

# BUSINESS PLAN

2015 - 2020





## 2015-2020 Business Plan

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## **FOREWORD**

In 2001, the decoding of the human genome transformed our understanding of human development, wellness and disease and, in so doing, empowered medicine to characterize, diagnose, and treat diseases more precisely. Novel technologies, such as next generation genome sequencing and large scale data analytics using sophisticated mathematics and advanced computing resources are now revolutionizing the health related sciences with a potential for transformative impact on health care.

Coupled with epigenetics, proteomics, metabolomics, gene targeting, imaging, drug discovery etc., the genomics revolution is transforming the way in which medicine can be best practiced. The era of personalized and targeted medicine has begun. Initial excitement and progress in the field of precision healthcare has been focused on developing novel, targeted interventions using genomics and large scale analytics in the areas of cancer care, rare diseases and drug therapeutics (pharmacogenomics).

Children pass through several developmental stages and each step is subject to unique health challenges with life-long personal, societal and economic consequences. Moreover, as the origin of all adult diseases emanates from interactions between genes and the environment - from conception through childhood to adulthood - it is ever more imperative that research efforts be focused on the developmental continuum. Such a paradigm enables new knowledge creation and a comprehensive understanding of gene-environment interaction, which forms the basis for precision medicine throughout life.

Only a few centres in the world are focused on deciphering the genetic basis of developmental disorders and their transition to adulthood. ACHRI is one such centre. We are committed to redefining how one envisages human development in the context of gene-environment interactions. Specifically, ACHRI is focused on becoming a global hub of research excellence for personalized child health and the science of genomics as it applies to human development and health. ACHRI's aspiration to become the nexus of child precision medicine has its origin in the foundational research and business plan that was put forward in the years 2010 – 2015. ACHRI's strategic plan inspired its membership to develop state of the art genomics, informatics and imaging platforms, which have since helped attract the best and the brightest minds to Calgary.

In June of 2015, the Alberta Children's Hospital Research Institute (ACHRI) released its 2015-2020 Strategic Plan:

[http://www.research4kids.ucalgary.ca/files/research4kids/achri-strategic-plan\\_2015\\_2020.pdf](http://www.research4kids.ucalgary.ca/files/research4kids/achri-strategic-plan_2015_2020.pdf)

The plan outlined the Institute's vision, mission and critical success factors. In addition, it provided a high level overview of the Institute's research themes, enabling research platforms, and documented our key partnerships and alignments.

The 2015-2020 ACHRI Business Plan now provides a more comprehensive review of the Institute's governance, organizational structure, recruitment priorities, emerging research programs, operational plans, enabling research platforms and budget. The document is prepared for submission to our partners as a research and innovation roadmap for our interdisciplinary research partnership and to inform a fund development initiative in support of the plan.

Background material helpful to the reader is attached in the form of appendices.

Yours sincerely,

Dr. R. Brent Scott  
Director, ACH Research Institute  
Husky Energy Chair in Child and Maternal Health

## **Note to Readers**

ACHRI's Business Plan was developed over a six month period, July-December 2015. ACHRI's leadership team is grateful for the time and commitment our members gave to create this plan. The leadership team also benefited and appreciated the constructive advice and encouragement offered by our child health research champions: the Alberta Children's Hospital Foundation, the Cumming School of Medicine, the University of Calgary and Alberta Health Services.

What has been developed is both a clear outline of the Institute's research agenda and an aspirational summary for the next five years. ACHRI's goal is to become Western Canada's leading child health research centre within the next five years. ACHRI is committed to achieving excellence and believes in the attainability of our goal, through this plan.

ACHRI's leadership team and our members are aware of, and sensitive to, the challenges of the current environment. Therefore, ACHRI's research agenda will be implemented prudently with the support of our research champions and funding secured from philanthropic resources, external grant competitions or other avenues. Consequently, this document does not include budgets as they are considered notional at this point. Effective April 1<sup>st</sup>, 2016, ACHRI's research business plan will have core operational funding provided for the next five years as a result of community philanthropy and the initiative of the Alberta Children's Hospital Foundation. Other elements of the business plan will be funded by previously approved ACHF commitments in support of our enabling research infrastructure and child health research programs. Additional elements will depend upon future philanthropy.

The next five years will be an exciting time for the growth of child health research and its impact. Locally, nationally and globally, new discoveries from genomics, developmental biology, and the health and clinical sciences will drive innovation, increase our knowledge and understanding of the fundamental biology of health and disease and lead to improved care and health outcomes for children.

ACHRI intends to deliver on our vision of developing "a healthier and more prosperous future for our children through research."



## Table of Contents

	Page
<b>Foreword.....</b>	<b>2</b>
<b>Note to Readers.....</b>	<b>3</b>
<b>Table of Contents.....</b>	<b>4</b>
<b>Executive Summary.....</b>	<b>5</b>
<b>A. ACHRI - An Overview.....</b>	<b>11</b>
<b>B. ACHRI's Research Environment, Alignments and Partnerships.....</b>	<b>13</b>
<b>C. ACHRI's Priority Themes .....</b>	<b>15</b>
1. Genes Development and Health.....	15
2. Behaviour and the Developing Brain.....	34
2.1 Acquired Pediatric Brain Injury and Rehabilitation.....	34
2.2 Pediatric Epilepsy.....	40
2.3 Neurodevelopmental Disorders and Child Mental Health.....	46
3. Healthy Outcomes.....	54
<b>D. ACHRI's Impact and Goals.....</b>	<b>69</b>
1. Impact Framework.....	69
2. Advancing knowledge – Academic Impact.....	70
3. Building research capacity – the fundamental elements of success.....	73
3.1 Personnel – Recruitment and Funding of Successful Research Scientists and Trainees.....	73
3.2 Infrastructure – Research Space and Platforms.....	77
3.3 Funding.....	85
<b>E. Governance and Organizational Structure .....</b>	<b>87</b>
<b>Appendices:</b>	
Appendix 1: ACHRI - The Historical Background.....	91
Appendix 2: ACHRI Membership Guidelines.....	92
Appendix 3: ACHRI's Communications Strategy.....	96
Appendix 4: ACH & ACHRI as a World Leading Academic Child Health Centre....	98
Appendix 5: CSM Precision Medicine Initiative.....	101
Appendix 6: CSM Annual Report 2014-15 – ACHRI and CSM.....	108
Appendix 7: ACHRI Recruitment Priorities by Theme.....	117
Appendix 8: Comprehensive Review of ACHRI Platforms .....	127
Appendix 9: ACHF Funding Commitments 2015-2020.....	159
Appendix 10: ACHRI Core Operating Budget Proposal 2015-2020.....	159
Appendix 11: ACHRI Philanthropic Funding Opportunities 2015-2020.....	159

## **Executive Summary: ACHRI 2015-2020 Business Plan**

### **ACHRI Aspirations 2015-2020**

By 2020, the Alberta Children's Hospital Research Institute (ACHRI) aspires to be recognized as the leading child health research institute in Western Canada. Over the next five years, ACHRI will lead in the emerging sciences and techniques of precision medicine for children encompassing basic, clinical, health services and population health research and utilizing genomics, bioinformatics and 'big data' techniques and applications.

ACHRI's scientists will be known and recognized for their research strengths in the fundamental understanding of human biology and development, pediatric brain health and rehabilitation, and the application of new knowledge to drive improvements in the prevention, diagnosis and treatment of pediatric illness that maximizes healthy outcomes for children – outcomes that create a societal return on investment with lifelong dividends.

ACHRI recognizes the ambitious nature of its plan. However, based on progress over the past five years, the shared aspirations of our major partners, the Cumming School of Medicine (CSM), University of Calgary (U of C); Alberta Children's Hospital (ACH), Alberta Health Services (AHS) and the Alberta Children's Hospital Foundation (ACHF), ACHRI believes that the goal is worth striving for and is achievable.

The following provides a high level executive summary of ACHRI's 2015-2020 Business Plan for Child and Maternal Health Research.

### **The Context for this Business Plan**

ACHRI has evolved over 35 years into a major Alberta and international resource for child health research focused upon the developmental origins of human health and disease and the translation and application of that knowledge from the bench to the bedside, to the community. ACHRI's scientists are drawn from across the U of C, and their research interests span the entire continuum of child health research. The new knowledge created is impacting policy and practice to improve lifelong health and wellness.

ACHRI's scientists collaborate with colleagues across Canada and internationally to advance child health. Locally, our most application-oriented partnership occurs with AHS as ACHRI is considered the research arm of the Alberta Children's Hospital.

ACHRI is one of seven research institutes of the CSM. ACHRI's current core research foci are the molecular and biological origins of disease and health, child brain and mental health, and healthy outcomes for children and mothers. The Institute is governed as a partnership between the U of C, AHS and the ACHF. It is the research home for 117 full and 146 associate members. The membership includes basic, clinical, population health and health services researchers engaging in the investigation of relevant and high impact child and maternal health research questions.

The range and scope of our members' research interests and our scientists' expertise position ACHRI to be a highly translational research institute which rapidly deploys the basic science and clinical discoveries into changes in health care practices in the clinic and community and into improved social and health policies that impact positively the health of children and mothers.

## **ACHRI Mission and Vision 2015-2020**

For the 2015-2020 Business Plan cycle, ACHRI's overarching goal is to be a flagship research institute of the CSM, the U of C and AHS, that is recognized as the leading child health research institute in Western Canada. The Institute's vision is to achieve a healthier and more prosperous future for our children through research.

To achieve this vision, ACHRI's mission will be to foster healthy biological and psychological trajectories for babies, children and youth through excellence in research, innovation, knowledge translation and education.

Success for ACHRI's Vision and Mission will require recruitment and retention of high quality researchers/faculty as well as leading edge research infrastructure. The success of the Institute will be built on the following three fundamental elements:

### **Fundamental Element 1: Recruitment and Funding of Successful Research Scientists**

This Institute's future success as Western Canada's leading child health research institute is dependent upon the recruitment and retention of researchers who can successfully compete nationally and internationally for external grant support of their research.

ACHRI therefore plans to recruit an additional 20-30 new scientists into our three priority research themes over the period 2015-2020. These new scientists will be recruited into the CSM and our other partner faculties across the University of Calgary.

Nationally and internationally, the hallmark of a strong researcher is the ability to successfully compete for external grant awards. However, young scholars at the start of their research careers require resources that launch their laboratories and research programs so that they can be successful with external grant applications. A major enabler for ACHRI to achieve its goals and to ensure new scholars get off to a successful start is the provision of adequate **start-up funds** for new recruits. Established scientists who are highly ranked, but unfunded in specific external research funding competitions, occasionally need **bridge funding** to sustain their laboratories to the next grant application cycle. To ensure uninterrupted operations and sustained productivity, ACHRI needs to provide bridge funding. In large national and international funding competitions (e.g. CIHR, Genome Canada and CFI), institutes are frequently expected to provide **matching funding** as an institutional requirement to successful applications. The need for matching funds from ACHRI has been in the millions of dollars annually which the institute has been supporting out of existing philanthropic support (where alignment permitted) or out of our core operating budget. Further details are available in the comprehensive ACHRI Business Plan document (please see pages 72-76).

Overall, for all three funding initiatives – start-up, matching and bridge funding – ACHRI is seeking philanthropic support for \$2 million per year in start-up funding, \$1 million per year in matching funding and \$200,000 per year in bridge funding for a total annual budget of \$3.2 million for the *ACHRI Start-up, Matching and Bridge Funding Program*.

### **Fundamental Element 2: Expanding Research Space**

A severe and critical need for additional space has been identified as the most significant challenge facing the Institute and a major risk to its ability to recruit, grow its research programs, achieve success and deliver on its aspiration of excellence.

Over the next 5 years, ACHRI will complete the redevelopment of approximately 2,000 m<sup>2</sup> in the Health Sciences Centre to support ACHRI's basic science precision medicine initiatives. In the longer term, ACHRI is planning for a comprehensive research space to be constructed (free-standing or co-located with new U of C research space) in close proximity to the Alberta Children's Hospital.

This new research building is a long-term aspirational goal for ACHRI. During the term of this business plan, ACHRI remains committed to further engagement with AHS and the U of C to develop an Academic Child Health Research Center within the Calgary Academic Health Sciences research environment.

### **Fundamental Element 3: Funding for Enabling Research Platforms**

ACHRI's research platforms are shared research infrastructure resources that are used collectively by the membership. ACHRI will support four research platforms over the 2015-2020 Business Plan Cycle:

- **ACHRI led CSM Centre for Health Genomics and Informatics**

In order to take the initiative to a new level, ACHRI has purchased new sequencing instruments to replace those purchased four years ago (technology has advanced and we can no longer purchase service agreements for the older machines) and is exploring a partnership with IBM to create a scalable pilot of a high-performance analytics platform, the architecture of which will support storage, computation, workload management, linkage and analysis of a variety of data sources (clinical, imaging, genomics and other metadata). The system will have the capacity to align with and complement computational infrastructure investments already made in the CSM Center for Health Genomics and Informatics, the CSM Clinical Research Unit and U of C IT.

The platform investment is foundational to the research agenda within the Genes Development and Health Theme and complementary or synergistic to basic and clinical research in the Behavior and the Developing Brain and the Healthy Outcomes theme. In addition it creates the necessary infrastructure for at least eight of the currently approved recruitments

- **ACHRI Clinical Research Support Platform**

Going forward, the Institute will build additional child health clinical research capacity in a sustainable fashion by supporting the recruitment of successful scientists with epidemiologic, methodological, biostatistical and clinical informatics skill sets who will in turn attract graduate and post-doctoral trainees to participate in collaborative research and further enhance clinical research capacity. ACHRI will maintain a modest clinical research consultation service specifically to support associate members striving to improve their clinical research proposals.

- **3T MRI/Child and Adolescent Imaging Research (CAIR) Program**

The platform permits visualization of brain structure, function and chemistry and supports an outstanding team of five imaging scientists. Currently the platform's strength is neuroimaging, but over time the scope of activities that this platform supports will expand to include teams conducting cardiac, cancer, bone and joint research. The 5-10 year vision for this platform is to become a nationally and internationally recognized center in pediatric imaging. To achieve this vision, the team must continue to grow their scientific capacity by recruiting leading researchers in the field. In addition, we must plan to expand and renew platform infrastructure including a research-dedicated 3T MRI, specialized fetal and neonatal imaging equipment, and possibly a PET-MRI system.

- **ACHRI Research Training Platform**

Through its Research Training Platform, ACHRI supports the development of excellent researchers of the next generation. Currently in its seventh year, and with the annual budget of approximately \$1 million, the Platform

offers a variety of incentives that enhance the research training environment in ACHRI. Trainee stipend support represents the majority of the Platform's budget, which not only increases training capacity in our Institute, but also enables ACHRI investigators to allocate more of their resources for enhancing research and training within their labs, given the fact that graduate students and postdoctoral scholars carry out the bulk of the work on research projects. Trainees are consistently at the centre of the research effort, which effectively makes them the backbone of research in the university system. Investing in our trainees and supporting them in their research careers ultimately translates into investing in the future of research.

## **ACHRI's Impact and Goals, 2015-2020**

### **Impact Framework**

ACHRI has adopted the Canadian Academy of Health Sciences (CAHS) Impact-Return on Investment Framework to guide development of our success metrics. (Please see page 68 in Business Plan document for details.)

Key foundational activities (with suggested metrics) in the CAHS framework relate to: Advancing Knowledge (quality and number of publications); and, Building Capacity (number of academic personnel recruited, number of students in training, amount of competitive research funding and available research infrastructure including space and research platforms).

Within the CAHS framework the research output from institutes like ACHRI contributes to a global knowledge pool from which innovations, cures, and improvements in health are drawn. In terms of health research achieving impact at the clinic, bedside or community, the CAHS framework describes how research that enters the global knowledge pool via a rigorous process of external peer-review is translated into policy and practice through collaboration and consultation with a broad array of health care, community, government and industry participants. The ultimate goal for all our research activities is to improve child health and wellness. Basic science research findings will take a longer and different translational path than a research finding from a technology assessment evaluation or clinical practice study. At each translational step, success can be defined either by proceeding onwards, or halting based on the nature and quality of the evidence.

ACHRI's contributions to this knowledge pool derive from hypothesis-driven research that spans each of ACHRI's themes. Often this work occurs in active partnership with colleagues across the CSM, the U of C, and AHS and can be directly or indirectly supported by the resources of the Institute's three partners. Translation into the clinical and community realm relies on strong partnerships with the academic, clinical, government, community and industry partners.

Over the last five years, there are many examples of ACHRI members' research having achieved high-impact national and global awareness. ACHRI is also performing solidly within the CSM, U of C and Alberta Children's Hospital AHS environment and is now a major element of partner success.

### **Goals for 2015-2020**

- Advancing Knowledge - Outcome Metrics**

Over the period 2015-2020, ACHRI plans to increase the number and cumulative impact factor of members' publications by 30 per cent over the last reported year 2013-2014. The CSM provides a comparative baseline count of publication activity, space and funding success for CSM faculty members and over the next five years similar baselines will be derived for ACHRI members in other U of C faculties.

- **Building Capacity - Outcome Metrics**

- **Personnel**

Over the period 2015-2020, ACHRI will recruit and nurture 20 to 30 new high-quality faculty members within its priority translational research programs. The ACHRI Research Training Platform will continue to attract the best and brightest students, enhance research performance and educate the next generation of child health research scientists.

- **Research Funding**

Over the period 2015-2020, ACHRI will increase competitive research funding by 30 per cent over the reported year 2013-2014.

- **Infrastructure (Space and Platforms)**

Over the period 2015-2020, ACHRI will:

- Renovate 2,000 m<sup>2</sup> of wet-laboratory space in the Health Science Centre at the Foothills medical campus;
- Lead the redevelopment of academic and service bioinformatics space of the former Sun Centre for Visual Genomics in partnership with the U of C and the CSM; and,
- Initiate planning with the U of C and AHS for new research space or a tower on the University campus adjacent to the ACH to complement the AHS/ACHF investment in the Alberta Children's Hospital on West campus and to thereby create the long-term research home for ACHRI.

## Specific ACHRI Research Theme Success Outcomes, 2015-2020

- **Genes, Development and Health**

This Theme will develop the MORPH/KidOmics program using multi-model organism research strategies to improve the early detection of rare diseases, the development of new diagnostic tools and therapies, and the elucidation of developmental pathways at the cellular and organ levels using genomics. The basic science will be conducted by the MORPH team. They will focus their exploration on fifteen genes selected in collaboration with the clinical medical genetics team. The KidOmics team will utilize a precision medicine clinical and genomics approach to the investigation of one thousand patients with rare or undiagnosed disorders over the next three years. The proposal will evaluate efficacy, efficiency and accuracy of next generation sequencing as a diagnostic tool with the capacity to improve cost-effectiveness of health care.

- **Behavior and the Developing Brain**

This Theme will conduct research in three focused areas of high relevance and potential impact. The long-term intended outcomes of each focus are as follows:

1. **Acquired pediatric brain injury and repair**

- Decrease the number of preventable pediatric brain injuries through identification of at-risk populations and the implementation of evidence-based prevention measures;
- Introduce more sensitive diagnostic and prognostic tools that can better identify pediatric brain injury and predict outcomes;
- Reduce long-term negative outcomes and improve the quality of life for children with acquired brain injury;

**2. *Pediatric epilepsy***

- Identify new antiepileptic drugs that can transform the treatment of current treatment-resistant epilepsy;
- Identify biomarkers as outcome predictors to provide targeted, precision medicine treatment;
- Develop novel metabolism-based therapies for drug-resistant epilepsy.

**3. *Neurodevelopment and child mental health***

- Generate the knowledge that can prevent, reverse or minimize the damaging effects of neurodevelopmental and mental health disorders in children;
- Optimize public resources for families and children with/at risk of neurodevelopmental and mental health disorders;
- Optimize clinical and community-based health care delivery as well as educational strategies through continuous translation and integration of research findings into practice; and,
- Improve the psychosocial, emotional and mental health of children with neurodevelopmental disorders and their families, thereby reducing the care challenges placed on families and the community at large.

• **Healthy Outcomes Theme**

- Achieve a recognized international prominence in outcomes-oriented child health research, evidence-based best clinical practice guidelines and care pathways;
- Theme-generated, outcomes-based research results will underpin new health and public policies, locally, nationally and internationally; and,
- Working with AHS, and other provincial, national and international partners, Theme-generated research will be used to improve specific health outcomes, reduce the costs of delivering healthy outcomes and improve the quality of life for children.

**ACHRI Business Plan 2015-2020 Resources Requested**

In order to power its 2015-2020 Business Plan, ACHRI is seeking a core operational funding support in the amount of \$5,302,000 annually. In addition to the \$58 million committed by ACHF to existing platform and theme program development, ACHRI is seeking funding in a total amount of \$79 million in research program and infrastructure growth opportunities contingent on philanthropic funding. The detailed budget documents can be found in Appendices 9, 10 and 11.

## A. ACHRI – An Overview

The Alberta Children's Hospital Research Institute (ACHRI) is a multi-disciplinary partnership institute within the Cumming School of Medicine, governed by a Memorandum of Understanding between the University of Calgary, Alberta Health Services, and the Alberta Children's Hospital Foundation. ACHRI's membership encompasses a diverse community of scholars in the university's faculties of Arts, Education, Kinesiology, Medicine, Nursing, Science, Social Work and Veterinary Medicine.

ACHRI's vision is:

*A healthier and more prosperous future for our children through research.*

And the Institute's mission is:

*To foster healthy biological and psychosocial trajectories for babies, children and youth through excellence in research, innovation, knowledge translation and education.*

ACHRI's vision and mission build upon the University of Calgary's *Eyes High* strategic direction with a goal of optimizing biological and psychosocial development and health – from before conception to adulthood. ACHRI is the research arm of the Alberta Children's Hospital and together we create an integrated academic child health center where our scientists deliver innovative health care solutions in partnership with Alberta Health Services.

ACHRI's high level goals are to:

- strive for research excellence,
- focus our investments and efforts on key priorities,
- create translational research pipelines with impact,
- secure transformative partnerships, and
- educate the next generation of child health scholars.

Of utmost importance to our future success is the recruitment and retention of high quality **people** (faculty). These are the dedicated basic, clinical, population health and health services research scientists who generate the innovative ideas that are pursued in collaborative research **programs** and are supported by **platforms** which are the foundational components of infrastructure that enables great science, which is translated into improved outcomes for newborns, children and youth.

The research programs of ACHRI members are organized into three priority themes, which drive research from the bench-to-bedside-to-community:

- Genes, Development and Health,
- Behaviour and the Developing Brain,
- Healthy Outcomes.

ACHRI has 117 full and 146 associate members with primary affiliations in the Institute's three research themes. Of the full members, forty are in Genes Development and Health, thirty-three in Behaviour and the Developing Brain and forty-four in the Healthy Outcomes theme.

Over the years, there have been various changes within and outside ACHRI's partnering organizations that have influenced the Institute's research environment and ultimately its governance and organization. Nevertheless, ACHRI has always made an effort to operate within a structure that ensures transparency, accountability to each Institute's partner, and sound operations of the Institute. Led by Dr. Brent Scott, Director, the Institute's leadership team includes Scientific Director, Executive Director (who acts as the academic lead for each of the three research themes), the Education and Training Director and the Senior Administrator. The Institute's operational activities

are supported by the Communications Manager, Finance and Business Operations Manager, two Program Managers who support ACHRI's themes and platforms, and a Grants Officer – all of whom report to the Executive Director. Additionally, research platform support teams (such as Manager of Sequencing, Manager of Informatics, Unix System Support) report to both Executive Director and to the scientific lead within their respective research facility. The Institute's operations, budgeting, future development and planning are governed by a committee structure which is outlined in detail in Section E.

ACHRI's primary operational responsibility is to establish and sustain an optimal research environment, with particular emphasis on the fundamental infrastructure (people, space and equipment) that enables Institute success across the four CIHR research pillars (biomedical, clinical, health systems and population health research). To support our three research themes, we have identified the following fundamental elements of success:

- Recruitment and retention of high quality personnel,
- Research infrastructure (space and research support platforms) and
- Funding

The Institute has established four research platforms that are critical enablers of programmatic success:

- ACHRI Research Training Platform,
- ACHRI led CSM Center for Health Genomics and Informatics,
- 3T MRI / Child and Adolescent Imaging Research (CAIR) Program and Platform,
- Clinical Research Support Platform.

Research, innovation, novel technologies and improved medical practices in the 21st Century have allowed a deeper and more integrated understanding of the origins of health and disease. Three recent advances stand out as being revolutionary and create new research opportunities for ACHRI that hold transformative promise:

- Next-generation genomic sequencing allows charting of the human genome and a greater understanding of how genes, proteins and molecules interact at the molecular and cellular level to define life-long health outcomes;
- New information technology supports multi-disciplinary research teams, large prospective cohort studies and clinical trials, massive databases, new imaging technologies and bio-banks to explore complex, multi-factorial influences of environment, medical care and the social determinants of health vis-à-vis our individual and societal well-being;
- The emerging science of epigenetics opens the doors to a better understanding of the interactions between an individual's genes and their environment including the effects on gene expression with long-term influences on the health of the current and future generations.

These advances have redefined the science and our ability to understand human biological, psychosocial development and clinical outcomes. The developmental origins of human health and disease are increasingly well recognized and accepted. Furthermore, interventions and investments during early life are being shown to yield the greatest long-term impact on individual and societal health and wellness.

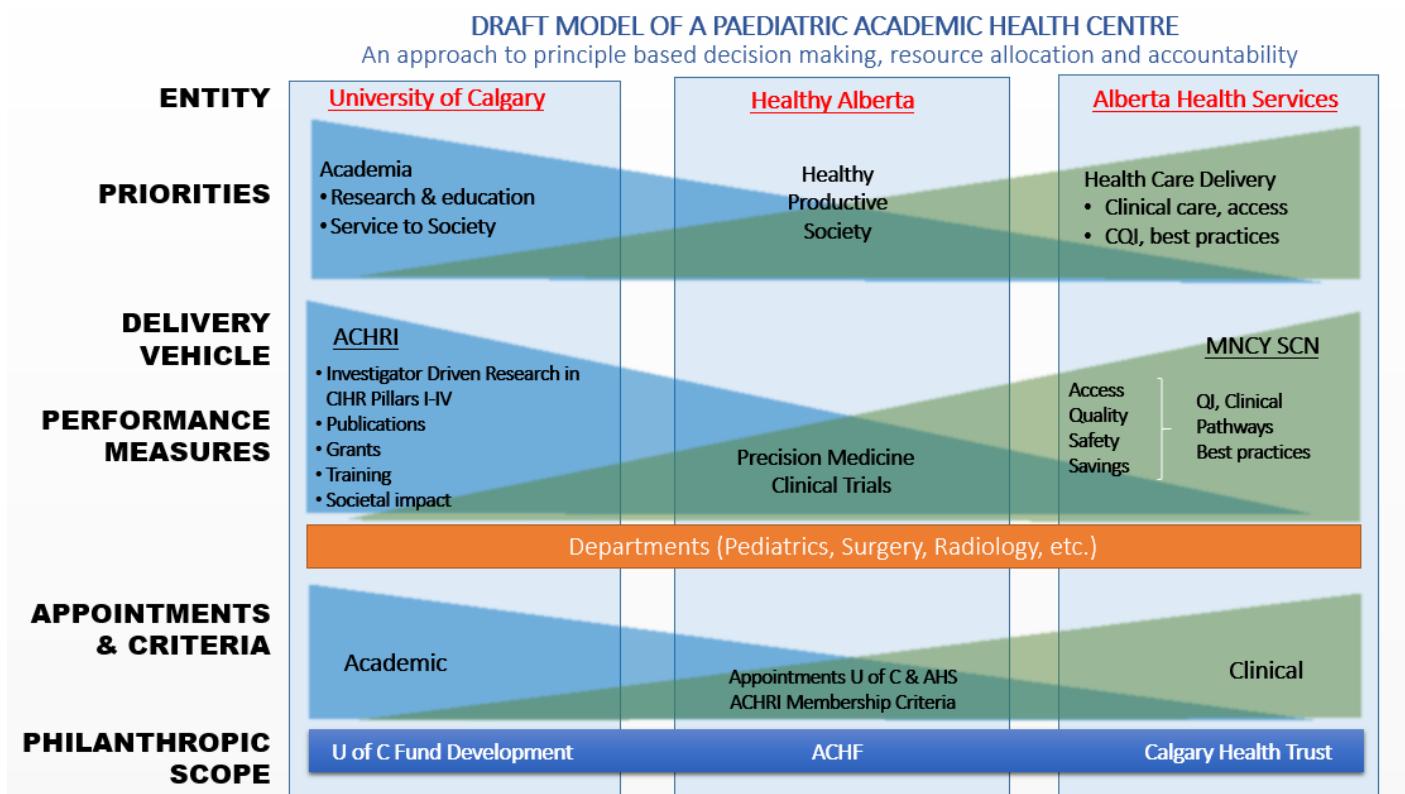
ACHRI is the research arm of the Alberta Children's Hospital and has committed itself to translational research that will increase understanding of the biological and psychosocial development of babies, children and youth. With our partners, we will create new knowledge to change practice and shape policy in ways that improve child health outcomes, enhancing the potential of children to mature as active, engaged and productive adults.

For additional information on ACHRI's historical background, evolution, communications strategy, as well as membership guidelines, please refer to *Appendices 1, 2 and 3*.

## B. ACHRI's Research Environment, Alignment and Partnerships

The Cumming School of Medicine, University of Calgary and Alberta Health Services, the two government-funded institutions to which ACHRI is accountable, both share a common goal of contributing to the health and well-being of Albertans. The institutional priorities and the performance measures by which their appointees/employees are assessed are different, but most overlap. *Figure 1* below depicts some of the interactions between U of C, AHS, ACHRI, ACH and the Alberta Children's Hospital Foundation as well as the key drivers within Calgary's integrated pediatric academic health centre. The figure illustrates each institution's priorities as wedge-shaped triangles, the bulk of which rests in the home organization, but in each case extends into the partner organization where there is a shared interest, responsibility and activity. While personalized medicine, patient centred clinical care and research are shared activities and priorities, different performance measures/output lenses do nevertheless reveal distinct foci which require unique approaches and resolution. These can, however, be synergistic and complementary through collaboration. Research institutes are primarily aligned with the U of C, while Strategic Clinical Networks (SCNs) reflect mainly AHS values regarding priorities, performance measures and outputs. In Calgary, Department Heads are jointly appointed as both the University academic and AHS Clinical Department Head. Each department member has both clinical and university appointments and a career activity profile that reflects the proportion of their role assigned to academic or clinical activities. ACHRI's membership options and criteria reflect a similar approach. Full members have a much greater proportion of their time, duties and performance assessment that falls within the academic sphere. Successful academic health centers integrate the strengths of both academics and clinicians in teams that greatly enhance performance and outcomes for clinical care, research and education. *Appendix 4* expands on the nature and potential benefits of an integrated academic child health centre.

*Figure 1. Depiction of relationships between U of C, AHS, ACHRI and ACH Foundation*



*Precision Medicine* has been articulated as a bold, comprehensive and inclusive new vision for the Cumming School of Medicine. (See Appendix 5 for details). It identifies a broad spectrum of infrastructure or platform needs: clinome analysis (i.e. clinical phenotype), genomics analysis, molecular diagnostics and phenomics analysis, microbiome analysis; bioinformatics capacity (“omics”, imaging, clinome, metadata), biobanking, imaging and novel technologies, exposome data, the fundamental science to understand disease mechanisms (e.g. model organisms research), tailored drug/vaccine/biological etc., clinical trials infrastructure, infrastructure for patient-centered care/patient-oriented research, ethical/economic/legal and social (EELS) implications of Precision Medicine.

The CSM’s precision medicine strategy is embedded within the health-relevant U of C priority research themes which include:

- Brain and Mental Health;
- Engineering Solutions for Health/Biomedical Engineering;
- Infection, Inflammation and Chronic Disease in a Changing Environment;
- Human Dynamics in a Changing World; and the most recent addition:
- Clinical, Health Services and Population Health Research which identifies the Precision Medicine, Optimal Health System Performance and Preventing Illness and Injury as Grand Challenges.

ACHRI’s three themes and four platforms have very strong alignment with the CSM’s Precision Medicine research direction, its platform development plans and the U of C health-related priority research themes. ACHRI is a strong partner and an avid contributor to both CSM and U of C key priorities; it also provides leadership in the area of genomics and informatics while championing the CSM Center for Health Genomics and Informatics.

From an AHS perspective, ACHRI is the research arm of the Alberta Children’s Hospital. Collaborations between U of C and AHS are essential for ACHRI and ACH to function as an integrated academic child health center. The synergies created by the integration of clinical care, research and education form the basis for high performing academic child health centres and are essential for translating new knowledge into better clinical practices, improved health care delivery and enhanced health outcomes. ACHRI supports the recruitment and retention of clinician scientists to U of C and AHS – the thought leaders and catalysts for innovations in clinical care, health services delivery and population health. ACHRI is also a member and supporter of the steering committee for the new AHS Maternal, Newborn, Child and Youth Health Strategic Research Network.

## **C. ACHRI PRIORITY THEMES**

### **C.1 GENES, DEVELOPMENT AND HEALTH THEME**

#### **Introduction**

Development from conception to adulthood is the most dynamic period of human life. Children pass through several developmental stages and each step is subject to unique health challenges with life-long personal, societal and economic consequences. Because the origin of all adult diseases emanates from interactions between genes and the environment from conception through childhood to adulthood, it is imperative that research be focused on the developmental continuum in order to fully comprehend and benefit from knowledge of gene-environment interaction.

Only a few centres in the world are focused on deciphering the genomic basis of developmental disorders and the impact of a healthy genome for the developmental transition from childhood to adulthood. ACHRI is one such centre.

In this business plan, ACHRI's Genes, Development and Health scientists have aligned their passion and interests to build on considerable expertise in clinical genomics and model organism genetics. This business plan further capitalizes on ACHRI's potential for dynamic interdisciplinary collaboration to propose a science plan that leads to the improved detection, prevention, amelioration or cure of rare childhood diseases, and to generate fundamental scientific discoveries that lead to ways that maintain or improve normal human development from the gene to the cell to the organ to the individual.

Over the period of this 2015-2020 ACHRI Business Plan, ACHRI's Genes, Development and Health Research Theme will establish two significant, linked initiatives - KidOomics at the Alberta Children's Hospital and Model Organism Research for Pediatric Health (MORPH) at the Foothills Medical Campus site – using the discovery potential of fundamental basic research to advance progress across the rare disease spectrum by the rapid translation of laboratory findings to clinical care accelerating Calgary as a global hub of excellence in rare disease understanding and treatment.

#### **Current State: Local**

ACHRI's Genes, Development and Health Theme is one of three research themes of ACHRI's scientific enterprise and is comprised of 40 basic and clinical research scientists from multiple University of Calgary faculties including the Cumming School of Medicine, the Faculty of Veterinary Medicine, the Faculty of Kinesiology, the Faculty of Arts and the Faculty of Science. The scientists of the Genes, Development and Health Theme compete for external grants through various granting agencies: Canadian Institutes of Health Research (CIHR), Alberta Innovates-Health Solutions (AIHS), The Canada Foundation for Innovation (CFI), Brain Canada, National Institutes of Health (U.S.A.), The Natural Sciences and Engineering Research Council (NSERC), The Canadian Cancer Society, and many others.

Some of ACHRI's members in the Healthy Outcomes and the Behaviour and Developing Brain research themes have research interests that are complementary to, or overlap with, their colleagues in the Genes, Development and Health theme. Collaboration is always encouraged such that the overall number of ACHRI scientists who could be said to have an interest in genomics and bioinformatics would likely be closer to 50 scientist members across the entire institute.

The Genes, Development and Health Theme has several clusters of research interest and activity that can be classified as established or emerging.

Established research clusters include scientists with common research interests and a track record of collaboration, or at least strong interaction, around a commonly understood and shared set of research interests, questions or investigative domains. At present, established areas of strength include the *Biological Basis of Development and Disease* research cluster that forms the core of the scientists contributing to the MORPH program and the *Genomic Basis of Health* research cluster that forms the core of KidOmics. These two research clusters are the most well-developed within the theme as reflected in the numbers of scholars in each, the ACHRI resources either invested to date or planned for future investment in each cluster, and the extent to which scientists from each cluster are involved in collaborative research within the theme and with scientific collaborators elsewhere.

In the emerging research clusters, collaborations are at an earlier stage of evolution and the shared research questions may not be as well drawn and defined. Current priorities for developing emerging clusters include the *Bioinformatics* and *Novel Therapeutics and Drug Discovery* clusters, which are developing areas of strength within the two established clusters listed above. Over the next five years, other emerging research clusters may develop and mature with the potential to become more prominent within ACHRI's panoply of research successes. These include pediatric cancer biology and therapy, the biology and epigenetics of maternal/infant reproductive health, and the biology and treatment of mitochondrial disease. All of these emerging clusters include scientists with external grant funding and philanthropic support. ACHRI is currently recruiting aggressively into the Bioinformatics group. The *Novel Therapeutics and Drug Discovery* cluster, which is in an early stage of development and collaboration, is strongly translational with a focus on drug discovery that employs high throughput robotic screening and information processing techniques. The *Maternal/Reproductive Health Research* cluster has the opportunity to advance a broad understanding of fetal development and development through the use of the "Alberta Birth Cohort Dataset".

Over the period September 2015-May 2016, approximately 2,000 m<sup>2</sup> of laboratory space (Health Sciences Center, Level 2, North-West wing) will be redeveloped primarily to house the *Biological Basis of Development and Disease* (MORPH) research cluster. The redevelopment costs have been supported by the generous donation of \$9.2 million from the Alberta Children's Hospital Foundation for both the design and construction phases.

By the end of May 2016, the estimated investment of ACHF funding in this theme's goals and priorities will have been about \$19.0 million, including the investment in ACHRI's genomics platform, the estimated requirement for the HSC renovation, the provision of investigator start-up funding, and CFI matching dollars from ACHF sources. It is anticipated that ACHRI will invest another \$1 million in an industry partnership to support implementation of the KidOmics and MORPH research proposals that form the core of a large CFI proposal to be resubmitted in 2016.

### **Current State: Canada and International**

Nationally, the Canadian Institutes of Health Research (CIHR) Institute of Genetics has identified two Signature Initiatives – Personalized Medicine and Epigenetics – relevant to this ACHRI research theme. The genomics "way forward" for research at the national level is well articulated in the Institute of Genetics Strategic Plan 2012-2017:

"How do we translate genomic information to advancements in diagnosing, preventing, and treating human disease? The answers are in the elucidation of gene function and in the understanding of how biological mechanisms are affected by specific mutations. Here is where model organism genetics, coupled with dynamic interdisciplinary dialogue and collaboration between medical scientists and basic researchers, will illuminate and be critical for decades to come."

Institute of Genetics Strategic Plan, 2012-17, page 20

Outside Alberta, various provinces have been willing to lead in advancing the development and dissemination of genomics through ambitious plans using focused and targeted approaches:

- In Newfoundland, a recent initiative to sequence 100,000 whole genomes has been announced. This initiative builds a major provincial partnership with IBM and Memorial University to launch a Translational and Personalized Medicine Initiative (TPMI). Newfoundland's TPMI represents an investment of about \$50M over the five years 2015-2020, with \$30M invested by IBM, nearly \$13M from the Government of Canada and \$7.2M from the Government of Newfoundland and Labrador. TPMI takes advantage of the fact that descendants of a limited number of Founder Families constitute a significant portion of Newfoundland's population, contributing to an unusual concentration of rare genetic disorders on the island. The TPMI research design targets families at high risk for certain diseases and aims at improving care while reducing healthcare costs and generating novel research findings.
- British Columbia has launched a "Roadmap for Bringing Personalized Medicine to British Columbians". This provincial roadmap takes advantage of near-term opportunities that leverage projects currently underway in British Columbia. These projects follow a model that applies the results of careful and fundamental genomics research with defined clinical objectives to deliver translational value. One example is the Pharmacogenomics in Primary Care and Community Pharmacies project which incorporates genomic information in a clinical decision support system to improve the therapeutic dosing of Warfarin, an important and commonly prescribed blood thinner which requires frequent and careful monitoring using traditional laboratory testing techniques.
- The Ontario Genomics Institute has received \$6 million in funding from Genome Canada to develop targeted treatments using genomic profiling for persons with cancerous tumours. The goal is to establish a genomic profile of various cancers so that healthcare providers such as Alberta Health Services can offer the right drug at the right time to a patient, thereby improving cancer treatment outcomes. This funding will support a partnership project between the Princess Margaret Hospital in Toronto and LifeLabs Medical Laboratory Services and is intended to generate knowledge that can be used across Canada.

Internationally, genomics initiatives tend to be large in scope and ambition, and more costly:

- The American Precision Medicine Initiative, announced by President Obama with a 2016 Budget investment of US\$215 million, will establish a genomics database of 1 million American volunteers to conduct research that improves diagnostics and treatments for disease, starting with cancer.
- In the United States, the US Department of Veterans Affairs has embarked on a major effort to establish a database of genomic and medical data to understand how genes affect health and disease in order to improve the healthcare of veterans. This project has already registered 345,000 volunteers, aiming for 1 million volunteers eventually. The databases will examine diseases such as diabetes and cancer and also examine post-traumatic stress disorders.
- In the United Kingdom, the 100,000 Genomes Project intends to establish a database of 100,000 genomes to enable new scientific discoveries and bring benefits to patients with rare diseases or cancer.

These examples represent a small selection of the many international initiatives underway to advance the genomic understanding of human development and how genomics can be harnessed to improve human health.

Canadian and international experience suggests that

- scholarly and clinical advances can be made using either large or small projects;
- genomics implementation projects can be usefully targeted to specific interventions;
- collaborative projects, between scientists and clinicians, are a frequently chosen path forward; and
- multiple partners, including significant private sector partners, can collaborate.

## ACHRI's Genomics Way Forward

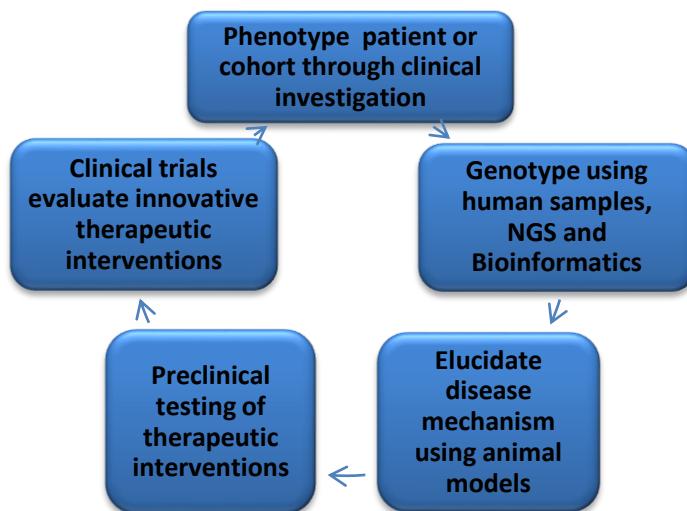
ACHRI's Genes, Development and Health scientists have identified specific goals that are well aligned with the framework articulated by the CIHR Institute of Genetics, and achievable over the five years of the proposed ACHRI business plan:

- To implement KidOmics, a translational research program that bridges the careful phenotypic characterization of a patient or patient cohort to genomic diagnostics and, at the other end of the pipeline, supports clinical trials of novel therapeutics. The KidOmics research program will create a foundation for the development of a diagnostics and therapeutics centre of excellence at ACHRI/the Alberta Children's Hospital, aligned with National and International Rare Disease Strategies.
- To implement *MORPH* (Model Organism Research for Pediatric Health), a structured investigation into the biological mechanisms underlying normal development and genetic disorders will be carried out, using experimental model organisms that will lead to the identification of potential therapeutic interventions including induced pluripotent stem cells (iPSCs) for tissue repair and preclinical drug screening in cell culture and animal models.
- To recruit, retain and nurture scientists working in the fields of human genomics, bioinformatics, and model organism developmental biology, whose research encompasses both fundamental and translational.
- To enhance the Genes, Development and Health graduate and postdoctoral programs to train the next generation of child health genomics scientists.

*The Theme's overarching goal in this business plan cycle 2015-20 is to develop a pipeline of basic and clinical precision medicine research that is characterized by translational cycles of patient to bench to bedside discovery (Figure 6).*

*The translational cycle begins with the detailed characterization of an individual patient or a patient cohort disease phenotype, flows to the discovery of the disease genotype using NGS technology and bioinformatics, to the elucidation of disease mechanism in animal models of human pathophysiology, to the identification of potential therapeutic interventions that can be evaluated in clinical trials resulting in improved child health.*

*Figure 6: Model of a pipeline of basic and clinical precision medicine research characterized by translational cycles of patient to bench to bedside discovery*



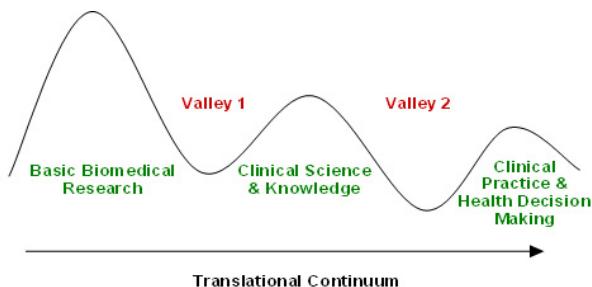
## The Scope of ACHRI's Genomics Translational Challenge

ACHRI recognizes that this is an ambitious direction for the Institute that will require our team to traverse Butler's translational "valley of death" (Declan Butler, *Nature* 453, 840-842, 2008. Published online June 11, 2008: <http://www.nature.com/news/2008/080611/full/453840a.html>). Butler's metaphor refers to the growing awareness of a widening gap between advances in basic science and the practical application of that knowledge.

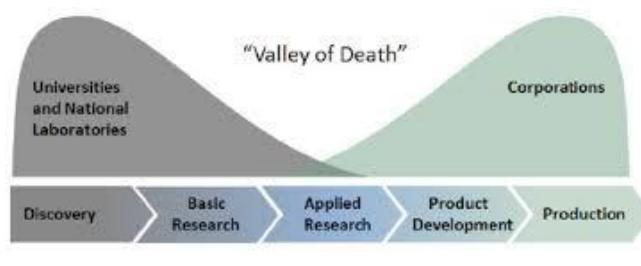
Others have explored Butler's metaphor and simplified it. A conceptually more direct simpler two-valley model is shown in *Figure 7* below (Meslin et al. *Clin Transl Med*. 2013; 2: 14. Published online Jul 27, 2013: doi: [10.1186/2001-1326-2-14](https://doi.org/10.1186/2001-1326-2-14)). *Figure 8* (below) illustrates the concept that effective translation of research from bench to bedside requires the major engines of biomedical research, the academic medical centers funded by the CIHR in Canada or NIH in the USA, to work effectively with industry. (Califf and Berglund, *Acad Med*. 2010 Mar; 85(3): 457-462. Published on line July 27, 2010 as doi: [10.1097/ACM.0b013e3181ccb74d](https://doi.org/10.1097/ACM.0b013e3181ccb74d)).

ACHRI is engaging with an industry partner that has genomic and health care expertise to develop a formal research partnership that will assist in bridging these gaps and developing an efficient, effective and productive research pipeline that can transform new knowledge into innovative business opportunities and improved health outcomes.

*Figure 7. Translation valleys of death*



*Figure 8. Academic-industry partnership*



Sections a), b), c), and d), following, describe how ACHRI's Genes, Development and Health Theme proposes to meet these goals over the next five years and bridge Butler's "valley of death".

### a) KidOmics:

Genetic Rare Disorders (RD) have a disproportionately high impact on the health of children and their families. Although individually rare, collectively these conditions are common and improving access to expert clinical care supported by cutting edge genomic technology remains one of Alberta's and Canada's greatest challenges.

There are over 7000 genetic disorders, of which just over half now have a known cause and less than 500 have a specific therapy. Genetic disorders in children can affect virtually every system and therefore can present with symptoms that include birth defects, epilepsy, recurrent infections, failure to thrive, autism and intellectual disorders, congenital heart defects, deafness, cancer, nephrotic syndrome, acidosis and metabolic disorders, short stature, obesity, scoliosis and inflammatory bowel disease.

Roughly 25% of children receiving ACH inpatient services have an underlying genetic condition and a similar proportion exists in many outpatient clinics. Children with genetic disorders experience more outpatient visits, inpatient admissions with extended length of stays, and are, sadly, more likely to die early in life. For many children their health care journey is characterized by lengthy diagnostic or treatment odysseys, during which delays to arrive at a diagnosis are common or multiple rounds of ineffective or even harmful therapeutic interventions are attempted.

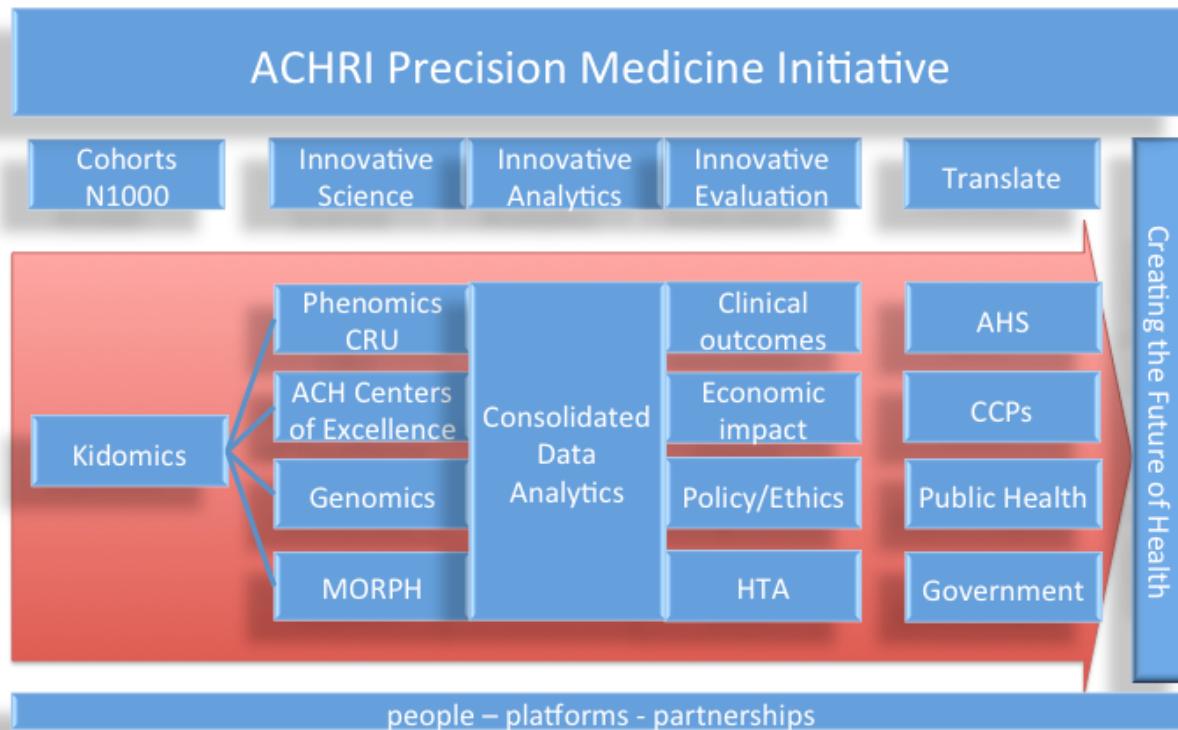
Without a definitive diagnosis, parents and providers are at a loss to understand the child's prognosis, best approaches to care and genetic risks to other siblings.

The revolutionary speed, cost and throughput of next generation sequencing (NGS) has brought genomic medicine to the doorstep of the clinical diagnostic and treatment services. The challenge and opportunity is to further drive scientific advances in RD research to the clinic.

Prior to implementation of genomic testing, analytical, interpretation, reporting and accreditation issues need to be addressed. Further, there is limited experience and there are few published standards on best clinical practices that address issues such as consent, privacy, return of results, incidental findings and clinical utility and cost effectiveness. It also remains unclear how access to genomic testing can be expanded beyond expert tertiary genetic clinics or how clinicians' lack of knowledge about the use/application of genomics can effectively be addressed.

The Genes, Development and Health Theme proposes to address these issues by establishing a KidOmics program (*Figure 9*) to support the development of a genomic testing pipeline at ACH. This clinic will partner with the Genome Canada funded Care for Rare Project as well the SickKids Genome Clinic and St-Justine Genome Centre. *KidOmics* aligns with Pillars One and Two of the Canadian RD Strategy and is aligned with activities as proposed in the PARTNERS SPOR research proposal. KidOmics is ACHRI's Precision Medicine Initiative, bringing together people, platforms and partnerships to provide cutting edge precision care based on integrating clinical, genomic and models systems researchers to improve the health and well-being of children. This model, if successful, could be expanded to support precision medicine initiatives across other ACHRI and CSM initiatives. The KidOmics program is tightly aligned with AHS Clinical and Laboratory Genetic services in order to bridge translational gaps and ultimately make genomic medicine broadly available to the children of Alberta.

*Figure 9: KidOmics program within the context of the ACHRI Precision Medicine Initiative*



## a. KidOmics Activity1 - Improving early detection and prevention of RDs

The advent of next-generation DNA sequencing (NGS), both whole-exome (WES) and whole-genome sequence (WGS), has increased the pace of RD gene discovery. Canada has set the international standard for RD gene identification; FORGE Consortium and its immediate successor Care4Rare have studied 587 RDs, achieving molecular diagnoses in more than 40% (249 diseases), which includes the identification of 78 novel disease genes. For a growing number of RDs, the challenge now is to translate gene discoveries into the development of accurate diagnostic tools.

**Main objectives:** *KidOmics a.1. will improve early detection of RDs by 1) Establishing in conjunction with the CSM Centre for Health Genomics and Bioinformatics and Alberta Health Services, a translational genomics pipeline to implement rapid advances in NGS-based sequencing into accurate and cost-effective diagnostic tools for ACH physicians and patients; and, 2) Developing cutting edge tools to improve the diagnoses of patients with RDs.*

### **Sub-activity a.1.1: Translate the rapid advances in NGS-based sequencing into accurate and cost-effective diagnostic tools for Canada.**

The decreasing cost of sequencing combined with improvement in informatics tools provides the opportunity to introduce exome sequencing into the clinic (“clinical exome”) dramatically improving the diagnosis (and hence the care) of individuals with RDs. Although early data from a Care4Rare pilot study on 250 undiagnosed RD patients suggest that exome sequencing early in the diagnostic process confers the most utility and cost-saving potential, there are several barriers to its widespread clinical uptake. This includes the unequivocal identification of: 1) optimal sequencing and analytical approaches; 2) optimal positioning of NGS in the clinical work-up of RD individuals, 3) clinical utility; and, 4) a more complete analysis of the economic impact of NGS. **To help answer these questions, we will expand the study to incorporate 1000 additional patients over the next three years.**

The work of Sub-activity a.1.1 will cluster around three major foci: clinical test development, determining diagnostic utility and developing an economic evaluation of the new approaches.

**Clinical test development:** For clinical integration, the sensitivity and specificity of NGS mutation detection, interpretation of variants, and the interoperability must be similar or better than the current methodologies. For all steps of the process, we will establish standard operating procedures (SOPs) that respect the best practice guidelines in diagnostics and in NGS. More broadly, genomic analyses will provide clinicians with both the opportunity and challenge of an unprecedented wealth of information. In close collaboration with clinicians, we will investigate best means to interpret and present genomic information at point-of-care.

**Diagnostic utility:** We will analyze pilot Care4Rare diagnostic positioning data to identify the most appropriate RD patients and scenarios for evaluation in a publicly funded system. The diagnostic yield for 1) first presentation to a subspecialist and RD suspected; 2) second visit to the subspecialist and first-line diagnostic tests unrevealing; and, 3) protracted series of diagnostic investigations (diagnostic odyssey) will be investigated. Additional data elements will be collected from this series of 2500 undiagnosed RD patients to facilitate the clinical utility and economic studies outlined below.

**Economic evaluation (Marshall).** Although clinical practice based on genomics is viewed as having the potential to ‘bend the healthcare cost curve’, whether systemic clinical adoption of NGS will actually reduce health care costs and, if so, to what degree, is unclear. For the 2500 individuals, health resources used in response to diagnostic results will be costed in the first post-test year according to the appropriate fee schedules. For pediatric patients, total health and social services used by the child will be measured prospectively using the Health and Social Service Utilization (HSSU) survey, a validated, parent-report tool (i.e. health and social service visits, community support services, medical procedures, blood tests, other diagnostic tests, hospital/emergency services, prescription drug use,

and complementary therapies). Indirect costs associated with parental lost time and reduced work productivity will be captured by HSSU. In addition, we will build on Care4Rare research to develop a cost-effectiveness analysis to compare NGS analyses of RDs with current non-NGS diagnostic pathways in routine care using decision analysis modeling. In this way, we will enumerate the differences in terms of potential health gains to patients and costs to the health system over the short and the long term – i.e. the downstream benefits, consequences and costs of the uptake and diffusion of NGS in clinical care pathways.

***Sub-activity a.1.2: Use of innovative approaches to improve diagnosis for undiagnosed RDs.***

The global RD community has identified the solving of *all* inherited RDs by 2020 as one of its primary goals ([www.irdirc.org](http://www.irdirc.org)), a bold vision which would, in essence, end the diagnostic odyssey for many RD patients. However, the exceeding rarity of many of the large number of RDs that remain unsolved complicates the ascertainment of additional families critical for variant identification. Moreover, the likely “non-exome” nature of the underlying genetic pathology will also complicate subsequent interpretation of variants as disease-causing; these challenges must be addressed if this ambitious goal is to be realized. We will consequently pilot international RD data sharing, WGS analysis and configure a functional genomic approach to address these issues.

As an increasingly larger proportion of unsolved RDs is caused by genomic variants that lie outside the exome, the ability to interrogate noncoding regions for variants and rearrangements with WGS becomes of particular importance. We will employ WGS analysis on 50 individuals with RDs refractory to exome sequencing. This activity will leverage the expertise and collaborative resources of previous investments in FORGE (2011-2013) and Care4Rare (2013-2017), as well as state-of-the art innovative infrastructures (RaPiD CFI). We will also use additional approaches, including gene-expression (RNA-Seq) and epigenetic analyses, to investigate the causes of these RDs.

**a. KidOmics Activity 2 - Providing timely, equitable and evidence-informed care**

Management of Rare Disease (RD) patients is often complicated by the lack of knowledge on care and therapies for any given condition. Access to credible experts and evidence informed care guidelines is also limited for most RDs.

Patients with unknown or undiagnosed RDs (see Sub-activity 1.2) represent a particular challenge for both clinicians and the families. In general, the rarer the disease, the sparser both the natural history and management knowledge.

Canada’s relatively low population density and large geographic size compounds this such that RD patients and their care providers in remote and rural communities are even less well-equipped. Furthermore, as patients with RDs grow older, and indeed treatment improvements have resulted in greater numbers of RD patients reaching adulthood, they are prone to develop further complications due to their disease or adverse drug long-term effects; the Canadian RD community has clearly articulated the significant gaps they experience in the area of transition care.

**Main Objectives:** *KidOmics a.2. will facilitate the provision of timely, equitable and evidence-informed care by tackling two main aspects contributing to unmet clinical needs: 1) Establishing an RD clinical centre of excellence at ACH for expert and coordinated care of patients with common, rare, ultra-rare, and undiagnosed RDs. 2) Develop a strategy to address RD clinical trials infrastructure in collaboration with ACHRI and AHS.*

***Sub-activity a.2.1 - Establish a RD centre of excellence model for expert and coordinated care of patients with common, rare, ultra-rare, and undiagnosed ACH RD patients.***

*Delivery of care framework.* We propose a series of collaborative workshops at ACH bringing together clinicians, patients and RD community organizations, to further the development of our local framework. Our framework is based on classifying RDs as ‘common’ (e.g. cystic fibrosis, neurofibromatosis type 1; prevalence >1/10,000; many centres will have a dedicated team of experts), ‘rare’ (e.g. Rett or Noonan syndrome; prevalence of 1/10,000 to 1/50,000; academic hospitals may have an expert physician), ‘ultrarare’ (e.g. Weaver syndrome; prevalence < 1/50,000; an academic hospital may have one to a few patients), and undiagnosed (1000s of patients at each academic hospital). While many issues are shared amongst clinical care delivery for RDs in any of these categories, the access to *availability of expertise* is predominant and is heavily dependent on prevalence.

We propose a model whereby expert diagnostic and clinical care of RD patients is provided at an RD clinical centre or through an RD virtual network. Through the workshops and consultative processes, we will prioritize the development of multidisciplinary RD clinical centres of excellence at ACH for select common and rare RDs. We will also establish at “**undiagnosed” RD clinic at ACH.** We will also pilot the development of a virtual network clinic for ultrarare RD patients whereby an ACH clinician would coordinate the care of select patients with a national or international expert in this disorder.

***Sub-activity a.2.2 - Develop a strategy to address RD clinical trials infrastructure in collaboration with ACHRI and AHS.***

With KidOmics, an innovative approach is required to advance RD clinical trials research. Through stakeholder consultation including AHS, ACHRI and RD community organizations, a business plan to establish an RD clinical trials centre will be developed.

**b) Model Organism Research for Pediatric Health (MORPH)**

MORPH is an interdisciplinary group of clinical specialists in molecular genetics who diagnose and treat patients, computational biologists who conduct *in silico* studies of genes across evolution, and developmental biologists who study model organisms to decipher the molecular and cellular bases of pediatric rare disorders. The group seeks to leverage existing advances in model organism research and technology to develop an innovative bioinformatics and deep phenotyping investigative platform in support of patient inquiry using the following four phases of discovery and application: gene selection, bioinformatics analysis, experimental analysis in model organisms, and knowledge translation.

The overall MORPH research program will interrogate rare disease gene function in cells and tissues at high resolution. The resulting gene characterization will accelerate investigations into disease-relevant pathways and will transform the health care system’s capacity to bring genetic diagnosis, pathophysiologic understanding, and the identification of therapeutic targets to the clinical repertoire of patient investigation and care.

**Impact of Genetic Childhood Diseases and the Genomics Revolution**

As outlined in the preceding description of KidOmics, rare genetic disorders present several diagnostic and treatment challenges and have, in aggregate, a profound impact on the health of Canadians. The advent of “next generation sequencing (NGS)” has revolutionized the identification of the genetic causes of rare disease to an extent unimaginable even a decade ago. This abrupt opening of the technological window onto the genetic causes of birth defects now anticipates the need for rapid and effective research tools that will provide insight into disease pathogenesis in months, not the years currently required.

The accumulated knowledge that basic research has acquired on the development of animals in general, model organisms in particular, combined with powerful new optical, microfluidic and molecular technologies, allow previously unimagined speed and precision in probing, reporting, manipulating and understanding genes and their mutations.

With the assistance of the proposed infrastructure and programs, and through the marriage of these powerful new technologies with the basic knowledge derived from model organism research, MORPH will make fundamental contributions to understanding and, ultimately, treating genetic disease. The World Health Organization and the International Rare Diseases Research Consortium (IRDiRC) have both stressed the need to improve the lives of children with birth defects and rare disorders, a need that MORPH will fill.

### **Model Organisms: Insight into Human Disease and Development**

Model organism research paves the way to novel, innovative, and transformative treatment directly benefiting families and their children.

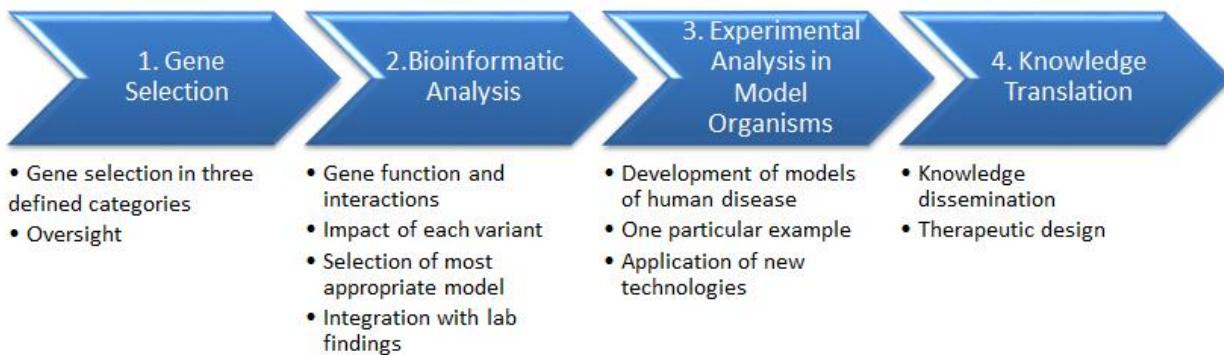
To date, model organism research has identified a multitude of fundamental biological processes that impact pediatric health. A partial list includes stem cell regulation, apoptosis and growth control, organogenesis, the wiring of the developing brain, angiogenesis, circadian rhythms, learning and memory. With this knowledge of developmental processes, modeling disease in simple organisms not only reveals the immediate impact of an uncharacterized gene mutated in a particular patient, but also reveals the collateral pathways and the tissue or cell types in which the gene participates.

Amongst the Genes, Development and Health theme are scientists who are experts in the four major model organisms used in genomic-based approaches to modeling human development and disease: mouse, zebrafish, fly, and worm. These animal models have been fully sequenced with annotated genomes, and they benefit from vast resources for genomic manipulation and functional analysis of genes. Recent introduction of CRISPR and TALEN genome editing technologies (recent Nature “Method of the Year”) for rapid and precise gene modification is revolutionizing the value of these organisms for disease modeling. These techniques will permit any patient mutation to be recapitulated, and will also permit targeting of associated gene pathways, dramatically enriching capacity to understand disease mechanisms in the broadest possible sense. These new tools are more precise, faster to use, and can reach across the genome, tissues and metabolism. The innovations that will come from applying these new technologies will transform the value of model organism research as a key component of patient investigations.

The work currently underway to re-develop and re-equip the MORPH team’s current laboratory space on the Second Floor Health Sciences Centre (FMC) combined with the ability to co-locate model organism biologists in the midst of investigators studying bioinformatics and human genomics, will allow MORPH research to occur within a state-of-the art physical and intellectual environment that will promote the creation of fundamental ‘translatable’ knowledge geared specifically to disease modeling and characterization.

The Theme proposes four “Activities” aimed at deciphering the biological and developmental basis of rare disorders in order to inform their diagnosis, management and treatment. These four Activities are: (1) gene selection; (2) bioinformatic analysis of the selected genes; (3) experimental analysis of the genes in model organisms, and; (4) knowledge translation, either to the clinic or to a pipeline leading to future therapeutics. As illustrated in *Figure 10*, MORPH will integrate model organism researchers into a “Model Organism Experimental Unit”, thereby establishing an investigational pipeline specifically designed to perform Activities 1, 2 and 3. Data from Activities 1, 2 and 3 will immediately be exploited for Activity 4, by knowledge translation and potential drug screens.

*Figure 10: Depiction of components within the Model Organism Experimental Unit (MORPH)*



The work of each activity is described in the following sections.

### **b. MORPH Activity 1 – Select and prioritize novel genes to be investigated computationally and experimentally**

Activity 1 builds upon prior work of the KidOmics leaders as part of FORGE Canada, the highly successful national collaborative effort to use NGS-based approaches to identify genes that, when mutated, are responsible for rare disorders (loosely referred to as “disease genes”). The Calgary group helped pioneer FORGE Canada and contributed significantly to ~300 genetic investigations referred by pediatric centres across Canada. Half of the gene identification projects were solved and >60 novel genes were identified. The FORGE Canada successor, Care for Rare, is the lead national program for rare genetic disease investigation with which MORPH is principally aligned. Care for Rare anticipates identifying a further 60 novel genes in the next three years. In addition to Care for Rare participation, KidOmics members are also identifying novel rare disorder genes in ACHRI’s genome centre. Overall, novel genes are being published at a pace of about ten per month, but for the majority of novel disease genes, the underlying biological or developmental mechanism remains completely unknown. This is the knowledge gap that MORPH will fill.

MORPH will investigate a select set of disease genes, either identified at the Alberta Children’s Hospital or particularly suited to model organism investigations, that will achieve two objectives: (i) to advance fundamental knowledge about these genes and the broader context in which they function, and; (ii) to establish a workflow for accelerated investigation, thereby maximizing the potential for model organism research to be directly useful to patients. Its membership includes clinical investigators, genome diagnostics specialists, bioinformatics specialists and developmental biologists. The MORPH Management Group prioritizes genes for MORPH projects and then formulates and monitors experimental strategies for the actual investigations (Activity 3 below). Genes for study will fall into three classes:

- (1) Class 1 genes: identified locally through clinical and genomics investigations at the Alberta Children’s Hospital (ACH) and further selected based on the capacity to contribute to ongoing clinical investigation, more specifically in translating actual research knowledge to patient counselling and management or therapeutic design.
- (2) Class 2 genes: aligned with ongoing research programs of MORPH investigators that have the potential for specific roles in development. These are likely to be the genes to which the most sophisticated analyses, the most comprehensive experience and the highest investigator interest can be applied, including those associated with the cardiovascular system (e.g., pediatric stroke and cardiomyopathies), neurological diseases, and muscular dystrophy.

(3) Class 3 genes: exhibiting clear, early developmental disruptions but best described as “black boxes”. These are the hardest ones to analyse because so little can be surmised about their mechanism of action. Class 3 genes also present the largest opportunity for fundamental discoveries, potentially with the collateral development of innovative technologies, through identification of mutations from whole genome investigations rather than from exome sequencing. Among Class 3 “genes” (strictly “loci”) will be sites of genome regulation, transcription factor binding sites, species of non-coding RNA etc. that are not normally examined in current NGS diagnostics. Compared to most other gene discovery and analysis programs, the MORPH team is notable for an approach that focuses on disruptions in critical signaling pathways, failed temporal or spatial patterns of gene expression, as well as other upstream and downstream effects of mutation that illustrate the intricate pattern of gene, protein and cellular interactions required to produce a healthy newborn.

The MORPH team will explore three genes in each of the three classes at any one time. Often a selected gene will belong to more than one class (e.g., a gene identified in the local clinic but also associated with cardiovascular defects in zebrafish) and these will be assigned a higher priority. The adjoining *Table 3* shows five genes already before the MORPH management group and subject of local investigations and local collaborations.

Table 3

<b>Disorder</b>	<b>Gene</b>	<b>Disorders and possible pathway</b>
<b>Nager Syndrome</b>	<i>SF3B4</i>	Craniofacial and limb malformation syndrome due to mutation in conserved splicing factor
<b>Cerebrocostomandibular Syndrome</b>	<i>SNRNPB</i>	Craniofacial & rib malformations - mutations in conserved non-coding exon of a splicing gene
<b>Dilated Cardiomyopathy and ataxia (DCMA)</b>	<i>DNAJC19</i>	Cerebellar atrophy, ambiguous genitalia and cardiomyopathy - mutation in mitochondrial import protein
<b>SHORT syndrome</b>	<i>PIK3R1</i>	Short stature, eye anomalies, characteristic facial features, lipodystrophy, hernias, hyperextensibility, and delayed dentition - mutation in phosphatidylinositol 3 kinase signaling cascade
<b>Recessive Limb Girdle MD</b>	<i>TRAPC11</i>	Limb girdle muscular dystrophy and myopathy with movement disorder and intellectual disability

#### b. MORPH Activity 2 - Comparative genomics for the functional characterization of genes.

Fundamental biological processes and pathways, such as replication, transcription and translation are highly conserved across organisms; subcellular processing, organelle structure and traffic, nucleic acid and protein turnover are also conserved, as are signaling pathways, much of metabolism, and cellular communications. Remarkably, many elements of development are regulated in a similar fashion in invertebrates and vertebrates and even employ the same repertoire of transcription factors. By and large, if humans and a simple model organism have a similar gene, this gene is likely to have the same function and even to share the same functional context (i.e., genetic or molecular pathway). Investigating the structure, function and biological context of a gene across evolution can lead to strong and reliable predictions about its role in biology that can then be tested in model organisms.

The initial role of Activity 2 will be to extend the computational studies that originally identified the disease gene selected for study. To this end, sets of genomic variants that are statistically associated with the disease phenotype will be characterized computationally to ensure that the correct target gene has been selected, before committing to potentially costly laboratory investigations. As described below, these analyses will be used further to assist Activity 3 investigations in an ongoing manner, including applying comparative analysis to the findings of the experimental

analyses. The computational hardware requested, including the computing cluster and data storage, will enable Activity 2 researchers to perform these tasks with high efficiency and speed.

#### ***Sub-activity b.2.1. Gene function and interactions.***

Predictions of the functional context of the candidate gene will first be used to develop working hypotheses about the regulatory and biochemical milieu in which the gene and its product(s) function. Regulatory interactions will be inferred by examining co-expression patterns in large-scale gene expression databases (e.g., ArrayExpress) and by probabilistically identifying transcription factor binding sites upstream of the gene, stringently guided by the position of nuclelease hypersensitive sites. Similarly, biochemical network databases will be mined to identify other proteins that may bind or interact. These and other functional and genomic data will be integrated to construct network models that capture all relevant information from public databases and will provide a starting point for investigations of the gene's function and interactions. These integrated models will be used to help guide experimental design with Activity 3 investigators, and will form working models that can be refined together by computational and experimental MORPH scientists.

#### ***Sub-activity b.2.2. Impacts of individual variants.***

The biochemical impact of individual mutations, including variants observed in patients, will be computationally interrogated using both comparative genomic data and protein structural information (when available). Existing variant impact prediction methods such as PolyPhen2, eXtasy, and CADD will be used to predict the severity of expected phenotypes caused by mutating key residues. Population genomic data (e.g., from the 1,000 Genomes and 6,500 exome databases) will be used to exclude recent targets of positive selection on the human lineage, which would otherwise be falsely identified as deleterious using comparative data alone. Other advanced evolutionary methods will also be used to model fitness distributions on the human lineage so that the impact of particular amino-acid substitutions can be interpreted. The outcome will be a set of sites within a gene that, if mutated, are likely to impart a disruptive phenotype when introduced into a model organism; a key member of this set of sites will be the putative disease mutation. This approach will extend the versatility of model organisms from complete gene disruptions (i.e., knockout mutations or full knockdown of expression) to the replication of specific disease mutations or to detailed investigations of active sites, regulatory sites or sites involved in macromolecule stability.

#### ***Sub-activity b.2.3. Selection of the most appropriate model organism.***

Model organisms differ substantially in the experimental techniques to which they are amenable but they may also differ in the degree to which they recapitulate specific human functions and phenotypes. Gene family evolution will therefore be explored across model organisms to assess the appropriateness of different model species for studying particular human gene defects. Gene family expansions and contractions will be identified using comparative genomic data and the results of high-throughput annotation pipelines (EnsEMBL Compara) and by quantitating sequence conservation within gene families. The appropriateness of individual model species will then be summarized based on the predicted similarity of the relevant gene families to humans.

#### ***Sub-activity b.2.4 Integration of ongoing laboratory findings into the comparative annotation of gene function and context.***

One of the strengths of the MORPH organization is the close proximity of computational and experimental biologists, thereby promoting continual collaborations. Rather than simply helping to define starting points for laboratory investigations, the computational analyses of Activity 2 will be fully integrated with the laboratory investigations throughout the research pipeline. As a result, existing databases of functional genomic data from high throughput experiments, genomic and transcriptomic sequence data, and comparative (evolutionary) information will be maximally leveraged with the local laboratory research to help integrate new findings into working models

of gene function. This close contact will be critical to support the rapid timelines proposed for knowledge transfer back to the clinic.

#### ***Sub-activity b.2.5 Expansion of computing and informatics capacity.***

In 2012, ACHRI (\$5M investment) and the U of C's Faculty of Medicine (\$2M investment) created a Genomics-Informatics Platform for next generation sequencing and bioinformatics analyses at the U of C, a necessary resource for the MORPH research program.

The initial computational component has been enhanced by a recently successful CFI LOF application (de Koning). The sequencing and computational-informatics components of the facility each have a Director and, for oversight, an Operations Committee that includes researchers. The existing ACHRI bioinformatics infrastructure consists of four main components: software, computers, networking, and storage, all housed (with the exception of continuous network-based off-site disk backup) in a purpose-built server room (Health Sciences Centre - HSC, room B151) with raised floor, dedicated chilled-loop air conditioning, central uninterruptible power supply, fire suppression, and automated environmental monitoring. A systems analyst and systems administrator maintain the more than 20 servers and clusters housed in B151, including four main ACHRI systems: 1) a cluster to process raw results from high throughput DNA sequencers, 2) a public Web portal for bioinformatics, 3) a university-users only portal of the same nature, and 4) a portal development server that also acts as backup for the DNA sequencers. As the MORPH group develops, additional dedicated servers for storage, processing and analysis will be incorporated within a highly expandable NetApp storage area network solution, which has a current total capacity of over 440TB. Multiple gigabit ethernet interfaces connect the server room to the main university network, the DNA sequencing lab, and the Alberta Children's Hospital Molecular Diagnostics Laboratory. The Web portals that act as the main user interface for nontechnical staff are installations of the popular open source Galaxy software for bioinformatics, and have been customized by the full time ACHRI Bioinformatics Support Specialist for the local genetic research community. The U of C and Compute Canada have agreed to co-support the facility.

The proposed computational infrastructure will be located in this server room, but will be functionally separated for the dedicated use of the MORPH group, yet supported by the platform resources. Proposed equipment has an estimated 10-year life expectancy and comes with a 3-year warranty. ACHRI's Genomics/Informatics platform budget contains contingency for equipment replacement and service.

The new infrastructure will provide bioinformatic tools to perform structure-function comparisons across species, and to analyze gene regulatory networks of disease genes. Comparative gene expression analyses will also utilise next generation sequencing technology, which results in the generation of a large amount of data. The MORPH bioinformatics faculty will assist in the analysis and mining of this data.

The computing cluster consists of a **PowerEdge blade server**, with 256 CPU cores, used for systems analysis of disease genes. A server of this calibre does not currently exist in ACHRI. In order to properly store raw and intermediate data files from genome investigations, an **enterprise-class file storage system** is requested, with 200 TB of disk storage and backup infrastructure from Long View Systems Corporation. Together, this infrastructure will be able to support the bioinformatic investigations of novel disease genes and pathways arising from large datasets generated by next generation sequencing technologies.

#### **b. MORPH Activity 3 - Deep phenotyping of human diseases in model organisms.**

Activity 3 is the experimental arm of MORPH, within which specialists in embryonic development, tissue and organ patterning, and developmental and metabolic regulation will delineate gene expression patterns, cell lineages and phenotypic consequences of gene mutations. Such deep phenotyping will require sophisticated cell imaging and cell/embryo isolation equipment as well as instruments that will allow precise analysis of gene and protein expression levels. The requested infrastructure will add speed, compared to the past, and precision and resolution,

compared to current experimental limitations. Overall, these studies will transform how we traditionally investigate genetic disease in patients. The basic knowledge derived from model organism research will be introduced into the patient workflow to produce timely, useful information, leading to improved care and diagnosis and potentially leading to treatment of the disease.

#### ***Sub-activity b.3.1 Development of multiple models of a human disease gene.***

Based on Activity 2 results and in consultation with the MORPH Management Group, diseases will be modeled in a minimum of two and often in three or four model organisms. The reason for choosing more than one model is primarily based on the often-distinct strengths of each organism to model human disease. This is a major strength of MORPH as individuals whose research is generally tied to distinct organisms will be working together within the context of the gene and treating their organisms as the available repertoire for mechanistic studies. The Model Organism Experimental Unit, specifically designed for pediatric disease gene studies, will be established through programmatic support by ACHRI as a flagship platform. It will be staffed by two research associates with postdoctoral experience with model organisms who will manage two technical staff and trainees. This unit will be responsible for performing the experiments in the investigational pipeline. A smaller pilot-program of this unit is being established supported by funds from the Gene Development and Health operating budget. Ultimately the Model Organism Experimental Unit will be funded externally through grant applications, including team-oriented operating grants, such as the Collaborative Research and Innovation Opportunities program, sponsored by the Alberta government (AIHS). Funding will also be sought through the CIHR-Genome Canada Rare Disease Research Catalyst Network, dedicated to investigating disease genes using model organisms. The strength of the Model Organism Experimental Unit is that it will be operated by a collaborative agreement of dedicated model organism researchers with the specific and only objective to investigate rare disease genes without the encumbrance of personal research projects. It will be a stand-alone entity working at the behest of the MORPH Management Group. It will be unique in Canada, and operate full-time with a team of highly qualified investigators.

#### ***Sub-activity b.3.2 Developmental Imaging and Genomics Infrastructure.***

New optical imaging and separation technologies have dramatically enhanced the ability to isolate small populations of normal or diseased cells in high purity, allowing *in vitro* analyses of their developmental potential and sampling of gene expression. These technological breakthroughs allow analysis of disease mechanisms and mutational effects with unprecedented precision. We will request funds from CFI and donor sources for this infrastructure that will allow MORPH to ask transformative questions of gene function. Other wet-lab investigators in the Genes Development and Health theme and other ACHRI themes will also be heavy users of this infrastructure.

Essential infrastructure to support the imaging platform includes a LightSheet or single plane illumination (SPIM) confocal microscope and a multiphoton microscope. The **multiphoton microscope** will facilitate 3D imagery of developing tissues/organs by performing deep-tissue imaging at a much greater depth than the ~200 micron currently available. The **Lightsheet** Single Plane Illumination Microscopy (SPIM) microscope configured for optical plane imaging of living cells, tissues and near microscopic organisms will allow imaging of dynamic biological processes in a field of cells labelled with a specific fluorescent reporter. It is designed for rapid dynamic imaging of an entire organism such as the developing zebrafish, worm or fly. This equipment will support morphological analysis of the effects of disease causing mutations in model organisms at the cellular and subcellular levels.

New methods of gene delivery in embryonic mouse organs allow for the rapid assessment of gene function without the expense and time required to generate transgenic lines. To deliver biomolecules (e.g., DNA expression constructs, pharmacological agents) into vascularized soft tissues in the mouse, such as the heart, pancreas and kidney, or across the blood brain barrier and into the CNS. A Vevo 2100 ultrasound targeted microbubble destruction (UTMD) will be purchased.

New separation technologies have also dramatically enhanced isolation of purified cell populations from whole embryos, allowing the sampling of gene expression and mutational effects on developmental potential to be assessed *in vitro* with unprecedented precision. To characterize RNA and protein expression levels or epigenetic profiles of cells within living organisms, or to experimentally assess the developmental potential of discrete cell populations, specifically labeled cells must be physically isolated. Recent advances in transgenic technology make it relatively easy to mark specific subsets of cells.

To isolate these labeled cells in high purity from mouse, zebrafish, fly or worm, a **Fluorescence activated cell sorter (FACS)** is being requested. A second recent innovation in the sorting field is the ability to sort whole organisms labelled with a fluorescent transgenic reporter. Small organisms such as zebrafish embryos, fly imaginal discs and worm embryos are ideal for this. Many thousands of embryos can be placed in the sorter and processed for the expression of cell-type specific markers, or markers of mutation (e.g., mutants that express green fluorescent protein while wild type embryos do not). This replaces tedious and inaccurate manual sorting and can dramatically increase the speed of isolating large numbers of embryos with desired characteristics for downstream applications.

As the sorter works with live samples, sorted embryos can continue to grow after the sorting event. For this, a **Biosorter-Pro large particle flow cytometer** from Union Biometrica will be requested. To support the isolation of cells and embryos that are sterile and therefore useful for downstream applications, four **biosafety cabinets** will be used to handle tissues, tissue cultures and embryos under sterile conditions both before and after sorting.

New technologies for DNA/RNA/Protein quantification will allow for gene sampling and protein expression more rapidly and more quantitatively than with currently available technology. Two **Droplet Digital PCR machines** comprise a system using a spray of nanolitre volumes of template for quantitative detection of nucleic acids by PCR in individual droplets. This new technology allows detection of absolute RNA/DNA numbers, and calculation of allele ratios after mutagenesis with outstanding accuracy and minimal variation between runs. The machine can detect copy number variations that may be present in genetic diseases as well as gene expression levels.

Protein quantitation will be accomplished with an **Amersham Imager 600 gel doc system**, a high sensitivity imaging system for gels and blots, both by chemiluminescence and by fluorescence, and electrophoretic mobility to shift assays for analysis of transcription factors binding to DNA. To quantitate RNA and DNA using low sample volumes, thus preserving the majority of samples with limited availability for functional tests, an **Agilent 2100 Bioanalyzer** is needed. There are applications for this equipment to all projects associated with *Activities 3 and 4*.

## **b. MORPH Activity 4 - Translational Exploitation**

### ***Sub-activity b.4.1. Knowledge dissemination.***

Traditionally, model organism research has been integral to the investigation of disease genes but not to the immediacy of the clinical problem. Although certainly important to future patients, a request for consent to conduct research rarely benefits the initial patient, MORPH has the opportunity to change this view. To assure timely delivery of research outcomes, MORPH has been designed to include ongoing involvement of the clinical research community in its organizational structure and to include knowledge translation as a key component of its mandate. The challenge is to create a workflow that, through the integrated team and a dynamic investigative approach, will transform research efforts from basic science to clinical investigation, anticipating outcomes achieved in months rather than years.

Research outcomes from *Activities 2 and 3* will be relayed to the MORPH Management Group, who, with clinical end users as part of the Group, will evaluate findings for transmission to the clinical domain. *Activity 4* participants will include: 1) clinical specialists and their trainees, who will disseminate information on disease cause to physicians and patients; 2) diagnostic lab technologists and their trainees, who may develop and validate new

diagnostic tests; 3) lab investigators who will pilot drug screens for therapeutic targets; 4) government agencies, who regulate and update medical policies; 5) specialized disease-based societies, who will inform patient groups and supporters of new insights into specific genetic disorders; and 6) IRDiRC and Care for Rare, whose goals include the delivery of new therapies for rare disorders.

#### ***Sub-activity b.4.2. Therapeutic design.***

MORPH's downstream interventional impact will be through therapeutic design work and will have three principal work foci: (a) the identification of therapeutic targets; drug screening; and cellular reprogramming.

##### **(a) Identifying Therapeutic Targets:**

The ultimate goal of MORPH model organism investigations, beyond understanding disease mechanism, is to reveal therapeutic targets. In addition, where the model organisms being studied prove to be ideal *in vivo* models for therapeutic investigations, the research will extend to drug screens in these selected cases (see next section). MORPH will also share knowledge and collaborate with investigators leading therapeutic platforms who are also focusing on genetic rare disorders.

Specifically, Dr. Kym Boycott at the University of Ottawa (CHEO), as lead investigator in Care for Rare, heads a merged CFI initiative from Ottawa (RD-MED), Dalhousie (IGNITE) and the Université de Montréal (RaPID), all of which examine rare disorder genes but are more directly focused on identifying novel therapeutics. MORPH's focus on disease mechanisms in developmental pathways combined with the Boycott group's focus on therapeutics will ensure the best potential for treating patients with complex genetic disorders. To accomplish this aim, the MORPH Management Group in consultation with RD-MED, IGNITE, and RaPID will review its findings on disease gene investigations and provide access to those systems that might benefit from their different approaches to target identification or therapeutics. For example, RD-MED has requested CFI support to establish a metabolomics facility. Where studies in mouse, zebrafish or *C. elegans* would indicate the benefit of metabolite surveys in the search for sites for intervention, MORPH would provide blood, tissue, or the relevant model for such investigations.

##### **(b) Drug Screening:**

Simple organisms, assayed *in vivo*, offer whole organism responses to drug screens; such readouts address both toxicity and efficacy. To this end, MORPH scientists are exploiting zebrafish as an *in vivo* model for evaluating small molecule drugs or other interventions as approaches to therapy. Zebrafish benefits are that they are vertebrates, hence closer to humans than the invertebrate models, but yet are amenable to large scale *in vivo* applications (unlike mice). GDH theme member Deborah Kurrasch, in collaboration with scientists from the Behaviour and Developing Brain Theme, has experience with a genetically modified zebrafish model of epilepsy. Normalization of a recognized behavioural phenotype will provide the functional assay for drug screens as part of Activity 4; step 1 will involve bioengineering zebrafish to possess the disease-causing mutation found in pediatric patients, leading to zebrafish models that phenocopy human disease.

CRISPR/TALEN technology will be used to conduct these gene-editing experiments, as currently employed by MORPH members. Step 2 will be to conduct drug screening of wild-type and 'diseased' zebrafish seeded into 96-well plates. Chemical libraries will come from various sources, for example, the NIH Clinical Collection (in house), comprised of 727 compounds, some of which are FDA approved and others that failed Phase III for missed endpoints. Importantly, all of these have already passed safety and toxicology analyses, thereby enabling rapid translation into the clinic.

Future expansions will exploit the Advantage Library from Enzo and the Pharmacon Library from Microsource

Discovery Systems, comprised of 786 FDA-approved and 1,600 world-wide approved compounds, respectively. Step 3 will involve phenotypic evaluations or readouts, with changes in gene regulation first monitored through screens so that the expected outcome is the up- or down-regulation of a transgenic reporter. In this approach, the screens will be automated using the Biosorter. Then, the team will take advantage of other screening equipment in the Kurrasch and Rho labs, including a ZebraLab (Viewpoint Life Sciences) behavioural activity chamber and a high throughput microscopy screening system. Further expansion of capacity to house and screen zebrafish, including expansion of the fish room, will be requested in a CFI application.

(c) Cellular reprogramming:

A major roadblock in treating patients with dysfunctional tissues/organs is the lack of readily available tissue sources for effective transplantation. With the advent of organ regeneration and cellular reprogramming strategies, as well as advances in tissue bioengineering, future treatment paradigms will one day be achievable for disorders not treatable by drugs. While these cellular reprogramming strategies may be a long way off and may not lead to immediate therapeutic interventions, the future of regenerative medicine will likely rely on these strategies. By including cellular reprogramming in the therapeutic platform, MORPH will remain at the forefront of current efforts to treat the most severe birth defects that are currently untreatable. Cellular reprogramming is an achievable goal. Two MORPH scientists have current cellular reprogramming projects aimed at converting skin cells to cone photoreceptors and to improving the myelinating capacity of skin-derived Schwann cells for transplant.

**c) Recruitment and Retention:**

*Recruit, retain and nurture scientists working in the fields of human genomics, bioinformatics, developmental biology and model organisms, whose research has translational potential*

Over the past three years, seven additional new start-of-career scientists have been added into the Genes, Development and Health theme with research interests in genomics and bioinformatics. Additional new recruits to support KidOmics and MORPH approaches are being sought through this business plan.

CSM Planning and Priorities Committee approved recruits that align with the MORPH initiative and who will be recruited over the period 2015-20 will be in the following areas of scholarly interest: four scientists in child health genomics (two junior AIHS Translational Chairs in Personalized Medicine, one NSERC Tier 2 in regulatory genomics, one medical geneticist specializing in genomics), six scientists specializing in bioinformatics (one assistant professor in Bioinformatics, one NSERC Tier 1 Bioinformatics, two junior AIHS Translational Chairs in Cancer Bioinformatics, two assistant professor level recruitments in bioinformatics subject to successful recruitment of the NSERC Tier 1 Bioinformatician), and one scientist specializing in primate behaviour.

These planned 2015-2020 recruitments, with the addition of planned and redeveloped research space at the Health Sciences Centre, represent a major rejuvenation of this the theme with new expertise in the areas of bioinformatics and genomics which will strengthen the research cluster of cell and human development science.

In response to the U of C Provost's recent commitment to fund twenty five new positions in CSM, and in alignment with the CSM's objective of having these positions support the School's initiative in Precision Medicine, ACHRI is submitting a proposal to the CSM for additional positions to fill gaps in the Schools genomic sciences capacity. The specifics and rationale for each requested position are identified in Appendix 7: ACHRI Recruitments Priorities by Theme.

#### **d) Education and Training of the Next Generation**

Training the next generation of scientists is a central mandate in ACHRI. The research activities in the KidOmics and MORPH programs will provide opportunities for training students and fellows at the post-doctoral, graduate and undergraduate levels.

The Theme will seek an additional \$200K annual funding to complement the ACHRI Training Program budget over the 2015-2020 term to support post-doctoral fellows, graduate and undergraduate students involved in this program. This funding will provide trainees with the opportunity to work in interdisciplinary research teams engaged in fundamental, translational and clinical research opportunities provided by the KidOmics/MORPH research pipeline.

Post-doctoral fellows will be given leadership roles, helping ACHRI scientists and clinicians to coordinate individual MORPH and KidOmics research initiatives, with graduate students working on independent aspects of the projects.

Bachelor's of Health Science students in the O'Brien Centre Biomedical and Bioinformatics Specialization, even as early as the first year of university, can be trained to contribute to ongoing Rare Disease research. ACHRI research programs will benefit from the added human resources and the benefit to the trainees of the multidisciplinary research environment will be considerable.

## C.2. BEHAVIOUR AND THE DEVELOPING BRAIN THEME

### Introduction

The Behaviour and the Developing Brain (BDB) Theme group comprises nearly six dozen full-time faculty members appointed in multiple Schools and Departments at the University of Calgary, spanning a wide breadth of expertise that is recognized both nationally and internationally for research excellence. There are three main areas of strategic focus, established after a comprehensive evaluation process that determined the highest priorities in terms of community needs, existing strengths and unique opportunities to improve health and well-being across the entire life span. These include pediatric brain injury (encompassing perinatal and childhood stroke, neurotrauma inclusive of concussion and moderate-to-severe traumatic brain injury, and neuroinflammation), epilepsy (and related co-morbidities such as sleep disorders), and the broad realm of neurodevelopmental disorders (including but not limited to attention deficit hyperactivity disorder, autism spectrum disorder, and developmental coordination disorder). A particular strength of the BDB Theme Group is the highly translational continuum of research within each of these areas, integrating important multi-disciplinary clinical research efforts aimed at optimizing cognitive and mental health outcomes, with cutting-edge bench laboratory programs and platforms addressing the molecular, genetic, anatomic, biochemical, physiologic, and *in vivo* behavioral underpinnings of brain-related disorders in the pediatric population. Supporting the bench-to-bedside research programs are advanced technologies that are enabling high-resolution structural and functional imaging of the human brain, next generation gene sequencing facility, and a clinical research core. Finally, the collective academic environment of the BDB Theme Group boasts a diverse array of training programs, and knowledge translation that has already significantly impacted public awareness and policy at the highest levels.

### C.2.1 Acquired Pediatric Brain Injury and Rehabilitation

#### Background

Pediatric brain injury encompasses a wide range of etiologies, including the broad categories of trauma, stroke, infection and systemic illness. Similarly, within each etiology the injury severity ranges from severe, life-limiting to mild, with no obvious consequences. Regardless of the severity of the primary injury, brain injuries can lead to long-lasting adverse effects, including neurological, mental and physical disabilities. The ultimate goal is to improve outcomes for these children through clinical and translational research.

**Traumatic brain injuries** (TBI) resulting from head trauma are by far the most common type of acquired brain injury in children. As many as 1 in 5 children in Canada are estimated to suffer a concussion or mild traumatic brain injury resulting in 65,000 emergency room visits, 5,000 hospital admissions and 120 deaths annually. This poses a major public health problem, resulting in total annual health care costs exceeding \$1 billion (Schneier, Shields, Hostetler, Xiang, & Smith, 2006). The most common measure of traumatic brain injury severity is the Glasgow Coma Scale (Teasdale & Jennett, 1974), on which scores range from 3 to 15. By convention, scores from 13 to 15 represent mild injuries, scores from 9 to 12 represent moderate injuries, and scores of 8 and less represent severe injuries. Studies have found that the majority of TBI even in the hospital setting fall under the mild category (71-77%). These numbers almost certainly underestimate the proportion of mild TBI, many of which go unreported entirely or are treated in outpatient settings and do not result in hospital visits. The diagnosis and management of concussion remains inconsistent, and lacks best practices guidelines.

**Stroke and cerebrovascular disease**, although less common, cause brain injury leading to lifelong neurological disabilities. The majority of childhood strokes occur perinatally: the highest period of risk for ischemic stroke is the first week of life. A term newborn carries a risk >1:3,500 in the first week, with an additional 50% of perinatal

strokes presenting later in infancy. Premature babies carry an even higher risk. Our work suggests that over 10,000 Canadian children and their families live with the consequences of perinatal stroke. It is the leading cause of hemiparetic cerebral palsy and most survivors suffer additional neurological sequelae including intellectual disabilities, language impairments, behavioural disorders, and epilepsy. Common occurrence combined with lifelong morbidity creates enormous burden on families, society and the health care system. Identification of direct causes remains elusive in most cases resulting in no prevention strategies to reduce burden or improve outcomes.

**Inflammatory brain diseases** are an increasingly recognized cause of devastating neurological deficits including childhood vascular stroke, epilepsy, movement disorders and cognitive decline. Inflammation is reversible, once recognized and treated rapidly. In 2001, all but one child world wide was only diagnosed after death on autopsy. Our work has dramatically increased the recognition of inflammatory brain diseases through a world-wide network of clinicians, researchers and families: BrainWorks. The morbidity has dramatically decreased, however, many children are left with significant disease related morbidity such as severe cognitive impairment resulting in a huge individual and societal burden.

Studies have repeatedly shown that breakthroughs in clinical care, and outcomes, emanate from the integration of basic and clinical science through the implementation of a strong translational focus. We have organised our research program to combine fundamental basic science labs with strong clinical programs to ensure that advances in basic science are translated into clinical practice.

**Mission:** To drive forward scientific knowledge and clinical care of pediatric brain injury and rehabilitation by creating new knowledge, guiding knowledge translation with the ultimate goal of preventing pediatric brain injuries whenever possible, and improving the lives of children who suffer from them.

**Vision:** A bench-to-bedside-to-community research program that advances our knowledge and drives evidence-based care to improve outcomes for children with different types of acquired brain injury, including traumatic brain injury, stroke and neuro-inflammation.

### **Strategic Goals:**

1. Understand the epidemiology, identify populations at risk, and find ways to prevent acquired brain injury;
2. Discern the underlying pathophysiology;
3. Improve assessment tools for accurate diagnosis and severity stratification;
4. Improve outcome predictions and prognoses
5. Establish evidence-based treatment and rehabilitation strategies to improve long-term outcomes

### **Current areas of research excellence and previous accomplishments**

Due to successful, targeted recruitments, both ACH and ACHRI now have a wealth of expertise in the spectrum of pediatric brain injury with internationally recognized clinical experts and research programs in TBI, stroke and neuroinflammation. We have also been building strengths and capacity in basic science programs in the same areas to better understand the mechanisms that underlie favourable and adverse outcomes after injury.

- The ***Alberta Children's Hospital TBI and Complex Concussion Research Program*** is a leader in clinical childhood concussion care and research. The program combines expertise from neurology, neurosurgery, physiatry, neuropsychology, psychology, and psychiatry, as well as allied health. The research program is targeted to clinically relevant projects with engagement of the community, children, and their families. The research explores the neurobiology of complex concussion by combining clinical, neuropsychological and novel imaging methods. Multiple studies employ the assets available at Alberta Children's Hospital include gait, sleep and neuropsychology laboratories, imaging suites, and functional brain monitoring facilities.

- The **Integrated Concussion Research Program (ICRP)** is a University-wide initiative to study concussion which brings together experts from the Faculties of Medicine, Kinesiology, and Arts, with support from the Alberta Children's Hospital Research Institute (ACHRI) and the Hotchkiss Brain Institute (HBI) under the leadership of Dr. Keith Yeates. The 10-year plan builds on existing strengths but will facilitate significant integration and expansion of university-wide research efforts. “Preventing and Treating Concussion and Brain Injury” is one of the four themes within the University of Calgary’s “Brain and Mental Health” research priority.
- **Pediatric Neurocritical Care (NCC) and Translational Research Program** – strong foundations have been laid to establish a strong, patient-centred pediatric NCC research program to facilitate the best care for all patients with brain injuries in the pediatric and neonatal intensive care setting. NCC is a novel, “brain-centred” approach that bridges the gap between basic and clinical neuroscience, and brings translational research to the bedside. A basic science laboratory and research program has been developed at ACHRI to investigate the effects of TBI across ages and severities on a validated experimental platform. The lab is capable of examining the behavioural outcomes of TBI using several modelling platforms, as well as analysing molecular changes from the level of DNA through to whole brain network organisation. Studies are driven by links to clinical research programs. This merging of basic and clinical science ensures the relevance of basic science studies, and rapid translation into clinical care.
- The **Sport Injury Prevention Research Centre** (SIPRC) in Kinesiology is conducting internationally recognized research and is one of only four International Olympic Committee (IOC) Centres of Excellence in Research in Injury & Illness Prevention in Sport in the world. Two prime areas of focus for the SIPRC are injury prevention in youth sport/recreation and concussion. The group has a 10-year history of CIHR funding related to concussion and has influenced public policies related to body checking in youth ice hockey, and also conducted novel trials in rehabilitation. Within the Faculty of Kinesiology, the SIPRC operates in partnership with the Sport Medicine Centre to both recruit participants and provide follow up care for study patients with the creation of the Sport Concussion Research Clinic at the University of Calgary Sport Medicine Centre.
- **The Calgary Pediatric Stroke Program (CPSP) at the ACH** is a leader in pediatric stroke care and research. The program has founded original research programs while assuming leading roles within global pediatric stroke research networks. New therapies have been successfully translated from CPSP clinical trials such as constraint-induced movement therapy. In collaboration with provincial partners, they have created the world’s largest population-based perinatal stroke cohort (>800 children). The team is also leading the perinatal section of the *International Pediatric Stroke Study (IPSS)* that now spans over 40 countries.
- **The ACH Pediatric Transcranial Magnetic Stimulation (TMS) Laboratory**, established in 2010, is the first dedicated facility of its kind in Canada. TMS can measure how a child’s brain recovers from injury while potentially guiding development toward better function. We recently established the ability of brain stimulation to improve motor function in children with stroke-induced cerebral palsy and other clinical trials are now underway.
- Through the **ACH/ACHRI Imaging platform and research team**, advanced neuro-imaging applications are available to help understand mechanism and outcomes of brain injury in children. Examples include MR imaging of neuroanatomy, pathways, functional activations, brain metabolism, and integrated neural networks. Using advanced imaging before and after interventional therapy helps understand how young brains develop following injury, and what changes in the brain occur when function improves.
- **The Calgary Neuroinflammation Program at ACH**, established in 2013 is a national and international leader in childhood inflammatory brain diseases. It is built on the CIHR funded BrainWorks platform, which includes the world’s largest cohort of more than 500 children with inflammatory brain diseases from 48 international

centers worldwide. It is partnered with leading national and international brain inflammation research institutes and captures the clinical phenotypes and course, neuroimaging studies, standardized outcome evaluation and partnered bio specimens. Through matched cytokine signature analysis and brain tissue gene expression from patient brain biopsies with a distinct subtype of inflammatory brain disease (small vessel CNS vasculitis), we recently identified a novel inflammatory pathway resulting in high levels of the proinflammatory cytokine TNF-alpha in the wall of brain blood vessels. Taking it further, and blocking TNF is the first step towards “real-life” precision medicine in children with brain injury.

## Research plan

1. **Epidemiology/prevention:** What are the factors that increase the risk of brain injuries, and what can be done to prevent them from occurring in the first place?

Several genetic, biological and environmental factors contribute to the risk of various types of brain injuries. Once we are able to identify factors that predispose to brain injury, and recognize the populations/individuals at risk, we can develop preventive measures.

Most previous research in TBI has focused on individuals identified either at hospitals (i.e., emergency departments) or in athletic settings; however, many mild TBI, and most concussions, do not come to the hospital and occur outside of sports. We will develop an injury surveillance program and concussion patient registry that involves community agencies, schools, primary care providers, and other institutions and individuals in the identification of concussion. This program will allow us to detect the broader population of concussions, to learn about factors associated with concussion; to monitor concussion outcomes; and to identify best practices in clinical care through studies of comparative effectiveness, while simultaneously providing a critical pipeline for research recruitment. Standardized data acquired through the community concussion registry and clinical research programs will help us identify risk factors and populations at risk for traumatic brain injury, and allow us to inform policy and practice on preventive measures and risk mitigation strategies.

The majority of childhood strokes occur in the perinatal period, defined as the time from the 20<sup>th</sup> week of gestation through the 28<sup>th</sup> postnatal day, which is a very sensitive developmental period for blood vessel maturation. The origins of perinatal stroke are not well understood, but they are thought to arise from vascular malformations pointing to genetic defects and/or from acquired causes such as placental disease. The Alberta Perinatal Stroke Project (APSP), the world’s largest study of its kind, is exploring the clinical epidemiology of perinatal stroke including clinical, prothrombotic, genetic, and placental mechanisms. These studies will take advantage of established ACHRI platforms and programs like the genetics-bioinformatics platform for exome sequencing and bioinformatic analysis to identify potentially pathogenic mutations; the MORPH program for modelling the effect of these mutations in model organisms; and the Imaging platform and CAIR program to identify morphological changes in blood vessels of these patients. Findings of these studies will inform strategies to develop safe and effective preventative measures.

Brain injury from inflammation is an intriguing, newly recognized and researched concept. Inflammation can be the sole mechanism of brain injury in previously healthy children. Distinct brain structures such as blood vessels or distinct neuronal receptors can be targeted by arms of the immune system resulting in devastating deficits in previously healthy children. We developed a multinational platform to capture children with inflammatory brain disease and provide diagnostic and therapeutic tools. We are now embarking on NIH partnered, population based studies aiming to identify distinct exposures associated with the risk of inflammatory brain injury, which will explore environment triggers and vaccination status in all countries. This work will inform prevention strategies, in particular the role of specific vaccinations.

**2. Pathophysiology:** What is the underlying neuropathology associated with pediatric brain injury and what does it imply about possible treatment?

When we are unable to prevent the initial injury, ameliorating the effects of secondary injury is a very realistic goal. To do this, we must better understand the pathophysiological mechanisms that underlie the secondary reaction through bringing an understanding of fundamental neuroscience to the bedside. With this brain-focused care approach applied by the NCC program, we will then be able to bring clinical questions to the lab to explore more deeply. Using a modified animal model of paediatric brain injury, ongoing research is examining the factors that determine short and long-term outcomes of early life TBI. Our experimental platform allows the exploration of many aspects of brain injury that span from genes to behaviour. A greater in-depth understanding of underlying pathogenic mechanisms has the potential to foster identification of novel therapeutic strategies for brain injured children.

**3. Diagnosis and assessment of severity:** What are the best methods/tools for the diagnosis and severity assessment of different types of acquired brain injury?

Since the diagnosis of mild TBI lacks a gold standard, one of the goals of the TBI research program is to establish standardized methods of assessment. Thus, the clinical program will focus substantial effort on developing new diagnostic methods and refining best practices for diagnosis. Along with existing, state-of-the art structural and functional imaging tools, novel technologies will play a vital role in this effort, including functional near infrared spectroscopy (fNIRS), robotic assessment, and computerized cognitive testing. fNIRS has the potential to be both an affordable and portable means to assess abnormalities in brain function associated with concussion, both at the time of injury and during recovery. Robotic assessment provides detailed quantitative assessment of reaction time, motor control, and cognitive functioning that is proving sensitive to sports concussion in children. Brief computerized cognitive testing in the Emergency Department setting has shown promise in identifying children with cognitive deficits after concussion.

One of the goals of the NCC Translational Research Program is to better bridge the gap between basic science and clinical care by providing state-of-the-art tools for diagnosis and therapeutic monitoring (so-called “theranostic” markers). These markers must have high clinical utility and be available for use by many different groups. There are many options for these theranostic markers including existing neuroimaging, and neurophysiological programs (EEG, evoked potentials or EPs) that have been in place for some time and have recently grown in prominence and in scope. New to the ACH/ACHRI, however, is the development of a BioCORE that will serve as a storage facility for “tissue” (blood, CSF, urine) as well as a platform for evaluating molecular markers of disease and treatment response (metabolites, lipids and proteins), for all pediatric patients with a brain injury. Once fully established, the resource will also become a core resource for all researchers within the ACH and ACHRI. The goal in the development of this BioCORE is to ultimately lead to the identification of a biomolecular signature that aids in risk stratification and will allow for real-time patient-centred, dynamic and personalized care.

A novel University of Calgary partnership was established to determine the inflammatory signature of children with all types of brain injury from plasma and CSF. It is the first of its kind in Canada and worldwide. A unique, comprehensive inflammation panel (65-cytokine, 21-cytokine receptor plus serum-amyloid A) is partnered with advanced clustering method readout and provides a platform for personalized cytokine signature analysis with high diagnostic precision while the child is in a refractory seizure status in the intensive care unit. This work is closely aligned with the NCC strategies and goals. Treatment targets and personalized therapeutic strategies can be rapidly identified. The detection of key inflammatory pathways enables the development and evaluation of transferrable targeted therapies, the critical step towards establishing real-life precision medicine.

Cytokine signatures open the door to understanding the biology of primary and secondary childhood inflammatory brain disease. When partnered with gene expression profiles from brain tissues of affected children new translational research discovery will become a reality.

**4. Outcome prediction/prognosis:** What are the markers that would accurately predict long-term outcomes?

Using the NCC Translational Research Program, our goal is to discover new biomolecular profiles (combination of biomarkers and other test results like MRI and neurophysiology) to stratify patients for maximum treatment utility, and as a result, best possible outcomes. Using this platform, we will improve the way diagnosis and predictions are made in the early stages of a child's presentation.

As part of the concussion/TBI clinical research program, in an effort to identify outcome predictors, we will systematically examine a broad pool of neurobiological and psychosocial markers and their likely interactions as predictors of TBI outcome. As an example, drawing on the expertise of the ACHRI Genomics facility, we can examine multiple genes that are implicated in response to neurotrauma, neural repair and plasticity, and cognitive reserve, and thus likely to affect the outcome of TBI.

All of the technologies relevant to TBI diagnosis can also be applied to the prediction of outcomes (i.e., fNIRS, robotic assessment, MRI, computerized testing). Transcranial magnetic stimulation (TMS) is another novel technology that may prove informative scientifically and useful clinically in the assessment of TBI. We plan to expand the TMS research program at ACH into cortical excitability and plasticity as predictors of recovery after TBI in children.

These research studies will inform clinical practice through the development of clinical pathways and associated best practices guidelines for the diagnosis of brain injury, disease progression, prediction of outcomes, and treatment response.

**5. Treatment/rehabilitation:** What are the most effective means of managing brain injury, from acute medical treatment to rehabilitation of persistent problems?

Considering the large variety of etiologies, symptoms and the range of disease severity, an individualized approach is needed in treating patients with different types of acquired brain injury from acute care to long-term, rehabilitative therapies. This embodies the comprehensive notion of precision or personalized medicine.

In the intensive care setting, closely evaluating neurobiological indicators of disease progression and individual treatment response will allow us to closely monitor and adjust treatment in all types of severe brain injury. This will help us develop patient-centred, dynamic and personalized care.

With the diversity of symptoms in mild traumatic brain injury, we need to customize our treatment approach. We will test a broad range of biomedical, neurocognitive, and psychosocial interventions for traumatic brain injury in randomized controlled trials that target interventions to patients' specific symptom profiles. We are exploring various types of novel treatments to improve outcomes, including physiotherapy, nerve blocks, electrical stimulation, pharmacotherapy (e.g., melatonin – a clinical study to validate this treatment is already funded by CIHR), cognitive behavioural therapy and computerized cognitive rehabilitation. These studies will help establish a personalized approach to concussion management.

The availability of personalized and precise diagnostic instruments leads to a better understanding of the pathways and the identification effector molecules of inflammation, traumatic and ischemic injury and repair. Each of these molecules and signaling pathways can be enhanced, modified or blocked by targeted biological therapies. We will integrate inflammatory signature not only at time of diagnosis but also during tailored

interventions to further enhance the therapy effectiveness, strengthen the safety and accelerate the recovery from all types of acquired brain injury in children.

We are developing non-invasive, neuromodulatory interventions to enhance function and life in children with disabilities previously considered untreatable. We have verified the ability of brain stimulation to improve motor function in children with stroke-induced cerebral palsy, and establishing new pediatric brain mapping and stimulation methods to measure complex neurophysiology and developmental plasticity. This translates into applications across other childhood neurological disorders including traumatic brain injury and adolescent mental health.

These, along with similar clinical studies and translational basic science research programs will give rise to a personalized approach to brain injury management to ensure the best possible outcomes for children.

## **Program Metrics, Outcome and Impact**

### **Academic Metrics:**

The metrics will be those commonly used to gauge impact in research and education, supplemented by metrics reflecting the engagement of clinical populations

- External research funding – TriCouncil or other peer-reviewed external funding
- Publications - number of publications in peer-reviewed, higher impact journals (relative to the field)
- Presentations - number of invited presentations, presentations at international, national, and local conferences, grand rounds, etc.
- Trainee outcomes – number of trainees and their success rate
- Clinical engagement - number of patients included in research studies

### **Clinical outcome measures:**

- Identified biomolecular profiles for diagnosis, outcome prediction and treatment monitoring
- New interventions to improve function and quality of life following brain injury
- Best practices guidelines, clinical pathways, policy statements

### **Long-term intended outcomes:**

Over the next 5-10 years, the program will improve human lives by:

- Decreasing the number of preventable pediatric brain injury through identification of at-risk populations and implementing prevention programs;
- Introducing more sensitive diagnostic and prognostic tools that can identify pediatric brain injury better and predict outcomes;
- Implementing evidence-based approaches to treating and managing brain injuries;
- Reducing long-term negative outcomes and improving quality of life for children with different forms of acquired brain injury.

## **C.2.2 Pediatric Epilepsy - Innovative Translational Epilepsy Research**

### **Background**

Epilepsy occurs with an estimated worldwide prevalence of 1-2% of the population. For Alberta, this translates to a prevalence of more than 75,000 epileptic patients. Importantly, fully three-quarters of newly diagnosed epileptic patients are 16 years of age or younger, thus making epilepsy primarily a problem of infancy and childhood. Of the many forms of epilepsy, the most devastating conditions begin in infancy and childhood and are universally

associated with cognitive impairment. In addition to the long-term impairment of quality of life for the child and psychosocial/economic impact for the family, epilepsy in childhood can be associated with daily seizures, systemic adverse effects of medications and even death. The potential years of life lost to epilepsy are second only to stroke within neurological disorders due to the early age of onset of seizures.

Common therapeutic practices include standard antiepileptic drugs as well as non-drug treatments like metabolic diets, immunomodulatory therapy and surgery. The single most important metric of successful treatment for children with epilepsy is seizure frequency with seizure freedom being the ultimate goal.

Regrettably, there have been no major breakthroughs in the successful treatment of epilepsy in the last hundred years. The overall range of patients who do not achieve seizure-freedom (intractability) remains between 20-30%. These children are at high-risk for disruption of normal development, behavioral co-morbidities such as Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) as well as premature mortality (i.e. Sudden Unexpected Death in Epilepsy, SUDEP). In addition to the human suffering of child and family, these children consume significant societal resources in the form of direct medical care, services provided in home and at school and loss of productivity by their parents while attending to the medical needs of their children.

New thinking and methodologies are required as those that currently drive therapy development have been unsuccessful in this population. The treatment of these patients clearly needs an individual approach. The strengths we have developed in Calgary offer us a unique opportunity to address therapy development for intractable seizures.

**Mission:** To use state of the art basic & clinical neuroscience methodologies to optimize the lives of children suffering from epilepsy and its behavioural co-morbidities, autism spectrum disorder (ASD) & attention deficit hyperactivity disorder (ADHD).

**Vision:** To create a platform by which novel anti-seizure compounds identified in animal model systems are translated into rapid cycle clinical testing thereby providing the ultimate in precision medicine for children with epilepsy.

### **Strategic Goals:**

1. Identify potential anti-seizure compounds by use of a high throughput testing on a zebra fish platform;
2. Test the anti-seizure properties of identified compounds in several established rodent models of epilepsy;
3. Leverage existing expertise to develop novel compounds based upon the role of oxidative metabolism in cellular and network excitability.
4. Create an ‘Intractable Epilepsy Research Clinic’ that will test compounds directly from the laboratory using N-of-1 trial design;
5. Identify biomarkers of responsiveness to interventions via modern electrophysiological, genomic and bio-banking methodologies.

### **Current areas of research excellence and previous accomplishments**

Our proposed research program builds on the existing strengths and successes of current ACHRI research scientists, programs and platforms while proposing a novel approach to the treatment of childhood epilepsy.

- ***Clinical outcomes research & implementation through advanced clinical informatics***

Our team has established a clinical informatics-based research program where we developed and implemented standardized diagnostic protocols and treatment algorithms. As part of the program, we have created a customized database of electronic health records that allows the near-time analysis and evaluation of our protocols by pre-determined outcome metrics including seizure reduction, treatment related medical &

neurological adverse effects, behavioural issues (e.g. ADHD), quality of life and health care delivery costs. Outcome dashboards for the individual patient and population of children with epilepsy are created every 24 hours in an automated fashion.

By continuously assessing the therapies applied, and adjusting pathways as necessary, this approach will lead to the establishment of optimal, outcome-based standards of care.

This standardized approach also allows us to identify patients who are not responding to customary antiepileptic treatments, and require a different therapeutic approach. This clinical informatics-based research program is unique to Alberta Children's Hospital, and, to our knowledge, a first of its kind in the world, and provides the basis for our proposed new research program.

- ***Bioengineered Zebrafish-Based research for Anticonvulsant Drug Development***

The ACHRI BDB research team has developed an innovative drug screening program (Kuriasch, Rho) which relies on the use of tropical zebrafish, which are 80-per-cent genetically similar to humans. The fish have been bioengineered to carry mutations in genes like those found in humans with epilepsy. Currently, the lab works with multiple genetic models, but it has the potential to rapidly engineer zebrafish to possess human mutations as new genetic underpinnings are discovered, taking us a step closer to individualized, precision therapy.

The rationale for this functional readout assay stems from the remarkable clinical efficacy of a metabolism-based therapy for epilepsy known as the ketogenic diet (KD). Although the underlying mechanisms of the KD remains poorly understood, we now appreciate that the use of ketones within the CNS as an alternative energy substrate is neuroprotective. There is also mounting evidence that neurometabolic alterations, such as those induced by fasting or the KD, may underlie many neurological disorders, including epilepsy, all of which show neuronal derangements in bioenergetics. Hence, screening for compounds that modulate cellular bioenergetics, we may identify drugs that restore normal cellular functioning and provide potentially disease-modifying effects.

The program design will allow for the rapid translation of the laboratory findings to the clinic, holding the potential to significantly improve epilepsy drug-discovery and treatment of patients throughout the world.

By initially screening libraries of established FDA-approved drugs, this strategic approach holds the potential for successfully identifying candidate drugs within a few years, in contrast to the usual 10 to 20 years. All promising candidate compounds will be verified in rodent models of epilepsy, prior to entry into the clinic. A future goal will be to test early-stage investigational compounds in partnership with pharma, other academic medical centers, and the NIH-sponsored Anticonvulsant Screening Project (ASP) Project prior to subsequent detailed preclinical toxicological studies and followed by clinical safety trials.

So far, this screening platform has uncovered six potential novel therapeutic compounds that are currently being validated in rodent models of epilepsy, before proceeding to clinical trials. This drug development program feeds directly into our proposed new research.

- ***Translational research in brain metabolism***

Currently there is no medical center in the world that comprehensively focuses investigation on the metabolic activity of the brain during seizures. This innovative approach has the opportunity of providing unique insights that will inform clinical therapies. ACH has already built a reputation as a leader in basic science research in neurometabolism. We need to build on this strength and translate our findings from the bench to the bedside. Specifically, over the past several years, ACHRI has developed the core infrastructure to assess tissue bioenergetics and metabolic profiles, with particular attention to mitochondrial function as aberrations in this organelle have been appropriately recognized as playing pivotal roles in disease processes, and hence may represent a therapeutic target for many neurological (and indeed many non-neurological) conditions. As an

example, ACHRI investigators have recently identified a key mitochondrial protein as a novel molecular target for epilepsy therapeutics, and the zebrafish-based experimental therapeutics platform has exploited and harnessed the fields of metabolism and bioenergetics to implement a highly innovative screening process that has already identified candidate compounds that might prove highly efficacious in humans. Moreover, our rapidly adaptable research program in brain metabolism holds great promise in advancing knowledge and novel treatments for disorders seemingly disparate from epilepsy, such as autism, brain cancer, cognitive impairment, and a host of other conditions. Our goal is to expand the multidisciplinary and translational research program in brain metabolism, and to further validate the field of metabolism-based treatments for neurological conditions.

- ***Established Research Capacity***

The proposed research program will utilize already established platforms in neuroimaging and genetics within ACHRI and will collaborate with local scientists who have well-established basic science research and bio-analytical skills necessary to implement tissue biobanking for research purposes and to mine the data generated to develop biomarkers and glean insights into disease pathophysiology, ontogeny and responses to interventions.

- ***ACHRI Imaging Platform***

The childhood imaging research platform and program was built over the last few years through investments from ACHRI, the ACHF, the University of Calgary and Governments of Canada and Alberta in both equipment and people. The state of the art pediatric neuroimaging research facility at ACH is geared towards the needs of children with a research dedicated 3 Tesla MRI scanner equipped with noise reduction and motion correction systems, an MRI simulator for training children before their scan, eye tracking equipment, state of the art pulse sequences and computer infrastructure. Dr Signe Bray is the lead of a cutting-edge pediatric imaging research program aimed at using the advanced neuroimaging capabilities offered on the new 3T scanner to identify brain abnormalities associated with various neurological disorders. These methods include fMRI, morphometric analysis, and simultaneous EEG-fMRI.

- ***Brain network analysis***

Dr. Andrea Protzner was recently recruited to the University of Calgary to establish a program in brain network analysis using advanced computational methodology to analyze brain electrical network, morphological and functional data captured simultaneously by the MR compatible EEG system.

- ***Bio-banking and bio-analytical core***

Dr. Michael Esser has funding to establish a biobank at the Alberta Children's Hospital to store biological tissues for later analysis, a necessary component of a true research-oriented bio-analytical core for uncovering relevant biomarkers of disease processes from these samples. ACHRI is one of few centers in Canada that already have the necessary and complementary expertise in the pediatric health field to integrate biobanking and real-time, full-scale clinical neurophysiological monitoring of patients in pediatric neurocritical care.

- ***ACHRI-led CSM Centre of Health Genomics and Informatics***

With ACHRI's leadership, the CSM has laid the foundation to create a facility that has the capability to provide population-based, as well as patient specific, state of the art genomic testing, data storage, linkage and analysis.

The coexistence of these strengths and platforms locally gives us a unique opportunity to tackle the serious issue of medically intractable epilepsy in a manner that will continue to enhance our already internationally recognized research programs and enable new knowledge which will be used to expedite the development of novel therapeutic strategies.

## **Research Agenda for the Translational Epilepsy Research Program**

The components and research flow within the Translational Epilepsy Research program are shown in *Figure 11* and has the following objectives:

1. To find new drugs/interventions for intractable epilepsy in a timely manner following a novel methodological approach in order to provide the best possible quality of life for our patients and their families.
2. To identify biomarkers for predicting treatment responsiveness:
  - Metabolic
  - Immunological
  - Electrophysiological networks
  - Structural and functional imaging
  - Genetic sequencing
  - Neuropsychiatric assessment

## **Research Plan**

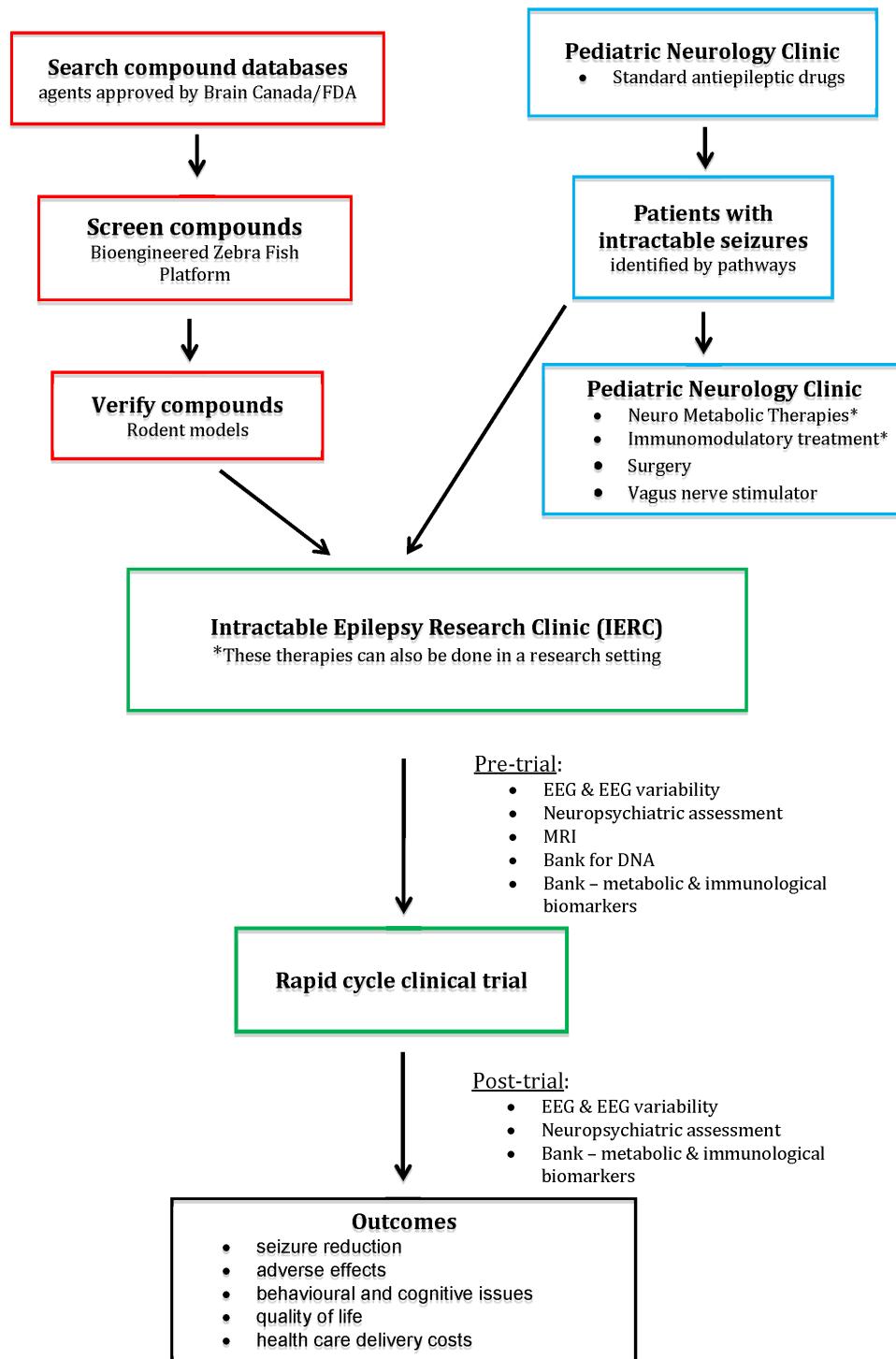
### **1. Finding treatments for intractable epilepsy**

Patients with intractable seizures, as identified by standard clinical pathways, will be referred to the Intractable Epilepsy Research Clinic if a research protocol is available and the patient/family consents.

In the proposed clinic, we will test potential therapeutic agents for 1-2 months in N of 1 clinical trials with the intent of identifying compounds that reduce seizures by 90% in individual patients. The compounds used will be those screened in the zebrafish platform and validated in rodents as described above. This approach is markedly different in several important ways. First, the threshold criterion of 90% seizure reduction represents a higher bar than the standard level of 50% or greater decrease in seizure activity for anti-seizure drugs. This will allow for the development of agents that exceed the clinical efficacy of existing medications. Second, our research protocol and platforms will more rapidly identify drugs in the affected patient populations than traditional approaches used in epilepsy clinical trials. Third, the initial focus on repurposing FDA- and Health Canada-approved medications will greatly decrease the time and investment required to uncover novel drugs, especially for medically intractable epilepsy. Finally, our translational research program in pediatric epilepsy will be unlike any in the rest of the world, and will further cement our reputation and leadership role in this field.

N-of-1 is an innovative trial design proven to be more effective than standard RCTs in certain chronic conditions where the study population is relatively small and clinically heterogeneous – as in the case of intractable epilepsies. Standard clinical trials of anti-seizure drugs involve 4-6 month testing in hundreds of patients that use reduction of seizures by 50% in 50% or more of patients as the metric of success. The major advantage of rapid cycle N-of-1 trials from the point of view of the patient and the treating physician is that the trial determines whether the treatment is actually of benefit in the individual patient as opposed to some percentage of a group of patients. So while it is important to study the pharmacogenomics (with implications to individual pharmacokinetics, pharmacodynamics, therapeutic efficacy and safety), the N-of-1 trial design approach is highly pragmatic and tailored to the unique characteristics of patients, and represents a readily available opportunity to implement precision medicine.

Figure 11: Translational Epilepsy Research program



## **2. Biomarkers as outcome predictors**

The population of patients with intractable seizures presents as a group with great clinical heterogeneity. We are planning to identify biomarkers of treatment responsiveness by performing a wide variety of assays pre- and post-interventions with the long-term goal of predicting which patient will respond to a specific intervention – that is, the actualization of personalized medicine. The use of most biomarkers would not only help determine which intervention would be optimal for a specific patient, but could also be used to monitor disease progression.

### **Program Metrics, Intended Outcome and Impact**

#### **Academic metrics:**

- External research funding – TriCouncil or other peer-reviewed external funding
- Publications - number of publications in peer-reviewed, higher impact journals (relative to the field)
- Presentations - number of invited presentations, presentations at international, national, and local conferences, grand rounds, etc.
- Trainee outcomes – number of trainees and their success rate

#### **Clinical Outcome Metrics:**

- Seizure reduction
- Treatment related medical & neurological adverse effects
- Behavioural issues (e.g. ADHD)
- Cognitive issues
- Quality of life
- Health care delivery costs

#### **Long term impact:**

- New antiepileptic drugs identified in a timely fashion that are effective in currently treatment-resistant epilepsy
- Biomarkers identified as outcome predictors – provision of targeted, precision treatment
- Novel metabolism-based therapies for drug-resistant epilepsy

## **C.2.3 Neurodevelopmental Disorders and Child Mental Health**

### **Background**

Neurodevelopmental disorders (NDD) represent a broad range of conditions, which result in an impairment in the normal development of a child's brain or central nervous system affecting their behaviour, memory and/or ability to learn. NDDs constitute one of the fastest growing health problems in the world with upwards of 15-20% of school-aged children suffering from one or more diagnosable disorders. The top 5 disabilities affecting children are neurodevelopmental and behavioural in origin.

The causes of NDDs are varied, often multifactorial, and at times unclear. Neurodevelopmental disorders arise from the disruption of the normal growth and maturation of the brain and nervous system - the science encompasses the disciplines of embryology, developmental biology, neuropathology, psychology and psychiatry. Additionally, there is an interaction between environmental and genetic factors that significantly impacts the life course. Known etiological factors include genetic and metabolic diseases, immune disorders, infectious diseases, nutritional factors, physical trauma, deprivation and toxic and environmental factors.

Children with NDDs experience medical, physical, emotional, learning, behavioural and social difficulties that vary drastically between disorders and also between children with the same diagnosis. These children are prone to experience mental health issues both as a direct result of the NDD and secondary to the behavioural, emotional and social challenges they face. The symptoms of these disorders – learning difficulties, anxiety, depression, compulsive behaviour, social isolation, to name just a few – exact a huge emotional cost on children and their families. Developmental, behavioural and emotional problems are now collectively the leading cause of disability affecting children and pose a substantial economic burden to individuals, their families, and to society as a whole. Given the social and economic costs and links between childhood neurodevelopmental disorders, childhood mental disorders and adult mental disorders, it is not surprising that the prevention of childhood neurodevelopmental and mental disorders has been viewed as a public health priority.

With the increasing complexity and co-morbidity in NDD populations, and the lack of standardized, evidence-based care, there is an urgent need to devote resources to uncover the developmental, psychosocial and environmental origins of these disorders. Health services research is warranted to identify the gaps in care and address the challenges of the health care system dealing with the complex medical and mental health needs of children and adolescents with NDD.

There are significant relevant academic resources and infrastructure within the Calgary region. Numerous researchers in various University of Calgary Faculties including Medicine, Nursing, Arts, Education and Research Institutes such as Alberta Children's Hospital Research Institute and the Hotchkiss Brain Institute, which leads the University of Calgary's Brain and Mental Health research priority, are focused on investigating the underlying antecedents, the outcomes of current management strategies, the development of innovative treatments for neurodevelopmental, child and youth mental health problems and translating these findings into improved policy and practice. "Optimizing Child and Adolescent Development and Behaviour" is an identified priority within the U of C's Brain and Mental Health research strategy.

With the recent opening of the Owerko Centre as a hub for collaboration, ACHRI is now in the position to lead and coordinate collaborative research in neurodevelopment and child mental health that spans the full spectrum from basic science to clinical studies to population health to health services research.

**Mission:** Become an international leader in neurodevelopmental and child mental health research and education, generate new knowledge and translate it into improved physical and mental health outcomes for children and youth through partnership in an innovative, integrated clinical / academic model that involves the University of Calgary (U of C), Alberta Health Services (AHS) and the community at large.

**Vision:** The advancement of research and education in childhood neurodevelopmental and mental health problems; implementation of effective interventions that reduce the prevalence, and improve outcomes for children at risk of, or affected by with these disorders.

### **Strategic Goals:**

1. Advance our understanding of biological and psychosocial development of children and improve health outcomes through translational research;
2. Determine prenatal and early childhood social-environmental predictors of neurodevelopmental and behavioural disorders;
3. Identify mechanisms (e.g., neural, endocrine, genetic, metabolic) underlying the relationships among antecedents and predictors of neurodevelopmental and mental health disorders in children and youth;
4. Improve the diagnosis of neurodevelopmental and mental health disorders by using and integrating psychosocial, imaging, genomic, and metabolomics approaches;
5. Evaluate and improve interventions that address clinical, rehabilitative and family needs for those at risk or affected by neurodevelopmental and mental health disorders

6. Reduce the prevalence of neurodevelopmental and mental health disorders through the development and implementation of effective programs/policies at local, provincial and national levels.

### **Current areas of research excellence and previous accomplishments**

ACHRI and has already made sizeable investments in the area of NDDs, including many key components required of a leading academic research program – i.e. people, space and critical research infrastructure.

#### **1. Clinical research:**

- Longitudinal follow-up studies of children with and without neurodevelopmental disorders and children with diseases/conditions that place them at risk for neurodevelopmental disorders and mental health issues are underway. Genetic, neurobiological and environmental factors that increase the risk for neurodevelopmental and mental health disorders in these children are being examined prospectively and retrospectively.
- Empirical studies have been established focusing on identification of factors leading to improved developmental outcomes of children, youth, and adults with various forms of NDD. Specific projects involve studies on social interventions for teens and young adults with ASD, peer victimization (bullying), social stigma, as well as building resilience and coping strategies.

#### **2. Basic science research:**

- The Developmental Neurosciences Laboratory was established with animal models of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) to elucidate the neurobiology of autism spectrum disorder and to uncover new treatments aimed at ameliorating the core symptomatology. The main research focus is on determining the pathophysiology of sensory processing problems in common neurodevelopmental disorders such as ASD, and on both pharmacologic and non-pharmacologic interventions to address core symptoms of these disorders. There are several ongoing research projects in this area.
- Neuro-metabolism in neurodevelopmental disorders  
There is growing evidence that dietary and other metabolism-based treatments may ameliorate the disabling behavioural and cognitive symptoms experienced by patients afflicted with ASD and ADHD. ACHRI has developed a full-scale translational neuro-metabolic research program aimed at identifying specific derangements in brain cellular metabolism, and exploiting this basic science information to develop new therapies that can restore normal neuronal function and behaviour. Specific attention has been focused on defects in mitochondrial structure and function, and on both molecular and genetic approaches that can mitigate these abnormalities.
- Animal model for drug discovery in ASD - zebrafish  
ACHRI has an established Zebrafish platform for high-throughput screening of previously FDA- and Brain Canada-approved compounds. The initial focus has been on epilepsy drug discovery with readouts that are based on fundamental principles of brain metabolism and bioenergetic homeostasis, but this experimental therapeutics platform has quickly pivoted to identifying compounds that address behavioural deficits seen in patients with ASD. The adaptability of this platform is well-recognized for the ease with which genetic models of human disease can be created, modified and tested using various interventional approaches.

#### **3. Population Health and Policy research:**

- Research methods and infrastructure to study the bio-psycho-social determinants of neurodevelopment and mental well-being of children and families have been established. Two large longitudinal pregnancy cohorts ( $n=3,200$  and  $n=2,200$ ) have been established with detailed data and biological samples from pregnancy to age 3. This large dataset has the capacity to provide data for cross-cutting research in the areas of public health, clinical, and health services research.

- We have established an extensive network of communication with health care providers to enable us to rapidly identify emerging issues of public health importance related to children's neurodevelopment and behavior, and generate evidence through research that addresses these issues. We contribute to strategic planning committees that inform provincial investments in programs and services relevant to children and families affected by NDDs and mental health issues.

#### **4. Health Services Research**

Much has already been invested and accomplished towards identifying the issues and addressing the challenges of the health care system dealing with the complex medical and mental health needs of children and adolescents with NDD, including:

- Collaborative development of ACEND Phase II (ACH Center of Excellence in Neuropsychiatric Developmental Disorders) and the Integrated Pediatric Brain Health Model of Care for Southern Alberta have provided us with roadmaps to support clinical and community service integration and enhance clinical research capacity within Calgary Zone NDD services. These roadmaps integrate leading practices identified in international site visits funded through ACEND Phase I.
- Clinical service redesign and streamlining within Child Developmental Services has created a central access point for referrals and improved access to diagnostic and treatment services. In the first 8 months since implementing the new service model, wait times across all service areas have been reduced, appointments scheduling is more timely and family oriented, and the service is more streamlined, less redundant and more accessible to referral sources in the community.
- Significant development of family oriented NDD resources and support in collaboration with community partners.

#### **5. Established ACHRI Research Platforms:**

- Child and Adolescent Imaging Research Centre  
A cutting-edge pediatric imaging research program has been established, with the aim of using the advanced neuroimaging capabilities offered on the new 3T scanner to identify brain abnormalities associated with various neurological disorders. Structural and functional imaging studies are in progress in large cohorts of typically developing children, as well as children with NDDs.
- ACHRI-led CSM Centre of Health Genomics and Informatics  
With ACHRI's leadership, the CSM has laid the foundation to create a facility that has the capability to provide population-based, as well as patient specific, state-of-the-art genomic testing, data storage, linkage and analysis.
- ACHRI Maternal and Child Health Research Support Platform  
The platform is providing support to advance the research capacity of ACHRI members and their teams, through consultation and direction at all stages of research, and by forging novel academic collaborations. Research support is offered through direct solicited consultation, regular seminars and lectures, and drop-in sessions to address specific methodological questions, or to initiate longer-term consultations, across several faculties.

### **Research Agenda**

#### **1. Clinical Research**

- Improve our understanding of various factors contributing to the development of NDDs, and undertake research to inform strategies and support systems to **prevent** at-risk children from developing NDDs.

- Improve the **diagnosis** of neurodevelopmental disorders, using the results of our basic and clinical research studies and develop evidence-based best practices for the assessment of pediatric neurodevelopment.
- Identify and implement innovative multidisciplinary **treatment and intervention** strategies that have the potential to prevent, reverse, or minimize the damaging effects of neurodevelopmental impairments and diseases. Apply research evidence to the establishment of outcome-based best practices for the management of NDDs.

## **2. Basic Science**

- Identify mechanisms (e.g. neural, endocrine, genetic, metabolic) underlying neurodevelopmental and behavioural disorders through basic laboratory research and translate the results to relevant clinical knowledge.
- Explore novel treatment strategies through the advancement of drug discovery as well as research into alternative treatment options (metabolic, immunological).

## **3. Population Health and Policy**

- Advance our understanding of the economic and social environment's influence on children's social, emotional, physical and cognitive development. Identify risk and resilience factors and design appropriate interventions to prevent and mitigate the impact of NDDs on child and family functioning.
- Advance our understanding of the outcomes associated with current screening policies and practices designed to identify child populations at risk for NDDs and mental health issues. Inform policy and practice based on research about optimal screening and intervention approaches.

## **4. Health Services Research**

- Analyze how the current health care system provides health promotion, relevant information, screening for developmental risk and access to early intervention. Based on new knowledge from research, inform the allocation of resources to optimize community and clinical health services.
- Analyze care pathways related to children with neurodevelopmental and mental health challenges to determine efficiencies and inform policy and practice to optimize service delivery.

## **Implementation plan**

### **1. Clinical Research**

Our clinical research will generate knowledge to improve our understanding of the basic mechanisms that result in suboptimal brain development and will identify risk factors, biomarkers and new treatment strategies.

One of the main goals is to advance our knowledge about the role of genetics in childhood neurodevelopment and mental health. With ACHRI's state of the art resources in genomics & informatics, as well as advanced neuro-imaging, we want to advance our understanding of the genetic basis of neurodevelopmental and mental health disorders and find out how genotype correlates with brain structure and function. We also plan to analyze the epigenetic changes triggered by the prenatal and early childhood environment as they influence disease outcomes.

Through collecting and analyzing data from our patients with NDDs and comparing them with control data, we will identify genetic and environmental risk and resilience factors that play a role in the development of NDDs. Once we are able to identify at-risk populations, we will design and test early interventions that will help prevent the development of NDDs. Our clinical research programs are also assessing current treatment outcomes, and exploring innovative treatment and intervention strategies.

Through genetic analysis, along with structural and functional neuro-imaging, we are expecting to be able to identify genetic and imaging biomarkers, which will improve our diagnostic skills, and enable the early diagnosis of NDDs. This is crucial in terms of clinical outcome, since treatment is most efficient if started early in the course of disease development.

In order to enable clinical research, we need to leverage and extend the development of existing data platforms and build a standardized database of electronic health records that captures relevant information from clinical settings. Ideally, clinical research would be embedded in the infrastructure of clinical practice with leading edge data capture, routine surveillance and analysis of data for timely identification of emerging issues and universal patient engagement. This clinical database would help us develop, monitor and evaluate standardized diagnostic protocols and treatment algorithms. By continuously assessing the therapies applied, and adjusting pathways as necessary, this approach could lead to the establishment of optimal, outcome-based standards of care.

As certain neurodevelopmental disorders are characterized by co-morbid medical conditions, another clinical research focus will be the intersection between ASD, epilepsy and sleep disorders. This will be implemented both in the basic science laboratory (with the generation and study of novel models of concomitant epilepsy and ASD) as well as in the clinical sphere (using advanced clinical neurophysiological monitoring technologies) to better understand and treat patients affected by these disabling medical co-morbidities. These neurodevelopmental brain linkages will be extended into the ADHD arena as well.

Neuroimaging studies are in progress to assess the effect of brain stimulation on neurodevelopmental disorders and child/adolescent mental health. Specific research studies are looking into the potentially beneficial effect of transcranial magnetic stimulation (TMS) as a possible new treatment for teen depression. The study is also trying to identify predictive imaging biomarkers that could help predict if this treatment may work for a specific patient. This would provide a high level of precision in the treatment of a condition where individualized therapy is crucial.

Additional research projects are investigating unique social, behavioural, and physical activity interventions that may improve outcomes of children and youth with NDD with a specific focus on ASD and ADHD. This work is aimed at enhancing and expanding the repertoire of interventions for children with an NDD.

## **2. Basic Science Research**

The Developmental Neurosciences Laboratory will continue using its animal models of ASD and ADHD to discover underlying pathophysiology focusing on defining behavioral abnormalities and sensory processing problems. The availability of ACHRI platform technologies will enable detailed molecular, biochemical, cellular and genetic characterization of behavioral and sensory disturbances in clinically relevant rodent models. The ultimate goal will be to identify novel treatments that might ameliorate, compensate for or correct the underlying molecular and cellular defects underlying these common clinical conditions.

Dietary and metabolic approaches in the treatment of neurological disorders are increasingly recognized as being both scientifically valid as well as therapeutically efficacious. The hallmark metabolism-based treatment is the high-fat, low-carbohydrate ketogenic diet (KD) which has been used for nearly a century to treat medically refractory epilepsy. The KD and its variants are also being increasingly explored for diverse neurological conditions such as brain cancer, ASD, cognitive disorders, pain and inflammation, and neurotrauma. Already internationally recognized, ACHRI's research program in epilepsy and brain metabolism will continue to identify the underlying mechanisms accounting for the broad anticonvulsant and neuroprotective properties of the KD.

The Behavioural Neuroscience Laboratory uses rodent models to study learning, motivation, and decision-making, as well as their underlying neural circuitry, to better understand functioning in health and disease. Specifically, they examine how brain dopamine systems operate following early-life adversity, reward learning, exposure to drugs of

abuse, and during decision making. Our goal is not only to understand these mechanisms, but also to generate prevention strategies and treatment options for addiction. This research is also relevant for autism, ADHD, schizophrenia, and OCD.

ACHRI's established Zebrafish platform for high-throughput screening of previously FDA- and Health Canada-approved compounds is also applicable for drug discovery in ASD. Our basic scientists have already developed several genetic zebrafish models of ASD that will be employed to rapidly identify compounds for therapeutic efficacy in this disorder. This would lead to rapid translation from animal models to early clinical trials.

### **3. Population Health and Policy**

The ABCD (Alberta Birth Common Data) is a collaboration for harmonizing two separate, well-established cohorts with detailed data and biological samples from pregnancy to age three. We will develop common follow-up strategies for children and their parents at ages five and eight years. ABCD will be a large prospective, population-based data source with detailed information on demographics, lifestyle, mental health, family functioning, parenting, child care, child development (social, emotional, physical, and cognitive) and biological markers that are critical to determine the early origins of child neurodevelopment, health and disease. This collaborative approach will offer an unprecedented opportunity to identify the risk and resiliency factors for suboptimal child development, including emotional and behavior problems, learning disabilities and mental health issues. The role of parenting, maternal mental health and stress, child care, environmental factors, school, and community in influencing family and child outcomes will be investigated. With input from community stakeholders and decision makers we will ensure our findings are relevant, address emerging needs and are translated into practice.

We will invest in long-term follow up to age 25 and beyond. This will enable unique investigation into early factors that influence neurological development, behaviour and mental health issues in adolescence and young adulthood-including familial and contextual factors. This information can be applied to understand risk and resiliency for substance use, school completion, interaction with the justice system and civic engagement.

The creation of a harmonized follow up will allow us to optimize the use of valuable resources. Creating an effective and efficient administrative infrastructure will optimize efficiency and reduce duplication. The ACHRI-led CSM Centre of Health Genomics and Informatics will enable the consolidation and efficient analysis of this large dataset. We will develop a training program to enhance analytic competency and content knowledge, recruit junior investigators and new faculty to investigate early origins of developmental concerns. We will establish a biobank for samples that include criteria for data access, and implement a leading edge, ethical data sharing process to enhance collaborations and the development of new knowledge. By implementing leading edge knowledge exchange and communication strategies, we will be able to share findings with stakeholders and ensure that the new knowledge is promptly translated into practice. Providing evidence about the influence of biological, social and environmental factors on children's neurodevelopment could lead to policy change, which, in turn, would contribute to the reduction of the burden of these disorders on society.

In partnership with health care providers, we will continue to design and implement research that addresses emerging issues of public health importance related to children's neurodevelopment and behavior. We will use the evidence arising from our research to inform policy and practices (including health, education and public services). Some current emerging issues that require investigation include child sleep patterns, food intake and habits, use of technology and screen time with respect to their effect on neurodevelopment and behaviour.

### **4. Health Services Research**

We will develop an efficient health services research platform for the linkage and analysis of relevant health services and administrative data sets to enable rapid description of gaps and emerging issues in health service processes. In collaboration with the Strategic Clinical Networks and others we will develop ethical strategies that facilitate data

access, linkage and analysis for discovery research in health. Our investigations would enhance understanding of the issues relevant to families who care for children with, or at risk of, neurodevelopmental problems such as where early screening occurs, what services are accessed and how timely they are, risk and protective factors, acute and tertiary care services, and transition to adult care.

Once we have identified gaps and emerging needs in the health services system, we will inform practice and policy in an effort to optimize outcomes for patients and families with NDDs and mental health issues. The goal is to deliver clinical and community health services in a coordinated, family-centred manner across the spectrum from the first point of access to transitioning to adult care. We will facilitate the development of a cohesive system with a single point of access, appropriate triage, ongoing coordinated management and system navigation support. We will actively participate in the development of common, consistent resources that meet family information and support needs.

## **Program Metrics, Intended Outcome and Impact**

### **Academic metrics:**

- External research funding – Tri-Council or other peer-reviewed external funding
- Trainee outcomes – number of trainees recruited and their success rate
- Publications - number of publications in peer-reviewed, higher impact journals (relative to the field)
- Presentations - number of invited presentations, presentations at international, national, and local conferences, grand rounds, etc.
- Partnerships/Leveraging - new partnerships/leveraging opportunities
- Knowledge translation - Policy statements, guidelines, clinical prediction rules, clinical pathways for assessment and management
- Membership on decision making and planning committees
- Clinical research engagement - number of patients included in research studies

### **Intended outcomes:**

- Develop early identifiers of children and families with/at risk of neurodevelopmental and mental health disorders;
- Design and verify methods of early intervention in at-risk populations to prevent the development of or minimize the damaging effect of neurodevelopmental and mental health disorders;
- Identify populations at risk of developing NDD and mental health issues;
- Inform programs and public policy and allocation of public resources for families with children with/at risk of neurodevelopmental and mental health disorders;
- Develop and implement evidence-based clinical pathways for the diagnosis and management of children with, or at risk of, NDD;
- Improve patient and family-reported outcomes such as functional status, quality of life and satisfaction;
- Identify novel treatment methods and drugs that improve patient outcomes.

### **Intended long-term impact:**

- Prevent, reverse, or minimize the damaging effects of neurodevelopmental and mental health disorders;
- Optimize public resources for families with children with/at risk of neurodevelopmental and mental health disorders;
- Optimize clinical and community-based health care delivery as well as educational strategy through continuous translation and integration of research findings into practice;
- Improve the psychosocial, emotional and mental health of children with neurodevelopmental disorders and their families, thereby reducing the burden on families and the community at large

### C.3. HEALTHY OUTCOMES THEME

#### Background

The focus of outcomes research is the scientific scrutiny of healthcare and health promoting practices and interventions to determine if there is benefit for patients, health care systems and/or society. The goal of child and family-centred outcomes research is to improve health outcomes and to conduct research that is aligned with the individual needs and preferences of the target population. Rigorous research methods and standards are needed to produce relevant and reproducible findings that improve health outcomes.

The Healthy Outcomes theme's broad goals are to use discovery and outcomes research techniques to improve clinical practice in acute and chronic child health care. The spectrum of interest includes: health promotion, prevention, diagnostic, treatment and rehabilitation interventions. The Institute promotes the creation of multidisciplinary teams with a diversity of talented members who share a passion for outcomes research designed to improve the health and well-being of children and families. We strive to advance health system sustainability through improved access, quality, safety, efficiency and reduced health care delivery costs (*Figure 12*).

The spectrum of our research initiatives includes: health promotion, injury and chronic disease prevention, diagnostic and therapeutic approaches to acute and chronic diseases, and rehabilitation practice. The development and evaluation of preventive and therapeutic interventions, targeting specific populations, has significant potential to improve child and family health, well-being and quality of life. Research teams typically focus on diseases and conditions that are highly prevalent and/or are associated with significant maternal, newborn, and child morbidity and mortality. These are the areas where child and family-centred outcome research provides the greatest impact.

To achieve our goals, our theme believes in creating strong strategic partnerships, promoting collaborations and leveraging alignments to achieve a greater impact than could be accomplished working in isolation. We have strong connections to leaders and members of other ACHRI themes, to other institutes within the Cumming School of Medicine, and with specific groups such as the CSM Clinical Research Unit, the ACHRI led Health Genomics and Informatics platform, and the Western Canadian Microbiome Centre. We have worked to align our strengths and research platforms with Alberta Health Services, the Maternal Newborn Child and Youth Strategic Clinical Network, and Alberta Innovates-Health Solutions to foster mutually beneficial collaborations.

*Figure 12: Healthy Outcomes approach to problem identification, discovery and implementation of new knowledge*



The Healthy Outcomes Theme strives to reduce suffering, improve outcomes and save lives. By 2020, the Healthy Outcomes research teams will translate knowledge into best practices, care pathways, and policy while promoting health system sustainability through improved access, quality, safety, and reduced health care delivery costs.

**Vision:** To improve the health and wellbeing of children and families by focusing on excellence in child and family-centred outcomes research and translating new knowledge into practice.

**Mission:** To conduct high-impact child and family-centred research, employing innovative research methodologies, that is focused on promoting the well-being of children and families, guided by the values of prevention, health promotion, and knowledge translation.

### **Strategic Goals:**

1. To create new knowledge in high priority areas across the continuum of health and illness from conception to adulthood.
2. To build sustainable child and family-centred research programs through the recruitment and retention of outstanding academics.
3. To assist in creating child and family-centred research infrastructure (methodological, biostatistical, health economic, data analytic and knowledge translation expertise) to support data-intensive research.
4. To integrate new knowledge into clinical practice through the creation of new, evidence-based clinical pathways, the shaping of health policy and the integration of quality improvement into pediatric care.
5. To promote collaborations and partnerships across disciplines, faculties and institutes to develop a comprehensive, translational clinical research program.

Two broad strategies for achieving these goals are as follows:

- Investing in scientists and infrastructure to complement areas of strength and promote success
- Recruiting a core team of child and family-centred outcomes research methodologists, biostatisticians and informatics experts

These goals and strategies will inform ACHRI's approach to new opportunities. ACHRI has embraced collaboration with the Vi Riddell Pain and Rehabilitation Centre at the Alberta Children's Hospital to create the Vi Riddell Pain and Rehabilitation Program. This program will bring together a multidisciplinary team of clinicians, child psychologists and basic scientists. The ACHRI team will improve pain management modalities to minimize the impact of medications, elucidate the fundamental mechanisms involved, characterize the genes underlying pain and determine novel treatments.

### **Current areas of research excellence and previous accomplishments**

The HO Theme's plan builds on its significant strengths in priority areas of child and family outcomes research as well as a Clinical Research Infrastructure platform. Select innovations and successes are highlighted below:

#### **1. Health Promotion and Disease Prevention**

- **Antenatal and Post-Natal Determinants of Health**
  - Implemented a common follow-up for two large pregnancy cohorts to determine the early influences on child development employing protocols for data depositing and sharing, enabling secondary use of research data to support investigation into uncommon childhood problems and the validation of new findings across studies.

- Demonstrated how an obstetric co-morbidity index can be employed to predict adverse obstetrical events and the safety of reduced duration post-natal inpatient monitoring of newborns.
  - Assisted with development of simple neonatal education programs to reduce mortality in resource limited areas of the world and led the development and implementation of a comprehensive Maternal Newborn Child Health (MamaToto) program in Uganda that has significantly decreased child morbidity and mortality.
  - Elucidated factors involved in respiratory control and normal post-natal oxygen saturations, and demonstrated the effect of maternal conditions, resuscitation and post-natal factors on outcomes of pre-term neonates.
- **Obesity**
    - Demonstrated how early dietary intake affects long term obesity risk and that prebiotic fibre consumption helps obese children improve their ability to maintain a healthy weight.
    - Employed composite knowledge of genetics, nutrition and metabolism to predict, prevent and treat chronic metabolic disease states that begin in childhood and early adolescence including obesity, type 2 diabetes and cardiovascular disease.
    - Documented the strategies used to market child-targeted foods, the nutritional profiles of these foods, provided policy recommendations on food labelling, marketing/packaging, and developed Media Literacy and Food Marketing Curricula for children and teenagers for schools in Alberta and British Columbia.
  - **Injury Prevention and Rehabilitation**
    - Evaluated strategies to reduce the public health burden of youth sport and recreation injury, including long term consequences of injury (e.g., decreased physical activity, obesity, osteoarthritis, post-concussion syndrome, health care utilization).
    - Interdisciplinary approach to evaluation of rehabilitation strategies informing practice across a diversity of pediatric populations (e.g., neuromotor impairment, concussion, developmental disorders, musculoskeletal injury and disease) to maximize function, physical activity and quality of life.
    - Informed injury prevention practice and policies in child and adolescent sport (e.g., body-checking policy and other ice hockey regulations, helmet and equipment standards, active transportation).
  - **Pain Management**
    - Created an interdisciplinary centre of excellence for child pain management and innovative research focused on developing novel therapies for children suffering from acute and chronic pain.

## **2. Infection, Inflammation and Chronic Childhood Diseases**

- **Vaccine Development and Evaluation**
  - Developed vaccines derived from bacterial surface antigens to eliminate Gram-negative pathogens responsible for meningitis, pneumonia and otitis media from the upper respiratory tract.
  - Developed an evaluation pipeline to quantify the safety, immunogenicity, cross-protection, and efficacy of new vaccines in healthy and immunocompromised individuals.
  - Evaluated asymptomatic and clinical disease states caused by vaccine preventable pathogens, particularly *Streptococcus pneumoniae*.
- **Diagnosis, Monitoring and Management of Autoimmune and Inflammatory Diseases**
  - Integrated basic and translational research findings from national and international cohort of rare rheumatologic diseases (particularly vasculitis) into clinical care to improve the understanding of pathogenesis, enhanced capacity to diagnose, classification, management and rehabilitation in children with disease to improve outcomes.

- Established a national observational cohort to study care variation in childhood nephrotic syndrome enabling the development of research platforms to understand disease pathogenesis, and to develop targeted treatments of childhood nephrotic syndrome.
- Established a national database of children with end-stage renal disease which has increased our understanding of outcomes related to age, ethnicity, and location of residence and the impact of transition to adulthood.
- **Advances in Childhood Cancer Care**
  - Developed a biorepository of pediatric tumours and body fluid samples from which cell-lines could be created, tumour modeling made possible, and avenues be created for metabolomic research.
  - Identified potential determinants of hematopoietic transplant failure, graft-vs-host disease, and infection to prospectively study through screening of blood stem cell donors.
  - Increased our understanding of the impact of cancer on the psychosocial well-being and relationships involving patients, survivors and families and have promoted appropriate physical activity and exercise.

### **3. Acute and Life Saving Care**

- **Simulation and Cardiac Arrest**
  - Demonstrated that a credit card sized Cardiopulmonary Resuscitation (CPR) feedback device improves CPR quality when children experience a cardiac arrest.
  - Discovered that simulation-based team training improves CPR.
  - Quantified how training performed in highly realistic environments results in improved clinical skills and task performance compared with low-realism simulation scenarios.
- **Respiratory and Intestinal Emergencies**
  - Evaluated and integrated use of antiemetic into clinical care dramatically enhancing the ability of children with vomiting and diarrhea to succeed with oral rehydration and reducing the use of intravenous rehydration by over 50%.
  - Generated knowledge directing optimal management of most common childhood respiratory emergencies and incorporated this evidence into clinical care pathways to ensure children receive the best care possible.
  - Designed clinical algorithms and generated knowledge through next-generation biomarker profiling (blood and urine) in pediatric appendicitis and sepsis.

### **4. Clinical Research Methods**

- **Child and Family Outcomes Research Methodology**
  - Employed economics based stated preference techniques to quantify family, patient and physician views about health interventions and programs.
  - Enhanced the design, conduct, and analysis of studies across all ACHRI core research strengths to produce optimally designed studies that lead to results that are accurate and impactful.
  - Investigated individual characteristics that result in frequent health care system use, both acute and primary care, by adults and children.
- **Implementation Science and Metrics**
  - Achieved a 50% increase in proportion of children and caregivers who are satisfied with pain management when brought for emergency department care with extremity injuries.
  - Developed quality indicators for high acuity pediatric emergency department conditions that have been adopted nationally for performance measurement.

## **Research plan**

The Healthy Outcomes theme's research development plans are focused on promoting the success of all members through the creation of a core of methodologic expertise that aligns with our vision, priorities and strengths. We believe that a solid methodologic research foundation and infrastructure (e.g. the child health research methods team comprised of faculty within the Departments of Paediatrics and Community Health Sciences) will catalyze a broad range of collaborative research within child and maternal health and best promote achievement of our goals. Expertise in epidemiology and biostatistical methods are key components enabling the conduct of high-quality and rigorous studies incorporating optimal database design and the conduct of data linkages and analytics that are core components of the Healthy Outcomes theme. We need to further strengthen our research methods expertise through recruitment of key faculty to support the creation of linkages between biological and psychosocial data, child and family-centred outcomes metrics, health-care system data, health economics, and to translate these findings into improved outcomes. Strength in bioinformatics has the potential to integrate our clinical data into emerging technologies and strengths at the University of Calgary, including the microbiome and genomics facilities. Our methodologic interests overlap with those of the O'Brien Institute of Public Health, there is extensive collaboration, joint membership and shared perception of common recruitment needs. While we are not interested in duplication, we are committed to building complementary clinical research capacity **specific to child and family health**. The 5-year recruitment plan proposed by the Theme is aligned with the U of C Clinical, Health Services and Population Health Research Strategy that is under development and will be submitted as a U of C *Eyes High* research priority. It is also aligned with the CSM strategic plan, most notably along the lines of precision medicine (clinical trials, bioinformatics).

The following positions reflect the needs of the Healthy Outcome theme and the gaps to be filled to help us achieve excellence (listed in order of priority):

1. **Patient and Family Centred Outcomes Research Methodologist (Goals #1, 2):** According to CIHR, patient-oriented research is the cornerstone of evidence-informed health care. It refers to a continuum of research, from initial studies in humans to comparative effectiveness and outcomes research, and the integration of this research into the health care system and clinical practice. It involves ensuring that the right patient receives the right clinical intervention at the right time, ultimately leading to better health outcomes. The vision of CIHR's Strategy for Patient-Oriented Research is to demonstrably improve health outcomes and enhance patients' health care experience through the integration of evidence at all levels in the health care system. These goals are currently being integrated into the currently being proposed U of C Clinical Research Strategy and we at ACHRI believe that we are well positioned to make huge strides in the conduct of patient-oriented research.

A key step to move ACHRI forward would be the addition of a mid-career, PhD methodologist with expertise in patient centred outcome metrics. Such an individual would provide benefits across research groups, institutes, and faculties. There is a movement within funding agencies such as CIHR, to focus on patient rather than health system outcome measures. Moreover their SPOR strategy has identified the importance of having patients (an overarching term inclusive of individuals with personal experience of a health issue and informal caregivers, including family and friends), researchers, health care providers and decision-makers actively collaborate to build a sustainable, accessible and equitable health care system and bring about positive changes in the health of people living in Canada. Engaging patients is thus an integral component in the development and implementation of CIHR's SPOR strategy. ACHRI and U of C currently lacks an outcomes methodologist with pediatric expertise. This initiative is directly aligned with our AHS partner's focus on delivering patient and family centred care and the recently established SPOR network here in Alberta.

2. **Implementation & Knowledge Translation Science Lead (Goal #4):** A proven leader with a track record in knowledge translation and implementation science research is needed to aid in integrating the vast amount of knowledge generated locally and nationally/internationally into clinical care and public health practice and

policy. By doing so, we would create the science that will guide the integration of optimal policy into clinical care. The focus would be on partnering with existing research groups to design optimal implementation strategies for our local institutes that could be adopted nationally and internationally thereby positioning ACHRI at the forefront of knowledge translation science. In addition to generating original science, this role would align with our strategic partners at Alberta Health Services, particularly the Maternal Newborn Child and Youth Strategic Clinical Network, the ACHF and our broader community. The translation of research findings into improvements in quality of life is a key element stressed in the Canadian Academy of Health Sciences report “Making an Impact; A preferred framework and indicators to measure returns on investment in health research”. By recruiting both an implementation scientist and a patient-centred outcomes research methodologist, ACHRI will be well positioned to demonstrate return on investment and research impact.

3. **Clinical/Bioinformatics (Goal #3):** As our members are increasingly linking their clinical data with emerging biologic data (e.g. microbiome, genetics) there is a need and an opportunity for ACHRI to become national and international leaders. Many of our members have large bio-repositories of data and specimens and the addition of a PhD with expertise in this emerging field will position ACHRI as a leader.
4. **Health Services Research (Goal #4):** To truly understand and evaluate the impact of health interventions and changing health care policies, a health services researcher is required. Such an individual would have access to some of the most robust and comprehensive data in the world, right here in Alberta. This expertise would complement the strengths of our Theme and those of the implementation science lead. Such an individual could help in priority setting, identifying priority diseases and issues while also improving our capacity to evaluate impact. These skills are crucial to completing the Gordian knot which is central to our theme’s perspective on research.
5. **Paediatric Clinical Pharmacologist/ Drug Safety Expert (Goal #1):** Drug safety and optimized therapeutics for children has been identified a top priority by key leading regulatory agencies (e.g., FDA), professional organizations and policy-makers in North America and Western Europe. Historically, children have been excluded from clinical trials and drug development, in an attempt to protect them from potential harm. Drug prescribing and dosing have been largely extrapolated from adults. This practice violates basic principles of pediatric physiology and ontogeny, and has led to a lack of knowledge on the effectiveness and safety of many medications, resulting in the common practice of administering medications to children ‘off-label’ (i.e., not for the approved clinical indication, age, dose or route of administration). Currently, *50-75% of all medications prescribed in hospitals to children are administered off-label*. This practice puts children at risk of adverse reactions and use of ineffective medications, which ultimately can compromise their health.

An individual with expertise in paediatric pharmacokinetics, pharmacodynamics and pharmacogenomics (“personalized medicine”) research would take drug-related research to the next level at ACH/ACHRI, while complementing the evolving U of C Strategic Plan (Health Research Strategy; led by Dr. Tonelli) and provide important partnership to several of our current research groups and position our institute as a leading site for the expanding field of pediatric drug studies. Such an individual would facilitate and foster new funding opportunities, building relationship with local and global pharmaceutical industry, as well as strong support for funding agencies applications, which involve novel therapies.

Our group focused on Childhood Cancers is a leader in early phase clinical trials and would benefit immediately from the addition of a clinical pharmacologist with expertise in this specific area. Other groups that employ and evaluate novel and expensive biologics (e.g. gastroenterology, rheumatology) would benefit from a clinical pharmacologist. The field of personalized medicine and tailored drug therapy is another important and under-explored area at ACH/ACHRI. Other aspects of drug safety, such as the prevention of medication errors are imperative to building a safe clinical environment, clinically, legally and financially and expertise in this realm would align with the requested Implementation & Knowledge Translation Science Lead. In addition ACHRI is

hopeful of securing a position as a KIDSCAN node and we are ideally suited to become a pharmacokinetic/pharmacodynamic hub of expertise. To achieve these aims, an established clinical pharmacologist is necessary. This desire is further strengthened and aligned with other ongoing Department of Pediatrics recruitment efforts.

6. **Health Economist (Goals #3, 4, 5):** Our theme is fortunate enough to have a health economist but the current expanding role and need to incorporate economic analysis into clinical studies has demonstrated our need to expand our strength in this field. Such strength would align with AIHS PRIHS grants, AHS' need to demonstrate economic costs of policies and the need to demonstrate health system sustainability.

These 6 individuals would join and strengthen our existing Research Methods Team, which includes Gillian Currie (PhD – health economics), Brent Hagel (PhD – epidemiology), and Alberto Nettel-Aguirre (PhD – biostatistics). They would also require a team of enabling personnel to enhance collective and individual efforts. These personnel would include graduate students and post-doctoral fellows along with a small, core group of non-faculty, service level personnel. A final key to success would be to create formal ties to Alberta's SPOR support unit, U of C's CRU, Data Integration, Measurement and Reporting (DIMR), and the Maternal Newborn Child and Youth Strategic Clinical Network.

## Program Metrics, Intended Outcome and Impact

### Academic Metrics:

- External research funding
  - Tri-Council or other peer-reviewed external funding
  - Research chairs
  - Competitive academic prizes
  - Return on investment from philanthropic funding (e.g. ACHF, Theme Based Funding)
- Publications
  - Number of publications in peer-reviewed journals
  - Impact of journals (to be considered relative to the field)
- Presentations
  - Number of invited presentations
  - Number of presentations at international, national, and local conferences, and grand rounds.
- Trainee outcomes
  - Number of trainees (all levels – Masters, PhD and post-doctoral)
  - Trainee success measured in terms of training awards, research productivity and final academic placement
- Leadership
  - Large research network, international societies
  - Participation in network, team, centre of excellence grants
- International profile
  - Keynote addresses, influence on global child health policy and practice

### Impact:

- Integration of findings into care or lead role in promoting knowledge translation
  - Evidence-based best practices guidelines
  - Care pathways
- New health and public policies shaped by outcome-based research results
  - Local (i.e. Alberta Health Services)
  - National (i.e. Canadian Pediatric Society, Sporting Associations)
  - International
- Improved disease specific health outcomes, reduced delivery costs and quality of life

- Select quality metrics to be determined based on research investments, priorities and alignment. This metric will require the support of the SCN and DIMR and thus will be negotiated in conjunction with external stakeholders.

## Select Established Research Program Summaries

The following are summaries of a select group of the Healthy Outcomes Theme's established, core research programs and their goals for 2015-2020:

### I. Childhood Cancer Research Program (CCRP)

The Childhood Cancer Research Program (CCRP) comprises a diverse group of investigators at the University of Calgary and the Alberta Children's Hospital who are dedicated to improving outcomes for infants and children with cancer and blood disorders under the leadership of Dr. Jennifer Chan, holder of the Kids Cancer Care Chair in Pediatric Oncology funded through the ACHF.

#### Background

Cancer is the second leading cause of death in children (after accidents). Fortunately, through clinical and biomedical research, great improvements have been made over the past decades in outcomes for children with cancer. In the 1950's, the chances that a child would survive at least 5 years after receiving a diagnosis of cancer was <40%. By the 70's, that number rose to nearly 60%. Today, over 80% of children diagnosed with cancer will live for 5 years or more.

Behind those encouraging numbers, however, are several serious realities about childhood cancer outcomes. Firstly, despite our progress, cancer remains the second leading cause of mortality in kids. For those 20% that do not survive, we still need more effective treatments to **increase the rate of cure**. Although overall progress has been good, with some cancers such as Hodgkin's lymphoma, retinoblastoma, Wilms tumour, and acute lymphocytic leukemia exceeding 90% 5-year survival, the outcomes for other cancers such as brain cancers and sarcomas have seen little improvement in decades. Furthermore, once a cancer recurs or metastasizes, the prognosis is exceedingly poor. We still need **more cures**. Secondly, with increasing long-term survival, we must work to **decrease the toxicity** of our therapies. Radiation, chemotherapy, and bone marrow transplant are staples of modern hematology-oncology practice. However, childhood cancer survivors often experience acute and long-term adverse effects from the treatments that can include neurocognitive decline, heart and lung problems, secondary malignancies, and graft-versus-host disease. We must not only improve the rates of cure, but also decrease the complications that survivors experience. Thirdly, because childhood cancer is a traumatic and life-altering experience for both the patients and their families, we must work to understand and **improve the cancer experience**, maximizing the quality of life for patients and families.

#### Goals

##### 1. Increase the cures

- *Understand the basis of childhood cancer origin, growth, and metastasis*

Although children and adults both are susceptible to cancer, we are learning that the genes and mechanisms underlying childhood cancer are often different than those in adults. To make progress in childhood cancer, we are developing more representative models of childhood cancer using patient-derived cells and tissues and genetically engineered models systems, with a particular need for better experimental models of solid tumours. Building on prior success in the brain tumour area, we are expanding and developing a pipeline for patient-derived cell cultures and patient-derived xenotransplants into animals. We are developing a next-generation biobank that is not only a source of clinically annotated biosamples but also one that contains xenograft-ready

samples to support preclinical experimental therapeutics studies. We are already using some of these types of models to focus on identifying determinants of cancer progression and metastasis through basic and translational research, as these determinants represent potential new therapeutic targets. One special focus of research is in the interaction of the immune system with cancer cells (see below). We are also linking our preclinical models and tissue samples studies into larger national/international initiatives in personalized oncogenomics (see below).

- ***Guide therapy selection with molecular information***

Precision cancer medicine for childhood cancer is a necessarily a team effort that requires integration of clinical efforts and research efforts across multiple disciplines and multiple institutions. Our investigators are advancing the science and bringing the hope of personalized oncogenomics to kids in Alberta through leadership roles and activities in two forming initiatives involving integrated molecular profiling (genomic, epigenomic, transcriptomic, proteomic) of a child's cancer linked with potential selection of a specific drug. These projects leverage local and national/international expertise in biobanking, experimental therapeutics, genomics, proteomics, and model systems. Over the next 5 years, our goal is to have programs in place such that every child with a rare/refractory/hard-to-treat cancer at ACH (and beyond) has the opportunity to enroll in such a study. At this stage, both the POETIC consortium (key involvement by CCRP investigator Dr. Aru Narendran) and investigators in the Terry Fox Foundation supported PROFYLE project (key involvement by CCRP investigator Dr. Jennifer Chan) have received funding to organize the first stages of these programs. Matching funds are needed to realize the full breadth of the projects.

- ***Identify and evaluate new therapeutic approaches***

Our investigators have a track record in experimental therapeutics through their work in cooperative group clinical trials and in the translational preclinical work that is necessary to launch early phase trials (through our involvement in POETIC, C17, and other consortia). With the recent addition of faculty recruits who have expertise in medicinal chemistry, immunotherapy, and virotherapy to our group, and the recent construction of a high throughput screening facility, our investigators are accelerating their work in experimental therapeutics. In addition to screening for compounds that might have direct effects on cancer cells, a special focus of our group is searching for genes or compounds that can allow us to harness immune cells and viruses to target cancer cells. We are also investigating whether existing therapies can be applied in new contexts to improve patient outcomes. An example is the innovative work of Dr. Greg Guilcher to expand the accessibility and use of bone marrow transplant to cure sickle cell disease.

## **2. Minimize adverse effects**

- ***Decrease graft-versus-host disease (GVHD) in allogeneic hematopoietic cell transplant patients***

Bone marrow transplant is a life-saving treatment for childhood blood cancers and other blood disorders. One of the most serious complications post-transplant is the development of GVHD. Our investigators are identifying genetic makers (KIR genes and others) that, when matched between donor and recipient, will improve graft survival and decrease the incidence of GVHD after transplant. This work has high potential to improve survival and quality of life of pediatric BMT patients.

- ***Reduce neurologic sequelae of cancer treatment***

Radiation to the brain and spinal cord is a standard part of therapy in children with brain cancers and some blood cancers. Although effective, radiation can be associated with neurological side effects, neurocognitive decline, and developmental delay; the younger the patient, the more severe the side effects. Dr. Lucie Lafay-Cousin is investigating radiation-sparing approaches for the treatment of infant brain tumours. Dr. Jennifer Chan is investigating how and why cell types in the developing and immature brain might be particularly sensitive to the effects of radiation therapy. Other researchers aim to investigate the therapeutic efficacy of radiation (or re-radiation in some settings), while quantitating neurocognitive outcomes (Drs. Doug Strother, Fiona Schulte et al.).

### **3. Improve the Cancer Experience**

- When a child, teen, or young adult is affected by cancer, it is a life-changing experience for the patient and the family. Young persons' cancer and its treatment can have lasting consequences for later success in school, work, relationships, and childbearing. This area of our research focuses on the physical, cognitive, psychological, and social impacts of cancer in young persons. Investigators in this group are working on understanding the many facets of cancer as experienced by the patient and the patient's family, and developing novel interventions to improve the quality of life during and after cancer treatment. Dr. Fiona Schulte is investigating social development and social competence in pediatric oncology survivors, and is testing interventions for social skills support. Dr. Nancy Moules is focused on understanding **patient and caretaker experiences**. Dr. Nicole Culos-Reed is investigating how **exercise** may improve patient outcomes and wellbeing. Dr. Lianne Tomfohr is evaluating the impact on **sleep** in cancer patients, and is interested in psychosocial aspects of cancer. Dr. Catherine Laing is determining the **social return on investment** for childhood cancer interventions. Finally, Drs. Lucie Lafay-Cousin and Fiona Schulte are investigating **innovative models of service delivery** to improve experiences and outcomes for childhood cancer patients and families; in the next 5 years, some of the goals of this program are to quantitate outcomes, and determine the value of the Hospital at Home program.

Although these themes, and the investigators in the group are diverse, some core infrastructure common to many of the investigative programs include the need for cancer biobanking/modeling, an integrated database solution for clinical and research/molecular data, and improved support for the collection of clinical data and tracking of patient outcomes.

## **II. Alberta Birth Common Dataset (ABCD) - Longitudinal, Genetic and Biomarker Data**

### **Background**

The ABCD (Alberta Birth Common Data) is a collaboration for harmonizing two separate, well-established cohorts with detailed data and biological samples from pregnancy to age 3. The All Our Babies (AOB, n=3200) and the Alberta Pregnancy and Nutrition (APrON n=2200) cohort studies have similar data elements from the prenatal period through 3 years of age and common follow up strategies for children and their parents at 5 and 8 years of age (Appendix 1). Current retention rates exceed 75%, indicating the feasibility of long term follow up (details below), and samples available for analysis from 4300 participants. The studies will follow up children and families over time, to analyze and catalogue biologic samples, including genetics and biomarkers. This unique longitudinal data will allow for leading edge investigation of the relative influences and timing associated with social, biologic, toxicant and genetic influences on health and well-being of children and families.

### **Objectives**

1. To establish a data platform which includes longitudinal cohort data, biomarker, neurotoxicant and genetic data to enable research on the factors that influence risk and resiliency for childhood disease/disorder;
2. To create a hub of research inquiry that answers complex questions about child development;
3. To partner with community stakeholders in the application of evidence into policy and programs to improve outcomes for children; and
4. To create a collaborative environment for research, training and education in maternal and child health

ABCD will create a large prospective, population-based platform with detailed information on demographics, lifestyle, mental health, family functioning, parenting, child care, child development (social, emotional, physical, and cognitive), genetic, toxicant and biomarker information that is critical to determine the early origins of child neurodevelopment, health and disease. The collection of data over time among the same individuals is critical to determine causal associations, the trajectory of health and well-being, and the identification of early markers of adverse outcomes.

The ABCD harmonized follow up optimizes resources because the number of children and families will less common conditions is large enough to answer questions about these special populations. Investigations on the trajectories of children and families provides insight into where interventions would be most effective to prevent or remediate problems. This approach is an unprecedented opportunity to identify risk and resiliency factors for suboptimal child development, including emotional and behavior problems, learning disabilities and mental health issues. This detailed longitudinal descriptive, genetic and biologic characterization of the cohorts is critical to understanding the early factors that influence neurological development, behaviour and mental health issues that appear in adolescence and young adulthood- including familial and contextual factors. Furthermore, we can investigate complex human issues including risk and resiliency for substance use, school completion, interaction with the justice system, work force attachment and civic engagement.

***We plan to follow the children to age 25 and analyze existing biologic specimens to create an unsurpassed data platform for the investigation of the social, genetic, toxicant and biologic influences on human development.***

To achieve these objectives, we will develop an infrastructure to optimize efficiency, reduce duplication, accelerate research and promote data sharing. The data platform will include information from the descriptive questionnaires, genetic, toxicant exposure and bio-specimen data. We will develop criteria for data access and implement a leading edge, ethical, sharing process to enhance collaborations and the development of new knowledge. The ACHRI-led CSM Centre of Health Genomics and Informatics will enable the consolidation and efficient analysis of this large dataset. Through our training program, we will enhance analytic competency, content knowledge and teamwork to better understand human development. Through integrated stakeholder engagement strategies, we will continue to design and implement research that addresses issues of social importance related to children's neurodevelopment and behavior. Leading edge knowledge exchange and communication strategies with our stakeholders will facilitate the inclusion of evidence into practice and policy, ultimately reducing the burden of these problems on society.

## **Key Components**

### **1. Descriptive Questionnaire Platform**

To set priorities for the follow-up questionnaires, we review government strategic plans and the child health literature. To ensure a coordinated approach, we convene team members, academic experts, funders, informed parents, and decision-makers interested in child and family health to identify content gaps and priority areas for research. Stakeholders identify evidence gaps (e.g., injury, nutrition, task completion, sleep) that could be addressed by the ABCD. They recommend measures and consensus is reached about a questionnaire that minimizes respondent burden, yet addresses areas of importance. We pilot test these questionnaires with families and revise them for clarity and acceptability; the questionnaires are approved by the ethics board. Questionnaire data will be collected both electronically and by paper to accommodate participant preferences. The data is stored in a secure data environment and each questionnaire is linked to previous waves of data and sample collection. Data management practices have been approved by ethics boards and the provincial privacy commissioner. Table 1 includes summary information on measures to date.

## **2. Genetic Platform**

An individual's DNA contains the genetic blueprint that will define their phenotype (observable traits, including behaviour). This genetic blueprint provides the code for proteins (functional component including enzymes, transporters and receptors), and any changes in the genetic code may result in variations in the function of these proteins. Variations in DNA include, for example, single nucleotide polymorphisms (SNPs), where change in a single base pair results in a change in the building blocks of the protein. Dependent on protein function, this may result in altered enzyme activity, transporter interaction or receptor binding, which results in an altered individual phenotype. There is evidence that specific gene systems have direct effects on human social behaviours, including parenting, empathy, and aggression.

## **3. Biomarker Platform**

Biomarkers are often used to classify individuals in terms of disease risk. For example, the components of a basic lipid panel identify people at risk of outcome such as diabetes, cardiovascular disease, and obesity. Biomarkers were selected based on measurement reliability, association with disease processes, use in clinical assessment or prediction, and overlap with other studies. These biomarkers will enable basic phenotyping of ABCD participants and improve the accuracy of risk classification above questionnaire data alone. For example, the validity of self reported disease may be questionable, however, the biomarker data can provide an objective marker of physiologic disorder. ABCD has samples for 4300 participants that could be analyzed. It is preferable that samples are analyzed in a single laboratory using standardized protocols to ensure high-throughput, high-quality, and robust measurements. The Alberta Tomorrow Project and The Canadian Longitudinal Study on Aging have identified Calgary Laboratory Services as an optimal facility. We propose a basic biochemical panel, and a placeholder for other biomarkers of specific disease relevance. The basic biochemical panel would include: Lipids, Total and HDL cholesterol, HbA1c, hsCRP, ALT, Albumin, Creatinine, Estradiol.

## **4. Neurotoxicant Platform**

Recent studies have shown that developmental outcomes of children are exquisitely sensitive to environmental contaminants, in particular Bisphenol A, phthalates, heavy metals (i.e., methyl mercury, lead, arsenic, manganese) and perfluorinated chemicals (i.e., perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)), which are abundant in the Canadian environment. These environmental contaminants cross the placenta and are believed to affect the activity of genes in the brain critical for development of pathways that drive behaviour of children later in life. In utero exposure of mice to BPA affected learning and memory, and permanently influenced behavior of offspring in adulthood, and recent data from the Kurrasch lab showed that BPA directly shifted the timing of neurogenesis in developing zebrafish, perhaps offering a potential mechanism for how BPA exposure in utero can manifest in neurodevelopmental disorders later in life. In humans, there is also an expanding body of evidence, including our own, associating maternal BPA and phthalate exposure with behaviour problems, ADHD, social impairments, and lower IQ and alterations in brain structure. The effect of these contaminants on genes is poorly understood, may be different for males and females and could explain the greater proportion of boys that are diagnosed with developmental disorders such as autism spectrum disorder, attention deficit/hyperactivity disorder and reading disability. Analyses of neurotoxicant biomarkers in this cohort will position us as leaders in research on developmental neurotoxicants. These data will be used to answer critical questions about the negative effects of exposure to environmental contaminants during pregnancy on children's brains and behaviour and could be used to inform risk mitigation strategies.

### **III. Alberta Provincial Pediatric Enteric Infection Research Program**

The APPETITE (Alberta Provincial Pediatric EnTeric Infection TEam) program represents a unique multi-disciplinary, bench to bedside collaboration that includes experts from across Alberta that has been assembled and is led by Dr. Stephen Freedman, holder of the ACHF Professorship of Child Health and Wellness. The team is externally funded by a \$5 million Alberta Innovates – Health Solutions Team CRIOT grant that runs until 2019.

#### **Background**

Each year in Canada there are 5 million episodes of acute gastroenteritis (AGE) with up to 70% attributed to an unidentified pathogen. In 2012, AGE was the discharge diagnosis assigned in 30,666 pediatric emergency department (ED) visits (10% of all pediatric ED visits) in Alberta alone. AGE ED visits are on the rise, increasing by 4% annually (data courtesy of Data Integration, Measurement, and Reporting, Alberta Health Services). At a cost of over \$1,000/AGE case, the annual cost of AGE in Alberta's children exceeds \$400 million; the cost to the entire country is \$3.7 billion.<sup>2</sup> These estimates, which rely heavily on non-Canadian data, are only the tip of the iceberg since 90% of individuals with AGE do not seek care when ill; thus, the estimates are limited by under-diagnosing and under-reporting. Moreover, we know little about the pathogens causing AGE as the majority of episodes are attributed to an “unidentified” etiology because **current testing:** **1)** identifies a pathogen in only 20 – 30% of submitted samples; **2)** usually requires caregivers to collect stool at home and return it for testing, which is an unappealing process with low compliance; and **3)** is only performed on “diarrhea” specimens, consequently individuals with AGE in which vomiting predominates rarely have specimens tested.<sup>4</sup>

The APPETITE team is evaluating a movement from cumbersome culture, microscopic and enzyme immunoassay (EIA) based diagnostics to a **21<sup>st</sup> century testing platform**, employing a multi-analyte polymerase-chain reaction (PCR) array. This single test approach, evaluated on 625 patients to date, has identified a pathogen in 75% of study participants, tripling our current diagnostic precision. The team is also evaluating a paradigm shift from stool collection (by parents at home) to **rectal and oral swab performance at the point of care**. This approach has boosted compliance from 25% to over 95%, eliminate delays in testing and treating, enabling the rapid identification of etiologic agents, including those causing infectious vomiting in the absence of diarrhea. These findings are already guiding high-level discussions regarding: **1)** the value of introducing a universal rotavirus immunization program in Alberta; and **2)** the integration of comprehensive enteric pathogen identification into provincial laboratories. The APPETITE team is delivering an unparalleled analysis of enteric diseases, including assessment of societal impacts, which is already serving as a model for global dissemination and the team has already played valuable roles in mitigating outbreaks of infectious agents such as Shigella. Our work focuses on the pediatric population (< 18 years) as they bear a disproportionate burden of disease (17% AGE monthly prevalence).

Our team integrates clinicians, scientists and end-user partners who are responsible for provincial decisions related to laboratory testing, program delivery, communicable disease surveillance, and vaccine policy. Our proposal emerges from substantial engagement by caregivers/patients, clinicians, and policy-makers and it integrates the needs and knowledge of these three groups into the research plan.

#### **Objectives**

Our team has the following objectives which are designed to enable Alberta Health (AH) to deliver an evidence-based, economically efficient, patient-centred enteric disease management plan:

- 1. Improve health through enhanced enteric pathogen identification.** We are evaluating novel specimen collection methods (rectal and oral swabs) and technology (multi-analyte PCR assay) that support **precision medicine** through point of care specimen collection and testing, leading to rapid pathogen identification, enabling more expeditious institution of therapy when indicated (e.g. antibiotics; volume expansion), providing anticipatory guidance to families, and interdicting outbreaks (e.g. public health – notifiable organisms).

- 2. Develop with team member policy-makers economic models incorporating pathogen burden and societal preferences to inform decision making about potential new enteric vaccine programs**, focusing on rotavirus (available) and norovirus (on the horizon). The discussions are being informed by extensive population sampling and specimen analysis leading to optimal resource use to reduce the population burden of disease.

### **Outputs/Outcomes**

- Knowledge of clinical presentations, care-seeking patterns, etiologic agents, burden of disease, and high risk clinical features (e.g. age, location, daycare) which will be used by decision-makers to build vaccine policy, by parents to make informed vaccine choices, and by clinicians to provide optimal care.
- Design of specimen collection protocols that incorporate patient and care provider preferences, test performance and economic analyses leading to improved uptake, pathogen identification, and surveillance.
- Knowledge of the economic impact on, and preferences of Albertans related to novel program implementation (e.g. vaccines, specimen collection, testing), leading to bidirectional discussions to optimize success.
- A clinical surveillance model to monitor other emerging infectious diseases and a variety of candidate vaccination programs (including but not limited to rotavirus and norovirus).

## **IV. Simulation Research Program: KidSIM-ASPIRE (Assessing Simulation in Pediatrics: Improving Resuscitation Events)**

### **Background**

Recently, Alberta Children's Hospital (ACH) has made the delivery of life-saving care one of the main pillars of clinical care and research. ACH clinical and administrative leadership recognize that the delivery of effective life-saving care for pediatric patients involves the complex interplay of an inter-professional healthcare team, and translational research assessing education and implementation of guidelines is necessary to improve outcomes from resuscitation. Outcomes from pediatric cardiac arrest are poor, and currently there is a paucity of research assessing the inter-professional process of delivery of care for critically ill patients. The International Liaison Committee on Resuscitation (ILCOR) recently published international guidelines for resuscitative care, which not only outline the current evidence for management of these conditions, but also clearly indicate the need for more research addressing knowledge gaps related to teamwork, techniques in resuscitation, procedural skills, treatment and processes of care. Our research program, comprised of a highly qualified team of researchers with a successful record of performance in clinical medicine, research, training and implementation, seeks to leverage existing resources with support from ACH to address our research goals and objectives.

The KidSIM-ASPIRE (Assessing Simulation in Pediatrics: Improving Resuscitation Events) Simulation Research Program, led by Dr. Adam Cheng, was established to bring together an inter-professional group of Alberta-based leaders in clinical care, research methodology, education, human factors and psychology from various institutions in Alberta (Alberta Children's Hospital (ACH), Stollery Children's Hospital (SCH), University of Calgary, and University of Alberta) interested in improving the delivery of life-saving care to critically ill infants and children. The KidSIM simulation program, based out of ACH, has evolved since its inception in 2005 to become one of the leading pediatric simulation programs in the world. Since then, research productivity in terms of number of projects and total amount of grant funding has taken off, thus verifying the need and enthusiasm for simulation-based research aimed at improving outcomes in life-saving care.

## Goals

The mission of the program is to conduct innovative, high-quality, simulation-based research to inform healthcare providers and families of best practices, which will optimize pediatric patient outcomes from critical illness. As life-saving treatment in pediatric patients involves effective interprofessional care, we strive to conduct single and multicenter studies that involve various professions (nursing, respiratory therapy, paramedics, physicians etc) in order to optimize the impact of our research on patient outcomes. In our collaborative research model, we also aim to facilitate the academic growth of young investigators by exposing them to established mentors and nurturing the skills necessary to become successful researchers, as evidenced by our current involvement with pediatric and emergency medicine trainees.

Additionally, our research goals directly address several areas of strategic priority, by targeting clinical questions in the vulnerable pediatric population who are suffering from critical illnesses (eg. infections, injuries). Studies will specifically be formulated to identify novel and innovative methods of healthcare delivery in order to improve effectiveness and efficiency of care.

- The **primary goal** of the KidSIM-ASPIRE program is to improve patient outcomes by conducting innovative research that (a) identifies gaps in resuscitation education and implementation of guidelines, and (b) assesses novel strategies to address these gaps.
- The **secondary goal** of the program is to apply and disseminate the knowledge from our research to maximize the impact on patient outcomes. To achieve these goals, we plan to: (1) collect and analyze quantitative and qualitative evidence to inform the development of new International Liaison Committee on Resuscitation (ILCOR) guidelines; (2) conduct research to evaluate innovative approaches to resuscitation education, assessment and implementation; and (3) translate the results of our research into peer-reviewed scientific publications, presentations, guidelines, and training materials.

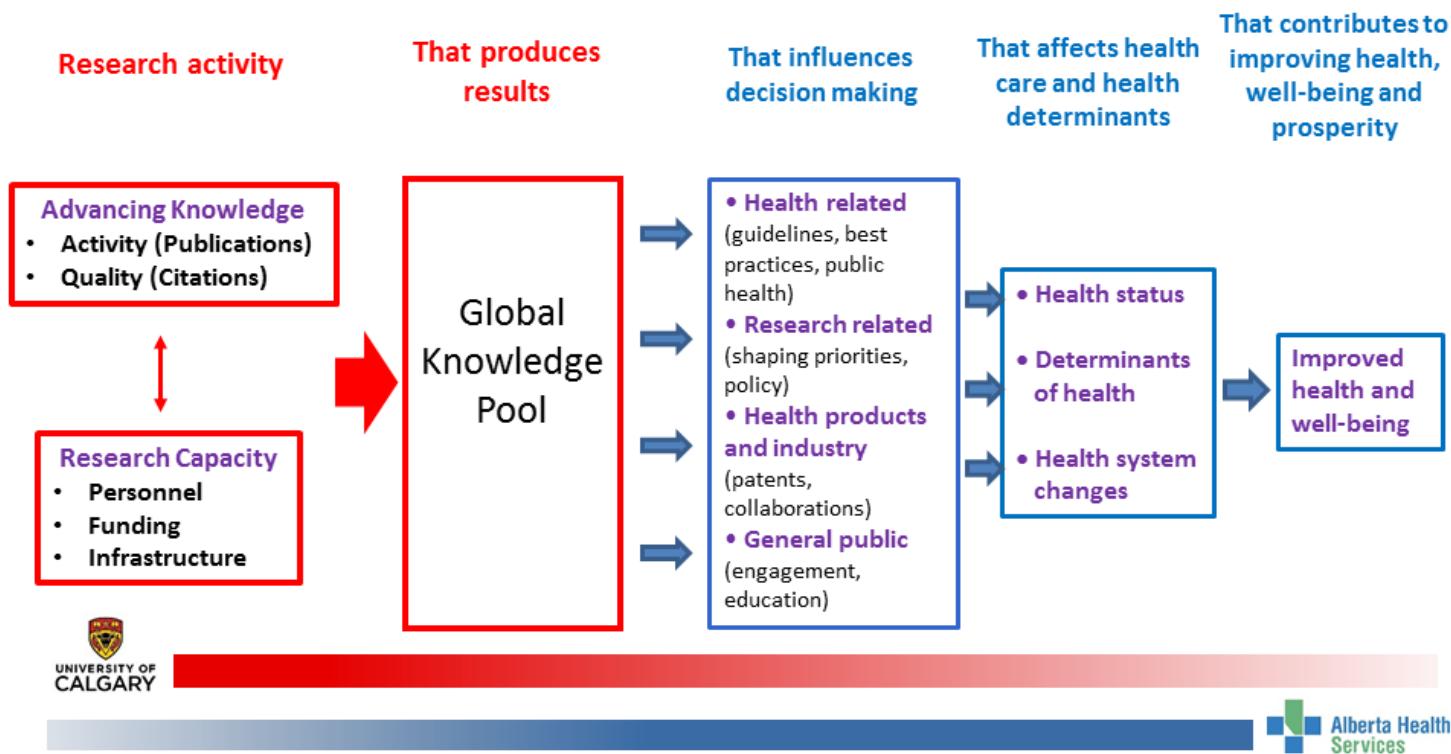
## D. ACHRI's Impact and Goals

### 1. Impact Framework

ACHRI has been asked to provide a framework with which our partners and donor community could assess ACHRI's performance and the return on donor investment. Frameworks such as this have been developed in many countries including the National Institute of Health (NIH) in the United States and the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The Canadian Academy of Health Sciences (CAHS) developed the equivalent framework in Canada. The framework is outlined in a document entitled "Making an Impact - A Preferred Framework and Indicators to Measure Returns on Investment in Health Research" ([http://www.caahs-acss.ca/wp-content/uploads/2011/09/ROI\\_EnglishSummary.pdf](http://www.caahs-acss.ca/wp-content/uploads/2011/09/ROI_EnglishSummary.pdf) ).

The overarching objective of the Canadian Academy of Health Sciences (CAHS) is to provide "scientific advice for a healthy Canada". Twenty-three different organizations (including the federal and provincial governments, the Canadian Institute of Health Research, universities, health care organizations, industries and foundations) sponsored development of this assessment approach. They all share an interest in defining the impacts of health research and learning how to improve the returns on investments in health research. CAHS's remit from these sponsors was: Is there a "best way" (best method) to evaluate the impacts of health research in Canada, and are there "best metrics" that could be used to assess those impacts (or improve them)? CAHS proposes a new impacts framework and a preferred menu of indicators and metrics that can be used for evaluating the returns on investment in health research in Canada.

Figure 13: Depiction of ACHRI's Impact Framework



**The CAHS impact framework** builds on the combined logic model and impacts approach of the “payback model” (Buxton, M.J., and Hanney, S.R., 1996 – adapted by CIHR in Canada in 2005 and 2008), and was revised by the CAHS panel into a “systems approach” to capture impacts. A simplified version of the model is shown in *Figure 13*. The systems model approach demonstrates how research activity informs decision making, eventually resulting in changes in health and economic and social prosperity. It is designed to be used as a roadmap to track health-research impacts in five main categories: 1) advancing knowledge, 2) building capacity, 3) informing decision-making, 4) health impacts, and 5) broad socio-economic impacts.

Within the CAHS framework the research output from institutes like ACHRI contributes to a global knowledge pool from which innovations, cures, and improvements in health are drawn. In terms of health research achieving impact at the clinic, bedside or community, the CAHS framework describes how research that enters the global knowledge pool via a rigorous process of external peer-review is translated into policy and practice through collaboration and consultation with a broad array of health care, community, government and industry participants. The ultimate goal for all our research activities is to improve child health and wellness. Basic science research findings will take a longer and different translational path than a research finding from a technology assessment evaluation or clinical practice study. At each translational step, success can be defined either by proceeding onwards, or halting based on the nature and quality of the evidence.

ACHRI’s contributions to this knowledge pool derive from hypothesis-driven research that spans each of ACHRI’s themes. Often this work occurs in active partnership with colleagues across the CSM, the U of C, and AHS and can be directly or indirectly supported by the resources of the Institute’s three partners. Translation into the clinical and community realm relies on strong partnerships with the academic, clinical, government, community and industry partners.

## **2. Advancing knowledge – Academic Impact**

The academic metrics used to assess research performance measure research *activity* by the number of publications, and research *quality* by the number of citations.

The CSM provides an annual assessment of School (Annual Report 2014-15 – CSM), department and institute (Annual Report 2014-15 - ACHRI) performance. The CSM and ACHRI Annual Reports are available for review in *Appendix 6*.

ACHRI members have had significant increases in their research performance every year since the Institute’s rebranding in 2009. ACHRI’s 2015-20 Strategic Plan calls for an increase in both the number and cumulative impact factor of publications, as well as the magnitude of competitive external funding by 30% over the 2013-14 CSM reported base year.

The following figures show metrics of ACHRI’s academic performance.

- Activity – number of publications (*Figures 14 and 15*)
- Quality – number of citations (*Figure 16*)

Figure 14: Total number of publications by year (CSM Members only- from CSM Annual Report)

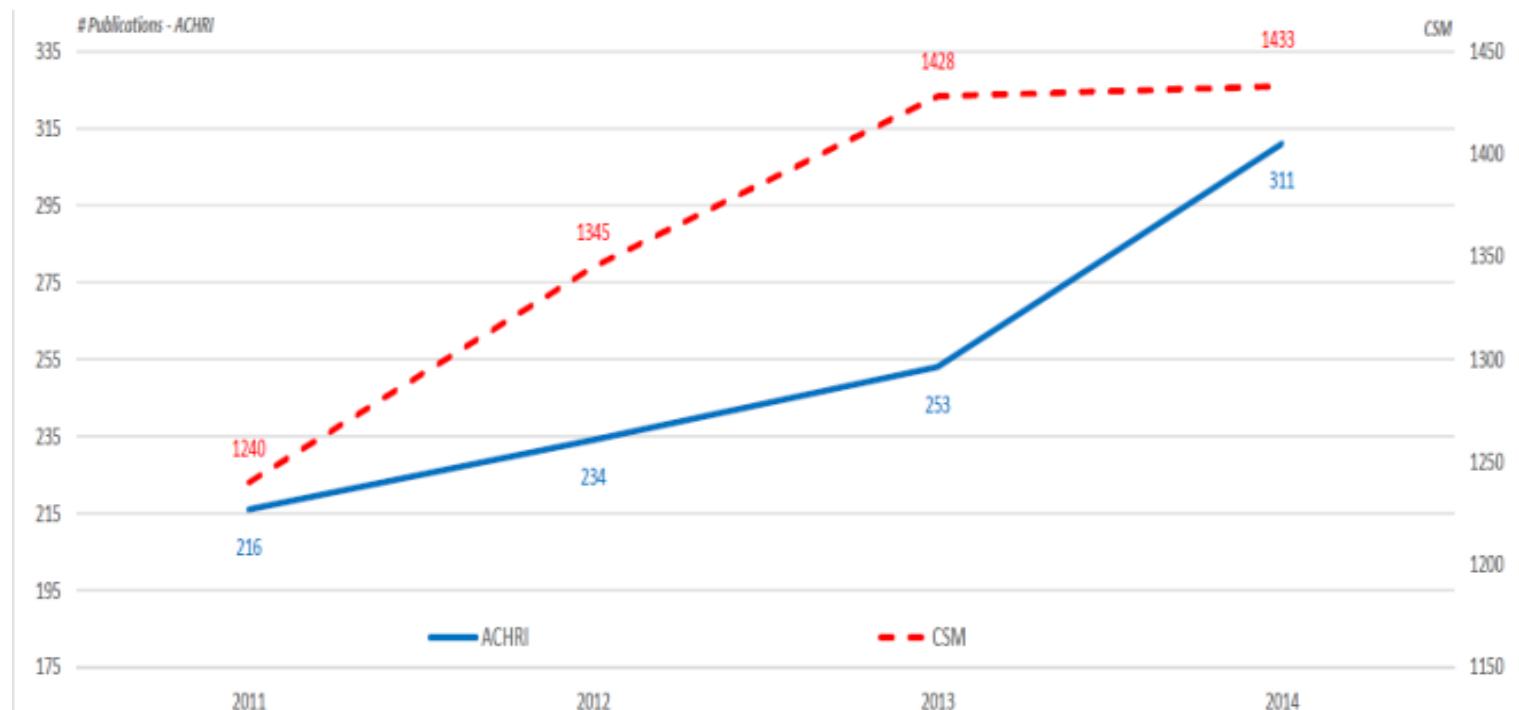


Figure 15: Average number of publications per Research Equivalent (CSM Members only- from CSM Annual Report)

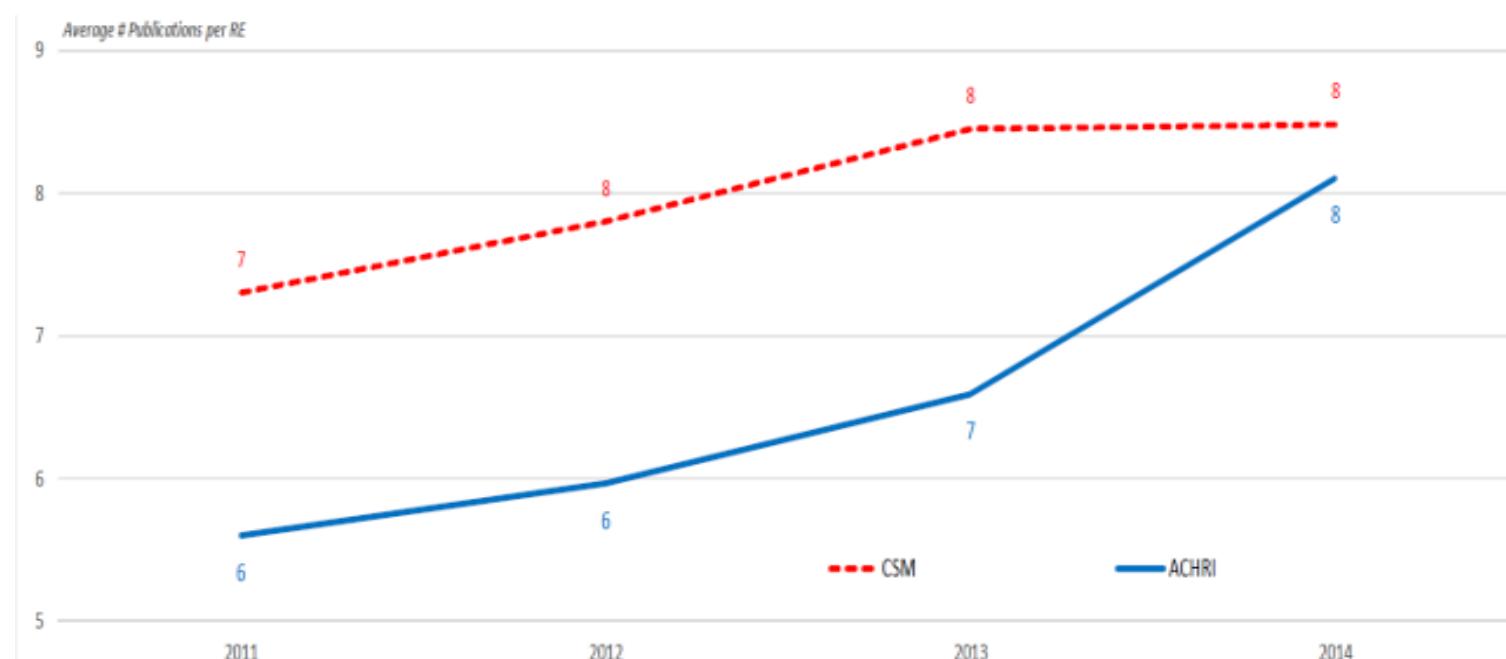
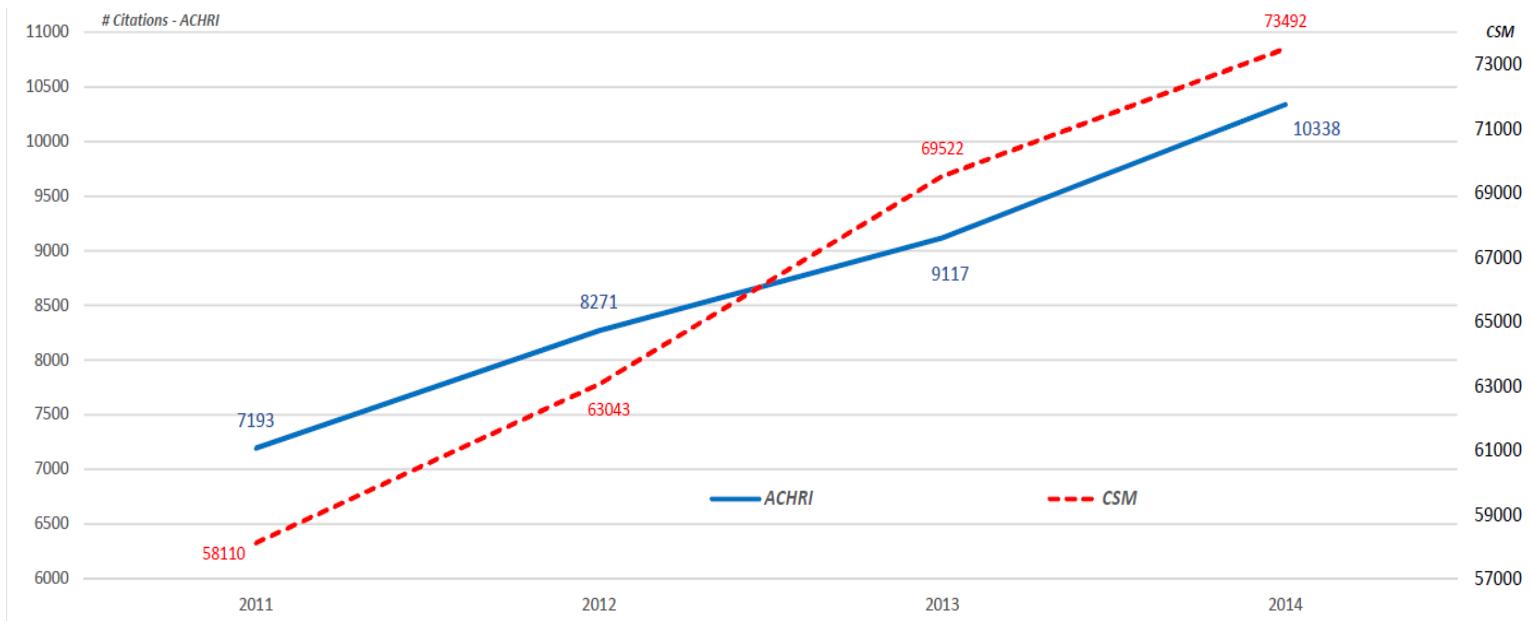


Figure 16: Total number of citations per year (CSM Members only - from CSM Annual Report)



ACHRI's research space allotment at the CSM is 38% lower compared to other institutes within the faculty. Our performance, however, is significantly stronger in terms of research funding and publication counts per square meter than CSM average. This substantial difference in academic performance is not explained by the space difference alone, which ultimately demonstrates ACHRI's outstanding performance despite the space constraints. (Table 1)

Table 1: Performance within CSM in 2014/15 (CSM Members only - from CSM Annual Report)

Space	ACHRI	All CSM institutes
Total	3,298 sq.m.	33,888 sq.m.
Per Member	35.84 sq.m. ( $\downarrow 38\%$ )	52.46 sq.m.
Funding/sq.m.	\$6,539 ( $\uparrow 74\%$ )	\$3,760
Publications/100 sq.m	9.43 ( $\uparrow 123\%$ )	4.23

### **3. Building Research Capacity – The Fundamental Elements of Success**

In line with the ACHRI's impact framework described above, we have identified the three key elements of a successful research institute that help build research capacity:

- Personnel: successful researchers and trainees
- Infrastructure: research space and research support platforms
- Funding

Leading edge research infrastructure as well as the recruitment and retention of high quality researchers/faculty are fundamental elements of Institute success. To create a supportive research environment that promotes recruitment, retention and productivity, ACHRI has identified the need to invest in the provision of:

- Leading edge research space and enabling research infrastructure/platforms
- Start-up funding to support new investigators in rapidly establishing productive research programs that set them up for success when applying for competitive external operating grant awards,
- Matching funding programs that facilitate securing competitive external awards (CFI, Genome Canada CIHR etc.),
- Bridge funding of highly ranked but unfunded competitive grant applications that sustains an investigator's research program until the next competition

ACHRI does not support internal operating granting competitions for the support of its full members. The hallmark of a strong researcher is the ability to successfully compete for competitive external grant awards. ACHRI considers that an internal granting program does not enhance the performance of its members in this measure.

The following sections provide detail on each of these factors critical to the overall success of ACHRI.

#### **3.1 Personnel: Recruitment and Funding of Successful Research Scientists and Trainees**

##### **a) Investing in successful researchers**

###### **i) Start-up Funding**

One of the key factors contributing to ACHRI's academic performance is the need to recruit and retain high quality faculty for renewal and growth. The Institute's ultimate success will reflect the collective efforts and achievements of its members; the sum of their individual performance in research, education and service to society. ACHRI has focused its resources on supporting the recruitment of full members with the skills, protected time and demonstrated capacity for innovative research and success as measured by the publication of high quality papers with translational impact and in success at competing for competitive external grant awards. To achieve a critical mass and impact, the Institute has focused on recruitment in its three priority research themes.

The alignment of ACHRI priorities with CSM and U of C priorities directly influences ACHRI's and collaborating Departments' success in being awarded a share of the School's limited recruitment opportunities. A salary, supported by the School's core operating budget or the University's allocation of a competitively awarded Canada Research or AIHS Translational Chair translates into an institutional commitment of about \$4 million over the 25-30 year career of a successful PhD scientist, and several times that for a clinician scientist. *Table 2*, below, lists the fifteen CSM and U of C approved recruitments to ACHRI and its departmental partners in the past 16 months. *Table 3*, lists 13 additional and ongoing, Planning and Priorities Committee approved recruitments. The total of 28 approved new positions over 2

years represents a \$96 million commitment from the Cummings School of Medicine to ACHRI over the next 25-30 years. When a recruitment opportunity is allocated to a Department and Institute by the School or University, there is an expectation that the alignment of priorities, critical mass, performance, translational impact and visible success will accrue recognition that results in philanthropic support and the institute's capacity to provide a nurturing and supportive research environment. This includes mentorship, team collaboration, internal peer review, research space, enabling infrastructure (platforms), start-up, matching and bridge funding.

Nationally, competitive start-up funding for new recruits at the assistant professor level is in the range of \$250,000 to \$500,000 for clinical researchers (dry lab) and \$500,000 to \$1 million for basic science researchers (wet lab) with variation depending upon the nature of the research being undertaken. The Institute already has 13 approved and ongoing recruitments and it is not unreasonable to expect that in the next few years we will be awarded several more for a total of 15 over the next 5 years. If start-up costs average \$500-750,000 per recruit there is a need for \$7.5 to \$11.3 million over 5 years or \$1.5 to \$2.27 million per year of start-up funding. This information is available by request on an Excel Spreadsheet: ACHRI Recruitment and Start-up Needs 2014/15 and 2015/16.

*Table 2: Recruitments from April 1, 2014 to December 1, 2015*

<u>Genes Development &amp; Health</u>		
Quan Long	Biochem. Mol. Biol.	Bio-Informatics
Edwin Wang	Biochem. Mol. Biol.	Bioinformatics, cancer
Amanda Melin	Anthropol/Cell Biol.Anat.	Primate behaviour/molecular genetics
<u>Healthy Outcomes</u>		
Darren Derkisen	Chemistry	ACHF Jr Chair in Medicinal Chemistry
Marco Gallo	Physiol. Pharm.	C3BD – brain cancer / genomics
Amy Metcalfe	Obstetrics & Gynecology	Epidemiology, medically complicated pregnancies
Melanie Noel	Psychology	Vi Riddell Pain Research Program
Marinka Twilt	Ped. Rheumatology	Clinician Scientist, rheumatologic disorders
<u>Behaviour and the Developing Brain</u>		
Keith Yeates	Psychology	Acquired brain injury/concussion
Vedran Lovic	Psychology	Neurodevelopment (basic science, behavior)
Sheri Madigan	Psychology	Neurodevelopment (clinician scientist)
Ashley Harris	Radiology	Child & Adolescent Imaging Research
Tim Shutt	Medical Genetics	Mitochondrial function in the brain
Jay Riva-Cambrin	Neurosurgery	Clinician scientist, acquired brain injury
Richelle Mychasiuk	Arts/Psychology	Developmental Neuroscience

*Table 3: Approved Recruitments in Process as of December 1, 2015*

<u>Genes Development and Health</u>	
Junior AIHS Translational Chair A	Medical Genetics
Junior AIHS Translational Chair B	Medical Genetics
Tier 1 NSERC Bioinformatics Recruit	Biochemistry & Molecular Biology
Junior AIHS Translational Chair, Cancer Informatics	Biochemistry & Molecular Biology
Medical Genetics (PPC #11-014 Pop Health Invest.)	Medical Genetics
NSERC Tier 2 in Regulatory Genomics	Medical Genetics
Junior Informatics Recruit (release of Sensen salary)	Biochemistry & Molecular Biology
Junior Informatics Recruit (release of Sensen salary)	Biochemistry & Molecular Biology
<u>Healthy Outcomes</u>	
Asthma Chair	Department of Paediatrics
<u>Behaviour and the Developing Brain</u>	
Core Child Psychopathology	Department of Psychiatry
Maternal Child/Epigenetics	Department of Psychiatry
Cuthbertson-Fischer Chair in Pediatric Mental Health	Department of Psychiatry
Developmental Paediatrics / NDD	Department of Paediatrics

## **ii) Matching Funding**

New recruits, as well as successful and established scientists often require specialized facilities and equipment. They have the opportunity to competitively apply for CFI JELF awards (40 per cent Federal Government, 40 per cent Provincial Government and 20 per cent other from institutions or industry), but the investigator and Institute are expected to guarantee the Provincial component for a period of 6-18 months until the province makes a funding decision. Usually the province awards the entire 40 per cent, but sometimes they do not, and the investigator and Institute funds are utilized.

Large granting agencies (e.g. CIHR, Genome Canada, CFI) and national organizations (e.g. Brain Canada, disease specific associations and foundations) frequently run funding competitions for program operating or infrastructure awards that can be in the range of hundred thousands to millions of dollars and require matching funding from the institution if awarded. These are typically highly competitive and prestigious awards. To compete for these awards the Institute requires a pool of matching funds. The magnitude of the current need (which reflects the current number and success of our researchers) can be estimated by the number and total amount of matching requests over the last several years.

In the 2014/2015 fiscal year there were eight requests for matching funds and ACHRI wrote conditional letters of support for a total value of \$4.9 million. Only six of the eight proposals were successful for a total commitment of \$2.8 million in matching funds. Of this \$2.8 million, \$1.14 million was for CFI JELF awards (infrastructure awards to new investigators) for which the Institute had to guarantee the Provincial 40 per cent of the award for a period of 6-18 months before the Province confirms its support. In this instance the Province agreed to support \$0.92 million. ACHRI recovered that amount, which was then reinvested to support other matching requests.

ACHRI commenced the 2015-2016 fiscal year with a positive balance of \$80,616 in its matching fund account. As of November 9th, 2015 the Institute has a total of eighteen matching requests for a cumulative value of \$11.1million. The Institute has provided letters of support that were commitments in four cases (for a total of \$4.45 million) where a match could be made from existing program approvals (e.g. the approved budget of the Vi Riddell Pain and Rehabilitation research programs is eligible as a match for CIHR SPOR applications), while the remaining fourteen were given conditional letters of support and have no available funding source. Of these, two applications to Brain Canada for \$910,000 were recently unsuccessful and the remaining twelve are outstanding requests for a total unfunded balance of \$3.48million: six CFI JELF infrastructure grants for new recruits, one CFI Large Grant application, two CSM-AHS Clinical Research Competition applications, two operating grant applications to the Canadian Diabetes Association and one CIHR Partnership for Health System Improvement application. This information is available by request on an Excel Spreadsheet: ACHRI Matching Fund Requests 2014/15 and 2015/16.

ACHRI is proposing an annual budget of \$1million to provide support for matching requests. Should funding be made available, ACHRI will be reviewing all such requests with consideration of the following factors:

- ACHRI's capacity to approve individual project/program budgets, Chairs, Professorships or other approved/available funding sources to provide the match through existing allocation or a new commitment;
- Capacity of ACHRI's discretionary Matching Funds Program;
- Alignment with Strategic Plan;
- Whether the investment can be recovered (e.g. CFI JELF Plan B funding offered by the Institute has a high probability of being 100 per cent recovered);

- Whether the application is submitted to a prestigious, national or international organizations? (e.g. CIHR, NSERC, Genome Canada, Brain Canada, etc.)
- Applicant's academic track record, and participation in meetings and activities of the theme/research program;
- Matching ratio – (Return on Investment);
- Whether the allocations leverage existing investments;
- Whether there is a contribution to the required matching funds from other partners (AHS, SCNs, AIHS, Departments and other Institutes, industry etc.);
- The potential impact of the investment for the Institute and its partners;
- Where the investment will be made (locally vs. provincially or nationally).

### **iii) Bridge Funding**

The research environment in Canada is highly competitive. Canadian Institute for Health Research (CIHR) grant awards are generally viewed as the academic gold standard performance measure for an investigator's success in terms of securing external nationally competitive grant awards. The success rate for applicants to the CIHR granting competitions is generally between 15 and 20 per cent. In the review process grants are ranked 0-5.0 with > 4.0 being excellent. It is common for some of the grants ranked as excellent to fall below the funding cutoff. Successful investigators who have their grants highly ranked, but unfunded have to reapply in the next competition, the result of which can be 12 months in the future. During this grant funding cycle "holding" interval, the laboratory operations supporting that research project are unfunded, have to be curtailed and the laboratory technicians skilled at that project may be let go, resulting in a significant reduction in productivity that reduces the likelihood that a reapplication will be successful.

Alberta Innovates Health Solutions, the University of Calgary and Cumming School of Medicine invest in a Bridge Funding Program that provides adequate bridge financial support to investigators that are unfunded, but ranked in the top 25 per cent so that they can maintain their research programs until the result of a reapplication. ACHRI and other CSM Institutes participate in this program to support their investigators. Over the last several years, the return on investment (total value of grant awards for resubmission in the next competition) has been fifteen times the amount of the bridge funding provided. ACHRI's financial contribution has averaged \$100,000 per year.

**Total Magnitude of the ACHRI Start-up, Matching and Bridge Funding Program:** ACHRI is seeking philanthropic support for \$2 million per year in start-up funding, \$1 million per year in matching funding and \$200,000 per year in bridge funding for a total annual budget of \$3.2 million for the *ACHRI Start-up, Matching and Bridge Funding Program*.

**Deliverables from an ACHRI Start-up, Matching and Bridge Funding Program:** This program is a priority for the Institute as it enables recruitment of new rising stars to our three research themes, enhances the success and retention of our strongest scientists and grows our research enterprise.

**An ACHRI Start-up, Matching and Bridge Funding Program would provide the following deliverables:**

- Permit ACHRI to apply and compete for CSM and U of C academic recruitments (the ability to provide a supportive research environment is a precondition);
- Provide competitive offers of start-up to potential new recruits (full members);
- Get new recruits off to a successful start with essential equipment and personnel that accelerates their early performance and in so doing enhances the likelihood that they will receive competitive external operating funds and establish a successful and sustainable research program;

- New recruits will (as an outcome of the CSM's process for approving recruitment and the U of C's process for allocating AIHS Chairs, CRC, NSERC, CIHR or other competitive awards) be aligned with the ACHRI 2015-2020 Strategic Plan, the CSM and U of C *Eyes High* strategic research priorities;
- Enhance local infrastructure through success at local, provincial and national infrastructure competitions;
- Enhance ACHRI's competitive performance locally (within CSM and U of C) and nationally;
- Allow research scientists to continuously develop and grow their programs aiming at improved child health outcomes;
- Leverage philanthropic investment by at least 1:1 through competitive external grants.

**Process:** Recruitment needs are identified by the Themes and reviewed by ACHRI leadership to ensure alignment with the strategic plan. Subsequently, ACHRI seeks every opportunity to support the recruitment through partnership with relevant Departments and Faculties or application for competitive salary awards and philanthropic funding. Requests for competitive salary awards are evaluated by the CSM Planning and Priorities Committee or by the VPR Office in the case of University-wide competitions.

For detailed recruitment strategies by Theme please refer to *Appendix 7*.

#### **b) ACHRI Trainees: Investing in the future generation of researchers**

The significance of the role that trainees play in academia and research in particular, is often overlooked. Undergraduate and graduate students, postdoctoral fellows, and medical residents are consistently at the centre of the research effort which effectively makes them the backbone of research in the university system. Graduate students and postdoctoral fellows carry out the bulk of the work on most projects led by their supervisors – principal investigators. Investing in our trainees and supporting them in their research careers translates into investing in the future of research. These trainees, when provided with nurturing research environments and mentorship, will become the outstanding researchers of their generation and fill an anticipated gap in the Canadian talent pool of child health experts. ACHRI, through its Research Training Platform, seeks to assure through a variety of incentives, that our Institute supports the development of excellent researchers of next generation. ACHRI trainee stipend support, awarded on a competitive basis, represents the majority of the Platform's budget at approximately \$1,000,000 per year for the last five years. By offering stipend support our Platform not only increases training capacity in our Institute, but also enables mentors to allocate more of their resources for enhancing research within their labs. Stipend support streams offered by the ACHRI Research Training Platform by far represent the single greatest impact on the success of ACHRI research of any aspect of the Platform.

For a detailed description of the ACHRI Research Training Platform, its accomplishments and future direction, please see *Appendix 8*.

### **3.2 Infrastructure: Research Space and Platforms**

**a) Research Space:** In ACHRI's December 2009 Research Strategic Plan, a severe and critical need for additional space was identified as the most significant challenge facing the Institute and a major risk to its ability to recruit, grow its research programs, achieve success and deliver on its aspiration of excellence over the short and medium term. At that time, an inventory of the Institute's available laboratory space indicated that its footprint to be approximately, 2,072.8 sq. m. of wet laboratory space, of which ~35% was actively occupied by researchers whose primary affiliation was with other institutes or the Faculty of Veterinary Medicine (investigators waiting to move into their own institutes' laboratory space in the new Health Research and Innovation Center).

With the support of its partners (U of C, AHS and ACHF) ACHRI developed short, medium and long-term plans

for addressing the space issue. In the short term, non-ACHRI investigators have been gradually relocated to their home institutes and ACHRI has refreshed the vacated space to accommodate new recruits.

**Medium term solutions** have involved the allocation and development of space on both the U of C and AHS sites with financial support from the ACHF:

**University of Calgary solutions:**

- On the 3<sup>rd</sup> floor of the Child Development Center, University of Calgary main campus, opposite the Alberta Children's Hospital, ACHRI initiated the functional planning, design development and construction of 1,000 sq. m. of undeveloped space as dry lab space. The design concept was to create facilities to support research in neurodevelopment and child mental health and the functional plan encompassed offices for 10 Faculty, workstations for 24 research staff and 43 trainees (graduate and post-doctoral students), observation rooms, testing rooms, records room, meeting rooms, secure server room, phlebotomy and lab specimen collection and preparation area, supplies and photocopy area, kitchen oasis and storage. Construction was completed and handover occurred in May of 2015. A generous donation through the ACHF covered construction costs and made a major investment in program development. In recognition of the donor family the site has been named the Owerko Center at ACHRI.
- In September of 2013, ACHRI initiated functional planning and a feasibility study regarding the redevelopment of its wet lab footprint in the aging and inefficient Health Sciences Center (2<sup>nd</sup> floor NW wing) as an open concept wet lab space that would accommodate a 50% increment in research lab capacity. In May of 2014 ACHRI, the CSM and ACHF proceeded to the next stage by hiring project management and design teams, creation of a decanting plan, schematic design, design development and preparation of complete construction documents. In September of 2015, complete construction documents (for a global construction cost estimate of \$8.8M) were tendered and in October 2015 Ellis Don Construction Services was identified as the General Contractor. Demolition started in November 2015 and construction should be complete in 10 months (August 2016).

**Alberta Children's Hospital/AHS solutions:**

- In the fall of 2013, ACHRI and AHS initiated functional planning for the Child and Adolescent Imaging Research program: offices for 5 research faculty, 20 workstations for research assistants, graduate students and post-docs and a mock scanner. The project was tendered May 2014 and construction was completed November 2014. The 5 offices and 8 carrels are located in 98 sq. m. at ACH Lower Level. The mock scanner and 5 carrels are located in 54 sq. m. on the 4th floor of ACH in the Neonatal development area.
- ACHRI received management accountability for the ACH Fourth Floor Behavioural Research Unit (BRU). The investigators and their trainees were relocated to the Owerko Center and ACHRI has repurposed the 350 sq. m. of vacated space to accommodate teams of PhD researchers and their research assistants and trainees if their research was conducted on inpatients and/or outpatients at ACH, but they were not employees of AHS and would not otherwise be provided space. The three patient assessment/observation rooms are used by ACHRI members conducting research on the site.

The above solutions allow us to better accommodate our existing researchers, and integrate current research teams. However, since recruitment is identified as key priority for ACHRI, space requirements for new recruits and expanding research teams need to be addressed. To ensure future growth, the Institute must

create new space and infrastructure to accommodate clusters of cross-cutting research programs into which targeted new recruitments could be embedded and fully integrated with maximum potential.

### **Long term solutions**

A long term solution for both wet and dry lab to space is still required. The external review of the Institute Director at the time of his recent reappointment recommended a research tower be built adjacent to the ACH. It could accommodate both dry and wet lab research as long as the wet lab research did not require colocation of animal care facilities. Wet lab research requiring colocation of animal care facilities will continue to be situated in the CSM's Foothills campus location.

ACHRI recruited 15 new and outstanding investigators in the year 2014 - 2015, and an equivalent number of recruitments are planned for the year 2016 - 2017. The majority of these research scientists and clinical investigators focus on child health research, and as such require access to and collaborations with the ACH. Moreover, the success of our imaging scientists and their research program has created a ground swell of new trainees, research funding and international collaborations – thus putting tremendous space pressure on the ACH. The success of any research program is contingent upon close physical proximity of all participating investigators and their trainees. Unfortunately, despite considerable efforts, our Imaging scientists are struggling to coalesce their trainees into one effective unit. Similarly, our child behavioral psychologists, pain and rehabilitation scientists etc. are also not fully integrated in close proximity to the Child Development Center. Moreover, with expanding child health clinical needs, the pressure is mounting on the ACH to meet the needs of exploding Alberta population - thus making it very difficult for ACHRI to secure additional research space within the hospital footprint. Thus the consolidation, expansion and growth potential of our Institute is being compromised by the lack of available research space. The paucity of appropriate research space and infrastructure will also hamper our ability to recruit the best and the brightest scientists and clinical investigators to Calgary.

A freestanding University of Calgary/ACHF research tower is being proposed to complement the Alberta Health Service/ACHF investment in the Alberta Children's Hospital on West Campus and to create the long term research home for ACHRI. Such a tower will not only consolidate our imaging and child behavior psychologists, neurodevelopmental, pain and rehabilitation scientists to further facilitate research excellence and collaborations but also accommodate new recruits; together we will create a center of excellence for child health, which will parallel Sick Kids in Toronto. This center will also allow us to consolidate clinical care, education and research activity to foster child and maternal health – all considered essential to securing the CSM precision medicine mandate.

ACHRI proposes a new 100,000 square foot facility that would allocate dry and wet lab space in equal proportions (50,000 square feet each). This tower will allow us to move our imaging scientists from the ACH to the newly developed space – thereby coalescing all of their infrastructure and trainees at one place. This will also free up space in the ACH to allow the expansion of its clinical programs. An entire floor will be dedicated to our Child Imaging Program thus further consolidating and strengthening their research activities. We will also relocate our dry lab genomics and informatics IT infrastructure and scientist and create additional wet lab space for genomics not requiring animal care facilities. This would ensure a consolidated and well-integrated child health genetics program. A full floor will be dedicated to this program. ACHRI also wishes to expand our clinical, health services delivery and population health research including pain and rehabilitation research programs to accommodate clinical investigation space and an outstanding cadre of child physiologists, behavior therapists etc. to serve children whose developmental trajectories are rendered compromised either due to illness, injury, trauma, medical procedures (pain management drugs and anesthetics, cancer medication etc.) and develop early and personalized interventions. We wish to dedicate a full floor to this research program. ACHRI intends to retain the wet

lab footprint at HSC/HMRB as it would support investigators whose research was supported by animal care facilities or other infrastructure on site. All of the space on both sites would support recruitment of top quality investigators from multiple faculties able to compete aggressively and successfully for external research support.

**b) Research platforms:** The Institute has established four research platforms that are critical enablers of programmatic success:

- ACHRI Research Training Platform.
- ACHRI led CSM Center for Health Genomics and Informatics
- 3T MRI / Child and Adolescent Imaging Research (CAIR) program,
- Clinical Research Support

A summary of each of these platforms follows. A more detailed description of the historical background, governance, leadership and team membership, operations, research programs supported, training activities, metrics and performance and vision for the future is available in *Appendix 8*.

## I. ACHRI Research Training Platform

**Background:** The ACHRI Research Training Platform has provided competitive access to clinical research fellowships, graduate and postdoctoral research traineeships and summer student scholarships since 2009. We take pride in the depth of the training programs that comprise this Platform, which has allowed to significantly increase training capacity within ACHRI and is helping to introduce our trainees to the rapidly evolving technologies and health challenges that characterize modern medical research. Trainees are the backbone of research in the university system. Whether conducting basic research on fundamental biological mechanisms or searching for the cause, treatment or prevention of a devastating disease or injuries, trainees are consistently at the centre of the research effort. These individuals, when provided with nurturing research environments and mentors, have the potential to become the outstanding biomedical researchers of their generation and fill an anticipated gap in the Canadian talent pool of child health experts. The ACHRI Research Training Platform seeks to assure through a variety of incentives, that our Institute supports the development of excellent researchers.

The ACHRI Research Training Platform was established in 2009 through a partnership between ACHRI, CIHR Training Grant, Faculties of Medicine and Veterinary Medicine, and the ACH Foundation with a common goal to foster excellence in research training and increase training capacity in the Faculty of Medicine, and particularly in ACHRI. With time, ACHRI introduced new, more specialized training support options through additional funding secured by the ACH Foundation. Today, the ACHRI Training Program, ACHRI Clinical Research Fellowship Program, Talisman Energy Fund Program and Dr. D. Grant Gall Traineeship comprise the ACHRI Research Training Platform, with a current budget of approximately \$1,150,000 per year. Governed by a committee structure that ensures effective operations and transparency, the Platform supports all trainees within each of ACHRI's theme structure which includes Genes, Development and Health; Behavior and the Developing Brain; and Healthy Outcomes, which span the spectrum of research in child and maternal health domains, from basic research in models of simple organisms through translational to clinical and population health science.

To date, the ACHRI Research Training Platform has developed several strong partnerships and secured funding that has allowed us to provide an enhanced educational and training experience in ACHRI to a wide spectrum of trainees: undergraduate and graduate students and postdoctoral scholars in both basic and clinical research disciplines; medical residents specializing in pediatrics, obstetrics/ gynecology, and genetics; trainees in the Canadian College of Medical Genetics certification program; and pre- and postdoctoral trainees in the highly competitive Canadian Child Health Clinician Scientist Program (CCHCSP). All our training partners work with our Platform to help enhance educational opportunities and streamline funding options for ACHRI trainees where

such opportunities exist. While the Platform does not offer specific graduate courses through a formal graduate program (these are the purview of the Faculty of Graduate Studies), the funding support and the extracurricular training opportunities it provides to ACHRI trainees is instrumental to our collective success. Currently in its seventh year, the Platform offers competitive trainee scholarships (including summer studentships, graduate studentships and postdoctoral fellowships); funding support for trainee recruitment, visiting speakers, workshops, research days and symposia; as well as travel funds for national and international meetings and scientific visits for ACHRI trainees.

ACHRI trainee stipend support represents the majority of the Platform's budget at approximately \$1,000,000 per year. Since 2009, the cumulative total number of trainees supported by the ACHRI Research Training Platform has reached 182: 70 undergraduate summer students, 33 Master's students, 30 PhD students (including 1 in the CCHSCP program), 43 Postdoctoral Fellows (including 6 in the CCMG program, 3 in the CCHCSP program), and 6 medical residents. This stipend support by far represents the single greatest impact on the success of ACHRI research of any aspect of our Research Training Platform. Most research carried out by ACHRI members is supported by external funding from provincial, federal and private agencies that award operating grants to individual faculty members. Graduate students and postdoctoral fellows carry out the bulk of the work on most of these projects. The salary awards provided by the ACHRI Research Training Platform allow our members to add more, and highly qualified, trainees to their research projects, beyond what was included in the budgets awarded for the projects. Thus faculty with ACHRI-funded trainees can accomplish much more than would otherwise be possible. This increased productivity in turn enables their work to have a greater impact on their research and enables ACHRI members to acquire more competitive external funding in the future. Similarly, the ACHRI funded trainees can point to their ACHRI stipend awards as evidence of success, which in turn increases their chances of obtaining external support at the provincial and national levels. For instance, over 20% of graduate and postdoctoral trainees supported through our program have competed successfully for other external awards, such as AIHS (provincial), CIHR (national), and NSERC (national), bringing in over \$970,000 in external funding since 2009.

In addition to trainee funding, the Platform puts emphasis on development of various valuable initiatives to further enhance the training and educational opportunities in ACHRI. To this end, our Platform provides funding support to ACHRI-centred and theme-organized research days and symposia, which include retreats and trainee research days involving oral and poster presentations by trainees and a seminar by a visiting scholar. Such theme research days provide ACHRI Trainees with an opportunity to present their work to a wide audience and better understand current research within their area of interest. Furthermore, with the aim of fostering connection and collaboration among trainees and mentors across the three themes and numerous research groups within the Institute, we take part in organizing ACHRI's annual Research Symposium. This event highlights innovation and diversity of research in ACHRI and typically features presentations from renowned visiting scholars in the field of child and maternal health, talks by ACHRI's members and trainees, as well as a poster session, showcasing trainee research accomplishments. Additionally, a part of the Symposium focuses on trainee career development featuring talks, workshops and activities that help trainees hone their 'soft skills' as well as learn more about career opportunities that may be available to them after graduation. We've also recently introduced an ACHRI-wide summer student research day - an event similar in format to the ACHRI Research Symposium, geared toward ACHRI summer students and showcasing research undertaken by the undergraduate trainees funded through our program. Both the ACHRI Symposium and the Summer Student Research Day have been a tremendous success, offering a wealth of development opportunities for trainees, further enhancing their training environment and broadening their skill set.

As part of our aim to foster trainee professional development, the ACHRI Training Platform partners with other local training initiatives, such as the Professional Development Program at CSM, providing professional development opportunities for trainees within the CSM through various training activities, workshops and seminars presented by local and invited experts. Additionally, our links with Let's Talk Science, as well as KT (Knowledge Translation) Canada, help expand the transdisciplinary training pursuits of ACHRI trainees. Furthermore, in the past year our Platform has been exploring options for partnerships and collaborations across the U of C campus so

as to further expand program and its training capacity through leveraging of funds and streamlining trainee recruitment process. Several such options presented themselves following the new strategy roll-out for the Cumming School of Medicine (e.g., the CSM Postdoctoral Scholar Program, and the CSM Graduate Student Scholarship Program) and U of C's Eyes High strategy (e.g., the Eyes High Postdoctoral Scholar recruitment program). In the coming months, we will be establishing a detailed process for these partnerships and integrating them into our Spring 2016 scholarship competitions.

**Future Plans:** ACHRI views its Research Training Platform as one of the highest priorities for investment. With the changing landscape of health research, characterized by the convergence of mathematics, humanities, physical, social, biological, behavioral and clinical sciences, plus emerging technologies, the criteria for success are more demanding than ever. ACHRI hopes to make a significant difference in the training landscape, creating an opportunity to recruit, develop and retain exemplary scientists in Calgary who will build new knowledge to help advance child health locally, nationally and globally. To this end, the ACHRI Research Training Platform continually explores ways to improve and enhance training to meet the needs of our trainees in the changing and highly competitive research environment. Going forward, as the Platform continues to provide competitive funding opportunities to ACHRI trainees through its various funding streams, these initiatives will be more attuned to the strategic priorities of the Institute, Cumming School of Medicine, and University of Calgary, as well as the needs of our trainees. In addition to existing awards, we will work with our partners to introduce scholarships for more specialized research training, through leveraging of existing funds, as well as fundraising opportunities. Undergraduate and graduate students, postdocs, medical residents are the backbone of research. ACHRI strongly believes that investing in our trainees and supporting them in their research careers translates into investing in the future of research. Given the fact that ACHRI-funded trainees dramatically enhance an ACHRI investigator's research program, by freeing up funds that enable them to carry out more and higher quality research than would otherwise be possible, the key to increasing the impact of the ACHRI Research Training Platform on ACHRI research output is to expand the funding base dedicated to our trainees. For instance, in 2015, out of 148 ACHRI trainees only 23 (or 15 percent) were funded by our Platform (15 graduate students and 8 postdoctoral fellows). Increased trainee funding would help ACHRI to achieve the goal of continually increasing our Institute's' training capacity, where having an ACHRI-funded trainee in a lab will be the norm rather than the exception. In addition to seeking opportunities for increased funding support for our trainees, the ACHRI Research Training Platform will also create avenues for our trainees to learn more about the research that takes place in the Institute to encourage collaboration and foster cross-disciplinary research opportunities. Lastly, the leadership of the ACHRI Research Training Platform are working on a long-term plan for development of an ACHRI-wide training program that would involve specific courses, seminars and educational activities. This would further address the Platform's goal of fostering excellence of the next generation of child health researchers.

## **II. Genomics and Informatics Platform**

**Background:** Recent advances in the technology of genome sequencing (specifically Next Generation Sequencing or NGS) and the emerging avalanche of information have initiated a revolution in the biologic and health sciences. The immediate beneficiary of this breakthrough has been precision genomic medicine with new diagnostic and health care management tools leading to prevention, rapid and earlier diagnosis, personalized, safer and more effective treatment. NGS technology has been one of the drivers of "big data" that is requiring new bioinformatics skills and capacity to interpret and present the information.

Recognizing the need and opportunity, and with the generous financial support of the Alberta Children's Hospital Foundation and the CSM, ACHRI created a state-of-the-art genomics-bioinformatics platform to enable leading-edge science, generate new knowledge, create intellectual property, business applications, improved diagnostics and new treatments – all ultimately leading to improved health and wellness. In the spring of 2012, ACHRI announced the opening of its Genomics and Informatics Platform to the CSM scientific community. Sequencing

was made available to all academic faculty members at the University of Calgary at the cost of consumables, while free access to a variety of bioinformatics tools was made available to all U of C users through a Galaxy web portal. Over the last 3 years, the Platform has been utilized by increasing numbers of scientists, supported multi-million dollar research initiatives and awards, facilitated several faculty recruitments, and had a significant impact on clinical research through collaborations. The Platform, still one of its kind at the U of C, is widely recognized to provide excellent quality service at a competitive price.

In its 2015-2020 Strategic Plan, the Cumming School of Medicine (CSM) identified personalized or precision medicine as a core concept around the School's pan-institute strategy for "creating the future of health". The scope of the initiative incorporates the four CIHR research pillars: basic, clinical, population health and health services delivery. The initiative's success will require enabling research platforms that include genomics, bioinformatics, advance imaging and clinical research infrastructure. The initiative will create incremental need for secure storage, linkage and integrated analytics for the data generated from each of these sources.

The Government of Alberta, Alberta Innovates – Health Solutions, Alberta Health Services, and the universities within Alberta, while recognizing the importance of the "big-data" problem, do not yet have a framework/plan for the provision of big data computational services that could support our collective needs into the future. A comprehensive solution encompassing all potential stakeholders will be very expensive, complex, and it is difficult to gauge support for such an endeavor in these trying economical times.

In response to these challenges, in May 2015, the CSM announced the creation of the Centre for Health Genomics and Bioinformatics, a partnership led by ACHRI, amongst the CSM, its institutes and other U of C faculties. The Centre is mandated to use the collective resources of the partners and provide genomic and bioinformatics research infrastructure and services in a collaborative, cost effective fashion and foster a robust training experience for graduate students and postdoctoral scholars.

**Future Plans:** In order to take the initiative to a new level, ACHRI has purchased new sequencing instruments from Illumina to replace the sequencers purchased four years ago (for which we can no longer purchase service agreements) and is exploring a partnership with IBM to create an affordable, consolidated, flexible, scalable pilot of a high-performance analytics platform, the architecture of which would support storage, computation, workload management, linkage and analysis of a variety of data sources (clinical, imaging, genomics and other metadata). The system will have the capacity to align with and complement computational infrastructure investments already made in the CSM Center for Health Genomics and Informatics, the CSM Clinical Research Unit and U of C IT.

The current IT infrastructure at CSM is built on a model of secure, but separate and independent servers. This is an inefficient model to carry into the future, and one, which does not have the necessary capabilities of linking various research datasets/applications and analyzing them in an integrated fashion.

In the next two years, ACHRI will need to invest at least \$1 million in compute and storage infrastructure for new recruits if the previous model is continued. Discussions with IBM have indicated that building a high-performance analytics platform capable of operating in a collaborative environment would be of similar cost yet provide enormous potential additional benefits. ACHRI will commit resources to this latter innovative approach.

Implementation will be focused around three key research programs that represent all three of the Institute's themes. This pilot will build capacity, leverage the success of our research initiatives, and serve as a CSM/U of C demonstration project for IT infrastructure that links and performs integrated analytics for clinical trials, imaging and metadata, and is scalable. Such a capability is foundational to the success of the precision medicine priority of the Cumming School of Medicine.

The proposed budget for the next five years for the ACHRI investment in the Genomics and Informatics Platform

is summarized in Appendix 1. The platform investment is foundational to the research agenda within the Genes Development and Health Theme and complementary or synergistic to basic and clinical research in the Behaviour and the Developing Brain and the Healthy Outcomes theme. In addition it creates the necessary infrastructure for at least eight of the currently approved recruitments.

### **III. Imaging Platform/Child and Adolescent Imaging Research (CAIR) Program**

**Background:** The Child and Adolescent Imaging Research (CAIR) platform was built in just a few years through significant institutional (AHS, U of C) and philanthropic (ACHF) investments complemented by successful competitive infrastructure grants to support the renovation of space, acquisition of equipment and the recruitment of imaging scientists. The state of the art MR imaging research facility at ACH is geared towards the needs of children with a research dedicated 3 Tesla MRI scanner equipped with noise reduction and motion correction systems, an MRI simulator for acclimatizing and training children before their scan, eye tracking equipment and computer infrastructure. The platform permits visualization of brain structure, function and chemistry and supports an outstanding team of 5 imaging scientists. Currently the platform's strength is neuroimaging, but over time the scope of activities that this platform supports will expand to include teams conducting cardiac, cancer, bone and joint research. Dr. Signe Bay is the scientific lead of the CAIR Program. She and her team have been extremely successful in obtaining external funding build a strong scientific program and leverage the philanthropic investment.

**Future Plans:** The 5-10 year vision is to become a nationally and internationally recognized center in pediatric imaging. To achieve this vision, the team must continue to grow their scientific capacity by recruiting leading researchers in the field and plan for investment in new equipment and space in the long term (to be consolidated in the new proposed tower). One of the key areas in which they could expand is cardiac imaging. There is already significant strength in clinical cardiac fMRI and the potential to collaborate on the recruitment of a PhD cardiac imaging scientist with the Stevenson Cardiac MRI Center and the Libin Institute. Another key area in which the team would like to expand is fetal and perinatal imaging. There is already significant clinical capacity in neonatology and research strength in the neurodevelopmental and child mental health focus of the Institute's Behaviour and the Developing Brain theme and our new Owerko Center. In order to identify abnormal neurodevelopmental trajectories from the earliest possible age, imaging fetal and neonatal brains is a clear path forward. We have seen tremendous technical growth in this area, creating an opportunity to hire a faculty member who will bring these capabilities to our site. In addition, the platform and research program would benefit from the recruitment of dedicated senior leadership to provide direction and oversight to our young, dynamic research team.

In order to grow imaging capacity in the future and remain at the leading edge, there need to be plans to expand and renew platform infrastructure including a research-dedicated 3T MRI, specialized fetal and specialized neonatal imaging equipment, and possibly a PET-MRI system.

### **IV. Clinical Research Support Platform**

**Background:** Expertise in research methodology, epidemiology and biostatistics are key components in enabling the conduct of high-quality, rigorous clinical research studies.

Clinical research infrastructure is generally agreed to be in significant need of development in Alberta. The Government of Alberta, Alberta Health Services, Alberta Innovates, the University of Calgary and the Cumming School of Medicine have each identified investment in clinical research infrastructure as a priority. Existing clinical research resources already available to our membership include:

- Cumming School of Medicine's Clinical Research Unit
- Alberta SPOR SUPPORT units
- Department of Paediatrics Research Methods and Research Advancement teams
- Department of Community Health Sciences, CSM
- O'Brien Institute of Population and Public Health, CSM
- Alberta Health Services Research Administration Pathway and Research Facilitation Services

ACHRI will not duplicate these investments, but rather wishes to collaborate and make synergistic, complementary investments that enhance clinical research capacity in child health in a sustainable fashion.

To increase child health clinical research capacity and critical mass, ACHRI provides ongoing salary support for a health economist and a biostatistician, and in 2014 ACHRI led recruitment and provided start-up for a second biostatistician (salary supported by CSM) whose research interests were in child health. In addition, ACHRI supports a modest clinical research consultation service, managed by an epidemiologist with an appointment as an Adjunct Assistant Professor, to specifically support clinicians with associate membership status who are striving to improve their clinical research proposals. The service is not intended to be a substitute for faculty members accessing the necessary training and acquiring the skills necessary to conduct clinical research. Support is offered through direct solicited consultations, regular seminars and lectures, and drop-in sessions to address specific methodological questions, or through direct academic collaboration with ACHRI members. Over the last 3 years, this individual has conducted more than 200 consultations, as well as 23 lectures and seminars to ACHRI members and their trainees to assist them at various stages of research.

**Future Plans:** Going forward, the Institute will build additional child health clinical research capacity in a sustainable fashion by supporting the recruitment of successful scientists with epidemiologic, methodological, biostatistical and clinical informatics skill sets who will in turn attract graduate and post-doctoral trainees to participate in collaborative research and further enhance clinical research capacity.

The proposed budget for the next five years for the ACHRI Clinical Research Support platform is summarized in Appendix 1. It is currently comprised of the salary cost of the Senior Research Methodologist providing the consultative service and two faculty salaries, which will be phased out April 2017. The sustainability model for building child health clinical research skills and capacity is built upon recruitment of faculty and in turn their recruitment of graduate and post-doctoral trainees. These costs are identified in the recruitment budget of the Healthy Outcomes Theme. This investment in high quality clinical research faculty and their trainees is foundational to the research agenda within the Healthy Outcomes, Behaviour and the Developing Brain and to a lesser extent the Genes, Development and Health Theme.

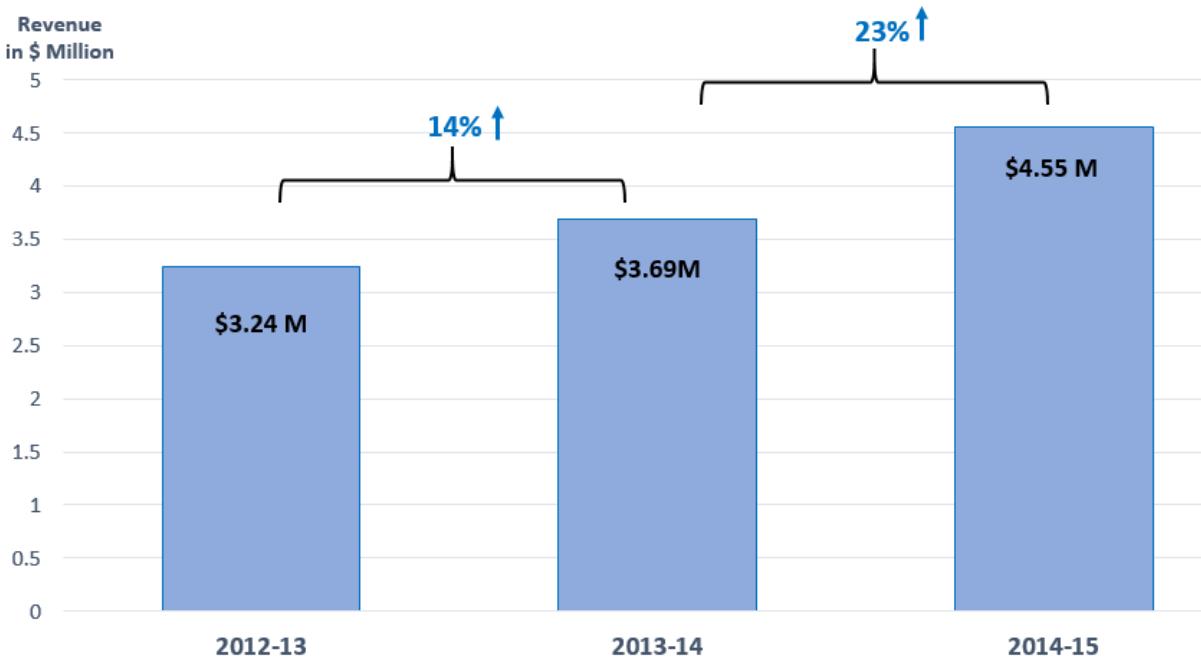
### 3.3 Funding

ACHRI's partners have made significant long-term commitments to support the institute. The current approved academic recruitments alone represent an approximate \$120M investment by CSM in ACHRI over 30 years. ACHF has a current commitment of nearly \$58 million to support ACHRI's operations, platforms and themes (for details see *Appendix 9*). The impact of philanthropic dollars is maximized when used to build infrastructure and introduce new programmatic capabilities that can support multiple research projects or agendas within the Institute. ACHRI members need to obtain competitive external grant funding to leverage philanthropic dollars, and fund their research operations. The hallmark of a strong researcher is the ability to successfully compete for external grant awards. ACHRI has a strong track record of CIHR Revenue, which is considered the gold standard within Canada for individual or institutional competitive external operating grant support. The annual amounts of ACHRI's research revenue over the last 3 years are shown in *Table 4*, and CIHR funding for the same period is also graphed in *Figure 17*. Over the period 2015-20, ACHRI will increase competitive research funding by 30% over the reported year 2013-14.

*Table 4: ACHRI Research Revenue (CSM Members only - from CSM Annual Report)*

	<b>Total Research Revenue</b>	<b>CIHR Revenue</b>		<b>Clinical Research Revenue</b>
<b>2012-13</b>	\$20.97 M	\$3.24M		\$2.73M
<b>2013-14</b>	\$23.92M	\$3.69M	<b>14% increase</b>	\$2.22M
<b>2014-15</b>	\$21.56M	\$4.55M	<b>23% increase</b>	\$4.37M

Figure 17: ACHRI CIHR Revenue by Fiscal Year (CSM Members only - from CSM Annual Report)



For 2015-20 ACHRI is proposing a core operational budget which includes funding for institute management/administration, a start-up, matching and bridge funding allocation to support strong academic researchers, and operational funds for two overarching enabling platforms: Training and Clinical Research support. Please see the detailed budget proposal in *Appendix 10*.

Beyond core operations, ACHRI is seeking support from all funding sources to further its research program and infrastructure growth across priority themes. We are also planning to make a sizeable investment in our Genomics and Bioinformatics platform which will lead the CSM Center for Genomics and Bioinformatics, and provide the necessary infrastructure for the precision medicine approach across our research themes. ACHRI's pressing research space need calls for a large investment in additional research space with the support and participation of ACHRI's partners: U of C, AHS and ACHF. Please see the detailed funding proposal in *Appendix 11*.

## **E. Governance and Organizational Structure**

### **a) Governance**

The May 2007 ***Memorandum of Understanding Concerning the Alberta Children's Hospital Institute for Child and Maternal Health***, signed by the Institute's founding partners (the Governors of the University of Calgary, the Calgary Health Region that has been superseded by Alberta Health Services, and the Alberta Children's Hospital Foundation), provides perspective on what the Institute was envisaged to become:

- “Be a centre of excellence in maternal, newborn, child and youth health research and education, translating discoveries into better maternal, newborn, child and youth health for Albertans and others;
- Facilitate the integration of research with care to ensure that discoveries in basic, translational and clinical research quickly lead to advances in maternal, newborn, child and youth health;
- Foster provincial networks that facilitate population health and services research, prevent injury, evaluate new therapies, and advocate for advancement of policy promoting healthy productive lives for newborns, children, youth and families;
- Recruit and train the next generation of basic, clinical, health service and population health researchers in disease and societal factors adversely affecting the newborn, child, youth and families;
- Create research and training opportunities in the pediatric sciences through interactions with academia, government, industry and other partners; and,
- Be an authoritative source of information on maternal, newborn, child and youth health for Albertans and others.”

Over the years, there have been: a) changes in the organization of health care in Alberta (creation of Alberta Health Services (AHS), b) a change in leadership at the University of Calgary (U of C) with adoption of the Eyes High strategic direction and release of the new Academic and Strategic Research Plans that have guided its implementation, and c) greater definition of funding priorities and an evolution of Alberta Children's Hospital Foundation (ACHF) processes – all of which have influenced ACHRI's governance and research environment.

ACHRI's governance is depicted in *Figure 18*. The Director reports directly to and is accountable to the Dean of the Cumming School of Medicine (CSM), U of C and the Calgary Zone Medical Director of AHS. The U of C and AHS are responsible for establishing the ACHRI Strategic Advisory Board (SAB) comprised of a Chair appointed by the U of C and AHS, three members appointed by the University, three members appointed by AHS and three members from the Alberta Children's Hospital Foundation.

The SAB is advisory to the Institute Director, reviewing and providing input regarding the Institute's annual budget, annual report, annual scientific and educational goals, establishing and engaging the Expert Advisory Committee (relevant representatives external to Calgary), developing internal and external communications and providing advice to the Institute Director that will facilitate Institute success. The Terms of Reference for the ACHRI SAB will be revised concurrent with renewal of the gift agreement.

Figure 18. Alberta Children's Hospital Research Institute Governance



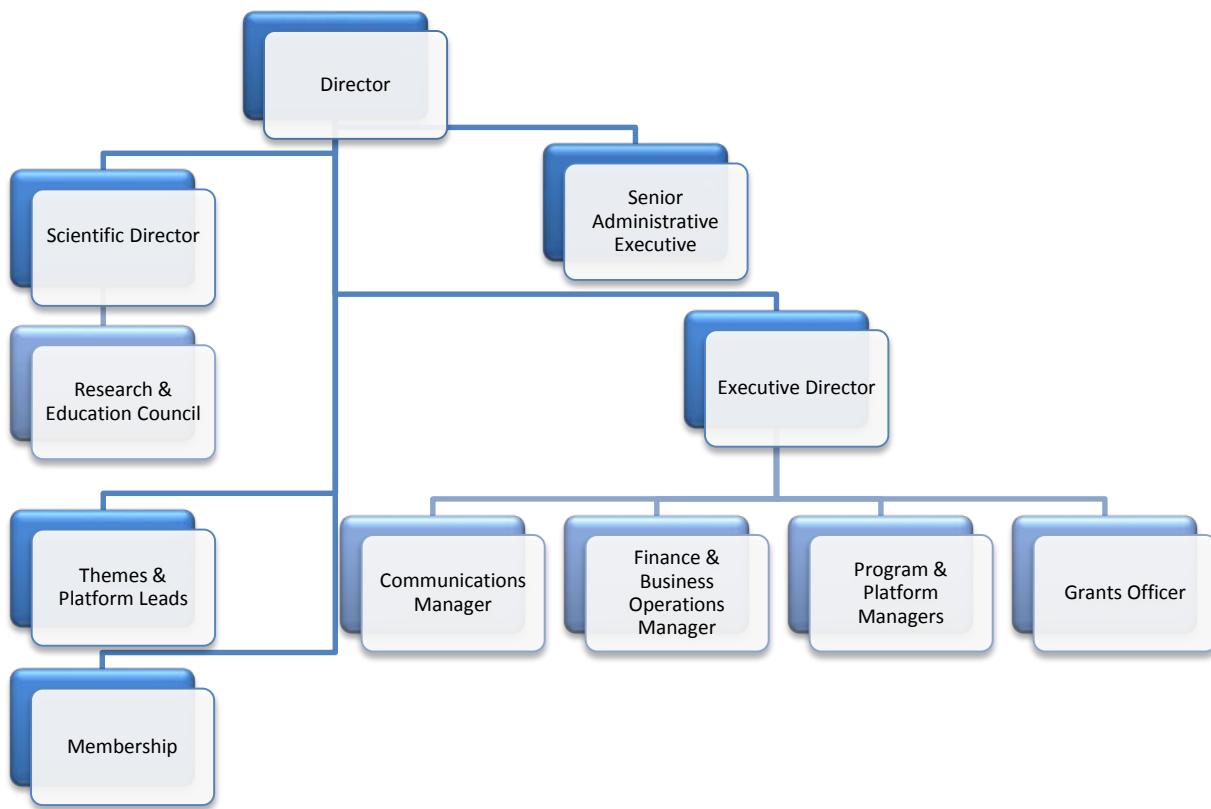
### b) Organizational Structure

The Institute's organizational structure is depicted in *Figure 19*. This is the team that is responsible for leading and managing implementation of the strategic and business plans.

ACHRI's executive leadership team overseeing the research enterprise is comprised of the Director, Scientific Director, Executive Director, the academic lead for each of the three research themes, the Education/Training Program Director and the Senior Administrator. The Institute's operational activities are supported by: a Communications Manager, Finance and Business Operations Manager, two Program Managers who support the Themes and platforms, and a Grants Officer – all of whom report to the Executive Director. ACHRI has led the development of a number of enabling research platforms and where there is a requirement for managers to be in place to support the operations of a University facility (Manager of Sequencing, Manager of Informatics, Unix System Support), these individuals report to the scientific leads from a research operations perspective and to the Executive Director from an HR perspective.

The **Director** is appointed by the Dean, CSM, U of C and the Calgary Zone Medical Director, AHS; but reports to the Senior Associate Dean Research CSM and the Calgary Zone Medical Director. The Institute Director is responsible for the day-to-day operations of the Institute; realizing the potential of the Institute as set out in the founding MOU; setting the Institute's annual budget and operating performance goals; managing the Institute's financial resources and developing annual budgets for review and input by the Strategic Advisory Board, and approval by the Dean of the Cumming School of Medicine and the Calgary Zone Medical Director; providing annual reports; and working with the Senior Associate Dean Research, Cumming School of Medicine and the Calgary Zone Medical Director to develop metrics to assess the Institute's performance.

*Figure 19. Alberta Children's Hospital Research Institute Organizational Structure*



The **Scientific Director** reports to the Director and provides scientific leadership for research and related activities within the Institute. The Scientific Director is responsible for promoting the science mission, enhancing the research portfolio through mentorship and grant review programs, representing the institute in the management of research and advising the institute on research and research-related budgetary matters. S/he is expected to ensure that ACHRI meets its scientific mandate, maintains strong partnerships and relationships with stakeholders and maintains good working relationships with the scientific community. (S)he should maintain open communication with the Director, Strategic Advisory Board and Expert Advisory Committee including regular updates on progress or issues.

The **Executive Director** reports to the Director and is responsible for supporting the Director in the day to day operations of the Institute and managing the team of personnel that support Institute activities from both a task allocation and human resources perspective. S/he is the primary contact and resource person regarding Institute and partner (CSM/U of C, AHS and ACHF) organizational, fiscal and administrative policies and procedures. The Executive Director is expected to assist in preparation and implementation of the strategic plan, business plan, annual report and annual budget.

The **Manager of Finances and Business Operations** reports to the Executive Director and is responsible for assisting the ACHRI leadership by tracking all financial aspects of the Institute's operations, including accounting, budgeting, forecasting and annual reporting, in compliance with the university's policy and procedures. The Manager serves as a liaison with external partners, funding agencies, and organizations to ensure compliance and reporting on all financial, legal, and/or contractual agreements, and works closely with the University's Research and Trust Accounting, and Research Services office on these matters. The Manager is the responsible ACHRI resource person for both the direct and indirect support of the University's Hyperion PeopleSoft module.

The **Program and Platform Managers** report to the Executive Director and support ACHRI's Theme and Platform leads by providing consultation and expertise regarding the day to day operations, analysis of issues, creation of project objectives, implementation plans, determining resource requirements and managing resources, supporting preparation and implementation of strategic and business plans. They design and manage all delegated phases of ACHRI programs or platform activities. Where relevant, they develop and maintain strong working relationships with colleagues in other Institutes, the ACHF, AHS, AIHS and key CSM academic Departments as well as important functional areas (e.g., Finance; Human Resources; Information Technology; Communications; Supply Chain Management, Research Services, etc.) and other child health service providers, to successfully plan, implement, monitor/evaluate and sustain projects/programs.

The **Communications Manager** reports to the Executive Director and is responsible for visioning, creation, and implementation of strategic communication plans that ensure the Institute's research output has societal impact and is communicated and well understood by both our partners, the donor community and broader Alberta and Canadian audiences. The Manager provides input into the preparation and communication of the strategic plan, business plan, annual report, press releases and in the development of materials as part of the stewardship of our partners and donors to the Institute. S/he will lead a communications/events team and support decision-making on all aspects of internal and external relations, communications, and strategic events.

The **Grants Officer** is a new position that reports to the Executive Director and supports the Scientific Director in the internal peer review process by tracking ACHRI members who are applying to granting agencies, supporting the creation of internal review committees, scheduling test your concept and subsequent full internal grant review, taking minutes and providing a summary of feedback to applicants, tracking outcome and collating external reviews and managing the bridge funding requests of unsuccessful candidates who are highly ranked. The Grants Officer will assist the Scientific Director in preparing Institute-wide submissions to national granting agencies (e.g. Genome Canada, CIHR).

The **Senior Administrator** reports to the Director and supports the scheduling, coordination of calls/meetings and preparation of documents/presentations and manages correspondence for the ACHRI leadership team. S/he supports ACHRI committees including the preparation of agendas, drafting minutes, coordination of communications with committee members; plays a major role in planning and supporting Institute events; manages phone inquiries to the Institute and assists the Communications Manager in supporting the ACHRI website.

## **Appendix 1: ACHRI - The Historical Background**

Alberta Children's Hospital Research Institute (ACHRI) has undergone transformative evolution from its origin within the old Alberta Children's Hospital on Richmond Road 35 years ago. The Behavioural Research Group (the catalyst to our current Neurodevelopment and Child Mental Health program in the Behaviour and Developing Brain theme) was created and funded by the Alberta Children's Hospital Foundation (ACHF) in 1978. The Genetics Research Unit was created and funded by the ACHF in 1982 (the precursor of the University of Calgary (U of C) Department of Medical Genetics and the human genetics component of ACHRI's current Genes, Development and Health theme). In the same year, the ACHF funded and built the Kinsmen Research Centre (adjacent to the old Alberta Children's Hospital on the Richmond Road site) to house the two research units, and an independent Kinsmen Research Centre Board was created to manage its activities. In 1990, the two existing research units were joined within a formally recognized and funded U of C research group, the Child Health Research Group, which focused on facilitating the growth of research across multiple child health related disciplines. In 1996, all of the research units/groups merged as the Child Health Research Centre that had a Child Health Research Centre Board with representatives from the community, Faculty of Medicine/University of Calgary and the ACH Foundation.

In 2004, Dr. J. Cross was appointed as the Director of the Faculty of Medicine/University of Calgary Institute for Child and Maternal Health and the Child Health Research Centre at the ACH merged with the Genes and Development Research Group in the Faculty of Medicine with the intent of developing into a center of excellence in research and education in maternal, newborn and child health. In preparation for the 2007 move of the ACH from the old site on Richmond Road to its current location on Shaganappi Trail, the Kinsmen Research Centre Board was dissolved and the research building reverted to the Calgary Health Region (now Alberta Health Services). In 2007, Dr. Cross was recruited as the Associate Dean, Research in the new Faculty of Veterinary Medicine. An external search for a new Director was initiated; however, a consistent theme of all the applicants was the perception that there was little vacant research space within which the Institute could grow.

In 2009, an internal candidate, Dr. B. Scott was appointed as Director, who accepted the challenges that needed to be resolved and the Institute was rebranded as the Alberta Children's Hospital Research Institute (ACHRI). In the fall of 2009, ACHRI initiated a grass roots-up, three stage, strategic planning process. A draft plan was created in alignment with the Faculty of Medicine and University of Calgary research strategic plans and the Alberta Health Research and Innovation Strategy (AHRIS) (Phase I). It was presented to our partners (Faculty of Medicine/University of Calgary, Alberta Health Services and ACH Foundation) in May of 2010 to stimulate discussion and to inform a Faculty mandated External Review of all of its Institutes in February of 2011 (Phase II). The draft plan and Institute operations were then revised and finalized in accordance with the recommendation the external review (Phase III).

The impact on Institute operations and performance, of the implementation of the recommendations of the 2011 External Review was assessed by the Expert Advisory Committee (comprised of the Chair of the initial External Review and two additional external reviewers) in October of 2013. In the following year, the Institute acted upon the additional recommendations of the Expert Advisory Committee. In April of 2014 the Executive Director of ACHRI was externally reviewed prior to the end of his initial five-year term, and reappointed to a second five-year term.

ACHRI released its Strategic Plan 2015-2020 in June of 2015 and submitted this Business Plan in December of 2015 to provide a more detailed account of its research programs, development of fundamental enabling infrastructure/platforms and projected budget to assist in obtaining philanthropic support and operationalizing the strategic plan.

## Appendix 2: ACHRI Membership Guidelines

<b>Section 1: ACHRI Membership Criteria</b>				
	<b>Associate</b>		<b>Full</b>	
	<b>Investigator</b>	<b>Associate Scientist</b>	<b>Scientist New-Investigator</b>	<b>Scientist</b>
<b>Allocated Time for Research</b>	20% or Less	50% or less	50% or more	50% or more
<b>Education and Research Experience</b>	At least 2 years research exposure and involvement	M.Sc./MPH level or higher with a record of at least 2 years of consistent research productivity	M.D. or Ph.D. level or equivalent with academic training and experience required to develop an exceptional independent research program	M.D. or Ph.D. level or equivalent, demonstrates consistent research productivity and operational grant support at the CIHR level or equivalent
<b>Affiliation</b>	Member of U of C, or AHS or an organization relevant to child and maternal health	May have full primary membership (or interest) in another Institute  Holds an academic, clinical or adjunct role in the University,  Privileged as a professional in an affiliated hospital	To be appointed to the Scientist-New investigator Track an investigator must have support of the ACHRI Executive Director, Scientific Director and Theme Leader	Holds an academic appointment at the University of Calgary (assistant, associate or full professor)  Works in child or maternal health or in basic science and conducts research relevant to the child and maternal health mission

<b>Section 2: Membership Expectations</b>				
	<b>Associate</b>		<b>Full</b>	
	<b>Investigator</b>	<b>Associate Scientist</b>	<b>Scientist-New Investigator</b>	<b>Scientist</b>
Research Activity and Expectations	Contributes intellectually as a team member in a research program, led by a Scientist/Associate Scientist. Team investigators may be capable of independently designing experiments but are not expected to have responsibilities for initiating or maintaining funding for research programs.	Participates or leads a research program relevant to child and maternal health recognized for its impact or significance within the academic scientific/clinical community.  Should participate in institute committees and related activities	Question-based or hypothesis-driven research of relevance to ACHRI.  Is a fully engaged, active participant in the research, teaching and service missions of a theme within the Institute  Participates on ACHRI research and educational committees, task forces or working groups  Contributes to the academic mission through active research funding support and publications  Participates in the trainee mission of the University and Institute through the supervision of students, fellows and other trainees  Provides appropriate recognition of ACHRI support on any published articles, abstracts or presentation material.	The ACHRI logo should also be included in research-related websites, email signatures and letterhead.

<b>Measures of Productivity</b>	<p>Publishes as author or co-author in high-ranking scientific/clinical journals.</p> <p>Participates as at least a co-investigator on peer-reviewed grants from provincial and national agencies.</p> <p>Contributions are intellectually based and related to expertise, beyond serving as a source of patient materials or data.</p>	<p>Publishes as primary or senior author in discipline-specific journals.</p> <p>Maintains peer-reviewed grant funding from provincial and national agencies.</p> <p>Invitations to:</p> <ul style="list-style-type: none"> <li>-major symposia in the field of research,</li> <li>-participate on grant reviews/panels</li> <li>-review manuscripts for journals.</li> </ul>	<p>Publishes as primary or senior author in high-ranking scientific journals.</p> <p>Maintains peer-reviewed grant funding from national/ international agencies.</p> <p>Participates in Theme and Institute activities (committees, seminar series, symposia, internal peer review)</p> <p><b>Scientist (not new investigators) receive</b></p> <p>Invitations to:</p> <ul style="list-style-type: none"> <li>-major symposia in the field of research,</li> <li>-participate on grant reviews/panels</li> <li>-review manuscripts for journals.</li> </ul>	
<b>Training/Education Roles</b>	<p>May Co-supervise training of clinical research fellows.</p> <p>Clinical Team Investigators will have access to the ACHRI clinical fellowship training program</p>	<p>Supervises training of clinical research fellows, and may supervise graduate students.</p> <p><u>Clinical</u> Associate Scientists will have access to the ACHRI clinical fellowship training program</p>	<p>Limited training responsibilities</p> <p>Access to ACHRI training programs</p>	<p>Supervises graduate students, PDFs.</p> <p>Access to ACHRI training programs</p>
<b>Review</b>	In-depth review every 3 years	In-depth review every 3 years	<p>Review after 2 years</p> <p>Maximum length of appointment is 5 yrs.</p>	In-depth review every 3 years

Section 3: ACHRI Membership Benefits			
	Associate	Full	
Investigator	Associate Scientist	Scientist - New Investigator	Scientist
Included in ACHRI scientific meetings, symposia, seminars Participate in research and education	Included in ACHRI scientific meetings, symposia, seminars Participate in research and education	Research and office space allocated based upon research grants and productivity  Access to ACHRI funded core facilities and services	
Eligible to apply to ACHRI Small grant competitions	Eligible to apply to ACHRI Small grant competitions  Clinical Associate Scientists will have access to the ACHRI clinical fellowship training program  May benefit from ACHRI program and platform development  Listing on the ACHRI mailing list  Access to ACHRI sponsored seminars, events	Establishment support determined in collaboration with Department/Faculty  Competitive access to ACHRI trainee programs  Access to bridge funding and other funding programs  Internal grant review and mentorship  <b>Scientist only:</b> Mentor junior faculty	

## **Appendix 3: ACHRI – Communications Strategy 2015-2020**

Communications and Community Engagement are important elements in the development of a public profile for the Institute and increasing community awareness of our research activities and successes. We work collaboratively with the communications team at the CSM and the six other faculties represented within ACHRI (Science, Arts, Social Work, Werklund School of Education, Nursing, Veterinary Medicine), the other six institutes in the CSM, the fund development and communications teams at the Alberta Children's Hospital Foundation and the CSM, the Communications team at Alberta Health Services and with Marketing at the University of Calgary.

We are responsible for communicating internally within the CSM, across the university, and externally at local, provincial and global levels through public engagement and by sharing compelling success stories about our research. This communications plan is designed to support ACHRI's strategic plan.

### **Vision**

Communicating the value of the Alberta Children's Hospital Research Institute.

**Mission** – To inform, educate and connect with local, national and international communities regarding ACHRI research initiatives and their impact on improving child and maternal health.

ACHRI's vision emphasizes that the provision of cutting edge, high quality child health research in Alberta relies on the Institute's presence.

Our team supports that vision and mission by increasing public awareness and understanding regarding ways the research activities of ACHRI's scientists result in innovation, new discoveries and improved health care delivery and health outcomes. We work to enhance the Institute's reputation and to increase meaningful engagement with internal and external partners and community groups. We adhere to the highest professional standards of communications with integrity as our guiding principle.

### **Objectives (in order of priority)**

#### **i. Communications internally**

Enhance communication links to strategic internal partners and our research scientists.

- Support institute symposia in a manner that showcases ACHRI's researchers and its education platform. There is potential to strengthen donor ties through lab tours and symposia visits. The overarching goal is to increase engagement of the public in our research.
- Our goal is to increase the number and quality of these research and community outreach stories for circulation in ACHRI's monthly newsletter, CSM media relations, UCalgary traditional and digital publications (alumni), AHS news releases, Apple magazine, Calgary Zone, as well as other community publications. The overarching goal is to create awareness of ACHRI's value and success.
- Create and promote ACHRI's brand identity with collateral such as banners, logo awareness in correspondence, research posters, and brochures for specific targeted audiences.
- Provide advice and support to the CSM communications team and internal theme groups along a spectrum of medium and high priority activities.
  - Create and/or support co-sponsored seminars and lectures such as Bea Fowlow Lecture, Next Gen and Owerko Conference.
  - Support calendars and e-mail blasts shared by all institutes and communicators.
  - Support media availabilities to create awareness of the institute's research.

## **ii. Strengthen our digital communications**

Create a stronger digital space with a specific emphasis on social media to strengthen research awareness within our institute, especially amongst ACHRI trainees, and to reflect the changing information consumption preferences of target audiences.

- Dedicate more resources to Drupal and social digital needs.
- Develop an interactive web experience for external audiences by writing/posting stories & videos more frequently.
- Use social media channels to strategically engage traditional media to increase awareness of ACHRI stories and value.
- Measure digital growth.

## **iii. Leverage internal communications**

We plan to strengthen our communication partnerships by sharing ideas, strategizing and undertaking collaborative initiatives with the ACHF, AHS and CSM. We can achieve efficiencies and enhance unified branding efforts with other institutes in key research theme areas: Brain and Mental Health; Infection Inflammation and Chronic Disease; and Precision Medicine.

## **iv. Effectively market the ACHRI brand externally**

This area has the most potential for our institute as it looks for ways to promote child health research in the Calgary community. Partnering with a stakeholder to support public interactive events would greatly enhance the Institute's visibility and value. Our goals in this area are the following:

- Strategically plan for opportunities to advertise/promote materials in national newspapers and the community to show the value of ACHRI.
- Create Annual Report Highlights for targeted groups, government relations and partners to promote and showcase ACHRI's values and successes.
- Search for external community stakeholders to partner in developing outreach efforts to highlight ACHRI's value to the community.

<b>Objective</b>	<b>Targets</b>	<b>Data Sources</b>
<b>Internal Communications</b>	Doubling of ACHRI stories internally year over year – measure outcomes in media/awareness/ google analytics.	Utoday hits, ACHRI web sessions, internal surveys /Cision Media
<b>Strengthen digital communications</b>	20% growth in social media reach by 2020	Google analytics
<b>Leverage internal communication growth</b>	Greater presence of key communications partners by 2020 in the three priority areas: BMH, IICD, Precision medicine	Connect regularly with the scientific directors and communication leads
<b>External communications</b>	Find external partner to create interactive displays, talks, raise community awareness	

## **Appendix 4: ACH and ACHRI Collaborate as a World Leading Academic Child Health Centre**

### **Background: Health Research and the Future of Research Hospitals**

“Child health is of the greatest importance for the future health of a nation, since today’s children grow up to become the next generation of parents and workers, and because health in early life is the basis of health in adult life. Early life health has lifelong effects that result from the interaction of biological development and social and environmental circumstances. The concomitants of good health in childhood are educational receptivity, good parenting, and good maternal health and education. Therefore, investment in physical and mental health and education of mothers and children has beneficial effects on the future health of a nation, as well as on the functioning and well-being of its citizens.”<sup>i</sup>

Weatherall<sup>ii</sup> recounts the rapid progress of medical science during the last century when the development of molecular biology led to the discovery of novel treatments for many diseases. Molecular biology was informed by, and likewise informed, the clinical knowledge and expertise of physicians. This partnership between the basic and clinical sciences played out largely within the walls of individual research hospitals. As the understanding of the nature and causes of the molecular basis of disease deepened, the search for effective treatments and therapies became more creative. The human genome was deciphered. New technologies, such as next generation sequencing, were developed. “Research harnessing the wealth of post-genomic sciences and the power of the (...) Health Services, offers unparalleled opportunity to improve the wellbeing of infants and children, turn the tide of the growing burden of the major non-communicable chronic diseases that have their origins in early life and lead to premature adult death, and benefit the health of future generations.”<sup>iii</sup>

As the last century closed, we also increased our understanding of the roles of human psychology and organization, the environment and society in health and disease. More disciplines became involved in generating the type of knowledge required to understand the complex, multi-factorial bases of many diseases and the equally complex array of factors that contribute to health. Medical epidemiologists, clinical scientists, and social scientists such as geographers and sociologists, worked in teams to study the social determinants of health. Complex research questions required the development of large cohort studies and bio-banks. Often this research took place outside the walls of research hospitals in settings as diverse as Universities, public schools and ski hills. Throughout, the broad research goal has always been breakthrough thinking to achieve improved health and reduce the burden of disease on individuals and the population.

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<sup>i</sup> Wadsorth,M. and Butterworth, S. Chapter 3 Early Life; in Social Determinants of health 2<sup>nd</sup> edition. Edited by Marmot, M and Wilkinson, R.G. Oxford University Press (Oxford, 2006), pages 31-53.

<sup>ii</sup> Weatherall, D., “Science and the Quiet Art: the Role of Medical Research in Health Care”, W.W. Norton (New York, 1995), pages 227-229.

<sup>iii</sup> Turning the Tide: Harnessing the power of child health Research. A report from the Royal College of Paediatrics and Child Health Commission on Child health Research. Executive Summary, November 2012. The full report can be accessed at: <http://222.rcpch.ac.uk/harnessing-the-power-of-child-health-research>

<sup>iv</sup> Canadian Academy of Health Sciences Assessment Report: Making an Impact. A Preferred Framework and Indicators to Measure Returns on Investment in Health Research. Report of the Panel on the Return on Investments in Health Research. January 2009. <http://www.cahs-acss.ca/making-an-impact-a-preferred-framework-and-indicators-to-measure-returns-on-investment-in-health-research-8/>

As this current century begins, these two broad directions for health research (how genes, proteins and molecules interact at the molecular and cellular level; and how social determinants interact to promote health or cause disease) have become linked. Epigenetics and the evidence from early childhood development studies now demonstrate that genes and the environment are highly interactive systems. Alterations in the environment (either beneficial or adverse) can influence the transcription of genes, the system biology and behaviour in the current and future generations.

Consequently, the traditional research hospital model requires transformation to keep pace with the demands for new and novel understandings of the causes and remedies of disease and the pathways for improving health. The questions driving research today require research hospitals to consider developing a broader role as knowledge networks that reach from the laboratory and clinic to influence people in their homes, workplaces and communities. Pediatric research hospitals, which care for some of the most vulnerable populations, have an opportunity to lead this development. The current proposal proposes a path that transforms Canada's collection of pediatric research hospitals into a hub and spoke network - horizontally and vertically organized - to do breakthrough research into the biological and social determinants of disease and health and then share, transmit and apply this knowledge to benefit children, families and communities.

Today's child and maternal health care institutions are focused primarily on the delivery of patient care. While they are often associated with or collaborate with academic institutions and do support research and education, their predominant focus is maximizing access to the highest quality and safest care possible within their budgetary envelopes. While these goals must remain paramount, we have not yet begun to achieve the kind of improvements in performance, productivity and patient outcomes that are possible if we truly integrate the clinical and academic mission and apply innovative thinking, iterative evaluation and rapidly translate new knowledge into practice. The academic partnerships, governance, administrative structures, core objectives, policies and procedures, budgets and performance measures of our child and maternal health care institutions need to be assessed and revised to facilitate the changes in values, culture, structure, health care delivery processes and infrastructure that drive family centred care and integrate community and partners into iterative cycles of innovative change, rigorous evaluation and the subsequent incorporation of new knowledge into best practices and care delivery pathways. Thoughtful questions, data acquisition, analysis and outcomes will need to refine policy and practice. When every member of the health care team (patient and family, health provider regardless of discipline, support staff, administrator, academic, and community partners) feels they can present a hypothesis that offers potential for system improvement, have it seriously considered, evaluated and potentially acted upon, we will have created a research hospital. It is unrealistic to expect that this will be achieved in 3, 5 or even 10 years, but the benefits over time justify seizing the opportunity, identifying an initial focus and the necessary steps to achieve the goal and embarking upon the journey.

### **The Value Proposition for Children and Families**

In the research hospitals of the future, both clinical care and research need to be child and family centred. The child and family can expect that they will be respected partners and participants in clinical care, research and its translation into best practices and the highest standards of evidence based care and treatment. Every patient will expect to participate in clinical trials that ensure compliance with best currently available practices and treatments, but within which there is evaluation of possible improvements. Patients and families will have representation on study design, implementation, communication of results and knowledge translation strategies. The new knowledge derived from clinical trials will be utilized to continuously improve patient outcomes and well-being.

## **The Value Proposition for Health Providers and Clinicians**

For health providers and clinicians, the research hospital of the future will support the enabling infrastructure for clinical, health services and population health research. Participation in research that enables continuous quality improvement, improved patient safety, more rapid knowledge translation and better clinical outcomes will create a culture of inquiry, a pride of participation and attract the best and brightest to centers that become internationally recognized for the provision of not only the best current care but continually striving to be leaders in advancing the quality of care and the health and well-being of Canadians.

### **The value proposition for Researchers**

Because the research hospital of the future will support the enabling infrastructure for clinical, health services and population health research, investigators will find that clinical research will be greatly facilitated by clear, standardized, principles/policies, processes and supports (e.g. ethics, legal, data acquisition, data storage, data management, administration of access to data, research methods consultation, data analysis, KT, training). There will be inter-institutional collaboration (hospitals, universities, government, NGO's) so that opportunities are maximized, duplication is reduced and funds are spent effectively to develop core shared infrastructure, facilitate multi-centred and population based research within provinces and across the country, build and retain clinical research capacity and improve health care delivery and health outcomes in Canada. The unique, existing clinical research and educational collaborations/networks within the child health sectors across this country provide a real opportunity to build upon and achieve these outcomes.

### **The value proposition to the health care system**

A research hospital of the future will benefit from the culture of inquiry, the pride of patients, families, health care providers and investigators in being active participants within a network of institutions that strive for continuous quality improvement, improved patient safety, more rapid translation of new knowledge into better practices/standards of care, better clinical outcomes and improved health and well-being of Canadians. Such an environment supports a healthy workplace, recruitment and retention, efficiencies that can be reinvested in clinical and research infrastructure that fosters further improvements in care and outcomes. Patients and families become meaningful participants in care and research and in so doing facilitate health care delivery, better outcomes and lead to an improved public perception of the health care system.

A recent report by the Canadian Academy of Health Sciences<sup>iv</sup> indicates that "It is practically impossible to 'identify the most appropriate data to collect for any potential evaluation of health research in Canada.'" However, the panel "...identified a 'menu' of potential indicators that can be brought together into sets for specific evaluations..." Their indicators covered five impact categories: advancing knowledge, capacity building, informing decision making, health impacts, and broad economic and social impacts. Moreover, "When used together in sets, indicators can help to create focused, appropriate, balanced, robust, integrated, and cost - effective evaluation (HM Treasury, Cabinet Office, et al. 2001)." Thus, if we move forward to develop a network of child health research hospitals use of these indicators will allow appropriate benchmarking, performance evaluation and assessment on return on investment.

## Appendix 5 : CSM Precision Medicine Initiative

### CREATING THE FUTURE OF HEALTH Precision Medicine as a bold new vision for the Cumming School of Medicine

#### 1. Background

In contemporary medical practice, physicians typically use clinical phenotypic data (symptoms, signs and laboratory results, and imaging including light microscopic analysis of tissues) as the basis for definitive diagnosis or hypotheses about the underlying cause and pathogenesis of their patients' illness. Although both patients and doctors often think of this process as culminating in a specific and irrefutable diagnosis and treatment, our current paradigm for classifying disease may not be as precise as we have been taught to believe. In the words of the U.S National Research Council, "Many disease subtypes with distinct molecular causes are still classified as one disease and, conversely, multiple different diseases may share a common molecular cause".

This sole focus on clinical phenotypes has served us well for over the last two thousand years – and has led to many important discoveries about health and disease. However, insights and technologies derived from the 'human genome project', molecular and cellular biology have extraordinary potential to identify new diagnostic and therapeutic capabilities that will transform clinical medicine over the next 25 years. Today, we can link clinical phenotypes to molecular pathogenesis to understand human health and disease in an unprecedented way. The cornerstones of this revolution in clinical medicine will be

- Continued advances in collecting population wide genomic data at high speed and low cost increasingly reasonable cost and translating this into distinct phenotypes
- Developing an integrated system for systematic collection of organ tissues, tumor and other biological samples to assess for molecular phenotypes and genetic mutations
- Advances in the secure storage and ultra-rapid analysis of "big data" from disparate sources
- Continued development of methods to accurately categorize intermediate clinical phenotypes
- Expand clinical trials infrastructure to test personalized therapies, based on genotypic, somatic and intermediate phenotype information
- Availability of low cost computing to merge clinical, genomic and molecular phenotypic data fueling discovery
- Increasing numbers of successes where genomic and molecular data revolutionizes diagnosis and therapy

This new paradigm will evolve slowly at first, and identifying the molecular causes and imprints of diseases in individuals will not diminish the importance of clinical skills, and studying population and public health. Precision medicine also applies in the context of public health, with a focus on health promotion, disease prevention and reduction in health inequities. In addition, although this approach may be more expensive at the outset, over time the incremental value of measured clinical outcomes, targeted resource utilization, and patient-centered care will exceed the ongoing costs of the status quo. The growing emphasis on 'patient-centered care' and the unprecedented access that today's patients have to health information will mean that new approaches to the communication of many benefits and limitations of molecular medicine will be needed. How to best deploy these innovations in a sustainable and equitable fashion also requires careful thought.

New paradigms will bring opportunities and challenges. The Cumming School of Medicine stand ready to embrace the molecular era of medicine and health and associate challenges. At retreats and planning sessions held during the development of the CSM Strategic Plan, all stakeholders delivered a clear message that Precision Medicine should be a key priority for our school. This document articulates a preliminary roadmap for achieving this objective.

#### 2. The vision

We are committed to a future where all Albertans receive the right treatment, at the right time, in the right setting, and with the information that they need to make good choices about their own health and health care. Some examples of how this "health care of the future" will look for patients are shown in Box 1.

## **Box 1: The vision for health care of the future**

### **Targeted treatment for inflammatory diseases**

A 55 y.o. woman has microscopic polyangiitis, a rare inflammatory disease that causes progressive kidney failure and lung hemorrhage. She underwent molecular testing to better define the status of her immune system and the inflammatory pathways that were damaging her lung and kidney tissues. As a result of this testing, she was found to have a subtype of microscopic polyangiitis that is associated with treatment-resistance or high risk of relapse using standard therapies. Based on this information, her physicians select a drug that targets a specific type of white blood cell, arresting the inflammation, and protecting her from further damage, and allowing her organs to heal. The patient goes into a long term remission.

### **Precision treatment for cancer**

A 35 year old South Asian mother of two developed chest pain and cough. Persistent symptoms led her doctor to order a chest x-ray. The x-ray and subsequent CT scan showed an inoperable tumour in the lung. A biopsy was performed: the tumour was an adenocarcinoma (cancer). She was healthy previously and a non-smoker. Because of this unusual story, other testing of her cancer took place. Her cancer was caused by a mutation in a molecule called the epidermal-growth-factor receptor (EGFR). She was treated with a drug that blocks abnormal EGFR signaling and dramatically improved. The pain, cough, and tumour disappeared shortly thereafter, and she continues to be well two years later.

### **Precision diagnostics for stroke**

A 67 year old man presents acutely to a small community hospital within one hour of onset with left hemiplegia. Rapid brain and neurovascular imaging with computed tomograph (CT), including use of a new CT contrast agent that identifies thrombus characteristics, shows an acute blockage of his right middle cerebral artery. The novel contrast agent combined with advanced image processing tells the attending physician that the thrombus will not dissolve with routine use of a clot-busting medicine (tPA). He is rapidly transported by helicopter to the tertiary centre and undergoes endovascular thrombectomy. After a short hospital stay and in-home rehabilitation therapy, he makes a full functional recovery.

### **Patient-centred care**

A 79 y.o. farmer is diagnosed with advanced non-small cell lung cancer. Based on genomic analysis of biopsy specimens, she is offered targeted treatment with rofetinib. Rofetinib would improve the likelihood of 2y survival by 32%, but has an appreciable risk of disabling neuropathy that would make independent living difficult or impossible. After discussion with her family (facilitated by state-of-the-art decision aids) that accurately presents her available options, she opts for palliative treatment at home.

## **What tools are needed?**

Fully capitalizing on the potential of Precision Medicine will require world-class platforms for routinely capturing detailed patient phenotypes from clinical practice, linking this to targeted information and specimens collected at point of care, efficiently measuring and analyzing molecular data in selected specimens, and a comprehensive biobanking strategy to preserve a wide range of specimens for future research. Multiple links between and among scientists, clinicians and patients will also be required to ensure that these data are used to optimally inform clinical care. The following represent areas in which the CSM's infrastructure already meets the requisite high standard, or in which critical new investments are needed to help propel the CSM to the forefront of Precision Medicine.

### ***Clinome (i.e. clinical phenotype) analysis platforms:***

Precision Medicine requires the ability to perform detailed and routine capture of patient clinical phenotypes. When coupled with state of the art bioinformatics, intermediate phenotype assessment, data capturing systems and data processing (i.e. machine learning), these data will help guide decision-making processes during interventions.

### ***Bioinformatics capacity:***

The huge quantities of data available from whole genome sequencing, metabolomics, microbiomics, immunobiomics and other molecular platforms mean that medicine is now a “data intensive science”, and tremendous computing power is required to fully utilize this information for the benefit of patients. Continued growth in personal mobile devices used to collect physiological and behavioral data on a huge scale further magnify the informatics capacity that is potentially required. Fortunately, parallel improvements in the efficiency and affordability of computer technology mean that this capacity is within reach. Central IT infrastructure is needed to link all of the molecular/genetic platforms to the clinome.

The CSM has developed a Clinical Research Unit that will support the Precision Medicine program, focusing on the acquisition, linkage, processing and anonymization of confidential clinical data and relevant metadata. In parallel, the University of Calgary and CSM are building a larger bioinformatics platform to support the collection of genomic data that will be considered in light of other data such as proteomics, gene expression, imaging and pathological data. More robust linkages of “research” data with the clinical data that are routinely collected in the health system will reduce duplicated efforts, allow comprehensive, inexpensive assessment of a wide range of clinical outcomes and prevent information silos. The CSM’s strong partnerships with the provincial Strategic Clinical Networks, Alberta Health Services and Alberta Health will be critical for achieving the Precision Medicine goal.

### ***Genomics:***

Genomics is one of the cornerstones of any Precision Medicine program: at present, genomic DNA is sequenced in germline or tumor tissue of patients and/or relatives, especially for those with genetic disorders and cancer. In the near future, genomic technologies may be extended to routine analysis of the microbiome and epigenome – and in broader populations such as those with inflammatory diseases and other chronic conditions. Furthermore, the Department of Medical Genetics has developed a program to diagnose and treat rare genetic disorders in children. The CSM has partnered with the Alberta Children’s Hospital Research Institute and the Charbonneau Cancer Institute to build a University-wide genomics platform. This will support both research and diagnostics, and will interface seamlessly with the bioinformatics platform in a secure and privacy-compliant fashion.

### ***Molecular diagnostics and molecular phenomics:***

In addition to genomic information, Precision Medicine also requires detailed insights into other types of biomarkers such as immune responses (immunobiome) and metabolomics. Through Mitogen International and Eve Technologies, the CSM supports a biomarker research and development platform that is unique in Canada and which serves a large patient population in Alberta and around the world. A metabolomics platform is located in the Faculty of Science (under the direction of Dr. Hans Vogel), which augments world-class capabilities at the University of Alberta (Dr. David Wishart). Together, these two Alberta-based facilities could support the large numbers of patient samples needed to implement Precision Medicine in clinical practice.

### ***Biobanking:***

Like detailed cataloging of patient clinomics data, it will be essential to routinely preserve and catalog patient tissue and biological fluid samples obtained for clinical indications. This will require a concerted effort for integrated state of the art biobanking with a common cataloging and retrieval protocol that links clinical and pathological samples to genomic, metabolomic and molecular phenotypic and clinomic data. Multiple biobanks are already in operation across the UC campus, but need to be integrated and eventually consolidated into a centralized system that ideally leverages clinical infrastructure.

### ***Microbiome data:***

It is becoming increasingly clear that many disease processes arise from specific interactions between the body and its external and internal microbial environment. Through major investments through the Cumming Medical Research Fund and the Western Economic Diversification opportunity, the CSM is uniquely able to execute detailed studies of the link between the microbiome and human disease. The microbiome data will be seamlessly linked with the genomics and other ‘omics platforms and the rich clinical data embedded in the health system. These data will enable CSM scientists to discover novel diagnostic and therapeutic technologies that are targeted at specific characteristics of an individual’s microbiome.

### ***Imaging and novel technologies:***

The CSM is supporting several critical human imaging platforms, particularly in the area of brain (within the Hotchkiss Brain Institute), heart (within the Libin Cardiovascular Institute), child health (Alberta Children’s Hospital research Institute) and bone and joint (within McCaig Institute) imaging that will be able to support efforts in Precision Medicine. This is particularly exemplified in the area of stroke neurology (see Box 1). These advanced human imaging platforms will also support links to related technologies that will drive commercialization efforts (e.g. Project Neuroarm for enhanced precision in brain surgery).

### ***Induced Pluripotent Stem Cells:***

Using cellular reprogramming, it is now possible to turn patient blood or skin cells into induced pluripotent stem cells (iPSCs). Being pluripotent, these patient-derived cells can be differentiated into specific cell types for diagnostic applications. For example, heart tissue can be derived from patients with cardiomyopathies in order to model the disease *in vitro* and to identify therapeutics that ameliorate disease. Similarly, by deriving patient liver cells, scientists are able to validate predicted pharmacogenomic profiles *in vitro*. Finally, clinical trials have also begun to investigate whether patient-derived iPSCs can be used to replace defective cells and or tissues in humans. Being patient derived, these iPSCs can circumvent current problems associated with immune rejection.

### ***“Expososome” data:***

Interactions between humans and their environment have long been known to cause and modulate disease. There is growing interest in how environmental factors in the broad sense (including air quality and occupational exposures, but also housing and neighbourhood characteristics, for example) together with lifestyle and behavioral characteristics such as diet and exercise might interact to promote health or illness. Together, these factors have been termed the “expososome”. Some elements of the expososome could be addressed directly through public health action (e.g. air quality, alcohol intake, tobacco use, UV exposure, oral health, sports injuries), whereas others might be used to customize treatment strategies (e.g. personalized chemotherapy doses for patients with prior occupational exposure to certain sensitizing agents). While it is not currently practical to comprehensively characterize an individual’s expososome, the CSM has existing strength in environmental epidemiology and in population health that could be leveraged to improve this aspect of Precision Medicine. These data can also be directly linked to the end organ effects, by studying tissues for the presence of somatic mutations.

### ***Fundamental science to understand disease mechanisms:***

There can be no Precision Medicine approach without a solid basis of fundamental biomedical research that aims to elucidate disease processes. Relevant fundamental research with translational potential will help guide

personalized treatment options. Platforms such as MORPH (based in the Alberta Children's Hospital Research Institute), the new microbiome center, cancer genomics and state of the art immunology research in the Snyder Institute already guides clinical practice, as do molecular neuroscience studies in the Hotchkiss Brain Institute. Strong platforms to support biomedical research such as state-of-the-art cell imaging facilities and the Clara Christie Center for Mouse genomics are salient examples of essential infrastructure that support the fundamental research enterprise of the CSM.

***Tailored drug, vaccine and other intervention development:***

Precision Medicine will require the development of tailored and targeted drug interventions that reflect the molecular basis for disease in an individual. This can be accomplished by using the bioinformatics platform to integrate clinomics, genomics and metabolomics data and select the best choices for existing approved drug treatments -- or alternatively by developing novel targeted therapeutics. For the latter, there is an existing relationship between the University of Calgary and the Centre for Drug Research and Development (a platform spun out of the University of British Columbia) that supports drug discovery efforts. In addition, it will be essential to work closely with the pharmaceutical sector to develop new partnerships for the development and testing of new therapeutics. This can be facilitated through close partnerships with Innovate Calgary and Tec Edmonton.

***Clinical trials infrastructure:***

The Precision Medicine strategy will also require a process for testing promising therapies in first-in-human clinical trials and other early phase clinical studies. This will require continued focus on the CSM phase 1 clinical trials unit and additional support for the clinical trials units already in existence at the CSM to test personalized testing and therapeutic strategies. Strong linkages with the health system and the bioinformatics platform will ensure that eligible patients are rapidly identified and offered the opportunity to participate in novel clinical trials. Indeed, a top tier clinical trials infrastructure will provide the Cumming School with an international profile, and will be essential for inclusion into consortia, networks, and multicenter trials.

Through its existing infrastructure, people and platforms, the CSM is poised to become a world leader in Precision Medicine. However, further support and investments in key areas will be required to capitalize on our existing strengths.

***Infrastructure for patient-centered care and patient-oriented research***

Today's increasingly informed and engaged patients are chiefly responsible for the momentum behind patient-centered care. Patient-centered care places less value on "one-size-fits-all" approaches to the management of cancer, cardiovascular and other chronic diseases – and emphasizes instead the presentation of options that incorporate the individual values and preferences of patients and their families. Given the cost and complexity of novel therapies, balanced presentation of such options in a way that can be understood by patients will become increasingly important as Precision Medicine becomes more widespread. This shift in emphasis requires new tools and approaches to facilitate shared decision-making: this in turn will require investment in human factors engineering, cognitive science, behavioral economics, knowledge translation, and multimedia and mobile computing platforms.

Precision medicine also spans pillar 3 research, precision/personalized health care delivery, as well as pillar 4, precision population/public health. Precision medicine in health services and health care delivery aims to ensure that the right patient receives the right treatment at the right time. This personalized and patient-centered approach addresses the risk-treatment paradox (i.e., the mismatch between patient profile and treatment received). Use of a variety of strategies and tools, such as risk-prediction tools, decision aids and mobile technology for patients and providers will be central to this approach. This personalized, patient-centered and risk based approach will transform health care to enhance the patient experience, improve outcomes, and potentially also to improve efficiencies to the health care system.

Precision medicine in population/public health extends the fundamental notions of precision medicine to populations. One size does not fit all in diagnostics and therapeutics for patients. Similarly, one size cannot fit all

for population and public health. Precision public health focuses on the targeted and detailed characterization of context-specific social determinants of health, so that targeted population-health interventions can be designed and delivered in ways that produce positive health impacts for specific populations. In this paradigm of precision public health, the ‘molecules’ of interest are the community-specific patterns of social determinants of health (i.e., the unique mix of demographic factors, ethnicities, socioeconomic factors, and cultural factors) that define populations and their associated health. As with precision medicine, precision public health involves the application of emerging technologies, including new methods for assessing the social determinants of health as well as assessing exposures, behaviors and susceptibility in populations. The use of big data and smart analytics will enhance the precision of public health surveillance, and rapidly transform this information to action through the detection of epidemics and related community health problems. Various mobile technologies and related tools will track health behavior and disease outcomes, and improve the timeliness of population/public health data for decision makers. A population-based approach can also be used for molecular and genomic applications to ensure early disease detection at a population level, and to identify high-risk populations for screening and interventions.

#### ***Ethical, economic, legal and social (EELS) implications of Precision Medicine***

Introduction of the novel, expensive and often highly efficacious treatments implied by Precision Medicine will likely raise critical new questions about these so-called EELS issues. Such questions will in turn have important implications for patients and society – and for payers such as government and private insurers. Addressing these questions will require a coordinated investment in ethical, social, environmental and legal sciences with the requisite expertise – as well as investment in the UC Health Technology Assessment unit that could be patterned after Genome Canada’s GE3LS.

#### **4. How do we get there?**

##### ***Research and analytics infrastructure:***

Clinomics, molecular phenomics, genomics, epigenetics and metabolomics have redefined the science and our ability to understand human biological, psychosocial development and clinical outcomes. In the short term, additional investments to strengthen existing infrastructure for research and analytics are needed, across all pillars of research. This includes investments into enhancing genomics and other ‘omics capabilities, bioinformatics infrastructure, machine learning, investments in basic biomedical research platforms such as live cells and two-photon imaging/microscopy, and the adoption of newly emerging technologies such as CyTOF. The developmental origins of human health and diseases are well accepted, and interventions and investments during early life have been shown to yield the greatest long-term impacts on individual and societal health and wellness. Incorporation of a component focus on child health and the developmental origins of health and disease will be essential. Development of state-of-the-art IT infrastructure and novel IT technologies, such as such as quantum computing, will be essential.

##### ***People:***

A successful Precision Medicine program will require targeted recruitment of researchers, clinician scientists and trainees whose research programs are relevant to the Precision Medicine Vision. This is particularly important in the area of genomics and bioinformatics, but also in more fundamental research areas targeted to identify disease mechanisms. Human resource capacity also needs to be strengthened in the area of training of HQP, and in the recruitment of staff scientists who manage core platforms and who engage in technology development.

##### ***Training Physicians and Health Care Providers of the Future***

The emergence of Precision Medicine will require integrated approaches to educating health care providers of the future. This will include adjustments to the pedagogy and curricula.

##### ***Integrated Precision Medicine building:***

Ultimately, to fully realize the vision of Precision Medicine in Alberta we need to seamlessly integrate research and patient care. Each contributes to, and is essential for the other. The Cumming School of Medicine currently conceptualizes this in the form of a new building on the Foothills Campus that will become the home of our teaching

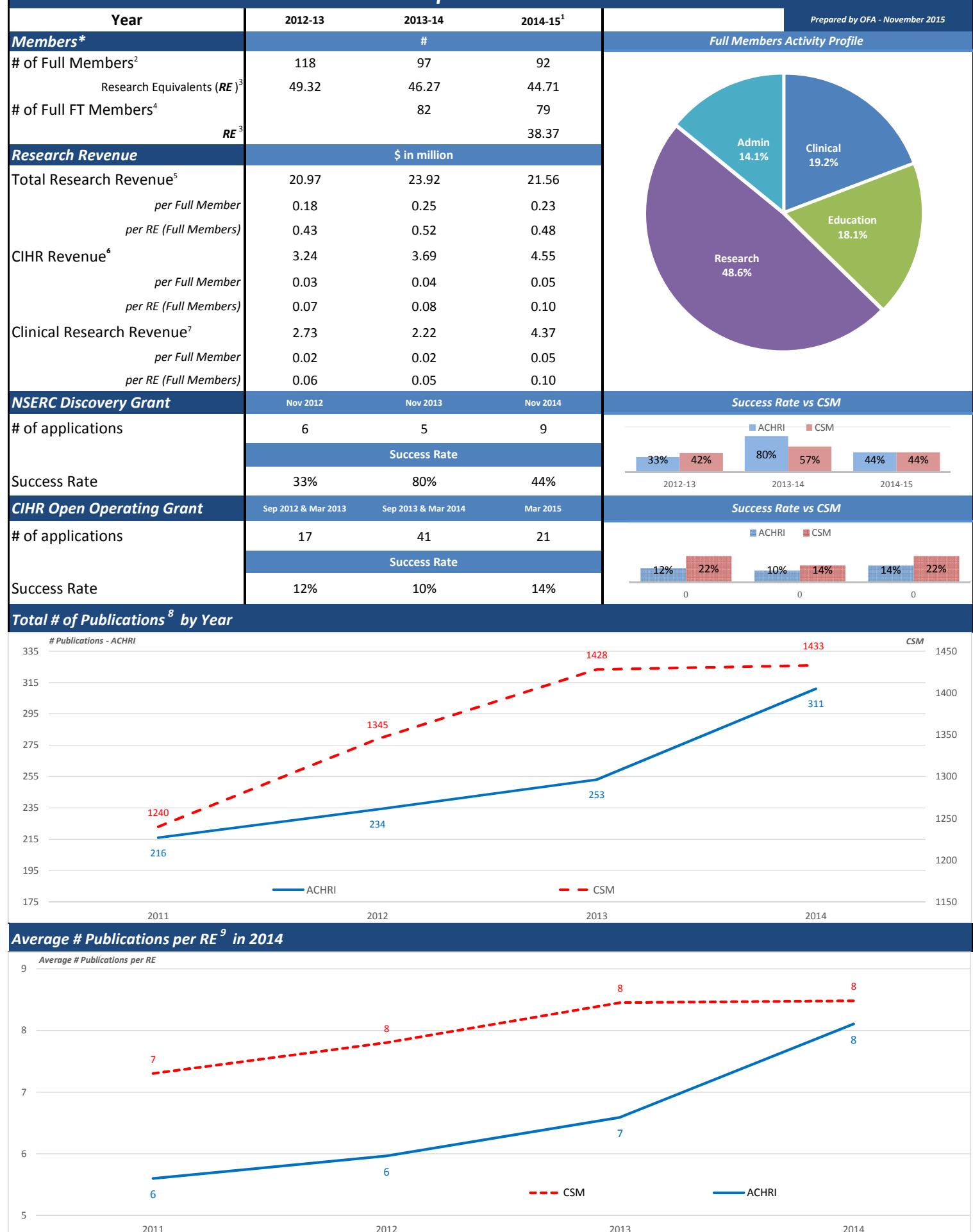
outpatient clinics. The “Calgary Center for Precision Medicine” would house primary care and subspecialty clinics along with core infrastructure for the delivery of precision medicine. Patients who came for care would be evaluated and treated using precision medicine and each in turn would be a research patient, with their data informing the care of future patients. Critical success factors for realization of the utility of expansion and ultimately partnership support for construction include 1) recognition that CSM has an academic leadership role for all Calgary Zone hospitals, including ACH, family practice and rural medicine, 2) alignment with AHS plans for service provision including academic support at all primary, secondary and tertiary care sites, and 3) defining the relationship to the new cancer center at Foothills medical campus. This will all contribute towards “bioengineering” the optimal healthcare system to implement change.

***Partnerships:***

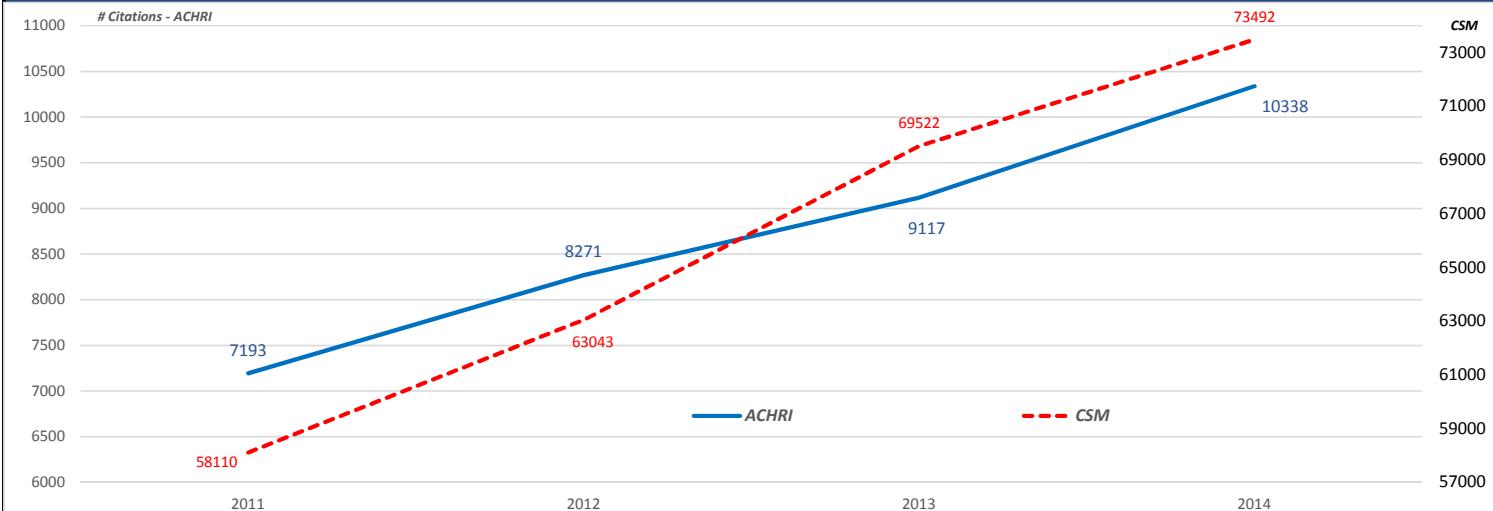
A crucial success factor will be the development and maintenance of key partnerships. This includes other faculties within the University of Calgary, our partners at the University of Alberta, Alberta Health Services, the Government of Alberta, funders such as Alberta Innovates-Health Solutions and CIHR, organizations such as the Centre for Drug Research and Development and various NGOs. Newly formed linkages with the pharmaceutical industry, diagnostics, imaging and medical devices sectors will be essential, as will partnerships that enhance philanthropic support to the CSM.

# Appendix 6: CSM Annual Report 2014-2015 - ACHRI and CSM

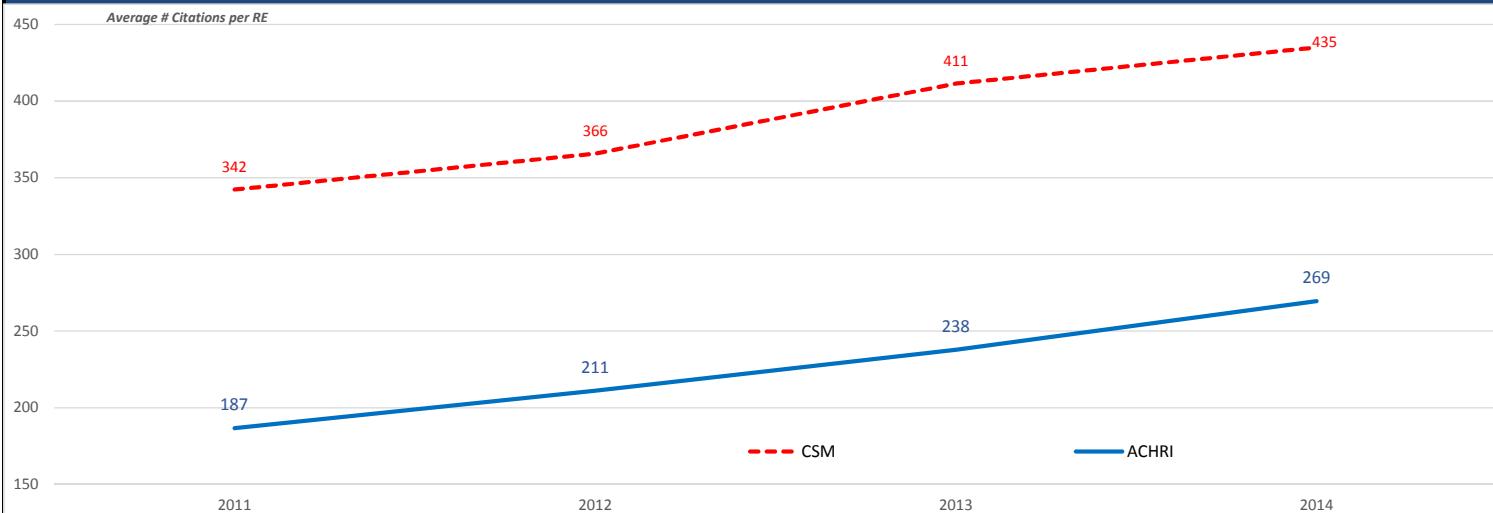
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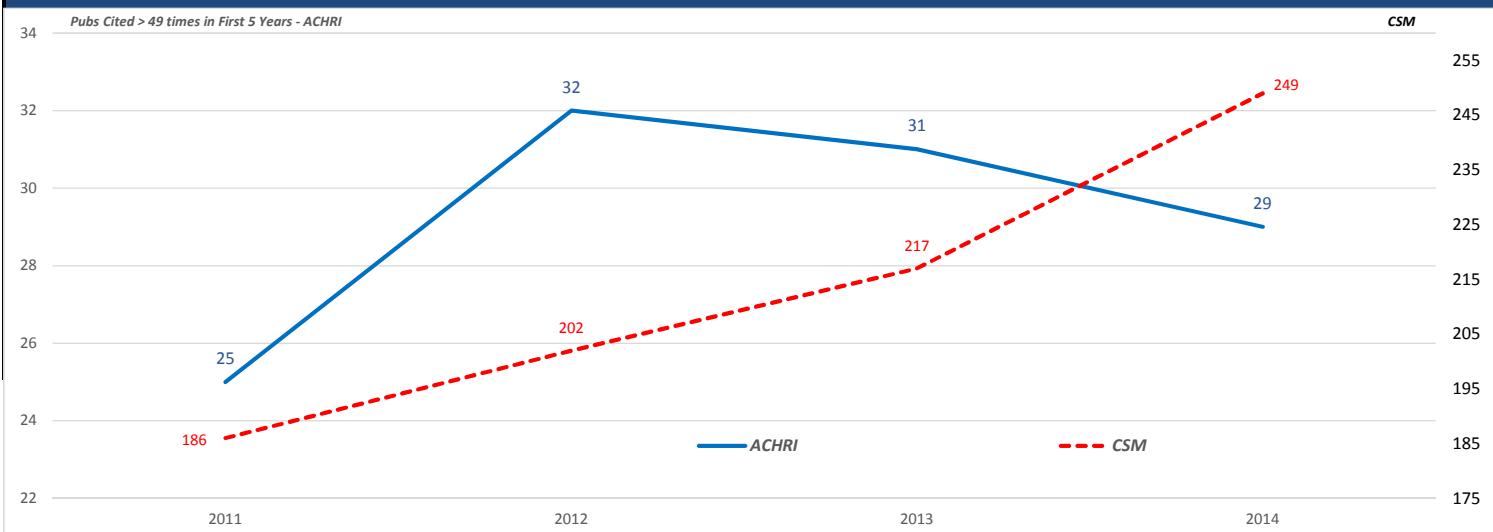
## Total # of Citations<sup>10</sup> by Year



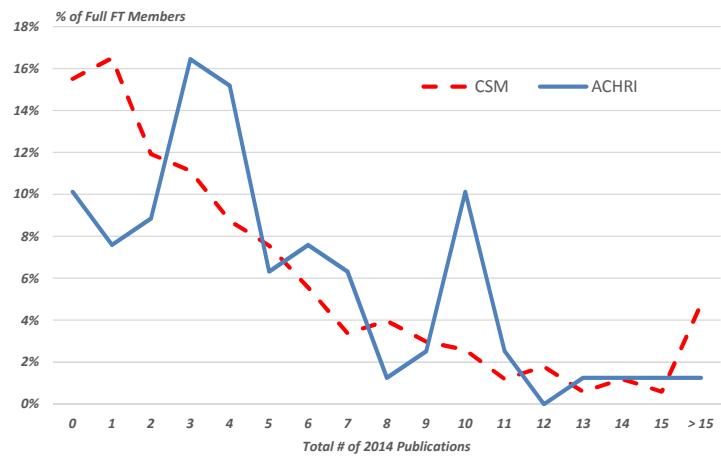
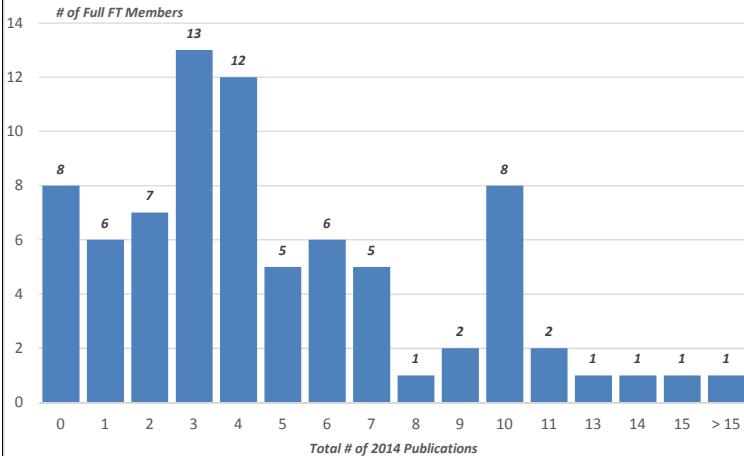
## Average # Citations per RE in 2014



## # Publications cited >49 times in first 5 years<sup>11</sup>



## Productivity among Full FT Members in 2014<sup>12</sup> - ACHRI



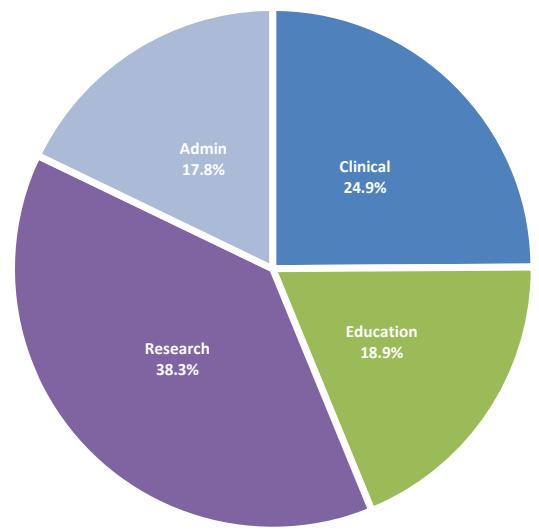
Year	2012-13	2013-14	2014-15 <sup>1</sup>	2014-15	
<b>Space</b>	<b>ACHRI</b>				
Space Allotment (Sq M) <sup>13</sup>	3,050	3,298	3,298	33,888	
Sq M / Full Member	25.85	34.00	35.84	52.46	
Research Revenue \$ / Sq M	6,875	7,254	6,539	3,760	
# of Publications / (Sq M/100)	7.67	7.67	9.43	4.23	

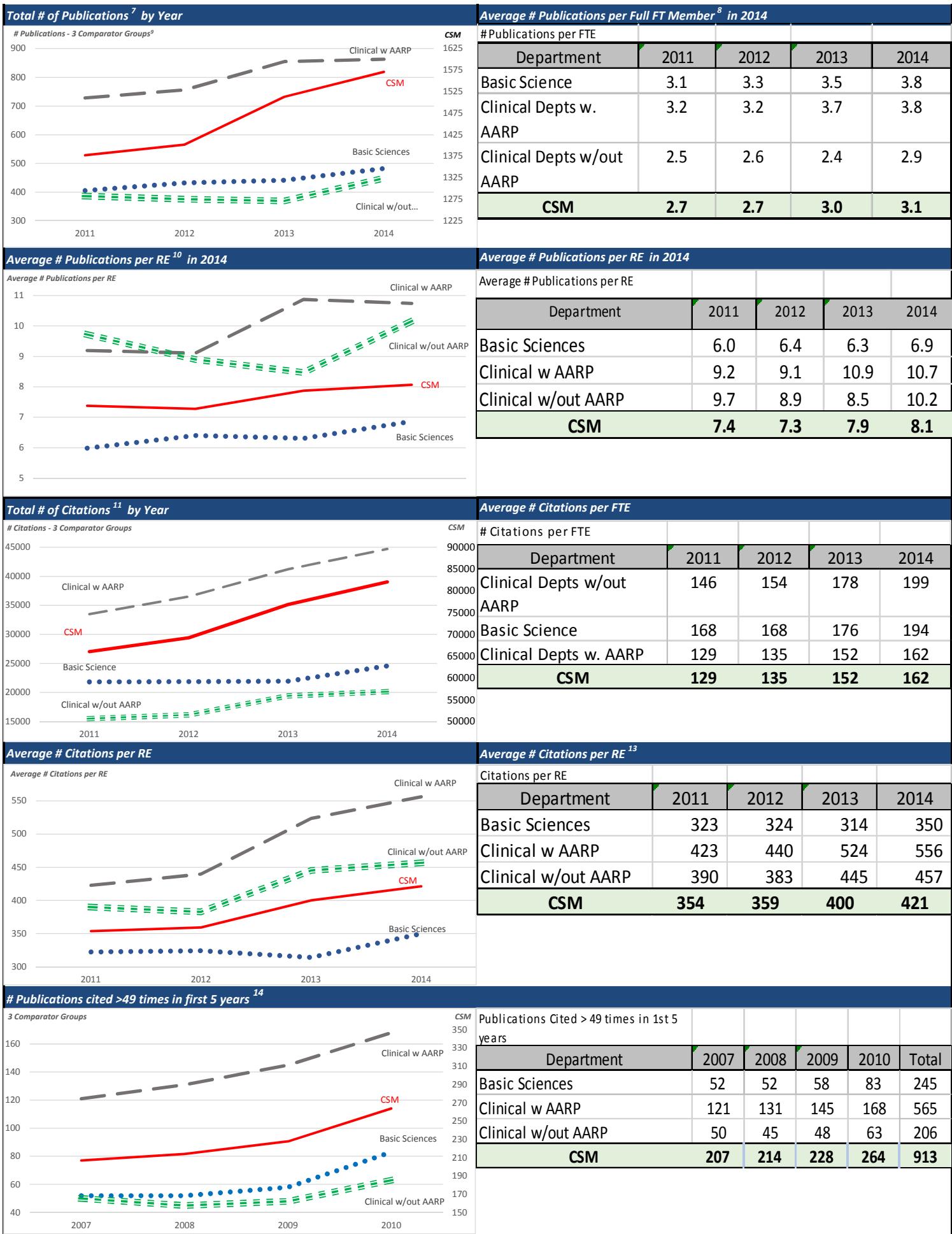
# Notes

Term	Description	Source of data
1. Year 2014-15	<p><i>Primary dates of measurement for 2014-15 reporting are:</i></p> <ul style="list-style-type: none"> <li>- 31 Dec 2014: FT for CSM;</li> <li>- Sept 2015: Membership;</li> <li>- Apr 2014: Space Allotment.</li> </ul> <p><i>Primary periods of measurement for 2014-15 reporting are:</i></p> <ul style="list-style-type: none"> <li>- 1 Jan-31 Dec 2014: Publications, Citations;</li> <li>- 1 Apr 2014-31 Mar 2015: Revenue;</li> <li>- 1 Jul 2013-30 Jun 2014: Activity Profile, Research Equivalent.</li> <li>- 1 Jul 2014 - 30 Jun 2015: Graduate Student Supervision.</li> </ul> <p><b>Note :</b></p> <ol style="list-style-type: none"> <li>1) The ARO (Academic Report Online) time allocation data - used to calculate the Activity Profile/Research Equivalents - was not yet available for the academic year 2014-2015, hence the 2013-2014 time allocation data is used in this report. This data is, however, adjusted to match the current Institute membership list.</li> <li>2) Due to renovations in parts of our infrastructure, the 2015 Space Allotment would give an incorrect number. Hence, the 2014 data is used.</li> </ol>	
2. Full Members	Full Members with current primary academic appointment at CSM.	Academic appointment information from Dean's Database; Membership Lists from Institutes sent to Office of Faculty Analysis (OFA)
3. Research Equivalent (RE)	<p>Sum of %Time for Research (as reported in ARO) / 100.</p> <p><b>Note :</b> To account for Institute members with no time allocations reported in the ARO, we have made the following adjustments:</p> <ul style="list-style-type: none"> <li>- <b>Full Members RE</b> : 20% of the 2014-15 ACHRI Full Members have blank time allocations - for those, we have assigned the average time of research based on the other (non-blank) ACHRI Full Members. [Similar adjustments have been made for 2012-13 and 2013-14]</li> <li>- <b>Full FT Members RE</b> : 6% of the 2014-15 ACHRI Full FT Members have blank time allocations - for those, we have assigned the average time of research based on the other (non-blank) ACHRI Full FT Members.</li> </ul>	Academic Report Online
4. Full FT Members	For <b>Institutes</b> - Full Member with current primary academic appointment with CSM in the ranks of Professor, Associate Professor or Assistant Professor.	For Institutes - Membership Lists from Institutes sent to Office of Faculty Analysis (OFA); Academic appointment information and ranks from Dean's Database
	For <b>CSM</b> - Full-time Academic Staff with ranks of Professor, Associate Professor or Assistant Professor.	For CSM - Fact Books published by Office of Institutional Analysis, University of Calgary
5. Research Revenue	Defined according to AFMC guidelines.	Enterprise Reporting\Research & Trust Accounting datamart
6. CIHR Revenue	Research revenue (see Note 5) received from CIHR.	Enterprise Reporting\Research & Trust Accounting datamart
7. Clinical Research Revenue	<p>Research revenue (see Note 4) with Purpose of Funds Desc = "Clinical Research".</p> <p><b>Note :</b> in previous annual reports, this category also included projects that had a Purpose of Funds Desc = "Clinical Trials". These "Clinical Trials" are now converted into "Clinical Research" in the Enterprise Reporting system.</p>	Enterprise Reporting\Research & Trust Accounting datamart
8. Total # of Publications	<p>Only publications of Document Types "Article", "Review", "Editorial", "Case Report", "Clinical Trial" and "Book" are included;</p> <p>This is the total number of publications in 2014 for each Institute/CSM. For publications co-authored by more than 1 Full FT or FT, they will be counted only once within the same Institute or CSM.</p>	Web of Science; - CV from Authors sent to Office of Faculty Analysis (OFA) in 2014 and 2015
9. Average # Publications per RE	= Total # of Publications (see Note 8) / RE (see Note 3) of Full FT Members	See Source 8
10. Total # of Citations	Total citations in a year for all unique publications by 2014 FTE members	See Source 8
11. Publications cited > 49 first 5 years	Unique publications cited > 49 in the first 5 years of 5 year publication date window (ie: For 2010, Sum of unique publications published in 5 year window 2010-14 with citation counts in years 2010-14 greater than 49)	See Source 8
12. Productivity among Full FT Members	All calculations for charts in this section are using the Total # of Publications for each Full FT Member. For example, 3 Full FT Members in same Institute co-authored an article, this article will be counted for all 3 members and thus will be counted as 3 in the Institute/CSM total.	See Source 8
13. Space Allotment	Total space assigned to Institute in Sq M.	Archibus
<p>* For bibliometrics, we only track Full FT Members. For all other report categories, we track Full Members.</p> <p>** Duplicates have been removed to account for Full Members of multiple Institutes:</p> <ul style="list-style-type: none"> <li>-Full Members of multiple Institutes are counted only once for the 'Total - CSM Institutes' # of Full Members</li> <li>-Research Revenue assigned to Full Members of multiple Institutes is counted only once for the 'Total - CSM Institutes' Research Revenue</li> <li>-Publications from Full Members of multiple Institutes are counted only once for the 'Total - CSM Institutes' # of Publications.</li> </ul>		

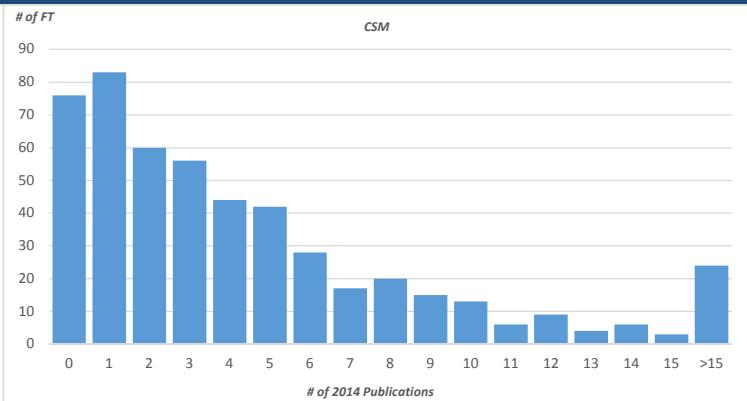
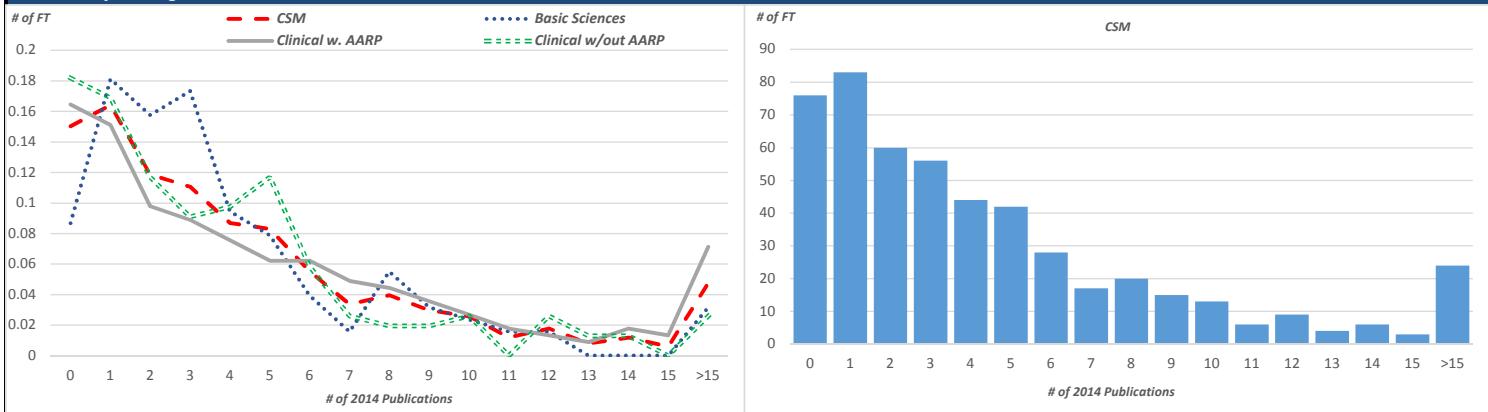
# Annual Report 2014-15 - Cumming School of Medicine

Year	2012-13	2013-14	2014-15 <sup>1</sup>		Prepared by OFA - November 2015
<b>FTE of Professors, Associate Professors and Assistant Professors</b>	<b>CSM</b>				<b>Activity Profile</b>
FTE <sup>2</sup>	513.8	507.6	506.1		
Research Equivalents ( <i>RE</i> ) <sup>3</sup>	195.11	192.19	193.99		
FTE Research Equivalents	129.8 68.65	125.8 68.50	126.3 68.51		
FTE Research Equivalents	237 83.64	228.8 79.19	224.8 79.50		
FTE Research Equivalents	147 42.82	153 44.50	155 45.98		
<b>Research Revenue (\$ in million)</b>	<b>CSM</b>				
Total Research Revenue <sup>4</sup>	168.04	158.58	172.71		
	per RE	0.86	0.83	0.89	
Total Research Revenue	per RE	47.25 0.69	48.28 0.70	45.75 0.67	
Total Research Revenue	per RE	49.47 0.59	53.92 0.68	54.43 0.68	
Total Research Revenue	per RE	22.85 0.53	27.24 0.61	25.88 0.56	
Total Research Revenue		48.47	29.14	46.65	
	<b>CSM</b>				
CIHR Revenue <sup>5</sup>	25.24	26.31	28.21		
	per RE	0.13	0.14	0.15	
CIHR Revenue	per RE	16.04 0.23	15.35 0.22	15.27 0.22	
CIHR Revenue	per RE	6.99 0.08	7.12 0.09	10.50 0.13	
CIHR Revenue	per RE	1.89 0.04	1.62 0.04	2.44 0.05	
CIHR Revenue		0.32	2.22	/	
	<b>CSM</b>				
Clinical Research Revenue <sup>6</sup>	12.05	14.36	14.77		
	per RE	0.06	0.07	0.08	
Clinical Research Revenue	per RE	0.09 0.00	0.22 0.00	0.03 0.00	
Clinical Research Revenue	per RE	10.10 0.12	11.31 0.14	12.31 0.15	
Clinical Research Revenue	per RE	1.83 0.04	2.84 0.06	2.42 0.05	
Clinical Research Revenue		0.04	/	/	
<b>NSERC Discovery Grant</b>	Nov 2012	Nov 2013	Nov 2014	<b>Success Rate</b>	
# of applications	24	22	36	■ CSM	
	<b>Success Rate</b>			42%      57%      44%	
Success Rate	42%	57%	44%	2012-13      2013-14      2014-15	
<b>CIHR Open Operating Grant</b>	Sep 2012 & Mar 2013	Sep 2013 & Mar 2014	Mar 2015	<b>Success Rate</b>	
# of applications	139	166	87	■ CSM	
	<b>Success Rate</b>			22%      14%      22%	
Success Rate	22%	14%	22%	2012-13      2013-14      2014-15	





### Productivity among Full FT Members in 2014<sup>15</sup> - CSM



Year	2012-13	2013-14	2014-15 <sup>1</sup>	
<b>Teaching</b>	<b># of students</b>			
Graduate Student Enrolment (Fall 2012/2013/2014) <sup>16</sup>	506	492	483	
Master's	274	258	237	
Doctorate	230	230	246	
Total per RE	2.59	2.56	2.49	
<b>Graduate Student Enrolment</b>				
	Master's	Doctorate		
2012-13	270	220		
2013-14	260	220		
2014-15	240	240		

# Notes

Term	Description	Source of data
1. Year 2014-15	<p><i>Primary dates of measurement for 2014-15 reporting are:</i></p> <ul style="list-style-type: none"> <li>- 31 Dec 2014: FTE</li> </ul> <p><i>Primary periods of measurement for 2014-15 reporting are:</i></p> <ul style="list-style-type: none"> <li>- 1 Jan-31 Dec 2014: Publications, Citations;</li> <li>- 1 Apr 2014-31 Mar 2015: Revenue;</li> <li>- 1 Jul 2013-30 Jun 2014: Activity Profile, Research Equivalent.</li> <li>- December 2014: Graduate Student Enrolment.</li> </ul> <p><i>Note : the ARO (Academic Report Online) time allocation data - used to calculate the Activity Profile/Research Equivalents - was not yet available for the academic year 2014-2015, hence the 2013-2014 time allocation data is used in this report. This data is, however, adjusted to match the current CSM FTE list.</i></p>	
2. FTE	<i>Full Time Equivalent of Full-time Academic Staff with Ranks of Professor, Associate Professor or Assistant Professor.</i>	<i>Human Resources [this data is also used in the Fact Books published by the Office of Institutional Analysis, University of Calgary]</i> <i>Note : the data is updated to include Senior Leadership roles (e.g. AVP Research).</i>
3. Research Equivalent (RE)	<p><i>Sum of %Time for Research (as reported in ARO) / 100.</i></p> <p><i>Note : To account for CSM Academic Staff members with no time allocations reported in the ARO (= 3 % the total 2014-15 CSM FTE count), we have assigned to those blank members the (department-level) average time of research based on the other (non-blank) CSM Academic Staff members. [Similar adjustments have been made for 2012-13 and 2013-14]</i></p>	<i>Academic Report Online</i>
4. Research Revenue	<i>Defined according to AFMC guidelines.</i>	<i>Enterprise Reporting\Research &amp; Trust Accounting datamart</i>
5. CIHR Revenue	<i>Research revenue (see Note 5) received from CIHR.</i>	<i>Enterprise Reporting\Research &amp; Trust Accounting datamart</i>
6. Clinical Research Revenue	<p><i>Research revenue (see Note 4) with Purpose of Funds Desc = "Clinical Research".</i></p> <p><i>Note : in previous annual reports, this category also included projects that had a Purpose of Funds Desc = "Clinical Trials". These "Clinical Trials" are now converted into "Clinical Research" in the Enterprise Reporting system.</i></p>	<i>Enterprise Reporting\Research &amp; Trust Accounting datamart</i>
7. Total # of Publications	<i>Only publications of Document Types "Article", "Review", "Editorial", "Case Report", "Clinical Trial" and "Book" are included; This is the total number of publications in 2014 for each Institute/CSM. For publications co-authored by more than 1 Full FT or FT, they will be counted only once within the same Institute or CSM.</i>	<i>Web of Science;</i> <i>- CV from Authors sent to Office of Faculty Analysis (OFA) in 2014 and 2015</i>
8. Average # Publications per Full FT Member	$= \text{Total # of Publications (see Note 8)} / \# \text{ of Full FT Members (see Note 4)}$	<i>See Source 8</i>
9. Average # Publications per RE	$= \text{Total # of Publications (see Note 8)} / \text{RE (see Note 3)} \text{ of Full FT Members}$	<i>See Source 8</i>
9.3 3 Comparator Groups	<p>1) Basic Sciences  <ul style="list-style-type: none"> <li>- Biochemistry,</li> <li>- Cell Biology &amp; Anatomy,</li> <li>- Community Health Sciences,</li> <li>- Microbiology Immunology &amp; Infectious Diseases,</li> <li>- Physiology &amp; Pharmacology</li> </ul> <p>2) Clinical with AARP  <ul style="list-style-type: none"> <li>- Cardiac Science</li> <li>- Clinical Neuroscience</li> <li>- Family Medicine</li> <li>- Medicine</li> <li>- Paediatrics</li> </ul> <p>3) Clinical without AARP  <ul style="list-style-type: none"> <li>- Anaesthesia</li> <li>- Critical Care Medicine</li> <li>- Emergency Medicine</li> <li>- Medical Genetics</li> <li>- Obstetrics &amp; Gynaecology</li> <li>- Oncology</li> <li>- Pathology &amp; Laboratory Medicine</li> <li>- Psychiatry</li> <li>- Radiology</li> <li>- Surgery</li> </ul> </p> </p></p>	<i>See Source 8</i>
10. Average # Publications per RE	$= \text{Total # of Publications (see Note 8)} / \text{RE (see Note 3)} \text{ of Full FT Members}$	<i>See Source 8</i>
11. Total # of Citations	<i>Total citations in a year for all unique publications by 2014 FTE members</i>	<i>See Source 8</i>
12 Average # Citations per Full FT Member	$= \text{Total # of Citations (see Note 11)} \text{ divided by } \# \text{ of Full FT Members (see Note 4)}$	<i>See Source 8</i>
13. Average # Citations per RE	$= \text{Total # of Citations (see Note 11)} \text{ divided by } \text{RE (see Note 3)} \text{ of Full FT Members}$	<i>See Source 8</i>

14. Publications cited > 49 first 5 years	Unique publications cited > 49 in the first 5 years of 5 year publication date window (ie: For 2010, Sum of unique publications published in 5 year window 2010-14 with citation counts in years 2010 -14 greater than 49)	See Source 8
15. Productivity among Full FT Members	All calculations for charts in this section are using the Total # of Publications for each Full FT Member. For example, 3 Full FT Members in same Institute co-authored an article, this article will be counted for all 3 members and thus will be counted as 3 in the Institute/CSM total.	See Source 8
16. Graduate Student Enrolment	Number of Graduate Students (Full-Time and Part-Time), categorized in separate totals for Master's and PhD. The overall total number of Graduate Students for CSM includes exchange, visiting and undeclared students that cannot be categorized into Master's or Doctorate.	Fact Books published by the Office of Institutional Analysis, University of Calgary.

## **Appendix 7: ACHRI Recruitment Priorities by Theme**

### **1. Genes, Development and Health Theme**

The Genes, Development and Health Theme has identified recruitments that would fill gaps in expertise and improve research performance and productivity. They are listed below and have common areas of collaborative alignment:

#### **i. Epigenetics**

While significant investments in the genomics infrastructure and informatics expertise have helped the CSM establish its center for health genomics and informatics, we lack significant expertise in the area of epigenetics. The influence/s of environmental/epigenetic factors on our genome are paramount, and these range from *in utero* maternal factors to an individual's microbiome. The emerging science of epigenetics opens the doors to a better understanding of the interactions between an individual's genes and its environment including the effects on gene expression with long-term influence on the health of the current and future generations. Emerging evidence continues to implicate epigenetic modifications to DNA and chromatin, as a significant risk factor for the development of chronic diseases and provide a mechanistic link between the observed association of environmental exposures, life experiences including physical and emotional stress with adverse health outcomes. The recruitment of epigenetics expertise is critical for the CSM to establish a comprehensive precision health genomics strategy; it will also help ACHRI and CSM researchers align with emerging provincial epigenetics network.

#### **ii. Gene editing technologies for investigating, modelling and treating human disease**

While an individual's genetic screening may help identify perturbed genes, "disruptive" technologies and approaches must be explored either to silence the abnormal gene/s or to modify their code manifesting the disease. Gene editing (TALEN and CRISPR) may be this decade's most revolutionary biomedical technology. The technique allows precise editing of specific DNA sequences in model organisms or cell lines (including induced pluripotent stem cells). Gene editing technology is currently being used in research applications to introduce specific mutations; however, it has potential to be applied to treat genetic disorders and provides the potential to provide unique precision therapies. The recruit will perform deep phenotyping of disease models and mechanistic analysis of genetic networks underlying human disorders. Emphasis will be on understanding the global genomic and epigenetic phenomena and the development and testing of preclinical therapies.

#### **iii. Complex traits genomics**

The inheritance of simple monogenic disorders (dominant or recessive) is well understood. However, most chronic diseases are the result of complex, multifactorial genetic, environmental and gene-environmental (epigenetic) interactions. The CSM lacks expertise in the area of genetics whereby multiple gene-gene and gene-epigenetics factors are studied in the context of complex genetic disorders. A scientist with such expertise would utilize network and other analytic modalities to characterize the genetic/"-omic" factors contributing to chronic disease and the potential for targeted interventions with the potential to modify disease course.

#### **iv. Pharmaco-genomics**

The efficacy of medications and vaccines is contingent upon myriad factors (such as genetics, epigenetics, microbiome etc.) – each of which likely influences and impacts personalized treatment regime. Moreover, it is now well established that exposure to inhalation anaesthetics, pain management medications etc. during early life and also in old age may render brain susceptible to learning, memory and cognitive deficit. Similarly, exposure to

radiation and chemotherapeutics given to cancer patients impacts their cardiac genomics thereby increasing the incidence of heart failure. Approximately 7% of FDA approved medications are affected by actionable inherited pharmacogenes, and approximately 18% of US outpatient prescriptions are affected by actionable germline pharmacogenomics. A translational scientist in this field would collaborate with clinician scientists to design patient centre and personalized drug therapy.

**v. Bioinformatics**

All OMICS platforms, imaging and best clinical practices benefit from large cohort studies that invoke population data collected from large sample sizes. A specialist in genomic and metabolomic informatics will develop approaches/techniques to analyse, visualize and interpret “omic” data. This recruit will collaborate with clinical informaticians to link and enable integrated analytics for large prospective cohort studies and clinical trials. This position will recruit an independent investigator who will develop and integrate multiple large databases (clinical, imaging, genomic and metadata) and will permit exploration of complex, multi-factorial influences and interaction between genes and the environment, including medical care and the social determinants of neurodevelopmental health.

**vi. Cellular reprogramming/ human induced Pluripotent stem cells**

A major roadblock in treating patients with dysfunctional tissues/organs is the lack of readily available tissue sources for effective tissue regeneration and transplantation. With the advent of organ regeneration and cellular reprogramming strategies, as well as advances in tissue bioengineering, future treatment paradigms will one day be achievable for disorders not treatable by drugs. These cellular reprogramming strategies are in their infancy and may not lead to immediate therapeutic interventions; however, any future precision medicine strategy will fail if we do not position ourselves immediately to recruit an expertise in the area of tissue engineering. There exists considerable capacity both at the CSM (also U of A) and also in the Biomedical Engineering (BME) group to generate cells, tissues and organs by exploring and exploiting tissue engineering technologies and expertise. We seek a basic scientist using *genome editing strategies* with induced pluripotent stem cells (iPSC) in human and/or model organism cells.

**vii. Fetal/maternal/environmental interactions**

We seek a scientist taking genomic/genetic approaches in a model system to understand epigenetic and/or metabolic prenatal programming from a genetic and gene-environment interaction standpoint. This will support initiatives in Alberta to reduce pre-term birth and worldwide interest in developmental origins of chronic disease.

**viii. Developmental Neurogenomics**

We seek a scientist working in a model organism to perform deep phenotyping of disease models and mechanistic analysis of genetic networks underlying human neurodevelopmental disorders including autism and epilepsy. Emphasis will be on understanding the global genomic and epigenetic phenomena associated with the disease states. Individuals working in either vertebrate or invertebrate systems would be appropriate. This would be part of a collaborative bench to bedside research initiative in precision medicine and neurodevelopment, which is broadly inclusive of genomics, informatics, inflammation, immunology and the enteric micro biome.

**Proposed UCalgary Theme Alignment:** Brain and Mental Health, IICD enteric micro-biome initiative.

**Proposed Departmental Partners:** Biochemistry and Molecular Biology, Cell Biology and Anatomy Clinical Neurosciences, Medical Genetics, Paediatrics, Psychiatry, Radiology, Physiology and Pharmacology

**Proposed Institute Partners:** ACCI, HBI, Snyder Institute, OIPH

**Space Implications:** Office and wet laboratory space within ACHRI or collaborating institute if appropriate.

**Proposed Program Collaborations:** KidOomics, MORPH, Enteric Microbiome

**Proposed Platform Collaborations:** CSM Center for Health Genomics and Informatics, CRU, Child and Adolescent Imaging Research Program

## **2. Behaviour and the Developing Brain Theme**

### **i. Lab-based epilepsy researcher**

Epilepsy is a common neurological condition, affecting approximately 1% of the general population. Despite the advent of many new anti-seizure drugs over the past 20 years, the proportion of patients who fail to respond adequately to medications has remained unchanged. Approximately 30-40% of patients with epilepsy continue to experience unremitting spontaneous seizure activity and attendant cognitive, behavioral and mental health problems. In the pediatric population, epilepsy represents one of the three most common disorders encountered in clinical practice. Importantly, the vast majority of medications used in infants and children were developed without due consideration of the intrinsic complexities and uniqueness of the maturing brain, and hence available drugs are used “off-label”. It is unclear whether existing pharmacological agents can be improved upon for pediatric patients. Further, the long-term safety of such medications is not entirely clear. The pediatric epilepsy research group has pursued an alternative approach based on the notion that neurometabolic targets might yield better efficacy and tolerability than conventional anti-seizure drugs. Our goal has been to grow basic metabolism-based research in a manner that helps us achieve a greater critical number of investigators.

The recruitment of a PhD basic scientist with an interest in the molecular biology, cell signalling and/or metabolomics of epilepsy would considerably strengthen the ACHRI – HBI partnership around epilepsy research and enhance the existing basic science program investigating the metabolic basis of epilepsy and new pharmacological and non-pharmacological treatments for epilepsy. The successful recruit would develop a research program exploring the links between cellular signaling pathways, ion channels and cellular membrane-bound ion channels, and their interactions with biochemical pathways and especially mitochondrial homeostasis. At present, there is no full-time faculty-level PhD research scientist within ACHRI having a focus on pediatric epilepsy. The addition of a PhD basic epilepsy researcher will complement the small core group of wet lab epilepsy researchers housed in the HBI, and enhance synergies amongst multiple faculties, departments and institutes.

**Proposed UCalgary Theme Alignment:** Brain and Mental Health

**Proposed Departmental Partners:** Biochemistry and Molecular Biology, Cell Biology and Anatomy, Clinical Neurosciences, Medical Genetics, Paediatrics, Physiology and Pharmacology

**Proposed Institute Partners:** HBI

**Space Implications:** Office and wet laboratory space within existing ACHRI footprint (or collaborating Institutes if appropriate).

**Proposed Program Collaborations:** KidOmics, MORPH, Enteric Microbiome

**Proposed Platform Collaborations:** Zebrafish drug screening platform

### **ii. PhD epilepsy health sciences researcher**

During the past three years, efforts related to clinical research have expanded significantly in several ways with the creation of the Children’s Comprehensive Epilepsy Centre (CCEC) at Alberta Children’s Hospital. We are now active collaborators in several trans-Canadian research projects including: Genome Canada, Pediatric Epilepsy Surgery Quality of Life, Electrical Status Epilepticus in Sleep Neuropsychological Consequences. In addition, we are a key part of a Brain Canada award to Dr. Deborah Kurasch at the University of Calgary. The major effort initiated from within the CCEC is the Pediatric Epilepsy Outcomes Informatics Project. The progress to date has included creation of multiple care pathways of standardized care laying the foundation for Quality Improvement-based studies. Thus far since early 2015, there has been robust data entry and analysis for over 1,000 children with epilepsy.

Using the outcomes-based informatics framework described above, we are now poised to initiate a series of unique clinical, translational, genetic and healthcare resources directed studies. In order to build upon what has already been created, a PhD level clinical research scientist is required. The ideal background would include either health resources-related or clinical trials as our program is focused on improving clinical outcomes and optimizing the expenditure of health resources. This person would add another expertise to that already present within ACHRI and will use existing resources in informatics, biostatistics and epidemiology. It is anticipated that this team would be very successful in securing extramural research funding to cover the costs of program personnel and other needs.

**Proposed UCalgary Theme Alignment:** Brain and Mental Health; Clinical, Health Services and Population Health Research

**Proposed Departmental Partners:** Clinical Neurosciences, Community Health Sciences, Medical Genetics,

**Proposed Institute Partners:** HBI, OIPH

**Space Implications:** Office space and dry lab within ACHRI

**Proposed Program Collaborations:** HBI Epilepsy Neuroteam, ACHRI Healthy Outcomes Theme

**Proposed Platform Collaborations:** Zebrafish drug screening platform

### iii. Academic pediatric neuropsychologist - neurodevelopmental and behavioral outcomes

Within the Behaviour and the Developing Brain Theme Group, there is a clear and present need for an academic pediatric neuropsychologist who has a research interest in studying cognitive and behavioural outcomes of neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). This need is all the more urgent given the recent transitions and imminent retirement(s) of investigators in the former ACH Behavioural Research Unit, now integrated under the larger campus-wide umbrella of the Owerko Centre on Neurodevelopment and Child Mental Health. This important recruitment is aimed at filling this gap in pediatric neuropsychology. The successful candidate for this position will contribute to the Owerko Centre's fundamental/translational research efforts to understand how indicators of early adversity and signs of distress influence mental health and developmental outcomes in children and youth. The translational aspect will emerge when modifiable risk factors are well understood. The primary developmental outcomes encompass learning, behavioural and emotional problems in children that are precursors to social, academic, occupational, and mental health problems in adolescence and later life. To permit exploration of these topics, expertise in a variety of behavioural/social indicators and possible biomarkers will be targeted. Examples of behavioural/social indicators include attachment and social support, and biomarkers may include measures of hypothalamic-pituitary-adrenal (HPA) axis function such as cortisol, which indicates physiological responsiveness to stress, and cytokine indices of inflammatory processes, known to be associated with both diet and with mental health vulnerabilities.

The new skills this recruitment will bring to the study of modifiable risk factors related to childhood adversity will significantly advance our understanding of important aspects of child development and mental health. This is a natural extension of existing academic strengths in child health, neurosciences, psychosocial modifiers, brain imaging and bioinformatics. There is much potential for interaction with other investigators with expertise in metabolomics and genomics that will be complementary and translational from a therapeutic, mechanistic and diagnostic perspective. The individual who fills this position will provide invaluable research expertise that is required to fully supplement the broad activities taking place in the study of child neurodevelopment at the University of Calgary.

**Proposed UCalgary Theme Alignment:** Brain and Mental Health

**Proposed Departmental Partners:** Paediatrics, Psychology, Education, Social Work, Nursing

**Proposed Institute Partners:** HBI

**Space Implications:** Office and dry lab space in the Owerko Centre at ACHRI

**Proposed Program Collaborations:** KidOmics, Enteric Microbiome, Integrated NDD, ABCD

**Proposed Platform Collaborations:** CAIR, NCC BioCORE, ACHRI Bioinformatics and Genomics Core

- iv. **Clinical bio-informatics shared with Healthy Outcomes recruitment priority #ii.**
- v. **Lab-based neurotrauma researcher (PhD)**

Pediatric brain injury encompasses a wide range of etiologies, including the broad categories of trauma, stroke, infection and systemic illness. Similarly, within each etiology the injury severity ranges from severe, life-limiting to mild, with no obvious consequences. Regardless of the severity of the primary injury, brain injuries can lead to long-lasting adverse effects, including neurological, mental and physical disabilities. The ultimate goal of the brain injury research program in the Behavior and the Developing Brain Theme Group is to improve outcomes for these children through clinical and translational research. Due to successful, targeted recruitments, both ACH and ACHRI now have a wealth of expertise in the spectrum of pediatric brain injury with internationally recognized clinical experts and research programs in TBI, stroke and neuroinflammation. There are currently multiple areas of research excellence – including the Alberta Children's Hospital TBI and Complex Concussion Research Program, the university-wide Integrated Concussion Research Program (ICRP), the Pediatric Neurocritical Care (NCC) and Translational Research Program, the Sport Injury Prevention Research Centre (SIPRC) in Kinesiology, the Calgary Pediatric Stroke Program (CPSP) and the Pediatric Transcranial Magnetic Stimulation (TMS) Laboratory at ACH, Child and Adolescent Imaging Research Program (CAIR) under ACHRI. However, one area that is currently in need of future growth is in the realm of basic science neurotrauma research, specifically a dearth of principal investigators focused on moderate-to-severe brain injury in animal models. Translational concussion research has already been developed in the ACHRI web lab footprint, but the biology and therapeutic implications of more serious forms of neurotrauma have yet to be addressed. Parenthetically, none of the other research institutes within the Cumming School of Medicine or other university stakeholders in this area have or are planning to develop such a research program. Hence, there is both a need and an opportunity that can be filled by ACHRI.

The ideal candidate for this faculty-level position would be a junior-to-mid level laboratory investigator who has expertise in various models of moderate-to-severe TBI such as controlled cortical impact (CCI), fluid percussion, and weight drop paradigms. Further, the desired individual would have a basic neurobiological emphasis on brain metabolism, epigenetics, and/or neuroinflammation to best integrate with existing research priorities and expertise within the Theme Group and more broadly through the University of Calgary. And finally, there should be a clear translational framework designed to exploit the basic neurobiology of TBI using innovative, high-throughput screening methods to uncover novel interventions to prevent or mitigate the long-term adverse consequences of TBI. The experimental therapeutics component of this research program should also be broadly defined to include not only investigational compounds with known molecular targets and repurposing of FDA- and Health Canada-approved medications, but also metabolism - and neuroinflammation-based treatments where there is already great expertise and research infrastructure.

**Proposed UCalgary Theme Alignment:** Brain and Mental Health

**Proposed Departmental Partners:** Biochemistry and Molecular Biology, Cell Biology and Anatomy, Clinical Neurosciences, Paediatrics, Physiology and Pharmacology

**Proposed Institute Partners:** HBI and Snyder Institute

**Space Implications:** Office and wet laboratory space within ACHRI

**Proposed Program Collaborations:** NCC, Integrated Concussion Research Program, KidOmics, MORPH, Enteric Microbiome

**Proposed Platform Collaborations:** NCC BioCORE, Seaman Centre Animal Imaging Facility, Zebrafish drug screening platform

- vi. **Neuroimmunologist**

The recruitment to and activation of immune cells in the brain defines certain devastating neurological conditions, notably multiple sclerosis and there is evidence that inflammation also plays a role in certain neurodevelopmental disorders, traumatic brain injury and epilepsy. There is increasing recognition that immunological mechanisms may

play a role in some psychiatric conditions. The recruitment of a Neuroimmunologist with expertise in live cell imaging will greatly strengthen many of the programs across the CSM. The Neuroimmunologist will play a major role in the proposed CSM Centre for Advanced Optical Imaging, being organized as a CSM-wide partnership, led by the Snyder Institute and HBI. It supports microscopy as an identified recruitment priority and CSM platform.

**Proposed UCalgary Theme Alignment:** Brain and Mental Health; Infection, Inflammation and Chronic Disease

**Proposed Departmental Partners:** Clinical Neurosciences, Cell Biology and Anatomy, Physiology and Pharmacology

**Proposed Institute Partners:** HBI, Snyder

**Space Implications:** Laboratory and office space is available using existing space across HBI, Snyder and the ACHRI footprints.

### **3. Healthy Outcomes Theme**

The Healthy Outcomes theme's broad goals are to use child and family-centred, discovery and outcomes research techniques to improve clinical practice in acute and chronic child health care. We believe a solid methodologic research foundation and infrastructure will catalyze a broad range of collaborative research within child and maternal health and best promote achievement of our goals. Our methodologic interests have significant overlap with those of the O'Brien Institute of Public Health, there is extensive collaboration, joint membership and shared perception of common recruitment needs.

The Healthy Outcomes theme has identified the six recruitments that follow which would fill gaps in expertise and enhance research performance and productivity. Those identified with an “\*” were independently prioritized by the O'Brien Institute of Public Health (OIPH) as recruitments that would benefit CSM and the emerging Eyes High Clinic/Health Services and Population Health Research Strategy of the U of C. All are supported by the Department of Paediatrics. The Departments of Paediatrics and Community Health Sciences would be the academic home for recruitments 1-5 while recruit #6 would reside in a shared appointment with Paediatrics and Emergency Medicine under the newly established Section of Clinical Pharmacology and Toxicology.

#### **i. \*Patient and Family Centred Outcomes Research Methodologist:**

The spectrum of our current research initiatives includes: health promotion, injury and chronic disease prevention, diagnostic and therapeutic approaches to acute and chronic diseases, and rehabilitation practices. The development and evaluation of preventive and therapeutic interventions, targeting specific populations, has significant potential to improve child and family health, well-being and quality of life. Our ultimate aim is to ensure that the right patient receives the right clinical intervention at the right time, ultimately leading to better health outcomes. Our goals align fully with CIHR's vision which claims that patient-oriented research is the cornerstone of evidence-informed health care. The vision of CIHR's Strategy for Patient-Oriented Research is to demonstrably improve health outcomes and enhance patients' health care experience through the integration of evidence at all levels in the health care system. These goals are currently being integrated into the proposed U of C Clinical Research Strategy. A focus on pediatrics is essential as examining patient and family centred outcomes for children and their families is fundamentally different than for adults. Working with this group requires different consent protocols, data collection and analytic techniques.

A PhD methodologist with expertise in patient centred outcome metrics would provide benefits across research groups, institutes, and faculties. There is a movement within funding agencies such as CIHR, to focus on patient rather than health system outcome measures. Moreover, the SPOR strategy has identified the importance of having patients (an overarching term inclusive of individuals with personal experience of a health issue and informal caregivers, including family and friends), researchers, health care providers and decision-makers actively collaborate to build a sustainable, accessible and equitable health care system and bring about positive changes in the health of people living in Canada. Engaging patients is thus an integral component in the development and

implementation of CIHR's SPOR strategy. This initiative is directly aligned with our AHS partner's focus on delivering patient and family centred care and the recently established SPOR network here in Alberta.

**Proposed UCalgary Theme Alignment:** Clinical/Health Services and Population Health Research

**Proposed Departmental Partners:** Community Health Sciences, Paediatrics,

**Proposed Institute Partners:** OIPH

**Space Implications:** Office space at ACH/ACHRI or Community Health Sciences

**Proposed Program Collaborations:** W21C, Research Methods Team, The Methods Hub, Community Health Sciences, APPETITE, Pain

**ii. \*Clinical Bioinformatics/Big Data Smart Analytics**

Clinical investigators are increasingly linking their clinical data with emerging biologic data (e.g. microbiome, “-omics”, imaging) and there is a need for CSM to recruit expertise in this field if we are to become nationally and internationally competitive. This expertise is required for clinical research in all organ-systems. Many of our research teams have large bio-repositories of data and specimens which, once analyzed and linked with clinical and administrative data, could lead to significant new discoveries. Examples include the Neurodevelopmental Research team which has compiled data and biological samples from large patients cohorts in order to discover factors contributing the early neurodevelopment; the Neurocritical Care research program which is looking to discover new biomolecular profiles (integrating data from neuroimaging, neurophysiological, as well as molecular markers) to be used for diagnosis and therapeutic monitoring in the intensive care setting. To store, analyze and link this “big data” we need bioinformatics capacity and analytical skills. This expertise will be utilized in clinical research in various areas, consequently the potential partners will vary by specific areas of interest.

**Proposed UCalgary Theme Alignment:** Clinical/Health Services and Population Health Research; Brain and Mental Health, IICD enteric micro-biome initiative

**Proposed Departmental Partners:** Clinical Neurosciences, Community Health Sciences, Critical Care Medicine Paediatrics, Radiology,

**Proposed Institute Partners:** HBI, Snyder Institute, OIPH

**Space Implications:** Office space at ACH, ACHRI, Community Health Sciences

**Proposed Program Collaborations:** ABCD cohort, NDD, NCC, Integrated Concussion Research Program, Clinical Research Unit (CRU)

**Proposed Platform Collaborations:** Genomics-Bioinformatics, Imaging

**iii. \*Health Services Research/ Innovative Models of Care for Chronic Disease**

To truly understand and evaluate the impact of health interventions and changing health care policies, health services researchers with expertise in administrative data are required. Such an individual would have access to some of the most robust and comprehensive data in the world, right here in Alberta. Such an individual could help in priority setting, identifying priority diseases and issues while also improving our capacity to evaluate impact.

**Proposed UCalgary Theme Alignment:** Clinical/Health Services and Population Health Research

**Proposed Departmental Partners:** Paediatrics, Community Health Sciences

**Proposed Institute Partners:** OIPH

**Space Implications:** Office space at ACH, ACHRI, Community Health Sciences

**Proposed Program Collaborations:** Transitions, AHS, DIMR, CRU, Department of Paediatrics. Maternal Newborn Child & Youth SCN, The Methods Hub, World Health Organization Collaborating Centre

**Proposed Platform Collaborations:** Bioinformatics

#### **iv. Health Economist**

The current expanding role and need to incorporate economic analysis into clinical studies and health technology assessment into policy and decision making has clearly demonstrated a need to expand CSM strength in this field. Such expertise would strengthen Genome Canada, CIHR and AIHS PRIHS applications. It is crucial to health system sustainability to have expertise in evaluating the economic costs/benefits of health care practice and policy. In addition, health economists who focus on preference elicitation methodologies contribute quantitative methods to understanding patient and family preferences which provide an important avenue to enabling patient and family centred care.

**Proposed UCalgary Theme Alignment:** Clinical/Health Services and Population Health Research

**Proposed Departmental Partners:** Community Health Sciences, Paediatrics

**Proposed Institute Partners:** OIPH

**Space Implications:** Office space at ACH, ACHRI, Community Health Sciences

**Proposed Program Collaborations:** Community Health Sciences, SCNs, Research Methods Team, Health Technology Assessment Unit, OIPH Health Economics/Health Technology Assessment group, Svare Professor in Health Economics.

#### **v. Implementation & Knowledge Translation Science Lead**

A proven leader with a track record in knowledge translation and implementation science research is needed to aid in integrating the vast amount of knowledge generated locally and nationally/internationally into clinical care and public health practice and policy. By doing so, we will create the science that will guide the integration of optimal policy into clinical care. The focus would be on partnering with existing research teams to design optimal implementation strategies for our local institutes that could then be adopted nationally and internationally thereby positioning CSM at the forefront of knowledge translation science. In addition to generating original science, this role would align with our strategic partners at Alberta Health Services, particularly the Strategic Clinical Networks. The translation of research findings into improvements in quality of life is a key element stressed in the Canadian Academy of Health Sciences report “Making an Impact: A preferred framework and indicators to measure returns on investment in health research”. By recruiting both an implementation scientist and a patient-centred outcomes research methodologist, CSM would be well positioned to demonstrate return on investment and research impact.

**Proposed UCalgary Theme Alignment:** Clinical, Health Services and Population Health Research

**Proposed Departmental Partners:** Paediatrics, Community Health Sciences

**Proposed Institute Partners:** OIPH

**Space Implications:** Office space at ACH, ACHRI, Community Health Sciences

**Proposed Program Collaborations:** Antenatal/Post-natal determinants of health, Injury Prevention and Rehabilitation, Pain, Acute and Life Saving Care

#### **vi. Paediatric Clinical Pharmacologist/ Drug Safety Expert**

Drug safety and optimized therapeutics for children has been identified as a top priority by key leading regulatory agencies (e.g., FDA), professional organizations and policy-makers in North America and Western Europe. Historically, children have been excluded from clinical trials and drug development, in an attempt to protect them from potential harm. Drug prescribing and dosing have been largely extrapolated from adults. This practice violates basic principles of pediatric physiology and ontogeny, and has led to a lack of knowledge on the effectiveness and safety of many medications, resulting in the common practice of administering medications to children ‘off-label’ (i.e., not for the approved clinical indication, age, dose or route of administration). Currently, *50-75% of all medications prescribed in hospitals to children are administered off-label*. This practice puts children at risk of adverse reactions and use of ineffective medications, which ultimately can compromise their health.

An individual with expertise in paediatric pharmacokinetics, pharmacodynamics and pharmacogenomics (“personalized medicine”) research would take drug-related research to the next level at ACH/ACHRI, while complementing the evolving U of C Strategic Plan (Health Research Strategy; led by Dr. Tonelli) and provide important partnership to several of our current research groups and position our institute as a leading site for the expanding field of pediatric drug studies. Such an individual would facilitate and foster new funding opportunities, building relationships with the global pharmaceutical industry, as well as strong support for funding agency applications that involve novel therapies.

Our team, focused on childhood cancers, is a leader in early phase clinical trials and would benefit immediately from the addition of a clinical pharmacologist with expertise in this specific area. Other groups that employ and evaluate novel and expensive biologics (e.g. gastroenterology, rheumatology) would benefit from a clinical pharmacologist. Our teams focusing on drug discovery (e.g. epilepsy, ASD, mitochondrial diseases) are also in need of an expert when new compounds are developed to the stage of early clinical trials. The field of personalized medicine and tailored drug therapy is another important and under-developed area. Other aspects of drug safety, such as the prevention of medication errors are imperative to building a safe clinical environment, clinically, legally and financially and expertise in this realm would align with the requested Implementation & Knowledge Translation Science Lead. In addition, ACHRI is hopeful of securing a position as a KIDSCAN node and we are ideally suited to become a pharmacokinetic/ pharmacodynamic hub of expertise. To achieve these aims, an established clinical pharmacologist is necessary.

**Proposed UCalgary Theme Alignment:** Basic Science/Clinical, Health Services and Population Health

**Proposed Departmental Partners:** Paediatrics, Physiology and Pharmacology

**Proposed Institute Partners:** SACRI

**Space Implications:** Office space at ACH, ACHRI, Community Health Sciences

**Proposed Program Collaborations:** APPETITE, Childhood Cancer Research Program, Translational Epilepsy Program, NDD

## vii. Pediatric Rehabilitation – Biomechanics

The Pediatric Rehabilitation program would greatly benefit from a PhD scientist in Human Movement Biomechanics with expertise in kinetics, kinematics, dual fluoroscopy, electromyography and machine learning who could lead a research program focusing on pediatric rehabilitation and clinical movement assessment in populations with musculoskeletal injury or disease, neuromotor impairment, and/or neurodevelopmental disorders. This individual would provide expertise in biomechanics in clinical populations, facilitate and foster new funding opportunities and play a significant role in graduate teaching and supervision.

**Proposed UCalgary Theme Alignment:** Clinical/Health Services and Population Health Research, Brain and Mental Health

**Proposed Departmental Partners:** Clinical Neurosciences, Paediatrics, Kinesiology

**Proposed Institute Partners:** McCaig Bone and Joint

**Space Implications:** ACH, ACHRI

**Proposed Program Collaborations:** Vi Riddell Rehabilitation Research Program, Integrated NDD Research Program

## viii. Pediatric Rehabilitation - Neuromotor Impairment

We seek a clinician-scientist with expertise in pediatric rehabilitation in clinical populations including cerebral palsy, pediatric stroke, and/or neurodevelopmental disorders. Several ACHRI clinical research programs would benefit from a health sciences PhD with an active Canadian license to practice (e.g., physiotherapist, occupational therapist) who would become a leader in pediatric rehabilitation research and make significant contributions to

ACHRI and the Cumming School of Medicine in graduate training and supervision.

**Proposed UCalgary Theme Alignment:** Clinical/Health Services and Population Health Research, Brain and Mental Health

**Proposed Departmental Partners:** Paediatrics

**Proposed Institute Partners:** HBI

**Space Implications:** ACH, ACHRI

**Proposed Program Collaborations:** Vi Riddell Rehabilitation Research Program, Integrated NDD Research Program, Pediatric Brain Injury Research Program.

## **APPENDIX 8: Comprehensive Review of ACHRI Platforms**

### **1. ACHRI Research Training Platform**

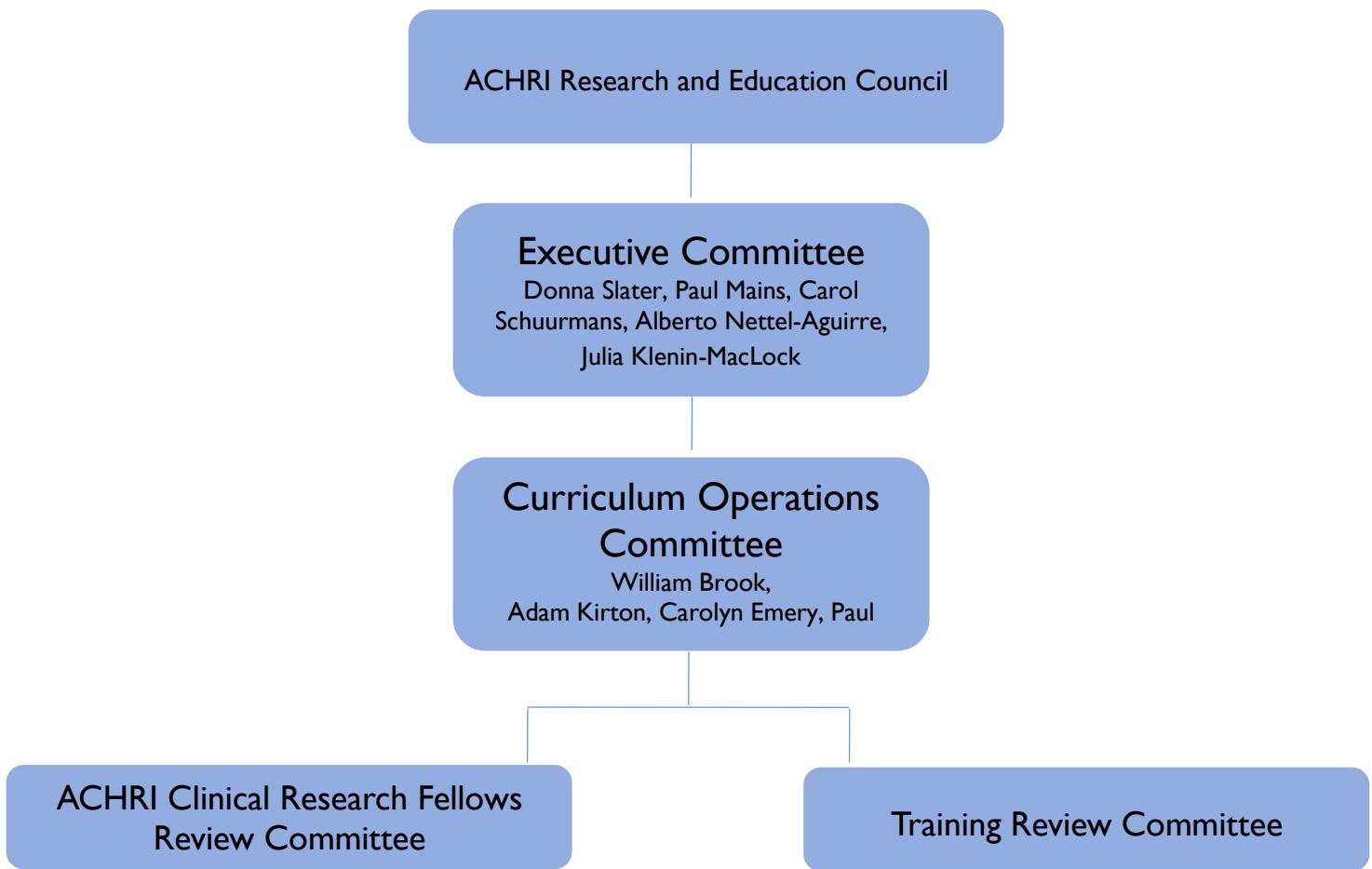
**a) ACHRI Research Training Platform: Historical Background:** The ACHRI Research Training Platform has provided training support on a competitive basis to undergraduate, graduate and postdoctoral scholars as well as medical residents in ACHRI since 2009. The Platform was established following a renewal of the CIHR-STIHR Training Grant in 2009 at \$325,000 per year, awarded to the members of ACHRI's Genes, Development and Health theme, for which ACHRI also received matching funds from the ACH Foundation at \$325,000 per year. Other matching contributions of \$40,000 per year and \$100,000 came from the Faculty of Veterinary Medicine and Faculty of Medicine respectively. This partnership between ACHRI, CIHR Training Grant, Faculties of Medicine and Veterinary Medicine, and the ACH Foundation significantly enhanced the grant's impact on training within the institute. Additionally, with the merge of the two separate ACHRI training initiatives - the ACH Foundation Clinical Research Fellowship Program (which provided additional annual funding at \$300,000) and the CIHR Training Grant – the ACHRI Research Training Platform was established. In the years that followed, ACHRI introduced new, more specialized training support options through additional funding secured by the ACH Foundation: the Talisman Energy Fund program to support trainee research in the areas of injury prevention and obesity at \$100,000 per year; and Dr. D. Grant Gall Traineeship, a joint scholarship in partnership with the Snyder Institute to support innovative and interdisciplinary graduate research in the area of infection, inflammation and immunity within the child health context, at \$20,000 per year. In 2015 CIHR discontinued the STIHR programs nationwide, which prompted ACHRI to increase its annual contribution to training in order to make up the difference of funds to continue this highly successful training initiative for the years to come. Today, the ACHRI Training Program, ACHRI Clinical Research Fellowship Program, Talisman Energy Fund Program, Dr. D. Grant Gall Traineeship, and Veterinary Medicine graduate awards currently comprise the ACHRI Research Training Platform, with a total annual budget of approximately \$1,150,000 per year. The Platform supports all trainees within each of ACHRI's theme structure which includes Genes, Development and Health; Behaviour and the Developing Brain; and Healthy Outcomes, which span the spectrum of research in child and maternal health domains, from basic research in models of simple organisms through translational to clinical and population health science.

To date, we have developed several strong partnerships that have proven to be of value to both our trainees and supervisors. These partnerships and the funding they have secured, have allowed the Platform to provide an enhanced educational and training experience in ACHRI to a wide spectrum of trainees: undergraduate and graduate students and postdoctoral scholars in both basic and clinical research disciplines; medical residents specializing in pediatrics, obstetrics/ gynecology, and genetics; trainees in the Canadian College of Medical Genetics certification program; and pre- and postdoctoral trainees in the highly competitive Canadian Child Health Clinician Scientist Program (CCHCSP). All of our training partners work with our Platform to help enhance educational opportunities and streamline funding options for ACHRI trainees where such opportunities exist. The Platform does not offer specific graduate courses through a formal graduate program (that is the Province-mandated responsibility of the Faculty of Graduate Studies), there are many natural affinities between ACHRI and existing graduate programs. The funding support and the extracurricular training opportunities that the ACHRI Research Training Platform provides to ACHRI trainees enrolled in those graduate programs is instrumental to the success of both ACHRI trainees and researchers. Currently in its seventh year, the Platform offers competitive trainee scholarships; funding support for trainee recruitment, visiting speakers, workshops, research days and symposia; as well as travel funds for national and international meetings and scientific visits and exchanges for ACHRI trainees. Through these initiatives outlined in more detail below, the Platform helps equip ACHRI trainees with the necessary tools to succeed in an increasingly complex medical research environment, thereby creating the next generation of highly skilled health researchers.

**b) Governance and Operations** The ACHRI Research Training Platform is governed by a committee structure that ensures effective operations and transparency. For the first six years after its launch, the Platform was governed by the Program Advisory Committee (PAC), composed of representatives of the Platform partners, whose role was to oversee the overall effectiveness of our training programs, make recommendations for future training, review the budget and make suggestions for its effective use. In an effort to streamline operations of the ACHRI platforms, in 2014 ACHRI established its Research and Education Council (AREC) – a central governing body providing direction and support to ACHRI research, funding, and education endeavors. This committee has replaced the Training Platform’s PAC in its function of supervision and audit of the ACHRI Research Training Platform operations.

Current committees of the ACHRI Research Training Platform include the Executive Committee, the Curriculum and Operations Committee and the Training Review Committee. The Executive Committee meets twice a month and manages the day-to-day activities of the program and addresses issues that require immediate attention. This committee also oversees the budget and is responsible for reviewing and approving the spending of the ACHRI Research Training Platform to ensure that expenditures remain within budget. This committee is comprised of the Program Director, Program Manager and three other members. The Curriculum and Operations Committee is responsible for determining how to allocate funding based on the peer review recommendations and feedback of the Training Review Committee. The Training Review Committee meets once a year (or more often, if needed) to rank student and postdoctoral salary applications. Members of the Training Review Committees rotate on a regular basis, to minimize conflict of interest, ease reviewer burden, and ensure a fair review process. Starting in 2016, we will be adopting a new format, where one review committee will adjudicate both basic and clinical science applications, as well as summer studentship applications. Every application will be evaluated by reviewers with both basic and clinical expertise, after which applications will be ranked for funding, and results will be submitted to the Curriculum and Operations Committee for final funding decisions. This committee considers the budget of the Research Training Platform and has the ability and authority to determine how to effectively allocate available training funds between graduate and post-graduate applications. A separate committee adjudicates the ACHRI Clinical Research Fellowship applications (this program has a separate funding envelope and very specific training requirements). Trainee recruitment and fast track visits (described in more detail below) are reviewed by members of the Executive Committee, who may call upon the expertise of members of the Training Review Committee.

**c) Leadership and Team Membership** Dr. Donna Slater acts as the Education Director of ACHRI, providing leadership and guidance to the ACHRI Research Training Platform, and reporting to ACHRI’s Scientific Director, Dr. Naweed Syed. The Education Director oversees all activities, including operations, finances and curriculum planning. Day-to-day management of all training components is coordinated by Project Manager, Ms. Julia Klenin-MacLock who has been in this position since the inception of the Platform in 2009.



**d) Research Programs** Since its inception, our Training Platform's primary focus has been to increase training capacity by providing stipend support to various categories of trainees. ACHRI trainee salary support represents the majority of the Platform's budget at approximately \$1,000,000 per year for the last five years. By offering stipend support our Platform not only increases training capacity at our Institute, but also enables mentors to allocate more of their resources for enhancing research and training within their labs. Since 2009, the cumulative total number of trainees supported by the ACHRI-CIHR Training Program has reached 182: 70 undergraduate summer students, 33 Master's students, 30 PhD students (including 1 in the CCHSCP program), 43 Postdoctoral Fellows (including 6 in the CCMG program, 3 in the CCHCSP program), and 6 residents.

The largest portion of the ACHRI training budget – approximately \$500,000 per year – is dedicated to providing funding salary support to ACHRI graduate students and postdoctoral fellows in basic and clinical research disciplines, on a competitive basis once a year. Typically, seven to twelve graduate students and three to four postdoctoral scholars are awarded each year through this funding stream.

ACHRI offers more specialized options for graduate stipend support through other award streams. The Grant Gall Graduate Traineeship promotes interdisciplinary research in immunology, inflammation and infectious disease in children and supports one student per year. The Talisman Energy Research Fund in Support of Healthy Living and Injury Prevention supports two to four graduate students and postdoctoral scholars each year. This funding stream will conclude in 2018. In the past, another funding stream

sponsored by the Veterinary Medicine supported research stipends of either one postdoc or two graduate students each year. This Program ended in 2014 – 2015 fiscal year.

In addition to graduate and postdoctoral trainee stipend support, our Platform provides funding to undergraduate summer students. Budgeting at \$32,000 - \$40,000 annually, this initiative supports eight to twelve undergraduates. In 2015, the Maternal Newborn Child and Youth (MNCY) Strategic Clinical Network (MNCY SCN) provided support for additional seven Summer Studentship Awards (\$30,000) through the ACHRI Research Training Platform. Summer student awards expose trainees to the research environment and its standard practices and enable students to decide if health research is their desired career path. All of our summer studentship awardees submit a written report on their projects at the end of the summer term, as well as deliver either a podium or poster presentation at ACHRI's annual Summer Studentship Research Day.

Our Platform also administers additional ACHF funds of \$300,000 per year for clinical research traineeships. These fellowships are for residents in pediatrics, obstetrics and gynecology, and genetics; trainees in certification programs, such as the Canadian College of Medical Genetics (CCMG); and pre- and postdoctoral traineeships in conjunction with the Canadian Child Health Clinician Scientist Program (CCHCSP) – a prestigious and highly competitive national program for clinician scientists. Competitions for ACHRI clinical research fellowships are held once per year. For CCMG fellows and trainees in the CCHCSP program, the ACHRI Clinical Research Fellowship is the only source of funds for their training.

These various salary support streams by far represent the single greatest impact on the success of ACHRI research of any aspect of our Research Training Platform. Most research carried out by ACHRI members is supported by external funding from provincial, federal and private grants awarded to individual faculty members. Graduate students and postdoctoral fellows carry out the bulk of the work on most of these projects. The salary awards provided by the ACHRI Research Training Platform allow our members to add more, and highly qualified, trainees to their research projects, beyond what was included in the budgets awarded for the projects. Thus faculty with ACHRI-funded trainees can accomplish much more than would otherwise be possible. This increased productivity in turn enables their work to have a greater impact on their research and enables ACHRI members to acquire more competitive external funding in the future. Similarly, the ACHRI funded trainees can point to their ACHRI stipend awards as evidence of success, which in turn increases their chances of obtaining external support at the provincial and national levels. The awards enhance their CV's to increase their ability to obtain future educational and professional positions.

Over 20% of graduate and postdoctoral trainees supported through our program have competed successfully for other external awards, such as AIHS (provincial), CIHR (national), and NSERC (national), securing over \$1.1M in external trainee funding since 2009. Their achievements underscore the high standard of trainees chosen by ACHRI for funding. ACHRI-funded trainees successful at acquiring external funding are given a one-time top up of \$3000 for graduate trainees and \$5000 for postdoctoral trainees that they can spend on research-related travel, subscription to scientific journals in their field, and training relevant to their research project. Unspent amounts of these trainees' ACHRI salary awards are returned to the funding pool and are subsequently reallocated to provide stipend support to other trainees.

In short, ACHRI trainee salary awards make a significant impact on the positive feedback loop of success for the trainee, supervisor, and our program as a whole.

**e) Training** In addition to salary support, the Platform puts emphasis on development of various valuable initiatives to further enhance the training and educational opportunities in ACHRI. Budgeting approximately \$45,000 annually, our Platform provides many smaller awards that are not restricted to trainees who have received a salary award. To ensure the competitiveness of both the Platform and its

trainees, we organize and support advanced training opportunities, focused on child health and transdisciplinary research. We also organize and sponsor numerous events throughout the year where our trainees can share their research with each other, faculty, and invited speakers from other institutions. The Platform intends to continue to offer these awards, and organize and sponsor various events and educational activities and hopes to develop a more extensive portfolio of these valuable trainee initiatives to further meet the needs of ACHRI trainees and members. Our existing programs are described in detail below.

**Trainee Recruitment** To facilitate recruitment of high-quality students and fellows to our Institute, the Program budgets \$10,000 per year for visits by potential graduate students and postdoctoral scholars. To date, we have funded 20 such recruitment visits, 16 of which were successful. Additionally, we offer fast track access to our studentship and fellowship support, so that the best trainees can secure their ACHRI stipends before they arrive. As the top candidates always have offers from multiple other institutions, the recruitment visits and fast track offers give our faculty a competitive advantage in recruiting the very best trainees. To date, we have awarded 4 trainees with Fast Track Scholarships.

**Travel Awards.** Budgeting \$12,000 per year, the ACHRI-CIHR Training Program offers travel awards for trainees to attend scientific meetings of their choice to present their research. Through these travel awards, ACHRI trainees have the opportunity to connect with top researchers and fellow trainees in their fields from across the country and around the world. Since 2009, the Program has received 154 applications and has provided travel support throughout North America and Europe for over 130 ACHRI trainees. This program has our single greatest impact to students not supported by salary awards.

**Trainee Research Visits.** Our Program budgets \$10,000 per year for funding trainees who wish to travel to attend courses or to visit a collaborating research group at other institutions. This allows them to acquire new, cutting edge techniques not available in Calgary. These visits also expose the trainee to new people, approaches and ideas and build foundation for future collaborations. Since 2009, 21 research visits have been funded.

**Events.** The Training Platform organizes trainee research days, workshops and on- or off-site retreats, budgeting \$18,000 annually. For instance, we provide funding support to ACHRI-centred and theme-organized research days and symposia, which include retreats and trainee research days involving podium and poster presentations by trainees and a seminar by a visiting scholar. Such theme research days provide ACHRI Trainees with an opportunity to present their work to a wide audience and better understand current research within their area of interest.

With the aim of fostering connection and collaboration among trainees and mentors across the three themes and numerous research groups within the Institute we take part in organizing ACHRI's annual Research Symposium. This event highlights the innovation and diversity of research within ACHRI. The two-day event features 3 to 4 visiting scholars in the field of child and maternal health, several presentations by ACHRI's own members and trainees, as well as a poster session, showcasing over 50 posters prepared by our students and fellows; the second day of the symposium is focused on trainee career development with an opportunity for all trainees within ACHRI to learn about various career paths and career opportunities and to harness expert advice, including from the invited external speakers.

We recently introduced an ACHRI-wide summer student research day - an event similar in format to the ACHRI Research Symposium. This event not only allows our undergraduate students to showcase their ACHRI-funded summer research accomplishments via podium or poster presentations; but also aims to introduce undergraduate trainees to reporting and presentation skills in used academic science.

We support and encourage participation of ACHRI trainees in events organized by other groups within the Faculty of Medicine, such as the annual Bea Fowlow Lectureship Day organized by the Department of

Medical Genetics, and the annual Cumming School of Medicine Symposium, organized entirely by graduate students in Cumming School of Medicine. Similarly, our Platform also partners with other organizations, for example, with KT (Knowledge Translation) Canada, which offers a variety of workshops on translating basic science to clinical and academic practice and policy.

**Visiting Speakers.** In 2009, the ACHRI Research Training Platform established a program for hosting visiting scholars who are invited to the U of C for the purpose of participating in a PhD examination committee and presenting a lecture to ACHRI trainees and faculty. Budgeting \$7,500 per year (up to \$1,500 per visit), these events include a seminar presented to trainees and faculty. The visitor meets with individual researchers in their field of expertise. A key component of the visit is a meeting with ACHRI trainees, usually an informal lunch. To date, 26 such visits have been funded by the Program.

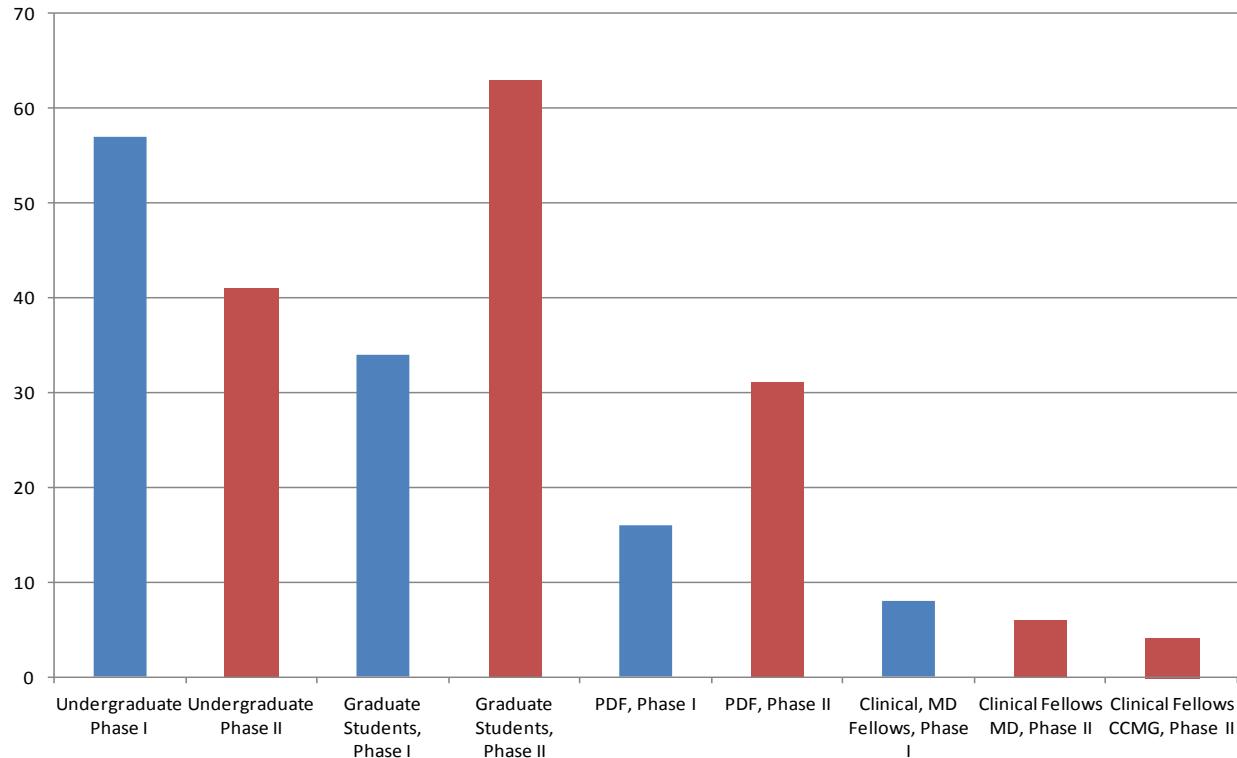
**Other Training Activities.** As part of our aim to foster trainee professional development, the ACHRI Training Platform partners with other local training initiatives, such as the Professional Development Program housed at the Graduate Science Education office at Cumming School of Medicine - a local initiative that provides an effective framework of professional development opportunities for trainees within the Cumming School of Medicine through various training activities, workshops and seminars presented by local and invited experts. Additionally, our trainees are encouraged to participate in activities of *Let's Talk Science*, an award-winning national outreach organization that aims to spark interest in science in junior high and high school students. This partnership provides our trainees with a rewarding volunteering opportunity as well as teaching and mentoring experience that will be critical to professional success of researchers and clinicians alike. Our Platform's links with *Let's Talk Science*, as well as KT (Knowledge Translation) Canada, help expand the transdisciplinary training pursuits of ACHRI trainees and have been able to provide them with access to a diverse array of internal and external workshops and events, and help facilitate advanced skill development. In the future, our Platform intends to explore avenues for partnering with other similar programs.

**f) Metrics and Performance** In order to make educated decisions regarding the future development and direction of the ACHRI Research Training Platform, we gather specific data on our funded trainees, such as trainee publication history and their successes at acquiring external awards. These are standard criteria in assessment of academic performance. We also keep track of all ACHRI students and fellows after completion of their training in ACHRI, in order to evaluate employment competitiveness of our trainees and to get a better understanding of our trainees' preferences in selecting a certain career path.

**Training Capacity.** Since 2009, the cumulative total number of trainees supported by the ACHRI Research Training Platform has reached 182: 70 undergraduate summer students, 33 Master's students, 30 PhD students (including 1 in the CCHSCP program), 43 Postdoctoral Fellows (including 6 in the CCMG program, 3 in the CCHCSP program), and 6 residents.

The diagram below demonstrates the impact of the ACHRI Research Training Platform's stipend support initiative on building and expansion of the training capacity within the institute for the last six years (i.e., the term of the current ACHRI Research Training Platform). As demonstrated by the diagram, the current phase of the ACHRI Research Training Platform is geared toward graduate and postdoctoral funding, as opposed to undergraduate support, as we recognize the increasing competition for external funding and growing demands of the research environment.

**Figure 1: Numbers of trainees funded through the ACHRI Research Training Platform stipend support stream: A comparison between Phase I (2002-2008) and Phase II (2009 – present) of the Platform**



**External funding.** Among the many trainees supported through ACHRI's various funding streams for the last two years, over 20% competed successfully for major external awards and internal awards, valued at over \$1,000,000 since 2009. The following table summarizes our trainees' achievements by trainee category and lists some of the agencies that granted their prestigious awards.

**Table 1: External Awards of ACHRI Research Training Platform -funded Trainees, 2009 -2015**

Trainee Category	Agency/ Award	Amount
Master's Student	External: AIHS, NSERC Internal: Queen Elizabeth II	External: \$85,500 Internal: \$20,800
PhD Student	External: AIHS, NSERC, Alberta IBD Consortium Internal: Queen Elizabeth II, HBI	External: \$156,000 Internal: \$52,000
Postdoctoral Fellow	External: AIHS Internal: Alberta Children's Hospital -Hematology, Oncology and Blood and Marrow Transplant Program	External: \$325,000 Internal: \$113,000

Their achievements showcase the high standard of trainee recruitment in the ACHRI Research Training Platform. As a result of these external awards, the funds allocated for stipend support were released back to the Platform, helping fund additional trainees, thereby further expanding the training capacity in ACHRI.

**Trainee Publications** Trainee productivity is evident through the trainees' publication track record. The following table summarizes publication numbers per trainee category over the last two years.

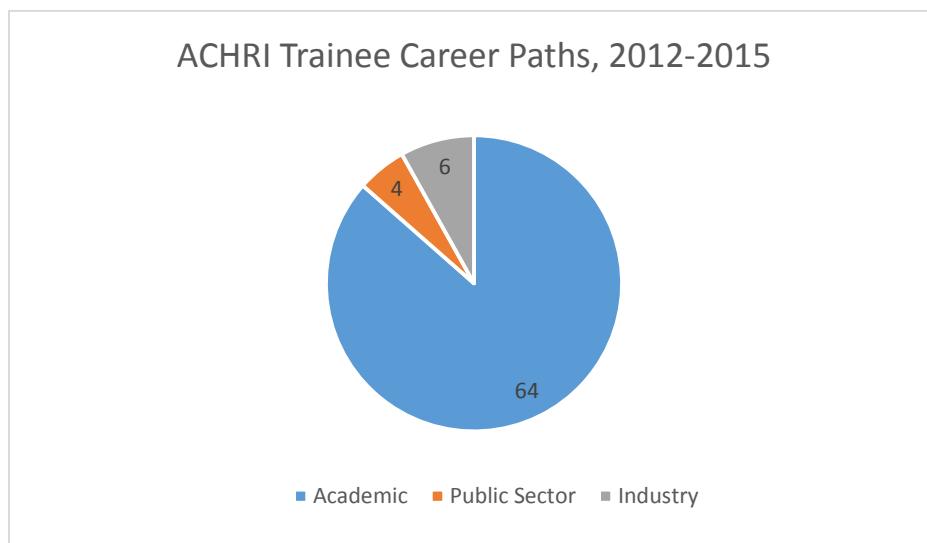
**Table 2: Trainee Publications of ACHRI Research Training Platform -funded Trainees, 2009-2015**

Trainee Category	Number of Peer-Reviewed Publications	Number of Publications Published in Top 5 Journals
Undergraduate Student	14	1
Master's Student	65	11
PhD Student	123	27
Postdoctoral Fellow	108	32

**Translational Impact:** In 2009, the ACHRI Research Training Platform established a relationship with the Knowledge Translation (KT) Canada (Calgary) initiative, whose activities and events, including the Summer Institute, KT Seminar Series, and Scientist Knowledge Translation Training workshops, have received a welcome response from the ACHRI trainees. Hence, our link with KT Canada Calgary has been providing our trainees with additional opportunities to participate in transdisciplinary research projects and education thereby enriching their training experience at ACHRI. We also hope that in the future, our involvement with KT Canada will help optimally leverage and streamline available training funds and educational opportunities for the trainees in both programs, as well as instill in this next generation of medical researchers the need for continuous transfer and sharing of knowledge within both the research community and general public.

**Trainee Career Success:** Our trainees' successful track record and dedication to research and continued training and education is evident in their career paths. Thus, of the 145 trainees funded by the ACHRI Research Training Program since 2009, 100 continued their training in academia and research, 13 pursued government and hospital roles utilizing their graduate and post-graduate training; and 7 chose to pursue industry careers.

The following chart demonstrates the breakdown of various career paths of ACHRI trainees for the past three years.



*Note: Does not include trainees who were unavailable to participate in the survey*

As seen in the above chart, the vast majority of our trainees pursue academic careers upon completion of their ACHRI training, and this trend is consistent across the different categories of trainees – undergraduate, Master’s, PhD students and postdoctoral fellows. Thus, 12 out of 15 undergraduate students enrolled in graduate training programs upon completion of their undergraduate education; 17 out of 20 Master’s students pursued further education (PhD or MD); 19 out of 20 PhD students pursued postdoctoral training; and 16 out of 19 postdoctoral fellows were recruited for academic positions.

The above data not only demonstrate the success of our trainees upon completion of their training in ACHRI, but emphasize their strong interest to remain part of the scientific community and academia as well as to continue contributing to scientific research. This indicates that as a training initiative, the ACHRI Research Training Platform should focus primarily on addressing the needs of trainees pursuing academic careers, while offering opportunities to explore other types of career paths and help them develop the necessary skills to be well-rounded professionals.

Taking into consideration the above-presented data and the ever-changing demands of the health research environment, ACHRI recognizes that much more needs to be done to help propel our trainees to success upon graduation, provide them with rich training environments, assist them with increased funding support, create novel opportunities for high quality research and collaboration – in other words, equip them with the necessary tools to become the best researchers of the next generation. The ACHRI Research Training Platform is prepared to help our trainees to fully realize their potential. The following section outlines the steps on how we propose to do this in the next five years.

**g) Platform Development and Business Plan** The leadership group of ACHRI view our Research Training Platform as one of the highest priorities for investment. We hope to make a significant difference in the training landscape, creating an opportunity to recruit, develop and retain exemplary scientists in Calgary who will build new knowledge to help advance child health locally, nationally and globally. To this end, the ACHRI Research Training Platform continually explores ways to improve and enhance training to meet the needs of our trainees in the changing and highly competitive research environment. As the Platform continues to provide competitive funding opportunities to ACHRI trainees through its various funding streams, these initiatives will be more attuned to the strategic priorities of the Institute, Cumming School of Medicine, and University of Calgary, as well as the needs of our trainees. In addition to existing awards, we hope to introduce scholarships for more specialized research training, as well as create avenues for our trainees to learn more about the research takes place in ACHRI to encourage collaboration and foster cross-disciplinary research opportunities.

With the recent review of the accomplishments and challenges of the ACHRI Research Training Platform over the last five years, and the new vision of the ACHRI and its partners, we have identified the following goals for the ACHRI Research Training Platform:

1. Build and enhance the quality of scholarship in ACHRI to help facilitate success in obtaining external trainee funding as well as employment success for ACHRI trainees;
2. Provide high quality training to meet trainee needs in scientific knowledge, professional development, and career planning.
3. Recruit high quality trainees
4. Increase training capacity
5. Build a stronger sense of community among ACHRI trainees and encourage collaboration

With these goals in mind, we have developed an action plan to help our Platform to take a new direction for the next five years. As we align our goals with the priorities of ACHRI, Cumming School of Medicine, and the University of Calgary, we strongly believe that this plan will competitively position the ACHRI Research Training Platform to further foster excellence in research training in our Institute.

### ***1. Build and enhance quality of scholarship in ACHRI***

We meet this goal by providing training opportunities to ACHRI trainees in a form of workshops, retreats and symposia, and various extracurricular activities. For instance, as a requirement of the graduate programs within the Cumming School of Medicine, trainees are expected to participate of a regular basis in Research in Progress meetings and Journal Clubs, where they are required to deliver a presentation on the progress of their research project or a selected publication. Not only does this practice allows trainees to showcase their accomplishments and get feedback from fellow students and fellows, but also allows them to practice presentation skills and develop critical thinking abilities. In addition to this practice, ACHRI trainee participation in workshops offered by the Professional Development Program at the Cumming School of Medicine, as well as activities presented as part of the ACHRI annual Research Symposium or ACHRI theme retreats and seminars allow our trainees to learn about research that takes place in ACHRI, explore grounds for potential collaboration and build a solid foundation for skills critical to academic success. Finally, with the trainee-oriented funding for conference travel and research visits (particularly travel to another laboratory where trainees can learn a new technique relevant to their research or collaborate on a project), we offer our trainees opportunities to become more knowledgeable and skilled scientist, and acquire skills that would aid them in advancing in their research. These initiatives help facilitate trainee publications, external trainee funding as well as competitively position them for employment opportunities after completion of their training.

In order to bridge the gap between basic and clinical research – a challenge that our Platform and ACHRI as a whole has faced due to the diversity of research in the Institute – we will organize more special workshop-type events that would bring ACHRI trainees from different disciplines together. We are developing a presentation series workshop for all ACHRI trainees who have gone on research visits to another lab or attended a conference. Passing the newly acquired knowledge to fellow trainees and having yet another chance to polish presentation skills so critical to academic science will be the main objective of this initiative. Additionally, we will explore avenues on putting forward a proposal for an ACHRI graduate program, which will offer a portfolio of courses beneficial to our trainees in basic, clinical and population health research disciplines.

### ***2. Provide high quality training to meet trainee needs in scientific knowledge, professional development and career planning.***

Similar to our first goal, we offer various opportunities to meet trainee needs. For instance to help trainees acquire specific scientific knowledge we supporting trainee research visits, conference travel, and theme-organized workshops and retreats. ACHRI's annual Trainee Development Day and our partnership with the Professional Development Program help our trainees continuously improve their soft skills, and get guidance in career planning. While continuing to offer these opportunities, we will explore options for expanding our educational offerings through collaborations with our partners on site, and outside of the University of Calgary.

Furthermore, starting in 2016, the ACHRI Research Training Platform will introduce the ACHRI Small Grant program – an initiative that will direct more funds toward ACHRI trainee research endeavors. With this program in place our Platform will not only be able to offer our more senior graduate students and postdoctoral fellows an opportunity to competitively obtain funds for their special research proposals, but also expose them to standard practices of grant writing and grant application in a supportive environment.

### ***3. Recruit high quality trainees***

Our Platform has allowed recruitment of high quality trainees through offering trainee recruitment funding to our members and by providing prospective trainees studentship and fellowship support through the Fast

Track stream. We will continue with these programs, and hope that through leveraging of funds via our partnerships with the Cumming School of Medicine and U of C graduate and postdoctoral programs we will be able to increase the number of trainees visiting our Institute for recruitment processes. Working closely with ACHRI leadership and the ACHRI Research and Education Council we hope to establish a formal process for trainee recruitment in conjunction with the graduate and postdoctoral recruitment programs of the Eyes High initiative and the Cumming School of Medicine.

#### ***4. Increase training capacity***

Our past and present partnerships with the Cumming School of Medicine, Faculty of Veterinary Medicine and Snyder Institute have not only allowed our Platform to encourage transdisciplinary research opportunities for our trainees and mentors, but also have helped secure matching funds, allowing our Platform to increase training capacity in the Institute even further. In the past year our Platform has been exploring options for partnerships and collaborations across the U of C campus so as to further expand our program and its training capacity through leveraging of funds and streamlining trainee recruitment process. Several such options presented themselves following the new strategy roll-out for the Cumming School of Medicine in 2015 (e.g., the CSM Postdoctoral Scholar Program, and the CSM Graduate Student Scholarship Program) and U of C's Eyes High strategy (e.g., the Eyes High Postdoctoral Scholar recruitment program). In the coming months, we will be establishing a detailed process for these partnerships and integrating them into our Spring 2016 studentship and fellowship funding competitions.

Furthermore, the research activities in the KidOmics and MORPH programs will provide opportunities for training students and fellows at the post-doctoral, graduate and undergraduate levels. Additional funding for these initiatives will specifically provide trainees with the opportunity to work in interdisciplinary research teams engaged in fundamental, translational and clinical research opportunities provided by the KidOmics/MORPH research pipeline.

In general, undergraduate and graduate students, postdocs, medical residents are the backbone of research. ACHRI strongly believes that investing in our trainees and supporting them in their research careers translates into investing in the future of research. Given the fact that ACHRI-funded trainees dramatically enhance an ACHRI investigator's research program, by freeing up funds that enable them to carry out more and higher quality research than would otherwise be possible, the key to increasing the impact of the ACHRI Research Training Platform on ACHRI research output is to expand the funding base dedicated to our trainees. For instance, in 2015, out of 148 ACHRI trainees only 23 (or 15 percent) were funded by our Platform (15 graduate students and 8 postdoctoral fellows). Additional trainee funding would help ACHRI to achieve the goal of continually increasing our Institute's training capacity, where having an ACHRI-funded trainee in a lab will be the norm rather than the exception.

#### ***5. Build a stronger sense of community among ACHRI Trainees and encourage collaboration***

Diversity of research in ACHRI has presented us with both advantages and challenges. To build a sense of community and to bring trainees together our Platform has participated in organizing ACHRI Research Symposium and ACHRI Trainee Development and Career Day since 2010. These events have proven to be highly valuable to our trainees in disseminating research findings, sharing ideas and establishing collaborations. However we recognize that more needs to be done to continue fostering the development of ACHRI culture. To this end, our Platform has recently initiated an idea for developing ACHRI Trainee presentation series available to all ACHRI trainees who have gone on research visits to another lab or attended a conference. This workshop-style series will present our trainees with the opportunity to present their research or what they have learned from their research visit, but also bring together ACHRI trainees from various research areas to help build a stronger sense of ACHRI community.

Additionally, our Platform will work closely with the Cumming School of Medicine and Faculty of Graduate studies to coordinate an ACHRI orientation day, where all ACHRI trainees – new and returning – will be welcomed, will have a chance to meet with the Training Platform management team, and will be made aware of various educational and funding opportunities available to them.

In addition to seeking opportunities for increased funding support for our trainees, the ACHRI Research Training Platform will also create avenues for our trainees to learn more about the research that takes place in the Institute to encourage collaboration and foster cross-disciplinary research opportunities. Lastly, the leadership of the ACHRI Research Training Platform are working on a long-term plan for development of an ACHRI-wide training program that would involve specific courses, seminars and educational activities. This would further address the Platform's goal of fostering excellence of the next generation of child health researchers.

## **2. Genomics and Informatics Platform**

**a) Historical Background:** In 2009, ACHRI's Genes, Development and Health researchers identified that the success of their priority research initiatives required access to a local genomics and informatics platform. The rationale was that advances in the technology of genome sequencing (specifically Next Generation Sequencing or NGS) and the emerging information were creating a revolution in the biologic and health sciences while tendering innovative and highly translational opportunities to advance health care. The immediate beneficiary of this breakthrough was deemed to be precision genomic medicine with new diagnostic and health care management tools leading to prevention, rapid and earlier diagnosis, personalized, safer and more effective treatments and health care delivery. Thus, to compete nationally and internationally in these fields, it was essential for ACHRI to acquire and develop expertise in the new NGS technologies and the related interpretive and informatics skill sets. It was also evident that strong and integrated genomics and informatics facilities would be a must for faculty recruitment and retention.

The genomics and informatics platform were envisaged to enable leading-edge science, generate novel knowledge, new intellectual property, business applications, improved diagnostics and opportunities for disease prevention, new treatments - leading to improved health and wellness. Such a platform would be essential to train the next generation of clinicians, technologists and scientists. There was also evidence demonstrating that a local facility that interacts with stakeholders in their experimental design would yield better outcomes, reduce errors in sequencing data/interpretation and ensure data and IP security. With there being no such facility at the University of Calgary, ACHRI prioritized the creation of a new genomic and informatics platform.

In 2010, the ACHF committed \$5.8M in funding over five years to support ACHRI in the creation of a genomics and informatics platform. In 2011, ACHRI approved a 5 year plan, purchased two Life Technologies 5500 sequencers, hired skilled genomics and informatics staff, established workflows and validated the accuracy of the sequencing and informatics pipeline against samples provided by the Alberta Health Services Genetic Laboratory Services facility in the Alberta Children's Hospital. In the spring of 2012, ACHRI announced the opening of its Genomics and Informatics Platform to the CSM scientific community. Sequencing was made available to all academic faculty members in the University of Calgary at the cost of consumables, while free access to a variety of bioinformatics tools was made available to all UofC users through a Galaxy web portal. In the same year, ACHRI submitted a proposal to a competitive CSM process and was awarded \$2M over 5 years to build up genomics and informatics capacity in the CSM.

In December of 2013, the Alberta research community at an AIHS Provincial Research Forum in Edmonton identified genomics and informatics as a key priority for investment. In the fall of 2014, ACHRI presented to the CSM Planning and Priorities Committee and proposed the creation of a CSM Center for Health Genomics and Informatics. A CSM Research Retreat in the spring of 2015 supported investment in such a platform and subsequently the CSM 2015-2020 Strategic Research Plan identified Precision Medicine as a strategic focus going forward. The CSM committed to a vision of pan-Institute initiatives in precision medicine and investment in platforms, i.e. genomics and informatics, clinical trials, imaging, and a microbiome gnotobiotic facility – all deemed essential to the success of its strategic plan. ACHRI was identified as the lead for the development of a genomics and informatics partnership amongst the CSM, its institutes and other U of C faculties in support of this and the university's strategic direction. This has since emerged as the CSM Center for Health Genomics & Informatics (CHGI).

**b) Governance:** The ACHRI Genomics and Informatics platform formally transitioned to become the CSM Center for Health Genomics and Informatics on April 1<sup>st</sup>, 2016. The platform is managed by an Operations Oversight Committee that is chaired by the ACHRI Director with representations from each of the partner institutes (ACHRI, Arnie Charbonneau Cancer Research Institute, Snyder Institute), faculties (CSM, Vet. Med., Science), the CSM Department of Medical Genetics, the UCalgary *Eyes High* strategic research theme on Infections/Inflammation and Chronic Diseases' Enteric Microbiome Initiative and the AHS/ACH Molecular Diagnostic Laboratory Services.

Committee members are accountable to their respective participating entities, whereas the Committee is collectively accountable to the Center for Advanced Technology, CSM (see Appendix 6, Memorandum of Understanding between the Founding Partners of the CSM Center for Health Genomics and Informatics). The collective goals of the partners are to enhance research, foster education/training, and to determine how best to utilize operational and philanthropic funding. The CHGI is mandated to reduce duplication, increase operational efficiency and reduce costs to investigators while providing and growing expertise in genomics and informatics.

**c) Platform Leadership and Team Membership:** Dr. Paul Gordon is Informatics Manager and Dr. Richard Pon is the Manager of Genomic Sequencing. They provide day-to-day operational leadership and technical expertise for the research services of the CHGI. A Unix administrator and a Unix analyst report to Dr. Gordon and have responsibility for maintaining the IT infrastructure. A lab manager, and two technicians report to Dr. Pon and have responsibility for sample preparation and operation of the sequencing equipment. All of these positions are funded by the core operating budget (\$1M/year for 5 years) provided to the CHGI by the CSM. The partners are each committed to additional complementary investments in personnel and equipment that support the sequencing and informatics service needs of their respective research programs for a total investment of more than \$20M over the next five years.

**d) Platform Operations:** The *sequencing service* of the CHGI has two synergistic operational elements: a core basic research component in the Cumming School of Medicine and a translational research component situated within the accredited AHS Genetic Laboratory Services diagnostic laboratory at Alberta Children's Hospital (ACH). Both sites have private high-speed network connections to a dedicated genomics server room in the basement of the Health Sciences Center and share a common, private and secure high-performance computational and storage facility that supports the *bioinformatic / analytic service*. Together, the sequencing and the bioinformatic cores of the CHGI comprise a full-service genomics facility that performs all of the sequencing, and bioinformatics required to go from isolated DNA/RNA to a list of variant calls or expressed genes. Both basic research and clinical research are supported for PI's and their PhD students, post-doctoral placements and international or national collaborators who choose to have sequencing work performed in the Calgary area.

**Core Basic Research Sequencing Facility at HSC:** Under the leadership of the Manager of Genomic Sequencing, Dr. Richard T. Pon, the facility offers a wide variety of NGS services. These include, but are not limited to, whole genome, shotgun metagenome, whole exome, amplicon (including 16S metagenomics), whole transcriptome, poly-A mRNA transcriptome and small RNA sequencing services. Very low sample input (down to single cell levels) services are also being rendered. Samples can be viral, bacterial, metagenomic, invertebrate, plant, or mammalian, but human and mouse samples make up the majority of the current workload.

The CGHI operates two laboratory suites in the basements of the Heritage Medical Research Building (HM B20A-D, the former Libin Gene Therapy suite) and the Health Sciences Centre (HSC B102-104). These two laboratory suites are intentionally physically separate to minimize cross-contamination. All sample preparations steps occur in the HM B20 suite (118 m<sup>2</sup>, 1270 ft<sup>2</sup>) where there are two air-lock separated laboratory areas for isolated sample input/pre-PCR and post-PCR operations. There are also RNase-free and library quantitation work areas. The actual sequencing is performed in the HSC B102-104 instrumentation suite where the next-generation sequencers are located. This suite was originally shared with separately operated Sanger DNA sequencing and microarray services with ~ 50 m<sup>2</sup> (540 ft<sup>2</sup>) available for NGS instrumentation. However, in 2014 the microarray service ended and now ~100 m<sup>2</sup> (1080 ft<sup>2</sup>) is available for NGS in the instrumentation suite. The sequencing instruments are adjacent to the server room and IT infrastructure located in HSC B151 (see details below) with direct data connections.

Next-generation sequencing at the CHGI has been available on five different platforms. Large-scale sequencing was originally performed on two Life Technologies SOLiD 5500xl instruments having a combined capacity of ~ 33 three-week long runs/year (sufficient for up to ~ 6 Tb/year). However, these older instruments were replaced in 2015 with two Illumina NextSeq 500 sequencers. The NextSeq instruments are smaller, less-expensive, and significantly faster (1 day/run vs 15 days/run) and increase our combined annual capacity approximately six-fold

to ~ 200 runs/year (~24 Tb/year). This is sufficient for up to 200 whole human genomes or 1600 exomes. Small-scale next-generation sequencing for basic research projects is performed by Dr. Pon's staff on the Ion Torrent PGM and Illumina MiSeq instruments located at the ACH (see below).

Long-read single-molecule DNA sequencing is also provided on an experimental basis (early access test site) using Oxford Nanopore Technologies MinION and MinION Mk 1 nanopore sequencers. These are novel and potentially “disruptive” sequencing technologies which sequence at a rate of hundreds of bases per second and generate sequence reads tens of thousands of bases long (compared to ~ 100-300 base-long reads with our other instruments). This technology is expected to create opportunities for new diagnostic and clinical applications as it develops. Already, it is the basis for new IP protection applications made on behalf of Dr. Gordon regarding signal analysis algorithms.

**Translational Research Sequencing Facility at ACH:** This element of the CHGI operates within a clinically certified diagnostic environment in the Molecular Diagnostics Lab at the Alberta Children's Hospital under the leadership of Dr. Jillian Parboosingh. The AHS/ACH Molecular Diagnostic Laboratory provides clinical diagnostic services for AHS. The four clinician scientists working in that laboratory are jointly appointed in AHS and UofC. ACHRI has provided two bench top NGS sequencers (an Ion Torrent PGM and an Illumina MiSeq) on site to support translational research. The translational research program is supported by the core, basic research sequencing facility at HSC through a private high-speed network connection to the dedicated genomics server room in the basement of the Health Sciences Center. Through the same link they share access to the CHGI's private and secure high-performance computational and storage infrastructure and bioinformatic / analytic software.

**Bioinformatics and Analytics:** The core bioinformatics and IT infrastructure is maintained by Dr. P. Gordon (bioinformatician) and two systems administrators. The service and academic bioinformatics capacity of the CHGI is being constantly expanded and now includes: a Lecturer in Bioinformatics, Bachelor of Health Sciences Program; Service Bioinformatician, Faculty of Veterinary Medicine; and multiple academic appointment within the CSM, Veterinary Medicine and Science with bioinformatics skills in the areas of infectious disease, enteric microbiome, rare diseases, cancer, veterinary medicine, plant, environmental/microbial biology. The CHGI has a philosophy of emphasizing the provision of tools and training to enable researchers to perform their analyses rather than recruiting a large number of staff bioinformaticians.

The server room in HSC B151 has a raised floor, main power supply from utility, 30 minute back-up power to protect equipment from utility power variations, air conditioning via chilled water loop, fire suppression, environmental monitor and alarm system, public and UofC Private Network Switches. The IT infrastructure supporting informatics services is comprised of three large shared memory servers (1 TB RAM each), 220 TB disk storage with remote backup, and a Galaxy server (<http://galaxyproject.org/>) for turnkey user-run analyses in the medical genetics domain.

The Galaxy Web Portal framework is used by over 70 bioinformatics service providers such as the U.S. National Institutes of Health, The Max Planck Institute for Immunology, and The International Rice Research Institute. The Centre's Galaxy portal has been designed to provide a user-friendly data analysis interface for biological and medical researchers. The portal takes advantage of open source and in-house developed algorithms to quickly identify and triage genetic variants related to disease and developmental processes. The galaxy interface is accessible by web browser (and userid/password) and provides a convenient portal to sequencing data files, Q/C tests, and over 100 analytical tools and custom in-house scripts. Examples of the bioinformatic tools include GATK, BWA, Tuxedo, Trinity, Eland, MACS, Oasis, Velvet, Picard, and SAMtools as well as a number of packages specifically for human annotation, i.e. GERP, SIFT. The Galaxy interface allows users to access high-performance IT hardware, (i.e. our three 64 CPU core servers each with 1 Tb RAM shared memory and 220 Tb of disk storage), without knowledge of the UNIX command line. Instead, users have links to their datasets, access to pre-configured and optimized analytical pipelines and the ability to easily share data and results. Galaxy also documents the complete history of how each analysis was performed for reproducibility and eventual publication. An example of

one of our Galaxy's uses is the collaboration with Alberta Health Services medical geneticists which has developed analysis outputs to meet clinical needs and streamline calculations. The results are rapid automated pipelines facilitating prioritization of disease causing variants in individuals, family trios (mother, father, child) and family pedigrees. Training workshops are held twice a year and presently there are about 70 active users of the system.

The Center's computation infrastructure has been supplemented by a successful three-year Compute Canada resource allocation request for public-facing disk and compute cycles mirroring the existing intramural bioinformatics portal. The allocation provides for 80 TB of rapid excessive bulk hard disk space, and 64 CPU years of compute time. The request was made in order to allow external users to access the University of Calgary's CHGI intramural bioinformatics portal that is currently being used by the University's medical genetics research community.

**e) Research Programs:** The CSM provides core operational support for the CHGI. Each partner has committed additional resources to meet its respective research needs, and these include:

- ACHRI focus - Genes, Development and Health
- Arnie Charbonneau Cancer Research Institute - Personalized Cancer Genomics
- UCalgary *Eyes High* Infection, Inflammation and Chronic Disease - Enteric Microbiome
- Faculty of Veterinary Medicine – Advancing Canadian Water Assets (ACWA)
- Faculty of Science – Environmental/microbial oil and gas; plant “omics”

The CHGI activities are operationalized by the partners through an Operational Oversight Committee which Administers resources (financial and otherwise) that the partners agree to contribute. It respects the specific research objectives, financial & operating independence of the partners. The partners recognize that they can achieve much more cooperatively and be far more cost effective than they can be independently. The Operations Oversight Committee of the CHGI is accountable to all partners, but reports through the Center for Advanced Technology, CSM. The typical commitments of a partner involves a contribution to renewal and expansion of the sequencing and bioinformatic infrastructure, salary support for laboratory technicians and service informaticians, and the recruitment of new faculty with relevant skills. In ACHRI's case, the Institute has two initiatives in the Genes Development and Health theme that this platform will support:

**Model Organisms Research for Paediatric Health (MORPH):** This program integrates an interdisciplinary group of clinical specialists in molecular genetics, computational biology, and developmental biology who exploit model organisms to decipher the molecular and cellular basis of pediatric rare disorders. The team interrogates disease gene function, uses advanced technologies to manipulate gene expression in model organisms, and examine abnormal development associated with genetic diseases in children. This initiative seeks to establish sophisticated, laboratory-based, mechanism-centred resources capable of revealing gene function in simple organisms to inform patient diagnosis, prognosis and treatment.

The rationale for MORPH derives from the evolutionary conservation of developmental pathways across species and the capacity to experimentally pursue these genes in simple organisms in which select genes and pathways are most amenable to study; this cannot be done in children. MORPH scientists investigate fundamental developmental processes in a repertoire of invertebrate and vertebrate models, including flies, worms, Zebrafish and mice. With this knowledge base and the advanced technologies described in this application, the MORPH team will investigate the developmental and cellular roles of genes identified in patients for which functional understanding is lacking.

The MORPH team, organized as the MORPH Management Group, includes: (i) clinical investigators (clinical genetics group and Care for Rare participants based at Alberta's Children's Hospital (ACH)); (ii) genomics diagnostics specialists in Calgary and across Canada, who will be the source of disease genes identified in pediatric patients; (iii) bioinformatics specialists, who will conduct comparative genomic analysis of the genes and assess the impact of identified mutations; and (iv) developmental biologists representing the model organism group that will undertake laboratory investigations. This innovative, translational health pathway beginning with model organisms

to model human mutations, determining the biological mechanisms of the genes involved, and translating this knowledge to benefit patient treatment, will have a transformative impact on the study of rare human diseases.

**KidOmics:** This program will assess the impact of implementing a local model of the provincial strategy for an integrated Genomic Health Program that could provide preventable, predictive, personalized and cost effective genomic health services for all Albertans across the lifespan. To ensure that new genetic knowledge is rapidly translated into improvements in diagnostics, prevention and treatment the theme's bedside research focus will be a collaboration with the Department of Medical Genetics and the AHS Genetic Diagnostic Laboratory at ACH to initiate a clinical trial evaluating the costs and benefits of a pilot "KidOmics" program. The goal is to use a person's DNA information to improve care by supporting early and accurate diagnosis, individualized treatment, avoid unnecessary and invasive diagnostics testing, and reduce harmful or ineffective interventions. The results of this research will inform future AHS decisions concerning implementation of the Provincial clinical genetics strategy document that Dr. Bernier was asked to provide to AHS and which has since been submitted to Alberta Health & Wellness. The platform is currently supporting the introduction of rapid clinical exome assays (clinome) into health care for individuals, in partnership with AHS and with funding support from Genome Canada via the Care for Rare research grant. To support this rapid sequencing, we have developed a novel turnkey bioinformatics pipeline to perform quality control, predict variant effects, and apply statistical rigor to gene-phenotype correlations.

**f) Training:** Dr. Gordon provides twice-yearly bioinformatics training workshops on RNA-seq and exome analysis, for attendees from U of C Faculties of Medicine, Veterinary Medicine, Science, Calgary Laboratory Services, Alberta Health Services, and Provincial Lab. Over 130 people have received training to date. A few co-op students and technicians have also received more extensive training through work-term or limited term job placements as data analysts or lab technicians.

Both Dr. Pon and Dr. Gordon frequently consult with principal investigators wishing to get started in the area of NGS and assist them with experimental design. This often includes help with preparing grant applications and generating preliminary pilot data or performing pilot analyses to support grant applications.

CHGI held its first day-long NGS outreach symposium on April 22, 2014 to promote and educate students and researchers on the use of NGS technologies. Seven local faculty or ACHRI members and two visiting speakers from industry discussed applications of NGS in the fields of cancer, medical genetics, bioinformatics, pathology, fish biology, rare diseases, biofilms, and energy bioengineering. Over 200 people participated and attendees came from southern Alberta, Edmonton, and Saskatchewan as well as from our local public, students and faculty. This symposium was so successful that we plan to hold a similar educational event annually as part of our outreach activities.

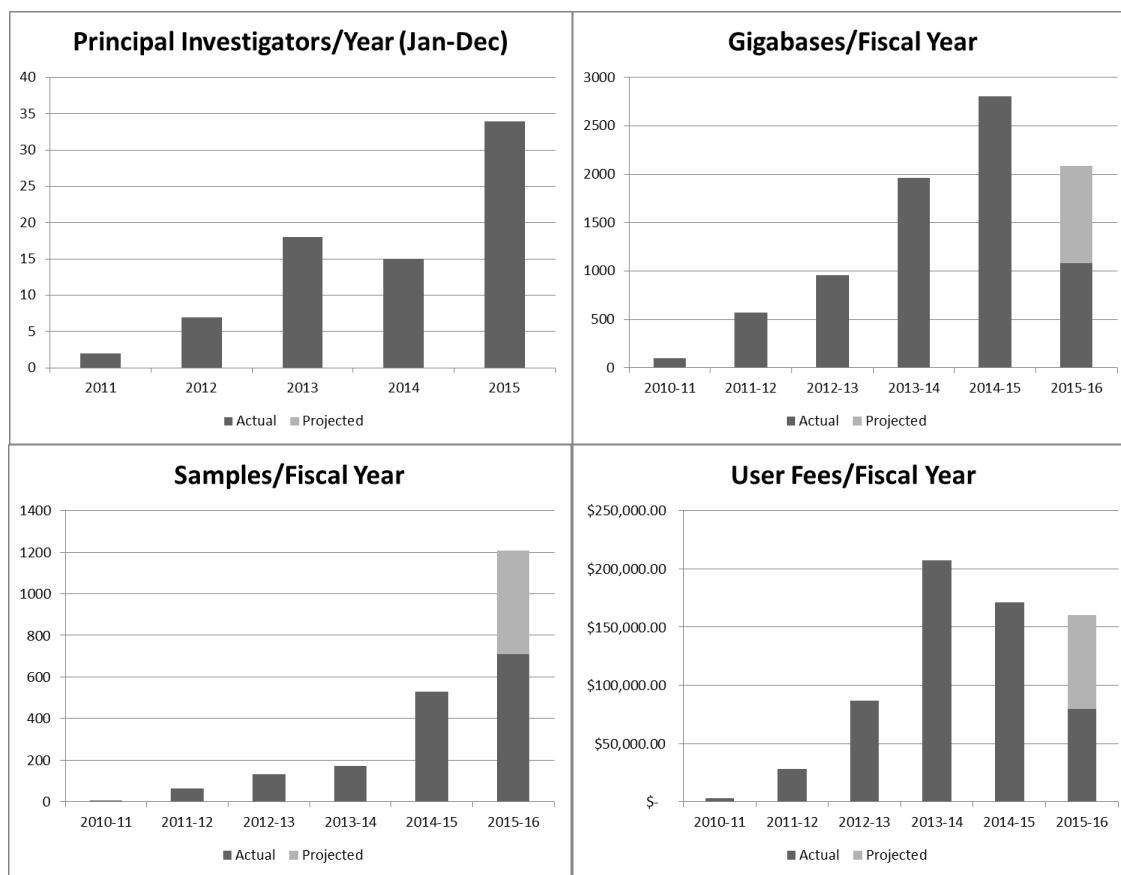
### **g) Metrics and Performance**

#### **Utilization Numbers**

CHGI began validating its sequencing and informatics services in 2011, but did not offer services to investigators until the spring of 2012 (start of fiscal 2012/13). By November 2015 there had been 203 job requests for sequencing and bioinformatics support comprising over 3400 pieces of work from 68 unique users and 54 Principal Investigator's or lab directors. The difference between the number of unique users and the number of PI's is due to the fact that often a PI was the point of contact for either: a) research consortia that were multi-centred and international, and b) multiple graduate and post-doctoral students. In terms of DNA sequence generated, the first four years showed marked increases in output each year. However, for 2015-16 output is expected to level off at about ~ 3 Terabases due to a shift towards projects requiring less sequencing/sample. Even so, after five years, we will have produced almost 10 Terabases of sequence.

The following four charts document how the number of Principal Investigators serviced, the number of samples

sequenced, the amount of sequence produced, and the amount of user fee revenue have increased since the genomic and informatics services were introduced.



## Utilization:

**Impact – Basic Research:** By its third year of operation (2014/15), CHGI was supporting six UofC and CSM AIHS Team, Genome Canada, individual CIHR, Brain Canada, or international consortia grants lead by CSM members. These successful awards represented many collaborative investigators with major multi-million and multi-year research commitments dependent on the genomic-informatics facility. In addition, CHGI infrastructure is fundamental to the ACHRI Model Organism for Pediatric Health (MORPH) CFI Large Grant application (\$5-10M), the Arnie Charbonneau Institute initiative in personalized genomics (\$8M), the CSM Precision Medicine priority, the Faculty of Veterinary Medicine ACWA research program, the UCalgary *Eyes High* Infection/Inflammation and Chronic Diseases enteric biome investment (estimated currently at \$26M) and is also supporting genomic/informatics research initiatives within the Snyder Institute, and Faculty of Science. On numerous occasions the Center has provided rapid turnaround to generate additional data required to resubmit CIHR grants or papers for publication. Seven members of ACHRI were also part of an international group coauthoring a Nature Cell Biology paper identifying regulators of ciliogenesis and ciliopathy genes ([dx.doi.org/10.1038/ncb3201](https://dx.doi.org/10.1038/ncb3201))

**Impact – New Intellectual Property:** CHGI is generating intellectual property in at least two areas. First, novel “Liquid Biopsy” assays using cell-free DNA sequencing have been developed for transplant monitoring. Second, novel signal processing algorithms for improved nanopore base calling are in development.

**Impact – Clinical Research:** CHGI's collaboration with the certified clinical site (AHS Genetic Laboratory Services at ACH) and ACHRI's bioinformatics expertise in medical genetics have facilitated translation of new NGS diagnostic applications into clinical practice. Already, one breast cancer gene panel on an Ion Torrent PGM sequencer has been designed, validated and put into clinical use and a second inherited diseases gene panel is being tested. A novel NGS method to monitor organ transplant rejection or stem cell uptake has been developed and a patent application filed. The CHGI was also instrumental in working with the Alberta Provincial Laboratory for Public Health (ProvLab) to sequence and characterize the only primary viral samples from the 2014 H5N1 influenza fatality (the first in North America) using the Ion PGM sequencer. In addition, we are using the Illumina MiSeq along with the Illumina TruSight One panel to evaluate a smaller, faster, cheaper version of exome sequencing (the “clinome”) containing only the ~ 4,800 clinically relevant genes rather than the more conventional whole exome (~ 22,000 genes). This research is supported by the Genome Canada funded Care for Rare program. Pre-programmed bioinformatic analyses along with the speed of the MiSeq platform allow three samples at a time to be run with four-day turnaround time for < \$500 each.

In 2015, the CHGI began providing microbiome sequencing to support an ongoing clinical trial with Dr. Thomas Louie into a new antimicrobial agent for treatment of *C. difficile* infection. The CHGI also assisted in preparing a proposal with Drs. Andrei Harabor and Belal Alshaikh (Alberta Health Services) for a study on “Florababy probiotic administration and microbiome changes in extremely preterm neonates” to treat necrotizing enterocolitis. Funding for this study was announced in October 2015 and the CHGI will perform the microbiome analyses.

**Impact – Recruitment:** CHGI is a platform that is essential for the recruitment of new faculty necessary for the success of the CSM's Precision Medicine initiative that includes platform capacity in genomics and informatics. ACHRI has helped recruit five recent recruits (Dr. J. de Koning, Informatician, BMB; Dr. Quan Long, Informatician, BMB; Dr. Edwin Wang, AIHS Translational Chair in Cancer Genomics, BMB; Dr. Amanda Melin, Primate Biologist/Enteric microbiome, Faculty of Arts/CBA; Dr. Paul Arnold, AIHS Translational Chair, Director of the Mathison Center, Child Mental Health/Psychiatry) and eight recruitments in process (Junior AIHS Translational Chair in Personalized Genomics x2; NSERC Tier 1 in Bioinformatics; Junior AIHS Translational Chair in Cancer Genomics; Medical Genetics; NSERC Tier 2 in Regulatory Genomics; Junior Informatics Recruits x2).

### Other Performance Metrics:

**Price Comparisons with other Canadian Genomics-Informatics Facilities:** Table 1 is a comparison of our NGS user fees with nine other Canadian next-generation sequencing facilities as of January 2015. The costs per sample are shown for various services assuming they are processed in full sequencing runs. The CHGI facility's prices compare very well with these nine other labs. Only Genome Quebec in Montreal has consistently offered lower prices. We were less expensive than the others in almost every example. The only exception was for whole human genome sequencing where the very big centres running HiSeq instruments had a clear advantage. This represents a known limitation of our SOLiD 5500 sequencers and is significantly addressed with the transition to use of the NextSeq instrumentation. In conclusion, CHGI's prices based on cost of consumables provide a competitive advantage to our local researchers, when compared to most other alternatives in Canada. This is in keeping with our objective of developing internationally competitive researchers in this field.

**Economies of Scale:** Multiple table top sequencers have been purchased by individual laboratories within UofC. However, as shown in Table 2 the full cost of ownership is substantial. This is because the equipment depreciates rapidly and because the cost of maintaining service agreements is very high: \$30,000 US/year per NextSeq and \$17,000/year per MiSeq. Unless individual instruments are used extensively, it is more cost efficient to have them placed in a multi-user core lab such as the CHGI. Additionally, the cost of sequencing is greatly affected by the choice of platform with different sequencers being better suited for different sized projects. Thus, there are opportunities to achieve economies of scale within CHGI.

The most cost effective choice for a given investigator, group of investigators or an institution is to use the largest machine that is suitable for the type of analysis being done and which can be run at as close to maximum capacity as possible. Machines typically have down times due to various failures, so it is desirable to have more than one with some excess capacity so that the facility is never in a position that it is effectively closed or has a backlog of work that creates delays in processing requests. The CHGI has addressed this issue by entering into instrument sharing arrangements with other partners. A second NextSeq 500 sequencer has been made available by the ACWA group (John Gilleard) to supplement the NextSeq purchased by ACHRI. For smaller-scale sequencing projects, the Snyder group's MiSeq (operated by Karen Poon) is available should the ACHRI purchased MiSeq be busy or out-of-service. A well-managed centralized facility that pays attention to the above issues and is transparently accountable to its investigators will provide high quality, cost-effective and competitive services in a timely fashion.

**Quality of CHGI Data:** A CHGI user who represents an international consortium of users compared the service he received locally from ACHRI/CHGI with two other commercial vendors and a major genome center (Table 3). This table compares the depth of sequencing coverage (how many times the target region was sequenced) and the % of target region covered (sequenced) at least 20 times. The data is retrospective; the PI spoke personally or corresponded with each vendor to indicate what the research objective was in each instance.

CHGI consistently met and exceeded the performance of the other commercial vendors. The reliability of interpretation of positive or negative findings is significantly impaired when depth of coverage and % of target region covered is reduced. In this PI's case, the whole genome sequencing that his research consortium chose to do in follow-up this year was done in CHGI because it could be done immediately (compared to a 4-12 month wait elsewhere) and because our platform provides significantly better data in terms of depth of coverage, % of region covered at least 20 times and therefore far better reliability of interpretation.

**Table 1: Comparison of Canadian Next-generation Sequencing Prices – January 2015**

	ACHRI	CHRIM	SRI	OHRI	BCGSC	TCAG	GQ	UBC-Biodiv	UBC-DMCBH	LRGC
<b>Major Instrumentation</b>	Life Tech 5500	LifeTech 5500	LifeTech 5500	ILM NextSeq	ILM HiSeq	ILM HiSeq	ILM HiSeq	ILM HiSeq	Ion Proton	Ion PGM
<b>Sample Preparation</b>										
DNA library	110.00				338.23			200.00		240.00
Poly-A mRNA library	180.00				463.11	296.00	146.00	200.00		250.00
Exome library and capture	470.00				638.54		358.00			
<b>Project per sample (library &amp; sequencing)</b>										
Exomes at 5 Gb each									750.00	
Exomes at 6 Gb each	811.11					900.00				
Exomes at 8 Gb each	981.67					1100.00				
Exomes at 15 Gb each	1493.33			1960.00	1279.41		613.00			
RNA-seq at 50M reads	691.67	1300.00	1750.00	950.00	1159.13	994.33	716.00	1020.67	850.00	
microRNA-seq at 10M reads	289.33		880.00							
Human genome, 20-25X depth	6250.00									
Human genome, 30-40X depth	7870.00				3538.00	3700.00				
Ion PGM 314 seq chip, 400 bp	630.00									950.00
Ion PGM 316 seq chip, 400 bp	880.00									1150.00
Ion PGM 318 seq chip, 400 bp	1140.00									1350.00

ACHRI = Alberta Children's Hospital Research Institute, Calgary

BCGSC = BC Genome Sciences Centre, Vancouver

GQ = Genome Quebec, Montreal

LRGC = London Regional Genomics Centre, London

CHRIM = Children's Hospital Research Institute of Manitoba

OHRI = StemCore Laboratories, Ottawa Health Research Institute, Ottawa

SRI = Sunnybrook Research Institute Toronto

TCAG = The Centre for Applied Genomics, Hospital for Sick Children, Toronto

UBC-Biodiv = NGS Sequencing Facility, The Biodiversity Research Centre, UBC Vancouver

UBC-DMCBH = Djavad Mowafaghian Centre for Brain Health, UBC, Vancouver

**Table 2. Cost of Ownership Estimates (Dr. R.T. Pon, 2015-01-20)**

	Cost of Ownership	Total Costs
	<u>per year over 4 years</u>	<u>per Gb</u>
<b><u>Small or Personal Scale Sequencers</u></b>		
Ion Torrent PGM	\$42,250	\$1,086
Ion Torrent Proton	\$153,700	\$143
Illumina MiSeq	\$51,790	\$133
<b><u>Mid-Scale Sequencers</u></b>		
Illumina NextSeq 500	\$155,000	\$49
Life Technologies 5500xl	\$305,925	\$159
<b><u>High-Capacity Production Sequencers</u></b>		
Illumina HiSeq 2500	\$431,300	\$79
Illumina HiSeq 4000	\$731,000	\$32
<b><u>Long-Read Length Sequencers</u></b>		
Pacific Biosciences RSII	\$367,675	\$1,195

**Table 3. Example Comparing Details of Exome Sequencing Services – CHGI vs Other Vendors**

Sequencing Site* (Capture Kit, Sequencing Platform, Aligner)	Description	Mean Depth of Coverage, Cohort Average (SD)	% of Target Region Covered at least 20x, Cohort Average (SD)
ACHRI/CHGI (Agilent SureSelect V5 + UTRs, Life Technologies SOLiD 5500XL, NovoAlign CS)	Probands (n=22)	132.7 ( $\pm$ 14.1)	91.79 ( $\pm$ 0.81)
	Tumors (n=4)	249.8 ( $\pm$ 40)	95.11 ( $\pm$ 0.54)
WASH U (Illumina All Exon 65MB, Illumina HiSeq 2000, BWA)	Proband	86.9	82.7
BGI (Agilent SureSelect V4, Illumina HiSeq V4, Aligner, Illumina HiSeq 2000, BWA)	Probands (n=7)	28.1 ( $\pm$ 1.7)	50.95 ( $\pm$ 1.79)
Perkin Elmer Corp (Agilent SureSelect Human All Exon 38MB, Illumina HiSeq 2000, BWA)	Proband	76.6	65.96

\*ACHRI/CHGI: Alberta Children's Hospital Research Institute/Center for Health Genomics and Informatics, Calgary, Canada; WASH U; Washington University, St. Louis, USA; BGI: Beijing Genome Institute, China

#### **h) Vision for the Future - Business Plan 2015-2020**

The Need: In its 2015-2020 Strategic Plan, the Cumming School of Medicine (CSM) identifies personalized or precision medicine as a core concept around the School's pan-institute strategy for "creating the future of health". The concept and scope of the initiative incorporates the four CIHR research pillars: basic science, clinical, population health and health services delivery. It will require enabling research platforms including: clinical trials infrastructure, bioinformatics, genomics, advanced imaging and advances in the secure storage and ultra-rapid integration and analysis of "big data" from multiple sources.

The Government of Alberta, Alberta Innovates – Health Solutions, Alberta Health Services, and the universities within Alberta, while recognizing the importance of the "big-data" problem, do not yet have a framework/plan for the provision of big data computational services that could support our collective needs into the future. A comprehensive solution encompassing all potential stakeholders is very expensive, complex, and it is difficult to gauge support for such an endeavor in these trying economical times.

The Opportunity: ACHRI is committed to a partnership with IBM to create a readily achievable, affordable, consolidated, flexible, scalable pilot of a high-performance analytics platform, the architecture of which would support storage, computation, workload management, linkage, and analysis of a variety of data sources (clinical, imaging, genomics and other metadata, see Figure 1 prepared by IBM). The system will have the capacity to align with and complement computational infrastructure investments already made in the CSM Center for Health Genomics and Informatics, the CSM Clinical Research Unit and UofC IT. ACHRI plans to fund the initiative out of investments that both the Institute and the CSM (e.g. CFI JELF awards) will make: a) to support the recruitment and start-up of multiple new investigators (including four PPC approved bioinformaticians), and b) from planned investment in platform development.

The information technology (IT) infrastructure that supports the CSM Centre for Health Genomics and Informatics is housed in a server room in the basement of HSC. The information technology architecture has been built on a model whereby each new partner/ major user purchases a separate server to provide capacity and secure, independent work environment for each partner/investigator. The cost has typically been in the range of \$250,000 for each new partner/informatician. This is an inefficient model to carry into the future, and one, which does not have the other necessary capabilities of linking various research datasets/applications and analyzing them in an integrated fashion. In the next two years, ACHRI anticipates a requirement to invest at least \$1,000,000 in IT infrastructure if the previous model is continued. Discussions with IBM have indicated that accelerating life science discovery using a high-performance analytics platform capable of operating in a collaborative environment would be of similar cost yet provide enormous potential additional benefits. ACHRI has decided that it will commit these resources to this innovative approach and provide a pilot environment in which we can move the precision medicine, clinical trials and the health outcomes research agendas forward within the Cumming School of Medicine and enhance the training opportunities for the next generation of clinicians and scientists. The initiative will further facilitate innovation, software and IT product development.

Within the pilot proposal, ACHRI plans to support three demonstration projects that are aligned with our theme and platform strategic plan:

- Alberta Birth Cohort Data (ABCD) set: This is a longitudinal patient cohort of 5500 maternal pairs with comprehensive antenatal, prenatal, postnatal, developmental and social determinants of health data, as well as fMRI imaging data and the potential for whole genome data on each patient.
- Model Organisms Research for Paediatric Health (MORPH): This program integrates an interdisciplinary group of clinical specialists in molecular genetics, computational biologists, and developmental biologists who exploit model organisms to decipher the molecular and cellular basis of pediatric rare disorders. The team will interrogate disease gene function, using advanced technologies to manipulate gene expression in model organisms, and to examine abnormal development associated with genetic diseases in children. This initiative seeks to establish sophisticated, laboratory-based, mechanism-centred resources capable of revealing gene function in simple organisms to inform patient diagnosis, prognosis and treatment.

- KidOmics: This translational research program will assess the impact of implementing a local model of the provincial strategy for an integrated Genomic Health Program that could provide preventable, predictive, personalized and cost effective genomic health services for all Albertans across the lifespan. The goal is to use a person's DNA information to improve patient care by supporting early and accurate diagnosis, individualized treatment, and avoid unnecessary and invasive diagnostics testing and harmful and ineffective interventions.

### **3. The 3T Imaging Platform/Child and Adolescent Imaging Research (CAIR) Program**

**a) Historical Background:** The vision for an Alberta Children's Hospital Research Institute Pediatric 3 T Imaging platform and program was identified as a high priority need of the child health research community in the 2009 planning process leading up to the 2010-2015 ACHRI Strategic Research Plan. Implementation of the vision was structured around the installation of the research 3 T MR scanner at ACH in 2012.

The goals of the imaging platform are to: 1) use imaging technology as a research tool to generate new knowledge about the pathophysiology, diagnosis and treatment of illness or injury in children and youth, 2) in collaboration with our partners in healthcare translate that new knowledge and apply imaging technology to improve patient care, safety and outcomes, 3) train the next generation of clinician investigators and scientists in the application of imaging technology to a better understanding of the pathophysiology and management of illness and injury affecting children and youth, and 4) leverage partner support and seek external funding/grants. These goals translate research and training into meaningful improvements in the lives of Albertan children and their families.

These activities require and build upon the close working relationship between the University of Calgary (UofC) and Alberta Health Services (AHS). The key stakeholders within the AHS and the UofC include the ACH, ACHRI and the AHS and UofC Department of Diagnostic Imaging/ Radiology. The successful realization of the initial vision through the purchase and installation of a turnkey scanner facility in 2012 (\$4.8M) with supporting research infrastructure, scanner warranty and service contract (\$1.4M), the renovation of space in the basement and on the 4<sup>th</sup> floor of the ACH for the Child and Adolescent Imaging Research program and mock scanner facility (\$0.75M), recruitment, start-up and graduate training funding (\$2.45M) has been achieved with the generous philanthropic support of the ACHF.

The renovation of the basement “dry lab” and 4<sup>th</sup> floor simulation scanner and “dry lab” imaging spaces within ACH was completed in the fall of 2014. In September 2014, the MR simulator was installed in the ACH 4<sup>th</sup> floor location along with behavioral testing and eye tracking technology, helping to create a state of the art pediatric neuroimaging research facility. The simulator is already proving useful for preparing children for their MRI scans. It is currently being used by six research teams in addition to the child life specialists who are developing protocols to reduce the need for anesthesia in clinical scans. To further this effort, a research competition was held in March 2015 seeking proposals to study the effectiveness of the mock scanner in reducing the need for a general anaesthetic. The \$150,000 grant was awarded to Dr. Catherine Lebel, PhD, and Dr. David Lardner, MBChB, FANZCA, Pediatric Anesthesiologist.

**b) Governance and Operation:** The scanner is operated and administratively managed by the AHS Department of Diagnostic Imaging with input from key stakeholders via a collaborative governance model outlined below. The Pediatric 3 T Imaging Program is accountable to both the AHS and UofC Department of Diagnostic Imaging and to ACHRI. Three committees have been established to oversee the activities associated with the program:

- The **Pediatric Imaging Research Program Steering Committee** has membership from ACHRI, ACH Administration, AHS and UofC Department Radiology and Section of Pediatrics Radiology and ACHF. It reports through the AHS Clinical Department Head Radiology to the AHS Senior Executive (SVP, Clinical

Support Services, VP Diagnostic Imaging, CMO Medical Affairs – Calgary) and through the UofC Head of Radiology and ACHRI to the Cumming School of Medicine, University of Calgary (Senior Associate Dean (Research)). The purpose of the Steering Committee is to: 1) provide a forum for the discussion of ideas, concerns and recommendations related to the operation, development and growth of the ACH/RI Pediatric Imaging Research Program, 2) discuss recruitment of scientific and support personnel, 3) to advise both the University of Calgary (UofC), and Alberta Health Services (AHS) on policy and procedures affecting research projects within the program, 4) ensure financial viability of the program, 5) promote effective communication between the UofC and AHS, 6) resolve conflict between research projects if agreement cannot be achieved at the operational level, and 7) to liaise with the ACHF. The Steering committee meets quarterly.

- The **Pediatric Imaging Research Program Operations Committee** includes representation from ACHRI's Child and Adolescent Imaging Research program, AHS and UofC Department of Radiology and Pediatric Radiology and ACH Administration. The Operations Committee reports to the Steering Committee. It is responsible for: 1) fostering MR research and development within the Pediatric Imaging Program, 2) ensuring the safe, efficient and effective operation of the 3 T magnet, 3) monitoring trial and funded research protocols on the 3 T magnet, 4) allocating scanning time on the 3 T magnet, 5) monitoring the performance of the MR system, Chair to correspond with vendor as required, 6) overseeing the selection, purchase, installation and operation of equipment related to the 3 T magnet, 7) overseeing operational issues relating to: scientists, clinicians, post-graduate trainees, MR technologists, nurses and other support personnel, volunteers, inpatients and outpatients, and other departments within the AHS and the University of Calgary, 8) advising the steering committee on policy, procedures and ongoing research activity as it relates to the Pediatric Imaging Research Program, 9) ensuring operational viability of the program, 10) the proper management of research imaging data, 11) promoting effective communication between the UofC and AHS, and 12) resolving conflict between research projects if agreement cannot be achieved at the operational level. The Operations Committee also hosts ACH Pediatric Imaging Program Investigator meetings every 4 months to facilitate communication and gather feedback from investigators on operational issues. The Operations committee meets monthly.
- The **Joint Scientific Review Committee** is comprised of imaging research scientists from ACHRI's Child and Adolescent Imaging Research program, the Seaman Family Centre and U of C Department of Radiology. A joint committee provides a degree of arm's length review of submitted proposals and ensures a broader base of scientific expertise. In order to promote translational research, membership includes both clinical and basic science investigators. It provides a forum for the discussion of ideas, concerns, and recommendations related to research and is responsible for: 1) reviewing, and approving all proposed research, 2) encouraging research, while ensuring continued fiscal viability. The Joint Scientific Review Committee reports to both the Pediatric Imaging Research Program and Seaman Family Centre Steering Committees.

**c) Leadership and Team Membership:** The platform's research team has expanded rapidly with the support of an ACHF Chair (Dr. Frank MacMaster in 2010), the ACHRI Scholars Program (Drs. Catherine Lebel and Signe Bray in 2013 and Ashley Harris in 2015) and a collaboration with General Electric (Dr. Marc Lebel in 2012) and is now comprised of five faculty members.

Dr. Signe Bray was appointed as Scientific Director of the CAIR program in 2015. She leads a team of PhD imaging scientists with the following interests and expertise:

- Dr. Signe Bray, Assistant Professor, Section of Imaging Science, Department of Radiology. The goals of her research program are to improve understanding of healthy brain and cognitive development, as well as atypical development related to disorders such as autism spectrum disorder, preterm birth and genetic syndromes.

- Dr. Ashley Harris, Assistant Professor, Section of Imaging Science, Department of Radiology. She is an expert in MR spectroscopy and its pediatric applications. She plans to build a research program applying spectroscopy and other imaging tools to understand the structure, function and chemistry of perceived pain and the progression of brain recovery after a traumatic injury
- Dr. Catherine Lebel, Assistant Professor, Section of Imaging Science, Department of Radiology. She specializes in the use of diffusion tensor imaging to assess white matter microstructure. Her research interests include brain plasticity in response to learning, treatment or intervention, and brain maturation in healthy children and those with fetal alcohol spectrum disorder or autism spectrum disorder.
- Dr. Marc Lebel, Adjunct Professor, Section of Imaging Science, Department of Radiology. As part of the negotiated research agreement with General Electric Healthcare (GEHC), he has been located to Calgary as a GEHC Scientist to support 3 T MR imaging research. He provides technical and scientific MR imaging expertise to other researchers using the 3 T scanner and develops new image acquisition and reconstruction techniques.
- Dr. Frank MacMaster, Associate Professor, Department of Psychiatry, Scientific Director of the AHS Mental Health Strategic Clinical Network. He has been studying the effect of two novel approaches to the treatment of depression in youth: 1) exercise and 2) repetitive transcranial magnetic stimulation (rTMS).

Collaborating with this core group of imaging scientists, are the imaging research scientists at the Seaman Family MR Research Center and other imaging scientists in the Department of Radiology, U of C, as well as the pediatric radiologists at ACH. In addition, Dr. Bruce Pike was recruited in 2013 as a senior imaging scientist, Head of the Section of Imaging Science and Deputy Head Research in the Department of Radiology. He has considerable experience in imaging in pediatric populations and brings a wealth of expertise and mentorship to the CAIR program.

The CAIR program has grown well beyond its faculty membership to include a total of 31 highly qualified personnel, including research staff and trainees at the MSc, PhD and postdoctoral levels. From May 2014 to August 2014, additional summer students joined the team. The growth exceeded the capacity of the newly renovated imaging space, and in 2015 the five faculty members were moved into ACHRI research office space in the 4<sup>th</sup> floor of ACH creating a total of 31 workstations in the basement (n=19), 4<sup>th</sup> floor mock scanner area (n=8) and an office space in the Department of Paediatrics administrative area (n=4).

**d) Research Programs Supported:** The 3T MR platform enables and the CAIR program supports the research initiatives of ACHRI's Behavior and the Developing Brain theme and aligns with the strategic priorities of each of the principal stakeholders. The existing research initiatives within the theme include: neurodevelopment and child mental health, epilepsy, acquired brain injury and rehabilitation with special focus on concussion. Over time, the scope of activities that this platform enables will expand to include research in other disorders/organ systems, e.g. cancer, cardiac, bone and joint imaging.

**e) Training:** The imaging platform and CAIR program creates opportunities for trainees of all levels – undergraduate and graduate students, postdoctoral fellows, medical students, residents, and clinical research fellows. Support for trainees is garnered from the ACHRI Training Platform, CSM and U of C graduate and post-doctoral programs, Alberta Innovates-Health Solutions (AIHS) and the new International and Industrial Imaging Training (I3T) Program recently funded by National Science and Engineering Research Council (NSERC). Preparing the next generation of researchers to use innovative imaging technology to answer critical questions centred on children and adolescents is a fundamental goal of this program.

**f) Metrics and Performance:** The metrics that will be used to measure accomplishment include: acquisition of competitive external funding, number and quality of publications, presentations and recognition,

translational impact and leveraging of philanthropic investments.

This past academic year, 2014/15, the group successfully obtained both national and provincial funding from the Canada Foundation for Innovation to support this new infrastructure; new research funding has been secured from CIHR (Canadian Institutes of Health Research), NeuroDevNet, and NSERC (National Sciences and Engineering Research Council of Canada)

The program is now supported by a full-time research assistant who facilitates imaging research for investigators outside the Department of Radiology.

The CAIR Program has 26 approved imaging studies underway lead by 13 Investigators. Investigators are drawn principally from the Departments of Radiology, Clinical Neurosciences, Psychology, and Psychiatry as well as the Hotchkiss Brain Institute (Full members: 1), and the Alberta Children's Hospital Research Institute (Full members: 12). Active research areas include: depression, Tourette's syndrome, pediatric stroke, childhood obesity, healthy brain development in preschool children, development of language and attention skills, autism spectrum disorder, attention deficit hyperactivity disorder. To build capacity, enhance utilization and productivity, the program is supported by a full-time research assistant who facilitates imaging research for investigators outside the Department of Radiology.

A total of 1350 MR scans were completed in the 2014/15 fiscal year, an increase of 187 scans over last year. Of these scans, 405 (30%) were research and 945 (70%) were clinical. Clinical scans were 73% Neuro, 22% Musculoskeletal and 5% other. The number of research scans has increased significantly from 2013/14 when only 153 (13%) research scans completed and the remaining 87% were clinical scans. The percentage of research scans is expected to continue to increase each year as the research program continues to expand.

Scan cost recoveries of \$222,750 were achieved due to the 405 research scans. With the success of the imaging program, the CAIR Program Steering Committee approved the creation of a pilot scan program which will allow investigators 5-10 scans free of charge to collect data which can be used for grant submissions to leverage additional funding. A maximum of 30 scans will be allocated each year.

**g) Vision for the Future-** ACHRI Business Plan 2015-2020: The CAIR program was founded in 2012 and was built through investments from ACHRI, the ACHF, the University of Calgary, and Governments of Canada and Alberta in support of people, programs and infrastructure. In a very few years, a platform has been built including a research dedicated 3 Tesla MRI scanner, an MRI simulator for training children before their scan, eye tracking equipment, state of the art image acquisition software, computer infrastructure and an outstanding team of 5 imaging scientists whose expertise spans all aspects of human brain imaging, including imaging of brain structure, function, blood flow, and chemical composition. Philanthropic investments have been successfully leveraged into competitive research grants. CAIR Program scientists have funding from tri-council agencies (NSERC, CIHR), Canadian Networks of Excellence (NeuroDevNet), private foundations (SickKids Foundation), industry (General Electric), and clinical networks (Alberta Mental Health Strategic Clinical Network). There are now two CIHR operating grants and two CIHR Foundation grants using this platform, in addition to NSERC, private foundation- and philanthropy-funded studies. To maintain, and truly capitalize on, this tremendous momentum, a continued investment in space, equipment, and people is needed. Our 5-10 year vision is to become a nationally and internationally leading center in pediatric imaging. To achieve this vision, we must focus on a few research goals, continue to grow our scientific capacity by recruiting leading researchers in the field, build on our infrastructure by investing in new equipment, and to consolidate our staff for enhanced interaction and productivity.

#### **Research Goals:**

- To discover imaging-based biomarkers of neurodevelopmental and mental health disorders as well as brain injury.
- To utilize imaging-based biomarkers to guide rational treatment approaches and monitor outcomes.

### **Faculty Recruitment:**

- Expand capacity in new and growing areas of pediatric imaging. Key areas in which we could expand include cardiac and fetal and neonatal imaging. We already have significant strength in clinical cardiac fMRI and the potential to collaborate on recruitment of a **PhD cardiac imaging scientist** with the Stevenson Cardiac MRI Center and the Libin Institute. Similarly, we have significant clinical capacity in neonatology and research strength our Behaviour and the Developing Brain theme and specifically in neurodevelopment. In order to identify abnormal neurodevelopmental trajectories from the earliest possible age, **imaging fetal and neonatal brains** is a clear path forward. We have seen tremendous technical growth in this area, creating an opportunity to hire a faculty member who will bring these capabilities to our site. Note that these recruitments would require specific additional infrastructure investments – e.g. fetal/neonatal-specific imaging coils, incubators, and transport systems.
- Recruit dedicated senior leadership

### **Equipment:** Program growth in the next five years requires investment in new equipment:

- A research-dedicated 3T MRI, over which the Institute has full administrative control. This system would ideally be sited on University of Calgary land.
- A PET-MRI system co-located with the research dedicated MRI
- Fetal/neonatal imaging equipment, and specialized head coils (e.g., pediatric-specific, multi-nuclear).

**Space:** As of October 2015, the CAIR Program members are spread out over four different spaces in the Alberta Children's Hospital. This configuration limits the spontaneous interactions between our students and fellows, which is detrimental to the training experience and results in inefficient sharing of knowledge and expertise. The foremost goal of our program is to identify a contiguous space with room for 60 trainees of varying levels (undergraduate, graduate, and postdoctoral), as well as 8-10 faculty members. Improved links with faculty and staff at the Foothills site is also desirable to promote interactions with the Seaman Family MR Research Centre and the Healthy Brain Aging Initiative.

**Engagement with scientific and local community:** We will host a 5-year anniversary event featuring top international speakers and local scientists. This event will include a research day and several days of workshops. Through this event we will both build capacity in our group by inviting experts in new areas of imaging acquisition, processing and analysis, and build our brand by showcasing our truly outstanding program to the international community. . The research day will conclude with a social event inviting the local community and recognizing philanthropic donors

## **4) Clinical Research Support Platform**

**a) Historical Background:** In the mid-1990s the Department of Paediatrics and the leadership of the Child Health Research Center were successful in a request to the ACHF for five years of seed funding to establish a Research Methods Team that would support the development of clinical research on the old Richmond Road Alberta Children's Hospital site. An epidemiologist, biostatistician and a health economist were hired with 50% of time allocated to pursue independent research with U of C academic appointments in the Department of Paediatrics, and 50% allocated to a consulting role to ACHRI membership. After the initial five years of funding, sustainability became an issue. The Child Health Research Center assumed ongoing financial support for members of the Research Methods Team as a transitional solution while alternatives were evaluated. One of the three investigators secured an AHFMR Scholar award and the CSM eventually assumed responsibility for ongoing salary support when the Government of Alberta terminated AHFMR and created Alberta Innovates. In 2010, there was concern expressed by the ACHF regarding academic salary support that was not of specific term or leveraging University support of child health research initiatives. There was little interest in the philanthropic

community for supporting the growth of clinical research in child health through the permanent funding of UofC academic salary lines. In 2012, ACHRI offered the remaining two ACHRI funded faculty in the Research Methods Team five years of salary support during which time they had no service responsibilities to ACHRI, but could focus their energy on developing their academic credentials. At the end of five years, the CSM would evaluate their performance and eligibility for ongoing tenure track positions. ACHRI continues to build clinical research infrastructure in sustainable ways and in 2014 ACHRI led the recruitment (and provided start-up funding) of a biostatistician, whose research is child-health focused, into a tenure track position in the Department of Community Health Sciences.

**b) Governance and Operation:** The Clinical Research Platform lead is accountable to the Scientific Director and through him to the Director of ACHRI; however, reports to the Executive Director ACHRI from a management/human resources perspective. The platform receives direction on high level operational priorities from the Scientific Director and advice on strategies for implementation from the ACHRI Clinical Research Operations Committee that is comprised of six representatives who are full members of ACHRI and are active clinical, population health and health services delivery researchers (predominantly from the Healthy Outcomes Theme).

**Platform Mandate:** To support and advance the clinical, population health and health services delivery research capacity of ACHRI members and their teams, through consultation and direction at all stages of research, and by ongoing novel academic collaborations. All ACHRI members have access to 6 hours of free research consultation per project, after which, additional services are available at the prorated cost of \$50 per hour. Research support is offered through direct solicited consultation, regular seminars and lectures, and drop-in sessions to address specific methodological questions, or to initiate longer-term consultations for ACHRI members across the faculties of Arts, Kinesiology, Nursing and the Cumming School of Medicine.

**Academic research support agenda:** The ACHRI Research Support Platform has evolved since its inception in July 2012, in response to the changing needs and capacity of ACHRI researchers, and institutional transition. The platform has developed *de novo* processes and provided excellence in research support aiming to augment research capacity through a changing institutional and economic landscape.

The platform provides ongoing consultation to all full and associate members of ACHRI and their trainees who have requested support since July 2012 in the following domains:

Project planning and development:

- Formulating research questions and hypotheses
- creating/refining study design to appropriately answer research questions
- Ensuring feasibility of research within budgets, time constraints and specific population characteristics
- Developing/redesigning methods to achieve research objectives and maximize scientific outputs and clinical/population impact
- Directing sample size calculations and analysis planning

Project execution and conduct:

- Directing and database design and coding, data collection and management
- Providing bias minimization strategies, adequate measurement of extraneous/confounding variables
- Creating and providing randomization modules
- Leading integrated interim data analysis techniques
- Directing and overseeing interim analyses, power projections and providing decision support
- Educating, directing and overseeing qualitative sampling recruitment and data collection strategies

Analysis and reporting:

- Directing data cleaning and preparation
- Planning, biostatistical analysis with ongoing direction and oversight
- Directing and conducting qualitative analysis and auditing
- Assisting with interpretation and appropriate reporting of biostatistical and epidemiologic results
- Conducting advanced analyses
- Contextualizing results and analyses in current state of knowledge

Academic collaboration:

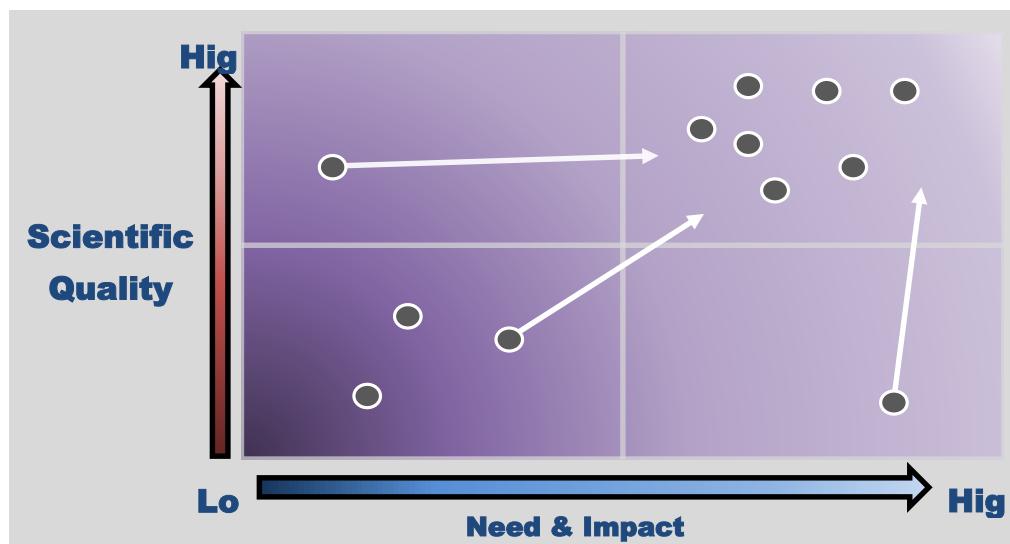
- Providing internal peer-review of grant applications and manuscripts for publication
- Co-investigating hypothesis-driven maternal and child health research questions
- Co-authoring peer-reviewed manuscripts
- Facilitating networking between academic researchers to forge excellence in maternal and child health research teams

**c) Leadership:** Katie H. Chaput, PhD. is the platform lead. She is an epidemiologist with over ten years of experience with quantitative, qualitative and mixed-methods research, and has advanced biostatistical training. She has an Adjunct Assistant Professor appointment in the Department of Paediatrics and Community Health Sciences. Her personal program of research focuses on perinatal maternal health interventions to improve maternal and infant health outcomes.

**d) Research Programs:** The platform supports ACHRI members conducting clinical, population health and health services delivery research.

**e) Training:** The platform encourages the involvement of graduate students and post-doctoral trainees in research projects, but the platform is not a substitute for their mentors having clinical research training and skill sets.

**f) Metrics and Performance:** Initially the platform was instigated to meet a broad array of demands assessed by systematic needs assessment survey and case-by-case evaluation:



- Studies with low scientific and methodologic rigour are elevated through direct methodological and biostatistical consultation.
- Studies with poor potential impact on child and maternal health systems and outcomes are elevated through broadening or redefining research questions and populations to fill crucial knowledge gaps and to generate important, needed evidence.

### **Platform achievements July 2012-October 2015**

Research support consultations:

<b>Category</b>	<b>Domain</b>	<b>Consultations to date</b>
<b>Quantitative Methodology</b>	Project planning and development	40
	Project execution and conduct	52
	Analysis and reporting	36
<b>Qualitative Methodology</b>	Project planning and development	15
	Project execution and management	22
	Analysis and interpretation	6
<b>Academic Collaboration</b>	Internal Peer Review	46
	Addressing reviewer comments and resubmission	18
	Co-investigation (grant)	6
	Co-authorship (manuscript/presentation)	14
<b>Total</b>		<b>210</b>

### **Lectures and Seminars July 2012 to October 2015**

<b>Topic</b>	<b>Number</b>
Qualitative Methodology	9
Biostatistics	6
Database design/setup	3
Grant/proposal development and writing	5
<b>Total</b>	<b>23</b>

Grants consulted on:

<b>Source</b>	<b>Status</b>	<b>Total Amount</b>
External	Received	\$5,306,000
	Pending	\$240,000
Internal	Received	\$39,000
	Pending	\$6,000
<b>Total</b>		<b>\$5,591,000</b>

**g) Vision for the Future:**

Clinical research infrastructure is generally agreed to be in significant need of development in Alberta. The Government of Alberta, Alberta Health Services, Alberta Innovates, the University of Calgary and the Cumming School of Medicine have identified investment in clinical research infrastructure a priority. ACHRI will not duplicate these investments, but rather wishes to collaborate and make synergistic, complementary investments that enhance clinical research capacity in child health. Significant clinical research resources are already available to our membership:

- Cumming School of Medicine's Clinical Research Unit <http://cru.ucalgary.ca/>
- Alberta SPOR SUPPORT units <http://www.researchalberta.ca/>
- Department of Paediatrics Research Methods and Research Advancement teams
- Department of Community Health Sciences, CSM
- O'Brien Institute of Population and Public Health, CSM
- Alberta Health Services Research Administration Pathway and Research Facilitation Services

ACHRI will maintain a modest clinical research consultation service specifically to support associate members striving to improve their clinical research proposals. The service is not intended to be a substitute for faculty members accessing the necessary training and acquiring the skills necessary to conduct clinical research. Currently, the platform is facing increasing demand for research support that will necessitate a triaging process that will prioritize:

- Project proposals being submitted for external funding
- Projects aligned with Institute strategic research priorities (the three themes)
- Highly ranked but unfunded projects requiring increased rigour and/or scope to achieve success

Going forward the Institute will build additional child health clinical research capacity in a sustainable fashion by: i) supporting the recruitment of clinician scientists into relevant academic departments (e.g. Paediatrics, Obstetrics and Gynaecology, Community Health Sciences) when retirement creates opportunities, and ii) competing for external salary awards such as Canada Research Chairs, CIHR New Investigator awards, AIHS Translational Chairs or opportunities to leverage philanthropic support for specific term salary support into long term CSM support of successful recruits (ACHRI Scholars Program). Successful clinician scientists with epidemiologic, methodologic, biostatistics, informatics and other skill sets recruited through these mechanisms would then attract graduate and post-doctoral trainees to participate in collaborative research and further enhance clinical research capacity and critical mass.

As the research capacity within ACHRI grows and research focus shifts increasingly toward ACHRI's strategic priorities, the need for more complex and involved research support will be necessary.

## **Appendix 9: Alberta Children's Hospital Foundation Funding Commitments 2015-2020**

## **Appendix 10: ACHRI Core Operating Budget 2016-2021**

## **Appendix 11: ACHRI Philanthropic Funding Opportunities 2016-2021**

### **Note to Readers**

ACHRI's Business Plan is both a clear outline of the Institute's research agenda and an aspirational summary for the next five years. ACHRI's leadership team and our members are aware of, and sensitive to, the challenges of the current environment. Therefore, ACHRI's research agenda will be implemented prudently with the support of our research champions and funding secured from philanthropic resources, external grant competitions or other avenues. Consequently, *this document does not include budgets* as they are considered notional at this point. Effective April 1<sup>st</sup>, 2016, ACHRI's research business plan will have core operational funding provided for the next five years as a result of community philanthropy and the initiative of the Alberta Children's Hospital Foundation. Other elements of the business plan will be funded by previously approved ACHF commitments in support of our enabling research infrastructure and child health research programs. Additional elements will depend upon future philanthropy.