AUSTRALIAN LIONS CHILDHOOD CANCER RESEARCH FOUNDATION FELLOWSHIP

Summary:

Childhood cancer is a devastating diagnosis for both patient and family. Whilst childhood cancer accounts for less than 1% of all cancers, it represents the most common cause of death from disease in children. Despite advances in modern medicine that have resulted in an increase in 5-year survival to 80%, children are often left with permanent disabilities and development of secondary malignancies as a result of their disease and aggressive therapies.

Clinician-scientists are ideally placed to identify clinically relevant problems, address them in a research laboratory, and then transfer this newly gained knowledge back into the clinic (bedside – benchtop – bedside). However, the career pathway to becoming a clinician-scientist is difficult, largely due to the financial burden resulting from sacrificing clinical hours to complete postgraduate studies in a research laboratory and concern over 'de-skilling'.

As a result the pool of trained Paediatric oncology researchers in Australia is very limited.

Here, we propose a 3-year fellowship, the "**Australian Lions Childhood Cancer Research Foundation Fellowship**" to provide a unique opportunity for a Paediatric oncologist clinician to train in and develop a Paediatric cancer research program. The highlight of this fellowship is the integration of clinical and research activities at both Monash Children's Hospital (MCH) and The Royal Children's Hospital (RCH) together with their associated research institutes, MIMR-PHI and Murdoch Children's Research Institute (MCRI).

This Fellowship for the first time will strongly unite the two major Victorian Children's Cancer Centre's, and their respective clinical and research staff. The aim is to catalyse further collaboration between all of the entities, leading to important basic and translational research outcomes to improve patient outcomes.

Benefits:

The benefits of Australian Lions Childhood Cancer Research Foundation Fellowship include:

- Unique opportunity for a talented, passionate and enthusiastic clinician to train and develop a research program whilst maintaining a clinical presence.
- Proposed joint clinical duties at MCH and RCH will further develop communication and interaction between Victorian hospitals treating children with cancer.
- Participation/presentation of cases at MCH and RCH multidisciplinary patient care meetings will allow greater discussion and sharing of expertise.
- For the first time structured clinical research collaboration between the clinical and research departments at MCH, RCH, MIMR-PHI and MCRI.
- Building research capacity and expertise in Paediatric oncology, with future opportunities to expand the collaboration to include PhD students.
- Advancement of preclinical research likely to benefit patient outcomes.

Collaboration:

The Australian Lions Childhood Cancer Research Foundation Fellow would be trained and supported by a senior research project team comprised of expert researchers and clinicians from MIMR-PHI (Cain), Monash Health (Algar – previously based at RCH/MCRI) and both MCH (Downie) and RCH/MCRI (Ekert). The proposed research will be undertaken in the Cain, Algar and Ekert laboratories, and will utilise resources and tissues from the Cancer Bio banks at both hospitals. The Fellow would be based at MCH for clinical duties and we propose the fellow will also conduct one clinic per week at RCH and attend all Paediatric cancer multidisciplinary care meetings across both hospitals, resulting in direct or indirect exposure to all Victorian Paediatric cancer

patients. This will facilitate closer integration with MCH and RCH clinical staff and expertise including A/Prof Michael Sullivan (RCH, Head of Solid Tumor and Neuro-Oncology Program).
Thus, the Fellow will provide a clear and important link between hospitals and research institutes as well as bridge research, diagnostic and clinical departments.
An important outcome of the research project is a critical clinical diagnosis and research tool not only for both Victorian hospitals but can be made available to all Australian hospitals treating children with cancer.

Recognition:

The generosity and support of the Australian Lions Childhood Cancer Research Foundation will be recognized as follows:

- Naming rights of fellowship (Australian Lions Childhood Cancer Research Foundation Fellowship).
- Logo display and/or acknowledgement in all resulting posters, presentations and publications.
- Logo display and acknowledgement on relevant websites (including but not limited to clinician/researcher profiles, department/institute pages).
- Community engagement (including but not limited to tours of facilities/laboratories for Lions members and associated groups, clinical/research presentations to Lions clubs/members and associated groups).
- Participation in Lions fundraising efforts by educating the public and potential donors by communicating where their support is directed and how it makes a significant difference.

Fellowship Research Proposal:

Selection of Candidate:

This fellowship will be offered to an outstanding clinical fellow, defined as a medical doctor currently undertaking or about to undertake specialised training in the area of Paediatric oncology. Therefore, the candidate will have direct interaction with and input into patient management whilst simultaneously engaging in relevant cutting-edge preclinical research. The position will be widely advertised in order to attract the most exceptional local, national or international candidate.

Background and Research Plan

Tumours effecting the brain and central nervous system (CNS) are the second most common cancer and most common cause of death in the Paediatric population with 150 new diagnosis annually. Therefore, there is an unmet need for improved clinical management and research in the area of Paediatric Neuro-oncology. In particular, our research proposal focuses on two devastating brain Tumours, Medulloblastoma and Diffuse Intrinsic Pontine Glioma (DIPG) that represent the most prevalent and most aggressive Paediatric brain Tumours, respectively.

Medulloblastoma (MB) is the commonest malignant brain tumor of childhood, and is a leading cause of childhood cancer related morbidity. Current treatment protocols include surgical resection, chemo- and radiotherapy. Although these treatments can cure some children with MB, their effects on developing brains can be catastrophic, resulting in severe developmental and neurological deficits. Genomic profiling studies have recently shown that MB can be divided into four distinct genetic subgroups; WNT, SHH, Group 3 and Group 4, each with distinct clinical outcomes. Treatment approaches that target distinct MB genetic subgroups have been recently adopted in overseas clinical settings and show extremely promising results. Thus, genetic classification of MB, when combined with treatments appropriately targeted to their tumour subgroup, has the potential to dramatically improve outcome for children with MB.

Diffuse intrinsic pontine glioma (DIPG) is a rare Paediatric brain stem tumor that accounts for 10-15% of all Paediatric brain Tumours. Because of the location of the tumor in the brain stem, resection is not an option and tumor biopsy material is scarce.
Despite the use of intensive radiotherapy and chemotherapies in DIPG there is presently no curative treatment and the median survival for these children is only 9 months. This makes DIPG the most lethal and devastating Paediatric tumor. With no effective treatment there is an urgency to better understand the underlying genetic and molecular biology in order to devise new therapeutic strategies.

Specific Aim 1. *Establish a local MB molecular subtyping service to provide accurate, reliable, rapid and cost-effective analysis of Victorian and Australian patients.*

In response to a growing demand from Paediatric oncologists and parents we have provided young Victorian MB patients access to the latest technologies for genetic subgrouping of their disease, through our collaboration with the Hospital for Sick Children in Toronto. However, the high cost of shipping samples, associated delay in generating relevant data, and inability of the Toronto group to continue to provide this service makes this arrangement unsustainable. MB subgroup analysis is not performed in Australia and with increased demand from clinicians and the families of MB patients for molecular subgroup testing, both in Melbourne and nationally, there is an urgent need to establish this technique locally. Integration of routine MB molecular tumor profiling in the Molecular Pathology laboratories at MCH and RCH will be a significant step forward in achieving best outcomes for these patients Australia-wide.

Specific Aim 2. *Investigate a role for the disruption of genomic imprinting in DIPG to better understand the biology of the tumour.*

Imprinted genes are developmentally critical genes that normally maintain monoallelic expression from either the maternal or paternal chromosome. Disruption of imprinting is a common mechanism in Paediatric Tumours but has not been explored in DIPG. By performing RNA-Seq on DIPG tissue, available from the MCH and RCH Cancer Bio banks, and on human DIPG cell lines available in Dr. Cain's laboratory this aim has the potential to identify new gene targets for potential therapeutic intervention.

Specific Aim 3. *Preclinical investigation of pharmacological epigenetic modifiers in DIPG to evaluate their therapeutic potential.*

Modulating the cellular histone acetylation/deacetylation state using specific inhibitors to histone deacetylases represents a potential approach for cancer therapy. DIPG is a tumour in which numerous modifications to gene expression are predicted due to the nature of the prevalent Histone H3.3 mutation in this disease. For this reason, drugs that directly modify chromatin are deserving of investigation. Here, we will explore the potential of pharmacological epigenetic modifiers in human DIPG cell lines *in vitro* and *in vivo*.
Since many pharmacological epigenetic modifiers are in advanced clinical trials, or are already FDA approved for other diseases, positive outcomes from this aim have the potential to be rapidly translated into the clinic.