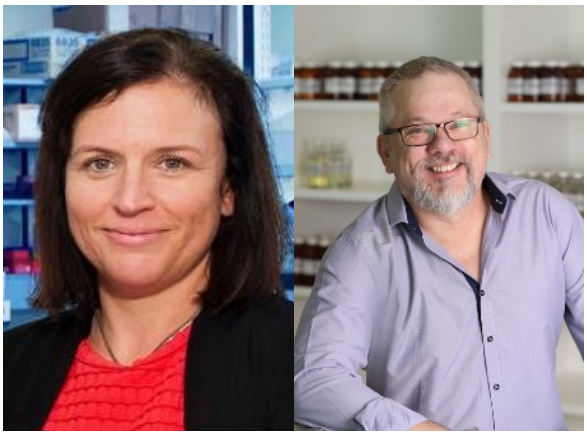
The *RUNX1* Research Program Quarterly Newsletter

Dear Friends,

In the winter newsletter we hinted at some exciting developments for our program and the FPD/AML field at large. This newsletter will introduce two exciting developments: firstly, an important study we are funding that will amalgamate existing research data on families across the world with the germline RUNX1 mutation, and, secondly, we will introduce our partnership with the National Institutes of Health (NIH) on a groundbreaking clinical and natural history study they will be undertaking. We would also like to announce upcoming dates for our next RRP-ALSF grant cycle (our grant partnering with Alex's Lemonade Stand for Childhood Cancer). November 4-6, 2018, will be our second annual RUNX1 Research Program Scientific Meeting, and this year the meeting will take place in our very own Santa Barbara, taking the form of a scientific retreat.



Dr. Anna Brown and Prof. Hamish Scott, Centre for Cancer Biology, University of South Australia

The RUNX1 FPD/AML Mutation Database

In the last newsletter, we mentioned that during one of last November's RUNX1 Scientific Meeting breakout sessions in Philadelphia, it was widely agreed upon that integral to the field was a better understanding of the relationship between a patient's germline *RUNX1* mutation and their secondary mutations. Aggregation of current national and international datasets was seen as a priority to help direct further research models and aims.

We are pleased to announce that we have awarded a one-year, $90,500 grant to Dr. Anna Brown and Professor Hamish Scott of the Centre for Cancer Biology at the University of South Australia and SA Pathology for this very purpose, in their creation of an 'FPD/AML RUNX1 Mutation Database'. Dr. Brown and Dr. Scott will present an update on the database at our November scientific meeting. Following is a description of the project:

Dr. Anna Brown and Prof. Hamish Scott, Centre for Cancer Biology at the University of South Australia and SA Pathology, 'FPD/AML RUNX1 Mutation Database'.

Recent advances in genetic sequencing technology applied by many FPD/AML research groups around the world have highlighted their value in understanding the somatic genetic changes that are associated with the development of malignancies in germline RUNX1 mutation carriers. Collectively, this information can lead to powerful insights that are essential in order to apply precision-medicine based diagnosis, risk assessment, monitoring, and therapeutic intervention. Dr. Brown, Prof. Scott and the team at the Centre for Cancer Biology in Adelaide are leading a project

to generate a data-sharing platform for investigators to contribute germline and somatic genomic sequence data from germline RUNX1-mutated individuals. The aim is to use genomics analysis software developed at the Centre for Cancer Biology to create a custom-designed web portal for RUNX1 genomics data. This will allow investigators from around the world to deposit data in a central location where it can be viewed and queried as a single cohort. Generating a RUNX1 world genomics cohort through data aggregation will allow significant genetic and biological questions to be asked and answered, providing a resource that will continue to grow with ongoing sequencing efforts.

Dr. Brown and Prof. Scott are currently contacting investigators who have published datasets, and if you are a researcher with questions or have data you wish to contribute to the project, please contact Dr. Brown directly referencing 'RUNX1 Research' at anna.brown@sa.gov.au.

The National Institutes of Health RUNX1-FPD Clinical Research Center and Study

The above-mentioned aggregation study will make great strides in our current understanding of the disease and in informing immediate research. Longer term, the field requires a comprehensive, longitudinal (patients will be followed over time), centralized, natural history study; collating genomic and phenotypic data to then use bio-informatics on the dataset, allowing any qualified investigators access. This was one of our organization's foundational goals, and thanks to the tireless efforts of one of our Scientific Advisors, Dr. Paul Liu, it will now become reality. We are absolutely thrilled to share with you a groundbreaking new Research Study that will be taking place at the National Institutes of Health commencing fall of 2018. In addition to providing a foundation for future research in the field, the Research Center will provide cutting-edge, best-in-kind therapeutics to those with RUNX1 FPD/AML who go on to develop leukemia, and at no cost to the patient.

Following is a brief review of the relevancy of this study to our disease understanding, along with a more detailed description of the Clinical Research Center and Study. In the coming months we will be reaching out to affected families, clinicians and researchers following FPD/AML families, genetic testing companies, AML groups, and more. If you are interested in participating in this study in any format, either personally or via recommendation, you will be taking an active role in pushing the field one step towards finding a cure. All data will be secured at a governmental level and kept completely anonymous for the purpose of research.

Dr. Paul Liu, NHGRI

Dr. Paul Liu, NHGRI, Dr. Dennis Hickstein, NCI, Dr. Lea Cunningham (Clinical Director), 'The National Institutes of Health RUNX1-FPD Clinical Research Center and Study'.

We know that a germline *RUNX1* mutation causes a syndrome known as familial platelet disorder with associated myeloid malignancies (FPDMM, or simply FPD. Note that originally it was believed that only AML resulted from the platelet disorder, hence the original name FPD/AML; whereas, it is now understood that varied types of acute leukemias may result.) Patients with FPD have a life-long risk of developing hematological malignancies with variable clinical presentation and disease penetrance among families with different germline mutation types, and even between affected individuals within the same family. Currently, there are no good biomarkers or assays to predict the development of leukemia, and the fact that many FPD

patients do not go on to develop leukemia suggests that the original *RUNX1* mutation in itself is insufficient for leukemogenesis; additional mutations (both somatic and inherited), followed by clonal evolution are needed.

To better understand the natural history of FPD, and to identify individuals at higher risk of developing leukemia, we are establishing a new clinical research program at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland dedicated to the study of FPD. This program has three components. The first component involves identifying or confirming RUNX1 mutations in index cases and family members by DNA sequencing. The second part consists of a longitudinal natural history study with phenotyping of FPD patients and identifying secondary mutations leading to progression of the disease. The third part consists of a therapeutic or treatment component with a uniform regimen for allogeneic hematopoietic stem cell transplantation. Collaborating and supporting components include the NIH Intramural Sequencing Center for genomic sequencing to identify secondary mutations, NIH CC Laboratory of Medicine for CLIA-certified diagnosis, genetic counseling service, and other clinical laboratories. There will be biospecimen and data sharing between this program and investigators in the extramural program. This program is designed to improve the understanding of FPD and enhance the care of these patients.

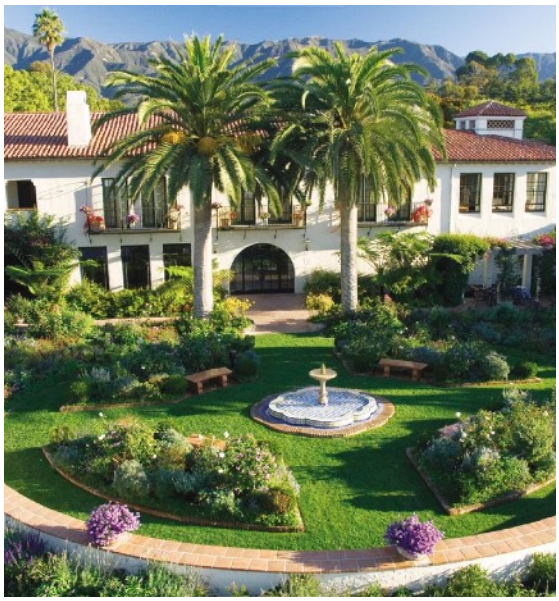
Dr. Liu is an expert on the development of leukemia using genetic and genomic approaches, and has been an instrumental advisor and friend of The *RUNX1* Research Program. In his role as the Deputy Scientific Director of the NIH's NHGRI (National Human Genome Research Institute), he advocated for the creation of the Clinical Research Center and Study within the NIH's Intramural Research Program. He will oversee its overall organization. We are pleased to announce that Dr. Lea Cunningham, a pediatric hematologist and oncologist with fellowship training from Hopkins and NIH and experience as an independent physician-scientist at St. Jude Children's Research Hospital, will direct the overall clinical activities for this program. Dr. Dennis Hickman is a Senior Investigator at the National Cancer Institute's Center for Cancer Research in the Experimental Transplantation and Immunology Branch, as well as being Head of the Molecular Oncology and Gene Transfer Section. Dr. Hickstein has headed the GATA2 Center and Study at NCI and will serve as Senior Advisor.

To ensure the field at large would benefit from the data using the latest in data analytics, we have enlisted the expertise of Dr. Casey Greene of the Perelman School of Medicine at the University of Pennsylvania's Greene Lab (greenelab.com) and Childhood Cancer Data Lab (CCDL). Dr. Greene has been funded by Alex's Lemonade Stand Foundation at the CCDL to democratize cancer genomics analysis. He is developing a system to capture and analyze complex datasets in a user-friendly interface for access to any qualified researcher globally.

Our organization's role in the Research Center and Study will be to encourage families worldwide to participate in the program and to encourage clinicians to collaborate. Moreover, we will aim to fund subsequent research proposals that make use of data generated by the Research Center and Study.

2018 *RUNX1*-ALSF Grant Cycle

We are about to embark upon our third grant cycle in partnership with Alex's Lemonade Stand for Childhood Cancer. We are indebted to Liz and Jay Scott for their support and partnership and for the impact this award has had on the field. Awards are for $250,000 for research leading to the prevention of the transition from pre-leukemia to leukemia for *RUNX1* FPD/AML patients. LOI's are due July 2, 2018 with full applications due October 1, 2018. If you are interested in learning more or applying for our grant program, please click here: https://www.alexslemonade.org/grants/runx1



The Biltmore, Montecito

Second Annual RUNX1 Research Program Scientific Meeting

This year our annual scientific meeting will take the form of a retreat in our own town of Santa Barbara. It will take place November 4 - 6, 2018, at the newly refurbished, historic Montecito Biltmore, a Four Seasons resort, https://www.fourseasons.com/santabarbara on the famed Butterfly Beach. We are happy to host this at a local establishment after the hotel was shut for what will be six months following the natural disasters of December and January. If you are a conference attendee, please stand by for a link to a page with more information on the conference details, such as booking information and agenda. We look forward to it!

Other Business

Our last newsletter announced that we had found and hired an executive director to help us manage the Program. Regrettably, it was not the right fit, and we have re-started our national search. Please reach out to either one of us (mbabich@runx1.com [Monica] or tbabich@runx1.com [Tim]) should you happen to have a suggested candidate for our consideration.

Please continue to follow our progress and spread the word about our efforts.

With thanks,

Tim and Monica Babich