The RUNX1 Research Program Quarterly Newsletter

Dear Friends,

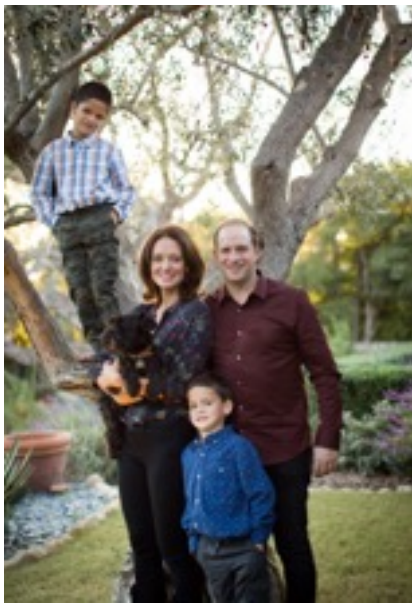
Welcome to our very first RUNX1 Research Program newsletter! Given that this communications marks our first written update, we thought it made sense to share some of our family history and hence the story of how this Program began. We would also like to take this opportunity to thank the people and institutions instrumental to the set-up of RUNX1, and to update you on the $1.25 million dollars of grants we've just awarded, giving a little synopsis of each project. Lastly, we wanted to announce that our first symposium will take place in November 2017, in conjunction with Dr. Nancy Speck and Dr. Paul Liu's International RUNX Conference.

What is the RUNX1 Research Program?

Our mission is to support patients and families with the germ-line RUNX1 mutation (FPD/AML - Familial Platelet Disorder with a propensity to Acute Myeloid Leukemia), functioning in both a research and advocacy capacity to unravel the mechanics of RUNX1 and its evolution to AML. We hope to improve therapeutic options and, ultimately, to find a cure.

Our Family's Story with FPD/AML

Tim's mother was diagnosed with AML in 1995 and received a bone-marrow transplant the following year. Subsequent to her treatment, it was identified that our family carried the mutated RUNX1 gene, which would a few years later be described in the seminal 1999 *Nature Genetics* paper (*Nature Genetics* 23, 166-175 (1999)). Although Mom's transplant was a success, she suffered from Graft-versus-host disease along with other secondary complications to this day. Years later, Tim's maternal aunt developed AML and ultimately passed away from complications. At the time, Tim was working 80+ hour weeks in London at his own investment firm. He came to the realization that given his mutated RUNX1, health needed re-prioritization. Additionally, we determined that some of our children, nieces and nephews shared his low platelet count and, most likely, the mutation. We felt we had to do more than just wait until AML knocked at our door again.



The Babich Family

How the Babich Family formed the Research Program

Dr. Morty Poncz, chief of the Division of Hematology at The Children's Hospital of Philadelphia and a specialist in platelet disorders, has been the Babich family's hematologist for over 30 years, and was the first person Tim approached for advice in the summer of 2015 when he decided to make an organized effort to fund

research into RUNX1. Dr. Poncz was instrumental in providing guidance, serving as chair of the committee of specialists that met in December of 2015 to formulate a plan for how best to develop a grant program. Since then, Tim has travelled and met over 40 leukemia researchers globally at the top of their field. Over a dozen other independent foundations were immensely generous with their time and wisdom. Of particular note is Dr. Michael Lewis of the Evans Foundation, who has been invaluable to us since our inception. Also, Dr. Nancy Speck, Chair of UPENN's Perelman School of Medicine's Department of Cell and Developmental Biology, and a RUNX1 authority, has provided guidance and planning from the start. Dr. Speck served on the Planning Committee and is our family's first point-of-call whenever we have a technical question.

Our Partners

Our mission could not have come to fruition without our grant program partners. We met with many cancer foundations before launching our program, and Alex's Lemonade Foundation (ALSF) stood out for their combination of thoroughness, innovation, and determination. ALSF's philosophy and values mirror our hopes for RUNX1, so we were fortunate to partner with Jay and Liz Scott for our first grant program. We are also very lucky to be working with the Leukemia and Lymphoma Society (LLS) for our second grant program. Dr. Lee Greenberger and Alice O'Rourke have been instrumental to our partnership with LLS. It is our intention to continue with both partners in annual grant programs until we reach our ultimate objective. The partnership with LLS for our current program will award up to $1.8 million across 3 grants intended to fund cutting-edge, translational research in RUNX1. Winners will be announced in the summer of 2017 - stay tuned!

Our Scientific Advisors

We are indebted to the scientific expertise and invaluable insight of our esteemed advisors. These scientists have assisted in developing the organizational plan and vision for the grant program and have also combed through numerous outstanding grant applications, applying thorough review procedures to select the best candidates. Currently, we are in the throes of expanding our website and hope to list and recognize the individuals who have assisted us in our one-and-a-half year journey shortly.

The RUNX1 FPD/AML Research Program and Alex's Lemonade Foundation Grant Awardees

Following is a brief introduction to the principal investigator and the primary topic of research for our first grant cycle. We are thrilled to have such a strong, diverse selection of renown researchers as partners.

Dr. Ravi Majeti, Stanford University, 'Characterization of Pre-Leukemia Associated with Familial RUNX1 Mutations'. Dr. Majeti and his team propose to investigate the disease pathogenesis and pre-leukemia by determining the effects of familial RUNX1 mutations on hematopoietic stem and progenitor cells using CRISPR methods and a mouse host model. Additionally, they aim to determine the contributions of familial RUNX1 mutations in HSPCs and the bone marrow microenvironment to aberrant pre-leukemic hematopoiesis.

Dr. Alan B. Cantor, Boston Children's Hospital, 'Pharmacologic Enhancement of Residual Wild Type RUNX1 Protein Activity in FPD/AML'. Dr. Cantor will investigate whether enhancing the residual wild type RUNX1 protein by pharmacologic means is able to reduce the chances of progression to MDS/leukemia as well as improve the platelet function of the disorder. The hope is to understand RUNX1 regulation in order to develop therapies for RUNX1-related hematologic malignancies. By using

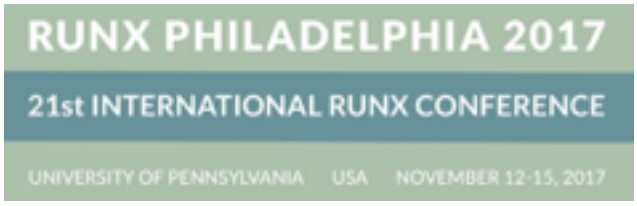
pluripotent (iPSC) cell lines from FPD/AML patients and an in vivo mouse model, the research aims to establish the extent to which SFK inhibitors enhance total RUNX1 activity as well as to establish a high throughput assay for RUNX1 transcriptional activity and screen about 100,000 compounds for additional enhancers.

Dr. Eirini Papapetrou, Icahn School of Medicine at Mount Sinai, 'Identifying Therapeutic Targets to Prevent Progression of Familial RUNX1 Disorder to AML using Novel iPSC Models'. Papapetrou's lab aims to develop an iPSC-based model of progression of familial RUNX1 disorder with the goal of identifying therapeutic targets to prevent leukemia progression.

Dr. Marshall S. Horwitz, University of Washington, 'Restoring RUNX1 Levels in FPD/AML'. Dr. Horwitz's research aims to inhibit the degradation of the wild-type RUNX1 protein through the ubiquitin-proteasome pathway by evaluating drugs currently in use or undergoing clinical trials in other forms of cancer. Additionally, his research will attempt to boost RUNX1 expression to reset its auto-regulatory circuit. Studies will be performed using patient-derived iPSC.

Dr. Leonard I. Zon, Boston Children's Hospital, 'Modeling RUNX1-associated Clonal Hematopoietic Disorders in Zebrafish'. Dr. Zon will use his 'famous' zebrafish program to model RUNX1 FPD/AML to study and understand the combination of secondary mutations to understand disease pathogenesis. This would allow for early recognition in order to reverse abnormally mutated clonal expansion and restore normal hematopoiesis.

Mark Your Calendar!



The RUNX1 Research Program is excited to be a co-sponsor of the bi-annual International RUNX Conference hosted by Dr. Nancy Speck and Dr. Paul Liu at the Abramson Cancer Center at the University of Pennsylvania. The conference will run Sunday to Wednesday November 12-15, 2017. Research Program grantees from both the ALSF and LLS sponsored programs will present to the group and have breakout sessions on Monday the 13th. Email us should you wish to learn more about the conference and its agenda. For more details visit: http://www.runx1.com/philly-2017.

Calling All Families with RUNX1

We are hoping to make contact with more individuals and families affected by the familial RUNX1 mutation. Please visit our website, join our private Facebook page (which is still in the works), and reach out to us via email. We hope to expand our reach to encompass patient and family support, but we also want to ensure we start establishing a confidential database of affected parties to be the first to know of breakthroughs, clinical trials, and relevant research.

Thank You

We are in the fledgling stages, but wanted to extend our gratitude and thanks to the researchers, individuals, friends and family who have supported us in this pursuit. We hope our Foundation encourages RUNX1 research to boost the understanding of the mutation and the pre-leukemic condition in order to identify a solution. We hope you continue to follow our progress and spread the word. Thank you.

Tim and Monica Babich