The RUNX1 Research Program Quarterly Newsletter

Dear Friends,

In this newsletter, you will find an update on our joint grant offering with the Leukemia and Lymphoma Society (LLS). Grants have been awarded to three different recipients, and below we outline a summary of each project. We also wanted to formally announce our Scientific Advisory Board, giving them the due thanks for their time and effort devoted to The RUNX1 Research Program's aims. Finally, please remember to mark your calendar for our first RUNX1 Symposium on November 13, as part of the larger RUNX Symposium taking place November 12-15, in Philadelphia.

RUNX1 - LLS Joint Grant Update

The RUNX1 Research Project has a long-term partnership with the Leukemia and Lymphoma Society (LLS) to provide grants of $200,000 per year for three years for translational leukemia research related to the germline RUNX1 disorder. The hope of the grant program is to encourage and advance therapeutics, and to obtain a greater understanding of familial platelet disorders associated with RUNX1 mutations that lead to acute myelogenous leukemia (AML). Three grants up to $600,000 will be awarded, and this year we are pleased to announce that all three have been granted, to be funded starting in October 2017. We look forward to observing their progress over the coming years and will duly keep you informed.

Dr. Guy Sauvageau, University of Montreal, Canada, 'RUNX1 mutations that confer exquisite sensitivity to glucocorticoids'. Dr. Sauvageau discovered that a class of steroid hormones called glucocorticoids selectively inhibits the growth of acute myeloid leukemia (AML) cells containing *RUNX1* mutations in cell culture. He plans to determine how glucocorticoids inhibit the growth of *RUNX1* mutant AML cells, and to test the ability of glucocorticoids to inhibit AML in a mouse model.

Dr. Benjamin Ebert, Harvard Medical School, USA, 'Interaction of RUNX1 and the cohesin complex in megakaryocyte development and myeloid disease'. Dr. Ebert will study the cooperation between mutations in *RUNX1* and in a gene encoding a member of the cohesin complex, *STAG2*. He plans to generate a mouse model for the combined *RUNX1* and *STAG2* mutations and study hematopoiesis and leukemia progression. He will also evaluate inhibitors of CDK8, a member of the transcriptional mediator complex, for their activity and mechanism of action in the context of *RUNX1* and/or *STAG2* mutations.

Dr. Stephen Nimer, University of Miami - Miller School of Medicine, USA, 'Epigenetic-modifying enzymes in FPD/AML'. Dr. Nimer will evaluate the ability of inhibitors or activators of epigenetic gene

regulation to promote the differentiation, or inhibit the self-renewal, proliferation, and survival of *RUNX1* mutant hematopoietic cells derived from cultures of human-induced pluripotent stem cells (iPSCs). He will also generate a mouse model with combined mutations in *RUNX1* and in a gene called *ASXL1*, which have been found to co-occur in a subset of FPD/AML patients with AML, and test the activity of inhibitors or activators of epigenetic gene regulation in this model.

Scientific Advisory Board

Our Scientific Advisory Board is a working body of researchers and research/clinicians, esteemed in their respective fields, fulfilling an important scientific advisory role for the RUNX1 Research Program. The team offers scientific advice, suggests the direction of our research, helps to review grant applications, and fosters collaborative relationships within the scientific community. We are indebted to their expertise, and for their insight and assistance.

Nancy A. Speck, Ph.D., *Chairman and Scientific Director, RUNX1 Research Program*

Dr. Speck chairs the Department of Cell and Developmental Biology in the Perelman School of Medicine at the University of Pennsylvania. She earned her Ph.D. in biochemistry from Northwestern University and completed postdoctoral research fellowships in retroviral pathogenesis and eukaryotic gene regulation at the Whitehead Institute for Biomedical Research and at MIT. She started her own laboratory at Dartmouth Medical School, progressing from Assistant Professor of Biochemistry to Professor. She then held the James J. Carroll Chair of Oncology at the school before joining the Penn faculty in 2008 as Professor of Cell and Developmental Biology. She became Chair of her department in 2015. She is also the Associate Director of Penn's Institute for Regenerative Medicine, Co-Leader of the Hematologic Malignancies Program at the Abramson Cancer Center, and is an investigator in the Abramson Family Cancer Research Institute.

Dr. Speck is well-known in the field of developmental hematopoiesis, especially as it pertains to translating research into fighting leukemia. She purified the proteins RUNX1 and CBFβ, and cloned their genes. Her biochemical and molecular characterization of them as they relate to leukemia has enabled much progress in the field of malignant blood-cell development. In addition to publishing in more than 100 peer-reviewed articles in leading journals, Dr. Speck has served on and/or chaired study sections at the National Institutes of Health, American Society of Hematology, and the Leukemia and Lymphoma Society, as well as many national and international grant review panels and committees. Her honors include the Leukemia Society of America Scholar Award and The Fogarty International Center Senior Fellow Award. Most recently she received the 2015 Henry M. Stratton Medal for Basic Science from the American Society of Hematology for her 'seminal contributions in the area of hematology research', and in particular for her work on RUNX1.

Paul Liu, M.D., Ph.D.

Dr. Liu is the Deputy Scientific Director of the National Human Genome Research Institute. He received his M.D. and residency training in internal medicine in Beijing, China. He then earned his Ph.D. in human genetics from the University of Texas M.D. Anderson Cancer in Houston. He received his postdoctoral research training at the University of Michigan before moving in 1993 to NIH's National Center for Human Genome Research, renamed the National Human Genome Research Institute (NHGRI) in 1995. Dr. Liu was promoted from Senior Staff Fellow to tenure track Investigator to a tenured Senior Investigator. Dr. Liu headed the Oncogenesis and Development Section of the NHGRI since 1995, when in 2011 he was appointed Deputy Scientific Director. Dr.

Liu's laboratory investigates the molecular mechanism of leukemia using genetic and genomic approaches. He was the first to show that the gene *CBFB*, which encodes the non-DNA binding partner of RUNX1, is mutated in leukemia. His group has a particular interest in the genetic control of hematopoiesis, the process through which pluripotent hematopoietic stem cells differentiate into all of the types of mature cells that circulate in the bloodstream. More recently, his focus has been on the development of targeted treatments for leukemia. Dr. Liu has received several honors for his achievements, including NIH Director's Award and elections to the American Society for Clinical Investigation and the Association of American Physicians.

Gary Gilliland, M.D., Ph.D.

Dr. Gilliland is President and Director of the Fred Hutchinson Cancer Research Center. He received his Ph.D. in Microbiology from UCLA and his M.D. from the University of California, San Francisco. He completed his Hematology and Medical Oncology training at the Brigham and Women's Hospital and the Dana-Farber Cancer Institute, respectively. He completed his internship and residency at Brigham and Women's Hospital, Harvard Medical School. He is board-certified in Internal Medicine and had his Fellowship training in Hematology and Oncology, all at Harvard Medical School. Dr. Gilliland spent 20 years on the faculty at Harvard where he served as Professor of Medicine at Harvard Medical School and Professor of Stem Cell and Regenerative Biology at Harvard University where his work focused on the genetic basis of blood cancers. He was also an Investigator at the Howard Hughes Medical Institute from 1996 to 2009, the Director of the Leukemia Program at the Dana-Farber/Harvard Cancer Center from 2002 to 2009, and Director of the Cancer Stem Cell Program of the Harvard Stem Cell Institute from 2004 to 2009. In 2009, Gilliland left Harvard to go to Merck Research Laboratories where he served as Senior Vice President and Global Oncology Franchise Head, overseeing both preclinical and clinical oncology development as well as licensing, including the development of pembrolizumab (anti-PD1) for treatment of cancer. In 2013, he returned to academia to become the inaugural Vice Dean and Vice-President of Precision Medicine at Perelman School of Medicine at the University of Pennsylvania, where he was responsible for synthesizing research and clinical-care initiatives across all medical disciplines including cancer, heart and vascular medicine, neurosciences, genetics and pathology, in order to create a national model for the delivery of precise, personalized medicine. In January 2015, he became President and Director of the NCI-designated Fred Hutchinson Cancer Research Center. Dr. Gilliland discovered that inherited mutations in *RUNX1* cause FPD/AML. He is an expert in cancer genetics and precision medicine and has unique experience working within both the clinical and academic medical communities as well as the pharmaceutical industry. Dr. Gilliland's several honors and achievements include the American Society of Hematology's William Dameshek Prize (2003), the American Society for Clinical Investigation's Stanley J. Korsmeyer Award (2007), and in 2015 he became a Member of the National Academy of Medicine.

Benjamin Ebert, MD, PhD

Dr. Ebert is a Professor of Medicine at Harvard Medical School, an Institute Member of the Broad Institute, and Leader of the Leukemia Program for the Dana-Farber/Harvard Cancer Center. Dr. Benjamin Ebert received a bachelor's degree from Williams College, a doctorate from Oxford University on a Rhodes Scholarship, and an M.D. from Harvard Medical School. He completed a residency in internal medicine at Massachusetts General Hospital and a fellowship in hematology/oncology at the Dana-Farber Cancer Institute before pursuing postdoctoral research at the Broad Institute. Dr. Ebert is also an attending physician at Brigham Women's Hospital and Dana-Farber Cancer Institute. The Ebert laboratory focuses on the molecular basis and treatment of hematologic malignancies, with a particular focus on myelodysplastic syndromes (MDS). The lab has also

developed novel in vivo models to study myeloid malignancies, elucidating the biological basis for the transformation of hematopoietic cells by somatic mutations. In 2009, Dr. Ebert founded Ligon Discovery, Inc. and serves as its Scientific Advisor, guiding internal drug discovery strategy and assisting in academic collaboration. Dr. Ebert was elected a Faculty Scholar by the Howard Hughes Medical Institute (HHMI) in 2016, received the McCulloch and Till Award from the International Society for Experimental Hematology (2016), and was recently awarded the American Society of Hematology's William Dameshek Prize (2017). He is President of American Society of Clinical Investigation.

Lucy Godley, M.D., Ph.D.

Dr. Lucy Godley is a Professor in the Hematology/Oncology Department at the University of Chicago. She completed her undergraduate degree at Harvard University, obtained her Ph.D. from the University of California, San Francisco (PhD), and her M.D. from Northwestern University. After completing her Internal Medicine and Hematology/Oncology fellowships at the University of Chicago, she then joined the faculty in 2003. Dr. Godley has a special interest in the molecular basis of bone marrow malignancies. Her laboratory studies the basis for cancer cells' abnormal patterns of DNA methylation, as well as inherited forms of bone marrow cancers. As an expert in the care and treatment of patients with diseases of the bone marrow, including families with FPD-AML, Dr. Godley brings to her research the perspective of a clinician serving patients with rare hematological malignancies and hereditary blood cancers. She has received numerous awards for her research, including the Howard Hughes Medical Institute Physician Postdoctoral Award, the Cancer and Leukemia Group B (CALGB) Foundation Clinical Research Award, the American Society of Clinical Oncology Young Investigator Award, the Cancer Research Foundation Young Investigator Award, the Schweppe Foundation Career Development Award and the Kimmel Scholar Award. She was inducted into the American Society of Clinical Investigation in 2012.

John F. Crowley

Mr. Crowley is Chairman and CEO of Amicus Therapeutics, Inc. He co-founded Novazyme Pharmaceuticals with William Canfield, which was later acquired by Genzyme Corporation, and founded Orexigen Therapeutics. John's involvement with biotechnology stems from the 1998 diagnosis of two of his children with Pompe disease, a severe and often fatal neuromuscular disorder. In his drive to find a cure, he left his position at Bristol-Myers Squibb and became an entrepreneur as the co-founder, President and CEO of Novazyme Pharmaceuticals, a biotech start-up conducting research on a new experimental treatment for Pompe disease (which he credits as ultimately saving his children's lives.) In addition to being profiled on the front page of the Wall Street Journal, John was the subject of a book by Pulitzer prize-winning journalist Geeta Anand, 'The Cure: How a Father Raised $100 Million - And Bucked the Medical Establishment - In a Quest to Save his Children'. In 2010, Crowley released his memoir, 'Chasing Miracles: The Crowley Family Journey of Strength, Hope, and Joy.' Crowley and his family were the inspiration for the film 'Extraordinary Measures' starring Harrison Ford in 2010. John is also a commissioned officer in the U.S. Navy Reserve. He graduated with a B.S. in Foreign Service from Georgetown University, earned a J.D. from the University of Notre Dame Law School, and an M.B.A. from Harvard. The Crowley family was the recipient of the 2011 Family Exemplar Award from the University of Notre Dame. John is a Henry Crown Fellow at the Aspen Institute and serves on the executive committee of the National Board of Directors of the Make A Wish Foundation of America.

Bob Löwenberg, M.D., Ph.D.

Dr. Löwenberg co-founded Skyline Diagnostics B.V. in 2005 and serves as its Chief Scientific Officer. He is also the Chairman of the Department of Hematology at Erasmus University MC in Rotterdam, the Netherlands, and serves as Editor-in-Chief of *Blood*, the Journal of the American Society of Hematology. Dr. Löwenberg graduated with an M.D. from Groningen University, and received his Ph.D., cum laude, from Erasmus University. From to 1982 to 1990, he served as Scientific Director of the Daniel den Hoed Cancer Center, a cancer institute in the Netherlands. In 1978 he was an Eleanor Roosevelt Fellow at UCLA. Dr. Löwenberg's research activities are in the treatment and the pathobiology of leukemia, lymphoma and hematopoietic stem cell transplantation. He is one of the three original founders of Introgene (biotech company, Leiden), now Crucell. He has been a Member of Scientific Advisory Board at AIMM Therapeutics BV since June 20, 2013, and serves on the editorial board of several international journals, including *The New England Journal of Medicine*. He founded the Dutch-Belgian Cooperative Group on Hemato-Oncology in Adults (HOVON Cooperative Group), and served as chair of the HOVON leukemia trial group. He was the Founder of European Hematology Association (EHA) and served as its President. He also served as President of the International Society of Experimental Hematology and the International Society of Hematology. He serves as Member at the Royal Academy of Sciences and Arts of The Netherlands and is Chairman of the Medical Advisory Council of the Dutch Royal Academy of Arts and Sciences. In 2004, Dr. Löwenberg received the Dr. P. Muntendam Cancer Prize of the Netherlands Cancer Society, and in 2006 he received the Jacqueline Seroussi Memorial Foundation for Cancer Research Award for his scientific contributions in the field of leukemia.

RUNX1 Research Project Conference

The RUNX1 FPD/AML Research Program is excited to co-sponsor 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, November 12, 2017, to Wednesday, November 15. November 13th will be our dedicated RUNX1 Research Program day, to include presentations from all eight of our present grant recipients through our shared programs with Alex's Lemonade Stand Foundation for Childhood Cancer (ALSF) and the Leukemia and Lymphoma Society (LLS). To complement the conference program, Breakout Sessions will take place with the investigators thereafter. Please email Dr. Speck at nancyas@upenn.edu should you wish to attend or learn more about the conference and its agenda. More details can be found at: http://www.runx1.com/philly-2017.

We are currently in the midst of the second offering of our shared grant program with ALSF and reviewing LOIs. In our next newsletter we will include a Q&A with one of the research recipients from the first RUNX1-ALSF grant cycle.

Thanks for your continued interest and support,

Tim and Monica Babich