Research in the Laboratory of Dr. Seth Corey, Chair, Division of Pediatric Hematology/Oncology.

We study why children develop leukemia in order to better understand both normal blood formation and the more common adult myeloid malignancies. Using inherited bone marrow failure syndromes that evolve into acute myeloid leukemia, we study the biochemical and genetic processes and integrate these data into formulating mathematical/computational modeling. Thus, we study clonal competition among hematopoietic stem cells and how the sequential acquisition of mutations results in clonal growth advantages.

In the first project, we are studying the genetic lesions of Severe Congenital Neutropenia (previously known as Kostmann Syndrome). The first genetic lesion is mutation in ELANE, the neutrophil elastase, which causes the neutropenia. Sequential acquisition of mutations in the gene encoding the Granulocyte Colony Stimulating Factor Receptor (CSF3R) and the transcription factor \( \text{RUNX1} \) results in leukemia.

Dr. Rishi Mehta, Assistant Professor of Pediatrics, is studying ELANE mutations and how the resulting mutant protein triggers the unfolded protein response (UPR). Rishi has created a novel inducible expression system for mutant \( \text{ELANE} \). UPR consists of three main pathways. Rishi and Dr. Ralph Kamel, visiting scientist from Lebanon, are interrogating each of these three pathways. In addition, Rishi and Ralph are studying oxidative stress responses and their interactions with UPR. These stress responses result in genomic instability (see Figure 1). The mutated CSF3R results in a truncated form, which promotes proliferation but impairs granulocytic differentiation. This provides a clonal growth advantage. Together with our collaborators, Marek Kimmel and Rosemary Braun, at Rice and Northwestern, we are developing mathematical and computational models of clonal evolution into leukemia. Dr. Javeria Aijaz, a rotating graduate student, is using DNA barcodes to provide greater quantitation of the clonal dynamics.

Figure 1. Stress responses in Severe Congenital Neutropenia.
In a related project, Dr. Frances Austin, a second-year pediatric hematology-oncology fellow, is investigating the spliceosome, a complex machinery that recognizes RNA and processes mRNA into alternative splice forms. In particular, we identified that tyrosine phosphorylation and U2AF35 are involved in the splicing of CSF3R. Our laboratory recently reported that the spliced form of CSF3R results in a truncated receptor, similar to that observed in Severe Congenital Neutropenia.

We are studying Shwachman-Diamond syndrome, which also transforms into leukemia. However, the cooperating mutations are not known. The disease results from mutation in SBDS, which encodes a ribosome maturation factor. Unlike Severe Congenital Neutropenia, the collaborating mutations are not known.

Dr. Usua Oyarbide has generated a zebrafish model for Shwachman-Diamond syndrome using the novel technique CRISPR/cas9 for genome editing. Usua generated a stable zebrafish lines with a 7 bp deletion sbds gene that generates a frame-shift mutation resulting in a premature stop codon (sbds$^{nu132}$). Unlike human and mice, the double mutant for the sbds truncation permits fish to live up to 6 weeks showing a characterized phenotype, while heterozygous shows normal phenotype. Western Blot showed the absent of protein in sbds$^{nu132/nu132}$ at 8 days post fertilization (dpf). Mutants were smaller since 15 dpf (Figure 2).

We also observed that sbds mutants showed neutropenia at 5 and 15 dpf while number of macrophages and erythrocytes were normal. Moreover, pancreas and liver showed atrophy at 21 dpf. Thus, our unique zebrafish model phenocopies the human syndrome. We hypothesized that this mutant line will be a powerful tool for understanding the onset and progression of myelodysplasia and leukemogenesis. We will scrutinize the effects of known leukemia causing gene mutations, e.g. KRASV12, and mutations of candidate tumor suppressor genes located on 7q, a chromosome abnormality frequented lost in children with leukemia associated with Shwachman-Diamond syndrome. CRISPR/Cas9 editing as well as morpholino-mediated knockdown to effect transient haploinsufficiency. Zebrafish will be followed for development of leukemic burden and their tumors will be characterized molecularly. The Dean and the School of Medicine have generously supported the construction of 700 sq ft zebrafish facility in Sanger (Figure 3) under our direction..

One project funded by the Leukemia and Lymphoma Society is identifying the role of fibrocytes in promoting bone marrow failure and testing the efficacy of TGFβ modifiers in preventing fibrosis.
<table>
<thead>
<tr>
<th>PI</th>
<th>Division</th>
<th>Title</th>
<th>Sponsor</th>
<th>Budget</th>
</tr>
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<tbody>
<tr>
<td>Accardo, Pasquale</td>
<td>Development</td>
<td>Comprehensive Specialty Services</td>
<td>Virginia Department of Health</td>
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<td>Accardo, Pasquale</td>
<td>Development</td>
<td>Child Development Services</td>
<td>Virginia Department of Health</td>
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<td>Bean, Melanie K.</td>
<td>Endocrinology and Healthy Lifestyles</td>
<td>Improving Adolescent Obesity Treatment: Exploring the Role of Parents</td>
<td>National Institute of Health</td>
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<td>Friedel, David J.</td>
<td>Infectious Diseases</td>
<td>SOLI-Solithromycin Pediatric Development Program</td>
<td>Duke University</td>
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<td>Irani, Anne-Marie A.</td>
<td>Allergy/Immunology</td>
<td>COMMITTEE: YR 4 Evaluation of Treat with Omalizumab</td>
<td>University of Virginia</td>
<td>15,407</td>
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<td>Lavoie, Suzanne</td>
<td>Infectious Diseases</td>
<td>Special Projects of National Significance (SPNS) Patient Navigation (PN) Linking Individuals in Need of Care (LINC) Program</td>
<td>Virginia Department of Health</td>
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<td>McVoy, Michael</td>
<td>Infectious Diseases</td>
<td>Letermovir Mechanism of Action</td>
<td>Merck and Co Inc</td>
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<td>Rubin, Bruce K.</td>
<td>Pulmonary Medicine</td>
<td>Citramel on CF Sputum</td>
<td>Breathe Easy Limited</td>
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<td>Rubin, Bruce K.</td>
<td>Pulmonary Medicine</td>
<td>ARTUS wet and dry weight</td>
<td>Respironics Inc</td>
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<td>Schmidt, Howard J.</td>
<td>Pulmonary Medicine</td>
<td>A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation and With a Second CFTR Mutation That Is Not Likely to Respond to VX-661 and/or Ivacaftor Therapy (F508del/NR)</td>
<td>Vertex Pharmaceuticals</td>
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<td>Schmidt, Howard J.</td>
<td>Pulmonary Medicine</td>
<td>A Phase 3, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation</td>
<td>Vertex Pharmaceuticals</td>
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<td>Fortunato, John E</td>
<td>Gastroenterology</td>
<td>Comprehensive Symptom Intake and Assessment Tracker</td>
<td>Atlantic Pediatric Device Consortium</td>
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<td>Rozycki, Henry J.</td>
<td>Neonatal Medicine</td>
<td>Improving chest wall rigidity in very preterm infants</td>
<td>Atlantic Pediatric Device Consortium</td>
<td>5,000</td>
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**New Grants & Contracts Awarded 7/1/15—12/31/15**
### New Grants & Contracts Awarded
**7/1/15—12/31/15**

<table>
<thead>
<tr>
<th>Name</th>
<th>Department</th>
<th>Title</th>
<th>Fund Source</th>
<th>Amount</th>
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<tbody>
<tr>
<td>Willson, Douglas</td>
<td>Critical care</td>
<td>Diagnosis, Outcomes, and Microbiome in Pediatric Ventilator-Associated Infection</td>
<td>VCU Presidential Research Quest Fund</td>
<td>46,045</td>
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<td>Bradley, Jennifer</td>
<td>Pulmonary Medicine</td>
<td>Mature adipocytes from obese individuals release IL-13, which increases inflammation and induces a goblet cell phenotype in normal human bronchial epithelial (NHBE) cells at air-liquid interface (ALI)</td>
<td>Children's Hospital Foundation Research Fund</td>
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<td>Dodson, Kelly</td>
<td>ENT</td>
<td>Longitudinal Evaluation of the sinus microbiome in cystic fibrosis</td>
<td>Children's Hospital Foundation Research Fund</td>
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<td>Miller-Ferguson, Nikki</td>
<td>Critical Care</td>
<td>Development and initial characterization of a novel diffuse pediatric traumatic brain injury model.</td>
<td>Children's Hospital Foundation Research Fund</td>
<td>8,820</td>
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<td>Rhodes, Jennifer</td>
<td>Plastic Surgery</td>
<td>Using sequencing and zebrafish as a model system to confirm the candidate genes play a role in craniosynostosis</td>
<td>Children's Hospital Foundation Research Fund</td>
<td>10,000</td>
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<td>Ritter, Ann</td>
<td>Neurosurgery</td>
<td>MicroCT and PCR array analysis of isolated samples of open, fused or fused sutures in infants with craniosynostosis</td>
<td>Children's Hospital Foundation Research Fund</td>
<td>10,000</td>
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<td>Zhao, Wei</td>
<td>Allergy Immunology</td>
<td>Characterize the impact of Enterovirus D68 on host innate immune response using human bronchial epithelia cells</td>
<td>Children's Hospital Foundation Research Fund</td>
<td>7,500</td>
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<tr>
<td>Rozycki, Henry J.</td>
<td>Neonatal Medicine</td>
<td>Type 1 alveolar epithelial cells and RAGE function in newborn lungs</td>
<td>CCTR Endowment Fund</td>
<td>50,000</td>
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</tbody>
</table>

Pediatric non-clinical revenue over last 4 fiscal years. Year over year growth has been 2.8%, 0.7%, 17.3% and 4.3% respectively.


Fortunato JE, Tegeler CL, Gerdes L, Lee SW, Pajewski NM, Franco ME, Cook JF, Shaltout HA, Tegeler CH. Use of an allostatic neurotechnology by adolescents with postural orthostatic tachycardia syndrome (POTS) is associated with improvements in heart rate variability and changes in temporal lobe electrical activity. Exp Brain Res. 2015 Dec 8. [Epub ahead of print]


CHOR@VCU on the move!
Honors and Awards
Presentations to National & International Meetings

Melanie K. Bean, PhD, LCP, Associate Professor, Endocrinology and Metabolism, Health Lifestyles Center
Presentations

Dec 9, 2015 Workshop Presenter, “Exploring Community Perspectives to Inform Program Development.” Cultural Competency and Humility Workshop, Greater Richmond Coalition for Healthy Children, Richmond, VA.


Bruce K. Rubin, M.Engr., M.D., M.B.A., FRCPCH
Jessie Ball duPont Distinguished Professor and Chair, VCU Department of Pediatrics
Award

October 2015—Honored by being awarded the Wizard Award by the International Brotherhood of Magicians in
Presentations

Nov 7-12, 2015 American Association for Respiratory Care. Tampa FL
Plenary lecture. Life threatening asthma: Identifying and minimizing the risk.
Year in Review Series: Asthma Year in Review 2015
Drug Delivery to the Lungs:

Plenary Lecture: Aerosol therapies for cystic fibrosis: The present, the promise, the potential, and the problems.
Michael Schechter, MD, Professor and Chair, Pediatric Pulmonology

Presentations:

October 8-10, 2015. 29th North American Cystic fibrosis Conference, Phoenix AZ

Workshop Session Chair: "Implementation of Mental Health Screening: Strategies & Successes".

Platform presentation: Recommendations for CFF Support of Prevention, Screening & Treatment of Anxiety & Depression in Individuals with Cystic Fibrosis & Caregivers.

Posters: Fink A, Sawicki GS, Morgan WJ, Schechter MS, Rosenfeld M, Marshall BC. Treatment Response to Ivacaftor in Clinic Practice

Sawicki GS, Ostrenga J, Fink A, Petren K, Rosenfeld M, Schechter MS. Continuity of Care Transfer from Pediatric to Adult Cystic Fibrosis Care Centers in the United States.

Dasenbrook E, Fink A, Schechter MS, Sanders D, Millar S, Pasta D, Myers V, Mayer-Hamblett N. Risk factors associated with rapid FEV1, Decline in Adults with Early-Stage CF Lung Disease: Cohort Study of the US CF Foundation Patient Registry.


October 26-29. Academy of Managed Care Pharmacies, Orlando FL

Rubin-Cahill JL, Thayer S, Watkins A, Wagener J, Hodgkins P, Schechter MS. Frequency and costs of pulmonary exacerbations and association with % predicted FEV1 in patients with Cystic Fibrosis

Cumulative Department of Pediatrics non-clinical revenue in current fiscal year vs last fiscal year. Research and contract services revenue up 6.3% over same period last year.
Due Date: February 29, 2016 at 5 PM

The Children’s Hospital Foundation has renewed its commitment to advancing children’s healthcare by continuing the Research Grant Program it initiated in 2014. The Foundation is providing up to $50,000 to support new researchers and new research projects.

The Program was developed based on the experience in technology start-ups. At the earliest stages, when something is just a well-thought out idea, it is not easy to judge whether it is worth investing venture capital. Similarly, in research, a new idea is not going to attract funding from sponsors like NIH until it has a significant amount of preliminary data. The Foundation took on the challenge of how to help get the necessary preliminary data. In Silicon Valley, earliest stage investment puts small amounts into a number of projects. The Grant Program provides one year grants of $2,500—$10,000, knowing that some of them may not be successful, in the belief that one of them will turn into the pediatric equivalent of Google.

The criteria for a successful grant application are simple: 1) A good idea—well-supported by the what is already known, and with the potential to impact children’s health in some form. 2) Feasibility—the proposed project can be accomplished in the grant period. 3) If it succeeds, it has the potential to attract further external funding— the applicants must discuss what the next steps will be if their hypothesis and plan work out.

In the first two years, 14 grants were awarded. The average grant was for $6150. Of the 8 awarded for 2014-15, three of the projects have gone on to get $50,000 grants from VCU and another has provided data in support of an NIH application.

One other unique feature is the review mentoring program. An excellent way to learn what goes into a good grant application is to watch how grants are reviewed and to review grants yourself. In the second year of the program, four junior faculty were shadow reviewers. Now that they have experience, they will contribute to review process. There is room to have one more junior faculty member who would like to act as a shadow reviewer this year.

Who Should Apply: Any member of the CHoR Faculty, including members of departments other than Pediatrics. Fellows are eligible BUT their project must fit into the research plans of their mentor. See criteria #3 above.

How to Apply: Email henry.rozycki@vcuhealth.org for the forms. It’s a 5 page application, with the usual format—background, hypothesis/specific aims, research plan, analysis and subsequent plans. If you have any preliminary data, by all means include it, but it is not required. The signed completed application should be sent via email (or hand delivered) to Liz Fredericksen-Trent at elizabeth.fredericksen-trent@vcuhealth.org by the due date.

Questions or Help: We would like to have as many people submit strong applications as possible. If you have questions or need help, we want to provide it. henry.rozycki@vcuhealth.org
Due Date: February 29, 2016 at 5 PM

For 2016-17, The Children’s Hospital Foundation has provided funds to support the appointment of a Research Scholar at CHoR. The Foundation will give up to $25,000 per year for two years for salary support for the selected individual. It is expected that the faculty member’s primary department will add $10,000 per year. The Scholar will then have a minimum of 20% of their time protected from other duties, and this time will be devoted to their research.

This aim of this program is to give a young faculty member time to pursue their research projects. The Scholar is also expected to have a successful CHF Research Grant application to fund the activity. The combination of the two should give the selected Scholar a better chance at developing the skills, experience, data and publication record that will ensure their success in a competitive external grant environment.

There will be only 1 Scholar at a time. This is a two year appointment, so if someone is selected this year, there will be no Scholar selection in 2017.

Applicants need to be CHoR Faculty, including members of departments other than Pediatrics. Fellows are not eligible. The applicant must be within 5 years of their first appointment as Assistant Professor. The applicant’s leader (division or department chair) must approve the 20% effort release, and the department chair must guarantee the $10,000 per year contribution.

The application is available from henry.rozycki@vcuhealth.org. While the Research Grant application asks about future plans for the research, the Scholar application asks for research career plans for the applicant. The signed completed application should be sent via email (or hand delivered) to Liz Fredericksen-Trent at elizbeth.fredericksen-trent@vcuhealth.org by the due date.

Research Scholar applications will be reviewed and scored by the Review Committee and these will forwarded to the Chair(s) of the applicant department(s) for final decision.

Interested parties are encouraged to contact henry.rozycki@vcuhealth.org with questions or for help.