Resident Research is Booming at CHoR

The pediatric residency at CHoR at VCU attracts some of the brightest medical school graduates from the US and abroad. A number of these young pediatricians enhance their education by doing research, under the mentorship of CHoR faculty. These valuable experiences are an opportunity to learn about research, to interact closely with faculty, to work in teams, to explore potential future careers and to satisfy their curiosity. Below are some examples. Other projects will be highlighted in future issues.

Dr. Jonathan Ma is a second year resident. He is working with Dr. Bruce Rubin on a project involving cystic fibrosis patients. “Mucus is a barrier to airway water loss and microbial invasion and serves to maintain homeostasis in the respiratory system. In patients with cystic fibrosis, the mucus secretions are thick and viscous, leading to abnormal mucus clearance, infection, inflammation, and airway remodeling. My current research project is a longitudinal epidemiological study to examine biophysical and transport properties of cystic fibrosis patient sputum in relation to clinical parameters such as FEV1 and pathogen infection. We hypothesize that this will allow us to better understand the natural history of the disease, and perhaps to develop a better means of disease surveillance or prognostic tool.” He is currently measuring the biophysical and transport properties and getting clinical data from the medical record. He will be presenting some of this work at the ATS International Conference in Denver in May, 2015.

Two second year residents, Drs. Amanda Schlak and Ashley Mazo, and two third year residents, Drs. Hadi Anwar and Ashley Tseng, worked with Dr. Clifton Lee from the Division of Hospital Medicine on a project titled “The predictability of using the EGAMI Score to identify children with refractory Kawasaki Disease: one institution’s analysis.” Kawasaki Disease (KD) is an acute systemic, self-limited inflammatory illness. Typical presentation is described as prolonged fever, bilateral conjunctivitis, cervical lymphadenopathy, oral-mucosal involvement, extremity changes, and rash. Intravenous immunoglobulin (IVIG) is the current standard therapy; however, IVIG unresponsiveness is a major predictor for the development of coronary artery lesions, and the identification of resistant patients would allow for earlier intervention. There are established models to evaluate IVIG unresponsiveness in Japanese children, but such models have not been well demonstrated within the United States.

(Continued on Page 2)
RESIDENT RESEARCH AT CHoR

The EGAMI score is one of these models that consider age at diagnosis, days of illness, platelet count, C-reactive protein (CRP), and alanine aminotransferase (ALT) to predict IVIG responsiveness. A retrospective chart review of pediatric patients discharged from the Children's Hospital of Richmond at Virginia Commonwealth University with the diagnosis of KD EGAMI scores were calculated from demographic and clinical information to evaluate efficacy in predicting refractory KD cases and risk for coronary artery aneurysms. In our patient population, the EGAMI score has not been shown to identify high risk patients for refractory KD or the development of coronary artery aneurysms. No specific risk factors were identified in our patient population that was associated with refractory KD or coronary artery aneurysms. Further long-term, multi-center studies will be needed to evaluate if certain risk factors can be identified to predict IVIG resistance and to further evaluate if the EGAMI score may be applicable to other patient populations in the United States.

Dr. Anwar has a second project with Dr. Lee focused on the family centered rounds that are the standard practice at CHoR. Studies show that family centered rounds (FCR) improve family satisfaction by involving the families in their children’s care (Pediatrics, 2003). Medical students consistently find FCR beneficial to families but have differing attitudes regarding benefits to the medical team. We developed an FCR simulation to aid third year medical students in FCR presentation during their pediatric clerkship. We wanted to determine if the simulation improved medical student attitudes toward FCR. On the first day of the clerkship, third year medical students presented a patient admission to two evaluators playing the role of a parent and an attending physician. They completed a survey that day and at the end of their clerkship. The survey asked if they thought FCR would benefit family, nurses, physicians, students, and efficiency of rounds. The post-clerkship survey also included questions regarding changes in student’s perception toward FCR. We currently have data for the first four blocks of medical students. We initially hope to improve medical students' perceptions of FCR as well as improve their presentations during their clerkships. In the future, we may investigate if faculty and housestaff find their presentations improved, and if families are more satisfied.

Dr. Adi Gupta, a second year resident, is in the planning stage on a neonatal project, working with Dr. Shadi Jurdi, a senior neonatal fellow, and Drs. Henry Rozycki and Russell Moores, Jr. to see if CHoR can develop a better Apgar Score. When the Apgar score was first originated, it was used as a tool to evaluate an infant immediately after birth and helped facilitate neonatal resuscitation. However in modern day, the Apgar score is not part of the resuscitation practices in the delivery room. Though an Apgar score less than 3 at 5 minutes seems to correlate to a higher risk of death, the data in the literature is inconsistent in regards to preterm infant outcomes. In 2006, the AAP released a statement discussing the limitations of the Apgar score and the need for a more encompassing score at birth. At our institution, a new neonatal score was developed by Dr. Shadi Jurdi, a soon to be graduating neonatology fellow. In addition to vital signs, the NRAS score incorporates the level of resuscitation required to sustain adequate perfusion and oxygenation in a newborn, assessed both at one and five minutes of life. In our study, an APGAR and NRAS score will be assigned to every infant for which a neonatal team is present for delivery. Outcomes within the first 48 hours of life will be collected. The primary objective is to determine the relevance of the NRAS score in the delivery room and after birth, and ultimately compare it to the Apgar score.

Another second year resident, Dr. Will Smitthart, is also working with Drs. Rozycki and Moores in the Division of Neonatal Medicine on a project. New techniques of non-invasive ventilation are being used increasingly in premature infants in the Neonatal ICU. One common ventilation mode for infants who have apnea or desaturation/bradycardia episodes is Nasal Intermittent Positive Pressure Ventilation (NIPPV), where a breath at a set pressure is pumped in at a set time, whether the patient is inhaling, or exhaling at the moment. A newer mod called non-invasive Neuromally Adjusted Ventilatory Assist (NAVA) coordinates the amount and timing of the breath with the patient using diaphragm electrical activity. While NAVA may be a better mode in theory, it is not known if it is as effective as NIPPV at preventing apnea, bradycardia or desaturation (ABD). The study plans to enroll premature infants who are already receiving NIPPV or non-invasive NAVA. Careful simultaneous measurements of ventilator and cardiorespiratory data will be collected for 4 hours in one randomly assigned mode and then for 4 hours in the other mode. The incidence of ABD events, as well as breathing coordination data will be compared between modes.

Dr. Nick Klaiber is a second year resident who will tell you that he chose to come to CHoR for his residency so he could pursue his studies into cancer therapy. Working with investigators from the School of Engineering (Dr. Hu Yang), the Department of Human Genetics (Dr. Xiang-Yang Wang), and Biostatistics (Dr. Guimin gao), he has developed a novel hypothesis and project, and found a way to investigate it while doing his pediatric residency. The project is titled “Development of a novel immune checkpoint inhibitor for treatment of disseminated neoplasms".
Metastatic solid tumors represent a significant source of morbidity and mortality among the general population with few effective therapies available. T regulatory lymphocytes (Tregs) have been found to act as a shield, beneath which such neoplastic growths are free to proliferate and metastasize. Recently, immune checkpoint inhibitors have provided the first consistent increases in overall survival among patients with advanced stage melanoma in over two decades. Current FDA approved immune checkpoint inhibitors target molecules expressed by Tregs including, CTLA-4 and PD-1. Combination therapy with these two agents yielded remarkable response rates in patients with malignancies refractory to traditional treatments, confirming the potential of immunotherapeutics. Despite these encouraging developments, this first generation of immune checkpoint inhibitors falls short of targeting Tregs directly. In addition these drugs have failed to synergize with anti-tumor vaccination strategies, leaving autoimmune side effects to be managed. Thus, the ultimate goal of inducing a sustained, tumor specific immune response remains elusive. The primary difficulty in directly targeting Tregs is the lack of any single class defining cell surface marker. CD25, the high affinity alpha chain of the IL-2 receptor, represents an extracellular surface marker which is upregulated on Tregs, but is also highly expressed by activated effector T cells, the very lymphocytes responsible for actuating the antitumor response. Antibodies targeting CD25 were found to be counterproductive in animal tumor models, likely due to this non-specificity for the Treg subclass. The single most specific marker for Tregs yet identified is the fork-head box transcription factor foxp3. Tregs depend upon high levels of this protein to remain viable. The integral role of foxp3 in Treg function was elucidated through study of immune polyendocrinopathy enteropathy X-linked syndrome (IPEX) in humans and the scurfy phenotype in mice, both of which result from loss of function mutations in foxp3 and leave affected individuals devoid of functional Tregs with intact effector responses. As foxp3 is a strictly intracellular molecule it remains inaccessible to monoclonal antibody based therapies. One potential methodology for targeting intracellular proteins such as foxp3, is RNA interference, a highly conserved innate cellular response to double stranded RNAs that results in robust post-transcriptional silencing of gene products via specific cleavage mRNAs homologous to the introduced double stranded RNA. In vitro short interfering RNA (siRNA) mediated knockdown of foxp3 in Tregs inhibited the expression of CTLA-4, PD-1, PD-L1, IL-10 and TGF-B. In addition, RNAi mediated knockdown of foxp3 also effectively abrogated Treg’s ability to suppress mitogen stimulated effector T cell proliferation in vitro. In 2013 human trials achieved safe and specific knockdown of several host genes using siRNAs for therapeutic purposes, demonstrating the translatability of this technology. Direct suppression of Treg functioning via RNAi mediated foxp3 knockdown may hold the potential to stimulate a more effective anti-tumoral immune response than current immunotherapies are capable of generating. The specific aim of our research is to synthesize a novel immune checkpoint inhibitor based upon nanoparticle delivered siRNAs targeting the Treg master transcription factor foxp3 and inducing immune mediated tumor rejection.
## New Grants & Contracts Awarded
### 7/1/14—12/31/14—$1,442,284

<table>
<thead>
<tr>
<th>PI</th>
<th>Division</th>
<th>Title</th>
<th>Sponsor</th>
<th>Total Costs</th>
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<tbody>
<tr>
<td>Pat Accardo</td>
<td>Developmental Pediatrics</td>
<td>Child Development Services</td>
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<td>Jeff Donowitz</td>
<td>ID</td>
<td>Pediatric Scientist Development Program</td>
<td>AMSPDC</td>
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<td>Sue Lavoie</td>
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<td>VA LINC</td>
<td>Virginia Dept. Of Health</td>
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<td>Michael McVoy</td>
<td>ID</td>
<td>An HBC-vector peptide-based cytomegalovirus vaccine</td>
<td>NIH</td>
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<td>Linda Meloy</td>
<td>General Pediatrics</td>
<td>A Four-Year Blinded-Outcomes Follow-Up Study of Patients Who Received Stannsoporfin or Placebo in Clinical</td>
<td>InfaCare</td>
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<td>Linda Meloy</td>
<td>General Pediatrics</td>
<td>A Phase 2 Multicenter, Single Dose, Randomized, Double Blind, Placebo Controlled, Parallel Group Study Evaluating the Safety and Efficacy of Two Doses of Stannsoporfin in Combination with Phototherapy in Neonates.</td>
<td>InfaCare</td>
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<td>Bruce Rubin</td>
<td>Pulmonology</td>
<td>The Anti-Inflammatory Effects of Tiotropium Bromide in IL-13 Transformed Human Airway Cells</td>
<td>Boehringer Inglehein</td>
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<td>Michael Schechter</td>
<td>Pulmonology</td>
<td>Success With Therapies Research ConsortiumSEARCH CONSORTIUM</td>
<td>CF Foundation</td>
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<td>Judy Voynow</td>
<td>Pulmonology</td>
<td>Inhaled 2-O, 3-O Desulfated Heparin is a Multifunctional Anti-Inflammatory Therapy for Cystic Fibrosis Lung Disease</td>
<td>CHRB</td>
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<td>Joel Schmidt</td>
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<td>eQUIP-CR Coaching Program Travel Grant</td>
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<td>Joel Schmidt</td>
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<td>Participation in the Cystic Fibrosis Registry 2014/2015</td>
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<td>Melanie Bean</td>
<td>Endocrinology</td>
<td>Low Intensity Weight Loss for Young Adults: Autonomous vs. Extrinsic Motivation</td>
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<td>Melanie Bean</td>
<td>Endocrinology</td>
<td>Improving Diet via a School Cafeteria Intervention: Optimizing NSLP Policy Impact</td>
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<td>Pennsylvania Mid-Atlantic AIDS and Education Training Center</td>
<td>U Pittsburgh</td>
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<td>India Sisler</td>
<td>Heme/Onc</td>
<td>Enhancing Use of Hydroxyurea In Sickle Cell Disease Using Patient Navigators</td>
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</table>

The listing only includes those grants and contracts for which the University has created an account and listed the award in its system. Grants and contracts which have been awarded but not yet been recorded in the VCU system will be listed in the next newsletter.

Irani AM. Food allergy and increased asthma morbidity in a school-based inner-city asthma study. Pediatrics. 2014 Nov;134 Suppl 3:S166-7


Lo MM, Bunchman TE: Chronic Renal Failure in Children. The five minute consult for Pediatric Urology , eds Koo H . LWW 2015


Nina Xiao, MD, Division of Pediatric Nephrology presented at the American Society of Nephrology Conference in Philadelphia, PA November, 2014:
- "Subclinical kidney injury before and one year after bariatric surgery among adolescents with severe obesity"

At the 2014 North American Cystic Fibrosis Conference, Atlanta GA, Oct 2014, CHoR presentations included:
- Wheat Butt E, Wentz D, Bitsko M, Schmidt J. Improving Psychosocial Care for Patients: Implementing an Annual Screening Program for Anxiety and Depression
- Sanders DB, Emerson J, Ren CL, Schechter MS, Gibson RL, Morgan WJ, Rosenfeld M, The EPIC Study Group. Early Childhood Risk Factors for Decreased FEV1 at Age 6-7 Years

Asadullah Khan, MD from the Division of Hematology-Oncology presented 3 papers at the annual Society for Neuro-oncology Meeting in Miami, FL, Nov 2014
- Asadullah Khan, Jocelyn Terry, Sarah Goggin, et al. TERT activation and SUV420-mediated heterochromatin changes in pediatric brain cancers.

Tim Bunchman, MD co-chaired the AKI and CRRT symposium put on by ESPNIC (European Society Pediatric and Neonatal Intensive Care) Barcelona Spain, Oct 16-17, 2014 and gave talks on:
- Vascular Access for RRT
- Prescriptions in RRT
- Nutrition in AKI and Critical Illness
- RRT for In Born Error of Metabolism

Bruce Rubin, MD, Chair of Pediatrics presented the following:
University of Sao Paulo. Aug 2014, Taught a 3 day workshop and magic course including:
- Therapy for mucus clearance disorders
- Nasal and sinus inflammation in airway diseases
- Beyond the guidelines: Fatal and near fatal asthma
- The science and practice of aerosol therapy
- Clinical case discussion at Children’s Hospital
- Dogma and great mistakes in respiratory care
- Pediatric pulmonary puzzles
- How to get your research published

Porto Alegre, Brazil: 30th National Practical Course on Pediatric Pulmonary. Lectures as follows:
- Therapy for mucus clearance disorders
- Severe and near fatal asthma
- Getting research published
- Clinical Pearls
- Atelectasis plastic bronchitis and the Middle lobe syndrome

The 2nd Affiliated Hospital & Yuying Children’s Hospital of Wenzhou Medical University
2014 International Pediatric Respiratory Conference Oct 2014
- Keynote Lecture The Science and Practice of Aerosol Therapy
Enze Medical Center, Taizhou, China, Oct 2014:
- How to publish your research
- Clinical case discussions

American Association for Respiratory Care. Las Vegas, NV Dec 2014
- Aerosol therapy during mechanical vent – what is the evidence?
- Asthma Open Forum
- Aerosol Open Forum
- Inhalation therapy – Not just albuterol
- How to read a scientific paper
- Summary of the RC Journal Conference on Aerosol Therapy

Karen Hendricks-Munoz, MD from the Division of Neonatal Medicine was nominated to be a standing reviewer for NIH Study Section IRAP - Infectious Diseases, Reproductive Health, Asthma and Pulmonary Disease- 2015-2021

**External Salary Support Growing**

**Six Month Total**

![Bar chart showing salary and fringes dollars from grants and contracts for the first six months of the last 3 fiscal years (7/1 to 12/31). The 2015 total of just under half a million dollars is a 29% increase over 2014 and 56% higher than in 2013!](chart.png)