Emory+Children's Pediatric Research Center

An Atlanta-based research alliance

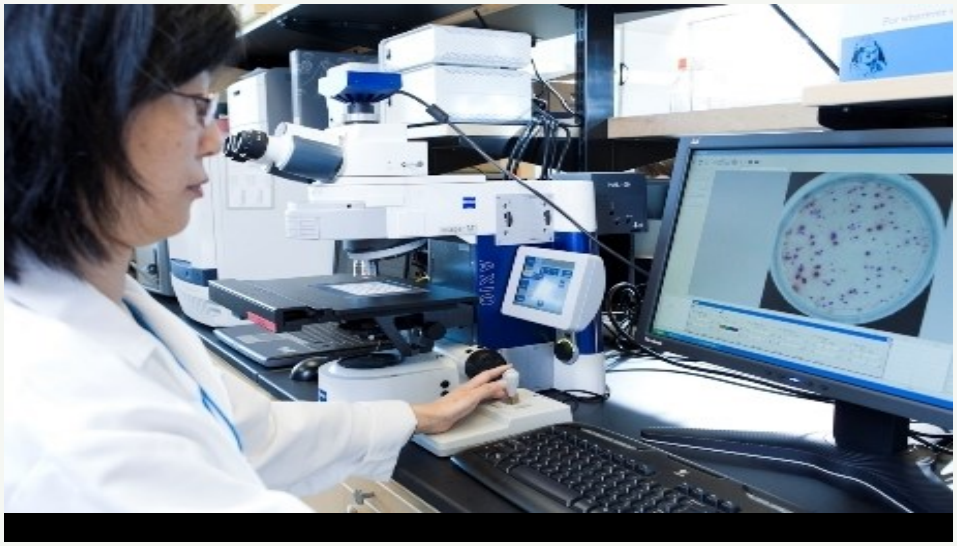
Children's Healthcare of Atlanta | Emory University | Georgia Institute of Technology | Morehouse School of Medicine

First Edition May 2014

Children's Center for Immunology and Vaccines

Welcome to our first CCIV newsletter!

Since this is our first (of many) CCIV newsletters, we should review the mission and purpose of CCIV. We are a broad-based group of investigators working in immunology, vaccinology, and infectious diseases. Our overall mission is to make new discoveries that will improve the lives of children through the development of improved diagnostics, therapeutics, and prevention of infectious diseases in children. One of the main ideas behind starting CCIV was to build a critical mass of investigators working in this area, allowing us to be more productive and to seek larger sources of research support such as training grants and multiple-PI or program project grants. This is an exciting time in pediatric research in Atlanta, and I think we have made a significant amount of progress in the past five years toward our CCIV goals. Through this newsletter, we will celebrate some of the successes of CCIV and highlight individual faculty and their projects. We plan to combine future letters with news from the Pediatric ID Division at Emory. To be clear, our Center includes important members both inside and outside of Pediatric ID at Emory. The significant degree of overlap, however, leads me to think that we should also highlight some of the people and progress in the ID Division, including our wonderful ID fellows. Kristen Herzegh will be coordinating the content for CCIV, while Tivia Woods will coordinate for Pediatric ID. Please help Kristen and Tivia as they work on future editions of this newsletter, and keep up all the good work!

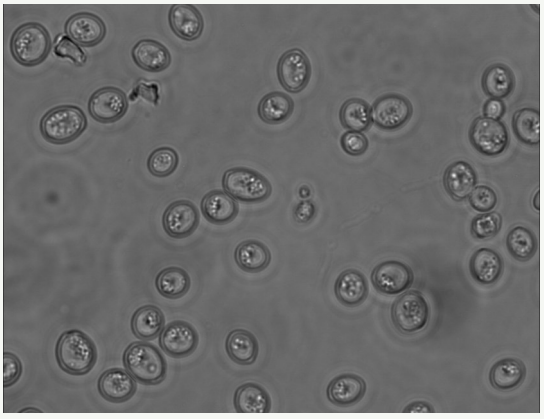


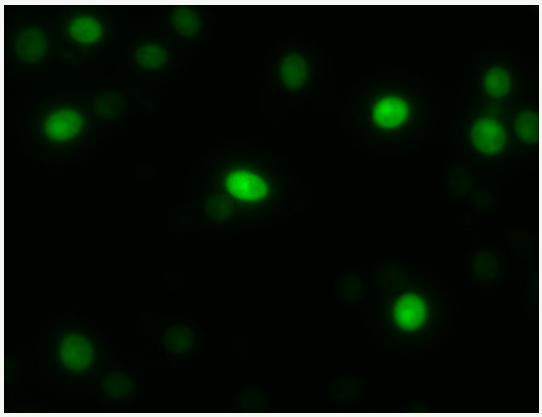
In This Issue

Tracey Lamb Awarded NIH Director's New Innovator Award

Tracey received the award to develop the probiotic yeast *Saccharomyces boulardii* as a novel vaccine delivery system. Needle-stick vaccines are expensive to manufacture and require trained medical personnel to administer. Dr Lamb's vaccine design is intended to tackle these issues by engineering *Saccharomyces boulardii*, a yeast species related to the common model yeast organism *Saccharomyces cerevisiae* (bakers yeast), to simultaneously produce and deliver vaccines orally. *S. boulardii* is a probiotic yeast often used in the clinic to treat diarrhea. The cell wall properties of *S. boulardii* allow it to survive passage through the harsh conditions of the gastrointestinal tract making it the perfect delivery vehicle for an orally-delivered vaccine. In addition, genetic manipulation strategies for *S. cerevisiae* are already well established allowing Dr Lamb's team to engineer *S. boulardii* yeast themselves to express the vaccine. It is hoped that this cost-effective manufacturing strategy will make such an approach affordable for developing countries where financing of vaccines for mass administration can be a road-block to prophylaxis against preventable diseases.

The NIH directors New Innovator Award of $1.5 million in research money is given to exceptionally creative new investigators who propose novel projects that have potential for exceptionally high impact in human health. Dr Lamb is the first recipient of one of these grants at Emory University. Her project also involves collaboration with researchers in Emory University School of Biochemistry (Professor Anita Corbett) and the VA Medical Center (Professor Jan Mead).





S. boulardii yeast (left) will be used as a vaccine delivery vehicle. They can be genetically manipulated to express proteins such as vaccine constructs and, as shown here green fluorescent protein (right).

Summer Seminar Series

Monday, June 2nd from 12:00pm—1:00pm

Anita McElroy, MD, PhD "Highly Pathogenic Viruses: Mechanisms of Immune Antagonism"

Monday, June 16th from 1:00pm – 2:00pm

Monika Bajorek, PhD "The Viral and Cellular Factors in Enveloped Virus Budding"

Thursday, July 17th from 12:30pm – 1:30pm

Tracy Ruckwardt, PhD "Defining Mechanisms of Age-Dependent Immunity in a Neonatal RSV Infection Model"

Marty Moore Receives 2013 Innovation of the Year Award

Written By: Mary Loftus

Respiratory syncytial virus (RSV) is the leading cause of bronchiolitis, viral pneumonia, and viral death in infants both in this country and worldwide, and it kills 200,000 infants annually.

Pediatrics infectious disease researcher **Martin Moore** runs a lab that has developed two RSV model systems, including one to develop live attenuated RSV vaccine candidates. He has gone beyond basic research, however, to a creative type of lab entrepreneurism, inventing and distributing tools needed by other researchers to study RSV.

"We have a culture of invention in the lab," he says. "We talk about tech transfer every week, it's central to the lab, and I actually think it creates optimism and excitement for trainees in a time of prevailing pessimism due to funding."

These materials—largely research reagents and RSV strains—are licensed to companies for fees, which are generally small.

"I didn't actually expect this to become an alternative funding source," Moore says. "But it builds up. We had 18 licensures for revenue last year. Now companies have started contacting me—can we test our therapeutics in your mucogenic RSV mouse model, or will you generate this particular RSV strain for us? So, in addition to licensing, the research tool distribution has led to research contracts."

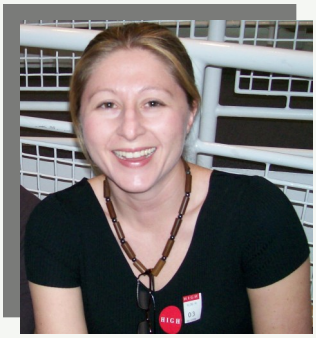
Intellectual Property Associate Clifford Michaels of Emory's Office of Technology Transfer (OTT) says Moore has created what he believes may be a model research lab of the future.

"Marty looks at his lab differently, in terms of, here we have an unmet need for a vaccine, but the problem is that there aren't good tools for people to use to make vaccines," Michaels says. "So he says, ‘Let me look at industry, let me make these tools to drive the whole field ahead.' "

The extra funding allows Moore to support post-docs in his lab, continuing the cycle of discovery and innovation.

"We have our own projects, basic science and vaccine development," he says. "But invention resonates with people. We invented something and got it to as many companies as possible to facilitate vaccines and antivirals, which is a lot better than having research materials just sitting in lab freezers."

Generating unique reagents is advantageous for NIH grants too. "Putting technology development at the front end of the goal of the lab, rather than seeing technology as a by-product of basic research, is enabling us to build an RSV and vaccine research program on multiple funding sources," he says.



“What the heck is Rift Valley fever virus?!” This is the question that I’m most often faced with when someone asks me about my research. “Rift,” as we like to call it, is a virus that causes disease in both people and livestock throughout Africa and areas of the Middle East. Mosquitos transmit the virus, and it can sporadically cause large outbreaks of disease in animals and people. Most people who get infected have mild non-specific disease characterized by fever, muscle aches, general unwellness and sometimes gastrointestinal or respiratory symptoms. However, up to 10% of those infected will develop severe disease, which can manifest as hepatitis, hemorrhagic fever or even encephalitis or retinitis.

One of the unique things about doing research with Rift (besides sometimes getting to go to Africa) is that the work requires biosafety level-3E containment. This means, for example, that before you can enter the lab you first have to undress, don a set of scrubs, knee high socks, and a smock. Then you put on a respirator, a double set of gloves and shoe covers over the lab-designated shoes. After doing your work, you have to take all of that off and take a shower before you can get back in your street clothes and go on with your day.

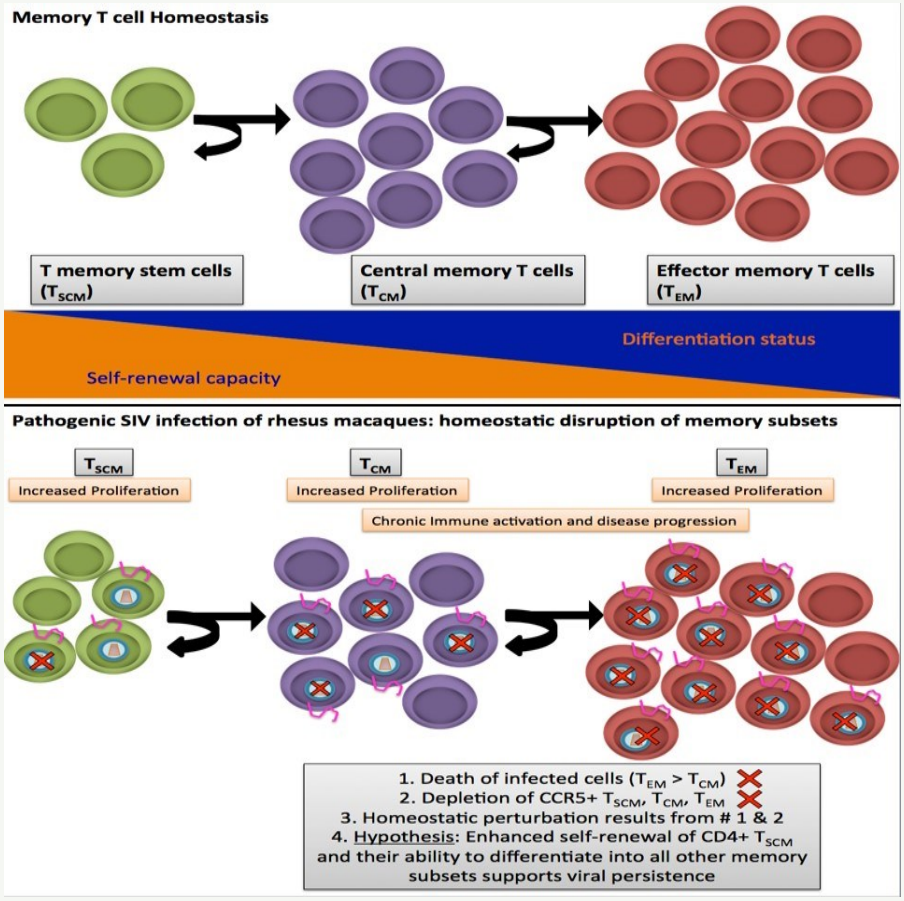
The fundamental question at the center of our work is why do some people get really sick while others get mild disease? If we can determine what protects individuals from developing severe disease, then maybe we can capitalize on that information and design therapies or vaccines to help mitigate disease in those who get infected. We are looking at this in two ways. First, we are examining the immune response in humans who have been exposed to a formalin-inactivated virus preparation to understand how humans form immune responses against the virus. And secondly, we are using the mouse model to help us understand which aspects of the immune response are necessary to provide protection from disease. The mouse model is especially useful for Rift studies because it allows us to alter certain aspects of the immune response to determine which ones are critical. We’ve already found that CD4 T cells are important for protecting mice from Rift-mediated encephalitis (J Virol. 2013 Jun;87(11):6161-71), and we’re following up on those results to gain a better understanding of the biological mechanisms at work.

Dr. Anita McElroy is an Emory Instructor who is also a guest researcher in the Viral Special Pathogens Branch at the Centers for Disease Control and Prevention.

Over 30 million people, including 2.5 million children, are infected with HIV. With the advent of combination antiretroviral therapy (cART), there has been a significant improvement in the mortality and morbidity of HIV infections, since HIV viral loads often go below detectable levels with this treatment. However, cART has drawbacks: it is associated with numerous adverse effects, particularly in the pediatric population, and viral rebound occurs quickly if treatment is stopped. Therefore, a sterilizing or functional cure of HIV infection is a key priority in HIV/AIDS research.

A major barrier to eradicating HIV/AIDS is the presence of a persistent reservoir of latently infected cells that are not eliminated by cART. There is limited knowledge of the cellular and anatomic sources of this reservoir, and the overall goal of our research is to identify such pools of latent infection so that targeted cure strategies can be developed. One newly described subset of T cells called T memory stem cells (Tscm) are of particular interest to us, as long-lived CD4+ Tscm have been shown to be latently infected with HIV and can undergo homeostatic proliferation without reactivating the virus.

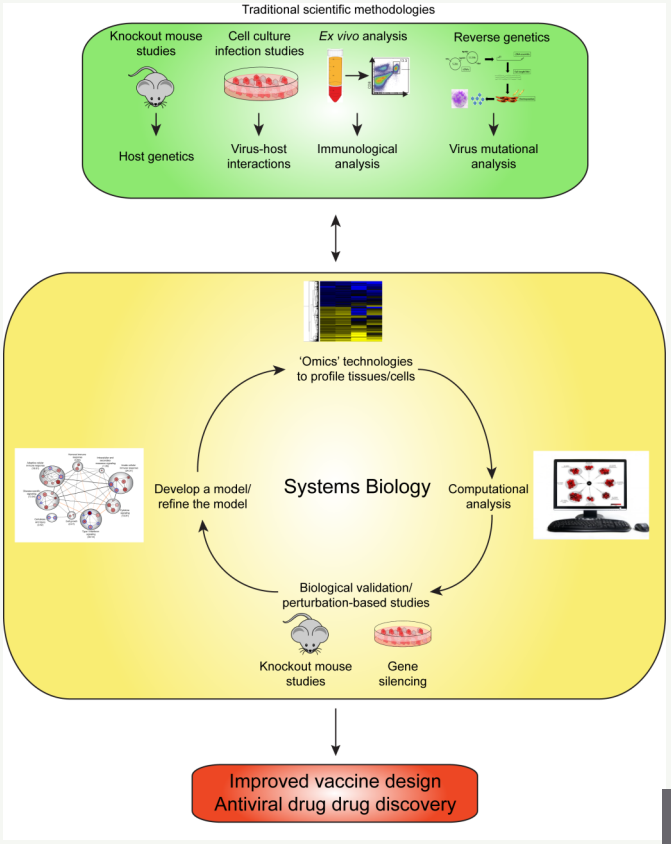
Like HIV infection in humans, some nonhuman primates can be infected by a simian version of the virus called SIV (simian immunodeficiency virus). In particular, we use experimental SIV infection of rhesus macaques, as it results in a pathogenic phenotype that leads to simian AIDS. In collaboration with members of the Yerkes National Primate Research Center, the goal of our study is to investigate, for the first time, the role of Tscm as a cellular reservoir of persistent SIV infection in rhesus macaques in the setting of cART. This work is funded by the NICHD Child Health Research Career Development Award / Atlanta Pediatric Scholars Program (Scholar = Ann Chahroudi / Co-mentors = Paul Spearman and Mirko Paiardini). We hope to elucidate key components of the persistent HIV/SIV reservoir, which will ultimately be used in developing a functional cure for HIV-infected patients.



Dr. Ann Chahroudi is an Assistant Professor of Pediatric Infectious Diseases at Emory University's School of Medicine.

Emerging/re-emerging mosquito-borne flaviviruses continue to be a significant threat to human health throughout the world.

Over the past decade, West Nile virus (WNV) and Dengue virus (DENV) have caused yearly epidemics of encephalitic and viscerotropic disease, respectively. In the United States alone, WNV has been estimated to cause more than 3 million infections, resulting in over 780,000 illnesses, 38,000 confirmed cases, and 1,500 deaths between 1999-2013. Although dengue has yet to gain a significant foothold in the United States, the World Health Organization estimates that throughout the world between 50 and 100 million people are infected each year and a total of 2.5 billion people are at risk of dengue infection. Infants, children under 5 years of age, elderly, and immunocompromised patients are considered the highest risk group for developing severe disease following WNV or DENV infection. Despite this ongoing risk to public health, there are still no approved vaccines or antiviral therapies for use in humans to treat these infections.



The innate immune system is the first line of defense against an invading viral pathogen. Nearly every cell in the body encodes pattern recognition receptors, otherwise known as innate immune sensors, that recognize distinct viral signatures and trigger a robust antiviral defense response. This culminates in the production of type I interferon, proinflammatory cytokines, expression of hundreds of antiviral effector genes, and activation of the adaptive arm of the immune system. My laboratory is focused on understanding how the RIG-I like receptors detect, respond, and regulate immunity to viral infection. A central theme in my laboratory is to use a systems biology approach that integrates multiple disciplines, including biology, virology, immunology, computer science, and mathematics, to develop a deeper conceptual understanding of immunity to flavivirus infection. Specifically, we are using these approaches to understand how the RIG-I like receptors program innate immune sentinel cells and promote humoral and cell-mediated immune responses during flavivirus infection. As part of our future goals, we hope to identify new host targets for therapeutic intervention and harness our findings to improve on current strategies for vaccine design.

Dr. Mehul Suthar is an Assistant Professor within the Department of Pediatrics and Emory's Vaccine Center.

BURROUGHS WELLCOME FUND

Congratulations Dr. Anita McElroy on receiving the Burroughs Wellcome Fund Career Award for Medical Scientists! The Career Awards for Medical Scientists (CAMS) program supports $700,000 awards over five years for physician-scientists to bridge advanced postdoctoral/fellowship training and the early years of faculty service. By increasing the number of physician scientists and keeping them in research, BWF believes that this bridging award, supporting the last year(s) of a mentored position in addition to supporting the beginning years of an independent position, will facilitate the transition to a career in research and buy time from service commitments.

Selected Recent Publications

Anderson, L "Respiratory syncytial virus vaccine development" Seminars in Immunology, Volume 25, Issue 2

Anderson, E, Weber, S. G. "Rotavirus infection in adults" Lancet Infectious Diseases, Volume 4, Issue 2

Camacho-Gonzalez, A., Spearman, P. W, Stoll, B. J. "Neonatal Infectious Diseases Evaluation of Neonatal Sepsis" Pediatric Clinics of North America, Volume 60 Issue 2

Wood, L. F, **Chahroudi, A,** Chen, H. L, Jaspan, H. B, Sodora, D. L. "The oral mucosa immune environment and oral transmission of HIV/SIV" Immunological Reviews, Volume 254

Flynn, P. M., Aldrovandi, G. M., Chadwick, E. G., **Chakraborty, R.,** Cooper, E. R., Schwarzwald, H., Martinez, J., Van Dyke, R. B. Comm Pediat, Aids "Infant Feeding and Transmission of Human Immunodeficiency Virus in the United States" Pediatrics, Volume 131, Issue 2

Eckard, A. R, Tangpricha, V., Seydafkan, S., O'Riordan, M. A., Storer, N., Labbato, D., McComsey, G. A. "The Relationship Between Vitamin D Status and HIV-related Complications in HIV-infected Children and Young Adults" Pediatric Infectious Disease Journal, Volumne 32, Issue 11

Abanyie, F, **Lamb, T. J. "**Implications of Ascaris Co-infection" Ascaris: The Neglected Parasite

Lee, S., Mittler, R. S., **Moore, M. L.** "Targeting CD137 Enhances Vaccine-Elicited Anti-Respiratory Syncytial Virus CD8(+) T Cell Responses in Aged Mice" Journal of Immunology, Volume 192 Issue 1

Dodd, Kimberly A., **McElroy, Anita K,** Jones, Megan E. B, Nichol, Stuart T, Spiropoulou, Christina F. "Rift Valley Fever Virus Clearance and Protection from Neurologic Disease Are Dependent on CD4(+) T Cell and Virus-Specific Antibody Responses"

Melikyan GB. HIV entry: a game of hide-and-fuse? Current Opin. Virol. 2013, vol. 4. p. 1-7.

J. Meng, C.C Stobart, and **M.L. Moore**. "An Overview of Respiratory Syncytial Virus." *PLOS Pathogens*, Pearls Series, *In press*.

Shane, A. L, Stoll, B. J. "Neonatal sepsis: Progress towards improved outcomes" Journal of Infection, Volumne 68

Suthar, M. S, Diamond, M. S, Gale, M. "West Nile virus infection and immunity" Nature Reviews Microbiology, Volume 11, Issue 2

R. C. Guerrero-Ferreira, and **E. R. Wright**. "Zernike Phase Contrast Cryo-Electron Tomography Of Whole Bacterial Cells." *Journal of Structural Biology*. 185 (1): 129-133 (2014).

Bodewes, R., Geelhoed-Mieras, M. M, **Wrammert, J,** Ahmed, R, Wilson, P. C, Fouchier, R. A. M, Osterhaus, Adme, Rimmelzwaan, G. F. "In Vitro Assessment of the Immunological Significance of a Human Monoclonal Antibody Directed to the Influenza A Virus Nucleoprotein"