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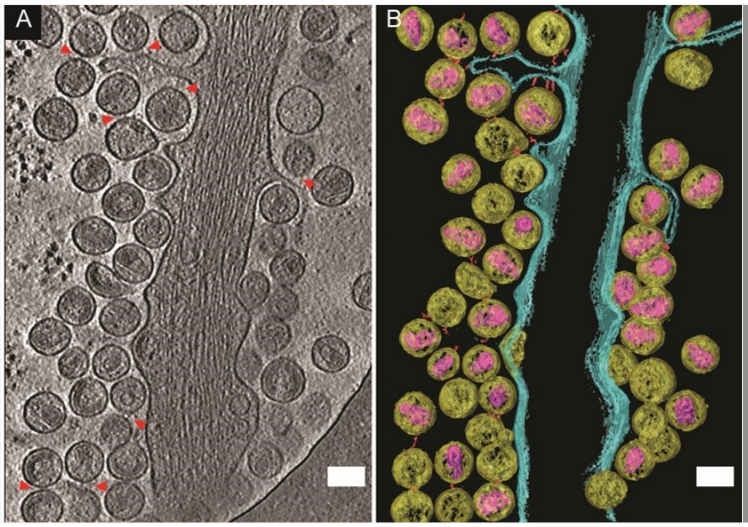
Volume 1, Issue 2 November 2014

# Center for Childhood Infections and Vaccines

Welcome to the Newsletter for the Center for Childhood Infections and Vaccines (CCIV). CCIV is part of a multi-institutional research partnership between Emory, Children's Healthcare of Atlanta, Georgia Tech, and Morehouse School of Medicine. We focus on many important infections that have been in the news lately, and we are developing treatments, preventions, and cures for childhood infections. There has been a lot of attention on the Ebola virus outbreak recently, and we are proud that CCIV member Anita McElroy has been helping with the Ebola patients who have been treated at Emory. You may have seen her quoted in the New York Times recently, because she has performed the only study to date examining inflammatory markers in Ebola-infected children. Its now RSV season, and we continue to work hard on RSV vaccines and interventions. Marty Moore, Larry Anderson, Liz Wright, and our Vaccine and Treatment Evaluation Unit (VTEU) are all engaged in research to battle this important pathogen. Please help me welcome two of our new members, Jumi Yi and Lisa Cranmer, who are featured in this edition of the newsletter. If you are interested in hearing more about CCIV please contact Karen Kennedy at kmurra5@emory.edu.

*-Paul Spearman, MD*

Paul Spearman, MD




Cryo-ET of Tethered HIV-1. (A) Selected slice from a three-dimensional cryo-electron tomographic reconstruction of HIV-1 virions tethered to a HT1080 cell F-actin microspike. Rod-like densities attributed to tetherin connecting virions to each other and to the plasma membrane are indicated by red triangles. (B) Corresponding segmented volume: rod-like densities (red), virions (yellow), mature HIV-1 cores (pink), and plasma membrane (blue ). Scale bars = 100 nm. Image from the laboratory of Liz Wright, PhD

**In This Issue**

# Research Highlight: RSV work in the VTEU

Respiratory syncytial virus (RSV) is the single most important cause of serious lower respiratory infections in children in the United States and infections in children are estimated to cause up to 200,000 deaths globally and 125,000 hospitalizations in the United States each year. It most often causes severe disease in children <1 year of age but causes repeat infection and disease throughout life. RSV has been a high priority for vaccine development since the 1960s but as yet no vaccine is licensed. Of the 4 potential target populations for vaccines, the infant <6 months or infants >6 months of age are the highest priorities. A critical next step in developing RSV vaccines for these children is clinical vaccine trials.

Through the VTEU, we received funding to address one gap in doing clinical vaccine studies in the infant, i.e. the need for a reliable test of RSV immune status. Presently RSV antibodies are used to detect past infection but the infected young infant does not reliably develop RSV antibodies and those that do may lose these antibodies over time. In this study, we will determine which memory CD8 and CD4 memory T cell responses, e.g. IFN-ɣ positive, lymphoproliferative, T regulatory, etc., induced by RSV stimulation of peripheral blood mononuclear cells (PBMCs) from children exposed to one RSV season of which about 50% will be from children previously infected with RSV, i.e. RSV primed, and cord blood mononuclear cells (CBMCs) obtained from normal births which should be RSV naïve, children hospitalized with an RSV positive acute respiratory infection, and children not exposed to an RSV season (RSV naïve). Through these studies we will identify a panel of T cell assays that detect past infection in antibody negative children. Since previously infected children are RSV primed, their response to a vaccine will not predict the response of the RSV naïve child in most need of the vaccine. This panel of T cell assays will improve our ability to accurately evaluate candidate vaccines and efficiently find one that works.

*-submitted by Dr. Larry Anderson*

Larry Anderson, MD

# Center Member Highlight: Jumi Yi, MD

During medical school at the Medical College of Georgia in Augusta, GA and pediatric residency at St. Christopher's Hospital for Children in Philadelphia, PA, I was involved in multiple community health outreaches and overseas mission trips and was always struck by the impact of common illnesses such as gastroenteritis and pneumonia in resource-poor settings. My project during my pediatric infectious diseases fellowship at the Emory University School of Medicine was a natural fit as it focused on norovirus, one of the most common causes of viral gastroenteritis in children and adults. I also developed an appreciation for the importance of well-planned studies in assessing disease burden and how they apply to vaccine development. Upon the completion of my fellowship, I was given an opportunity to join the Vaccine Trial and Evaluation Unit and am excited to participate in meaningful research that will potentially affect the population. In addition, I am grateful to continue to work with my talented mentors and colleagues.

Outside of work, I enjoy spending time with friends and family, playing guitar, and crafting gifts for others.

Jumi Yi, MD

*-submitted by Dr. Jumi Yi*

# Research Highlight: ICGEB-Emory Vaccine Center

CCIV faculty, Dr. Murali Krishna Kaja, has been working to develop an international collaborative partnership basing the activities at the ICGEB-Emory Vaccine Center, New Delhi, India. The ICGEB-Emory Vaccine Center is a unique international partnership between Emory and the International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, India. The goal of the joint center is to conduct vaccine research on infectious diseases that disproportionately affect the developing world. In the past 3 years, Dr. Kaja's leadership in the Emory-India program, combined with the expertise of the other Emory investigators and collaborators from India led to an International Collaborations infectious Disease Research (ICIDR) program on dengue virus infection India.


ICGEG Joint Center, New Delhi

Patients waiting at pediatric clinical ward at AIMS, New Delhi, during dengue season

Dengue is a mosquito-borne viral infection that is rapidly spreading globally with recent entry into the Americas. Over 40% of the world's population is now at risk from dengue, with India having the largest number of infections. Currently there are no available antivirals or vaccines and thus there is a compelling need for a better understanding of the immunology and virology of human dengue virus infections.

ICIDR programs are prestigious NIH competitive awards to support international collaborative research projects. The Emory ICIDR program application on dengue virus infection in India received top percentile with impact score of perfect 10. The program is expected to pay $500,000 direct costs per year for 5 years.

The overall objective of the Emory ICIDR on dengue virus infection in India is to build capacity for dengue research in India using state-of-the-art tools and technologies; and use these tools to address critical scientific questions important to the health and well-being of dengue exposed populations.

Other investigators from Emory include Drs. Bali Pulendran, Jens Wrammert, Rama Akondy along with Dr. Rafi Ahmed serving as the over all PI. Other participating institutions and investigators include Dr. Jeffrey Ravetchfrom Rockefeller, Dr. Navin Khanna from ICGEB (India), Drs. Sushil Kara and Rakesh Oldham from All India Institute of Medical Sciences (AIMS, New Delhi, India), Dr. Asha Abraham and colleagues from Christian Medical College (CMV, Vellore, India), and Dr. Cecilia Dayana from National Institute of Virology (NIB, Pune, India).

*-submitted by Dr. Murali Kaja*

Dr. Kaja and colleagues working at the ICGEB-Emory Vaccine Center, New Delhi

# Pilot Grant Program Success

Pilot grants have been a **major success** for CCIV. In only a few years, we have had **six** of our Center's pilot grants turn in to major awards from NIH, a total of more than $8M in funding. This is an unmatched record for success, with over than fifty percent of our pilot grants resulting in solid extramural funding and more expected in the near future. One of our earliest pilots to Richard Plemper and Jan Pohl resulted in R01AI083402, titled "Cryo-electron and biochemical analysis of native paramyxovirus fusion complexes." Pilot funding for Marty Moore and Phil Santangelo resulted in both an R01 and R21 grant. A pilot for Tracey Lamb and Jan Mead resulted in an NIH Innovators award of $2,329,500. A pilot for Paul Spearman and Biao He at UGA resulted in a new R01 for developing an HIV vaccine with total funding of $2.8M. Supporting funds from the center for a "pre-K" award for Nitika Gupta resulted in a successful NIH K award. Kudos to all! And many thanks to past awardees who gave research updates at the Annual CCIV Symposium on August 22, 2014.

See page 5 to learn about the other grant success of CCIV members.

# Center Member Highlight: Lisa Cramer, MD

Lisa M. Cranmer, MD, MPH trained in clinical medicine and public health at Johns Hopkins and completed her pediatric residency and infectious disease fellowship at the University of Washington/ Seattle Children's Hospital. She joined Emory and Children's Hospital of Atlanta in August 2014, and is excited to continue her research pursuits within such a dynamic and interdisciplinary research community. Dr. Cranmer's translational research has focused on detection and prevention of tuberculosis among HIV-infected mothers and their children. Prior to joining Emory, she lived in Kenya for 2 years, where she co-led an ongoing clinical trial on early initiation of antiretroviral treatment in HIV-infected children, and was the PI of the Maternal-Infant Mycobacterial Immunity Study to evaluate the role of maternal immunity on infant BCG vaccine responses. She aims to continue research in understanding predictors of infant TB immunity and vaccine response.

Outside of the workplace, Dr. Cranmer can be found biking or hiking with her husband John and their 3-year old son, Solomon.

*-submitted by Dr. Lisa Cranmer*

Lisa Cranmer, MD

# Clinic Research Highlight: VTEU

The Emory/Peds VTEU recently led the nation in H3N2 influenza vaccine protocol enrollment. CCIV has a major focus on vaccine testing, and frequently leads the country in testing vaccines in children. We recently had the opportunity to enroll seven children at once from one very willing and helpful family. The Freeman family is pictured in the middle of this photo, flanked by VTEU investigators and staff Brooke Hartwell, Melanie Johnson, Evan Anderson, and Teresa Ball.

# Recent Grants to CCIV Members

CCIV members have been busy securing funding this year for clinical trials and research grants. Congratulations!

Clinical Trials

- Evan Anderson: “PXVX-VC-200-005: A Phase III Randomized, Double-blind, Placebo-Controlled Study in Older Adults to Assess Immunogenicity, and Clinical Acceptability of a Single-dose of the Live Oral Cholera Vaccine Candidate PXVX0200, *Vibrio cholerae* O1 Serotype Inaba Vaccine Strain CVD 103-HgR,” $33,578
- Evan Anderson: “PXVX-VC-200-004: A Phase III Randomized, Double-blind, Placebo-Controlled Three-Lot Consistency Study in Healthy Adult Volunteers to Assess Immunogenicity, and Clinical Acceptability of a Single-dose of the Live Oral Cholera Vaccine Candidate PXVX0200, *Vibrio cholerae* O1 Serotype Inaba Vaccine Strain CVD 103-HgR,” $69,088
- Evan Anderson: “A Phase III, Double Blind, Randomized, Multicenter, Controlled Study to Evaluate the Immunogenicity, Safety, and Tolerability of VARIVAX New Seed Process (NSP) Administered Concomitantly with M-R-R II V210-063-001,” $3,318
- Rana Chakraborty: "GS-US-183-0160: A Phase 2/3 Multicenter, Open-Label, Multicohort, Two-Part Study Evaluating the Pharmacokinetics (PK), Safety, and Antiviral Activity of Elvitegravir (EVG) Administered with a Background Regimen (BR) Containing a Ritonavir-Boosted Protease Inhibitor (PI/r) in HIV-1 Infected, Antiretroviral Treatment-Experienced Pediatric Subjects," $18,225
- Rana Chakraborty: “GS-US-216-0128: A Phase 2/3, Multicenter, Open-label, Multicohort, Two-Part Study Evaluating Pharmacokinetics (PK), Safety, and Efficacy of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir (DRV/co), Administered with a Background Regimen (BR) in HIV-1 Infected, Treatment-Experienced, Virologically Suppressed Pediatric Subjects,” $19,200
- Rana Chakraborty: “GS-US-292-0106: A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents,” $19,200
- Paul Spearman: “PTN T025 ABS01 SCAMP: Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections,” $4,000

Research Grants

- Larry Anderson: Gates Foundation “Develop biomarkers of RSV disease severity for vaccine trial,” $807,988
- Ann Chahroudi: ACTSI/URC Pilot, $30,000
- Ann Chahroudi: Foundation for AIDS Research “Impact of early ART on SIV reservoirs,” $180,000
- Theresa Guathier and Marty Moore: R21 “Modulation of neonatal alveolar macrophage by CFTR mutation,” $234,000
- Tracey Lamb: R21 “Ephrin Ligands as Novel Targets for an Adjunct Therapy in Cerebral Malaria,” $241,653
- Anita McElroy: Burroughs Wellcome Fund “Defining the roles of CD4+ T cells in generating a protective immune response against Rift Valley fever virus,” $700,000
- Jan Mead: URC Pilot “Effects of Infection on Gene Expression of the parasite Cryptosporidium and its Host,” $30,000
- Jan Mead: R56 with University of Houston, “Optimizing IMPDH Inhibitors for the Treatment of Cryptosporidiosis,” $148,200
- Jan Mead: R33 with University of Georgia, “Targeting Host + Apicomplexian Isoprenoid Pathways,” $62,030
- Greg Melikian: R01 Equipment supplement “Identification and Characterization of Small Molecule Inhibitors of HIV-1 Fusion,” $50,000
- Marty Moore and Richard Plemper: R01 “Novel Therapeutics against Respiratory Syncytial Virus,” $622,945
- Paul Spearman and Biao He: R01 “PIV5 Mucosal Protection Against HIV Generated by PIV5,” $682,841
- Paul Spearman, David Guidot, Lou Ann Brown: R01 “HIV-induced redox stress and the alveolar macrophage as a resistant reservoir,” $687,678
- Paul Spearman and Mark Mulligan: RTOP-RSV, $59,634
- Paul Spearman and Mark Mulligan: RTOP-CMV, $994,454
- Mehul Suthar: U19 with University of Washington, “RIG-I-like receptor regulation of T cell immunity against flavivirus infection,” $398,681
- Mehul Suthar: R56 “Regulation of T cell immunity by the cytosolic RIG-I like receptors,” $443,306
- Cheng Zhu and Greg Melikian: Children’s Center for Pediatric Nanomedicine Pilot “Analysis of receptor binding kinetics and conformational change of HIV envelope protein,” $60,000

# Recent Papers Published by CCIV Members

2014 has been a busy year of publications for CCIV members:


1. Alonas E, Lifland AW, Gudheti M, Vanover D, Jung J, Zurla C, Kirschman J, Fiore VF, Douglas A, Barker TH, Yi H, Wright ER, Crowe JE Jr, Santangelo PJ. Combining single RNA sensitive probes with subdiffraction-limited and live-cell imaging enables the characterization of virus dynamics in cells. ACS Nano. 2014 Jan 28;8(1):302-15. PMID: 24351207
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3. Bernstein DI, Jackson L, Patel SM, Sahly HM, Spearman P, Rouphael N, Rudge TL Jr, Hill H, Goll JB. Immunogenicity and safety of four different dosing regimens of anthrax vaccine adsorbed for post-exposure prophylaxis for anthrax in adults. Vaccine. 2014 Sep 16. pii: S0264-410X(14)01240-7. PMID: 25239484
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8. Chakraborty R, Lacy KD, Tan CC, Park HN, Pardue MT. Refractive index measurement of the mouse crystalline lens using optical coherence tomography. Exp Eye Res. 2014 Aug;125:62-70. PMID: 24939747
9. Conrardy C, Tao Y, Kuzmin IV, Niezgoda M, Agwanda B, Breiman RF, Anderson LJ, Rupprecht CE, Tong S. Molecular detection of adenoviruses, rhabdoviruses, and paramyxoviruses in bats from Kenya. Am J Trop Med Hyg. 2014 Aug;91(2):258-66. PMID: 24865685
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11. Dodd KA, McElroy AK, Jones TL, Zaki SR, Nichol ST, Spiropoulou CF. Rift valley Fever virus encephalitis is associated with an ineffective systemic immune response and activated T cell infiltration into the CNS in an immunocompetent mouse model. PLoS Negl Trop Dis. 2014 Jun 12;8(6):e2874. PMID: 24922480
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21. Kiss G, Chen X, Brindley MA, Campbell P, Afonso CL, Ke Z, Holl JM, Guerrero-Ferreira RC, Byrd-Leotis LA, Steel J, Steinhauer DA, Plemper RK, Kelly DF, Spearman PW, Wright ER. Capturing enveloped viruses on affinity grids for downstream cryo-electron microscopy applications. Microsc Microanal. 2014 Feb;20(1):164-74. PMID: 24279992
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## Continued: Recent Papers Published by CCIV Members


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# Upcoming Events/Seminars

**Pediatric ID Seminar Series**

*Thursdays at 1 pm in HSRB Auditorium*

November 20: Paul Spearman
December 4: Kendra Quicke (Mehul), Eduardo Da Sileira (Wrammert)
December 11: Rebecca Dillard (Wright), Mariana Marin (Melikian)
December 18: Siddhartha Bhaumik (Kaja), Kristen Lamb (Wright)

**Special Events**

December 3: "Using Electronic Medical Records for Research at Children's: How to Turn Myth into Reality": HSRB Auditorium, lunch at 11:30 am, noon seminar, watch for emails to RSVP for lunch

December 10: Eric Pamer, MD, Sloan Kettering will be visiting and giving two talks at Children's and Emory
-Grand Rounds: 7:30 am, Egleston Classroom 5
-Noon Seminar: HSRB Auditorium, lunch at 11:30 am, watch for emails to RSVP for lunch

## Visit Our Website

To keep up to date on all that is happening in the CCIV, check out our website:

www.pedsresearch.org/centers/detail/immunology-vaccines