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PEDIATRIC RESEARCH ALLIANCE

December 2016

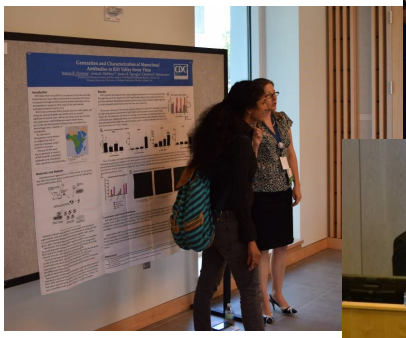
Center for Childhood Infections and Vaccines

First Annual CCIV Symposium

Each December brings a time of reflection on the year, and 2016 has been a great year for CCIV. Our faculty were successful in obtaining funding, including a first R01 for Ann Chahroudi (page 2). In June, the center awarded two pilot grants on Zika virus, one to Jens Wrammert and one to Ann Chahroudi. Anita McElroy and Mehul Suthar both received Junior Faculty-Focused pilot awards, making CCIV researchers the most represented group in Pediatric Research Alliance center pilots in 2016. Dedication and perseverance in the lab led to a number of publications as well. The impact of CCIV scientists on understanding and tackling important pediatric infectious diseases, such as Zika and RSV, can be seen in our many publications this year (link on page 4).

Our most notable center accomplishment came in October when CCIV hosted its second Annual Symposium. We had two keynote speakers: John V. Williams, Chief of the Division of Pediatric Infectious Diseases, Children's Hospital of Pittsburgh of UPMC spoke about human metapneumovirus and Julie Waterbury, Executive Director, Strategic Licensing & Acquisitions Lead, Vaccines at Merck spoke about vaccines for ebola. In addition, six CCIV faculty presented short talks about their work. The full gambit of CCIV work was showcased, from basic science and pathogenesis to vaccine development and clinical trials. A poster session allowed trainees from CCIV labs to share their projects, with nearly every CCIV lab represented. Thank you to everyone who participated for making our inaugural symposium such a success! You can see photos of the day and recordings of the talks on CCIV's website on the news page: http://www.pedsresearch.org/research/centers/cciv/newsletters/

Happy Holidays,
Marty Moore, PhD
CCIV Director



Inside this issue:

Ann Chahroudi awarded NIH R01

Ann Chahroudi, MD, PhD

The use of antiretroviral therapy (ART) typically results in reduction of plasma viral loads to below detectable levels in human immunodeficiency virus (HIV)-infected individuals. However, infection with HIV persists despite suppressive ART and treatment interruption results in rapid viral rebound. In absence of ART, CD8+ T cells have been shown to inhibit virus replication during HIV infection and depletion of CD8+ lymphocytes in vivo during simian immunodeficiency virus (SIV) infection of rhesus macaques (RMs) results in increased viral loads. The precise role of CD8+ lymphocytes in controlling virus replication and/or production during continuous, highly active ART is unknown. Understanding the mechanisms controlling HIV/SIV reservoir dynamics under ART, and particularly the role of host immune responses, is critical to design effective strategies to reduce the size of these reservoirs and promote HIV/SIV remission.

In our first study of CD8+ lymphocyte depletion in ART-treated SIV-infected RMs, we treated 13 animals in which viremia was suppressed by ART for a period variable between 8 and 32 weeks with a single dose of the CD8a-directed mAb M-T807R1 (Cartwright EK et al Immunity 2016 Sep 20;45(3):656-68). Similar to previous in vivo CD8 depletion experiments, we observed reduction of CD8+ T cells by >95% in peripheral blood, 70-85% in lymph nodes, and ~60% in rectal mucosa. NK cell numbers in peripheral blood were reduced by 40-99% in this study. Importantly, CD8+ lymphocyte depletion resulted in increased virus production in both plasma and lymphoid tissues in 13 out of 13 (100%) of the animals (Figure 1), with levels of viremia up to ~1000 copies/ml of plasma. We also observed that, upon CD8+ T cell repopulation (that occurred between three and seven weeks after depletion), viremia became undetectable again. Taken together, these data indicate that CD8+ lymphocytes are required to maintain full virus suppression in ART-treated SIV-infected RMs, thus revealing a previously unrecognized antiviral function of CD8+ lymphocytes and providing unprecedented rationale to explore immunotherapeutic approaches in ART-treated HIV-infected individuals. This exciting result forms the basis for our recently funded NIH R01 grant (R01 AI125064), in which we plan to elucidate the mechanism(s) responsible for CD8-mediated virus suppression under ART.

In this new project, we will build upon our preliminary data indicating that CD8+ lymphocytes act in concert with ART to maintain virus suppression. Using the highly relevant SIV/RM model, we will answer three important questions regarding the mechanism(s) of CD8+ lymphocyte-mediated virus suppression. First (Aim 1), we will determine if the antiviral effect of CD8+ lymphocytes is present in SIV-infected ART-treated RMs with prolonged suppression

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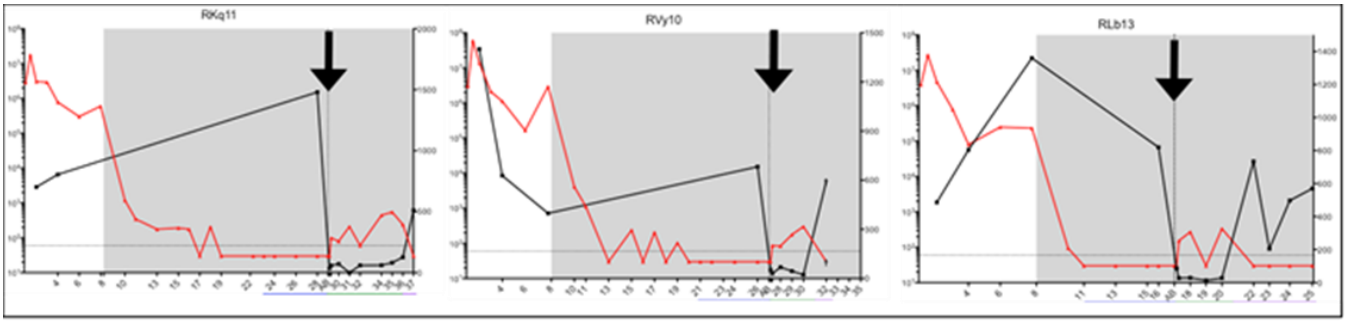

Figure 1. CD8+ lymphocyte depletion results in measureable increase in plasma viral loads in ART-treated SIV-infected RMs. Viral load (red line) and CD8+ T cell counts (black line) in SIV-infected RMs treated with ART (shaded area) and who received the CD8a depleting mAb M-T807R1 (indicated by arrows). Note that as CD8+ T cells reconstitute following mAb-mediated depletion, viral loads are again controlled to undetectable levels. Three representative RMs are shown (out of 13 total who underwent this protocol).

Bernardo Mainou awarded Winship ACS IRG Pilot

The American Cancer Society Institutional Research Grant, operated through the Winship Cancer Institute, is designed to provide funds for pilot projects to obtain preliminary results to enable investigators to compete for national research grants. Our project seeks to develop targeted viral oncolytic therapeutics against triple-negative breast cancer by using mammalian orthoreovirus (reovirus). In the United States, one in eight women will develop invasive breast cancer, with over 200,000 new cases and more than 40,000 deaths per year. A subset of breast cancers, termed triple-negative breast cancer (TNBC), for their lack of expression of estrogen receptor (ER) and progesterone receptor (PR) and absent amplification of the human growth factor receptor 2 (HER2) gene, account for approximately 15% of all breast cancers and more frequently affect younger patients and African American women. Because of the genetic heterogeneity within this subtype of breast cancer there is an absence of targeted therapies, with cytotoxic chemotherapy being the only treatment available to women with metastatic TNBC. Reovirus preferentially infects and kills transformed cells and is in Phase I-III clinical trials to determine its efficacy against a variety of cancers, although TNBC cells are not efficiently killed by current oncolytic reoviruses. Using funds from this research grant, we will genetically engineer reovirus to enhance its cytolytic properties against TNBC, identify cellular mechanisms used by reovirus to kill TNBC cells, and enhance reovirus killing of TNBC cells by screening a library of small molecule inhibitors. Our studies will improve our understanding of the host and viral factors used by oncolytic reovirus to efficiently kill TNBC cells and develop an improved targeted therapeutic against this disease.

—submitted by Bernardo Mainou, PhD

Mainou Lab: Bernardo Mainou, PhD, Angela Berger, PhD and Roxana Rodriguez

Chahroudi R01 continued

of viremia (as an extension of our preliminary results demonstrating this effect in the setting of short-term virus suppression). In this study, we will perform CD8 depletion in SIV-infected RMs treated with ART for at least one year to more closely mimic long-term ART-treated HIV-infected individuals with a stable virus reservoir. Second (Aim 2), we will determine if the observed antiviral effect of CD8+ lymphocytes under ART is mediated by CD8+ T cells vs. CD8+ NK cells. This critical experiment is made possible by a newly available monoclonal antibody (mAb) that targets cells expressing CD8b (i.e., CD8ab+ T cells, but not CD8a+ NK cells) for depletion. Third (Aim 3), we will quantify the contribution of CD4+ T cell activation/proliferation to the increase in viremia that follows in vivo CD8 depletion. By using a neutralizing anti-IL-15 mAb together with CD8 depletion we can selectively block homeostatic CD4+ T cell activation and measure subsequent virologic outcomes.

This work will allow us to understand how the host antiviral cellular immune response works in concert with ART to suppress SIV replication and/or production. These results will refine and clarify the evidence to explore cure-directed interventions, such as therapeutic vaccination and checkpoint blockade inhibitors, aimed at boosting the virus-specific CD8+ lymphocyte response in ART-treated HIV-infected individuals. The knowledge we gain will be important for designing novel immune-based approaches to induce HIV remission.

—submitted by Ann Chahroudi, MD, PhD

Recent Publication Highlights

View all recent publications on CCIV's website or click here.

Rotavirus and Norovirus in Pediatric Healthcare-Associated Gastroenteritis

Yi J, Sederdahl BK, Wahl K3 Jerris RR, Kraft CS, McCracken C, Gillespie S, Kirby AE, Shane AL, Moe CL, Anderson EJ. Open Forum Infect Dis. 2016 Aug 30;3 PMID: 27807589

Jumi Yi, MD

Rotaviruses and noroviruses are important causes of community-acquired gastroenteritis and can lead to severe disease resulting in hospitalizations. However, their importance in pediatric healthcare-associated gastroenteritis is not well understood. We collected residual stool specimens from patients with diarrhea and/or vomiting hospitalized at least ≥48 hours at 2 Children's Healthcare of Atlanta campuses from 2012-2013. All (total 207) stool specimens were from children with an underlying medical condition, who were hospitalized for a prolonged period of time, median of 285 hours (about 12 days), at time of specimen submission. About half were immunocompromised. We found that rotavirus and noroviruses were important pathogens in healthcare-associated gastroenteritis with 10% positive for rotavirus and 3% positive for norovirus. Of note, the year studied was a peak year for community-acquired rotavirus and norovirus. However, although rotavirus testing of clinical specimens was routinely available during this time, only 31% of children had standard of care (SOC) rotavirus testing ordered. In contrast, 89% and 47% of children had SOC Clostridium difficile (11% positive) and stool culture performed (0% positive), respectively. These findings highlight the need to consider rotavirus and norovirus in healthcare-associated gastroenteritis especially in peak years of community-acquired disease.

Furthermore, 34% of children were age eligible for rotavirus vaccination and 44% of them did not receive any dose of vaccine. This observation may have been secondary to contraindications associated with an underlying medical condition and stresses the importance of vaccinating eligible children for not only direct protection, but also indirect protection of those who are unable to be vaccinated.

-Submitted by the authors, please find the article here: https://www.ncbi.nlm.nih.gov/pubmed/27807589

Human antibody responses after dengue virus infection are highly cross-reactive to Zika virus.

Priyamvada L, Quicke KM, Hudson WH, Onlamoon N, Sewatanon J, Edupuganti S, Pattanapanyasat K, Chokephaibulkit K, Mulligan MJ, Wilson PC, Ahmed R, Suthar MS, Wrammert J. Proc Natl Acad Sci U S A. 2016 Jul 12;113(28). PMID: 27354515

Zika virus (ZIKV) is a mosquito-borne flavivirus of significant public health concern. Due to its association with Guillain-Barre Syndrome in adults, and neurological and ocular complications in neonates, it has become increasingly important to understand the immunology and pathobiology of ZIKV infections. ZIKV shares a high degree of sequence and structural homology with other flaviviruses, including dengue virus (DENV), resulting in immunological cross-reactivity. In this study, we addressed the issue of cross-reactivity between DENV and ZIKV by testing sera and plasmablast-derived monoclonal antibodies from acutely infected secondary dengue patients against ZIKV. We observed that both acute and convalescent dengue sera could potently bind and neutralize ZIKV. A majority of the dengue plasmablast-derived mAbs we tested bound to whole virus, and a small subset was also able to neutralize virus in vitro. In addition, we also demonstrated antibody dependent enhancement of ZIKV infection in the presence of dengue antibodies. Taken together, these findings suggest that preexisting immunity to DENV may impact protective immune responses against ZIKV. In addition, the extensive cross-reactivity may have implications for ZIKV virulence and disease severity in DENV-experienced populations.

-Submitted by the authors, please find the article here: https://www.ncbi.nlm.nih.gov/pubmed/27354515

Lalita Priyamvada & Kendra Quicke

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Visit our website: www.pedsresearch.org/research/centers/cciv
The CCIV website was recently redesigned, check out the new features on it and www.pedsresearch.org!

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Upcoming Events

Pediatric ID Seminar Series
Meets each Monday at 9 am in the Emory-Children's Center Room 302

Pictures & Archive

To see pictures from the CCIV Annual Symposium and our newsletter archive, check out:
http://www.pedsresearch.org/research/centers/cciv/newsletters/