Center for Childhood Infections & Vaccines

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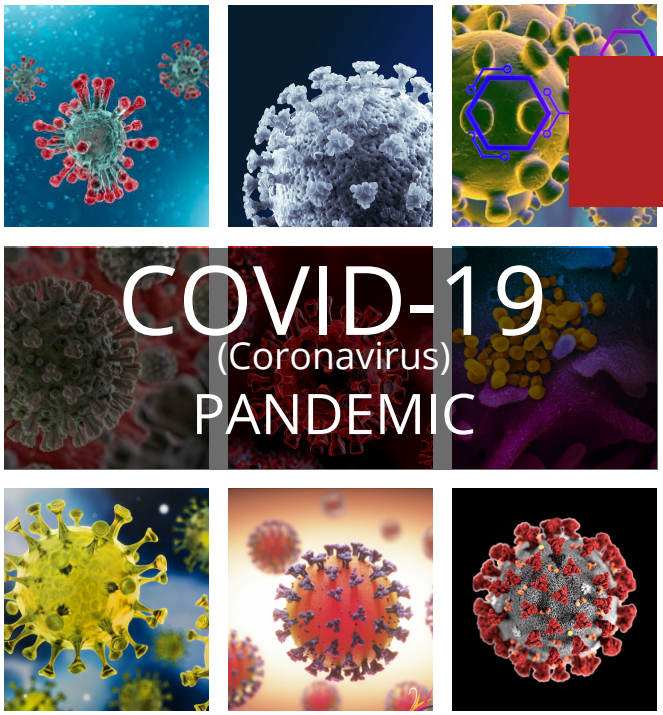

IN THIS ISSUE

Ann Chahroudi, MD, PhD

Director, Center for Childhood Infections & Vaccines

Associate Division Chief for Basic/Translational Research, Division of Infectious Diseases

Associate Professor of Pediatrics, Division of Pediatric Infectious Diseases

Medical Director, Ponce Family & Youth Clinic, Infectious Diseases Program, Grady Health System

FEATURE

Andi L. Shane, MD, MPH, MSc

Chief, Division of Pediatric Infectious Disease

Marcus Professor of Hospital Epidemiology and Infection Control

Emory University School of Medicine and Children's Healthcare of Atlanta

COVID-19 Preparedness at Children's Healthcare of Atlanta

While CCIV research colleagues have been engaged in efforts toward the development of diagnostics and treatments for COVID-19 infections and understanding the pathogenesis of SARS-CoV-2, our clinical teams have been preparing to care for children with COVID-19 infections.

Despite a significant burden of disease among older adults and those with chronic medical conditions, children between 0-17 years of age currently comprise less than 1% of the laboratory confirmed infections among people in the state of Georgia. COVID-19 infections appear to result in relatively mild upper respiratory symptoms in healthy children. This disparate burden of disease in the young is fascinating and is an active area of research.

Children's Healthcare of Atlanta has been actively engaged in a system-wide response effort to ensure that children with COVID-19 infections and the healthcare workers

FEATURE
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who care for them are able to do so in an appropriately safe environment. Clinical and operational leaders have partnered to develop guidance on the topics of screening and pre-hospital management, clinical care, diagnostics and testing, personal protective equipment (PPE) and supply chain, employee health and workforce management, and communications. With twice daily teleconferences, using Children's HEICS (Hospital Emergency and Incident Command Structure) topic leaders provide updates, discuss plans and barriers in the morning and outline progress during afternoon teleconferences.

Children's has adapted guidance from the Centers for Disease Control and Prevention (CDC) and the Georgia Department of Public Health to the unique needs of providing care to children. National and international shortages of PPE and diagnostic test kits as well as ongoing updates to guidance as we learn more about SARS-CoV-2, have created a need for flexibility for those on the front line as well as those who are developing guidance.

With a committed executive team and clinical and dedicated operational leaders, Children's strives to ensure that we are providing the best care to all patients. Acting on limited information and rapidly accruing data from the experiences of colleagues in countries around the world reminds us that the clinical – research partnerships that CCIV seeks to foster are essential, to optimize our response to the COVID-19 pandemic.

Atlanta Rotary Club - March 2, 2020

Colleen Kraft, MD and Andrea "Andi" Shane, MD, MPH

CCIV Response to COVID-19

Special CCIV Call for Pilot Grant Applications

SARS-CoV-2 and COVID-19 ONLY

CCIV has released an RFA focusing on COVID-19 studies only, with applications due April 3rd and funding available May 1st. A second RFA will be released early in April in the general call for pilots with applications due in July. This staggered RFA call is intended to allow investigators to apply for funds with a rapid turnaround as COVID-19 research programs are increasing.

RESEARCH

Publication Highlights

Maud Mavigner, PhD

Assistant Professor of Pediatrics, Division of Pediatric Infectious Disease, Department of Pediatrics, Emory School of Medicine

nature

Identification of Effective Strategies to "Shock" HIV Out of Latency as an Important Step Toward Curative Therapies

There is no cure for HIV that persists in latently-infected cells and requires lifelong antiretroviral therapy (ART). A widely-recognized theory to eradicate HIV reservoir relies on the "shock and kill" model, in which latency-reversing agents, or LRAs, induce viral reactivation from latently-infected cells (shock) to allow their elimination by the reactivated virus, the immune system, or therapeutic agents (kill). Candidate LRAs tested so far have been modestly effective at reactivating HIV.

Identification of Effective Strategies to "Shock" HIV Out of Latency as an Important Step Toward Curative Therapies

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However, in two articles recently published in Nature, we report successful "shock" interventions in animal models that induced the most robust and persistent HIV latency reversal observed to date.

In a first study, the drug AZD5582 targeting the non-canonical NF-KB pathway regulating HIV transcription, was tested in RMs displaying undetectable plasma viral load for over a year. AZD5582 induced on-ART increases in plasma viral loads in 9/12 RMs with sustained high-level viremia in 5/12 RMs, as well as increases in cell-associated SIV RNA levels in resting CD4+ T-cells, the main component of the reservoir. Concordant results were obtained in ART-treated HIV-infected bone marrow–liver–thymus humanized mice.

The second study, performed in the same animal models, evaluated immunological interventions combining CD8+ T-cell experimental depletion and treatment with the drug N-803 that strongly activates IL-15. This approach induced high-level on-ART viremia in 14/14 RMs as well as substantial increases in viral RNA in lymphoid tissues.

These studies identified novel pharmacological interventions able to reactivate HIV and advanced our understanding of HIV latency. While activation of the non-canonical NF-κB pathway could be used to induce HIV latency reversal as part of shock and kill approach, modulation of the pathways used by CD8+ T-cells to promote latency could potentiate the reactivating activity of any LRAs.

1: McBrien JB, Mavigner M, Franchitti L, *et a*l. Robust and persistent reactivation of SIV and HIV by N-803 and depletion of CD8(+) cells. Nature. 2020 Feb;578(7793):154-159. doi: 10.1038/s41586-020-1946-0. Epub 2020 Jan 22. Erratum in: Nature. 2020 Feb 4. PubMed PMID: 31969705.

2: Nixon CC, Mavigner M, Sampey GC, *et al*. Systemic HIV and SIV latency reversal via non-canonical NF-κB signalling in vivo. Nature. 2020 Feb;578(7793):160-165. doi: 10.1038/s41586-020-1951-3. Epub 2020 Jan 22. PubMed PMID: 31969707.

Bernardo Mainou, PhD

Assistant Professor of Pediatrics, Division of Pediatric Infectious Disease, Department of Pediatrics, Emory School of Medicine

A Review: Viral Interactions with Bacteria

The outcome of viral infection depends on the interplay between the virus, host factors, and the environment. The host microbiota, the constellation of microbes inhabiting an organism, plays a key role in the outcome of infection. Microbes and microbial products can directly interact with viral particles. Although bacteria do not support eukaryotic virus infection, they can promote viral fitness by enhancing virion stability, promoting infection of eukaryotic cells, and increasing coinfection rates. Virus binding of bacteria can also impact bacterial biology, including bacterial adherence to eukaryotic cells. The interactions between viruses and bacteria can also indirectly affect the host response to viral infection. In this Pearl, we focus on how direct and indirect interactions between viruses and bacteria impact viral biology and touch on recent findings that illustrate how bacterial biology can also be impacted by interactions with eukaryotic viruses.

Neu U, Mainou BA. Virus interactions with bacteria: Partners in the infectious dance. PLoS Pathog. 2020;16(2):e1008234. Published 2020 Feb 11. doi:10.1371/journal.ppat.1008234

PROFILE

Lab Profile

MELIKIAN LAB

Professor, Division of Infectious Disease, Department of Pediatrics
Emory University School of Medicine

Gregory Melikian, PhD

Melikian lab focuses on applying quantitative imaging and spectroscopy tools to delineate key steps of enveloped virus entry into cells, including HIV-1, Influenza virus, and, more recently, Lassa Fever virus. The following projects are ongoing in the lab

First, in collaboration with other investigators, including Dr. Salaita (Chemistry), we study mechanobiology of HIV-1 interactions with the cell plasma membrane.

Second, we are implementing correlative light-cryo-electron microscopy (CLEM) techniques to gain structural insights into key intermediate steps of virus entry – from fusion to nuclear import of viral complexes.

Third, we investigate the mechanism of virus restriction by host transmembrane innate factors that block viral fusion, using biochemical and biophysical techniques, including protein purification and reconstitution into lipid bilayers.

Fourth, we study the lipid-dependence and intermediates of viral fusion by reconstituting single virus fusion with supported lipid bilayers.

Fifth, we perform long-term live-cell experiments to visualize single virus entry and nuclear import in the context of productive infection.

Sixth, we are developing tools to study early stages of HIV-1 maturation by single-particle FRET measurements.

Seventh, we employ single-molecule localization microscopy to analyze the distribution of Env glycoproteins on single HIV-1 particles to assess the effect of host restriction factors incorporated into virions.

Eight, in collaboration with Dr. Sarafianos (Pediatrics) and investigators from other Universities, we investigate molecular mechanisms of HIV-1 interactions with the nuclear pore complex leading to nuclear import and integration into the host genome.

Greg Melikian was the 3rd most well funded investigator in the Department of Pediatrics in 2019.

AWARDS

Tooting Our Horn

2019 Notable Member Accomplishments

- In 2019, CCIV received the the second highest amount of external funding ($10.7 million) of any of the pediatric centers.
- Center member Greg Melikian was the 3rd most well funded investigator in the Department of Pediatrics.
- Center member Evan Anderson was awarded a $9 million grant from Pfizer to study an RSV vaccine in adults (one of the top 5 largest grants to the DOP in FY19).
- CCIV pilot award investment through 2017 has had a 21.6 multiple of return ($600K of pilot award investment converted into $12.9 million extramural award dollars through June 2019).

Promotions

Andi Shane
Promoted to perminent Division Chief!

Ann Chahroudi
Promoted to Associate Division Chief (Basic/Translational Research) !

Evan Anderson
Promoted to Associate Division Chief (Clinical Research) !

Jens Wrammert
Promoted to Associate Professor!

Awards/ Accomplishments

Jens Wrammert

Mehul Suthar

The joint R01 submitted by Jens and Mehul entitled “Understanding the Mechanisms of Antibody-mediated Transcytosis of ZIKV within the Placenta” scored in the 3rd percentile in study section.

Christina Rostad

Awarded the “Significant Event of 2019” by the Emory Office of Technology Transfer for RSV technology she developed in the lab of former CCIV Director Marty Moore that contributed to developing vaccine technology licensed to Meissa Vaccines, Inc. The vaccine received Series A funding and is currently in phase I clinical trials.

Ashwanth Francis

Awarded an R21 from the NIAID for the project entitled "Delineating a Role for CA in HIV-1 Nuclear Transport to Sites of Integration"

Meissa Vaccines:
Marty Moore Ph.D.,
Founder and Chief Executive Officer (former CCIV Director):
Meissa Vaccines received U.S. FDA Fast Track Designation for respiratory syncytial virus vaccine, MV-012-968.
Funds from a CCIV Pilot Grant contributed to initial research efforts leading to development of this vaccine.

EVENTS

Save-the-Date

CCIV Weekly Seminars

CCIV Monday Seminars will be held via Zoom web conference during the COVID-19 remote work schedule for the remainder of spring/summer season. All seminars will be are Mondays from 1-2 PM. Check out the most current seminar schedule and find the Zoom link to participate on the CCIV website.

Call for CCIV Pilot Grants

Submit your application for a CCIV Center Pilot Grant during the primary center request for applications in beginning in early April. Submissions are due by July 1, 2020 at 6:00 PM.

These grants are intended to encourage new research projects and collaborations, and increase extramural funding for pediatric research. Proposals should be aimed towards generating preliminary data for subsequent extramural grant applications. Selected applications may be awarded up to $50,000 for a 12 month project period (October 1, 2020 - September 30, 2021).

Visit the CCIV Website for eligibility and submission details.

RESOURCES

Resources

CCIV and Children's Publication Citation

Remember to cite CCIV and Children's Healthcare of Atlanta in your publications. This is vital to ensure recognition of our work by both Emory and Children's. This request/requirement applies to all center members, whether lab-based on non-lab based. Children's has been a significant supporter of the research operations that make all of our work possible and should be acknowledged.

The proper affiliation citation is: Center for Childhood Infections and Vaccines (CCIV) of Children's Healthcare of Atlanta and Emory University Department of Pediatrics, Atlanta, GA USA.

CCIV Website

Visit our website:
pedsresearch.org/research/centers/cciv/overview/

Social Media

Follow us on Twitter:
@EmoryCHOA_CCIV

Center Director

Ann Chahroudi, MD, PhD
ann.m.chahroudi@emory.edu

Program Coordinator

Karol Flowers
karol.flowers@emory.edu

Children's Healthcare of Atlanta

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