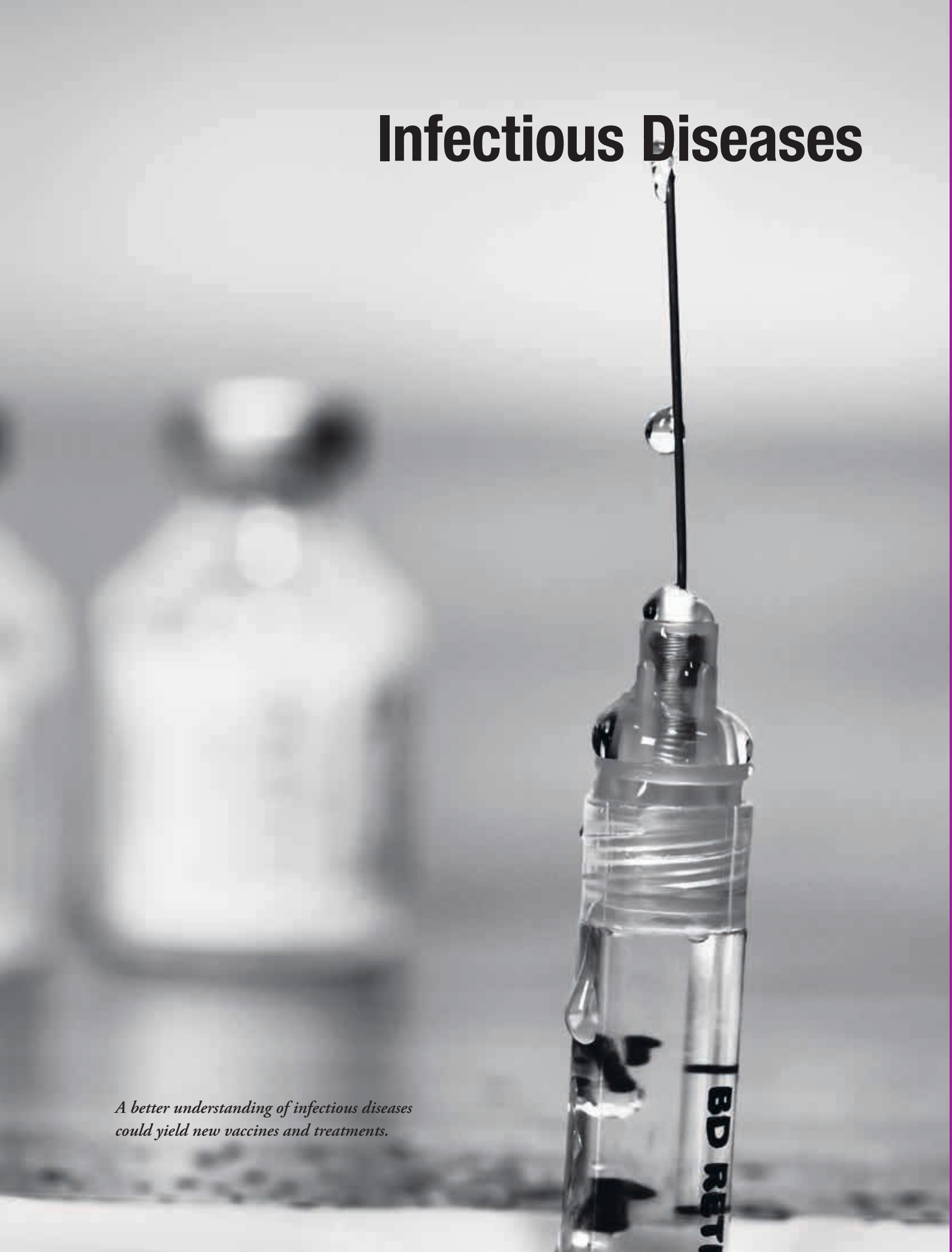
When you do infectious diseases well, you can have a huge impact in the community, throughout the hospital and with individual patients. Nothing affects quality of care more than preventing and eliminating infection. Nothing.

– Octavio Ramilo, MD
Chief, Infectious Diseases

Infectious Diseases



A better understanding of infectious diseases could yield new vaccines and treatments.

INFECTIOUS DISEASES

Study Helps Explain How Immune System Responds to Influenza Vaccine

While seasonal influenza vaccines protect 60 to 90 percent of healthy adults from "the flu," the mechanisms providing that protection were not well understood—until now. Infectious disease scientists in The Research Institute at Nationwide Children's Hospital have found that certain T cells in the blood are stimulated to provide protective antibody responses to seasonal flu vaccines. The work was published in *Science Translational Medicine*.

Led by **Octavio Ramilo, MD**, chief of Infectious Diseases and an investigator in the Center for Vaccines and Immunity at Nationwide Children's, the study identified this important mechanism after analyzing antibody responses in blood samples from three groups of healthy study participants taken before and after influenza vaccination. The groups included two sets of adults, one receiving flu vaccines during the 2009-2010 winter and the other receiving vaccination during the 2011-2012 winter. The third group included children receiving the flu vaccine during the 2010-2011 winter.

Antibodies are produced by specific white blood cells or B cells, which serve as an immune defense against foreign bodies such as the influenza virus. Helper T cells, another type of white cell, are essential for the generation of B cells. When they examined the blood samples, researchers found that a temporary increase in a unique subset of helper T cells expressing the co-stimulator molecule ICOS added to the immune response by helping B cells produce influenza-specific antibodies.

Results indicated that seven days after the administration of a flu vaccine, stimulated T cells were evident in all groups, contributing to the development of the immune response. The T cells positively correlated with increased antibodies against each flu virus strain examined, with the exception of the children's group against the swine-origin H1N1 virus.

"Given that seasonal influenza vaccines induce antibody responses mainly through boosting the recall response of the immune system, this lack of correlation might reflect the lack of H1N1-specific immunity in some children," explains study co-author Emilio Flano, PhD, a principal investigator in the Center for Vaccines and Immunity at Nationwide Children's.

"We're gratified that our study provides evidence of one of the essential events associated with the immune response following seasonal influenza vaccination," says Dr. Ramilo. "Understanding these processes is a key step toward developing more effective vaccines."

Bentebibel SE, Lopez S, Obermoser G, Schmitt N, Mueller C, Harrod C, Flano E, Mejias A, Albrecht RA, Blankenship D, Xu H, Pascual V, Banchereau J, Garcia-Sastre A, Palucka AK, Ramilo O, Ueno H. Induction of ICOS+CXCR3+CXCR5+ TH Cells Correlates with Antibody Responses to Influenza Vaccination. *Science Translational Medicine*. 2013 Mar 13;5(176):176ra32. PMID: 23486778.

INFECTIOUS DISEASES

The specialists in the Division of Infectious Diseases at Nationwide Children's Hospital provide expertise in diagnosis and management for children with all types of acute and chronic infections or immunodeficiency disorders. Physicians provide direct care for patients admitted to Nationwide Children's Specialized Infectious Diseases Unit. In addition, our physicians see patients with complicated infectious diseases or immunodeficiency disorders throughout the rest of the hospital, in close partnership with the primary care teams. We have developed close collaborations with physicians in hematology/oncology/BMT, pediatric critical care, cardiology, lung and heart transplant, neonatology, and the different surgical departments to optimize the infectious diseases-related care of those patients. Patients are evaluated as outpatients following referral to the Infectious Diseases Clinic, the Pediatric Tuberculosis Clinic, the Immune Deficiency Clinic, and the International Adoption Clinic.

STAFF PHYSICIANS AND FACULTY

Octavio Ramilo, MD
Chief
Professor of Pediatrics

FULL-TIME NCH FACULTY

Monica I. Ardura, DO
Assistant Professor of Clinical Pediatrics
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Associate Professor of Clinical Pediatrics
William J. Barson, MD
Professor of Pediatrics
Michael T. Brady, MD
Professor of Pediatrics
Dennis J. Cunningham, Jr, MD
Associate Professor of Clinical Pediatrics
Jonathan R. Honegger, MD
Assistant Professor of Pediatrics
W. Garrett Hunt, MD
Associate Professor of Clinical Pediatrics
Preeti Jaggi, MD
Assistant Professor of Clinical Pediatrics
Katalin I. Koranyi, MD
Professor of Clinical Pediatrics
M. Asuncion Mejias, MD
Assistant Professor of Pediatrics
Dwight A. Powell, MD
Faculty Emeritus
Rebecca G. Wallihan, MD
Assistant Professor of Pediatrics

OSU-AFFILIATE FACULTY

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Professor of Clinical Internal Medicine
David A. Wininger, MD
Associate Professor of Internal Medicine

CENTER FOR MICROBIAL PATHOGENESIS

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Professor of Pediatrics

Jennifer L. Edwards, PhD
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Steven D. Goodman, PhD
Associate Professor of Pediatrics
Sheryl S. Justice, PhD
Assistant Professor of Pediatrics
Samantha J. King, PhD
Assistant Professor of Pediatrics
Benjamin T. Kopp, MD
Assistant Professor of Pediatrics
Kevin Mason, PhD
Assistant Professor of Pediatrics
Robert S. Munson, PhD
Professor of Pediatrics
Santiago Partida-Sanchez, PhD
Associate Professor of Pediatrics
Peter White, PhD
Assistant Professor of Pediatrics

CENTER FOR VACCINES AND IMMUNITY

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Jonathan R. Honegger, MD
Assistant Professor of Pediatrics
M. Asuncion Mejias, MD
Assistant Professor of Pediatrics
Mark E. Peeples, PhD
Professor of Pediatrics
Octavio Ramilo, MD
Professor of Pediatrics

The clinical and translational research programs of the Division of Infectious Diseases continue to expand through integration and collaboration with scientists from the Center of Microbial Pathogenesis, the Center for Vaccines and Immunity, and the Department of Clinical Microbiology to develop an outstanding research environment. The integration of clinical and research activities is one of the key aspects of the Nationwide Children's Infectious Diseases Strategic Plan. We are fully committed to bringing state-of-the-art molecular assays, genomics capabilities, statistical skills and other research tools to the relevant clinical setting to advance the clinical care of our patients. The infectious diseases faculty, and clinical and research fellows are currently involved in a variety of research projects funded by the NIH and other agencies including hepatitis, Kawasaki disease, influenza immunization, respiratory viral infections, otitis, urinary tract infection, development of novel vaccine strategies, and application of genomics in infectious diseases. These studies provide additional training opportunities for junior physicians and facilitate collaborations with colleagues in our hospital as well as other national and international scientists.

Teaching of medical students and residents has always been one of the major academic missions of the Division of Infectious Diseases. Members of our division are generally among the highest-rated teachers among The Ohio State University Department of Pediatrics faculty. Over the years, several faculty members have been honored with teaching awards from medical students and residents as a testimony of their dedication to excellent teaching and medical education. Another major contribution of the division to the development of academic physicians is the fellowship training program. The division sponsors a three-year fellowship in pediatric infectious diseases that offers excellent opportunities for training in clinical and research aspects related to infectious diseases. The program is growing with the number of fellows and the diversity of research programs that are offered to help develop their academic and research skills. The infectious disease fellows play a critical role in the research and clinical activities of the division and have become successful in their research activities, as documented by the number of scientific presentations and manuscripts they have authored.

Center for Microbial Pathogenesis
The emphasis of the Center for Microbial Pathogenesis is to develop a greater understanding of the molecular mechanisms by which microorganisms cause infectious diseases as well as how the host responds to these disease states. Faculty within the center focus on identifying virulence mechanisms and defining host response patterns, with an overall objective of elucidating a detailed description of the structure, function, and control of biological systems in health and disease, utilizing molecular and cellular, as well as genomic and proteomic, approaches. In the past year, the Center for Microbial Pathogenesis progressed closer to vaccine development, described new bacterial biological functions, and continued its influence as an international leader in pathogenesis.

The Bakaletz Lab was the first to define how a copy number variation in gene cluster for an important immune effector was related to otitis proneness. The lab continued their efforts to develop a novel immune-based method of pathogenic biofilm disruption, and elucidated how the ability of *Haemophilus influenzae* to rapidly modify gene expression influenced pathogenesis in the highly prevalent pediatric disease otitis media. Importantly, the lab devised a method to prevent, as well as to resolve, existing experimental otitis media by noninvasive transcutaneous immunization – or immunization by "Band-Aid." This is an important first step toward developing a new pediatric vaccine that is cheaper, easier to deliver, likely to increase compliance, and accessible beyond the borders of the developed world.

The Edwards Lab became the first to identify the human receptor mediating *Neisseria meningitidis* colonization of the human airway, the platelet activating factor receptor (PAFr), an immunomodulatory molecule known to

play a role in promoting bacterial sepsis. They have also shown that two posttranslational modifications (PTMs), glycosylation and phosphorylcholine, are subject to phase variation (high frequency, reversible on/off switching of gene expression), and that they are closely associated on adjacent neisserial pilin (adhesin) subunits. Synergy between these PTMs modulates is required for PAFr engagement. These data define a new role for PTMs in meningococcal adherence and provide insight into the selective pressures that underlie their phase-variable expression as well as the pathobiology of meningococcal meningitis. These data were selected by the editors of *PLOS Pathogens* as a featured research paper.

The Goodman Lab has initiated projects on the structure and function of the extracellular matrix of biofilms to create tools to disrupt pathogenic biofilms and build better, and more lasting, probiotic biofilms.

The Justice Lab investigates the effect of host-pathogen interactions that enhance the virulence of uropathogenic *Escherichia coli*. We also are investigating bacterial traits that are associated with renal scaring and adverse perinatal outcomes following urinary tract infection.

The King Lab has defined a novel mechanism of pneumococcal adherence in which carbohydrate-binding modules present in the cell surface β-galactosidase BgaA mediate binding to host cell surface carbohydrates. They are currently exploring if this is a common and conserved mechanism that also explains adherence of other bacterial pathogens.

The Kopp Lab was initiated in July 2012 and had two national presentations and receipt of a cooperative PHPID grant related to autophagy-mediated clearance of *Burkholderia cenocepacia* infections in patients with cystic fibrosis. Additionally, the Kopp Lab received intramural funding to investigate pathogenic biomarkers in infants with cystic fibrosis in conjunction with Drs. Thompson and Mejias.

The Mason Lab received a NIH/NIDCD on a grant entitled "*Disease severity of otitis media: Biofilms, invasion, and host responses.*" The data supporting this application were recently accepted for publication in the high-profile journal *PLOS Pathogens*.

The Munson Lab is working on several projects designed to understand the virulence of the opportunistic gram-negative pathogens *Acinetobacter baumannii* and *Haemophilus influenzae*. Areas of interest include characterization of pili and other surface appendages as well determination of how these organisms resist oxidative stress.

The Partida-Sanchez Lab continues to define the functional role of macrophages during infection. They established that a nonclassical monocyte-derived macrophage cell subtype is essential to prevent pyelonephritis during urinary tract infection. They also focused on elucidating how a phagocyte calcium channel may regulate the production of reactive oxygen species, and bacterial killing, in a model of *Helicobacter pylori* infection.

Dr. Peter White, PhD, was selected as the Inventor of the Year finalist in the 2012 TechColumbus Innovation Awards for his teams work on "Churchill," a revolutionary computational approach that fully automates the bioinformatics process of human genome sequence analysis, reducing the analysis time from weeks to hours. This technology is being employed in our NIH-funded research to discover novel mutations that give rise to congenital heart defects, muscular dystrophy, autism, and other rare genetic disorders across both research and clinical domains.

Center for Vaccines and Immunity

The Center for Vaccines and Immunity is focused on improving the health of children through fundamental and applied research leading to a new generation of safe, protective vaccines against infection, cancer, and allergy. Faculty members from the center seek to understand how viruses cause disease and the role of the immune system in controlling infections. Some of the viruses studied, such as hepatitis C virus and human immunodeficiency virus, cause life-long infections with potentially catastrophic consequences. Center investigators are studying how these and other viruses evade the immune system, so that intervention by vaccination might one day be possible.

RESEARCH FUNDING (OVER $50,000) AWARDED

July 2012 – June 2013

Bakaletz, Lauren
Novel Immunotherapeutics for the Management of Otitis Media Due to H. influenzae
National Institutes of Health (NIH)
National Institute on Deafness & Other Communication Disorders (NIDCD)
$563,222

Determinants of H. influenzae Virulence in Otitis Media
National Institutes of Health (NIH)
National Institute on Deafness & Other Communication Disorders (NIDCD)
$481,705

Antimicrobial Peptides & Innate Immunity in Otitis Media
National Institutes of Health (NIH)
National Institute on Deafness & Other Communication Disorders (NIDCD)
$397,388

Impact of Phase Varions of Non-typeable haemophilus Influenzae on Otitis Media Pathobiology and Vaccine Development
Griffith University, Gold Coast Campus
National Health and Medical Research Council
$97,450

Development of a Transcutaneous Immunization Patch and Assessment of the Efficacy Afforded Against Experimental Otitis Media Due to Nontypeable Haemophilus influenzae
The Ohio State University
$50,000

Edwards, Jennifer
The Affect of Hormones and Oxygen-Limitation on Gonococcal Pathophysiology
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
$311,731

Goodman, Steven
Regulatory Mechanisms Controlling Expression of P. gingivalis
The Forsyth Institute
National Institutes of Health (NIH)
$70,000

King, Samantha
Mechanisms of Pneumococcal Adherence
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
$317,553

Mejias, Maria
A Multi-center, Outpatient, Surveillance Study of Respiratory Syncytial Virus (RSV) Infection and RSV-related Hospitalizations Among Subjects < 24 Months of Age With a Medically Attended Respiratory Tract Infection
Industry Sponsor
$155,900

Partida-Sanchez, Santiago
Novel Calcium Release Mechanism Regulates Dendritic Cell Function
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
$340,280

Peeples, Mark
Respiratory Syncytial Virus Targeting of the Human Airway Epithelium
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
$325,800

Mechanism of Respiratory Syncytial Virus Fusion
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
$325,800

Ramilo, Octavio
Blood Transcriptional Biomarker Profiles of Category B Pathogens
Benaroya Research Institute at Virginia Mason
National Institutes of Health (NIH)
$152,248

Systems Analysis of Vaccine Responses in Healthy and Hyporesponsive Humans
Baylor Research Institute
National Institutes of Health (NIH)
$140,630

Use of Microarrays to Understand Systemic Arthritis
Baylor Research Institute
National Institutes of Health (NIH)
$69,000

Walker, Christopher
HCV-Specific T Cell Responses
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
$660,754

Persistent Hepatitis C Virus Replication and T Cell Immunity in Pregnancy
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
$549,473

PUBLICATIONS

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Aquino VM, Cost C, Gomez A, Bowers DC, **Ramilo O**, Ahmad N, Winick N, Leavey PJ. "Predicitive value of interleukin-5 and monocyte chemotactic protein-1 for bacteremia in children with febrile neutropenia." *Journal Pediatric Hematology Oncology.* 2012;Aug;34(6):e241-e245.

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FAST FACTS

July 2012 – June 2013

Total Discharges: 3,353
- Inpatient Discharges: 2,977
- Observation and Outpatient-in-a-Bed Discharges: 376

Total Patient Days*: 7,552
- Average Length of Stay*: 2.5
- Average Daily Census*: 20.7

Total Clinic Visits: 2,406
- Inpatient Consults: 678
- Dublin Tuberculosis Clinic Visits: 54
- Hilltop Tuberculosis Clinic Visits: 88
- Infectious Disease Clinic Visits: 1,060
- International Adoption/Travel Clinic Visits: 38
- Westerville Adoption Clinic Visits: 82
- Northland Tuberculosis Clinic Visits: 335
- Tuberculosis Clinic Visits: 748
- Westerville Tuberculosis Clinic Visits: 1

**Excludes Observation and Outpatient-in-a-Bed Cases.*