Cincinnati Children's

2015 Research Annual Report

Immunobiology

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	19
Research Fellows	18
Research Students	19
Support Personnel	29
Direct Annual Grant Support	$3,873,956
Direct Annual Industry Support	$78,897
Peer Reviewed Publications	49

CLINICAL ACTIVITIES AND TRAINING

Clinical Fellows	1

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Research Highlights

Research Advances

The Division of Immunobiology continues to play a critical role in pursuing fundamental research explorations in the immune system and the applications of such insights to the understanding and treatment of inflammatory and autoimmune

disorders. Several recent findings of our faculty are particularly noteworthy. Given the excitement and rapid advances in tumor immunotherapy, Dr. Janssen and colleagues have shown that anti-tumor CD8 T cell responses are critically dependent on type I IFN production by dendritic cells after sensing DNA that is released from cryoablation of tumors, via the STING-TBK1-IRF3 pathway. The results suggest that the STING pathway could be targeted to modify the magnitude and nature of the immune responses to tumor-associated antigens. Dr. Lewkowich and colleagues have gained new insights into PD-1 signaling in T cells. They have shown that blocking PD-1 signaling in experimental asthma enhances disease severity, not by modifying the intensity of the inflammatory Th2 response, but by relieving the inhibitory influence of PD-1 on the development of a disease-modifying Th17 response. Blockade of PD-1 is proving to be of remarkable therapeutic benefit for a diverse set of tumors and the results from the Lewkowich lab suggest an underlying cellular basis. Drs. Fred Finkelman and Rick Straight, along with their colleagues, have demonstrated that certain Ig isotypes that poorly aggregate pathogens or activate complement and weakly bind to stimulatory Fc receptors can be protective in suppressing diseases mediated by immune complexes. These results imply that antibodies such as human IgG4 might be useful for treating people who have diseases caused by more pro-inflammatory antibody isotypes.

Faculty Promotions and Awards

In the past year, Drs. Kasper Hoebe and Edith Janssen were promoted to associate professors with tenure, and Lee Grimes became a full professor. In each case, the promotions were richly deserved as they reflected substantial research accomplishments that were recognized by testimonials from leading faculty at other institutions. All three continue to provide exemplary service within and outside of the Institution. Kasper Hoebe was recognized as a highly cited researcher in *The World's Most Influential Scientific Minds 2014*. Fred Finkelman was awarded the Daniel Drake Medal by the University of Cincinnati College of Medicine.

Faculty Recruitment

Two new faculty were recruited to the division in the past year. Theresa Alenghat completed her PhD and postdoctoral research at the University of Pennsylvania before joining Cincinnati Children's faculty as an assistant professor within the University of Cincinnati College of Medicine. Her research focuses on host-microbe interactions and she is currently exploring molecular mechanisms that underlie how the microbiota regulates health and disease. Her research may lead to new treatments for disorders in which the host-microbiota interactions are dysregulated such as in allergy, diabetes, and inflammatory bowel disease. Theresa was among 22 top next generation U.S. scientists to be recognized for their potential in biomedical sciences with a PEW Scholar’s Award.

Andrew Herr joined the division as an associate professor with an affiliate appointment in the Division of Infectious Diseases. Before joining the faculty at Cincinnati Children's, Andrew was an Ohio Eminent Scholar in Structural Biology at the University of Cincinnati College of Medicine and served as an associate director of the Cincinnati Medical Scientist (MD/PhD) Training Program. Dr. Herr received the 2014 Emerging Entrepreneurial Achievement Faculty Award from the University of Cincinnati for his work to commercialize a novel anti-infective therapy based on his lab’s research. Dr. Herr solved the first structure of a human IgA1 antibody bound to its cognate Fc receptor while a postdoctoral fellow at Caltech, and his lab has continued to study antibodies and immune receptors implicated in autoimmune diseases. The Herr Lab also studies mechanisms of bacterial pathogenesis. They have discovered a zinc-dependent mechanism of intercellular adhesion in bacterial biofilms formed by Staphylococcus epidermidis and S. aureus. Biofilms are specialized bacterial colonies that are highly resistant to antibiotics and therefore developing novel therapies to prevent biofilm formation is of high clinical importance.

Inter-disciplinary Collaborations

Faculty in the division spearheaded two inter-disciplinary collaborative proposals that were selected by the Academic Research Committee (ARC) for support through a new internal funding mechanism. Senad Divanovic, teaming up with Drs. Takahisa Nakamura in the Division of Endocrinology and Tom Inge in the Division of Pediatric General and Thoracic

Surgery have successfully launched a major research initiative in obesity and inflammation. Drs. Dave Hildeman, Jonathan Katz, Mike Jordan and Harinder Singh collaborated with Lara Danziger-Isakov in the Division of Infectious Diseases and John Bucuvalas in the Division of Gastroenterology, Hepatology and Nutrition to establish a Center for Transplantation Immunology. A research retreat was organized by Drs. John Perentesis in the Cancer and Blood Diseases Institute (CBDI), James Geller in the CBDI, Edith Janssen and Harinder Singh to nucleate research and clinical efforts in tumor immunotherapy. Discussions that have begun are expected to yield concrete research initiatives in the coming academic year.

Academic Retreat and Seminar Series

As in years past, the Division of Immunobiology played the lead role in organizing the annual Immunology retreat. The event was expanded to a day and a half at the Shawnee Lodge and Conference Center in Portsmouth, OH, and featured research presentations from accomplished graduate students and postdoctoral fellows as well as faculty. It brought together approximately 140 participants from various divisions, including Allergy and Immunology, Asthma Research, Infectious Diseases, Neonatology, Pulmonary Biology, Gastroenterology, Hepatology and Nutrition Research and the Center for Autoimmune Genomics and Etiology. Immunology, Allergy and Rheumatology colleagues from UC also participated. This retreat has now become the key annual event to showcase the breadth and depth of immunology research at Cincinnati Children's and UC. It is instrumental in spawning new research interactions and collaborations. To enhance academic interactions within the immunology community the division organized and hosted a substantial number of prominent seminar speakers from other institutions including Drs. Steve Smale (UCLA), Rafael Casellas (NIH), David Artis (U Penn), Katherine Siminovitch (U Toronto), Barry Sleckman (Wash U), Alexander Rudensky (Memorial Sloan Kettering), Ellen Rothenberg (Caltech), Anjana Rao (LIAI), Al Singer (NIH) and David Baltimore (Caltech).

Significant Publications

Klarquist J, Hennies CM, Lehn MA, Reboulet RA, Feau S, **Janssen EM**. STING-mediated DNA sensing promotes antitumor and autoimmune responses to dying cells. *J Immunol.* 2014 Dec 15;193(12):6124-34.

Adaptive immune responses to self antigens released by dying cells play a critical role in the development of autoimmunity, allograft rejection, and spontaneous as well as therapy-induced tumor rejection. Janssen and colleagues show that the induction of this adaptive immune response is critically dependent on type I IFN production by dendritic cells upon sensing DNA from dying cells via the STING-TBK1-IRF3 pathway. Targeting this pathway improved anti-tumor responses and interfered with disease progression in experimental models of autoimmune disease. Together these findings identify the STING pathway as a novel target to modify the magnitude and nature of the immune responses to cell-associated self-antigens.

McAlees JW, Lajoie S, Dienger K, Sproles AA, Richgels PK, Yang Y, Khodoun M, Azuma M, Yagita H, Fulkerson PC, Wills-Karp M, **Lewkowich IP**. Differential control of CD4(+) T-cell subsets by the PD-1/PD-L1 axis in a mouse model of allergic asthma. *Eur J Immunol.* 2015 Apr;45(4):1019-29.

PD-1 is expressed by exhausted CD8+ T cells in chronic viral infections and markedly inhibits CD8+T cell activity, limiting the ability of these cells to clear virus. While also expressed by activated CD4+ T cells, the role of its PD-1 in regulating individual $CD4^+$ T-cell subsets is not well defined. Work from the Lewkowich Lab demonstrates that PD-1 does not provide an inhibitory signal to all $CD4^+$ T-cell subsets. PD-1 does limit cytokine production by effector Th1 and Th17 cells and permanently reduces cytokine-producing capacity if engaged during Th1/Th17 differentiation. However, in Th2 cells, PD-1 engagement enhances GATA3 expression, increasing cytokine production by established and developing cells and supporting Th2 differentiation under non-polarizing conditions. Despite this Th2-enhancing activity, blocking PD-1/PD-L1 in experimental asthma enhances disease severity, not by modifying the intensity of the

Th2 response, but by relieving the inhibitory influence of PD-1 on the development of a disease-modifying Th17 response. These studies highlight the complex of role of PD-1 in immune regulation, and with the advent of PD-1 blocking therapy for the treatment of solid tumors, a greater recognition of this complexity is an important contribution.

Niss O, Sholl A, Bleesing JJ, **Hildeman DA**. IL-10/Janus kinase/signal transducer and activator of transcription 3 signaling dysregulates Bim expression in autoimmune lymphoproliferative syndrome. *J Allergy Clin Immunol.* 2015 Mar;135(3):762-70.

David Hildeman collaborating with Jack Bleesing and colleagues show that the Bcl-2 pathway is dysregulated in ALPS, a human disorder of the extrinsic apoptotic pathway. They demonstrate that Bim is significantly elevated in the pathologic double-negative (CD4-CD8-) T (DNT) cells of ALPS patients, at least partially through an IL-10/Jak/Stat3 mechanism. ABT-737, a pro-apoptotic BH3-mimetic that interferes with Bcl-2-mediated survival, is shown to have a promising role in treating ALPS by targeting the pathologic lymphoproliferative DNT cells, rather than global lympholysis. Furthermore, the effectiveness of ABT-737 was restricted to those ALPS patients that had increased expression of either Bcl-2 or Bcl-xL. Overall, the work provides new insight into the overlap between Fas and Bcl-2 pathways in a human disorder of T cell homeostasis.

Shehata HM, **Hoebe K**, **Chougnet CA**. The aged nonhematopoietic environment impairs natural killer cell maturation and function. *Aging Cell.* 2015 Apr;14(2):191-9.

Aging is accompanied by a reduced ability to control malignant transformation and viral infections, ultimately translating to an increase in the incidence and severity of these diseases in the elderly. It has recently become obvious that all arms of the immune system are affected by aging. Chougnet et al., report that aged mice have reduced proportions of mature NK cells, and this decreased maturation underlies NK cell functional deficits. Importantly, it is demonstrated that the aged environment in which NK cells develop is responsible for this reduced maturation, and consequently their impaired functionality. Determining the environmental factors responsible for the aged NK cell phenotype could have important implications for improving NK function in the elderly.

Strait RT, Posgai MT, Mahler A, Barasa N, Jacob CO, Koehl J, Ehlers M, Stringer K, Shanmukhappa SK, Witte D, Hossain MM, Khodoun M, **Herr AB**, **Finkelman FD**. IgG1 protects against renal disease in a mouse model of cryoglobulinaemia. *Nature.* 2015 Jan 22;517(7535):501-4.

Antibodies protect against pathogens, in large part, by aggregating them and by activating complement and stimulatory Fc receptors. Surprisingly, the most common IgG isotype in mice, IgG1, and an analogous IgG isotype in humans, IgG4, are relatively defective in their ability to aggregate pathogens, activate complement, and bind to stimulatory Fc receptors. Finkelman and Straight hypothesized that these “wimpy” isotypes provide a selective advantages by suppressing antibody-mediated disease. Consistent with this, they found that IgG1-deficient mice develop lethal kidney disease when immunized with an antigen that stimulates a large, rapid antibody response and immune complex production, while IgG1-sufficient mice fail to develop disease. Kidney disease in immunized IgG1-deficient mice was complement and Fc receptor-independent and was caused by increased production of IgG3, an isotype that forms large immune complexes that precipitate in glomerular capillaries; kidney disease was prevented by treating mice with antigen-specific IgG1. These observations demonstrate that wimpy Ig isotypes can protect against antibody-mediated disease and that immune complex kidney disease can be complement- and Fc receptor-independent; they imply that antibodies such as human IgG4 might be useful for treating people who have diseases caused by more pro-inflammatory antibody isotypes.

Division Publications

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2. Alenghat T, Artis D. **Epigenomic regulation of host-microbiota interactions**. *Trends Immunol*. 2014; 35:518-25.

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5. Chougnet CA, Moreno-Fernandez ME, Rueda CM. **Role of Regulatory T Cells During HIV Infection**. In: TJ Hope, M Stevenson, D Richman, eds. *Encyclopedia of AIDS*. Springer New York; 2014:1-9.

6. Cumaraswamy AA, Lewis AM, Geletu M, Todic A, Diaz DB, Cheng XR, Brown CE, Laister RC, Muench D, Kerman K, Grimes HL, Minden MD, Gunning PT. **Nanomolar-Potency Small Molecule Inhibitor of STAT5 Protein**. *ACS Med Chem Lett*. 2014; 5:1202-1206.

7. Endale M, Aksoylar HI, Hoebe K. **Central role of gimap5 in maintaining peripheral tolerance and T cell homeostasis in the gut**. *Mediators Inflamm*. 2015; 2015:436017.

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15. Herold MJ, Stuchbery R, Merino D, Willson T, Strasser A, Hildeman D, Bouillet P. **Impact of conditional deletion of the pro-apoptotic BCL-2 family member BIM in mice**. *Cell Death Dis*. 2014; 5:e1446.

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Faculty, Staff, and Trainees

Faculty Members

Harinder Singh, PhD, Professor

Leadership Director, Division of Immunobiology; Director, The Center for Systems Immunology

Research Interests Analysis of transcriptional and signaling networks that orchestrate the development and functioning of immune cells.

Theresa Alenghat, VMD, PhD, Assistant Professor

Research Interests Epithelial cell biology, mucosal immunology, and host-microbe interactions.

Julio Aliberti, PhD, Associate Professor

Research Interests Induction and regulation of immune responses to intracellular pathogens.

Claire A. Chougnet, PhD, Professor

Research Interests Mechanisms of immune dysregulation in HIV and aging; ontogeny of immune responses in early life.

Senad Divanovic, PhD, Assistant Professor

Research Interests Role of the innate immune system in obesity and its sequelae. Role of innate immune system in induction of preterm labor.

Fred Finkelman, MD, Professor

Research Interests Allergy/asthma; intestinal parasites.

H. Leighton Grimes, PhD, Professor

Leadership Director Cancer Pathology Program

Research Interests Leukemia/lymphoma.

Andrew Herr, PhD, Associate Professor

Research Interests Structural biology and biophysics of antibodies; immune receptors; and proteins involved in bacterial pathogenesis.

David A. Hildeman, PhD, Professor

Leadership Director, Immunology Graduate Program

Research Interests T-cell biology.

Kasper Hoebe, PhD, Associate Professor
Research Interests Forward genetic analysis of the host immune response using ENU mutagenesis.

Edith M. Janssen, PhD, Associate Professor
Research Interests Mechanistic analysis and translational exploitation of adaptive immune responses to antigens expressed by apoptotic cells.

Michael B. Jordan, MD, Associate Professor
Research Interests Childhood immunodeficiency diseases.

Christopher Karp, MD, Adjunct
Research Interests Molecular mechanisms underlying regulation and dysregulation of inflammatory responses in infectious, allergic, and genetic metabolic diseases.

Jonathan Katz, PhD, Professor
Research Interests The immunology of type 1 diabetes mellitus.

Joerg Koehl, MD, Adjunct
Research Interests Regulation of innate and adaptive immune responses by the complement system.

Ian Lewkowich, PhD, Assistant Professor
Research Interests The role of PD-1 family members in differential control of immune responses/mechanisms of severe allergic asthma.

Jochen Mattner, MD, Adjunct
Research Interests Autoimmune liver diseases.

Yrina Rochman, PhD, Instructor
Research Interests Regulation of memory CD4 T cell functions.

Marsha Wills-Karp, PhD, Adjunct
Research Interests Immunopathogenesis of asthma.

Trainees

- **Maha Almanan, BS**, GSY-3, University of Khartoum, Khartoum, Sudan
- **Monica Cappelletti, PhD**, PGY-4, University of Milan, Milan, Italy
- **Kaitlin Carroll, BS**, GSY-2, Beloit College, Beloit, Wisconsin
- **Shan Chandrakasan, MD**, PGY-4, Children's Hospital of Michigan, Detroit, Michigan
- **Virendra Chaudhri, PhD**, PGY-5, ICGEB (International Centre for Genetic Engineering & Biotechnology), New Delhi, India
- **Rama Dhenni, BS**, GSY-1, University of Indonesia, Jakarta, Indonesia
- **Jordan Downey, BS**, GSY-6, Hendrix College, Conway, Arkansas
- **Mehari Endale Mengistu, PhD**, PGY-4, Kyungpook National University, Daegu, Korea
- **Maria Fields, PhD**, PGY-1, University of Cincinnati, Cincinnati, Ohio
- **Daniel Giles, BS**, GSY-4, Case Western Reserve University, Cleveland, Ohio
- **Vishnu Gudimetla, BS**, GSY-2, The Ohio State University, Columbus, Ohio

- **Courtney Jackson, BA**, GSY-2, University at Buffalo - SUNY, Buffalo, New York
- **Jared Klarquist, BA**, GSY-4, Dartmouth College, Hanover, New Hampshire
- **Durga Krishnamurthy, PhD**, PGY-2, Medical University of Vienna, Vienna, Austria
- **Kun-Po Li, MS**, GSY-4, Graduate Institute of Immunology, National Taiwan University, Taiwan
- **Kevin Lomasney, PhD**, PGY-1, University of Chile Clinical Hospital, Santiago, Chile
- **Jaclyn McAlees, PhD**, PGY-6, The Ohio State University, Columbus, Ohio
- **Christopher McKnight, MD**, GSY-2, Indiana University Bloomington, Bloomington, Indiana
- **Jonathan McNally, BS**, GSY-6, St. Mary's College, St. Mary's City, Maryland
- **Sara Meyer, PhD**, PGY-6, University of Cincinnati, Cincinnati, Ohio
- **Scott Millen, PhD**, PGY-4, University of Cincinnati, Cincinnati, Ohio
- **Edward Muench, MEng**, GSY-3, University of Louisville, Louisville, Kentucky
- **Nazanin Navabi, PhD**, PGY-1, University of Gothenburg, Gothenburg, Sweden
- **Andre Olsson, PhD**, PGY-9, Lund University, Lund, Sweden
- **Andrew Patterson, BS**, GSY-2, University of North Carolina Chapel Hill, Chapel Hill, North Carolina
- **Jana Raynor, PhD**, PGY-1, University of Cincinnati, Cincinnati, Ohio
- **Michelle Reed, PhD**, PGY-1, University of Michigan, Ann Arbor, Michigan
- **Cesar Rueda Rios, PhD**, PGY-4, Universidad de Antioquia, Medellin, Antioquia, Colombia
- **Ankur Saini, PhD**, PGY-1, National Institute of Immunology, New Delhi, India
- **Hesham Shehata, BA**, GSY-5, Transylvania University, Lexington, Kentucky
- **Sadiq Silbak, BS**, GSY-2, University of Cincinnati, Cincinnati, Ohio
- **Anna Sliz, BS**, GSY-1, Austin College, Sherman, Texas
- **Sara Stoffers, MS**, GSY-4, University of Cincinnati, Cincinnati, Ohio
- **Kathryn Sullivan, BS**, GSY-1, Wooster College, Wooster, Ohio
- **Marjan Tajrishi, PhD**, PGY-4, University of Louisville, Louisville, Kentucky
- **Nikhil Wilkins, BS**, GSY-1, The Ohio State University, Columbus, Ohio
- **Zhiguo Wu, PhD**, PGY-2, Wuhan University, Wuhan, China
- **Heping Xu, PhD**, PGY-2, Tsinghua University, Beijing, China

Grants, Contracts, and Industry Agreements

Grant and Contract Awards	Annual Direct

Alenghat, T

Epigenomic Regulation of the Host-Commensal Relationship

Burroughs Wellcome Fund (University of Cincinnati)

	9/1/2014-8/31/2019	$140,000

Epigenetic Regulation of Intestinal Homeostasis

National Institutes of Health

K08 DK093784	9/19/2014-3/31/2017	$258,141

Chougnet, C

Host-Microbe Cross-Talk and Pregnancy Outcomes

Burroughs Wellcome Fund (University of Cincinnati)

	6/1/2013-3/30/2017	$150,000

Chougnet, C / Hildeman, D

Homeostasis and Function of Regulatory T Cells in Aging

National Institutes of Health

R01 AG033057	8/1/2008-4/30/2017	$301,905

Chougnet, C / Muglia, L

Maternal Temperament, Stress, and Inflammation in Preterm Birth

National Institutes of Health

R01 HD078127	9/1/2013-8/31/2017	$485,643

Divanovic, S

Immunopathogenesis of Non-Alcoholic Fatty Liver Disease

National Institutes of Health

R01 DK099222	9/5/2013-7/31/2018	$273,500

Role of Type I IFNs/IFNAR Axis in Inflammation-Induced Preterm Birth

Burroughs Wellcome Fund (University of Cincinnati)

	6/01/2015-3/31/19	$150,000

Grimes, H

MicroRNA in Acute Myeloid Leukemia

National Institutes of Health

R01 CA159845	7/1/2011-4/30/2016	$207,500

Developing Novel STAT5 Protein Inhibitors for Treatment of Leukemias

National Institutes of Health

R21 CA186945	9/1/2014-8/31/2016	$113,766

Summer Fellowship Program

St. Baldrick's Foundation

	5/1/2015-8/31/2015	$5,000

RNA Therapeutics for Leukemia

The Leukemia and Lymphoma Society

	10/1/2012-9/30/2015	$180,018

Herr, A

Studies of Metal-Dependent Intercellular Adhesion in Staphylococcal Biofilms

National Institutes of Health

R01 GM094363	8/1/2014-6/30/2015	$310,906

Hoebe, K

T Cell-Specific Lysosome Dysfunction as a Primary Cause of IBD in Gimap5sph/sph Mice

Crohn's & Colitis Foundation of America

	7/1/2012-6/30/2015	$105,300

Janssen, E

CD244 Targeting Therapeutics in SLE

Lupus Research Institute

	1/1/2015-12/31/2017	$100,000

Jordan, M

Creating an "Off" Button for Harmful Immune Responses

University of Cincinnati

	7/1/2014-6/30/2015	$77,744

Jordan, M / Hildeman, D

Exploiting the DNA Damage Response to Selectively Sculpt the T Cellrepertoire

National Institutes of Health

R01 AI109810	7/15/2014-3/31/2018	$250,000

Katz, J / Hildeman, D

Control of Diabetes by Manipulation of Bc12 Family Members

National Institutes of Health

R01 DK081175	7/1/2011-6/30/2015	$217,500

Krishnamurthy, D

Induction of Food Allergy in Mice by Allergen Inhalation

Department of Defense (Cincinnati Educ & Res for Veterans Fdn)

W81XWH-13-1-0497	9/30/2013-9/29/2016	$141,441

Rapid Suppression of Food Allergy with Anti-FcR Antibody

Intermountain Medical Center (University of Cincinnati)

	7/22/2014-9/30/2017	$74,206

Lewkowich, I

Mechanisms of IL-17A-Mediated Enhancement of Asthma Severity

National Institutes of Health

R01 HL122300	5/1/2014-2/28/2019	$246,250

Meyer, S

Environmental Carcinogenesis And Mutagenesis

National Institutes of Health (University of Cincinnati)

T32 ES007250	2/1/2013-6/30/2015	$24,385

Porollo, A

Suppression of IgE-Mediated Disease by Polyclonal Rapid Desensitization

National Institutes of Health (University of Cincinnati)

R01 AI113162	7/15/2014-6/30/2018	$54,251

Rochman, Y

The Molecular Mechanism of Thymic Stromal Lymphopoietin - Mediated TH2 Cell Differentiation

University of Cincinnati		
	5/1/2015-4/30/2016	$6,500
	Current Year Direct	**$3,873,956**

Industry Contracts

Finkelman, F		
Janssen Research & Development, LLC		$43,313
Lewkowich, I		
Janssen Research & Development, LLC		$35,584
	Current Year Direct Receipts	**$78,897**
	Total	**$3,952,853**

Additional Information
Immunology Graduate Program

The Immunology Graduate Program (ImmGP) is an inter-departmental program within the University of Cincinnati and Cincinnati Children's Hospital Medical Center that offers PhD and MS degrees in immunology. The program is managed by director Dr. David Hildeman and a steering committee composed of members of several departments and divisions at Cincinnati Children's and UC. Dr. Jonathan Katz is the director of the MS program.

The ImmGP provides broadly based instruction in immunology along with rigorous research training that emphasizes cutting-edge approaches to understanding the function of the immune system in health and disease. To this end, the program currently has 51 faculty members from six departments and 15 divisions within the University of Cincinnati College of Medicine and Cincinnati Children's. The program currently has a total of 55 outstanding students (38 PhD students and 17 MS students) from around the country and abroad. This academic year we celebrated the graduation of nine PhD students and eight MS students. Graduates are bolded on the below student lists. Our students have distinguished themselves already by receiving several travel and research awards (AAAAI, Yates Scholarship Award, Albert J Ryan Fellowship Award, Distinguished Dissertation Fellowship, and an NIH F30 Award). This year three ImmGP students won Ryan Fellowships (out of the five that were awarded).

The program is supported financially by a variety of sources. This year tuition support was provided through University Graduate Scholarships awarded by the University of Cincinnati. Student stipends were supported through a variety of sources including funds from the University of Cincinnati, NIH NRSA grants, external grants to their advisors, and funds from Cincinnati Children's Research Foundation. Also, due to a superb external review spearheaded by UC's 2019 program, the ImmGP received funding from UC and Cincinnati Children's to support two new pilot projects. The first is a student research grant proposal award in which students will compete for a research grant supporting a novel and innovative aspects of their work. The second is a travel award which students can use to go to another lab to learn a technique not already existing at UC/Cincinnati Children's. Thus far five students were awarded research grants and two

students took advantage of travel awards, one traveling to Germany and the other to California. After seven years of continued growth the program is now focused on maintaining its current size, planning on a target class size of six to eight students per year.

In the spring of 2013, the ImmGP has established an International Research Training Group (IRTG) with the University of Lübeck and the Research Center Borstel in Lübeck, Germany.

The research focus of the IRTG is:

1. Humoral and cellular pathways of allergic inflammation
2. Immuno-regulation of infection-driven inflammation

Students interested in research projects encompassed by these areas may have the opportunity to study and perform research in the beautiful city of Lübeck in north-central Germany for a three to six month period.

Over this last year, the ImmGP hosted five research scholars (four grad students and one faculty member) from the University of Lubeck and the Research Center Borstel in Germany. In addition, two ImmGP students went to Germany for two months to participate in research projects related to their dissertation work.

Doctoral Students

Admission Year	Student	Mentor
2008	Jana Raynor	David Hildeman
2008	Samuel Vaughn	John Harley
2009	Jordan Downey	Marsha Wills-Karp
2009	Naina Gour	Marsha Wills-Karp
2009	Jonathan McNally	Jonathan Katz
2010	Kyle Bednar	William Ridgway
2010	Roger Fecher	George Deepe
2010	Wenting Huang	William Ridgway
2010	Jennifer Leddon	Timothy Cripe
2010	Ke Liu	John Harley
2010	Hesham Shehata	Claire Chougnet
2011	Rahul D'Mello	Marc Rothenberg
2011	Dan Giles	Senad Divanovic
2011	Mike Horwath	George Deepe
2011	Jared Klarquist	Edith Janssen
2011	Kun-Po Li	David Hildeman
2011	Sara Stoffers	Ian Lewkowich
2012	Maha Almanan	David Hildeman

2012	Laura Brungs	Sue Thompson
2012	Benjamin Davis	Marc Rothenberg
2012	Jeremy Kinder	Sing Sing Way
2012	Xioaming Lu	John Harley
2012	Shannon Rapovy	Joe Qualls
2012	Carolyn Rydyznski	Steve Waggoner
2012	Kristi Betz	Sean Moore
2013	Paige Bolcas	Neeru Hershey
2013	Kaitlin Carroll	Jonathan Katz
2013	Jonathan Fletcher	Nancy Ratner
2013	Courtney Jackson	Claire Chougnet
2013	Zubin Patel	John Harley
2013	Andrew Patterson	Kasper Hoebe
2013	Jared Travers	Marc Rothenberg
2014	Caimei Li	Rotating
2014	Tony Jiang	Rotating
2014	Katelyn Melgar	Rotating
2014	Nikhil Rajagopalan	Rotating
2014	Anna Sliz	Rotating
2014	Kathryn Sullivan	Rotating

Master's Students

Admission Year	Student	Faculty Mentor
2010	Olivia Ballard	Ardythe Morrow
2011	Kristina Bielewicz	Non-Thesis MS
2011	Lindsay Dunn	Non-Thesis MS
2011	Yuan Li	John Harley
2012	Upasana Parthasarathy	Andrew Herr
2012	Samet Oksuz	Artem Barski
2013	Chesney Castleberry	Jonathan Katz
2013	Angelika Gasilina	Non-Thesis MS

2013	Mariam George	George Deepe
2013	Vishnu Gudimetla	Fred Finkelman
2013	Reshmi Indulga	Non-Thesis MS
2013	Christopher McKnight	Fred Finkelman
2013	Sadiq Silbak	Jonathan Katz
2014	Rama Dhenni	Michael Jordan
2014	Michael Moran	Steve Waggoner
2014	Nikhil Wilkins	Lee Grimes
2014	Amnah Yamani	Simon Hogan

Student Honors

TRAVEL AWARDS

Xiaoming Lu 2012

- 2015 Joint Meeting Travel Award, 2015 ASCI/AAP/ APSA Annual Meeting, Chicago, IL, USA.

Shannon Rapovy 2012

- Travel Award, National Multiple Sclerosis Society Autumn Immunology Conference.

Carolyn Rydyznski 2012

- Immunology Graduate Program travel award to the lab of Dr. Juan Carlos de la Torre at The Scripps Research Institute.

PRESENTATION AWARDS

Maha Almanan 2012

- Abstract Award, American Association of Immunologists, New Orleans.

Kyle Bednar 2010

- Poster Award, Immunology Retreat.

Rahul D'Mello 2011

- First Place, UC Graduate Student Research Forum Poster Award.

Daniel Giles 2011

- Second Place, Cincinnati Children's Digestive Health Center Symposium.

Vishnu Gudimetla 2013 (MS)

- Poster Award, Immunology Retreat.

Jeremy Kinder 2012

- Oral Presentation Award, Immunology Retreat.

Jared Klarquist 2011

- Honorable Mention, UC Graduate Student Research Forum Poster Award.
- AAI Young Investigator Award Chicago, Autumn Immunology Conference, Nov. 22.

Kun-Po Li 2011

- Abstract Award, American Association of Immunologists, New Orleans.

Xiaoming Lu 2012

- Abstract Award, American Association of Immunologists, New Orleans.

Jonathan McNally 2009

- Abstract Award, American Association of Immunologists, New Orleans.

Michael Moran 2014 (MS)

- Abstract Award, American Association of Immunologists, New Orleans.

Carolyn Rydyznski 2012

- Second Place, UC Graduate Student Research Forum Poster Award.
- Second Place, Ohio River Valley Cytometry Association (ORVCA) poster competition.

Hesham Shehata 2010

- Oral Presentation Award, Immunology Retreat.

FELLOWSHIPS AND GRANTS

Tony Jiang 2014

- Albert J. Ryan Fellowship.
- Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral MD/PhD Fellowship.
- Antifungal immunity controlled by commensal intestinal bacteria. Principle Investigator. NIDDK. July 1, 2015-June 30, 2020. F30-FDK107199A.

Xiaoming Lu 2011

- Albert J. Ryan Fellowship.

Shannon Rapovy 2012

- 2015 American Association of Immunologists Careers in Immunology Fellowship.

Carolyn Rydyznski 2012

- Albert J. Ryan Fellowship
- Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship.

- A follicular regulatory subset of natural killer cells. Principle Investigator. NAID. May 2015-April 2018. F31-AI118179.

Sadiq Silbak 2014 (MS)

- University Research Council, Graduate Student Research Fellowships.

Student Publications

Maha Almanan 2012

- Raynor J, Karns, R, Almanan M, Li, K-P, Divanovic, S, Chougnet, C, DA Hildeman. **IL-6 and ICOS Antagonize Bim and Promote Regulatory T Cell Accrual with Age.** *J Immunol.* 2015 Aug 1;195(3):944-52.

Kyle Bednar 2010

- Bednar KJ, Tsukamoto H, Kachapati K, Ohta S, Wu Y, Katz JD, Ascherman DP, Ridgway WM. **Reversal of New-Onset Type 1 Diabetes With an Agonistic TLR4/MD-2 Monoclonal Antibody.** *Diabetes.* 2015 Oct;64(10):3614-26.
- Bednar KJ, Ridgway WM. **Targeting innate immunity for treatment of type 1 diabetes.** *Immunotherapy.* 2014;6(12):1239-42.

Kristie Betz 2012

- Moore SR, Guedes MM, Costa TB, Vallance J, Maier EA, Betz KJ, Aihara E, Mahe MM, Lima AA, Oriá RB, Shroyer NF. **Glutamine and alanyl-glutamine promote crypt expansion and mTOR signaling in murine enteroids.** *Am J Physiol Gastrointest Liver Physiol.* 2015 May 15;308(10):G831-9.

Laura Brungs 2012

- Brungs LA, Lele A, Kottyan L, Levy B, Moncrieffe H. **Genetic Basis of Rheumatic Diseases and the Importance of GWAS in Paediatric Rheumatology.** *Ann Paediatr Rheum.* 2014; 3(3): 105-115.

Benjamin Davis 2012

- Kottyan LC*, Davis BP*, Sherrill JD, Liu K, Rochman M, Kaufman K, Weirauch MT, Vaughn S, Lazaro S, Rupert AM, Kohram M, Stucke EM, Kemme KA, Magnusen A, He H, Dexheimer P, Chehade M, Wood RA, Pesek RD, Vickery BP, Fleischer DM, Lindbad R, Sampson HA, Mukkada VA, Putnam PE, Abonia JP, Martin LJ, Harley JB, Rothenberg ME. **Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease.** *Nat Genet.* 2014 Aug;46(8):895-900. **Denotes co-first authorship*

Roger Fecher 2010

- Horwath MC, Fecher RA, Deepe GS Jr. **Histoplasma capsulatum, lung infection and immunity.** *Future Microbiol.* 2015;10(6):967-75.

Daniel Giles 2011

- Giles DA, Moreno-Fernandez ME, Divanovic S. **IL-17 Axis Driven Inflammation in Non-Alcoholic Fatty Liver Disease Progression.** *Curr Drug Targets.* 2015;16(12):1315-23.

Michael Horwath 2011

- Horwath MC, Fecher RA, Deepe GS Jr. **Histoplasma capsulatum, lung infection and immunity.** *Future Microbiol.*

2015;10(6):967-75.

Wenting Huang 2010

- W Huang, K Kachapati, D Adams, Y Wu, P Leung, G Yang, W Zhang, A Ansari, R A Flavell, M Eric Gershwin, and William M Ridgway. **Murine autoimmune cholangitis requires two hits: cytotoxic KLRG1(+) CD8 effector cells and defective T regulatory cells.** *J Autoimmun.* 2014 May;50:123-34.
- Ando Y, Yang GX, Kenny TP, Kawata K, Zhang W, Huang W, Leung PS, Lian ZX, Okazaki K, Ansari AA, He XS, Invernizzi P, Ridgway WM, Lu Q, Gershwin ME. **Overexpression of microRNA-21 is associated with elevated pro-inflammatory cytokines in dominant-negative TGF-β receptor type II mouse.** *J Autoimmun.* 2013 Mar;41:111-9.

Tony Jiang 2014

- Kinder JM, Jiang TT, Ertelt JM, Xin L, Strong BS, Shaaban AF, Way SS. **Cross-Generational Reproductive Fitness Enforced by Microchimeric Maternal Cells.** *Cell.* 2015 Jul 30;162(3):505-15.
- Jiang TT, Chaturvedi V, Ertelt JM, Xin L, Clark DR, Kinder JM, Way SS. **Commensal enteric bacteria lipopolysaccharide impairs host defense against disseminated Candida albicans fungal infection.** *Mucosal Immunol.* 2015 Jul;8(4):886-95.
- Xin L, Jiang TT, Chaturvedi V, Kinder JM, Ertelt JM, Rowe JH, Steinbrecher KA, Way SS. **Commensal microbes drive intestinal inflammation by IL-17-producing CD4+ T cells through ICOSL and OX40L costimulation in the absence of B7-1 and B7-2.** *Proc Natl Acad Sci U S A.* 2014 Jul 22;111(29):10672-7.

Jeremy Kinder 2012

- Kinder JM, Jiang TT, Ertelt JM, Xin L, Strong BS, Shaaban AF, Way SS. **Cross-Generational Reproductive Fitness Enforced by Microchimeric Maternal Cells.** *Cell.* 2015.
- Jiang TT, Chaturvedi V, Ertelt JM, Xin L, Clark DR, Kinder JM, Way SS. **Commensal enteric bacteria lipopolysaccharide impairs host defense against disseminated Candida albicans fungal infection.** *Mucosal Immunol.* 2015 Jul;8(4):886-95.
- Xin L, Jiang TT, Chaturvedi V, Kinder JM, Ertelt JM, Rowe JH, Steinbrecher KA, Way SS. **Commensal microbes drive intestinal inflammation by IL-17-producing CD4+ T cells through ICOSL and OX40L costimulation in the absence of B7-1 and B7-2.** *Proc Natl Acad Sci U S A.* 2014 Jul 22;111(29):10672-7.

Jeremy Klarquist 2012

- Klarquist J, Hennies CM, Lehn MA, Reboulet RA, Feau S, Janssen EM. **STING-mediated DNA sensing promotes antitumor and autoimmune responses to dying cells.** *J Immunol.* 2014 Dec 15;193(12):6124-34.

Ke Liu 2010

- Kottyan LC*, Davis BP*, Sherrill JD, Liu K, Rochman M, Kaufman K, Weirauch MT, Vaughn S, Lazaro S, Rupert AM, Kohram M, Stucke EM, Kemme KA, Magnusen A, He H, Dexheimer P, Chehade M, Wood RA, Pesek RD, Vickery BP, Fleischer DM, Lindbad R, Sampson HA, Mukkada VA, Putnam PE, Abonia JP, Martin LJ, Harley JB, Rothenberg ME. **Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease.** *Nat Genet.* 2014 Aug;46(8):895-900. **Denotes co-first authorship*

Xioaming Lu 2012

- Lu X, Zoller EE, Weirauch MT, Wu Z, Namjou B, Williams AH, Ziegler JT, Comeau ME, Marion MC, Glenn SB, Adler A,

Shen N, Nath SK, Stevens AM, Freedman BI, Tsao BP, Jacob CO, Kamen DL, Brown EE, Gilkeson GS, Alarcón GS, Reveille JD, Anaya JM, James JA, Sivils KL, Criswell LA, Vilá LM, Alarcón-Riquelme ME, Petri M, Scofield RH, Kimberly RP, Ramsey-Goldman R, Joo YB, Choi J, Bae SC, Boackle SA, Graham DC, Vyse TJ, Guthridge JM, Gaffney PM, Langefeld CD, Kelly JA, Greis KD, Kaufman KM, Harley JB, Kottyan LC. **Lupus Risk Variant Increases pSTAT1 Binding and Decreases ETS1 Expression.** *Am J Hum Genet.* 2015 May 7;96(5):731-9.

- Vaughn SE, Foley C, Lu X, Patel Z, Zoller EE, Magnusen AF, Williams AH, Ziegler JT, Comeau ME, Marion MC, Glenn SB, Adler A, Shen N, Nath S, Stevens AM, FreedmanBI, Tsao BP, Jacob CO, Kamen DL, Brown EE, Gilkeson GS, Alarcón GS, Reveille JD, Anaya J, James JA, Moser KL, Criswell LA, Vilá LM, Alarcon-Riquelme ME, Petri M, Namjou B, GaffneyPM, Langefeld CD, Kaufman KM, Kelly JA, Harley ITW, HarleyJB, Kottyan LC. **Lupus risk variants in the PXK locus alter B-cell receptor internalization.** *Front Genet.* 2015 Jan 8;5:450.

Katelyn Melgar 2014

- Varney ME, Melgar K, Niederkorn M, Smith M, Barreyro L, Starczynowski DT. **Deconstructing innate immune signaling in myelodysplastic syndromes.** *Exp Hematol.* 2015 Aug;43(8):587-98.

Michael Moran 2014 (MS)

- Rydyznski C, Daniels KA, Karmele EP, Brooks TR, Mahl SE, Moran MT, Li C, Sutiwisesak R, Welsh RM, Waggoner SN. **Generation of cellular immune memory and B-cell immunity is impaired by natural killer cells.** *Nat Commun.* 2015 Feb 27;6:6375.

Zubin Patel 2013

- Vaughn SE, Foley C, Lu X, Patel Z, Zoller EE, Magnusen AF, Williams AH, Ziegler JT, Comeau ME , Marion MC, Glenn SB,Adler A, Shen N, Nath S, Stevens AM, FreedmanBI, Tsao BP, Jacob CO, Kamen DL, Brown EE, Gilkeson GS, Alarcón GS, Reveille JD, Anaya J, James JA, Moser KL, Criswell LA, Vilá LM, Alarcon-Riquelme ME, Petri M, Namjou B, GaffneyPM, Langefeld CD, Kaufman KM, Kelly JA, Harley ITW, HarleyJB, Kottyan LC. **Lupus risk variants in the PXK locus alter B-cell receptor internalization.** *Front Genet.* 2015 Jan 8;5:450.

Jana Raynor 2008

- Raynor J, Karns, R, Almanan, M, Li, K-P, Divanovic, S, Chougnet, C, DA Hildeman. **IL-6 and ICOS Antagonize Bim and Promote Regulatory T Cell Accrual with Age.** *J Immunol.* 2015 Aug 1;195(3):944-52.

- Kurtulus S, Sholl A, Toe J, Tripathi P, Raynor J, Li KP, Pellegrini M, Hildeman DA. **Bim controls IL-15 availability and limits engagement of multiple BH3-only proteins.** *Cell Death Differ.* 2015 Jan;22(1):174-84.

Carolyn Rydyznski 2012

- Rydyznski C, Daniels KA, Karmele EP, Brooks TR, Mahl SE, Moran MT, Li C, Sutiwisesak R, Welsh RM, Waggoner SN. **Generation of cellular immune memory and B-cell immunity is impaired by natural killer cells.** *Nat Commun.* 2015 Feb 27;6:6375.

- Brandt EB, Gibson AM, Bass S, Rydyznski C, Khurana Hershey GK. **Exacerbation of allergen-induced eczema in TLR4- and TRIF-deficient mice.** *J Immunol.* 2013 Oct 1;191(7):3519-25.

- Kinder JM, Jiang TT, Ertelt JM, Xin L, Strong BS, Shaaban AF, Way SS. **Cross-Generational Reproductive Fitness Enforced by Microchimeric Maternal Cells.** *Cell.* 2015 Jul 30;162(3):505-15.

Hesham Shehata 2010

- Shehata HM, Hoebe K, Chougnet CA. **The aged nonhematopoietic environment impairs natural killer cell maturation and function.** *Aging Cell.* 2015 Apr;14(2):191-9.

Jared Travers 2013

- Travers J, Rothenberg ME. **Eosinophils in mucosal immune responses.** *Mucosal Immunol.* 2015 May;8(3):464-75.

Samuel Vaughn 2008

- Vaughn SE, Foley C, Lu X, Patel Z, Zoller EE, Magnusen AF, Williams AH, Ziegler JT, Comeau ME , Marion MC, Glenn SB, Adler A, Shen N, Nath S, Stevens AM, Freedman BI, Tsao BP, Jacob CO, Kamen DL, Brown EE, Gilkeson GS, Alarcón GS, Reveille JD, Anaya J, James JA, Moser KL, Criswell LA, Vilá LM, Alarcon-Riquelme ME, Petri M, Namjou B, GaffneyPM, Langefeld CD, Kaufman KM, Kelly JA, Harley ITW, Harley JB, Kottyan LC. **Lupus risk variants in the PXK locus alter B-cell receptor internalization.** *Front Genet.* 2015 Jan 8;5:450.

Student Presentations

Maha Almanan 2012

- CD4+ FoxP3+ Regulatory T cells Control Effector T cell Responses to Murine Cytomegalovirus, Annual Meeting of the American Association of Immunologists, New Orleans, LA.

Kristi Betz 2012

- Undernutrition and Augmented Levels of LPS in the Colon Additively Impair Small Intestinal Barrier Function in Weanling Mice Poster Presentation, Cincinnati Children's Annual Immunology Retreat, Cincinnati, OH, October 2014.
- Undernutrition and Altered Gut Secretory IgA Synergistically Increase Bacterial Burdens in the Mesenteric Lymph Nodes. Poster Presentation, Cincinnati Children's Digestive Health Center Annual Scientific Retreat 2015, Cincinnati, OH, February 2015.
- Undernutrition and Altered Gut Secretory IgA Synergistically Increase Bacterial Burdens in the Mesenteric Lymph Nodes. Poster Presentation, University of Cincinnati Graduate Student Research Forum 2015, Cincinnati, OH, February 2015.
- Undernutrition and Altered Gut Secretory IgA Synergistically Increase Bacterial Burdens in the Mesenteric Lymph Nodes. Poster Presentation, Cincinnati Children's Nutrition Hot Topics Poster Session 2015, Cincinnati, OH, April 2015.
- Undernutrition and Altered Gut Secretory IgA Synergistically Increase Bacterial Burdens in the Mesenteric Lymph Nodes. Poster Presentation, Digestive Disease Week 2015, Washington DC, May 2015.

Daniel Giles 2011

- Liver Metabolism and Nonalcoholic Fatty Liver Disease, Keystone Symposia, Whistler, BC.

Jeremy Kinder 2012

- T cells: Regulation and Function, Albert J Ryan Foundation Conference, 2015.
- T cells: Regulation and Function, Keystone, 2015.
- Cross-generational reproductive fitness sustained by tolerogenic microchimeric maternal cells.

Jared Klarquist 2011

- T cells: Regulation and Function, Albert J Ryan Foundation Conference, 2015.
- T cells: Regulation and Function, Keystone, 2015.
- STING-mediated DNA sensing promotes antitumor and autoimmune responses to dying cells. 43th Annual Autumn Immunology Conference, Chicago, IL, Nov 2014.

Kun-Po Li 2011

- Levels of the pro-apoptotic molecule Bim are determined early in the response and positively correlated with memory T cell fate, Annual Meeting of the American Association of Immunologists, New Orleans, LA.

Xiaoming Lu 2012

- Lupus risk-variant increases pSTAT1 binding and decreases ETS1 expression. Poster presentation. The American Association of Immunologists 2015 Annual Meeting, New Orleans, LA.
- Lupus risk-variant increases pSTAT1 binding and decreases ETS1 expression. Poster presentation. 2015 ASCI/AAP/APSA Annual Meeting, Chicago, IL.
- Genetic variant at ETS1 locus increases lupus risk and affects Stat1 binding. Poster presentation. 2014 ACR/ARHP Annual Meeting, Boston, MA.
- Genetic variant at ETS1 locus increases lupus risk and affects Stat1 binding. Oral presentation. The American Association of Immunologists 2014 Annual Meeting, Pittsburgh, PA.

Jonathan McNally 2009

- The rational targeting of the DNA damage response pathway for the selective elimination of encephalitogenic T cells, Annual Meeting of the American Association of Immunologists, New Orleans, LA.

Michael Moran 2014 (MS)

- The anatomic redistribution of natural killer cells within secondary lymphoid organs during viral infection, Annual Meeting of the American Association of Immunologists, New Orleans, LA.

Zubin Patel 2013

- Identification of SLE-associated risk variants in the *STAT1-STAT4* locus. Annual American Physician Scientist Association Meeting, Chicago, IL, April 2014.
- Identification of SLE-associated risk variants in the *STAT1-STAT4* locus. Annual GSRF Poster Session, March 2014.

Sara Stoffers 2011

- Molecular mechanisms of synergy between IL-13 and IL-17A in severe asthma. Poster presentation. American Thoracic Society, Denver, CO, May 2015.
- Dissecting molecular mechanisms of synergy between IL-13 and IL-17A in severe asthma. Poster presentation. The American Academy of Allergy Asthma and Immunology, Houston, TX, Feb 2015.
- Molecular mechanisms of synergy between IL-13 and IL-17A in severe asthma. Oral and poster presentation. Autumn Immunology Conference, Chicago, IL, Nov 2014.

Jared Travers 2013

- IL-33 is selectively expressed by esophageal epithelial cells during allergic inflammation, Presented poster at the 9th Biennial Symposium of the International Eosinophil Society, Chicago, IL, 2015.

Targeting MicroRNA Emerges as Potential Weapon Against Acute Myelogenous Leukemia

H. Leighton Grimes, PhD

RESEARCH AND TRAINING DETAILS

Faculty	19
Research Fellows	18
Research Students	19
Support Personnel	29
Direct Annual Grant Support	$3.8M
Direct Annual Industry Support	$78,897
Peer Reviewed Publications	49

Velu CS, Chaubey A, Phelan JD, Horman SR, Wunderlich M, Guzman ML, Jegga AG, Zeleznik-le NJ, Chen J, Mulloy JC, Cancelas JA, Jordan CT, Aronow BJ, Marcucci G, Bhat B, Gebelein B, Grimes HL. Therapeutic antagonists of microRNAs deplete leukemia-initiating cell activity. *J Clin Invest.* 2014 Jan 2;124(1):222-36.

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When acute myelogenous leukemia (AML) strikes, five-year survival rates vary dramatically (15 percent-70 percent) depending upon the AML subtype. Children diagnosed with AMLs with 11q23 translocations have experienced especially poor outcomes.

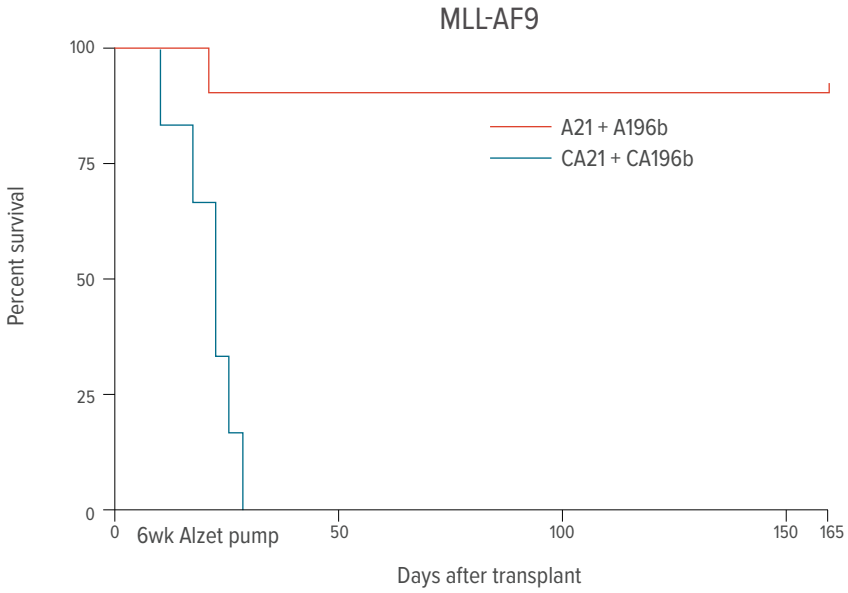
However, a new approach based on silencing targeted microRNAs that was developed by a Cincinnati Children's research team led by H. Leighton Grimes, PhD, has shown intriguing early success in mouse models. MicroRNAs have long been thought to play an important role in oncogenesis, but so far, converting this concept into therapeutics has been slow. Grimes and colleagues found one potential solution by exploiting an ancient competition between GFI1 and HOX transcription factors, which both act as leukemia-initiating "gatekeeper" pathways.

As the team studied the competing transcription factors, they found two microRNA that appeared to play important roles in AML relapse. The team went on to test antagomir treatment as a tool to silence the targeted microRNA.

"Therapeutic inhibition of microRNA-21 and microRNA-196b inhibited *in vitro* leukemic colony forming activity and depleted *in vivo* leukemia-initiating cell activity of HOX-based leukemias, which led to leukemia-free survival in a murine AML model and delayed disease onset in xenograft models," Grimes and co-authors wrote.

The study establishes microRNA as functional effectors of endogenous HOXA9 and HOX-based leukemia oncoproteins. At one level, this means the research world now has a mouse model that can serve effectively as an *in vivo* platform to test RNA-based cancer therapies. At another level, it means children who develop notoriously hard-to-treat forms of AML may have increased hope for longer-term survival.

"Overall, our studies provide a strong rationale to develop microRNA antagonists for clinical use in AML," Grimes says.



This figure shows the Kaplan-Meier survival curve of partially conditioned mice transplanted with one million leukemic splenocytes. Four days later, six-week osmotic pumps containing active A21+A196b or control CA21+CA196b anti-microRNA therapy were implanted. Treated mice were analyzed by flow cytometry for CD45.1 versus CD45.2 to identify leukemic cells at time of death (CA21+CA196b) or at the termination of the experiment at 165 days (A21+A196b).

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