The 56th Midwinter Conference of Immunologists at Asilomar

January 28 -31, 2017

Asilomar Conference Grounds, Pacific Grove, California

Christel Uittenbogaart, Executive Director

Roberta Meyers-Elliott, Treasurer

Rachel R. Caspi and Daniel J. Campbell

Chairpersons

The Dan H. Campbell Memorial Lecture

Sponsored by The American Association of Immunologists

Saturday, January 28, 8:00 PM

The Chapel Auditorium

Yasmine Belkaid

The National Institutes of Health

"Microbial Imprinting"

Council Members

Gregory Barton
Daniel Campbell
Michael Cancro
Rachel Caspi
Hilde Cheroutre
Nicholas Crispe
Shane Crotty
Jason Cyster
Laurie Dempsey
Pamela Fink
Ananda Goldrath
Jessica Hamerman
Wendy Havran
Stephen M. Hedrick
Kristin Hogquist
Christopher Hunter
Mitchell Kronenberg
Michael Kuhns
Terri Laufer
David Lewis
Ann Marshak-Rothstein
Diane Mathis
Roberta Meyers-Elliott
Tomas Mustelin
Roberta Pollock
David Scott
Dan Stetson
Jenna M. Sullivan
Tennille Thelen
Shannon Turley
Christel Uittenbogaart
David Webb
Arthur Weiss
Steven Ziegler
Martha Zuniga

NAME BADGES are issued at the time of Registration and must be worn at all Conference meetings and Receptions. Guests are issued a badge at the time of their Registration for admittance to Receptions. All names remain on the **CONFERENCE e-LIST** for two years after last attendance. Update your e-mail address with the Registrar for assured delivery of notices.

The 2017 Midwinter Conference of Immunologists

gratefully acknowledges the following contributors

The American Association of Immunologists
Amgen
BioLegend, Inc.
Bio-Techne
Bristol -Myers Squibb
California Institute for Regenerative Medicine
Celgene
Cellular Immunology (Elsevier)
CTL Cellular Technologies
Five Prime Therapeutics
Genentech
Janssen Research and Development, LLC
Juno Therapeutics
Kyowa Hakko Kirin
Merck Research Laboratories
Nature Immunology

Contributions by Members of the Midwinter Conference of Immunologists

The MCI website is hosted by courtesy of the La Jolla Institute for Allergy and Immunology

The 2017 Midwinter Conference of Immunology at Asilomar
Pacific Grove, California (USA) www.midwconfimmunol.org

CONFERENCE SCHEDULE

All Sessions: The Chapel Auditorium

Saturday, January 28th		
3:00 pm	**Registration**	
8:00 pm	***The Dan H. Campbell Memorial Lecture***	
9:00–11:00 pm	***Reception in the Nautilus Room***	
.Sunday, January 29th		
8:30–12:00 Noon	**Session I**	**Tumor Immunology, TSCM and Immunotherapy**
4:00– 6:00 pm	**Poster Session**	***Fred Farr Forum and Kiln Room***
7:30–10:00 pm	**Session II**	**Innate and Adaptive Responses to Infection**
10:00–11:00 pm	***Reception***	***Fred Farr Forum and Kiln Room***
Monday, January 30th		
8:30 – 12:00 Noon	**Session III**	**Mucosal Immunology and Barrier Function**
2:30 – 3:30 PM	**Peter Lee**	**Immunity "Meet the Editor"**
3:30 – 4:00 PM	**Conrad Mallia**	**NIAID**
4:00 – 6:00 PM	**Oral Presentations**	***The Chapel Auditorium***
7:30 – 10:00 PM	**Session IV**	**Immune Regulation and Tolerance**
10:00–11:00 PM	***Reception***	***Fred Farr Forum and Kiln Room***
Tuesday, January 31st		
8:30–12:00 Noon	**Session V**	**Innate and Adaptive Immune Pathways**
Saturday through Sunday	**Posters on Display**	***Fred Farr Forum and Kiln Room***

CONFERENCE PROGRAM

SESSION I — Tumor Immunology, Tumor Memory Stem Cells and Immunotherapy

Sunday Morning
8:30 -12:00 Noon

Chairperson: Drew Pardoll

Drew Pardoll, Johns Hopkins University
"Establishment of Immunotherapy as the Fourth Pillar of Cancer Treatment"

Max Krummel, University of California, San Francisco
"Dynamic Cellular Mosaics in the Tumor Microenvironment"

Luca Gattinoni, National Institutes of Health
"Generation of Long-Lived Cancer Antigen-Specific CD8+T Memory Stem Cells"

Ming Li, Memorial Sloan Kettering Cancer Center
"Immunity and Tolerance in Cancer"

Two short presentations chosen from abstracts and an informational presentation about the California Institute for Regenerative Medicine (Ross Okamura, CIRM)

Sunday Afternoon
4:00 – 6:00 PM

POSTER SESSION and informal discussion groups.

SESSION II

Sunday Evening
7:30–10:00 PM

Innate and adaptive responses to infection
Chairperson: Nicole Baumgarth

Nicole Baumgarth, University of California, Davis
"Innate and adaptive B cell immunity to influenza"

Kenneth Cadwell, New York University
"Host-microbiome interactions in inflammatory disease"

James Chen, University of Texas Southwestern
"The cGAS Pathway of Cytosolic DNA Sensing and Its Role in Health and Disease"

Ellen Robey, University of California, Berkeley
"What makes a protective anti-*Toxoplasma* T cell response?"

SESSION III

Monday Morning
8:30-12:00 Noon

Mucosal Immunology and barrier function
Chairperson: Mitchell Kronenberg

Rachel Caspi, National Institutes of Health
"The good and the bad: two faces of microbiota in the eye"

Cathryn Nagler, University of Chicago
"Regulation of allergic responses to food by commensal bacteria"

Rachael Clark, Harvard University
"Resident memory T cells in human health and disease"

Mitchell Kronenberg, La Jolla Institute for Allergy & Immunology
"HVEM: a TNF family receptor with a protective role in acute infections and in intestinal tissue homeostasis"

Two short presentations chosen from abstracts

Monday Afternoon
2.30 – 3.30 PM Immunity: "Meet the Editor"- Peter Lee
3.30 – 4.00 PM NIAID:information-Conrad Mallia

4:00 – 6:00 PM **ORAL POSTER PRESENTATIONS**

SESSION IV Immune regulation and tolerance

Monday Evening
7:30 -10:00 PM

Chairperson: Eric Meffre

David Scott, Uniformed Services University of Health Sciences
"Driving CARs to BARs: Engineered antigen-specific human Tregs for tolerance"

Eric Meffre, Yale University
"Tregs control peripheral autoreactive B cell selection"

Megan Levings, University of British Columbia
"Cellular and molecular biology of human regulatory T cells"

Jonathan Kipnis, University of Virginia
"Repertoire and function of meningeal immunity in healthy and diseased brain"

Awards Presentations to Graduate, Postdoctoral and Young Investigators

Poster Awards:

Ray Owen Poster Awards **(Sponsored by AAI)**
Council Poster Awards **(Sponsored by MCI Council)**
Ray Owen Young Investigator Poster Awards **(Sponsored by AAI and Cellular Immunology)**

Oral Presentation Awards:

Ray Owen Young Investigator Awards **(Sponsored by AAI)**
Young Investigator Presentation Awards **(Sponsored by BioLegend)**
Young Investigator Travel Awards **(Sponsored by BioLegend)**

SESSION V Innate and adaptive immune pathways

Tuesday Morning
8:30-12:00 Noon

Chairperson: Marc Jenkins

Daniel Campbell, Benaroya Research Institute
"Novel signaling pathways that control effector, memory, and regulatory T cell responses"

Dale T. Umetsu, Genentech
"Innate lymphoid cells regulate asthma phenotypes"

Gabriel Nunez, University of Michigan
"Role of interleukin-22 in host defense against bacterial pathogens"

Marc Jenkins, University of Minnesota
"How the helper T cell repertoire responds to infection"

Establishment of Immunotherapy as the Fourth Pillar of Cancer Treatment

Drew Pardoll

Bloomberg~Kimmel Institute for Cancer Immunotherapy
Johns Hopkins University School of Medicine

Major advances have been made in the immune-based therapy of cancer by antibody blockade of immune inhibitory pathways such as CTLA-4 and PD-1. Anti-PD-1 antibodies have produced objective responses in one third to one half of patients with advanced, chemotherapy refractory melanoma and renal cancer and one quarter of patients with non-small cell lung cancer. These responses are highly durable, the majority lasting significantly greater than one year and beyond cessation of therapy. Further, expression by tumor cells of ligands for PD-1 is associated with higher response to anti-PD-1 therapy. In exploring the basis for up-regulation of the major PD-1 ligand, PD-L1, on tumor cells, we found that its expression is not constitutive, but rather, is highly associated with lymphocytic infiltration. We identified IFN-γ as an immune signal sensed by the tumor cell that induces PD-L1 expression. In addition to IFN-γ, genes associated with Th1 responses, CTL responses and other inhibitory molecules, such as LAG-3, are up-regulated in lymphocytic infiltrates associated with PD-L1+ tumor cells. Two significant factors in tumors that are involved in the generation of anti-tumor immunity are mutational load and the presence of a virus driving the cancer. Thus, mismatch repair deficient cancers, which have 20-50 times the mutational load of their mismatch repair proficient counterparts, show a >50% response rate to PD-1 blockade. In contrast, Merkel Cell cancers, that are caused by integration of Merkel Cell Polyomavirus and possess only 10 mutations/exome, also demonstrate a >50% response rate to anti-PD-1. We have developed a new assay, termed MANAFEST, that sensitively, specifically and quantitatively measures T cell responses to tumor neoantigens. Initial findings using this analysis platform will be discussed.

Dynamic Cellular Mosaics in the Tumor Microenvironment

Matthew F. Krummel

Edward W. Roberts[1], Mark B. Headley[1], Adriana Mujal[1], Mikhail Binnewies[1,2], Adriaan Bins[1,3], Audrey Gerard[1] and Matthew F. Krummel[1]

[1] Department of Pathology, University of California, San Francisco, 513 Parnassus Ave, HSW512, San Francisco, CA 94143-0511, USA
[2] Precision Immune Inc. 953 Indiana St. San Francisco, 94107, USA
[3] Netherlands Cancer Institute. Plesmanlaan 121, 1066 CX Amsterdam

The nature of an immune response is rarely defined by a unanimous decisions by the participating cells; cells with seemingly opposing functions pervade many immune sites and tumors are no exception. Multiple DC and Macrophage subsets exert push/pull on T cell responses in tumors. Fundamentals of this are gleaned by live-imaging in connection with conventional flow-cytometry and immunofluorescence. Here, we broadly treat real-time imaging as a discovery tool to understand the diversity of cellular interactions that comprise host-tumor interactions. We focus heavily on understanding how information about the tumor is encoded in APC compartments and how this is passed from APC to APC. In considering this, we consider the concepts of seeking 'allies' for tumor therapies as well as for understanding the balance of push/pull signals that likely contribute to determine the consensus immune response.

This work was supported in part by a Department of Defense post-doctoral fellowship to M.B.H. (W81XWH-13-1-0009) and NIH grants U54 CA 163123, PO1 HL024136 and R21CA167601.

Generation of Long-Lived Cancer Antigen-Specific CD8+T Memory Stem Cells

Luca Gattinoni

National Cancer Institute, USA

Immunotherapies based on the adoptive transfer of naturally occurring or gene-engineered tumor-reactive T cells can result in durable complete responses in patients with metastatic cancers. There is now evidence that stem cell-like T cells with enhanced capacity for self-renewal and the ability to derive potent effector T cells might be used to improve persistence and long-term anti-tumor immunity. I will describe the molecular, metabolic and cellular aspects of T cell differentiation and their relevance to cancer immunotherapy. I will also discuss current efforts and new approaches that might potentiate T cell-based immunotherapies through the modulation of T cell fate and differentiation.

Relevant bibliography

*1. **Gattinoni L**, Speiser DE, Lichterfeld M, Bonini C. T memory stem cells in health and disease. Nature Med 2016 doi:10.1038/nm.4241*
*2. Sabatino M, Hu J, Sommariva M, Gautam S, Fellowes V, Hocker JD, Dougherty S, Qin H, Klebanoff CA, Fry TJ, Gress RE, Kochenderfer JN, Stroncek DF, Ji Y, **Gattinoni L**. Generation of clinical-grade CD19-specific CAR-modified CD8+ memory stem cells for the treatment of human B-cell malignancies. Blood 2016, 128:519–528*
*3. **Gattinoni L.** Memory T cells officially join the stem cell club. Immunity 2014, 41:7–9*
*4. Lugli E, Dominguez MH, **Gattinoni L**, Chattopadhyay PK, Bolton DL, Song K, Klatt NR, Brenchley JM, Vaccari M, Gostick E, Price DA, Waldmann TA, Restifo NP, Franchini G, Roederer M. Superior T Memory Stem Cell Persistence Supports Long-Lived T Cell Memory. J Clin Invest 2013, 123:594–599*
5. **Gattinoni** L, Klebanoff CA, Restifo NP. Paths to stemness: building the ultimate anti-tumour cell. *Nature Rev Cancer 2012, 12: 671-684*
6. **Gattinoni L** , Lugli E, Ji Y, Pos Z, Paulos CM, Quigley MF, Almeida JR, Gostick, E, Yu Z, Carpenito C, Wang E, Douek DC, Price DA, June CH, Marincola FM, Roederer M, Restifo NP. A human T cell memory subset with stem cell-like properties. Nature Med 2011, 17:1290–1297
7. **Gattinoni L**, Zhong XS, Palmer DC, Ji Y, Hinrichs CS, Yu Z, Wrzesinski C, Boni A, Cassard L, Church L, Paulos CM, Muranski P, Restifo NP. Wnt signaling arrests effector T cell differentiation and generates CD8+ memory stem cells. Nature Med 2009, 15:808-813

Immunity and Tolerance in Cancer

Ming O. Li

Memorial Sloan Kettering Cancer Center, Immunology Program, New York, NY

Cancer develops as a result of intricate interactions between tumor cells and their environment. How the immune system responds to tumors is of interest not only for understanding disease mechanisms but also for cancer immunotherapy. Using oncogene-induced breast and prostate cancer models, we have started to reveal novel modes of cancer-elicited inflammatory responses with anti-tumor and pro-tumor activities mediated by distinct lineages of lymphoid and myeloid cell populations. The cellular identity and molecular regulation of tumor-associated immunity and tolerance responses will be discussed.

References

1. M.K. Donkor, A. Sarkar, P.A. Savage, R.A. Franklin, L.K. Johnson, A.A. Jungbluth, J.P. Allison, **M.O. Li.** T Cell Surveillance of Oncogene-induced Prostate Cancer is Impeded by T Cell-derived TGF-beta1 Cytokine. *Immunity* 2011, 35: 123-134.
2. R.A. Franklin, W. Liao, A. Sarkar, M.V. Kim, M.R. Bivona, K. Liu, E.G. Pamer, **M.O. Li.** The Cellular and Molecular Origin of Tumor-associated Macrophages. *Science* 2014, 344: 921-925.
3. C.T. Luo, W. Liao, S. Dadi, A. Toure, **M.O. Li.** Graded Foxo1 Activity in Treg Cells Differentiates Tumour Immunity from Spontaneous Autoimmunity. *Nature* 2016, 529: 532-536.
4. S. Dadi, S. Chhangawala, B.M. Whitlock, R.A. Franklin, C.T. Luo, S.A. Oh, A. Toure, Y. Pritykin, M. Huse, C.S. Leslie, **M.O. Li.** Cancer Immunosurveillance by Tissue-resident Innate Lymphoid Cells and Innate-like T Cells. *Cell* 2016, 164: 365-377.

Innate and adaptive B cell immunity to influenza

Nicole Baumgarth

Nicole Baumgarth, Savage, Hannah P., Waffarn, Elizabeth E., Rothaeusler, K.

nbaumgarth@ucdavis.edu
Center for Comparative Medicine & Dept. Pathology, Microbiology and Immunology, University of California, Davis

B cell responses to influenza virus infection are complex and multi-layered. Preexisting antibodies, either natural or infection-induced, provide an early layer of immune protection, effectively reducing initial rapid viral replication and dissemination in the respiratory tract. $CD5^{pos}$ B-1a, but not $CD5^{neg}$ B-1b cells, in the plural cavity are one of the first responders to influenza infection. They migrate to the draining mediastinal lymph nodes (MedLN), where they accumulate in a CD11b-dependent manner, following activation by infection-induced Type I IFN. B-1a cells that differentiate to IgM-secretors in the MedLN change their phenotype and lose CD5, thus taking on a B-1b phenotype. Infection-induced IL-1-stimulated B-1a also enhance IgM production by conventional MedLN B-2 cells, thus becoming regulators of the adaptive immune response. The strongest early production of class-switched and high affinity antibodies following infection does not result from germinal center-derived B cell responses, but from the rapid differentiation of high-affinity B cells in short-lived, extrafollicular foci. The response generates high amounts of IgM, IgG and IgA production in the MedLN and correlates with the rapid clearance of influenza virus in sublethal infections. Despite the short-lived nature of the extrafollicular foci in the MedLN, extrafollicular-derived antibodies are present in the serum of mice lifelong, in the absence of measurable memory B cell responses or long-lived plasma cells derived from these responses. Instead, their production appears to be derived solely from self-renewing, short-lived plasmablasts present in the respiratory tract. Germinal center responses develop largely after the virus infection is cleared. Given the kinetics of the germinal center response, and the rapidly mutating influenza virus, we propose that high affinity B cell responses, generated in germinal centers after the infection is cleared, serve mainly as a means to broaden the repertoire of virus-binding B cells, not to serve the production of protective high affinity antibodies.

References:

1) Baumgarth, N. 2013 How specific is too specific? B cell responses to viral infections reveal the importance of breadth over depths. *Immunol. Rev* **255**: 82 -94.

2) Waffarn, E.E. Hastey, C.J. Dixit, N., Choi, Y.S, Cherry, S., Kalinke, U., Simon, S.I, and Baumgarth, N. 2015. Infection-induced type I interferons activate CD11b on B-1 cells for subsequent lymph node accumulation. *Nat Commun* **6**, 8991 -9002.

3) Rothaeusler, K. and Baumgarth, N. 2010. B cell fate decisions during influenza virus infection. *Eur J Immunol*. **40**: 366-3774

4) Baumgarth, N., Waffarn, E.E. and Nguyen, T.T. 2015. Natural and induced B-1 cell immunity to infections raises questions of nature versus nurture. *Ann N Y Acad Sci* **1362**, 188-99.

“Host-microbiome interactions in inflammatory disease”

“Insights from a viral member of the microbiome”

Kenneth Cadwell

New York University

The trillions of bacteria that are part of the gut microbiome provide key benefits to the host, but are also implicated in various disorders such as inflammatory bowel disease (IBD). For this reason, a large-scale effort has been placed in elucidating the mechanisms that determine how intestinal bacteria evoke beneficial and adverse responses from the host. However, the mammalian gastrointestinal tract can also harbor other infectious agents including viruses, fungi, protozoa, and helminths. The extent to which these infectious entities interact with the bacterial microbiome and shape the development of the mucosal immune system is unclear. We previously found that mice with a mutation in the IBD susceptibility gene Atg16L1 develop inflammatory pathologies in the intestine upon infection with murine norovirus (MNV), a single-stranded RNA virus. Remarkably, we found that MNV mimics the beneficial properties of the bacterial microbiome in a wild-type setting. MNV was sufficient to direct the proper development of the intestine and associated mucosal immune system in germ-free and antibiotics-treated mice. Also, MNV protected these mice from intestinal damage caused by chemical injury and pathogenic bacterial infection. Therefore, like certain bacterial members of the microbiome, MNV can be beneficial, but induces disease in a genetically susceptible host. Is the mechanism by which MNV provides beneficial cues to the host similar or distinct from bacteria? Why does mutation in Atg16L1, a gene that is essential for the cellular degradative pathway of autophagy, make an otherwise beneficial virus into a disease-causing agent? We will discuss these and related questions surrounding the characterization of a viral member of the microbiome.

References:

1. Cadwell K, Patel KK, Maloney N, Liu TC, Ng ACY, Storer CE, Head RD, Xavier R, Stappenbeck TS, Virgin HW. Virus-plus-susceptibility gene interaction determines Crohn’s disease gene Atg16L1 phenotypes in intestine. Cell. 2010. Jun 25;141(7): 1135-45. PMC2908380
2. Kernbauer L, Ding Y, Cadwell K. An enteric virus can replace the beneficial function of commensal bacteria. Nature. 2014 Dec 4;516(7529):94-8. PMC4257755
3. Cadwell K. The Virome in Host Health and Disease. Immunity. 2015 May 19;42(5):805-813. PMC4578625
4. Ramanan D, Bowcutt R, Lee SC, Tang MS, Kurtz ZD, Ding Y, Honda K, Gause WC, Blaser MJ, Bonneau RA, Lim YA, Loke P, Cadwell K. Helminth infection promotes colonization resistance via type 2 immunity. Science. 2016 Apr 29;352(6285):608-12. PMC4905769

The cGAS Pathway of Cytosolic DNA Sensing and Its Role in Health and Disease

Zhijian 'James' Chen. Ph.D.

Howard Hughes Medical Institute; Department of Molecular Biology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9148

In animal cells, DNA is normally present in the nucleus and mitochondria. When microbes infect cells, the presence of microbial DNA in the cytoplasm is perceived by the host as a danger signal that triggers defensive immune responses. We have recently identified cyclic GMP-AMP synthase (cGAS) as the sensor of cytosolic DNA that triggers the type-I interferon (IFN) pathway and other innate immune responses. Upon binding to generic double-stranded DNA (dsDNA), cGAS undergoes a conformational change that induces its enzymatic activity, which catalyzes the synthesis of a unique isomer of cyclic GMP-AMP containing both 2'-5' and 3'-5' linkages (2'3'-cGAMP). This cGAMP molecule functions as a second messenger that binds and activates the adaptor protein STING, which in turn activates the protein kinases IKK and TBK1 to induce IFNs and other immune modulators. Genetic experiments have shown that cGAS plays an essential role in IFN induction by a variety of DNA-containing pathogens, including DNA viruses, retroviruses (*e.g,* HIV) and bacteria (*e.g*, mycobacterium tuberculosis). As an enzyme activated by any dsDNA independently of the DNA sequence, cGAS can also be activated by self DNA that inadvertently enters the cytoplasm. In these cases, cGAS activation can cause autoimmune and autoinflammatory diseases. This has been demonstrated recently in several autoimmune diseases caused by functional deficiencies of cellular nucleases, such as Trex1 and DNaseII. In addition, cGAS can presumably detect tumor DNA in antigen presenting cells to activate anti-tumor immunity. Thus, cGAS is a general DNA sensor that plays a pivotal role in host defense against microbial pathogens and malignant cells; however, aberrant activation of cGAS by self DNA can also cause autoimmune diseases. Recent progress in understanding the regulation and function of the cGAS pathway will be presented.

References

1. Gao, D., Li, T., Li, X-D., Chen, X., Li, Q-Z., Wight-Carter, M., and Chen, Z.J. (2015) Activation of cyclic GMP-AMP synthase by self DNA causes autoimmune diseases. ***Proc Natl Acad Sci U S A.*** *112*, *E5699-705*. doi: 10.1073/pnas.1516465112.
2. Sun, L., Wu, J., Du, F., Chen, X., and Chen, Z.J. (2013). Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. ***Science*** *339*, 786-791.
3. Wu, J., Sun, L., Chen, X., Du, F., Shi, H., Chen, C., and Chen, Z.J. (2013). Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. ***Science*** *339*, 826-830.

What makes a protective anti-*Toxoplasma* T cell response?

Ellen Robey

Hamlet Chu[1], Alexandra Tsitstiklis[1], Shiao Wei Chan[1], Anita Koshy[2], Anna Salvioni[3], Nicolas Blanchard[3], John C. Boothroyd[4], Yang Wang[5], Nilabh Shastri[1], Shaodong Dai[5], and Ellen A. Robey[1]

[1]Division of Immunology and Pathogenesis, Department of Molecular and Cellular Biology, University of California, Berkeley, CA 94720-3200, USA
[2]Department of Neurology, University of Arizona, Tuscon, AR 85721-0240, USA
[3] Center of Pathophysiology of Toulouse-Purpan, INSERM UMR1043 - CNRS UMR5282 – University of Toulouse, 31024 Toulouse Cedex 3, France.
[4]Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA 94305-5124, USA
[5]Department of Biomedical Research, National Jewish Health, Denver, CO 80206

Immune control of the intracellular protozoan parasite *Toxoplasma gondii* in the mammalian host relies on a robust CD8 T cell response, but why certain CD8 T cell responses are particularly effective at controlling the parasite is not well understood. We are addressing this question by visualizing T cell-parasite interactions *in vivo* and by identifying and characterizing T cell responses to natural parasite antigens in genetically resistant mice. We previously identified a parasite antigen that elicits a dominant and highly protective CD8 T cell response (Blanchard et al., 2008; Chu et al., 2016). I will present recent data from our labs comparing this “elite controller” T cell responses to sub-dominant T cell responses, revealing unique features of the protective CD8 T cell response. I will also discuss how protective and non-protective T cells interact with parasites and parasite-invaded cells in the brain during chronic infection of mice (Schaeffer et al., 2009).

Blanchard, N., Gonzalez, F., Schaeffer, M., Joncker, N. T., Cheng, T., Shastri, A. J., et al. (2008). Immunodominant, protective response to the parasite Toxoplasma gondii requires antigen processing in the endoplasmic reticulum. *Nature Immunology*, *9*(8), 937–944. http://doi.org/10.1038/ni.1629

Chu, H. H., Chan, S. W., Gosling, J. P., Blanchard, N., Tsitsiklis, A., Lythe, G., et al. (2016). Continuous Effector CD8(+) T Cell Production in a Controlled Persistent Infection Is Sustained by a Proliferative Intermediate Population. *Immunity*, *45*(1), 159–171. http://doi.org/10.1016/j.immuni.2016.06.013

Schaeffer, M., Han, S.-J., Chtanova, T., van Dooren, G. G., Herzmark, P., Chen, Y., et al. (2009). Dynamic imaging of T cell-parasite interactions in the brains of mice chronically infected with Toxoplasma gondii. *Journal of Immunology*, *182*(10), 6379–6393. http://doi.org/10.4049/jimmunol.0804307

The good and the bad: two faces of microbiota in the eye

Rachel R Caspi

National Institutes of Health, Bethesda, Maryland, USA

Microbiota can play very different roles in inflammatory disease affecting the eye, depending on the context and the location. Autoimmune uveitis is a blinding disease driven by autoreactive T cells specific to tissue-specific antigens within the eye. Because these antigens are sequestered from the immune system as part of ocular immune privilege, it was a puzzle where these autoreactive T cells are initially activated. Our data suggest that intestinal microbiota can serve as a source of crossreactive antigenic material that activates retina-specific T cells that happen to migrate through the gut, and endow them with the ability to cross the blood-retinal barrier and fuel autoimmune disease in the eye. In view of the great diversity of the gut microbiome, we speculate that activation of autoreactive TCRs by commensals in the gut may be more common than is currently appreciated. On the other hand, microbiota on the surface of the eye may play a positive role. Mucosal sites such as the intestine, oral cavity, nasopharynx, and female reproductive tract all have their associated commensal flora. The surface of the eye (conjunctiva) is also a mucosal site, but because of the antibacterial environment, existence of a resident microbiome on the ocular surface is highly controversial. We have isolated an organism from the murine conjunctiva, which represents a stable resident of the ocular surface. Its presence tunes local immune function and protects from ocular surface infection by pathogens. Furthermore, loss-of-function and gain-of-function experiments demonstrate that this organism fulfills all 4 Koch's postulates for a causative agent, providing direct support for existence of a true resident microbiome on the ocular surface.

1. Reiko Horai* Carlos R. Zárate-Bladés*, Patricia Dillenburg-Pilla, Jun Chen, Phyllis B. Silver, Yingyos Jittayasothorn, Chi-Chao Chan, Hidehiro Yamane, Kenya Honda and Rachel R. Caspi. Activation of an autoreactive T cell receptor by commensal microbiota provokes autoimmunity in an immunologically privileged site. *2015 Immunity*; 43:343-53. PMID: 26287682. *Equal contribution.

2. Microbiome-dependent modulation of mucosal immunity at the ocular surface. Rachel R Caspi, Rebecca Drummond, Jigarkumar Desai, Phyllis B Silver, Michail S Lionakis and Anthony J St. Leger. http://www.jimmunol.org/content/196/1_Supplement/67.17.abstract.

Regulation of allergic responses to food by commensal bacteria

Cathryn R. Nagler, Ph.D.

Department of Pathology, Committee on Immunology, The University of Chicago

Immunoregulatory responses induced by commensal bacteria are critical to preventing intestinal inflammation. Whether the intestinal microbiota also plays a role in regulating non-responsiveness to the other major luminal constituent - food - has been poorly understood. We have shown that sensitization to a food allergen is enhanced in mice that have been treated by neonatal antibiotic administration (Abx) or are devoid of commensal microbes (germ free, GF). Selective colonization of GF mice demonstrated that the allergy-protective capacity is contained within the Clostridia, a class of anaerobic spore-forming Firmicutes that resides in close proximity to the intestinal epithelium. Microarray analysis of intestinal epithelial cells isolated from gnotobiotic mice identified a novel innate mechanism by which Clostridia protect against sensitization to dietary antigens. Clostridia colonization induces the production of the barrier protective cytokine IL-22 by both innate lymphoid cells and T cells in the intestinal lamina propria. IL-22-mediated effector functions, including the production of mucus and anti-microbial peptides, collectively contribute to protection against sensitization by reducing the access of dietary antigen to the systemic circulation. Our mouse model work is supported by translational studies comparing the fecal microbiota of healthy infants to that of infants with cow's milk allergy (CMA). We find that the CMA infant microbiome has the diverse community structure typical of adults. Treatment of CMA infants with a tolerance inducing formula supplemented with the probiotic *Lactobacillus rhamnosus* GG (LGG) is associated with changes in microbial community structure that include the expansion of butyrate-producing Clostridia and significantly higher levels of butyrate detectable in feces. Further elucidation of the mechanisms by which innate immune signals from commensal bacteria and their metabolites regulate the intestinal epithelial barrier will inform the development of novel microbiome modulating approaches to prevent or treat sensitization to food.

1. Stefka AT, Feehley T, Tripathi P, Qiu J, McCoy K, Mazmanian SK, Tjota MY, Seo GY, Cao S, Theriault BR, Antonopoulos DA, Zhou L, Chang EB, Fu YX, Nagler CR. Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci U S A. 2014 Sep 9;111(36):13145-50. PubMed PMID: 25157157; PubMed Central PMCID: PMC4246970.
2. Feehley T, Nagler CR. Cellular and molecular pathways through which commensal bacteria modulate sensitization to dietary antigens. Curr Opin Immunol. 2014 Dec; 3:79-86. PubMed PMID: 25458998; PubMed Central PMCID: PMC4255329.
3. Berni Canani R, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, Calignano A, Khan AA, Gilbert JA and Nagler CR. *Lactobacillus rhamnosus* GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. ISME J. 2016 Mar; 10(3): 742-750. PubMed PMID 26394008
4. Wesemann, D.R., Nagler, C.R. Windows of Opportunity: The microbiome, timing and barrier function in the context of allergic disease. Immunity 2016 Apr 19;44(4):728-38. PubMed PMID: 27096316

Resident memory T cells in human health and disease

Rachael A. Clark, M.D., Ph.D.

Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA

Resident memory T cells (T_{RM}) are non-recirculating memory T cells that persist long term in epithelial barrier tissues, including the gastrointestinal tract, lung, skin and reproductive tract. The skin of a healthy adult contains nearly 20 billion memory T cells, approximately half of which are T_{RM}. These cells persist long term in the absence of antigens, have impressive effector functions and provide rapid on-site immune protection against known pathogens in peripheral tissues. Human skin T cells are almost universally $\alpha\beta$ T cells and the TCR repertoire of human skin T_{RM} is very diverse. The most frequent T_{RM} clones from skin, gut and lung were non-overlapping, suggesting distinct T cell pools. Human T cells tropic for different barrier tissues were enriched for specificity against pathogens and commensal organisms commonly encountered through those tissues. In mouse models, local viral infection of skin led to seeding of the entire skin surface with highly protective T_{RM}. Moreover, skin infection also led to seeding of the lung and gut with protective T_{RM}, leading to partial protection of at least two other epithelial barrier tissues. T_{RM} have a fundamentally distinct gene expression program as compared to circulating T cells and the signals that allow T_{RM} to survive long term in tissues in the absence of antigen exposure are unknown. Although the T_{RM} differentiation program likely evolved to provide rapid immune protection against pathogens, autoreactive, aberrantly activated and malignant resident memory cells contribute to numerous human inflammatory diseases including psoriasis, contact dermatitis and mycosis fungoides. This lecture will discuss both the science and medicine of resident memory T cells, exploring how these cells contribute to healthy immune function and discussing what is known about how these cells contribute to human inflammatory and autoimmune diseases.

Funded by the NIH (NIAMS, NCI, NIAID, NIMH)

References:

1. Clark RA. Resident memory T cells in human health and disease. Sci Transl Med 2015;7(269):269rv1.
2. Watanabe R, Gehad A, Yang C, Scott LL, Teague JE, Schlapbach C, et al. Human skin is protected by four functionally and phenotypically discrete populations of resident and recirculating memory T cells. Science Translational Medicine 2015;7(279):279ra39.
3. Jiang X, Clark RA, Liu L, Wagers AJ, Fuhlbrigge RC, Kupper TS. Skin infection generates non-migratory memory CD8+ TRM cells providing global skin immunity. Nature 2012;483(7388):227-31.

"HVEM: a TNF family receptor with a protective role in innate immunity and tissue homeostasis"

Mitchell Kronenberg, Ph.D.

La Jolla Institute for Allergy & Immunology

The herpes virus entry mediator (HVEM) is a member of the TNF receptor super family (TNFRSF14) that binds to three ligands, including a TNF super family member called LIGHT (or TNFSF14), and Ig super family members BTLA and CD160. HVEM is expressed by a variety of hematopoietic cell types, including mast cells, but we have explored the role of HVEM expression in epithelial cells for promoting barrier immunity. During *Citrobacter rodentium* infection by oral gavage, *Hvem*$^{-/-}$ mice had impaired colonic epithelial responses, resulting in higher bacterial burdens, inflammation and increased mortality. HVEM is engaged in the intestine by CD160, which is expressed by intraepithelial lymphocytes (IEL). HVEM was also important for signaling to promote innate epithelial responses in mice to pulmonary infection with the pathogen *Streptococcus pneumoniae*, but in the lung the critical ligand for HVEM-mediated host defense was BTLA. Using conditional knock out mice, we have shown that HVEM expressed by lung epithelial cells interacted with BTLA expressed by a CD11c^{+} myeloid cell. In the small intestine, HVEM signals in epithelial cells occurred not only during acute infection, but also at steady state to influence the homeostasis of intestinal tissue, the microbiome and the resident T cells. Mice deleted for HVEM specifically in intestinal epithelia cells (*Hvem*$^{\Delta IEC}$ mice) exhibited a variety of changes, including reduced synthesis of basement proteins and decreased fucosylation of proteins on the cell surface. These mice developed increases in segmented filamentous bacteria (SFB) leading to increased CD4^{+} Th17 cells in the lamina propria. While the increased SFB and Th17 cells could be reversed by antibiotics, the epithelial cell changes were not reversed, indicating a primary effect of HVEM signals in regulating the biology of epithelial cells.

Shui, J.-W., Larange, A., Kim, G., Véla, J.L., Zahner, S., Cheroutre, H., and Kronenberg, M. HVEM signaling at mucosal barriers provides host defense against pathogenic bacteria. *Nature*, 488:222-225, 2012.

Krause, P., Zahner, S.P., Kim, G., Shaikh, R.B., Steinberg, M.W., and Kronenberg, M. The Tumor Necrosis Factor Family Member TNFSF14 (LIGHT) is Required for Resolution of Intestinal Inflammation in Mice. *Gastroenterology*. 146: 1752-1762, 2014.

Sibilano, R., Gaudenzio, N., DeGorter, M.K., Reber, L.L., Hernandez, J.D., Starkl, P.M., Zurek, O.W., Tsai, M., Zahner, S., Montgomery, S.B., Roers, A., **Kronenberg, M.**, Yu, M., Galli, S.J. A TNFRSF14-FcεRI-mast cell pathway contributes to development of multiple features of asthma pathology in mice. *Nat Commun*. 7:13696, 2016.

Driving CARs to BARs: Engineered antigen-specific human Tregs for tolerance

David W. Scott

Yong Chan Kim, Aihong Zhang, Jeong Heon Yoon, Kalpena Parvathaneni, Anja Schmidt*, Christoph Königs* and David W. Scott

Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD

*Department of Pediatrics, University Hospital Frankfurt, Goethe University, Frankfurt, Germany

Regulatory T cells (Tregs) have been proposed as a potential clinical therapy for a variety of adverse immune disorders, ranging from autoimmune diseases to the development of anti-drug antibodies, such as inhibitor formation in monogenic diseases. Treg therapies have also been applied in clinical studies for prevention of graft versus host disease. However, specific Tregs are relatively low in frequency. Moreover, polyclonal Tregs include a repertoire of diverse specificities and could potentially be globally immunosuppressive [1]. To increase efficacy and specificity, we have engineered human T cells to express chimeric antigen receptors (CARs) using either T-cell receptors from MS or hemophilia patients or specific single chain Fv's, Thus, we modified the CAR approach utilized successfully for leukemia therapy (e.g., CD19 CAR CD8's) to create specific T regulatory cells recognizing either myelin basic protein (for MS) or factor VIII (FVIII) for hemophilia [2, 3]. Such cells can actively suppress effector T cell proliferation and cytokine formation *in vitro*. These cells can mediate suppression even in the presence of strong inflammatory signals. Mechanistic studies suggest both contact dependent and contact-independent pathways. Further developments with B-cell targeting strategies have also been successful by expressing *antigen domains* in regulatory T cells (BARs) that are recognized by and can target specific B cells, as was recently reported with CD8 T cells [4]. Application of these engineered T cells to modulate pathogenic responses *in vivo* in disease models [3, 5] will be presented and further discussed.

(Supported by NIH grants HL126495, HL127495 and a grant from the National Multiple Sclerosis Society [DWS] and the German Society of Thrombosis and Hemostasis Research, and a Günter Landbeck Excellence Award [AS])

1. Brunstein, C.G., et al., *Adoptive transfer of umbilical cord blood-derived regulatory T cells and early viral reactivation.* Biol Blood Marrow Transplant, 2013. **19**(8): p. 1271-3.
2. Kim, Y.C., et al., *Engineered antigen-specific human regulatory T cells: immunosuppression of FVIII-specific T- and B-cell responses.* Blood, 2015. **125**(7): p. 1107-15.
3. Yoon, et al., *FVIII-specific human chimeric antigen receptor (CAR) T-regulatory cells suppress T-and B-cell responses to FVIII*. Blood, 2017 *in press*.
4. Ellebrecht, C.T., et al., *Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease.* Science, 2016. **353**(6295): p. 179-84.
5. MacDonald, K.G., et al., *Alloantigen-specific regulatory T cells generated with a chimeric antigen receptor.* J Clin Invest, 2016. **126**(4): p. 1413-24.

Tregs control peripheral autoreactive B cell selection

Eric Meffre

Department of Immunobiology, Yale University, New Haven, CT

Patients with autoimmune diseases display a defective peripheral B cell tolerance checkpoint, which results in accumulation of autoreactive mature naïve B cells in the periphery (1-2). Analysis of B cell tolerance in IPEX patients with FOXP3 mutations pointed to regulatory T cells (Tregs) as a potential regulator for this peripheral checkpoint (3). To determine a role for Treg on peripheral B cell tolerance, we analyzed two humanized NSG mouse models engrafted with human fetal HSCs with or without matched thymic graft. Both models recapitulated central B cell tolerance (4), whereas the prevention of the accumulation of autoreactive B cells in the periphery was only observed when a human fetal thymic graft was transplanted. The depletion of Tregs in NSG + Thymus mice resulted in the positive selection of autoreactive clones in the mature naïve B cell compartment, demonstrating the important role of these T cells in the regulation of the peripheral B cell tolerance checkpoint. To further characterize functional Tregs that developed in NSG + Thymus mice from defective Tregs that failed to prevent the expansion of autoreactive B cells in NSG mice, we performed RNA-sequencing and TCR repertoire-sequencing experiments on sorted Tregs from both mouse models. Tregs in NSG mice displayed an activated T cell phenotype with heightened expression of cell cycle genes, while lacking expression of key genes of T cell lineage specification such as TCF-1 and LEF-1. In contrast, Tregs from NSG + Thymus mice were similar to Tregs isolated from healthy donors. TCR repertoire sequencing also revealed an abnormal TCRVB gene usage in Tregs from NSG mice that likely reflects selection on mouse instead of human MHC, whereas the TCRVB gene repertoire of Tregs from NSG + Thymus mice was similar to that of healthy donors. We conclude that proper Treg development in the thymus is essential for ensuring peripheral B selection and preventing the accumulation of autoreactive clones.

References:

1. E. Meffre. The establishment of early B cell tolerance in humans: lessons from primary immunodeficiency diseases. 2011. *Ann. N.Y. Acad. Sci*. 1246: 1–10. PMID: 22236425.
2. Kinnunen T., Chamberlain N., Morbach H., Cantaert T., Lynch M., Herold K., Hafler D., O' Connor K., and E. Meffre. Specific peripheral B cell tolerance defects in patients with multiple sclerosis. 2013. *J. Clin. Invest.* 123(6): 2737-41. PMID: 23676463.
3. Kinnunen T., Chamberlain N., Morbach H., Choi J., Kim S., Craft J., Mayer L., Cancrini C., Passerini L., Bacchetta R., Ochs H.D., Torgerson T.R., and Meffre E. Accumulation of peripheral autoreactive B cells in the absence of functional human regulatory T cells. 2013. *Blood.* Feb 28; 121(9): 1595-603. PMID: 23223361.
4. Schickel J.N., Kuhny M., Baldo A., Bannock J.M., Massad C., Wang H., Katz N., Oe T., Menard L., Soulas-Sprauel P., Strowig T., Flavell R. and Meffre E. PTPN22 inhibition resets defective human central B cell tolerance. *Science Immunol*. 2016. In press.

Cellular and molecular biology of human regulatory T cells

Megan K. Levings

BC Children's Hospital Research Institute and University of British Columbia

Regulatory T cells have a major role in the induction and maintenance of peripheral tolerance through their ability to control the activation of multiple types of immune cells. These suppressive properties have the potential to be harnessed for disease therapy either via adoptive cell transfer or by strategies to increase their numbers and/or function in vivo. Indeed, multiple clinical trials of Treg cell therapy are underway, with promising early data illustrating their potential therapeutic effect. However, even as clinical studies are underway, the mechanisms of human Treg function still remain largely unknown, and it is difficult to track changes in their function. Strategies to tailor the function of Tregs to maximize their therapeutic potential as well as to track changes in their function overtime will be discussed.

Representative publications:

Alloantigen-specific regulatory T cells generated with a chimeric antigen receptor.
MacDonald KG, Hoeppli RE, Huang Q, Gillies J, Luciani DS, Orban PC, Broady R, Levings MK. J Clin Invest. 2016 Apr 1;126(4):1413-24. doi: 10.1172/JCI82771.PMID: 26999600

T regulatory cell chemokine production mediates pathogenic T cell attraction and suppression.Patterson SJ, Pesenacker AM, Wang AY, Gillies J, Mojibian M, Morishita K, Tan R, Kieffer TJ, Verchere CB, Panagiotopoulos C, Levings MK. J Clin Invest. 2016 Mar 1;126(3):1039-51. doi: 10.1172/JCI83987. PMID: 26854929

A Regulatory T-Cell Gene Signature Is a Specific and Sensitive Biomarker to Identify Children With New-Onset Type 1 Diabetes. Pesenacker AM, Wang AY, Singh A, Gillies J, Kim Y, Piccirillo CA, Nguyen D, Haining WN, Tebbutt SJ, Panagiotopoulos C, Levings MK. Diabetes. 2016 Apr;65(4):1031-9. doi: 10.2337/db15-0572. PMID: 26786322

Discarded Human Thymus Is a Novel Source of Stable and Long-Lived Therapeutic Regulatory T Cells. Dijke IE, Hoeppli RE, Ellis T, Pearcey J, Huang Q, McMurchy AN, Boer K, Peeters AM, Aubert G, Larsen I, Ross DB, Rebeyka I, Campbell A, Baan CC, Levings MK, West LJ. Am J Transplant. 2016 Jan;16(1):58-71. doi: 10.1111/ajt.13456. PMID: 26414799

Repertoire and function of meningeal immunity in healthy and diseased brain

Jonathan Kipnis

University of Virginia

Immune cells and their derived molecules have major impact on brain function. We have shown that a proper T cell compartment is critical for higher brain function. Mice deficient in adaptive immunity have impaired cognitive function compared to that of wild-type mice. Importantly, replenishment of the T cell compartment in immune deficient mice restored proper cognition. Our recent works also demonstrates the effect of the immune system on social behavior. Despite the robust influence on brain function, T cells are not found within the brain parenchyma, a fact that only adds more mystery into these enigmatic interactions between T cells and the brain. Our results suggest that meningeal space, surrounding the brain, is the site where CNS-associated immune activity takes place. We have recently discovered a presence of meningeal lymphatic vessels that drain CNS molecules and immune cells to the deep cervical lymph nodes. This communication between the CNS and the peripheral immunity is playing a key role in several neurological and psychiatric disorders and, therefore, may serve as a novel therapeutic target that is worth in-depth mechanistic exploration.

References:

1. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J. (2015) Structural and functional features of central nervous system lymphatics. *Nature*, Jul 16;523(7560):337-41. doi: 10.1038/nature14432.
2. Gadani SP, Walsh JT, Lukens JR and Kipnis J. (2015) Dealing with Danger in the CNS: The Response of the Immune System to Injury. *Neuron*. Jul 1;87(1):47-62. doi: 10.1016/j.neuron.2015.05.019.
3. Louveau A, Harris TH and Kipnis J. (2015) Revisiting the mechanisms of CNS immune privilege. *Trends Immunol*, Oct;36(10):569-77. doi: 10.1016/j.it.2015.08.006.

Novel signaling pathways that control effector, memory, and regulatory T cell responses

Daniel J. Campbell

Immunology Program, Benaroya Research Institute, Seattle, WA 98101

During activation, T cells integrate signals from the T cell receptor, cytokines, and co-stimulatory/co-inhibitory receptors, resulting in the development of specialized effector, memory and regulatory populations. Of the key signaling pathways engaged, activation of the phosphoinositide 3-kinase (PI3K) signaling cascade has particularly dramatic consequences on T cell responses by influencing cell proliferation and survival, metabolic reprogramming, cellular migration and tissue-tropism, acquisition of effector function and generation of long-lived memory cells[1,2]. In $CD8^+$ T cells, strong PI3K-dependent Akt activation favors the generation of short-lived effector cells (SLECs) at the expense of the long-lived memory precursor effector cells (MPECs)[2–4], and manipulation of PI3K signaling can be used to alter the balance of effector and memory T cell generation[5]. Similarly, in $CD4^+$ T cells PI3K activation plays a central role in effector differentiation; high levels of PI3K activation promotes the generation of strongly inflammatory Th1 effector cells, whereas low or absent PI3K activity promotes the generation of peripherally-induced $Foxp3^+$ regulatory T (Treg) cells[6,7]. Finally, within Treg cells, PI3K signaling is required for the differentiation of 'effector' Tregs that localize to non-lymphoid tissues and restrict ongoing immune responses[8]. However, despite the dramatic impact of PI3K signaling on T cell responses, the mechanisms by which PI3K is activated and regulatored during T cell differentiation are not completely understood. In this presentation I will highlight new data from my lab demonstrating that PI3K signaling downstream of the co-stimulatory receptor ICOS is critical for proper Treg cell localization and function due in part to its impact on activity of the transcription factor Foxo1, and identifying B cell adaptor for PI3K as a novel signaling scaffold that is expressed in T cell upon activation, and influences effector, memory and regulatory T cell development.

1. Han, J. M., Patterson, S. J. & Levings, M. K. The Role of the PI3K Signaling Pathway in CD4(+) T Cell Differentiation and Function. *Front. Immunol.* **3,** 245 (2012).
2. Kim, E. H. & Suresh, M. Role of PI3K/Akt signaling in memory CD8 T cell differentiation. *Front. Immunol.* **4,** 20 (2013).
3. Rao, R. R., Li, Q., Odunsi, K. & Shrikant, P. A. The mTOR kinase determines effector versus memory CD8+ T cell fate by regulating the expression of transcription factors T-bet and Eomesodermin. *Immunity* **32,** 67–78 (2010).
4. Rao, R. R., Li, Q., Gubbels Bupp, M. R. & Shrikant, P. A. Transcription factor Foxo1 represses T-bet-mediated effector functions and promotes memory CD8(+) T cell differentiation. *Immunity* **36,** 374–387 (2012).
5. Heikamp, E. B. & Powell, J. D. Sensing the immune microenvironment to coordinate T cell metabolism, differentiation & function. *Semin. Immunol.* **24,** 414–420 (2012).
6. Delgoffe, G. M. *et al.* The mTOR kinase differentially regulates effector and regulatory T cell lineage commitment. *Immunity* **30,** 832–844 (2009).
7. Haxhinasto, S., Mathis, D. & Benoist, C. The AKT-mTOR axis regulates de novo differentiation of CD4+Foxp3+ cells. *J. Exp. Med.* **205,** 565–574 (2008).
8. Luo, C. T., Liao, W., Dadi, S., Toure, A. & Li, M. O. Graded Foxo1 activity in Treg cells differentiates tumour immunity from spontaneous autoimmunity. *Nature* **529,** 532–536 (2016).

Innate lymphoid cells regulate asthma phenotypes

Dale T. Umetsu, MD, PhD, Genentech

Our understanding of the pathogenesis of asthma has been recently radically transformed, such that we no longer think of asthma as a simple Th2-mediated disease, but rather as a heterogeneous syndrome with an assortment of distinct phenotypes. These phenotypes include not only an allergic asthma phenotype, but also non-allergic eosinophilic asthma as well as non-Type 2 neutrophilic asthma phenotypes. The immunological pathways leading to these phenotypes include adaptive as well as innate ones, involving CD4 T cells and innate cell types, including several types of innate lymphoid cells.

Type 2 innate lymphoid cells producing IL-5 and IL-13 were first shown to affect asthma in mouse models only five years ago, and their role in human asthma is only now being understood. Type 3 innate lymphoid cells producing IL-17 are present in human lung, and may play a role in some forms of non-Type 2 asthma, such as asthma associated with obesity.

The idea that asthma is heterogeneous is consistent with the movement towards precision medicine and the use of individualized treatments for each patient.

References

Chang YJ, Kim HY, Albacker LA, Baumgarth N, McKenzie AN, Smith DE, Dekruyff RH, Umetsu DT. Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. Nat Immunol. 2011 May 29;12(7):631-8.

Kim HY, Lee HJ, Chang YJ, Pichavant M, Shore SA, Fitzgerald KA, Iwakura Y, Israel E, Bolger K, Faul J, DeKruyff RH, Umetsu DT. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. Nat Med. 2014. 20(1):54-61.

Iwasaki A, Foxman EF, Molony RD. Early local immune defences in the respiratory tract. Nat Rev Immunol. 2016 Nov 28. doi: 10.1038/nri.2016.117.

Monticelli LA, Buck MD, Flamar AL, Saenz SA, Tait Wojno ED, Yudanin NA, Osborne LC, Hepworth MR, Tran SV, Rodewald HR, Shah H, Cross JR, Diamond JM, Cantu E, Christie JD, Pearce EL, Artis D. Arginase 1 is an innate lymphoid-cell-intrinsic metabolic checkpoint controlling type 2 inflammation. Nat Immunol. 2016 Jun;17(6):656-65.

Role of interleukin-22 in Host Defense Against Bacterial Pathogens

Gabriel Nuñez

Department of Pathology and Comprehensive Cancer Center, University of Michigan,
Ann Arbor, MI, USA

The mechanisms that allow enteric pathogens to colonize the intestine and the immunity system and the indigenous microbiota to inhibit pathogen colonization remain poorly understood. Our laboratory is using *Citrobacter rodentium*, a mouse pathogen that models human infections by enteropathogenic *E. coli*, to understand the mechanisms that regulate the colonization and clearance of the pathogen in the gut. These studies have shown how the pathogen colonizes and replicates successfully in the intestine early during infection and how the host immune system and the indigenous microbiota cooperate to eradicate the pathogen in the later stage of the infection. In addition, recent studies have revealed a critical role for interleukin-22, a cytokine best known for its ability to promote epithelial barrier function, in the systemic control of *Citrobacter rodentium* and the symbiotic bacterium *Escherichia coli*, a major cause of sepsis in humans.

References:

Kamada, N., Kim, Y.G., Sham, H.P., Vallance, B.A., Puente, J.L., Martens, E.C., Núñez, G. (2012). Regulated virulence controls the ability of a pathogen to compete with the gut microbiota. Science 6086: 1325-1329.

Kamada, N., Sakamoto, K., Seo, S.U., Zeng, M.Y., Kim, Y.G., Cascalho, M., Vallance, B.A., Puente, J.L., Núñez, G. (2015). Humoral Immunity in the Gut Selectively Targets Phenotypically Virulent Attaching-and-Effacing Bacteria for Intraluminal Elimination. Cell Host & Microbe. 17:617-27.

How the helper T cell repertoire responds to infection

Marc K. Jenkins

University of Minnesota Medical School, Center for Immunology,
Minneapolis, MN 55455

The effector and memory $CD4^+$ T cell response to a foreign antigen arises from a repertoire of naïve cells that is formed before the antigen enters the host. Very little is known, however, about individual antigen-specific naïve T cell populations largely because of their small size in a vast repertoire. We have been working on this problem using sensitive single cell detection methods. We found that the secondary lymphoid organs of uninfected mice contain about 100 $CD4^+$ T cells with T cell receptors (TCRs) specific for an MHCII-bound peptide from the bacterium *Listeria monocytogenes*. This population was a clonally diverse mixture dominated by conventional naïve cells but also containing thymus-derived regulatory T cells. The conventional naïve T cell population generated an equal mixture of Th1 and Tfh effector cells after infection but did not generate peripheral regulatory T cells. Different individual conventional naïve T cells in the population, however, generated different Th1/Tfh ratios and cells with high affinity TCRs tended to produce more Th1 cells. Each conventional naïve T cell clone-derived effector cell population contracted and produced a memory cell population with the Th1/Tfh ratio of its effector cell predecessor population. The thymus-derived $Foxp3^+$ cells in this pre-immune repertoire also proliferated after infection but rapidly disappeared from the effector cell population. These experiments revealed previously unappreciated complexity in the composition and response potential of the pre-immune $CD4^+$ T cell repertoire. My talk will focus on the molecular factors that influence the activation and differentiation of conventional naïve cells and thymus-derived regulatory T cells from the same MHCII-foreign peptide-specific pre-immune repertoire.

References:

Pepper, M., A.J. Pagán, B.Z. Igyártó, J.J. Taylor, and M.K. **Jenkins**. 2011. Opposing signals from the Bcl6 transcription factor and the interleukin-2 receptor generate T helper 1 central and effector memory cells. *Immunity* 35:583-95.

Tubo, N.J., A.J. Pagán, J.J. Taylor, R.W. Nelson, J.L. Linehan, J.M. Ertelt, E.S. Huseby, S.S. Way, and M.K. **Jenkins**. 2013. Single naïve $CD4^+$ T cells from a diverse repertoire produce different effector cell types during infection. *Cell* 153:785-96.

Tubo, N. J., B. T. Fife, A. J. Pagan, D. I. Kotov, M. F. Goldberg, and **M. K. Jenkins**. 2016. Most microbe-specific naïve $CD4^+$ T cells produce memory cells during infection. *Science* 351:511-514.