Columbia University
College of Physicians and Surgeons

Department of
Microbiology & Immunology

M&I

The Department of Microbiology & Immunology in the Graduate School of Arts and Sciences at Columbia University bridges modern molecular biology with research on infectious disease and immunology.

The Department publishes M&I, its newsletter, once a year. Highlighting exciting new research discoveries, exceptional faculty achievements, and department-wide initiatives, M&I provides a comprehensive summary of the goings-on in the department. A digital version is also available at: *www.microbiology.columbia.edu*

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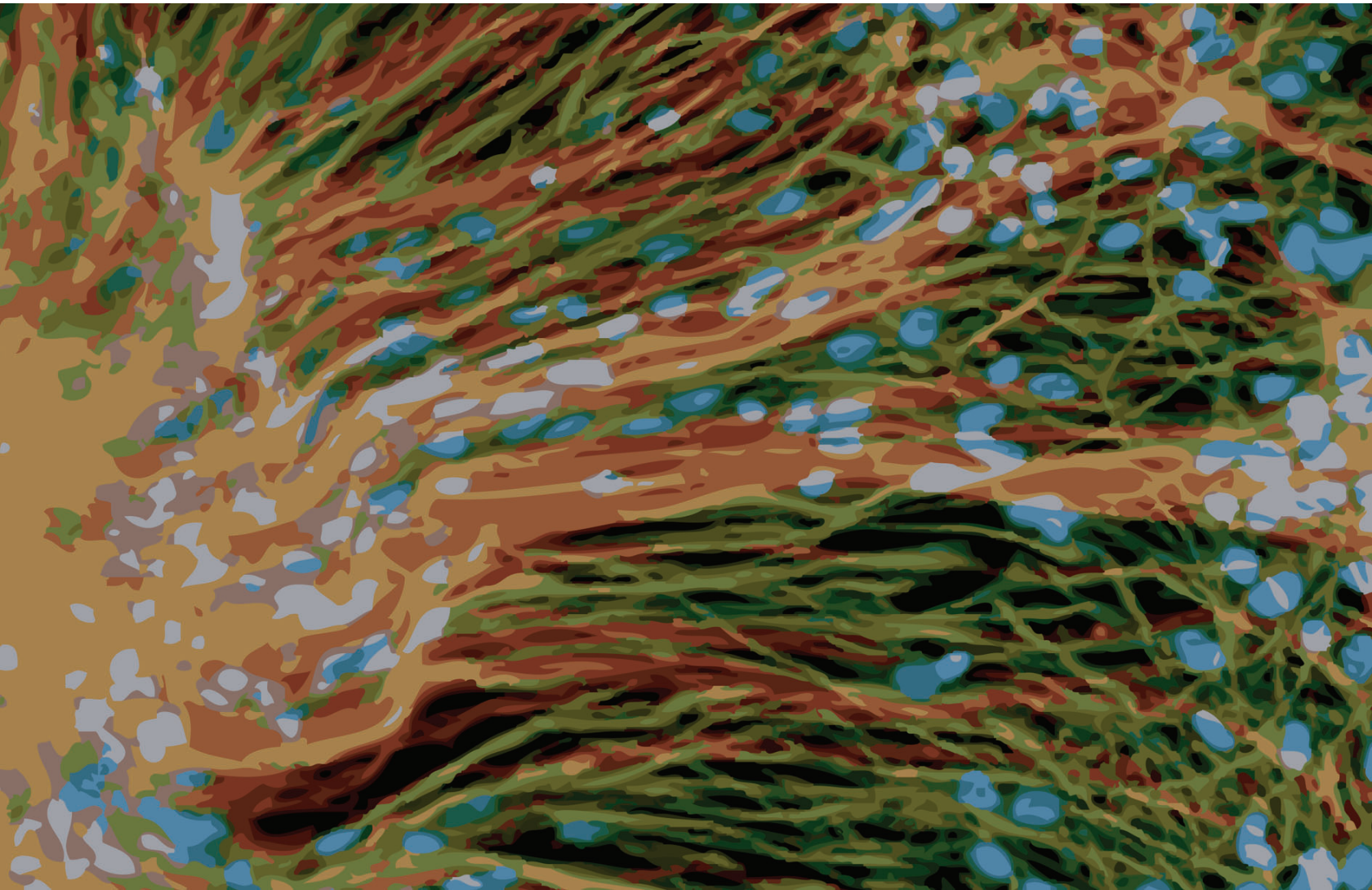

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Message from the Chair

Dear friends and colleagues,

Welcome to the 2012 edition of M&I, the newsletter for the Department of Microbiology & Immunology. There are numerous events to report on since the last newsletter, and we have highlighted many of them here. Amongst the most important was the successful recruitment of Dr. Steven Reiner at the beginning of this year from the University of Pennsylvania. Professor Reiner is a highly distinguished immunologist who has made fundamental discoveries in the process that guides T-cell differentiation, and we are delighted to welcome him to the department. We have also added three new joint appointees to our roster, Dr. Hans Snoeck, Dr. Matthew Hayden and Dr. Sagi Shapira. David Fidock, who is the Director of Graduate Admissions, was recently promoted to Full Professor, congratulations on this very well-deserved honor! We are also excited that Uttiya Basu, one of the junior faculty in the department was chosen for the NIH Directors Innovative Researcher Award. Finally, the past year also saw the passing of two long-time emeritus members of the faculty, Ben Pernis and Bernie Erlanger. Both of these distinguished immunologists leave a legacy of fundamental discoveries as well as many notable trainees. They were both remembered in a memorial service that drew many colleagues, friends and acquaintances. We will miss them deeply.

Our graduate program continues to flourish under the able guidance of David Fidock and Boris Reizis, the Director of Graduate Studies and we will welcome 5 new students to the program this fall. The past year saw completion of the major renovations on the 9th and 15th floors of Hammer. We have just begun a cosmetic refreshing of the 13th floor, completion of which will make all the M&I floors stylistically united. There has also been a major updating of the air conditioning system of the Hammer building and although this renovation was completed after the hottest days this summer, hopefully we will have cooler summers in the future.

As I noted in the last newsletter, we continue to encourage our alumni to contact us and hopefully get involved in the department's rebuilding and growth. I would also like to thank the members of the departmental office, Edie, Carol, Marisol, Joan and Anna, the operator of the FACS facility, Amir, and my assistant Elizabeth for all their work in help running the department. Finally I would like to thank Oliver and Shomik, once again, for putting this newsletter together. I hope you enjoy reading this newsletter and I wish you all an exciting and productive year!

Sankar Ghosh, Ph.D.
Chairman, Silverstein & Hutt Family Professor
Microbiology & Immunology

New Student Center

A new architectural landmark will be seen on the campus of Columbia University Medical Center. A 14-story tower, the new student center's south side is connected with terraces and glass facades offering perfect views of the Hudson River. The center's north side will offer modern classrooms and a high tech simulation center along with encompassing views of the Washington Heights neighborhood.

Hammer

The Hammer Health Sciences Center serves as the nucleus of departmental life here at the medical center. The building features a newly renovated library, cafe, student study area, as well as five newly designed and renovated floors for researchers and students in the department.

Retreat

Members of the department chat and mingle during dinner at the 2011 Microbiology & Immunology Retreat. The retreat was held at the Basking Ridge Conference Center on September 8th to 9th.

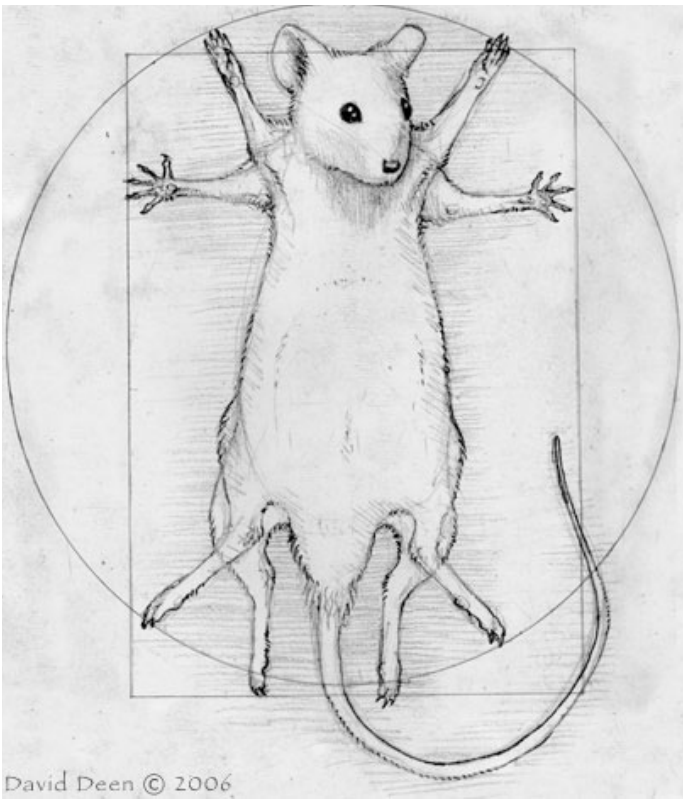
Pictured: Megan Sykes

Personalized Immune Analysis

A model for personalized *in vivo* analysis of human immune responsiveness may allow better understanding of gene-autoimmunity relationships and individualized immunotherapy

Megan Sykes, Professor of Microbiology & Immunology

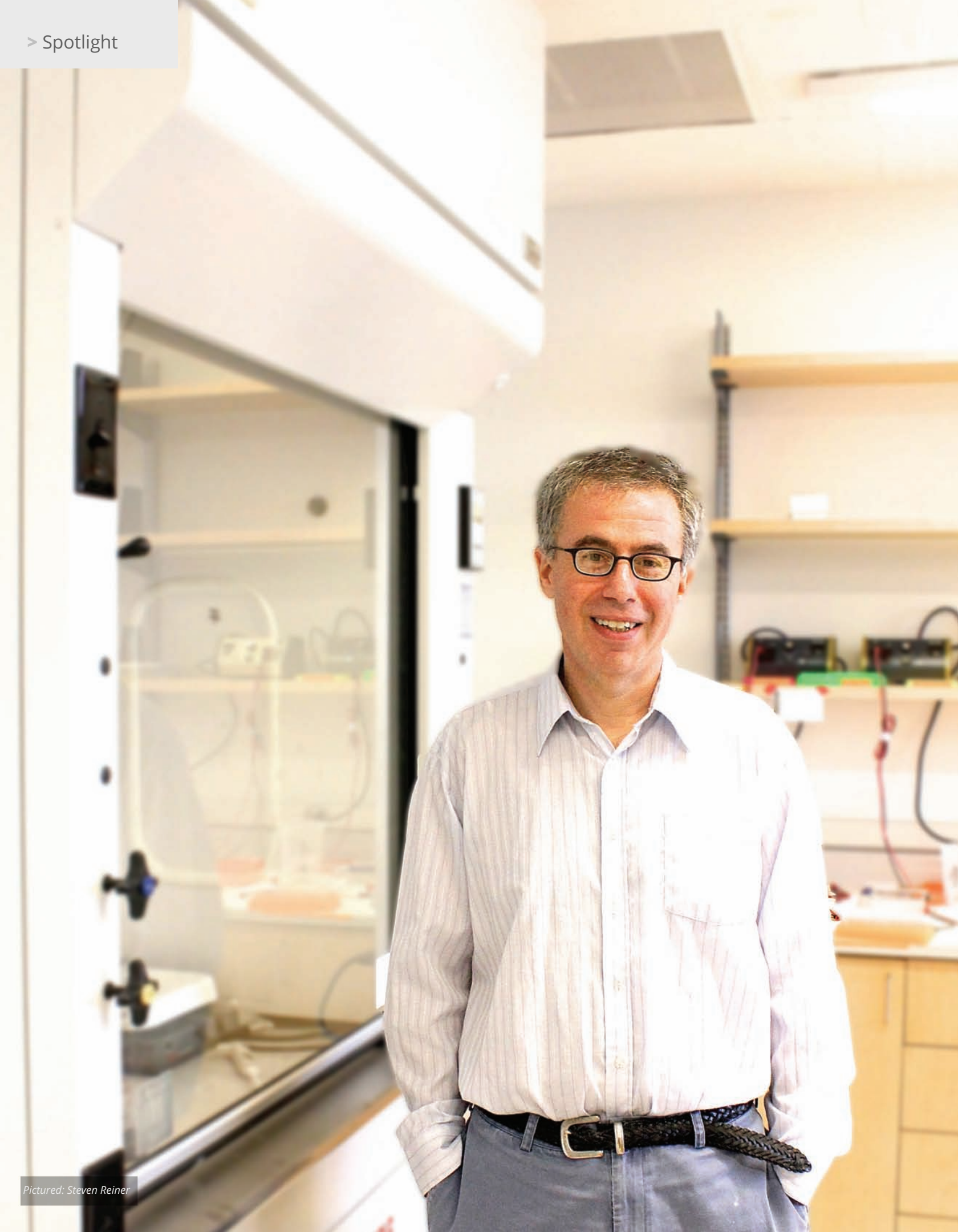
Large-scale studies of human populations have provided important clues to the genetic basis of autoimmune diseases, but have offered little information about the specific role that genes play. It is difficult to isolate these underlying mechanisms when looking at groups of patients who have had disease for different lengths of time, or have been receiving different treatments. The fact that the patients already have the disease makes it difficult to distinguish what underlies and propagates the autoimmune process. To address these issues, it would be advantageous to recreate an individual's immune system in a mouse, creating a "personalized immune" (PI) mouse. Such a model system would provide researchers with an unprecedented tool for individualized analysis of abnormalities that contribute to autoimmune diseases such as type 1 diabetes, starting before the onset of disease. It might also prove useful for developing individualized immunotherapies for fighting infection or cancer or for lessening a patient's rejection of transplanted tissue. Such a model would need to meet several challenges, including generating the full complement of immune cells and overcoming incompatibilities between tissues used to recreate the human immune system, leading to rejection and graft-versus-host disease. Unfortunately however, to date, such PI mouse models have not been developed.



In our recent study, we took the approach of transplanting human bone marrow stem cells (CD34+ cells), along with a small amount of human leukocyte antigen (HLA) matched immature thymus tissue, into an immunodeficient mouse (the HLA system mediates interactions amongst various immune cells.) The thymus tissue was implanted under the mouse's kidney capsule, a thin membrane that envelops the kidney and keeps the tissue in place while it becomes vascularized from the recipient. Within six to eight weeks, the transplanted thymus tissue had generated T cells from circulating human CD34+ cells (which are infused into the mouse's bloodstream), and other human immune cells that were also derived from the CD34+ cells. A key to the model's success was our discovery that freezing and thawing the transplanted thymus tissue, as well as administering antibodies against CD2 (a glycoprotein that mediates T cell development and activation), depletes mature T cells from the tissue graft. This prevents rejection of the human CD34+ cells and graft-versus-host disease, while preserving thymus tissue function.

We examined PI mice derived with human CD34+ cells from both healthy and type 1 diabetic individuals and found that T cells that arose from subjects with type 1 diabetes were more likely to have an antigen-experienced phenotype. Since the T cells developed in similar environments, this suggests that intrinsic differences in CD34+ cells may contribute to autoimmune pathology in type 1 diabetes. Further development of this PI mouse model and additional studies could reveal more about the pathogenesis and genetics of type 1 diabetes, and may prove useful in the study of other diseases.

Citation Kalscheuer, H.*, Danzl, N.*, Onoe, T., Faust, T., Winchester, R., Goland, R., Greenberg, E. Spitzer, T.R., Savage, D.G., Tahara, H., Choi, G., Yang Y.-G. and Sykes, M. (2012) A Model for Personalized *In Vivo* Analysis of Human Immune Responsiveness. ***Sci. Transl. Med.*** 4: 125ra30. (*equal contribution)



Pictured: Steven Reiner

Stem Cells and Protection

Asymmetric B cell division in the germinal center reaction.

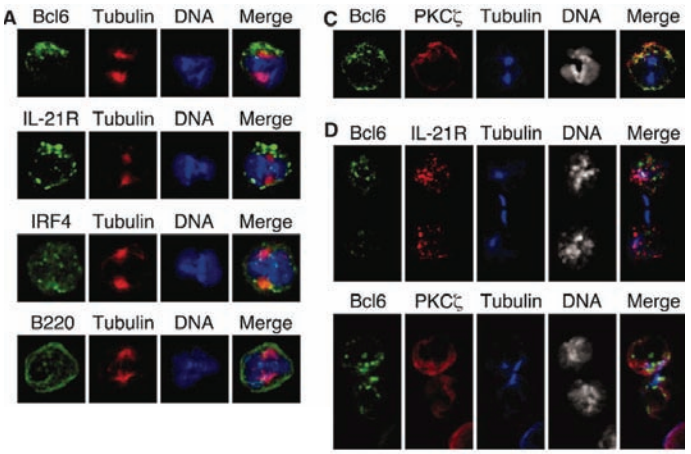
Steven Reiner, Professor of Microbiology & Immunology

Many essential, lifelong functions are performed year after year by cells that only live for a few days, like the cells on the upper layer of our skin or our oxygen-carrying red blood cells.

The paradox for how we obtain lifelong function from short-lived cells can be explained by the unusual power of stem cells. A stem cell is unique because it does two contradictory things – when it divides into two daughter cells it produces one daughter cell that is just like itself, incapable of a specialized task, and another daughter that is trained to have a new job. The daughter cell that carries out the specialized job, such as carrying oxygen or acting as a barrier to the outside world, sometimes dies within days of their generation. On the other hand the stem cell provides a lifetime source of replenishment for our tissues because when it divides, it simultaneously replaces itself with one daughter stem cell and another daughter cell to carry out the specialized functions.

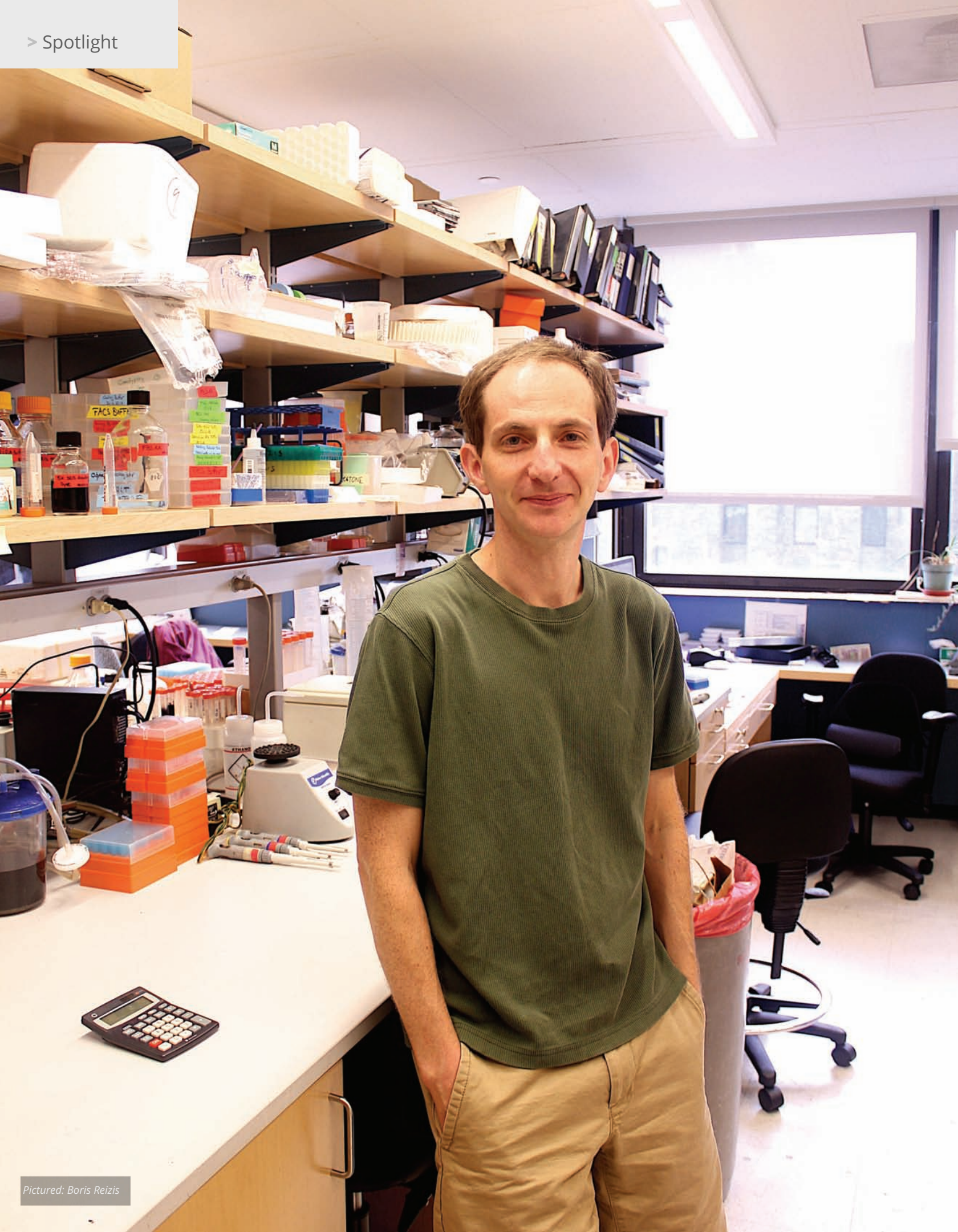
Our laboratory has shown that our immune system creates stem cells when it eliminates germs that invade our body. The ability of immune cells to produce two different types of daughter cells at once has provided an explanation for why our immune system "remembers" infections we have had earlier in life and why we respond faster and better the second time we get infected.

Recent papers from our group showed that the immune system can create two daughter cells that are different from one another because a mother cell donates unequal amounts of her working parts to the sister cells. The unequal inheritance makes a difference in their ability to perform jobs and how long they live, so the two daughter cells are fated to have different destinies. The goal of our research program is to influence the inheritance that sister cells of the immune system receive from their mother cell. This strategy should help us make better vaccines against infections and cancer, and it should lead to better treatments to fight auto-immune diseases, asthma and allergy.



Microscopic images showing asymmetric division of various molecules in germinal center (GC) B-cells.

Citation Barnett, B.E., Ciocca, M.L., Goenka, R., Barnett, L.G., Wu, J., Laufer, T.M., Burkhardt, J.K., Cancro, M.P. and Reiner, S.L. (2012) Asymmetric B cell division in the germinal center reaction. ***Science*** 335: 342-344.



Pictured: Boris Reizis

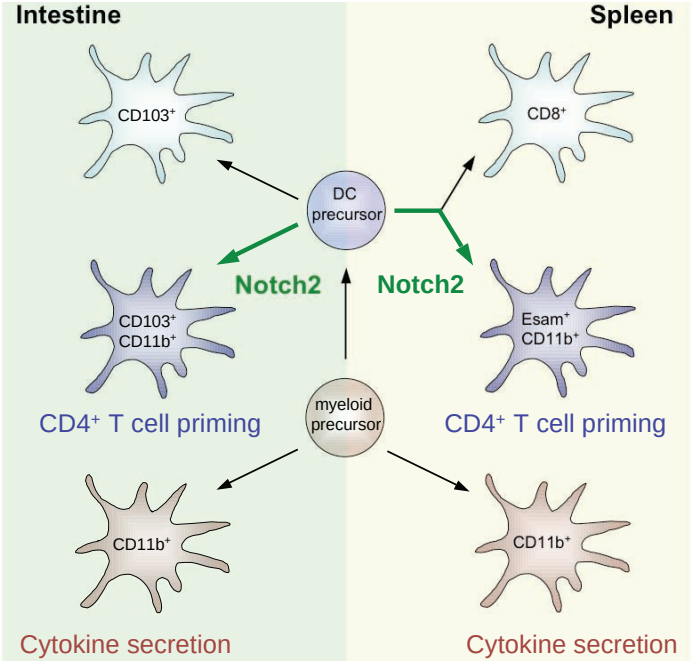
Notch Signaling Controls Dendritic Cell Development

A novel dendritic cell subset with unique immune functions is defined in the spleen

Boris Reizis, Associate Professor of Microbiology & Immunology

Dendritic cells (DCs) are immune "sentinels" that rapidly recognize pathogens and activate pathogen-specific T lymphocytes. The key role of DCs in the immune system has been highlighted with last year's Nobel Prize for their discovery to the late Ralph Steinman. Unlike most immune cell types, DCs differentiate in peripheral lymphoid organs and tissues, where they comprise distinct functional subsets. One major open question in the field is the nature of tissue-derived signals that guide DC differentiation in tissue- and subset-specific manner. Notch is an evolutionarily conserved signaling pathway that specifies cell fates dictated by their microenvironment, e.g. T lymphocyte lineage commitment in the thymus. However, the role of Notch signaling in DC differentiation remained moot.

Previously, our lab has developed a system for *in vivo* gene targeting specifically in the DC lineage. Michele Caton, a former postdoc, and Kanako (Kana) Lewis, a graduate student in the Microbiology/Immunology program, have applied this system to the Notch signaling pathway. They discovered that Notch2, one of the four mammalian Notch receptors, is a key determinant of DC differentiation in the spleen. Moreover, Kana has defined a novel splenic DC subset that is entirely dependent on Notch2 signaling, and showed its unique role in the priming of helper T lymphocytes. These studies were greatly helped by Dr. Kang Liu, a faculty member in the department who is a top expert on DC development.



Model showing regulation of differentiation of dendritic cells in the spleen and intestine by Notch2

An intriguing extension of the work focused on the regulation of DC development in the intestine. The intestinal immune system, which has to effectively control billions of commensal microbes present in the intestine, harbors unique DC subsets such as the CD103+CD11b+ DCs. However, little was known about the development and *in vivo* function of this subset. In collaboration with Dr. Miriam Merad's lab at Mount Sinai School of Medicine, Kana showed that this DC subset is strictly Notch2-dependent, providing a unique opportunity to examine its function. Our next-door neighbor Dr. Ivo Ivanov, a leader in the study of the intestinal immune system, then found that these DCs facilitated the development of pro-inflammatory helper T lymphocytes in the gut. These findings highlight a "supersymmetry" of DC development in the lymphoid organs (spleen) and tissues (intestine), both of which contain a unique Notch-dependent DC subset required for helper T cell responses. Because Notch pathway inhibitors represent promising new drugs, these studies also provide therapeutic opportunities for the modulation of DC function.

Citation Lewis, K.L., Caton, M.L., Bogunovic, M., Greter, M., Grajkowska, L.T., Ng, D., Klinakis, A., Charo, I.F., Jung, S., Gommerman, J.L., Ivanov, I.I., Liu, K., Merad, M. and Reizis, B. (2011) Notch2 receptor signaling controls functional differentiation of dendritic cells in the spleen and intestine. ***Immunity*** 35: 780-791.

Pictured: Sankar Ghosh, Matthew Hayden, Ramkumar Mathur

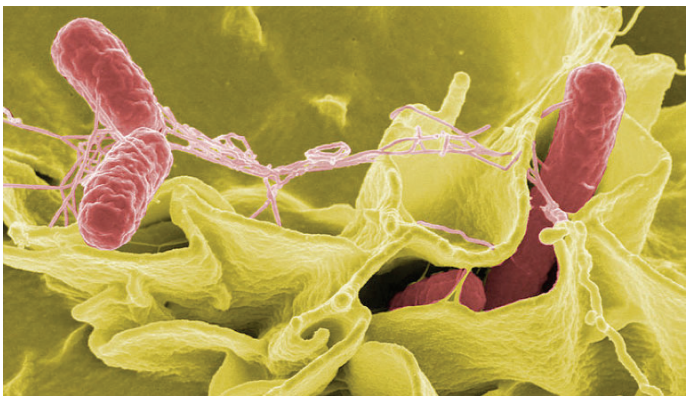
A Mouse Model for Typhoid

Evolution of the innate immune system determines host tropism

Sankar Ghosh, Professor of Microbiology & Immunology

Salmonella spp. are gram-negative flagellated bacteria that can cause food and water-borne gastroenteritis and typhoid fever in humans. Typhoid fever resulting from *S. typhi* infection affects 20 million people world-wide and is believed to be responsible for over 220,000 deaths annually. Bacteria of the gram-negative *Salmonella* sp. are widely used in laboratory studies aimed towards understanding the basis of mucosal immune responses, and diseases such as gastroenteritis and typhoid. Most laboratory studies are carried out using *S. typhimurium* in mice, where a disseminated infection with some similarities to human typhoid is observed. However typhoid disease in humans is caused by the specific *Salmonella enterica* serovars Typhi and, to a lesser extent Paratyphi which do not infect mice. There are marked genetic differences between *S. typhimurium* and *S. typhi,* which presumably account for the notable differences in the disease states caused by these organisms in people. As a result, animal models of *S. typhi* infection are of significant interest in efforts to understand the biology of this important pathogen. Furthermore, transmission of typhoidal serovars only occurs between infected humans, and hence establishment of hygienic conditions and pure drinking water is likely to have a major effect in curtailing transmission of the disease. However as typhoid is endemic in third-world countries, it is unlikely that adequate improvements in sanitation and water supply can be achieved in a timely fashion to have an impact on the disease. Clearly what is required is effective vaccination strategies, unfortunately the approved vaccines have only modest efficacy (50-80% protection). The development of better vaccination would require a more complete understanding of the immune response to bacteria as well as the availability of experimentally tractable small-animal models that can be infected by *S. typhi.*

Toll-like receptors (TLRs) have emerged as critical sensory mechanisms for recognizing and responding to infectious microbes. While most TLRs are shared between humans and other species such as mice, a subclass of them, namely TLR11, 12 and 13, are not expressed in humans. TLR11 is expressed in many species such as birds, dogs, cows but are absent in humans. Our previous studies have shown that TLR11 recognizes profilin, a protein ligand from the apicomplexan parasite *Toxoplasma gondii,* and plays a critical role in the mounting of innate immune responses to this organism. In addition we also showed that TLR11 specifically responds to uropathogenic *E. coli* (UPEC) strains



A scanning electron micrograph showing Salmonella *attaching to a macrophage cell surface*

that typically infect the urogenital tract causing urinary tract infections. The expression of TLR11 in epithelial cells, as well as macrophages and dendritic cells, likely explains its involvement in mediating responses to these different pathogens.

We have now discovered that flagellin from *Salmonella* spp. and UPECs is recognized in mouse intestine by the Toll-like receptor 11 (TLR11). Absence of TLR11 renders mice more susceptible to infection by *S. typhimurium,* with increased dissemination of the bacteria and to enhanced lethality. As TLR11 is expressed in mice but not humans, we hypothesized that the presence of TLR11 in mice provides species-specific protection against *S. typhi,* a human obligatory pathogen that causes typhoid fever, but is normally unable to infect mice. Remarkably, we found that tlr11-/- mice are efficiently infected with orally-administered *S. typhi* and the absence of TLR11 primarily impacts immunity against *S. typhi* at the intestinal epithelial surface. We have also found that tlr11-/- mice can be immunized against *S. typhi* and transfer of the serum from immunized animals to unimmunized animals leads to protective immunity. Therefore, tlr11-/- mice represent the first small animal model for the study of the immune response to *S. typhi,* and for the development of vaccines against this important human pathogen.

Citation Mathur, R., Oh, H., Zhang, D., Park S.-G., Seo, J., Koblansky, A., Hayden, M.S. and Ghosh, S. (2012) A mouse model of *Salmonella typhi* infection. ***Cell*** (in press)

IN & AROUND

The Goings-on in Hammer

Department News

Departmental Retreat

Keynote presented by Dr. Ian Lipkin

The 2011 Microbiology & Immunology annual retreat was held at the Basking Ridge Conference Center on September 8th to 9th. Dr. Ian Lipkin, Director of the Center for Infection and Immunity and the Northeast Biodefense Center, John Snow Professor of Epidemiology, and Professor of Neurology and Pathology at Columbia University presented the keynote lecture.

The 2012 M&I retreat will be held again at Basking Ridge on September 6th-7th.

Heidelberger-Kabat Lecture

Presented by Dr. Mark M. Davis

The 2012 Heidelberger-Kabat Lecture, "Mammalian Stress Sensors in Health and Disease" was presented on April 11, 2012 by Dr. Mark M. Davis, Investigator, Howard Hughes Medical Institute and Burt and Marion Avery Family Professor of Immunology, Stanford University. Dr. Davis is well-known for identifying the T-cell receptor genes. The lecture honors Dr. Michael Heidelberger and his student Dr. Elvin Kabat, a former member of the Department of Microbiology & Immunology.

Parker Lecture

Presented by Dr. C. David Allis

The 26th Richard C. Parker Memorial Lecture, "Beyond the Double Helix: Varying the 'Histone Code'" was delivered on February 22, 2012 by C. David Allis, Ph.D., Tri-Institutional Professor, Joy and Jack Fishman Professor and Head of the Laboratory of Chromatin Biology and Epigenetics, Rockefeller University. C. David Allis's research has elucidated the dynamic nature of chromatin through the post-translational modification of histone proteins.

In Memoriam

Drs. Erlanger and Pernis

The Department regrets to note the passing late last year of two dear colleagues and friends, Dr. Bernard F. Erlanger, Professor Emeritus of Microbiology & Immunology, and Dr. Benvenuto G. Pernis, Professor Emeritus of Microbiology & Immunology and Medicine. Dr. Erlanger joined the department in 1952 while Dr. Pernis joined in 1976. Both will be deeply missed.

Faculty Awards

Dr. Uttiya Basu

Dr. Uttiya Basu received the NIH Director's New Innovator Award. The NIH Director's New Innovator Award seeks to support exceptionally creative new investigators who propose highly innovative projects that have the potential for unusually high impact.

Dr. Vincent Racaniello

Dr. Vincent Racaniello, Higgins Professor of Microbiology & Immunology, received the Peter Wildy Prize for Microbiology Education, awarded annually by the Society for General Microbiology for outstanding contributions to microbiology education.

Dr. Jonathan Dworkin

Dr. Jonathan Dworkin, Associate Professor of Microbiology & Immunology, received the Burroughs-Welcome Scholar in Infectious Disease Award. The award is given to "accomplished investigators" researching areas of pathogenesis.

Faculty

David Fidock

Promoted to Full Professor

Dr. David Fidock was recently promoted to Professor of Microbiology & Immunology and Medicine. Dr. Fidock's work on malaria drug resistance, chemotherapy, pathogenesis, fatty acid metabolism, and cell development has been featured in numerous publications. Dr. Fidock received his Ph.D. from the Pasteur Institute of Paris before coming to the department in 2005 from Albert Einstein Medical College. He currently serves as the Director of Graduate Student Admissions for the department.

Steve Reiner

Immunologist Joins Department

Steven Reiner, M.D., renowned for his contributions to immunology, in particular the study of T cells, joined CUMC as Professor of Microbiology & Immunology and Pediatrics at the beginning of this year. Dr. Reiner came to Columbia from the University of Pennsylvania School of Medicine, where he spent six years, most recently as a Professor in the Department of Medicine. Dr. Reiner received his B.A. from Haverford College and his M.D. from Duke University School of Medicine.

Joint Appointments

Hans Snoeck, M.D., Ph.D.

Dr. Hans Snoeck is an Associate Professor of Medicine and Microbiology and Immunology. Dr. Snoeck obtained his M.D., Ph.D and training at the University of Antwerp before moving to Mount Sinai where he was faculty from 1998 to 2011.

Matthew Hayden, M.D., Ph.D.

Dr. Matthew Hayden is an Assistant Professor of Dermatology and Microbiology & Immunology. Dr. Hayden obtained his M.D., Ph.D. and training at Yale University before moving to Columbia University.

Sagi Shapira, Ph.D., MPH

Dr. Sagi Shapira is an Assistant Professor of Systems Biology and Microbiology and Immunology. Dr. Shapira received his Ph.D. at the University of Pennsylvania before moving to the Broad Institute for his postdoctoral research.

Students

Hammer 2.0

Renovations Breathe Life into HHSC

Hammer Health Science Building at Columbia University Medical Center is the home for the Microbiology & Immunology Department, which occupies over four floors (9th, 12th, 13th, 15th and a portion of 14th). The building houses one of the largest academic health sciences libraries in the country, which was recently renovated to include two new floors of space for student work, featuring new study rooms, lounges, meeting spaces, and café.

New Students

Five New Students Join Department

Yen-Hua Chen, National Taiwan University

Alexander Dahmani, University of Wisconsin-Madison

Joo Hyun Im, Grinnell College

Benjamin Sally, University of Chicago

Kyra Zens, University of California - Berkeley

Student Awards

Keim and Vitiello Win Parker Award

The recipients of the 2012 Richard C. Parker Graduate Student Award are Celia Keim and Christal Vitiello. Celia Keim's research has focused on understanding the mechanisms by which Activation induced Cytidine Deaminase (AID) functions in the generation of antibody diversity. Christal Vitiello's research has focused on understanding the mechanism of transcription elongation and arrest by investigating the Nun protein of the bacteriophage HK022.

Alumni Notes

Pamela Schwartzberg, M.D., Ph.D.

Dr. Pamela Schwartzberg, who completed her doctorate in the Goff lab and received the department's first Richard C. Parker Award, is now Acting Chief & Senior Investigator, Genetic Disease Research Branch and Head, Cell Signaling Section at NIH.

Erik Lium, Ph.D.

Dr. Erik Lium, who completed his doctoral work in the Silverstein lab, is the Assistant Vice Chancellor of Research at University of California San Francisco Medical Center. Dr. Lium is also leading UCSF's new Office of Innovation, Technology and Alliances

Alumni Advisory Board

The Alumni Advisory Board has begun to plan future alumni events. If you have any interest in getting involved in the Alumni Advisory Board or have suggestions for alumni events, please contact David Fox, J.D., Ph.D., at dlf84@columbia.edu.

Research Review

Antimalarial Drug Discovery

A review by David Fidock, touching upon recent developments in the field.

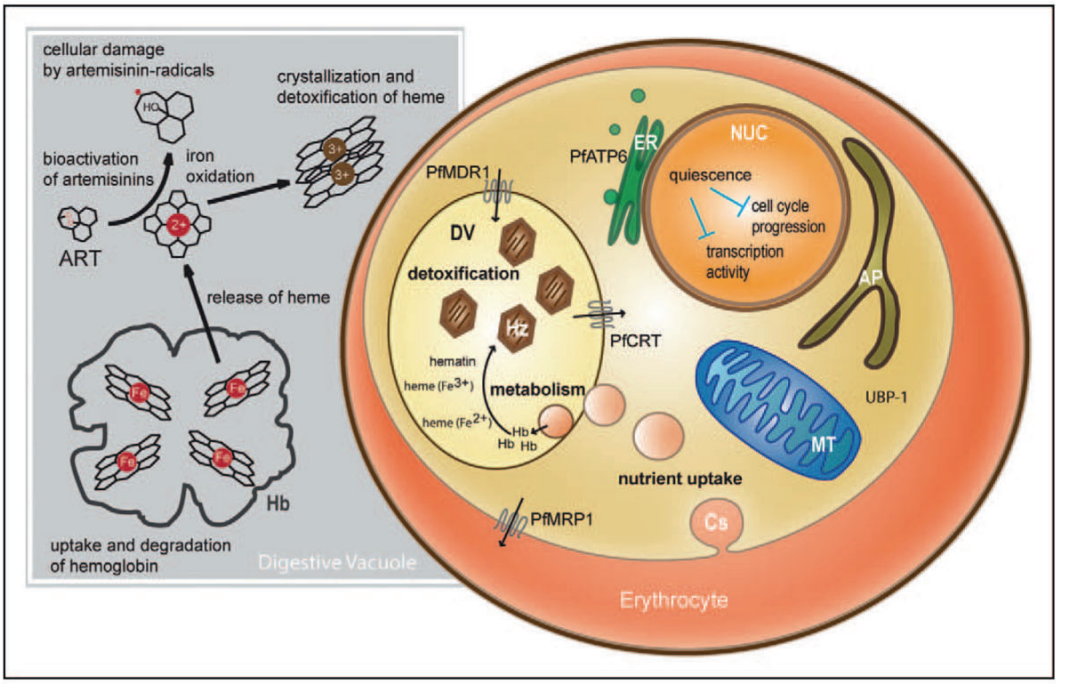
The human malarial pathogen *Plasmodium falciparum* is the most lethal infectious disease in children under the age of five, and the second leading cause of death from a single infectious agent in older children and adults. According to the most recent World Health Organization (WHO) Malaria Report, there were 216 million cases of malaria and 655,000 deaths from malaria in 2010. The vast majority of those deaths occur in African children. Since 2000, global efforts to control malaria have resulted in malaria mortality rates falling by 26% worldwide, and by 33% in Africa. These recent reductions in malaria mortality rates are very encouraging, but these gains are fragile. A major threat is emerging resistance to the antimalarial drug artemisinin and its derivatives, currently the most effective treatment for malaria.

P. falciparum is an ancient pathogen that has likely caused malarial infections for the entire history of the human species, but only began to have a major impact on human survival approximately 10,000 years ago, coinciding with wide-scale transition to agricultural societies and settlements. The first effective recorded treatment for malaria was described in 340 by the Chinese alchemist Hong Ge, who recommended treating malarial fever with the herb *Artemisia annua* in his manuscript *Zhou hou bei ji fang* ("Pocketbook of emergency prescriptions kept up one's sleeve".) The method Ge prescribed for preparing the herb produces extracts with remarkably high artemisinin concentrations and was instrumental in the development of the modern low-temperature ether extraction method developed by Youyou Tu in 1972, for which she received the 2011 Lasker Award. This work was part of a vast, secret Vietnam War era military project to develop antimalarial therapies, involving approximately 600 Chinese scientists in 50 institutes. They screened 200 herbs used to treat fever in a variety of traditional Chinese medicine preparations and identified 10 herbs with antimalarial activity, of which *Artemisia annua* was by far the most potent.

The antimalarial properties of artemisinins were unfamiliar outside of China and Southeast Asia until quite recently, and as a result, artemisinin and its derivatives were previously not widely used to treat malaria. Prior to 1972, herbal extracts or raw herbs containing artemisinin were used as treatment for malaria primarily in China, with varying efficacy, depending on the method of preparation. Between 1972 and 2006, artemisinins became more widely used to treat malaria in Vietnam and China, initially as monotherapy, then as in combination therapies to reduce recrudescence (the reappearance of asexual blood stage *P. falciparum* after treatment). In 2006, artemisinin-based combination therapies (ACT) began to be used globally.

Artemisinin-based combination therapies proved highly effective and have greatly contributed to the recent global decline in malaria mortality rates. Unfortunately, recent evidence for the emergence of *P. falciparum* parasite resistance to artemisinins suggests that in a few short years we may be faced with the loss of this vital drug. Despite significant effort, currently no other effective antimalarial agents or vaccines exist. To prevent a resurgence in malaria, research to better understand the mechanism of artemisinin's antimalarial activity and how tolerance to that activity is acquired is essential. There is ample his-

Figure 1 Depiction of an intra-erythrocytic *Plasmodium falciparum* parasite showing proteins and biological processes implicated in artemisinin action



Several parasite proteins have been implicated in decreased susceptibility to artemisinins (ARTs), including PfATP6 (proposed to be in the endoplasmic reticulum [41]), PfMDR1 on the digestive vacuole [42], PfMRP1 on the parasite plasma membrane [43], and UBP-1 whose ortholog in *Plasmodium chabaudi* is associated with ART resistance [44]. The digestive vacuole protein PfCRT is also indicated as mutations that confer chloroquine resistance have been shown to significantly increase susceptibility to ARTs [45]. Host hemoglobin is delivered via cytostomes to the digestive vacuole, wherein it is proteolytically degraded. This liberates iron-heme (Fe-protoporphyrin IX) moieties, with subsequent oxidation of iron. Iron-heme is detoxified via its incorporation into hemozoin crystals. Iron-heme is thought to activate ARTs via interaction with the endoperoxide bridge, with the resulting ART radicals causing cellular damage [46••]. Investigations of field isolates and drug-pressured laboratory lines have implicated quiescence or dormancy of early ring-stage parasites in resistance to ART action [47•–49•]. ART, artemisinin; AP, apicoplast; Cs, cytostome; DV, digestive vacuole; ER, endoplasmic reticulum; Hb, hemoglobin; Hz, hemozoin; MT, mitochondria; NUC, nucleus.

torical precedent for this. The massive use of chloroquine in the 20th century heralded substantial gains in the global fight against malaria, but these advances were later lost as chloroquine resistance arose and spread throughout malaria-endemic areas. Every useful antimalarial agent besides artemisinins has been rendered ineffective due to a gradual rise of resistant *P. falciparum,* and without intervention, artemisinins faces the same fate.

Artemisinins share a number of useful antimalarial properties, including the ability to very rapidly decrease numbers of asexual blood stage *P. falciparum* (killing parasites within minutes), activity against a broad range of developmental stages (including the immature ring-stage forms as well as the more mature trophozoite stages), and the ability to inhibit the development of immature sexual stage parasites (gametocytes). This gametocytocidal activity reduces the transmission of *P. falciparum* parasites to their *Anopheles* mosquito vector. These drugs have an excellent safety profile in human subjects. One limitation is their short-half life in plasma, typically on the order of one to three hours. Pharmacologically amenable derivates of artemisinin are now commonly used, including artesunate, artemether (ATM), and dihydroartemisinin (DHA). Artemisinin monotherapy must be administered for a week to be curative, and recrudescence is common, therefore combination therapies with longer lasting partner drugs have become the treatment of choice. The most widely used partner drug in ACT is lumefantrine (paired with ATM), other commonly used partner drugs include amodiaquine, mefloquine and sulfadoxine-pyrimethamine (all paired with artesunate), and piperaquine (paired with DHA). These combination therapies are typically curative with three day treatments, substantially reduce recrudescence, and hinder the emergence of resistance to the paired artemisinin derivative.

The mechanism by which these drugs kill *P. falciparum* is still not well understood. Artemisinin contains an unusual peroxide bridge that is believed to play a critical role in disturbing redox homeostasis in the parasite. The exact target of artemisinins, however, remains unclear, and their activity may well involve

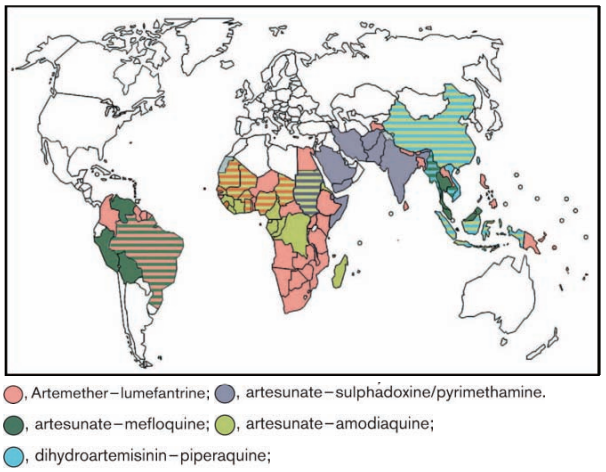
multiple targets. Developing a better understanding of the exact mechanism of action is essential to understanding the genetic and molecular basis of decreased parasite susceptibility to artemisinins.

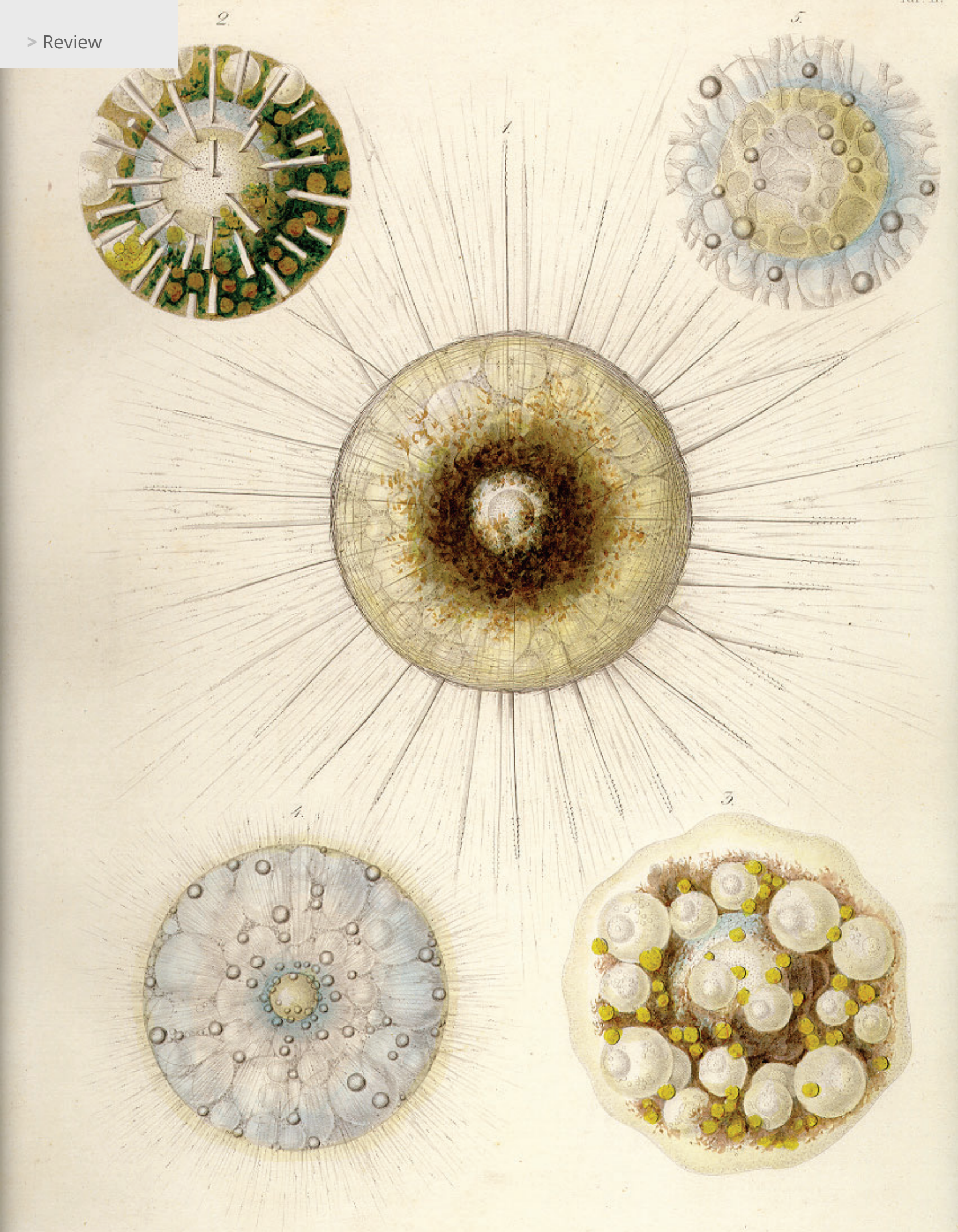
The first signs of developing resistance to ACTs were observational studies of artesunate-mefloquine treatment failures near the border of Thailand and Cambodia in the early 2000s. A subsequent report from western Cambodia by Noedl et al. in 2008 identified two patients with clear evidence of artesunate-resistant infections. These patients had prolonged parasite clearance times despite having adequate drug levels. *Ex vivo* drug dose-response measurements showed that these patients also had DHA half maximal inhibitory concentration (IC50) values four times higher than cured patients. A study by Dondorp et al. in 2009 showed delayed parasite clearance rates in the Pailin province of western Cambodia (near the border with Thailand), compared with the distant Wang Pha district of northwestern Thailand following artesunate monotherapy or artesunate-mefloquine combination therapy. A number of factors may have played a role in this localized emergence of resistance to artemisinins, including 30 years of previous monotherapy (now officially banned), substandard drugs, improper use of drugs, parasite genetic backgrounds that favor the emergence of multi-drug resistance and low rates of transmission resulting in insufficient immunity to eliminate resistant parasites.

Because ACTs are currently our most effective treatment for malaria, the rise and spread of artemisinin resistance poses a major threat to global efforts to control malaria. Developing a better understanding of the biological basis of artemisinin resistance is key to defining molecular markers to monitor its spread, learning to use partner drugs more effectively to hinder the rise of resistance, and discovering therapeutic strategies that effectively treat drug-resistant strains. The historical parallels are striking. The most effective treatment for malaria prior to artemisinins was chloroquine. Chloroquine began to be used for the prophylactic treatment of malaria in 1947, resistant parasites began to appear in the 1950s, and the effectiveness of chloroquine has greatly declined, with resistant strains of P. falciparum now common in Africa, Asia and South America. In 2000, the basis of resistance to chloroquine was identified by Fidock et al. as mutations in *pfcrt,* a previously unrecognized gene encoding the putative chloroquine transporter in the food vacuole. Subsequent analysis of *pfcrt* alleles by Wootton, et al. in 2002 showed that chloroquine mutations from African isolates actually originated in Southeast Asia and spread to Africa.

To prevent a similar spread of artemisinin-resistant parasites from occurring, a global plan for artemisinin resistance containment is underway, led by the WHO Global Malaria Programme and the Roll Back Malaria Partnership. The need to effectively diagnose, confirm, characterize, and contain resistance to artemisinins is clear, as a resurgence of malaria would be devastating to endemic countries. One goal of the research conducted in the Fidock lab in the Department of Microbiology & Immunology at Columbia University is to develop a better understanding of the genetic and molecular basis of drug resistance in *P. falciparum,* including emerging resistance to artemisinins. These efforts are coupled with a focus on drug discovery and elucidation of antimalarial modes of action, conducted in coordination with Medicines for Malaria Venture, the Bill & Melinda Gates Foundation, and academic and industrial partners. By applying molecular genetic techniques to these problems, the goal of the Fidock lab is to contribute scientifically to the global effort to reduce the burden of disease and drive towards its ultimate elimination.

Figure 2 Current global distribution of artemisin-based combination therapies as the first-line treatment of uncomplicated falciparum malaria

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Historical Highlight
In the Beginning, There Were Microbes

The foundation and early history of the department of Microbiology & Immunology

The Department of Microbiology & Immunology currently occupies 36,000 square feet on four floors of the Hammer Health Sciences Center at Columbia University Medical Center, with faculty occupying additional space in the Russ Berrie Medical Science Pavilion, Black Building and Irving Comprehensive Research Center. Yet, the historical origins of the department can be traced to a corner of a single, poorly lit pathology laboratory, located between a harness shop and an ice cream parlor.

In 1876, the Association of Alumni of the College of Physicians and Surgeons proposed funding an Alumni Laboratory in which original research related to pathology could be performed. The Laboratory of the Alumni Association was established in 1878 on the ground floor of a College owned building at 23rd Street and Fourth Avenue. Francis Delafield, a pathologist, was appointed the director. As Director of the Alumni Laboratory, Delafield drew no salary, and actually contributed over $2,000, a significant sum in those days, towards the running of the laboratory. The Alumni Association paid for all the equipment and expenses, and in addition had to pay the Faculty of Medicine an additional $750 a year in rent ($15,000 annually, adjusted for inflation).

Shortly after the founding of the Alumni Laboratory, Delafield hired Theophil Mitchell Prudden, a young doctor from Yale, as an Assistant in Pathology. Prudden had a strong interest in not only pathology, but in establishing a scientific understanding of disease, which would have a critical impact on the research of the Alumni Laboratory. In 1882, Delafield was appointed a Professor in Pathology, and Prudden replaced him as Director of the Alumni Laboratory. The timing was fortuitous. Prudden's interests in developing a scientific understanding of disease coincided with a rising interest in bacteriology and awareness of the germ theory of disease among not only scientists, but the general public, based on Robert Koch's pioneering research in Germany. In 1873, the mathematician and chemist Frederick A.P. Barnard, President of Columbia College, lectured at the American Public Health Association on "The Germ Theory of Disease and Its Significance to Hygiene". A number of such lectures led to an increased awareness of bacteriology among the general public, inspiring Mark Twain to begin writing a story in 1897 called "The General and the Cholera Microbes," in which he wrote: "The globe is a living creature, and the little stinking human race and the other animals are the vermin that infest it – the microbes."

Under Prudden's leadership, research in the Alumni Laboratory began to focus on bacteriology, and in 1883, he published the College's first original research in the field, a Medical Record paper titled "Occurrence of the Bacillius Tuberculosis in Tuberculous Lesions". Delafield and Prudden worked to establish a standard curriculum of pathology electives, initially meant for medical graduates, but soon became recommended for undergraduates. One of the major limitations facing the Alumni Laboratory and the bacteriological research done there was the awkward set-

ting of the laboratory, memorably described by Prudden as:

It was a narrow store on the ground floor, on Fourth Avenue, with a scanty strip of sky just visible through an iron grating, and with scarcely a feature adapting it to the needs of a microscopic laboratory, save that its walls kept out the wind and rain. An ice-cream store on one side and a harness shop on the other; the clatter of wagons and horse-cars and pedestrians sweeping endlessly along the street in front; the small boy peering curiously between the iron bars of the windows at the strange performances within, linked science to the busy world in a fashion truly cosmopolitan. The great brewery wagons rumbling heavily along the pavement set every microscope a-tremble; and the frequency with which microscopic observation must for this reason be suspended, while a severe strain upon the temper of the devotee to science, often left him free to muse upon the important role which beer plays in modern metropolitan life.

Just then the significant announcement of the importance of bacteria in the causation of infectious disease began to stir the medical world; and a small corner of the dark and crowded room was partitioned off with second-hand glass sashes – the wreckage of a livery stable – and devoted to bacteriology. So small was this apartment that the worker standing at his table with its twilight illumination could touch the walls in all directions, while at frequent intervals he must beat a hasty retreat for a breath of fresh air, lest he risk the ministrations of the coroner.

– T. Mitchell Prudden, ''Pathology and the Department of Pathology'' Columbia University Bulletin, March 1898.

In 1886, in part thanks to contributions by the Vanderbilt family, the College of Physicians and Surgeons moved to 59th Street and Tenth Avenue. The Alumni Laboratory moved with the College, into far more spacious quarters, with laboratories dedicated to instruction and a large general laboratory dedicated to bacteriology. In 1892, the College of Physicians and Surgeons formally merged with Columbia University, and the Alumni Laboratory became part of the Department of Pathology. A Faculty of Pure Science was also established, and Prudden was appointed a Professor of Pathology. In 1894, the Alumni Laboratory electives developed by Delafield and Prudden became required for obtaining a medical degree. The Department of Pathology rapidly expanded, eventually occupying 21,000 square feet on two floors.

Research in bacteriology continued to be heavily emphasized, and the department established a doctoral program to recommend students for the degree of Doctor of Philosophy in the Faculty of Pure Science. The first of these doctorates was awarded was to Harrison G. Dyar in 1895, for his dissertation on airborne bacteria in New York City. The subsequent doctorates awarded to members of the department continued to focus heavily on bacteriology and sanitary issues. Most of the research published by the department focused on bacteriology, including work on diphtheria, gonococcus, tuberculosis, and the sterilization of milk and water supplies. Over the next decade, the department actively recruited faculty interested in bacteriology, including Philip Hiss, who studied enteric bacteria, A.B. Wadsworth, who studied penumococcus and Hans Zinnser, who studied anerobic bacteria. The new faculty often collaborated, with Hiss and Wadsworth developing tests to differentiate streptococcus and pneumococcus, and Hiss and Zinsser studying the therapeutic properties of leucocytic extracts and cowriting "The Textbook of Bacteriology", which became the standard in the field.

In 1907, the Department of Pathology formally recognized the focus on research in bacteriology within the department that had begun in the Alumni Laboratory, and the department split into the Department of Pathology and the Department of Bacteriology & Hygiene. The new Chair of Bacteriology & Hygiene was Philip Hiss, at the time a Professor of Pathology. The Department of Bacteriology & Hygiene continued teaching medical and graduate students and performing research in bacteriology, but under the auspices of Hiss and Zinsser, research in immunology began to flourish. Zinsser moved to Stanford University in 1910 and become the Chair of Bacteriology there, where he began to work on his textbook "Infection and Resistance" (later "Immunity"), which became the standard textbook of immunology. In 1912, the department was renamed the Department of Bacteriology, and in 1913, after the death of Philip Hiss, Hans Zinsser returned as Chair of the Department of Bacteriology.

The department has seen many changes since, including a move in 1928 to new quarters at the medical center at 168th Street and Fort Washington Avenue, a change in name and focus to the Department of Microbiology in 1952 under Chair Harry M. Rose, and most recently, becoming the Department of Microbiology & Immunology in 2009 under Chair Sankar Ghosh. Our beginnings were indisputably humble, so we hope our future will prove correspondingly prosperous.

THE DEPARTMENT

Lab Notes/Publications

Lab Notes

Basu Lab

Uttiya Basu's laboratory is interested in the developmental fate regulation of B-lymphocytes, a vital component of the adaptive immune system. Recent research from his laboratory has identified a key regulatory complex known as "RNA exosome" that promotes genomic alterations in the immunoglobulin loci such that high affinity antibodies can be generated via processes like class switch recombination and somatic hypermutation. The RNA exosome is an eleven-subunit non-coding RNA degradation/processing complex whose role in various cellular function constitutes current topic of investigation. Ongoing research in the Basu laboratory is focused on probing the RNA exosome-dependent co-transcriptional regulation of non-coding RNA biogenesis in the immunoglobulin loci. Potentially, these findings will provide significant insight into the mechanism of B cell development during adaptive immunity and initiation of oncogenesis.

Chang Lab

Fred Chang's laboratory studies fundamental mechanisms underlying cell morphogenesis. Research topics include cytokinesis, cell polarity, nuclear positioning and the regulation of actin and microtubules. The lab uses the rod-shaped fission yeast *Schizosaccharomyces pombe* as a model cell, although recent work has also taken them into animal cell models. One of the questions that the lab has been trying to answer is how the site of division is positioned during cytokinesis. In fission yeast, the division site is determined by the position of the nucleus, through a process involving the peripheral membrane protein mid1p. The lab is studying how mid1p is localized to a series of dots on the cortex near the nucleus, which then recruit other cytokinesis factors to assemble the contractile ring, a complex process that involves multiple inputs, including nuclear shuttling, the endoplasmic reticulum, and a cortical gradient of a protein kinase pom1p emanating from the cell tips. This system represents one of the best-understood examples of division site placement in any organism.

Dworkin Lab

Jonathan Dworkin's laboratory studies the synthesis and modification of peptidoglycan of the bacterial cell wall, and how peptidoglycan derived muropeptides serve as an inter-bacterial signal. In the last year, the lab has focused on trying to understand how these bacterial molecules are recognized by vertebrates, and has found a previously uncharacterized protein, LysMD3, that is present on the surface of human cells and serves as a peptidoglycan receptor. They recently showed that LysMD3 is involved in activation of NF-κB, a key innate immune transcription factor, as well as cyotokine production in response to bacteria and peptidoglycan. The lab identified the domain of LysMD3 responsible for binding peptidoglycan and interestingly, found related domains in other bacterial, yeast and plant proteins. LysMD3 homologs are also found in flies and nematodes, suggesting that this mechanism of bacterial recognition may be widespread. They are currently trying to understand how this receptor functions in greater detail, including studying the signal transduction cascade that it stimulates.

Fidock Lab

David Fidock's laboratory studies the malarial parasite *Plasmodium,* with a central focus on what parasite factors determine treatment outcome. They are particularly interested in the genetic basis of antimalarial drug resistance, and use molecular techniques to genetically modify known or candidate determinants of resistance (including *pfcrt* and *pfmdr1*) and study their impact on drug potency, uptake, fitness and transmission. While most studies focus on the human parasite *Plasmodium falciparum,* the Fidock lab also uses the rodent model *P. berghei* to study pharmacological properties of antimalarial drugs when used to treat drug-resistant strains of malaria. They work with several teams to identify novel antimalarial agents and study their mode of action and mechanisms of resistance, using *in vitro* resistance selection and genome-wide methods of analysis of mutant lines. Another research area of interest is lipid and fatty acid metabolism and the pathways that are essential as the parasite progresses through its life cycle that alternates between the vertebrate and mosquito host. Finally, the Fidock lab investigates mechanisms of cytokinesis and protein trafficking in blood stage forms of *P. falciparum.* This past year, one major discovery of the laboratory was that methylene blue is highly effective at blocking transmission of *P. falciparum.* The laboratory also recently identified a highly mutated allele of *pfcrt* from Cambodia that manifests high-level multi-drug resistance and that displays greater fitness *in vitro* than the wild-type allele in drug-sensitive parasites.

Figurski Lab

David Figurski's laboratory studies the 14-gene *tad* locus for tenacious adherence of the oral pathogen *Aggregatibacter actinomycetemcomitans.* They discovered this locus, which encodes a secretion apparatus for adherent pili. Recent studies have concerned the pilin gene (*flp-1*) and a unique gene (*tadZ*). Though evolutionarily related to other Type IV pilins, the Tad pilin (Flp1) is much smaller. To begin to understand the unprecedented adherence of *A. actinomycetemcomitans,* the pilin gene was recently mutated by

them. All non-alanine amino acids of mature Flp1 were converted to alanine by mutating cloned *flp-1*. Four distinct classes of mutants were identified. The Figurski lab believes that these mutants will aid in understanding how Flp1 assembles into pili and mediates extremely strong adherence to surfaces. Their research has also shown that *tadZ* genes (which have been found in about 40% of sequenced bacterial genomes) form a family that belongs to the *parA/minD* superfamily of genes. The TadZ protein of *A. actinomycetemcomitans* fused to enhanced green fluorescent protein forms a polar focus in the cell without any other tad protein. The essential TadA ATPase also localizes to a pole, but its localization depends on the presence of TadZ. These results suggest that TadZ mediates polar localization of the Tad secretion apparatus.

Ghosh Lab

Sankar Ghosh's laboratory is striving to understand how the transcription factor NF-κB shapes various aspects of the immune response. Last year the Ghosh lab demonstrated that one component of the NF-κB signaling pathway, IκB-β, plays a surprisingly crucial role in the expression of the pro-inflammatory cytokine TNF. This insight into how NF-κB regulates TNF is likely to be important for understanding the etiology of chronic inflammatory and autoimmune diseases and suggests novel approaches for therapeutic targeting of inflammation. In other work, the Ghosh Lab identified γδ T cells as a new target of regulatory T cells and elucidated the mechanism whereby regulatory T cells suppress γδ T cell activation. They went on to show that in the absence of functional regulatory T cells, γδ T cells become hyperactivated, causing the development of colitis. Current efforts in the Ghosh lab seek to more fully characterize the role of NF-κB in regulatory T cells. Current work in the Ghosh lab seeks to further understand the contribution of mitochondria to bacterial clearance and inflammation. Other ongoing projects are focused on the role of non-coding RNAs in inflammation and immunity, the intersection of Ras-like and NF-κB signaling pathways in inflammation and cancer, the role of NF-κB in the skin, and the function of novel Toll like receptors in the recognition of both prokaryotic and eukaryotic pathogens.

Goff Lab

Stephen Goff's laboratory studies retrovirus replication and the host restriction systems that inhibit virus replication. The lab has identified and characterized a novel host protein, termed ZAP for zinc finger antiviral protein, that blocks gene expression of many viruses, including the murine leukemia viruses, Ebola, Sindbis, and HIV-1, by degrading viral mRNAs. The lab has also characterized a protein complex responsible for the silencing of retroviral DNAs in embryonic stem (ES) cells, and identified a zinc finger protein, ZFP809, as an ES-cell specific recognition molecule that binds the proviral DNA and brings TRIM28 to locally modify chromatin. In the last year, the lab has isolated proteins associated with HIV-1 mRNAs and identified Upf1, a component of the nonsense-mediated decay machinery. Upf1 binds to the 3'UTR of mRNA to measure 3'UTR length and trigger mRNA decay. Finally, the lab has studied the TRIM5a-mediated restriction of retroviruses, showing that the SUMO-Interacting Motifs (SIMs) in TRIM5a, and likely SUMO conjugation of the viral capsid, are important for this restriction.

Gottesman Lab

Max Gottesman's laboratory investigates the mechanism of transcription termination in *E. coli* and how termination affects other cellular processes. Blocking the release of elongating RNA polymerase leads to clashes with the replisome and the formation of DNA double-strand breaks. Transcription termination is linked to translation. NusG protein forms a molecular bridge that couples RNA polymerase and the first translating ribosome. *nusG* mutants that fail to form this bridge are exquisitely sensitive to the protein synthesis inhibitor, chloramphenicol; slowing translation probably leads to failure to terminate transcription and replisome clashes. The interactions among ribosomes, RNA polymerase and DNA polymerase are being investigated by the lab using genetic and biochemical approaches. In addition, the laboratory has recently begun work on a cryoEM structure of the ribosome-NusG-RNA polymerase complex.

Ivanov Lab

Ivaylo Ivanov's laboratory studies the mechanisms by which different resident gut bacteria (a.k.a. commensal bacteria) affect the mucosal and systemic immune systems. The lab has focused on investigating the action of one particular commensal – segmented filamentous bacteria (SFB). SFB are unique in that they are one of the very few commensals that penetrate the mucus layer and attach themselves to epithelial cells. SFB were described more than 100 years ago, but are currently unculturable *ex vivo*. During his postdoctoral work Dr. Ivanov found that SFB specifically induce Th17 cells in the gut, which are involved in mucosal immune responses. In an effort to examine the mechanisms by which the bacteria modulate the immune system, the lab has recently sequenced the SFB genome. They are currently trying to utilize the data from the genome to design strategies for culturing the bacteria and to assess the role of specific bacterial products in immunity.

Klein Lab

Ulf Klein's laboratory focuses on elucidating the molecular mechanisms that govern the differentiation of B lymphocytes into memory B cells and plasma cells, and on trying to understand how these mechanisms are disrupted in B-cell lymphomas. Recently, it has emerged that lymphomas frequently harbor genetic mutations that lead to the constitutive activation of the nuclear factor-κB (NF-κB) transcription factor complex, thereby promoting oncogenesis. Despite extensive knowledge about the biology of NF-κB, surprisingly little is known on the function of NF-κB in the precursor cells of these tumors. NF-κB signaling can occur via two different routes, mediated by specific NF-κB subunits. In the last year, the lab has characterized the expression pattern of the five NF-κB transcription factor subunits in the various B-cell subsets. Interestingly, they obtained evidence suggesting a differential activation of the separate NF-κB pathways in memory B-cell versus plasma cell precursors. The lab is now studying the *in vivo* function of the separate NF-κB pathways in the differentiation of memory and plasma cell precursors using conditional knockout systems. They are also undertaking a genome-wide identification of NF-κB pathway-specific targets. The results are expected to provide new insights into the role of NF-κB in normal B-cell differentiation and in lymphomagenesis.

Liu Lab

Kang Liu's laboratory studies the development and function of dendritic cells (DCs) and monocytes. They recently identified a population of DCs in the steady state mouse brain located along the "gates" of T cell entry into the central nervous system (CNS). They demonstrated that developmentally and functionally, these brain DCs are related to spleen DCs and distinct from microglia. They are currently investigating how CNS infection alters brain DC development and function in shaping CNS T cell immunity. The laboratory also continues to do research using a humanized mouse model to study molecular mechanisms controlling human DC and monocyte development.

Racaniello Lab

Vincent Racaniello's laboratory studies picornaviruses, the RNA-containing viruses that cause a variety of human diseases including paralysis (e.g. poliomyelitis), myocarditis, conjunctivitis, and the common cold. Their research focuses on the interaction of viruses with the innate immune system, viral pathogenesis, and viral discovery in wild animals. Innate responses to viral infection are triggered when cellular pattern recognition receptors engage viral macromolecules. The ensuing signal transduction cascade leads to induction of IFN and other cytokines and establishment of an antiviral state. Research in this lab has revealed that RIG-I, MDA-5, and IPS-1 are degraded in cells infected with picornaviruses. Experiments are ongoing to determine whether cleavage of these sensor molecules benefits viral replication. The poliovirus proteinase $2A^{pro}$ renders this virus relatively resistant to the antiviral effects of IFN. Experiments are currently in progress to identify which IFN-induced proteins that are the targets of $2A^{pro}$. Insertion of the gene encoding poliovirus $2A^{pro}$ into the genome of the IFN-sensitive picornavirus, encephalomyocarditis virus (EMCV), renders that virus resistant to IFN. Passage of the recombinant EMCV in the presence of IFN has permitted the isolation of viruses that are even more resistant to the antiviral effect of IFN. Identification of the amino acid changes that lead to this phenotype will permit a better understanding of how IFN-stimulated gene products block viral replication, and how viruses evade this innate immune response.

Reiner Lab

Steven Reiner's laboratory studies developmental biology and regeneration during the mammalian immune response. Upon engagement in an immune response, a naive T lymphocyte undergoes a program of rapid proliferation and many of its cellular progeny undergo terminal effector differentiation. After an immune response has ended, some antigen-specific daughter cells remain as long-lived replicas of the useful clone, so-called memory cells, which form the basis for successful vaccination. Using lymphocytes as a model system, they have provided evidence that asymmetric cell division may be a way for many mobile, non-polarized cells to generate cell fate diversity among their progeny. They are using static and time-lapsed imaging, genetic, and biochemical methods to better understand the nature and extent of asymmetric cell division in multicelled beings. It is predicted that this will have immediate relevance for the way in which blood stem cells and metastatic cancer stem cells can generate diverse progeny despite their lack of obvious polarity. Studies of lymphocyte differentiation during the immune response should continue to become an increasingly useful model for inquiry into the fundamental problem of regulated gene expression in dividing, differentiating, and highly mobile cells.

Reizis Lab

Boris Reizis' laboratory studies the molecular control of immune system development and stem cell function. Of particular interest are dendritic cells, which represent the key sentinel cells that orchestrate immune responses against pathogens. In the last year, the lab has characterized the transcriptional regulation of plasmacytoid den-

dritic cells (pDCs), which provide the first line of defense against viral infections. The results have identified transcription factor E2-2 as a key molecular switch that specifies and maintains the pDC cell fate, preventing spontaneous differentiation into the "default" classical dendritic cell fate. In ongoing studies, conditional gene targeting of E2-2 has been used to generate mice that constitutively lack pDCs in the steady state. These mice cannot efficiently control chronic viral infections, revealing a novel role of pDCs that is relevant to such human infections as human immunodeficiency virus and hepatitis C virus.

Schindler Lab

Christian Schindler's laboratory studies how cytokines, like interferons (IFNs), mediate their potent immunomodulatory effects on target tissues. Macrophages and some dendritic cells (DCs) are an important source and target of IFNs, which the lab had previously demonstrated to transduce signals through the JAK-STAT pathway. Macrophages are widely distributed throughout the body, where they appear to regulate tissue homeostasis in addition to functioning as immune sentinels. Known for their antiviral activity, IFNs have more recently been shown to regulate the innate response towards a number of bacterial pathogens, including Streptococci, *Staphylococcus aureus* and *Legionella pneumophila.* Yet, the mechanism by which these bacteria induce macrophage IFN expression has not been fully elucidated. Intriguingly, studies exploring *Legionella pneumophila* infection have identified the bacterial regulator 3',5'-cyclic diguanylate (c-diGMP) as an important trigger of IFN expression. The Schindler laboratory is currently exploiting biochemical and genetic approaches to characterize the mechanism by which macrophages sense and respond to c-diGMP.

Sykes Lab

Megan Sykes' research is in the areas of hematopoietic cell transplantation, achievement of graft-versus-leukemia effects without GVHD, organ allograft tolerance induction and xenotransplantation. Her research program aims to utilize hematopoietic cell transplantation as immunotherapy to achieve graft-versus-tumor effects while avoiding the common complication of such transplants, graft-versus-host disease. Work in this area is currently focused on understanding the iNKT cell-dependent pathway by which intentional rejection of an established hematopoietic allograft promotes the development of anti-tumor immunity. Another aim has been to utilize hematopoietic stem cell transplantation for the induction of transplantation tolerance, both to organs from the same species (allografts) and from other species (xenografts). Approaches in the lab to achieving allograft tolerance have been applied in the first successful human studies of allograft tolerance induction and the lab is performing *in vitro* analyses to understand the mechanisms of allogeneic tolerance in these patients. The lab's work has also extended into the area of xenogeneic thymic transplantation as an approach to tolerance induction. In this area, the lab is currently focused on understanding and overcoming the immunoregulatory consequences of differentiation of human T cells in a porcine thymic xenograft. The lab has investigated the mechanisms by which non-myeloablative induction of mixed chimerism reverses the autoimmunity of Type 1 diabetes (T1D) and has recently developed a way of generating robust human immune systems in mice using adult volunteer bone marrow donors. This model is being used to dissect the genetically-determined, HSC-intrinsic immunoregulatory abnormalities that predispose to T1D.

Symington Lab

Lorraine Symington's laboratory studies the mechanisms for repair of DNA double-strand breaks and genome integrity in the model eukaryote, *Saccharomyces cerevisiae* (budding yeast). The focus of the lab is identifying the proteins that act in homology-dependent double-strand break (DSB) repair, and understanding how cells decide between homology-dependent repair and direct ligation of DNA ends. In the last year, they solved the longstanding question of how mitotic crossovers are formed by showing a complete defect in this process in the absence of two partially redundant nucleases, Mus81 and Yen1. Furthermore, they identified gross genomic instability in the absence of these two nucleases. The other major accomplishment was showing that Ku, a DNA end-binding protein that is essential for direct ligation of DNA ends, interferes with homology dependent repair by blocking access to the Exo1 nuclease. They identified an essential role for Sae2 (homolog of the BRCA1 interacting protein CtIP) in counteracting the negative effect of Ku on homologous recombination.

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Events & Seminars

Things are always going on at the Department of Microbiology & Immunology—from "Research in Progress" seminars to weekly happy hours to guest lectures. This Fall, we're particularly excited about the group of speakers that are coming to the department, along with our annual retreat at the Basking Ridge Conference Center in Basking Ridge, NJ. A full list of all events can be found on our website, www.microbiology.columbia.edu

Sep. 19	**John Boothroyd** *Rose Lecture*
Sep. 26	**Richard Ebright**
Oct. 3	**Bonnie Bassler**
Oct. 10	**Saeed Tavazoie**
Oct. 17	**Kevin Tracey**
Oct. 24	**Harmit Malik**
Oct. 31	**Beatrice Hahn**
Nov. 7	**Sue Jinks-Robertson**
Nov. 14	**Ioannis Aifantis**
Nov. 28	**Margaret McFall-Ngai**
Dec. 5	**Christine Biron**

M&I Summer 2012 Newsletter

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