

A detailed scanning electron micrograph (SEM) of a plant cross-section. The central part of the image shows a dense cluster of green, rounded cells, likely mesophyll cells, which are arranged in a somewhat regular pattern. Surrounding this central cluster is a thick, orange-brown layer of fibrous material, possibly sclerenchyma or lignified cell walls, which provides structural support. The overall appearance is that of a cross-section of a stem or root, showing the internal cellular structure and the surrounding protective layers.

# M & I

2014

# **M&I** is the annual newsletter of the Department of Microbiology & Immunology at Columbia University

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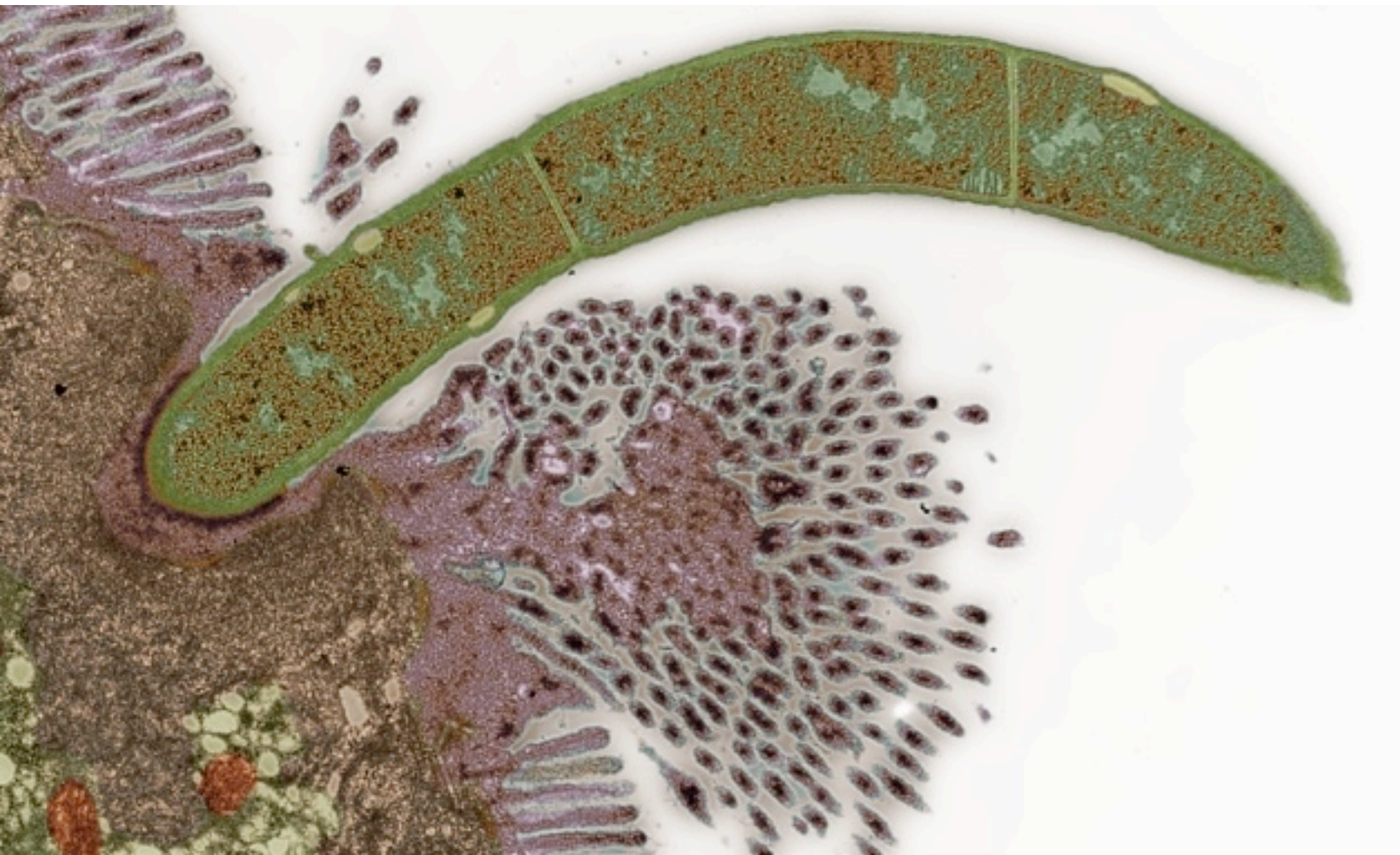
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*M&I highlights exciting new research discoveries, exceptional faculty achievements, and department-wide initiatives, providing a comprehensive summary of the goings-on in the department, which bridges modern molecular biology with research on infectious disease and immunology. Digital versions and back issues are available at: [www.microbiology.columbia.edu](http://www.microbiology.columbia.edu)*

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# Message from the Chair

**I AM PLEASED** to present the 2014 issue of M&I, the Department of Microbiology & Immunology's annual newsletter.

In this issue, we have once again highlighted the science being carried out in the department, as well as different departmental activities and departmental news. We have profiled exciting, recently published research from the laboratories of two of our junior faculty members, Uttiya Basu and Ivaylo Ivanov. We have also highlighted the study of the human microbiome, an emerging area of great interest that we would like to become more prominent at Columbia in the future. Also continuing our tradition of articles that highlight our history, we feature a biographical piece on Harry M. Rose, a prominent virologist who served as chairman of the department from 1952 to 1973. We hope that as we compile these articles we will have created a record of our past for the future.

The past year saw the departure of Ms. Edith Shumansky, our long-serving departmental administrator, who retired after 26 years of dedicated service. We wish her all the best in her retirement. Edie's departure also coincided with a turnover of our office personnel, and we are using this opportunity to reorganize our business office with new staff.

Jessica Sama, the departmental administrator of the Department of Genetics & Development, has been helping us during the transition and is serving as interim DA. James Lapin is our new Deputy DA, while Andrew Wong is our new HR/Pre-award coordinator. They will join Carol Duigou who will continue as our Financial/Accounting officer. Unfortunately we lost Sujatha Gurunathan, who took a new position at NYU. Sujatha was serving as a scientific writer for the department who worked on multiple projects (including writing many of the articles in this newsletter) and we are currently looking for her replacement.

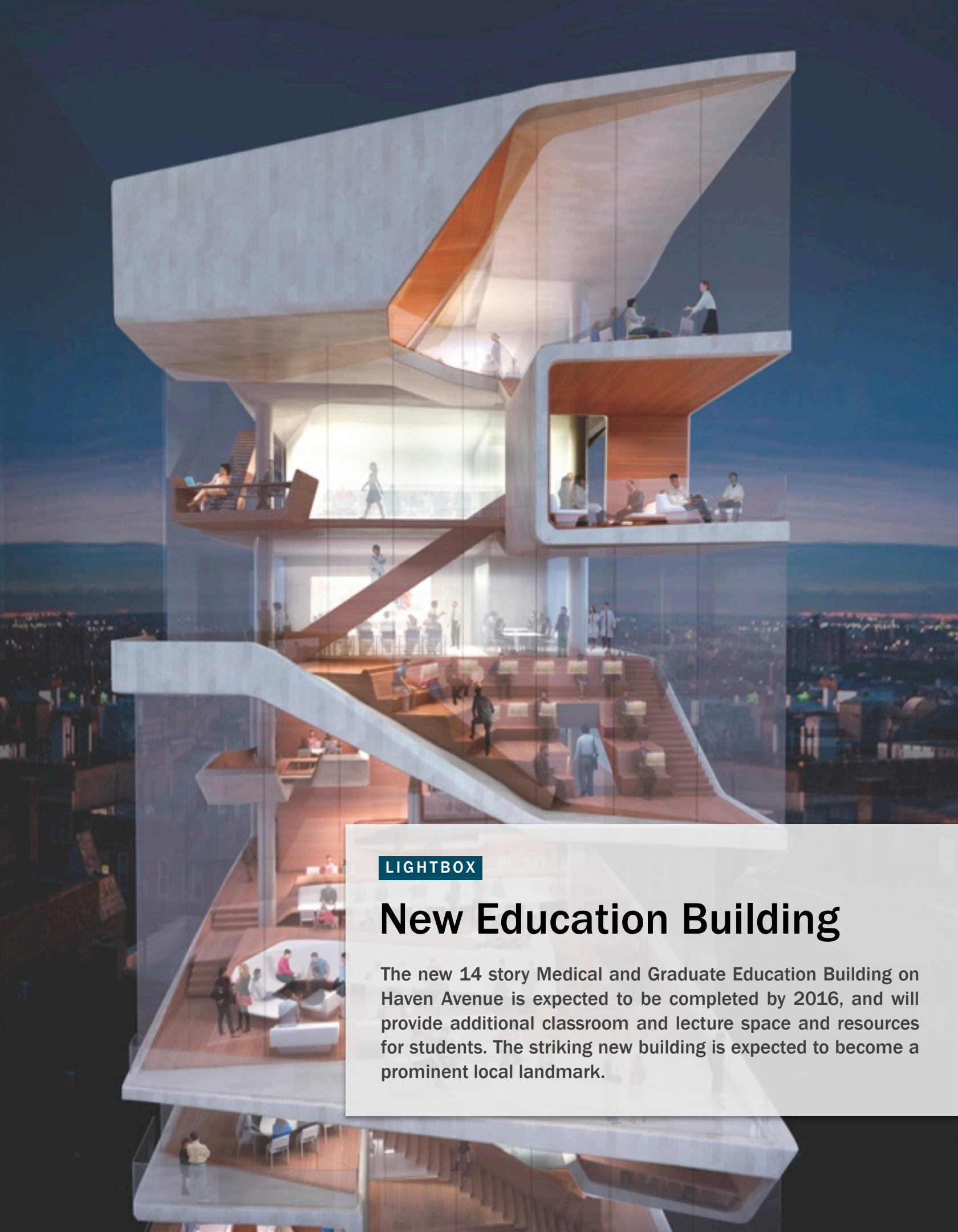
Our graduate program continues to flourish and we have four outstanding new students this fall. Under the direction of David Fidock, who serves as the Principal Investigator, we successfully reinstated our training grant, which will help us admit and train more students in the future. Boris Reizis, our Director of Graduate Studies has been deeply involved in mentoring students in the program, including helping the first-year students choose suitable laboratories for their rotations. We are also delighted that Steve Reiner was selected to become the head of the M.D.-Ph.D. program at Columbia, and we hope that with him at the helm, the department will become more attractive to M.D.-Ph.D. students as they seek laboratories to carry out their thesis research.

I want to end by thanking all the people who help ensure that the department runs smoothly, including the staff in the business office (as mentioned above), Oliver, Carla in my office, and Amir in the FACS/Microscope facilities. As in previous years, the editing and development of content of the newsletter was the work of Oliver and Suja, while the typesetting, formatting and graphics was the work of Oliver and Shomik.

I hope you enjoy reading this newsletter and I would like to thank all of you for your efforts in making M&I a great place to be.

**Sankar Ghosh, Ph.D.**





**LIGHTBOX**

## New Education Building

The new 14 story Medical and Graduate Education Building on Haven Avenue is expected to be completed by 2016, and will provide additional classroom and lecture space and resources for students. The striking new building is expected to become a prominent local landmark.



DR. UTTIYA BASU

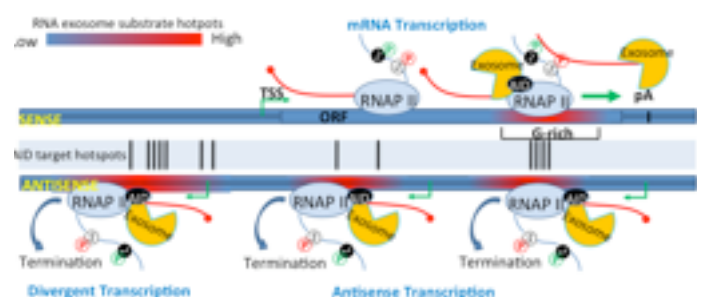
# Non-coding RNA Transcription Targeting

**FOLLOWING THE ADVENT** of high-throughput sequencing and systems biology-based genome evaluation technologies, the non-coding RNA transcriptome has been a field of immense scientific curiosity. One difficult aspect of identification of rare non-coding RNA species is their low abundance in cells, a problem compounded by their rapid degradation. Regulatory factors tasked with controlling spatio-temporal events tend to exist only for short periods of time and non-coding RNAs (ncRNAs) are no exception. To identify ncRNAs that may have rapid turnover rates in primary mammalian cells, we have generated a mouse model in which we can efficiently inactivate the cellular non-coding RNA 3'-5' degradation complex, RNA exosome, conditionally by *in vivo* and *ex vivo* methods. This mouse model has unique features that provide us the opportunity to study a protein complex that is essential, ubiquitously expressed, and required for mammalian cell function. The conditional allele of our gene of interest is deleted in this system using a "COIN" conditional-inversion system that utilizes some novel improvements over traditional gene targeting strategies. The recent advances in the non-coding RNA biogenesis field have, in turn, generated great interest in the RNA exosome complex and our conditional mouse model is an excellent system for understanding both the role of RNA exosome in regulating the function of various ncRNAs in mammalian cells and the non-coding RNAs themselves.

In this particular study we have evaluated the expression of various subsets of non-coding RNAs that are direct targets of the RNA exosome complex. One standout effect of RNA exosome deletion is a rapid and significant increase of short antisense non-coding RNAs that flank transcription start sites at numerous genes genome-wide which we collectively categorize as RNA exosome substrate Transcription Start Site non-coding RNA (xTSS-RNA). The presence of these transcripts in primary mammalian cells, beyond what has been described in knockdown studies for a few selected genes expressed in cell lines, has not been previously reported. In this study we report widespread expression of these antisense transcripts with physical and functional properties significantly different from what has been postulated previously. These xTSS-RNAs are greater than 500 bps in length, are expressed divergently from the TSS of coding genes, and have their own cognate transcription start sites.

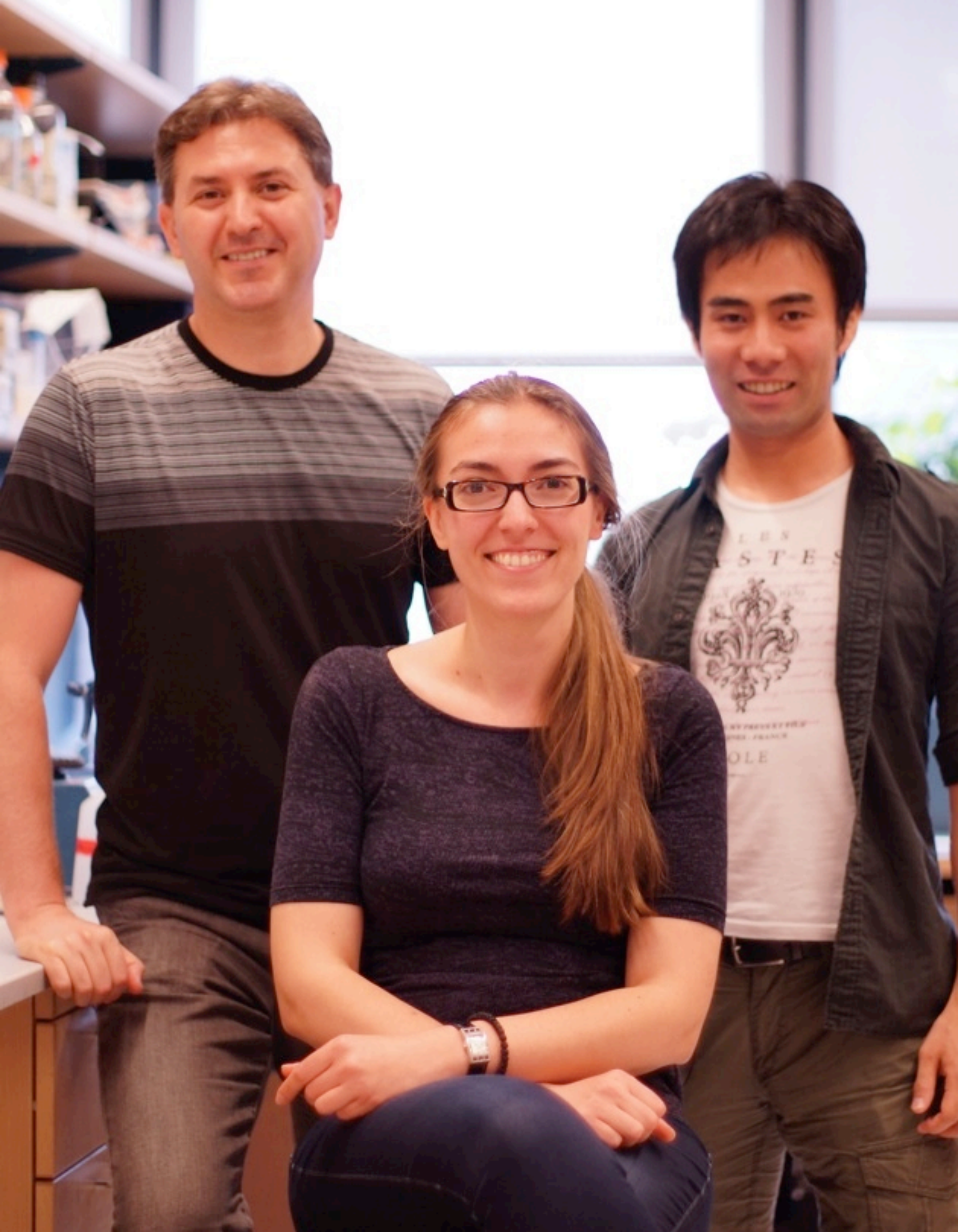
When we investigate the expression of these transcripts in primary B cells, we find their presence at genomic regions

where the B cell genome mutator Activation Induced Deaminase (AID) binds and mutates. AID is a ssDNA cytidine deaminase that we previously showed interacts with RNA exosome to enhance its DNA deamination activity and catalyze class switch recombination (Basu et al., Cell 2011), a chromosomal recombination-deletion event that leads to isotype switching in mature B cells. Moreover, we find that regions in the B cell genome that have been shown previously to be chromosomal translocation hotspots, express xTSS-RNAs at high levels. Indeed xTSS-RNA expression is highest at genes that are known targets of AID in B cells and are found mutated in human B cell lymphoma samples, namely Pim1, c-Myc, Pax5, Cd79b and Cd83. Regions of the B cell genome that have chromosomal translocations in the body of the gene, express antisense (as) RNAs that function similarly to xTSS-RNAs in marking translocation hotspots. Based on the fact that RNA exosome processing of ncRNAs (TSS-RNA or asRNA) expressed at divergently transcribed genes can generate ssDNA bubbles, we propose a mechanism of AID targeting to the B cell genome which is dependent upon the activity of the RNA exosome complex. Overall, our studies provide evidence of regulation of ncRNA expression in primary mammalian cells and identify a key functionality in antibody diversification mechanisms and maintenance of B cell genome integrity via the regulation of the oncogenic deaminase, AID.



**A model of RNA exosome recruitment to divergently transcribed promoters or at DNA sequences that promote RNA polymerase III stalling.** Divergent transcription of mRNA in the sense direction recruits RNA exosome and AID following stalling due to various transcription impediments (G-richness in IgH switch sequences is one example). Transcription stalling leading to RNA exosome recruitment occurs more often on the antisense strand due to formation of short antisense RNAs. Similarly in the body of transcribed genes, stalled RNA polymerase III generates antisense RNA transcripts leading to RNA.

**Reference:** Evangelos Pefanis, Jiguang Wang, Gerson Rothschild, Junghyun Lim, Jaime Chao, Raul Rabadan, Aris Economides and Uttiya Basu (2014) Non-coding RNA transcription targets AID to divergently transcribed genes in B cells. *Nature* 514: 389–393.





DR. IVAYLO IVANOV

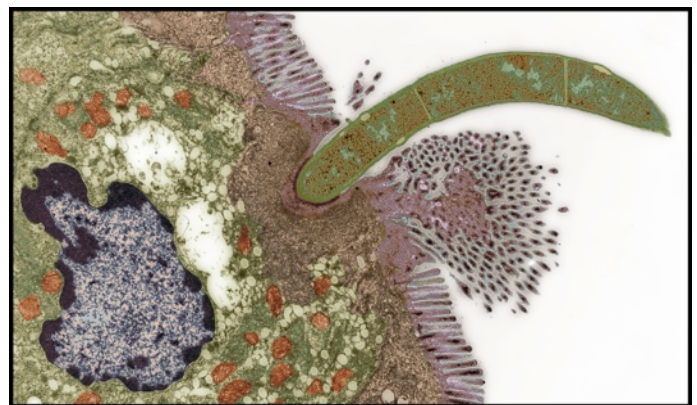
# Fine-tuning Gut Immunity

**THE HUMAN BODY** is permanently colonized by a complex and dynamic microbial ecosystem called commensal microbes or microbiota. We rely on our microbiota for many biological functions, ranging from basic metabolic and physiological functions to protective immunity and normal brain function. Our laboratory is interested in characterizing the mechanisms by which intestinal commensal bacteria fine-tune the immune system. Commensal bacteria have long been known to induce the accumulation of immune cells in the gut and boost mucosal immunity. Several years ago we discovered that, in addition to these immunostimulatory functions, the microbiota can perform immunomodulatory functions by directing the type of immune cells present in the gut. Moreover, we found that unique microbiota members are differentially involved in this process and identified the first specific example of such commensal immune modulation. We found that commensal Segmented Filamentous Bacteria (SFB) specifically induce a subset of pro-inflammatory helper T cells in the intestinal lamina propria, called Th17 cells. Th17 cells provide protection from bacterial infections at mucosal surfaces and contribute to pathogenicity in a number of autoimmune inflammatory conditions, e.g. IBD, psoriasis, multiple sclerosis. SFB control Th17 cell numbers and mice that have high levels of SFB are better protected from intestinal infection, but also more susceptible to autoimmunity. The concept that differences in microbiota composition translate into differences in immune cell composition throughout the body and contribute to differences in immune responses at steady state and during disease has now been expanded to many other commensal-immune interactions. We have termed such autochthonous immunomodulatory microbiota species, *autobionts*.

The identification of *autobionts*, and their specific effects on the immune system, has made it possible to focus studies on the cellular and molecular mechanisms involved. In our latest publication, we examined how SFB induce Th17 cells in the small intestine. Previous publications have suggested that commensal bacteria produce metabolites that affect the local cytokine environment in the gut and skew T cell differentiation. We found that the cytokine environment induced by SFB is not sufficient to direct Th17 cell differentiation. Instead, SFB-derived antigens are required for the process. We showed that the SFB antigens are acquired and presented by lamina propria dendritic cells (DCs) in an MHCII-dependent manner. Interestingly, at steady state, virtually all SFB-induced Th17 cells recognize

SFB and all SFB-specific T cells are Th17 cells. Therefore, SFB antigens direct not only the specificity, but also the type of T cell differentiation in the LP. How this occurs is an important question. Peyer's Patches (PPs) and mesenteric lymph nodes (MLN) are the standard way of sampling of intestinal antigens and induction of antigen-specific responses.

Interestingly, we find that Th17 cell priming and differentiation in response to SFB occurs locally in the small intestinal lamina propria and does not require organized secondary lymphoid organs, including PPs and MLN. Therefore, induction of mucosal Th17 cell responses requires commensal antigen delivery by alternative mechanisms. Because SFB is one of the very few commensal microbes that interact directly with intestinal epithelial cells (IECs), it may be able to deliver unique antigens in unique ways or to unique subsets of DCs. Identification of these antigens and pathways may, for example, allow us to generate vaccines targeted to boost mucosal Th17 cell responses. Our study also examined the role of other innate immune subsets in mucosal Th17 cell responses. Interestingly, ablation of MHCII-expression on type 3 innate lymphoid cells (ILCs) resulted in an increase of Th17 cells in SFB-negative mice, demonstrating that ILCs curb Th17 cell responses at steady state. This study under-scores the complex interplay between microbiota and innate immune cell subsets in modulating intestinal effector T cell responses.



**Transmission electron microscopy.** Segmented Filamentous Bacteria (green exterior) interacting with intestinal epithelial cells in the terminal ileum.

**Reference:** Yoshiyuki Goto, Casandra Panea, Gaku Nakato, Anna Cebula, Carolyn Lee, Marta Galan Diez, Terri M. Laufer, Leszek Ignatowicz and Ivaylo I. Ivanov (2014) Segmented Filamentous Bacteria Antigens Presented by Intestinal Dendritic Cells Drive Mucosal Th17 Cell Differentiation. *Immunity* 40: 594-607.



# Department News

## NIH Training Grant Awarded

**THE DEPARTMENT WAS AWARDED** a NIH NIAID Ruth L. Kirschstein National Research Service Award Institutional Research Training Grant (T32) on May 27, 2014 for a predoctoral Columbia University Graduate Training Program in Microbiology and Immunology. The grant was written by Dr. Fidock and Dr. Jovanovic, Dr. Fidock and Dr. Reizis will respectively serve as Director and Co-Director, Drs. Basu, Farber, Fidock, Ghosh, Gottesman, Reiner, Reizis and Symington will serve on the Steering Committee, and all of our training faculty have appointments in Microbiology & Immunology. The grant will serve to fund up to four graduate trainees a year over a period of five years. Trainees are selected for funding through an application process from graduate students that have attained dissertator status. Applications are due by June 1st of each year.

## Departmental Retreat

**THE 2013 MICROBIOLOGY & IMMUNOLOGY** annual retreat was held at the Hamilton Park Hotel and Conference Center in Florham Park, NJ on September 9th and 10th. It featured research talks by faculty members and a poster session presented by students and postdoctoral fellows, as well as a collegial after party. During down time, attendees were welcome to enjoyed numerous impromptu activities including swimming, basketball, walking, and foosball. The 2014 Microbiology & Immunology retreat will also be held at the Hamilton Park Hotel and Conference Center on September 4th and 5th, 2014, and will feature keynote speaker Dr. Andrea Califano, founding chair of the Department of Systems Biology at Columbia University and Director of the J.P. Sulzberger Columbia Genome Center.

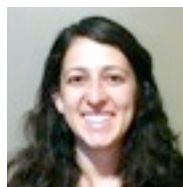
## Four New Students Join Department



**Julian Berger**  
*University of Chicago*



**Yeojin Lee**  
*Korea University*



**Michelle Miron**  
*Colgate University*



**Barbara Stokes**  
*University of Massachusetts*

## Professor Donna Farber Joins Department

**DR. DONNA FARBER, PH.D.**, Professor of Surgical Sciences (in Surgery) now has a joint appointment in Microbiology & Immunology. Dr. Farber is an accomplished immunologist with ongoing research collaborations with our faculty, and several of our students have trained in her lab. Dr. Farber received her Ph.D. from the University of California at Santa Barbara before coming to the Columbia Center for Translational Immunology in 2010 from the University of Maryland. The focus of her lab's research is on immunological memory, in particular on memory T cells, which direct and coordinate anamnestic immune responses to pathogens, and can mediate immunopathology in autoimmune disease and in transplantation.

## Department Welcomes Professor Han

**DR. YIPING HAN, PH.D.**, has recently joined the College of Dental Medicine as Professor of Microbial Sciences, with joint appointments in Dental Medicine and Microbiology & Immunology. Dr. Han received her Ph.D. from the University of Illinois at Urbana-Champaign and was most recently a Professor of Periodontics at Case Western Reserve University's School of Dental Medicine, before joining Columbia University earlier this year. Her research is focused on the role of oral bacteria in extra-oral infection and inflammation, in particular the role *Fusobacterium nucleatum*, an oral commensal, plays in pregnancy complications and colorectal cancer.

## Departmental Administrator Retires

**THE DEPARTMENT BIDS FAREWELL** to our long time departmental administrator, Edie Shumansky, who retired from Columbia University on February 7, 2014. Edie came to the department from Albert Einstein College of Medicine in 1988, brought in by former department Chair Lucy Shapiro, who had previously worked with Edie at Albert Einstein. Edie served the department as its administrator for 26 years before retiring. She successfully steered numerous faculty grants through the application and funding process, and saw three decades of our graduate students through to their doctorates. Edie played a critical role in the functioning of this department, and we wish her all the best in her well-deserved retirement. In addition, Joan Skeith, a long serving administrator in the department, fully retired from Columbia University on April 2, 2014, and will also be missed.

## Lorraine Symington Appointed to Named Professorship

**PROFESSOR LORRAINE S. SYMINGTON** of our department was appointed Harold S. Ginsberg Professor of Microbiology & Immunology on July 1, 2014. This named professorship was established to honor Dr. Harold S. Ginsberg, Chair of Microbiology & Immunology from 1973 to 1985, a renowned virologist whose contributions to the field helped pave the way to our current understanding of viral replication and pathogenesis. Dr. Symington is one of our most distinguished and accomplished faculty members and just recently completed 25 years of service to the department. Dr. Symington received her Ph.D. from the University of Glasgow and performed postdoctoral research at Harvard Medical School and the University of Chicago before joining our department. Her laboratory uses genetic, biochemical and molecular approaches to understand mechanisms of homology-directed double-strand break (DSB) repair using the yeast *Saccharomyces cerevisiae* as an experimental system.

## Boris Reizis Promoted to Full Professor

**ASSOCIATE PROFESSOR BORIS REIZIS** of our department was promoted to full Professor of Microbiology & Immunology on July 1, 2014. Dr. Reizis is an accomplished and highly productive faculty member who also serves as the department's Director of Graduate Studies. Dr. Reizis received his Ph.D. from the Weizmann Institute of Science and performed postdoctoral research at Harvard Medical School before joining our department. His laboratory's research is focused on the molecular control of stem cell function, blood cell development and malignant transformation, and immune response to pathogens.

## Memorial Lectures

**THE 2014 RICHARD C. PARKER LECTURE**, "Shaping of Host Immunity by the Microbiota in Health and Disease" was presented on March 19, 2014 by Dr. Dan R. Littman of New York University.

**THE 2014 HARRY M. ROSE LECTURE**, "Sirtuins are Viral Restriction Factors" was presented on April 16, 2014 by Dr. Thomas E. Shenk of Princeton University.

**THE 2014 HEIDELBERGER-KABAT LECTURE**, "Aire, a Transcriptional Regulator that Controls Immunological Tolerance" was presented on June 4, 2014 by Dr. Diane Mathis of Harvard Medical School.

## Richard C. Parker Memorial Award

**THE RECIPIENT OF** the 2014 Richard C. Parker Graduate Student Award was Huan Chen. Her research in Lorraine Symington's laboratory used a heat-inducible system to show that the essential budding yeast *Saccharomyces cerevisiae* replication protein A (RPA) is not only required to generate single-stranded DNA (ssDNA), but also protects ssDNA from degradation and inappropriate annealing that could lead to genome rearrangements. The award was presented to Huan Chen on March 19, 2014 at the 28th Richard C. Parker Memorial Lecture, delivered by noted immunologist Dan R. Littman.

# Alumni News

## 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](mailto:dlf84@columbia.edu).



## Department Alum Wins EMBO Gold Medal

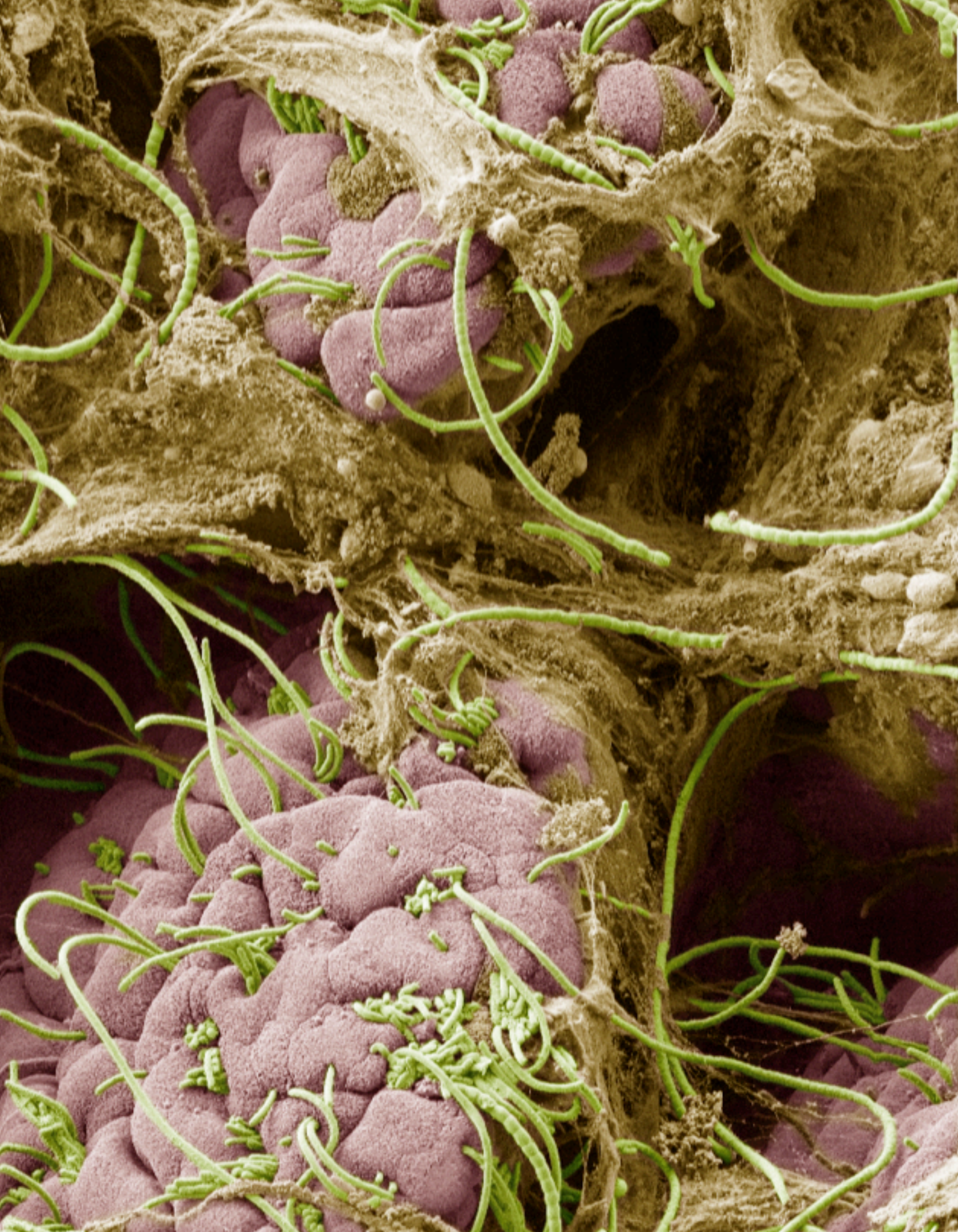
**DR. SOPHIE MARTIN** performed postdoctoral research in the laboratory of Dr. Fred Chang on the cytoskeleton in fission yeast. She subsequently joined the Center for Integrative Genomics at the University of Lausanne as a Swiss National Science Foundation Professor, where Dr. Martin continued to study cellular polarity in fission yeast. On April 23, 2014 EMBO awarded her the 2014 EMBO Gold Medal in recognition of her research to understand the organization and development of the cell.

### Alumni Spotlight

**DR. ELAINE A. SIA** completed her doctorate in our department in 1995 studying the broad host range plasmid RK2 in the lab of David Figurski. She went on to do postdoctoral research in the lab of Dr. Thomas Petes at the University of North Carolina at Chapel Hill. In 2000, Dr. Sia joined the University of Rochester as a faculty member, where she was promoted to Associate Professor in 2006, and was appointed a full Professor of Biology earlier this year. Her lab performs research on replication, repair, and maintenance of mitochondrial DNA.

### Alumni Spotlight

**DR. IRWIN GELMAN** completed his doctorate in 1987 in our department mapping herpes simplex virus regulatory circuits in the lab of Saul Silverstein. He was an American Cancer Society Postdoctoral Associate in the lab of Hidesaburo Hanafusa at Rockefeller University, then joined the faculty of Microbiology and Infectious Diseases at Mount Sinai School of Medicine in 1990. In 2003, he moved to the Roswell Park Cancer Institute, where he is now the John and Santa Palisano Chair of Cancer Genetics, Professor of Oncology, Director of the Advanced Cancer Genomics Program and co-leader of the Molecular Epidemiology and Functional Genetics Program, and also Chair of the Cell and Molecular Biology Program at SUNY Buffalo.



## FEATURE ARTICLE

# The Human Microbiome

**OUR UNDERSTANDING OF** human health and disease has shifted radically in the last two decades, with the recognition that the human body is home to vast populations of microorganisms. We now know that there are 10-fold more microbial cells (100 trillion) in the body than human cells (10 trillion), and 100 times as many microbial genes (3.3 million) as human genes (30,000). These microorganisms, known as the human microbiome or microbiota, are comprised mainly of bacteria, though viruses, fungi, archaea, and protozoans are also present. They live on the major epithelial surfaces of the body, including the nasal passages, the oral cavities, the skin, the gastrointestinal (GI) tract, and the urogenital tract. The human intestine contains more bacteria than any other part of the body, and is home to hundreds of distinct bacterial species, often called commensal species. Under normal conditions, many of these resident gut bacteria exhibit a mutualistic relationship with the human host, enjoying ideal living conditions, while providing benefits to the host such as immune protection and enhanced digestion. However, it is now becoming apparent that genetic and environmental factors can alter the composition of the gut microbiome, and that such alterations may correlate with changes in human health. Researchers are currently trying to understand how dysregulation of the microbiome is related to the progression of a plethora of human diseases, including allergic diseases and asthma, autism, autoimmune diseases, diabetes, obesity, eczema, and inflammatory bowel disease (IBD).

## Colonization from Birth to Death

Human babies are born with sterile gastrointestinal tracts, but upon birth, microbial colonization of the gut begins. The route of birth appears to be one of the earliest factors influencing the development of the infant microbiome. Vaginally delivered infants present with bacterial communities resembling their mothers' vaginal microbiota, while infants delivered by C-section harbor bacterial communities similar to those found in the environment and on their mothers' skin. As babies grow, breast-fed infants and formula-fed infants also exhibit differing composition of the gut microbiome. Human breast milk itself is a significant source of healthy bacteria for infants. Over the first weeks and years of life, the gut microbiome is thought to change extensively; it is initially colonized by oxygen tolerant species, which in turn, create a reduced environment that is

favorable for later colonization by anaerobic species. It has been suggested that the initial infant microbiome may be comprised of bacteria that facilitate the digestion of milk, and that breast milk may even have evolved to contain particular sugars to cultivate these beneficial bacteria. Furthermore, it has also been suggested that the microbiome composition shifts upon the transition to solid foods, to include bacteria essential for the breakdown of complex sugars and starches found in plant-based foods. However, in-depth characterization of the gut microbiome of infants is necessary to truly understand the composition and role of gut bacteria in the early weeks and years of life. The gut microbiome continues to change until it ultimately resembles an adult gut microbiome, which has been proposed by one study to occur by the third year of life.

From birth to death, the exact composition of the gut microbiota changes based on diet, infection, and antibiotic use, amongst other factors. Though it has been proposed that the combination of specific environmental factors and host genetics can lead to the establishment and maintenance of defined gut bacterial species in human populations, few studies have been able to confirm the existence of these discreet "enterotypes". More compelling evidence suggests that resident microbes at specific body sites likely perform the same symbiotic functions for the host, even though the precise microbial species may differ between different individuals. Thus, rather than ascribing symbiotic functions to single microbial species, researchers are becoming more interested in the function of groups of similar microbes in human health and disease.

## Symbiosis

Hundreds of distinct microbial species inhabit the human intestine and exhibit a mutualistic relationship with the human host. Using gnotobiotic animal models, it has been shown that the intestinal microbiota play a crucial role in the development of the innate and adaptive immune systems, both locally in the gut and systemically. Though the mechanistic details are incompletely defined, a number of reports have suggested that the microbiota is important for local changes in the gut such as enlargement of the mucosa-associated lymphoid tissue, enhanced cellularity, and enhanced barrier function, as well as for systemic changes such as increased antibody production, altered

lymphocyte migration patterns, and even development of T cell populations.

Importantly, bacteria in the gut have also been shown to protect against infection by pathogenic microbes. Our own Dr. Ivaylo Ivanov demonstrated an interesting example of this beneficial role of gut bacteria in a 2009 paper in the journal *Cell*. Dr. Ivanov showed that colonization of mice with the commensal species segmented filamentous bacteria (SFB) correlated with induction of Th17 cells and expression of anti-microbial genes, thereby resulting in protection of the mice from infection with the intestinal pathogen *Citrobacter rodentium*.

Finally, gut bacteria are also thought to be important for host metabolism, and to help in digestion and absorption of otherwise indigestible matter, such as complex carbohydrates found in plant-based foods. Microbial fermentation of ingested carbohydrates leads to generation of short chain fatty acids, which are a major energy source

for human cells and which play important roles in the intestine such as stimulation of epithelial cell proliferation and differentiation. In addition, production of vitamins important for human health, such as biotin, folate, and vitamin K, as well as the ability to absorb important minerals such as calcium, magnesium, and iron, are also essential functions ascribed to gut bacteria.

## Mechanisms of Intestinal Immune Homeostasis

Though the gastrointestinal tract harbors trillions of microbes, the host intestinal immune system specifically mounts a robust immune response against harmful pathogens, while dampening immune responses against commensal microbes. Studies in mice have allowed the characterization of protective mechanisms that limit the immune response to the gut commensal bacteria. First, layers of protective mucus allow for spatial separation of the microbiota and the intestinal epithelium, thereby limiting

## Advent of the Hygiene Hypothesis

In addition to colonization with commensal microbes, it has been suggested that infection with pathogenic microbes may shape human health as well. The decrease in infectious burden in industrialized countries has been associated with a meteoric rise in allergic and autoimmune diseases, leading to the theory known as the hygiene hypothesis. The hygiene hypothesis was first formally proposed by David P. Strachan, of the London School of Hygiene and Tropical Medicine, in a 1989 report detailing an inverse correlation between the number of older siblings and the incidence of hay fever in a longitudinal study of over 17,000 British children born in 1958. These findings led Strachan to conclude that allergic diseases might be prevented by childhood infection, transmitted by older siblings. Furthermore, he speculated that the decline in family size and higher standards of cleanliness in the modern era might explain the increased incidence of allergic disease.

Another canonical study lending support for the hygiene hypothesis was performed in the late 1990s by Dr. Erika Von Mutius. Dr. Von Mutius demonstrated that children growing up in the poorer, dirtier, and less healthy cities of East Germany had a lower prevalence of allergic reactions and fewer cases of asthma than children growing up in the cleaner and more modern cities of West Germany. Von Mutius also noted that the East German families were larger, with more children, and that there was more widespread use of daycare for young children in East Germany. Similar to Strachan, she hypothesized that exposure to microbes early in life, through contact with other children, could lead to immune tolerance for the irritants that cause asthma.

As the hygiene hypothesis has gained more support, the theory has been further developed. It was proposed in 2003 by Graham Rook and colleagues that colonization by ancient organisms that co-evolved with humans, such as certain species of bacteria, worms, and viruses, plays an important role in the development and function of the immune system. Another related theory, proposed in 2010-2011 by two groups, suggested that exposure to a diverse and dynamic subset of microorganisms is required for proper priming and regulation of the immune system. There is now a substantial amount of evidence supporting the hygiene hypothesis, and it is believed that reduced microbial exposure may contribute to increased incidence of a broad range of chronic inflammatory diseases.



epithelial cell responses to the bacteria. Not surprisingly, ulcerative colitis patients and mice with experimental colitis exhibit bacteria within these normally impenetrable mucus layers. Epithelial cell secretion of anti-bacterial peptides also limits the interaction of bacteria in the intestinal lumen with the epithelium. Next, microbe-specific IgA represents an important adaptive immune mechanism that both controls the response to the microbiota, and furthermore, may shape the composition of the microbiota. Dendritic cells that sample the microbiota stimulate B cells in the Peyer's patches to produce IgA. This secreted IgA exhibits specificity for host commensal bacterial species, and limits both epithelial cell invasion by the commensals and exposure of commensal antigens to systemic, adaptive immune cells.

A number of other microbe-host interactions have been proposed to help establish and maintain immune homeostasis in the intestine. There is some evidence that microbial metabolites, such as short chain fatty acids produced by particular clades of Clostridia, induce a response by regulatory T-cells in the intestine. In addition, innate lymphoid cells (ILCs), which are known to play a vital role in intestinal barrier function and integrity, have been proposed to limit the CD4+ T-cell response to the microbiota in the intestine. Next, it has been reported that the NLRP6 inflammasome may regulate the composition of the microbiota, as mice deficient for the NLRP6 inflammasome complex exhibited altered composition of the intestinal microbiota, as well as increased sensitivity to DSS-induced colitis. These are a just a handful of the numerous mechanisms to promote intestinal homeostasis in response to commensal microbes that have been described. It is hypothesized that various autoimmune or inflammatory diseases may result from the breakdown of the mucosal barrier or other mechanisms regulating mucosal immunity, thereby leading to inappropriate immune responses against microbial components in the intestinal lumen.

## The Microbiome and Disease

The link between alterations in the microbiota and human disease is of great interest. It has been proposed that changes in gut microbes correlate with diseases ranging from allergic diseases and asthma, autism, multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis, diabetes (T1D), obesity, eczema, to

IBD. Human migration studies have shown that children of immigrants often acquire the same incidence of diseases such as T1D, MS, and SLE as residents of the host country, thereby suggesting that acquired factors such as gut microbes might contribute to the predilection to these diseases. More recently, the transplantation of fecal microbiota from humans into germ-free mice has been shown to directly transfer health conditions such as obesity from humans to mice. However, the metabolic changes associated with fecal transfer from obese individuals are reversible through the concomitant introduction of "good" bacterial species or modification of diet. Such studies reveal that the microbiome is a modifiable entity that may transmit risk factors for disease, but which also has the potential to be therapeutically modified to improve health.

IBD, in particular, involves environmental, host genetic, and commensal microbial factors and therefore represents a comprehensive model for understanding the role of the human microbiome in inflammatory disease. A number of reports, from the early studies using culture-based techniques for microbial community characterization to the more current high-throughput sequencing studies, have suggested that IBD patients, especially those with Crohn's Disease (CD), exhibit reduced diversity of gut bacteria, as well as preferential colonization of particular bacterial species. Observed changes in the composition of the gut microbiota in IBD patients could be the cause or the effect of the disease, or a combination of the two. It is thought that factors such as diet, infection, or antibiotic use could alter the composition of the microbiota, thereby triggering disease processes through unknown mechanisms.

Experimental models of IBD have helped to define factors that may contribute to IBD onset. Some studies have indicated that the commensal bacterium *Bacteroides fragilis* contributes to homeostasis in the gut through production of immunomodulatory products such as polysaccharide A (PSA) and sphingolipids, and furthermore that colonization with *B. fragilis* protects mice from a bacterially-induced model of colitis. As mentioned previously, there is also some evidence that microbial metabolites shape the anti-inflammatory Treg response in the intestine, and furthermore, that induction of Tregs by microbial products, such as SCFAs, suppresses experimental colitis. Finally, mouse models recapitulating

genetic alterations found in IBD patients are being used to dissect the contribution of genetic mechanisms to disease. For example, a mutation in the autophagy-related gene *ATG16L1* is associated with CD, and mice with this mutation exhibit defective clearance of the intestinal pathogen *Yersinia enterocoliticas*, as well as a sustained inflammatory response. More than 160 polymorphisms and mutations have been associated with IBD, many of which have been proposed to affect microbe-host interactions. *Nod2* mutations, in particular, have been highly associated with Crohn's disease. *Nod2*-deficient mice exhibit increased bacterial load in their terminal ileum, suggesting that the disease-associated *Nod2* mutations might contribute to disease through an effect on the ileal microbiota.

Currently, intestinal microbial profiles only modestly distinguish between patients and healthy controls, and thus, cannot be used as a reliable diagnostic tool for IBD. However, some therapies leveraging knowledge of the microbiome have shown promise. Fecal microbiome transplants, which are intended to re-introduce healthy species of gut bacteria to patients thereby restoring immune homeostasis, have been successful against *Clostridium difficile* infection, though similar approaches against IBD have had mixed results. Interestingly, a few small studies have shown that probiotics may actually improve irritable bowel syndrome (IBS) symptoms, including bloating, abdominal pain, and flatulence. In addition, in support of the hygiene hypothesis, pilot clinical trials with helminth infection have also shown promising results against IBD.

## The Human Microbiome Project

Despite the recent interest in the human microbiome, the influence of commensal bacteria upon human development, physiology, immunity, and nutrition has yet to be clearly defined. The NIH Human Microbiome Project (HMP) began in 2007, with the goal of generating resources to facilitate comprehensive characterization of the human microbiota, as well as analysis of their role in human health and disease. The program, funded by the NIH Common Fund, was scheduled in 2 phases. The first phase, from fiscal years (FY) 2007-2012, characterized the microbial communities that inhabit the five major mucosal surfaces of the human body, namely the nasal passages, the oral cavities, the skin, the

gastrointestinal tract, and the urogenital tract. A major difficulty in the study of the microbiome has been that the majority of human-associated microbial species have never been successfully isolated, presumably because their growth requires as-of-yet undefined conditions. Thus, the HMP utilized a metagenomics approach, which allowed analysis of the genetic material harvested directly from human microbial communities without prior culturing. In addition to characterizing the site-specific species of the microbiome, the first phase of the HMP also created computational tools for analysis of the data generated by the HMP. The second phase of the HMP, which is currently underway and is scheduled from FY2013-2015, is focused on generating an integrated dataset of biological properties, including transcriptomics, proteomics and metabolomics data, from both the microbiome and the host from cohort studies of human diseases. Together, the studies of the HMP are providing insights into how the microbiome and human host interact to support health or to trigger disease. The NIH HMP is just one of several international efforts to encourage the study of the microbiome in human health. The long-term objective of these initiatives is to develop datasets and tools that the worldwide research community can use to identify microbial and host factors that contribute to human health and disease.





## HISTORICAL FEATURE

# Harry M. Rose

**ON JULY 1, 1975**, the University Trustees of Columbia bestowed upon Dr. Harry M. Rose, former Chair of the Department of Microbiology & Immunology, the distinction of John E. Borne Professor Emeritus of Medical and Surgical Research, stating, "...you are officially a permanent member of the Columbia community, even though in retirement." Dr. Rose spent more than half of his life in the service of Columbia University, and he is fondly remembered for his exceptional teaching, excellence in research, and important contributions to clinical medicine.

former students. Dr. Rose trained and inspired a generation of doctors and scientists. His own son, Stuart Rose, both attended his Microbiology class and followed in his footsteps into medicine. The late Dr. Bernard Erlanger affectionately recounted the following anecdote about the exceptional father and son, "Dr. Stuart Rose took Microbiology here at P&S when his father was Chairman. We had to ask Harry Rose to leave the conference room before we could give Stuart his grade for the course!"

**"Dr. Harry Rose placed great emphasis on teaching, and memorized the name and face of every graduate and medical student in his classes, even for large classes with over 100 students."**

## Background

Harry M. Rose was born May 30, 1906 in Niles, Ohio. As a young man, Rose attended Yale University. He went on to medical school at Cornell University Medical College, and received his medical degree in 1932. Dr. Rose came to Presbyterian Hospital as an intern in 1938 and received his first faculty appointment at the College of Physicians and Surgeons in 1940 as an Assistant in Medicine, assigned to Bacteriology. With the outbreak of World War II, he also served as secretary of the Medical Division of the Society of American Bacteriologists and a member of the Armed Forces Epidemiological Board. During this time, he performed research on tropical diseases for the United States government.

In 1952, Harry M. Rose was appointed as John E. Borne Professor and Chair of the Department of Microbiology & Immunology. At the time, it was known as the Department of Bacteriology, but Rose changed the name to the Department of Microbiology, to better encompass the other research taking place in the department.

## Teaching

Dr. Rose placed great emphasis on teaching, and memorized the name and face of every graduate and medical student in his classes, even for large classes with over 100 students. As a result, he was fondly remembered by many of his

## Research

Dr. Rose was also an accomplished researcher, and is best known for developing the first reliable test for rheumatoid arthritis, which became known as the Rose-Waaler or Waaler-Rose test, since it was independently developed by both Rose and the Norwegian bacteriologist, Erik Waaler. In 1948, Dr. Rose conducted tests on the blood of patients with rickettsialpox, and noticed that blood from a patient that also had rheumatoid arthritis caused an agglutination reaction in which cells mixed in from sheep's blood clumped together. In collaboration with Dr. Charles Ragan, Rose applied the test to blood from a large number of rheumatoid arthritis patients, and found that the agglutination reaction had predictive value in diagnosing rheumatoid arthritis. These findings led to the creation of a diagnostic test for rheumatoid arthritis that was 90% accurate. At the time, this test was considered the first and only practical laboratory test that allowed for diagnostic differentiation of rheumatoid arthritis from other diseases. It was later shown that the autoantibody known as rheumatoid factor was responsible for the agglutination reaction detected by the Rose-Waaler test, and that this factor contributed to the generation of immune complexes, thereby contributing to disease.

In addition to his work on rheumatoid arthritis, Dr. Rose carried out pioneering studies in antibiotic mechanisms and virology, and made great contributions to the development of the influenza vaccine. He also served as Editor-in-Chief of

the Journal of Immunology, and was a fellow of the American College of Physicians and the American Medical Association, as well as a member of the National Academy of Sciences. Dr. Rose's contributions to research and medicine were recognized by the Gairdner International Award, an Award of Distinction from Cornell University, the Gorgas Medal, and the Squibb Award from the Infectious Disease Society.

## Family and Children

On top of his impressive professional life, Rose had a thriving family life with 3 children. His son, Dr. Stuart Rose, continued his father's legacy of excellence in medicine, and is now an authority in the field of travel medicine. He is the author of the International Travel Health Guide, a comprehensive resource for travelers, founder of Travel Medicine, Inc., which is a company that specializes in products and information for travelers, and founder and Medical Director of the Travel Medicine Center of Western Massachusetts. He is also an Assistant Professor of Emergency Medicine at Tufts University, a Fellow of the American College of Emergency Physicians, a member of the International Society of Travel Medicine, and an attending physician in the Department of Emergency Medicine at Noble Hospital in Westfield, Massachusetts. As the saying goes, the apple does not fall far from the tree.

## Retirement

After over 30 years of service as a faculty member, of which over 20 were as Chair of the Department of Microbiology, Harry Rose retired on June 30, 1973 and moved to New Hampshire. Remarkably, after retiring from Columbia University, Dr. Rose recertified as a Diplomate in Internal Medicine and continued to practice medicine by maintaining his own practice in Sandwich, NH, and working on the medical staff of the Lakes Region General Hospital in Laconia, NH and Huggins Hospital in Wolfeboro, NH until 1984. He also served as chair of the medical committee in Sandwich, NH, as well as the Carroll County Coroner for several years.

Despite the various phases of his long and active career, Dr. Rose placed special importance on his extensive time at Columbia. In his resignation letter, written on April 6, 1973 to

the then Dean, Paul A. Marks, Dr. Rose eloquently wrote, "I have spent more than half my life in this place. Certainly the better half...The associations and friendships I have made here have had a vital effect on me...For this I want to express my most profound appreciation to you and to the host of other people who have made this great institution what it is, and who have given happiness and inspiration to me." Dr. Rose reciprocally inspired the students and colleagues around him.

## The Harry M. Rose Memorial Lecture

After his death on November 4, 1986, the Department of Microbiology & Immunology established the Harry M. Rose Memorial Lecture in Infectious Diseases with the Department of Medicine. This was made possible by donations from many of Dr. Rose's former students and colleagues, and by the generous assistance of the family of Dr. Rose. From the first lecture by Dr. J.A. Levy in 1988 to the most recent lecture by Dr. Thomas Shenk in 2014, 20 lectures from renowned infectious disease researchers, including three Nobel laureates, have been given to honor Dr. Rose for his contributions to scientific research, medicine, and education.

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## NOTES

# 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 11 subunit non-coding RNA degradation/processing complex whose role in various cellular function constitutes a current topic of investigation. Ongoing research is focused on probing the RNA exosome-dependent co-transcriptional regulation of non-coding RNA biogenesis in the immunoglobulin loci. These findings should lead to a better understanding of 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, including 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, as well as 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 studies 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 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.

## Dalla-Favera Lab

Riccardo Dalla-Favera's laboratory is focused on three major goals: (1) identifying the lesions and genes involved in the development of human B cell lymphoma, (2) determining the mechanism by which these lesions occur and (3) elucidating the contribution of each lesion to tumor development. The lab identifies novel oncogenes and tumor suppressors involved in the pathogenesis of lymphoma by virtue of their involvement in tumor-associated chromosomal translocations or by "positional cloning" from chromosomal regions involved in tumor-associated deletions. They study the function of the BCL-6 gene, a recently identified proto-oncogene which codes for a transcription factor expressed in B cells and is altered in its regulatory region in a significant fraction of human lymphoma. Finally, they seek to elucidate the role of chromosomal translocations involving the c-myc proto oncogene locus and immunoglobulin loci in the development of Burkitt's lymphoma.

## Ding Lab

Lei Ding's laboratory studies hematopoietic stem cells (HSCs), which play critical roles in the generation, repair and homeostasis of the blood and immune system via self-renewal and multilineage differentiation. The lab is investigating extrinsic mechanisms that

regulate HSC self-renewal, and how mis-regulation of niche/HSC interactions contributes to diseases such as cancer and anemia. Understanding the HSC niche is a key step in helping design better strategies for in vitro expansion of HSCs, and for treatment of niche related diseases such as leukemia and anemia.

## 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. The lab has recently focused on trying to understand how these bacterial molecules are recognized by vertebrates, and found a previously uncharacterized protein, LysMD3, that is present on the surface of human cells and serves as a peptidoglycan receptor. They showed that LysMD3 is involved in activation of NF- $\kappa$ B, a key innate immune transcription factor, as well as cytokine 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.

## Emerson Lab

Stephen Emerson's laboratory studies the transcriptional regulation of hematopoietic stem cell (HSC) proliferation, self-renewal and differentiation. In particular the lab focuses on NF- $\kappa$ B, the inducible transcriptional regulator of Hox-X4 genes, Bmi-1, the polycomb complex protein, and telomerase. The lab also studies the orphan nuclear hormone receptor Nur77 with the laboratory of Jennifer Punt. Within the context of HSC engraftment, they are interested in immune inputs into HSC proliferation, including the effects of interferons and other products of activated T lymphocytes in the context of graft-versus-host disease.

## Farber Lab

Donna Farber's laboratory studies immunological memory, and in particular memory T cells, which direct and coordinate anamnestic immune responses to pathogens and can mediate immunopathology in autoimmune disease and in transplantation. Memory T cells are generated following an initial encounter with antigen and can persist in multiple lymphoid and non-lymphoid peripheral tissue sites. The lab has recently found that lungs contain a resident population of memory T cells that are retained in the lung and mediate optimal protective responses to influenza virus. They are investigating how these tissue resident memory T cells are generated and retained in mucosal sites in mouse virus infection models, and how pancreas-homing autoreactive memory T cells are generated and maintained in a mouse model for Type I diabetes. Biochemical and molecular approaches are being used to elucidate mechanisms controlling the rapid recall response of memory T cells and their homeostasis and maintenance in mouse models with conditional deletion of key signal transduction intermediates. The lab recently began translational studies on

human memory T cells, with a focus on characterizing tissue-specific immune responses in multiple lymphoid and non-lymphoid human tissue obtained from organ donors in collaboration with the New York organ donor network. Other translational studies in progress include analyses of T cell homeostasis and function in human transplant recipients and in Type I diabetes.

### 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 *pfprt* 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*. The laboratory recently identified a highly mutated allele of *pfprt* 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.

### Ghosh Lab

Sankar Ghosh's laboratory is striving to understand how the transcription factor NF- $\kappa$ B shapes various aspects of the immune response. Last year the Ghosh lab demonstrated that one component of the NF- $\kappa$ B signaling pathway, I $\kappa$ B- $\beta$ , plays a surprisingly crucial role in the expression of the pro-inflammatory cytokine TNF. This insight into how NF- $\kappa$ B 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  $\gamma\delta$  T cells as a new target of regulatory T cells and elucidated the mechanism whereby regulatory T cells suppress  $\gamma\delta$  T cell activation. They went on to show that in the absence of functional regulatory T cells,  $\gamma\delta$  T cells become hyperactivated, causing the development of colitis. Current efforts in the Ghosh lab seek to more fully characterize the role of NF- $\kappa$ B 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- $\kappa$ B signaling pathways in inflammation and cancer, the role of NF- $\kappa$ B 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. The lab has recently 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.

### Hayden Lab

Matthew Hayden's laboratory investigates cytokines in the inflammatory response and seeks to elucidate how corruption of signaling contributes to immune-mediated diseases. The lab is currently focused on understanding signaling by the pro-inflammatory cytokine tumor necrosis factor (TNF), as well as other members of the TNF family. Although TNF blocking agents are a mainstay of therapy for several autoimmune and chronic inflammatory diseases, there are fundamental aspects of TNF biology that remain puzzling. For example, while TNF can trigger both cell death and inflammation, we do not fully understand how these two functions are coordinated. The laboratory is working both to understand the cellular and molecular mechanisms that govern these dichotomous outcomes and to develop more nuanced therapeutic approaches that function by altering the consequences of TNF signaling rather than blocking all TNF functions.

### Han Lab

Yiping Han's laboratory studies the role of oral bacteria in extra-oral infection and inflammation. Increasing evidence suggests that

microbial communities specific to particular regions of the body are not isolated from each other, but rather, are mobile and interchangeable. For example, oral bacteria are not limited to the confines of the mouth and are frequently detected at extra-oral sites associated with infections and inflammation. The lab uses culture-independent approaches to investigate the impact of the oral microbiome and oral health on pregnancy complications and gastrointestinal (GI) disorders. *Fusobacterium nucleatum* is a gram-negative anaerobic oral commensal prevalent in pregnancy complications including preterm birth, stillbirth and neonatal sepsis. It has also been associated with GI disorders, including inflammatory bowel disease, colorectal cancer and appendicitis. The lab identified a unique adhesin, FadA, from *F. nucleatum* that plays an essential virulent role, and is thus a potential diagnostic and therapeutic target. The lab continues to study the structure, function and regulation of FadA, as well its clinical relevance in patient cohorts. The Han lab was also the first to utilize ultrasound to facilitate DNA delivery (sonoporation) into bacteria and construct a double-crossover allelic exchange mutant in *F. nucleatum*, and developing bacterial genetic tools continues to be a focus.

### 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*. 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. The lab is 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- $\kappa$ B (NF- $\kappa$ B) transcription factor complex, thereby promoting oncogenesis. Despite extensive knowledge about the biology of NF- $\kappa$ B, surprisingly little is known on the function of NF- $\kappa$ B in the precursor cells of these tumors. NF- $\kappa$ B signaling can occur via two different routes, mediated by specific NF- $\kappa$ B subunits. In the last year, the lab has characterized the expression pattern of the five NF- $\kappa$ B transcription factor subunits in the various B-cell subsets. Interestingly, they obtained evidence suggesting a differential activation of the separate NF- $\kappa$ B pathways in memory B-cell versus plasma cell precursors. The lab is now studying the *in vivo* function of the separate NF- $\kappa$ B pathways in the differentiation of memory

and plasma cell precursors using conditional knockout systems. They are also undertaking a genome-wide identification of NF- $\kappa$ B pathway-specific targets. The results are expected to provide new insights into the role of NF- $\kappa$ B 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 2Apro renders this virus relatively resistant to the antiviral effects of IFN. Research is in progress to identify which IFN-induced proteins are the targets of 2Apro. Insertion of the gene encoding poliovirus 2Apro 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 multi-celled beings. This should allow for better understanding how 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 dendritic 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.

### Shapira Lab

Sagi Shapira's laboratory is focused on deciphering the genetic and molecular circuitry that is at the interface of host-pathogen interactions. The lab would like to understand how this circuitry controls cellular responses to infection, imparts selective pressure on viruses and affects disease progression. They use animal models of infectious disease, molecular biology, and genomic and

computational methods to generate mechanistic models of the dynamic interactions between host and pathogen. The efforts are aimed at developing general strategies for the study of host-pathogen dynamics. A mechanistic understanding of these relationships provides important insights into cellular machinery that control basic cell biology and have broad implications in human translational immunology and infectious disease research.

### 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 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 is 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.

## EVENTS

## 2014 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 are looking forward to a great group of speakers at our weekly “Seminars in Microbiology & Immunology” series, listed below, as well as our annual retreat at the Wyndham Hamilton Park Hotel & Conference Center in Florham Park, NJ. A full list of events can be found on our website, [www.microbiology.columbia.edu](http://www.microbiology.columbia.edu)

Sep. 24	Robert Roeder	<i>Rockefeller University</i>
Oct. 1	J.C. Zúñiga-Pflücker	<i>University of Toronto</i>
Oct. 8	Marc Feldmann	<i>University of Oxford</i>
Oct. 29	John Coffin	<i>Tufts University</i>
Nov. 5	Caroline Harwood	<i>University of Washington</i>
Nov. 19	Kris Hogquist	<i>University of Minnesota</i>
Dec. 3	Marc Jenkins	<i>University of Minnesota</i>

