M&I

Summer 2011

Columbia University
College of Physicians and Surgeons

Department of
Microbiology & Immunology

M&I

SUMMER 2011

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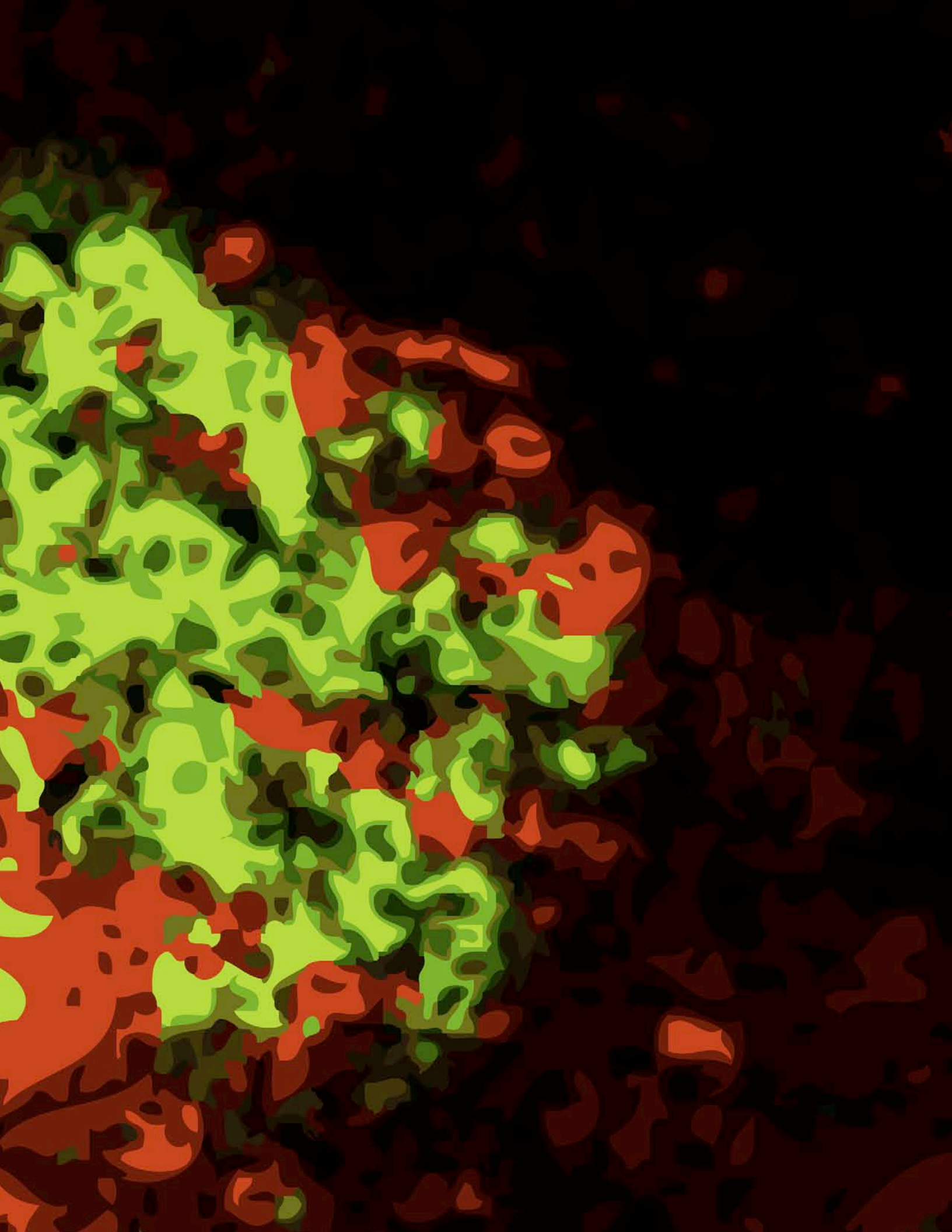



EXIT

Message From the Chair

Dear friends and colleagues,

I am pleased to present to you the Summer 2011 Issue of M&I, the biannual newsletter from the Department of Microbiology & Immunology.

In this inaugural issue, I would like to update you with changes that have happened in the Department since my move nearly two and a half years ago. We have recruited three outstanding young faculty members, Uttiya Basu, Kang Liu and Ivaylo Ivanov, and they are all busy establishing their research programs. In addition, we are delighted to welcome three outstanding joint appointees, Megan Sykes, Riccardo Dalla-Favera and Ulf Klein, to the department. Megan Sykes, in particular, has been busy setting up the Columbia Center for Translational Immunology (CCTI), a cross-departmental initiative that will emphasize translation of basic immunological research to humans.

I believe we are well on our way in establishing a vibrant program in immunology at Columbia that will complement our traditional strength in microbiology. To better reflect these developments we have changed the name of the department to Microbiology & Immunology. I am hopeful that going forward, the department will become a leading center for fundamental research on immunological mechanisms, microbial biology and host-pathogen interactions. I am excited to report that over the past couple of years, members of the department have made many new and exciting discoveries in fields of immunology, pathogenesis, and model systems, and a list of publications from the department over the last year is included in this newsletter. To provide better insight into some of the exciting research that is being carried out, we have highlighted research reported in three major publications this year. We hope to enhance this section of the newsletter in the future by also including descriptions of particular research programs.

I am also pleased to note that after a few difficult years, our graduate education program has been revived. Under the able supervision of David Fidock, who is the Director of Graduate Admissions, we have recruited 12 students in three years, and along with students from the Integrated Graduate Program and the M.D.-Ph.D. program, Microbiology & Immunology now has enough students to provide a community that is so essential for an exciting graduate school experience. The graduate students in the program are now overseen by Boris Reizis, who is the new Director of Graduate Studies. I am hopeful that going forward, the department will attract the best graduate students on campus.

Probably most visible among the recent changes has been the extensive renovations of our physical facilities, including a complete reconstruction of the ninth floor of Hammer. In addition, we have established several essential core facilities, including those for flow cytometry and confocal microscopy. These long-deferred investments have made our physical appearance welcoming and functional; however, significant challenges still remain, including inadequate facilities for housing laboratory mice. Still, I am optimistic that these intractable issues will be addressed in the near future.

I would also like to use this newsletter to reach out to our alumni, and welcome them to join us in establishing an alumni network. We would like to invite you to visit the department, and would love to hear your comments and suggestions as we move forward in revitalizing the department. We will use both traditional (e.g. this newsletter) and modern (e.g. Facebook) approaches to make you aware of the events that we plan to organize in the future. We are fortunate that David Fox, J.D., Ph.D. '90, has agreed to continue to serve as the Chair of the Alumni Advisory Board. Please feel to reach out to David or myself about any issues that may arise or any suggestions you may have. Finally, I would like to thank Oliver Jovanovic and Shomik Ghosh for helping to put this newsletter together. They are also working to redo our website, which should be completed over the summer. The administration of the department continues to be in the capable hands of Edie Shumansky, who with the members of the office including Carol, Angielina, Joan and Elizabeth, makes sure that bills get paid and we all keep to our budgets.

I would like to end by thanking all of you for your support and help as we go about making the department the preeminent place for cutting-edge research and education in microbiology and immunology.

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

Happening at Hammer

Heidelberger-Kabat Lecture

This year's Heidleberger-Kabat lecture, which is part of the Dean's lecture series but administered by the Department of Microbiology & Immunology, was presented by Dr. Laurie Glimcher, the Irene Heinz Given Professor of Immunology at the Department of Immunology and Infectious Diseases at the Harvard University School of Public Health. Dr. Glimcher is renowned for her seminal discoveries on T-cell development and function and on mechanisms of osteoblast differentiation. Her lecture was titled "Mammalian Stress Sensors in Health and Disease." This year's lecture was very well attended, and was followed by a reception at the HHSC Riverview lounge.

The Heidelberger-Kabat Lecture's foundations date to the mid-1950s when the university instituted a lecture series to honor Dr. Michael Heidelberger, Columbia's first professor of immunochemistry and the founding father of the field. Subsequently, the university established a symposium named for Dr. Elvin Kabat, a Columbia professor in the Department of Microbiology & Immunology who studied under Dr. Heidelberger and whose research led to the identification of the proteins responsible for antibody activity. In 2001, the families of Dr. Michael Heidelberger and Dr. Elvin A. Kabat, in conjunction with the University, formally established the Heidelberger-Kabat Distinguished Lectureship in Immunology to honor Drs. Heidelberger and Kabat, longtime colleagues and friends, by sponsoring an annual lecture by a scientist representing the best current research in immunology.

AID Targeted to Both DNA Strands by RNA Exosome

A role for non-coding RNA surveillance machinery in antibody diversity

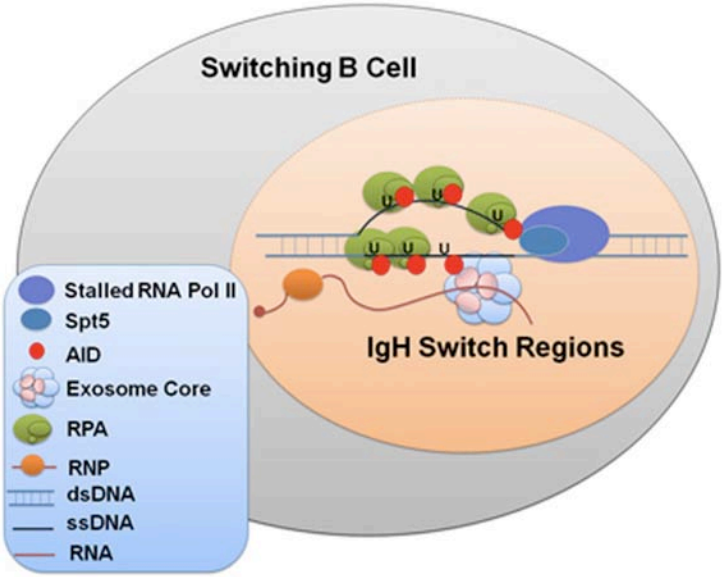
Uttiya Basu, Assistant Professor of Microbiology & Immunology

Antigens that can elicit an immune response are almost infinite in number. However, there are only a very finite number of genes at our disposal to synthesize antibodies specific for each of these potentially harmful antigens. B lymphocytes resolve this seemingly insurmountable challenge by undergoing three impressive processes, each making a powerful contribution to the organism's ability to fend off attacks by potential pathogens.

First, immature B lymphocytes in the bone marrow undergo V(D)J recombination, which dramatically increases the immunoglobulin (Ig) repertoire of the organism. Then, these B cells migrate to secondary lymphoid organs, where they go through somatic hypermutation to increase the affinity of an immunoglobulin for the epitope it binds. Finally, they undergo class switch recombination (CSR) to diversify and best tailor the kind of effector function that results from interacting with an antigen. These last two genetic alterations, which establish antibody memory, absolutely require the activity of the ssDNA cytidine deaminase AID.

It is imperative to understand the mechanism of function of AID, since loss of AID activity leads to immune-deficiencies known as hyper IgM-syndrome, whereas hyper-AID activity initiates aberrant chromosomal lesions and translocations that lead to oncogenesis. In this regard, most B cell lymphomas are caused by chromosomal translocations of the Ig locus that lead to deregulated expression of proto-oncogenes. Furthermore, a large number of germinal center derived B-cell lymphomas are associated with hypermutation of proto-oncogenes at signature AID substrate motifs. Although the importance of AID as a key regulator of adaptive immunity and potential oncogene is well established, the molecular mechanism by which AID performs its function is not completely understood. How AID identifies its physiological target sequences in the B cell genome and imparts mutations on DNA is an active area of investigation.

In our recently published work we have implicated the cellular non-coding RNA-processing/degradation complex, RNA exosome, in targeting AID to both DNA strands. In B cells activated for CSR, the RNA exosome associates with AID, accumulates on IgH switch regions and promotes optimal CSR. Moreover purified RNA exosome complex imparts robust AID- and transcription-dependent DNA deamination of both strands of transcribed DNA substrates in vitro, thus providing vital mechanistic insight into molecular mechanism of AID action. Our findings reveal a role for non-coding RNA surveillance machinery in generating antibody diversity. Future work will focus on the role of non-coding RNAs and RNA exosome complex during generation of adaptive immune response using various mouse model systems.



Citation Basu, U.*, Meng, F.L., Keim, C., Grinstein, V., Pefanis, E., Eccleston, J., Zhang, T., Myers, D., Wasserman, C.R., Wesemann, D.R., Januszyk, K., Gregory, R.I., Deng, H., Lima, C.D., Alt. F.W.*. (2011) The RNA exosome targets the AID cytidine deaminase to both strands of transcribed duplex DNA substrates. *Cell* **144:** 353-363. (*corresponding authors)

Left Graphical abstract highlighting targeting of AID to both strands of DNA by the RNA exosome cellular RNA-processing/degradation complex.

More than Just Powerhouses

Once considered only in terms of energy production, mitochondria have now been found to play a key role in the innate immune response.

Sankar Ghosh, Professor of Microbiology & Immunology

The phagocytic response of the innate immune system is critical for the effective clearance of microbial pathogens and is indispensable for host defense. Macrophages and neutrophils sense microbes and initiate phagocytosis upon engagement of a diverse repertoire of receptors, some of which directly recognize microbial products, such as Toll-like receptors and scavenger receptors, while others detect opsonized microbial products, such as Fc- and complement receptors. Upon internalization, phagosomes mature and fuse with lysosomes leading to proteolysis and microbial killing. Phagosomal maturation is also coupled to the production of reactive oxygen species (ROS) via the NADPH oxidase-dependent respiratory burst, a necessary effector response for the destruction of intracellular microbes. Although signaling via TLRs and other innate immune receptors is necessary for robust ROS production, the exact molecular mechanisms that couple TLR signaling to ROS production remain to be determined.

In addition to NADPH oxidase, the mitochondrial oxidative phosphorylation (OXPHOS) machinery generates ROS when electrons prematurely escape OXPHOS complexes I and III and react with molecular oxygen to generate superoxide. Mitochondria are major sites of ROS production in most cells; however, mROS have traditionally been regarded as byproducts of oxidative respiration, and therefore their synthesis was believed to be unregulated. Several studies have suggested that mitochondrial ROS (mROS) also contribute to macrophage bactericidal activity, although the mechanisms linking innate immune signaling to mitochondria for mROS generation remain unclear.

In our recent study, we demonstrated that engagement of a subset of Toll-like receptors (TLRs 1, 2 and 4) results in the recruitment of mitochondria to macrophage phagosomes and augments mROS production. This response involves translocation of the TLR signaling adapter TRAF6 to mitochondria where it engages ECSIT, a protein implicated in mitochondrial OXPHOS complex I assembly. Interaction with TRAF6 leads to ECSIT ubiquitination and enrichment at the mitochondrial periphery, resulting in increased mitochondrial and cellular ROS generation. ECSIT and TRAF6 depleted macrophages exhibit decreased levels of TLR-induced ROS and are significantly impaired in their ability to kill intracellular bacteria. Additionally, reducing macrophage mROS by targeting catalase to mitochondria results in defective bacterial killing, confirming the role of mROS in bactericidal activity. Our results therefore reveal a novel pathway linking innate immune signaling to mitochondria, implicate mROS as important components of antibacterial responses, and further establish mitochondria as hubs for innate immune signaling.

Citation West, A.P., Brodsky, I.E., Rahner, C., Woo, D.K., Erdjument-Bromage, H., Tempst, P., Walsh, M.C., Choi, Y., Shadel, G.S. and Ghosh, S. (2011) TLR signalling augments macrophage bactericidal activity through mitochondrial ROS. *Nature* **472:** 476–480.

Left A review by Ghosh and West on the role of mitochondria in innate immunity was recently featured on the cover of Nature Reviews Immunology.


MICROSCOPE / OBJECTIVE SHUTTER PARTS
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SUTTER INSTRUMENT CO.

Cell Shape and Division

New research suggests how cells sense their shape and may predict how cells of any shape will divide.

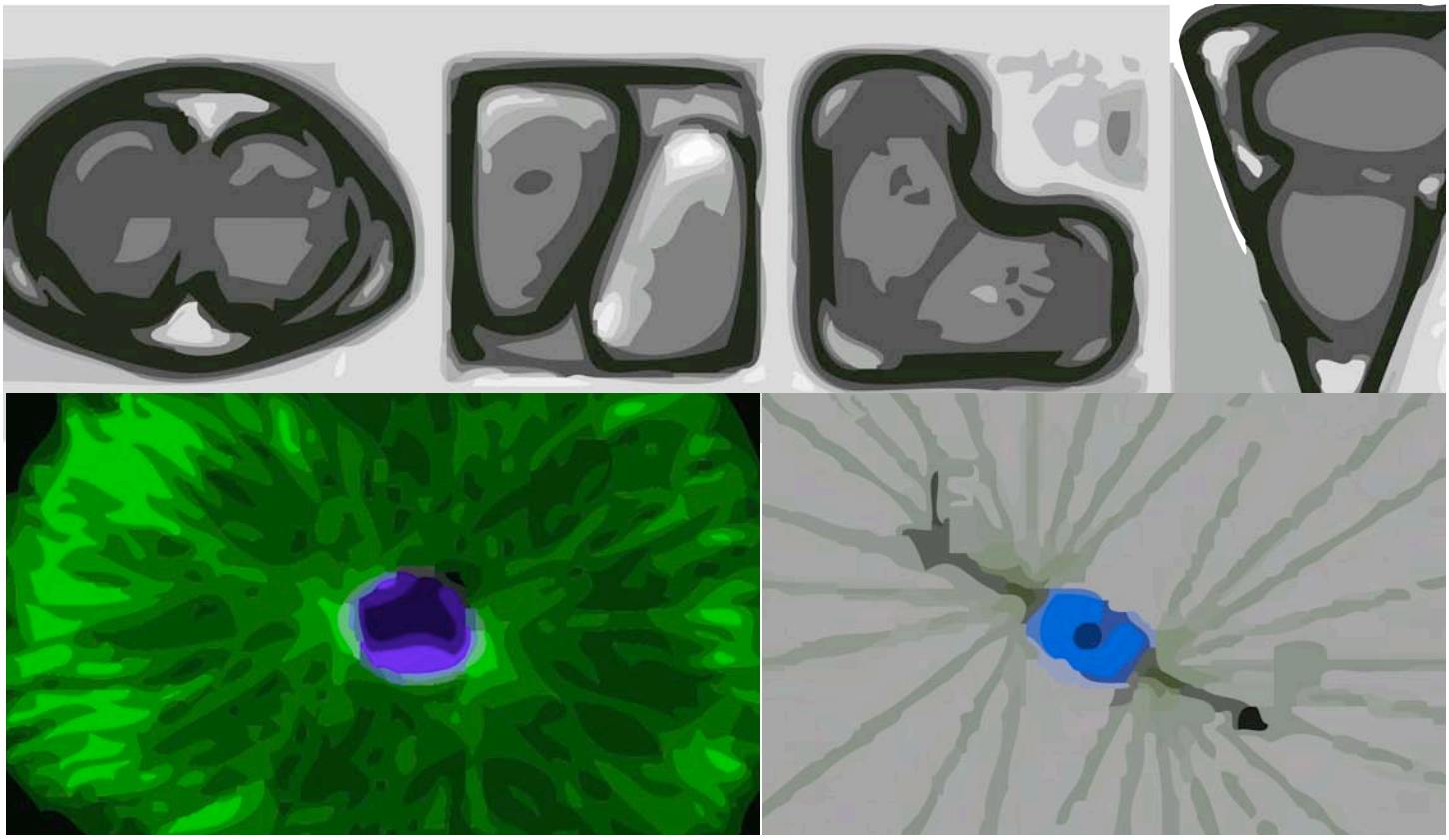
Fred Chang, Professor of Microbiology & Immunology

How do cells sense their own shapes? During development, cells adopt a wide variety of geometrical configurations, such as spherical, ellipsoidal, and polyhedral shapes. It has been appreciated since the 1800s that the shape of cells somehow influences where cells divide during cytokinesis. In this paper, we investigated how cell shape affects the positioning of the nucleus, which ultimately determines the positioning of the cell division plane. We devised a way to manipulate cell shape in a systematic manner, by placing individual sea urchin eggs into microfabricated chambers of defined geometry (e.g., triangles, rectangles, and ellipses).

In each shape, the nucleus was rapidly positioned at the center of mass by microtubules. We further noticed that the nucleus was stretched by microtubule-dependent forces along an axis that was perpendicular to the future division plane; the nucleus could be used then as a force-sensor for these microtubule-based forces. To test mechanisms, we developed a simple computational model that posits that microtubules sense cell geometry by probing cellular space and orient the nucleus by exerting pulling forces that scale to microtubule length. This model quantitatively predicted the division plane for a wide variety of cell shapes, even in multicellular contexts. This work suggests that cells sense their shape using microtubules that probe the cell boundaries. Further, these studies reveal a simple and possibly universal rule that predicts how cells of any shape will divide.

Citation Minc, N., Burgess, D. and Chang, F. (2011) Influence of Cell Geometry on Division-Plane Positioning. *Cell* **144:** 414-426. (A Cell Research Highlight)

Below Graphical abstract highlighting cell shape and sensing through length-dependent microtubule forces, which in turn impacts positioning of the nucleus, spindle and division axis.



IN & AROUND

The Goings-on in Hammer

Renovations

Rebuilding the Department Floor by Floor

We have completed renovations of the 12th floor of the Hammer Health Services Building. In addition to housing our administrative offices, a brand new conference room, and a number of research laboratories, the 12th floor is now home to our Flow Cytrometry Core and our Microscopy Core.

Our new Flow Cytometry Core is located in HHSC 1211A. The shared resource operates three flow cytometers: two LSRII designed for multi-fluoresence analysis and a custom configured FACSAriaII-SORP high-speed cell sorter. We will add more systems as demand increases.

In addition to these systems, our new Microscopy Core facility, which is located in HHSC 1201, has a state-of-the-art Zeiss LSM710 ConfoCorr confocal imaging microscope system, a Zeiss AxioVert Microscope, and a Typhoon Gel Imaging system.

The 9th floor of the Hammer Health Sciences Building had not seen any renovations since 1977, and had suffered from flooding. It has been completely renovated with state of the art research facilities.

In addition, the Hammer 15th floor lobby and corridors have also been renovated, along with improvements to the mechanical infrastructure.

Promotions

Dworkin and Reizis

Two of our junior members of the faculty (well, not so junior any more) were promoted to Associate Professor with tenure over the past year. Boris Reizis joined the department in 2003 and during his tenure here has made major contributions to our understanding of stem cell identity and dendritic cell differentiation. Jonathan Dworkin joined us in 2004 and his work has focused on understanding the mechanism of peptidoglycan synthesis and the pathways used for sensing of peptidoglycan. Congratulations to them both for this well-deserved accomplishment.

Alumni News

Lori Sussel, Ph.D.

Lori Sussel obtained her doctorate in the laboratory of David Shore in the Department of Microbiology & Immunology in 1993, and was also a recipient of the departmental Richard C. Parker Award. After performing postdoctoral research at the University of California at Berkeley and San Francisco, Lori returned to Columbia University as a faculty member in the Department of Genetics & Development, where she is currently an Associate Professor. The research in her lab combines molecular biology techniques and mouse embryology to study the role of transcriptional regulatory factors in specifying the development and differentiation of the pancreatic islet during mouse embryogenesis. The knowledge gained from these studies will contribute to the generation of new sources of beta cells for the treatment of type 1 diabetes.

Peter Covitz, Ph.D.

Peter Covitz obtained his doctorate in the laboratory of Aaron Mitchell in the Department of Microbiology & Immunology in 1993, and was also a recipient of the departmental Richard C. Parker Award. After performing postdoctoral research in genomics and bioinformatics at Stanford University, Peter worked as a research scientist and manager at Incyte Pharmaceuticals and Molecular Applications Group, and then at InforMax as Vice-President of Professional Services. He then joined the National Cancer Institute in Bethesda, Maryland, where he served as Chief Operating Officer at the NCI's Center for Biomedical Informatics and Information Technology. In 2008, Peter joined Nordion, where he has been Senior Vice-President of Innovation since 2010.

Retreat

2011 Microbiology & Immunology Retreat at Basking Ridge

The Department of Microbiology & Immunology will hold its annual retreat on September 8 and 9, 2011 at the Dolce Basking Ridge Conference Center in Basking Ridge, NJ. We are grateful that 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 will be our guest and will present the keynote lecture. Dr. Lipkin is a physician-scientist who is internationally recognized for his work with the West Nile and SARS viruses, and for pioneering a number of techniques for the identification of emerging pathogens. Dr. Lipkin is a fellow of the American Society for Microbiology and the American Association for the Advancement of Sciences and is the winner of numerous scientific prizes and honors.

Gottesman Elected to Academy

Max Gottesman, Professor of Microbiology & Immunology, was elected a Fellow of the American Academy of Arts & Sciences on April 19, 2011. Dr. Gottesman was selected for his studies of transcription termination in *E. coli* bacteria. He has shown that translation and transcription are coupled by the NusG protein and that failure to terminate transcription leads to chromosome breaks. Failure to repair such breaks can have catastrophic effects, including cancer. Other work involves the mechanism of DNA double-strand break repair and the linkage between repair and DNA methylation. Dr. Gottesman and his colleagues have determined that PTPD1, the protein tyrosine phosphatase that activates Src, is up-regulated in bladder cancer.

Silverstein Elected to AAAS

Saul Silverstein, Professor of Microbiology & Immunology, was elected a Fellow of the American Association for the Advancement of Sciences on January 11, 2011. Dr. Silverstein was selected for "distinguished contributions to the field of biology and medical sciences." In particular, Silverstein was recognized for "development of the process of cotransformation of mammalian cells," which allows foreign DNA to be inserted into a host cell to produce certain proteins. Other notable accomplishments by Silverstein include the development of diagnostic reagents for the identification of human papillomaviruses, unraveling the transcriptional cascade of herpes simplex virus and most recently the interplay of viruses with host restriction factors.

2011 Alumni Advisory Board

The Alumni Advisory Board for the Department of Microbiology & Immunology has begun to plan future alumni events, including an alumni picnic in New York City as well as other alumni get-togethers or meetings. David Fox, J.D., Ph.D. is the current Chair of the department's Alumni Advisory Board. David obtained his doctorate in the laboratory of Alex Goldfarb in the Department of Microbiology & Immunology in 1990, then went on to study law at Loyola University New Orleans, becoming an attorney practicing intellectual property law with a focus on biotechnology. He is currently the sole author of U.S. Patent Opinions and Evaluations, an annual treatise by Oxford University Press, and Of Counsel at Osha Liang, an intellectual property law firm with offices in Texas, California, France, and Japan. If you have any interest in getting involved in the Alumni Advisory Board or have suggestions for alumni events, please contact David at dlf84@columbia.edu.

New Students

David Corrigan joins us from Johns Hopkins, where he completed an M.S. in May. **Veronkia Grinstein** attended SUNY Stony Brook as an undergraduate, majoring in Biochemistry. **Joseph Thome** attended Oberlin College as an undergraduate.

Dalla-Favera Joins Department

Renowned Cancer Researcher Newest Addition to Department

Riccardo Dalla-Favera, M.D., distinguished investigator in the molecular genetics of cancer, joined the Department of Microbiology & Immunology on July 1st. Dr. Dalla-Favera currently serves as the Director of the Herbert Irving Comprehensive Cancer Center at Columbia University and the Percy and Joanne Uris Professor of Pathology and Genetics & Development.

A luminary in the field of cancer research, Dr. Dalla-Favera is internationally regarded for his work on the molecular pathology of lymphoid malignancies, and was the first investigator to identify and clone several human protooncogenes and to demonstrate their involvement in cancer-associated chromosomal amplifications and translocations. Among his numerous contributions to the field, notable accomplishments include the identification of myc and myb oncogene amplification and translocations in human leukemias, identification of myc target genes, characterization of BCL-6 associated translocations in human cancers and the delineation of molecular mechanisms associated with BCL-6 function in normal and malignant cell growth and differentiation. A prolific researcher, Dr. Dalla-Favera has authored over 250 articles in peer-reviewed journals, and has served on numerous editorial boards throughout his career. He has been recognized with several national awards, including the Stohlman Award from The Leukemia Society of America and two NIH MERIT Awards, and was recently elected into the Institute of Medicine.

Dr. Dalla-Favera completed both his M.D. and residency training at the University of Milan before joining the National Cancer Institute as a visiting fellow. In 1983, he joined the New York University School of Medicine as an Assistant Professor, later moving to the Columbia University College of Physicians and Surgeons in 1991.

Kang Liu

Recruitment

Dr. Kang Liu, Assistant Professor, joined the Department of Microbiology & Immunology on July 1, 2010. Dr. Liu previously worked at the Laboratory of Molecular Immunology with Michel Nussenzweig at Rockefeller University.

Dr. Liu studies molecular regulation of dendritic cell development and function with the long-term goal of finding novel ways to manipulate DC development and activity and apply the findings to vaccine development and treatment of infectious disease and cancer.

Uttiya Basu

Recruitment

Dr. Uttiya Basu, Assistant Professor, joined the Department of Microbiology & Immunology on September 1, 2009. Dr. Basu previously worked in the laboratory of Frederick W. Alt at the Immune Disease Institute and Harvard Medical School.

Dr. Basu studies genomic alterations and generation of adaptive immunity, with a focus on the activity of the enzyme activation induced cytidine deaminase (AID). Human patients with inactivating mutations in the AID gene suffer from severe immunodeficiency leading to Hyper-IgM syndrome (HIGM2), whereas hyperactivity of AID leads to various B and T cell malignancies.

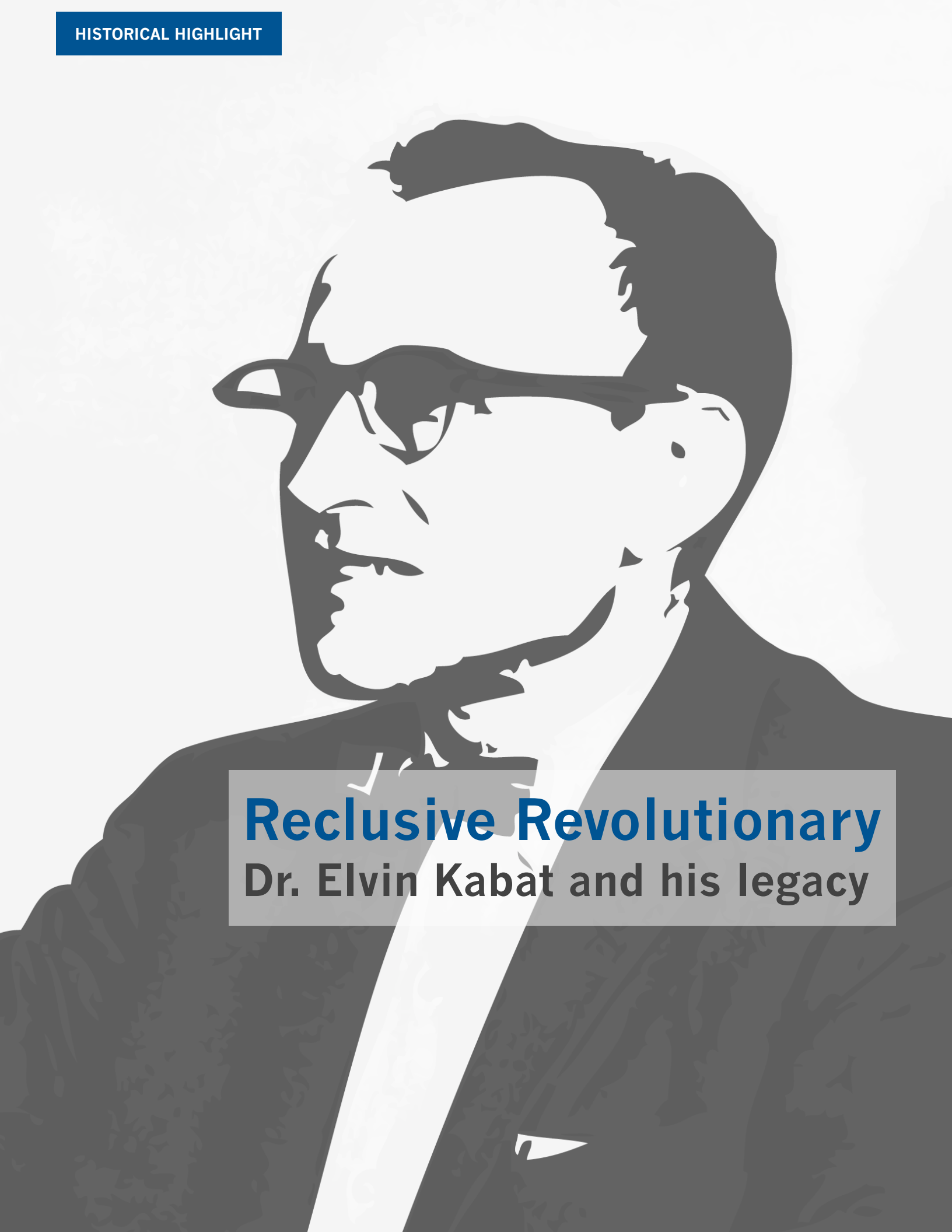
Ivaylo Ivanov

Recruitment

Dr. Ivaylo Ivanov, Assistant Professor, joined the Department of Microbiology & Immunology on January 1, 2011. Dr. Ivanov previously worked in the laboratory of Dan R. Littman at the New York University School of Medicine.

Dr. Ivanov studies the role of intestinal commensal microbiota in TH17 cell differentiation and function with the long-term goal of identifying bacterial species or products that can be used to modulate the immune response to protect from infections with enteric pathogens to treat chronic inflammation.

HISTORICAL HIGHLIGHT



Reclusive Revolutionary

Dr. Elvin Kabat and his legacy

The Reclusive Revolutionary

From both the bench and beyond, Dr. Elvin Kabat had an immeasurable impact, leaving behind a legacy that remains with us to this day.

Dr. Elvin A. Kabat, one of the founding fathers of modern immunochemistry, was a respected and beloved member of the faculty in the Department of Microbiology & Immunology for over half a century. In addition to his remarkable contributions to immunology, including over 470 publications and several leading textbooks, Kabat was an outstanding teacher and mentor, whose students, including Nobel Laureate Baruj Benacerraf, went on to make outstanding contributions to the field. The extent of Kabat's contributions are astounding, particularly considering the unexpected challenges his career faced.

Kabat began working in Dr. Michael Heidelberger's immunochemistry lab at Columbia in 1933, at the age of 18, first as a lab assistant, then as a graduate student. Kabat was Dr. Heidelbergers''s first student to be awarded a Ph.D. in 1937, for his graduate research on the immunochemical and physical properties of antibodies. Afterwards, Kabat spent a year as a postdoctoral researcher, funded by the Rockefeller Foundation, in the laboratory of The Svedburg at the Institute of Physical Chemistry in Uppsala, Sweden, where he worked with Arne Tiselius and performed the first immunochemical characterization of immunoglobulin G, using electrophoresis to show that immunoglobulins comprise the "gamma globulin" fraction of human serum. In late 1938, Kabat returned to the U.S. as an Instructor in the Department of Pathology at Cornell University, where he worked on purifying Rous sarcoma virus. In 1941, Kabat returned to Columbia University as a Research Associate in the Department of Biochemistry assigned to Neurology, where he was to perform research on multiple sclerosis.

The involvement of the United States in World War II starting in December 1941 had a major impact on Kabat's research and career. Kabat's research shifted to working on immunization against meningitis, developing more accurate tests for syphilis, and performing classified research for the National Defense Research Committee (NDRC) on detecting and neutralizing the plant toxin ricin. Part of this classified research involved immunizing a pair of horses with ricin to prepare a stock of antitoxin, which Kabat had to purchase at a horse auction and keep stabled at Rockefeller University at an exorbitant monthly rate. When Kabat tried to cut costs by selling the horse that failed to produce antibodies, he had to justify its lower resale value to the NDRC in the following manner: "...as a consequence of the numerous injections which the horse had received, it had developed many unsightly blemishes and had acquired a very intractable disposition, which in my judgment had reduced its value from $125 to $25." This incident eventually led to a ruling that government supported investigators could dispose of research animals in any way they saw fit, including sale.

During the war, Kabat hired Hilda Kaiser to work in his laboratory. Her husband, Samuel Kaiser, had been dismissed from Brooklyn College as a consequence of the New York State Legislature's anti-communist Rapp Coudert Committee, one of many similar committees that formed between WWII and the end of the

McCarthy era. Kabat also began to write his seminal textbook, *Experimental Immunochemistry,* with Manfred Mayer, and served as a consultant for the US Army at Fort Detrick, writing a report with Theodor Rosebury on potential biological warfare agents. Kabat and Rosebury had voluntarily refrained from publishing the report during the war, but once the war ended, they obtained clearance from the War Department and Columbia University to publish their review. The publication resulted in a burst of publicity, including an article in Time magazine that implied that Kabat was a communist supporter and had published classified information. Although this was untrue, it immediately resulted in an FBI investigation of Kabat, with FBI agents interviewing his landlord and opening his mail.

In 1946, after being passed over for promotion to Assistant Professor from Research Associate in the Department of Biochemistry, Kabat accepted a faculty appointment as an Assistant Professor in the Department of Bacteriology (now the Department of Microbiology & Immunology). By 1947, Kabat's new laboratory was performing research on blood group substances, encephalomyelitis, and quantitating allergic reactions. In 1948 Kabat was promoted to Associate Professor, and began to perform research on developing diagnostic assays for multiple sclerosis, initially funded by the National Multiple Sclerosis Society, and then Public Health Service. Kabat also began collaborating on histochemical localization of enzymes with Abner Wolf at the Bronx Veterans Administration (VA) Hospital as an attending consultant. This collaboration had unexpected consequences.

In 1947, after Kabat had started working at the VA, an Executive Order was issued by President Truman mandating loyalty investigations of every Federal employee, formation of loyalty boards, and the development of a central master index of each person investigated. A former colleague of Kabat's in Sweden, biochemist and Nobel Laureate James B. Sumner, informed the FBI that he suspected Kabat of being a communist sympathizer. This triggered a series of investigations of Kabat by the FBI and the Bronx VA Hospital Loyalty Board, and the dismissal of Kabat from his VA position by the hospital loyalty board. Kabat appealed his dismissal to the Presidential Loyalty Review Board, which reversed the decision and reinstated him, but continued pressure led Kabat to resign his VA position and abandon his work on the histochemical localization of enzymes. The hospital loyalty board had also issued a recommendation to the Passport Office that Kabat not be allowed to travel, after which Kabat's passport was rescinded, and not returned upon his reinstatement. As a result, Kabat was not able to attend international conferences or travel internationally until 1955, after which a DC district court decision, *Boudin v. Dulles,* held that passports could not be denied based on undisclosed information.

Fortunately for Kabat, he had the full support of the Department of Microbiology & Immunology during this difficult period. When Harry M. Rose was appointed Chair of the department in 1951, he accepted the position under the conditions that Kabat would be promoted to full Professor and have his salary supported by departmental funds, which took place in 1952. Kabat also received support from an unexpected source – the US Navy. In 1950, Kabat was invited to speak at the Naval Biological Laboratory, the Navy's equivalent of Camp Detrick. In 1952, the Office of Naval Research offered Kabat a grant for immunochemical criteria of purity of proteins and polysaccharides, which as it turned out, was most fortuitous. A year later, in 1953, at the peak of McCarthy era hysteria, the Public Health Service (at the time, the equivalent to the NIH) refused to renew Kabat's research grant on multiple sclerosis due to the political climate, suggesting that perhaps another name could be substituted as the responsible investigator, which Kabat refused to do. At the time, Kabat had developed the first reliable immunodiagnostic test for multiple sclerois, developed a successful animal model of multiple sclerosis, established the autoimmune character of this disease, and was running the only monkey colony in the world devoted to multiple sclerosis. Public Health Service also terminated Kabat's blood group grant. Kabat never again requested or accepted funding from them. His future research would be funded by the Office of Naval Research and the National Science Foundation.

Despite the tremendous blow suffered to two of his primary areas of research from the sudden termination of these grants, Kabat continued to perform pioneering research. In 1951, Kabat showed that dextran, commonly used as a blood plasma substitute at the

time, could provoke an immune response in humans. He took advantage of his expertise in carbohydrate chemistry to test the impact of a series of oligosaccarides on dextran binding antibodies, and used this data to provide the first estimates of the size and shape of an antibody's antigen binding site, confirmed decades later by X-ray crystallography.

In 1970, Kabat began to perform bioinformatics research in immunology, decades before sequence analysis became widely accepted. He realized that the amino acid sequence data for immunoglobulins now being published could be used to predict the locations of antigen binding regions. Kabat developed the Wu-Kabat plot with Tai Te Wu, which identified hypervariable and framework regions, and used this data to correctly predict the location of antigen binding regions in antibodies. Lacking modern tools, Kabat had to locate, enter and align immunoglobulin sequences from the published literature by hand. The data was eventually distributed in collaboration with the NIH as a textbook, called Sequences of Proteins of Immunological Interest, which had an enourmous impact on the field of immunology. In 1974, Kabat spent a year at the NIH as a Fogerty Scholar, and subsequently divided his time doing research at Columbia and working on immunological sequence data at the NIH.

Kabat was awarded the Louisa Gross Horwitz Prize by Columbia University in 1977 along with Michael Heidelberger and Henry G. Kunkel, and in 1991 was awarded the National Medal of Science, the nation's highest award for scientific achievement. This last award had particular significance to Kabat, given his shabby treatment at the hands of the government and Public Health Service in the 1950s.

Dr. Elvin A. Kabat remained an active member of the Department of Microbiology & Immunology until his death in 2000. He is deeply missed and remembered by his colleagues in Microbiology & Immunology not only for his outstanding scientific mind but also for his high standards, his forthrightness, and his wonderful sense of humor.

In 2001, the families of Dr. Michael Heidelberger and Dr. Elvin A. Kabat, in conjunction with Department of Microbiology & Immunology and the University, formally established the Heidelberger-Kabat Distinguished Lectureship in Immunology to honor Drs. Heidelberger and Kabat, longtime colleagues and friends, by sponsoring an annual lecture by a scientist representing the best current research in immunology. The Heidelberger-Kabat Lecture has emerged as one of the country's premier forums for the discussion of new developments and discoveries in immunochemistry.

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.

Carlson Lab

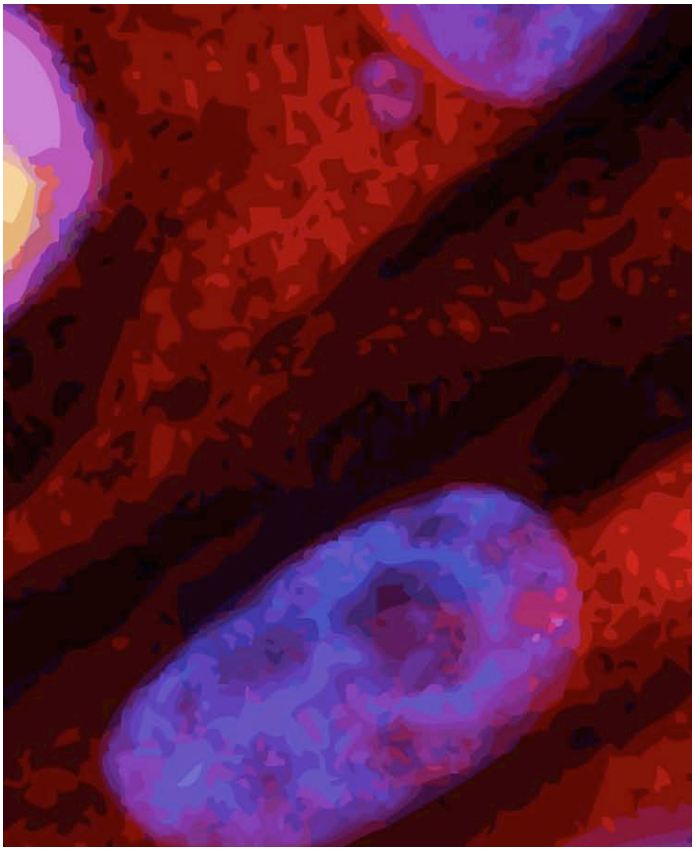
Marian Carlson's lab uses genetic analysis in yeast to study the function and regulation of the highly conserved SNF1/AMPK protein kinase signaling pathway. SNF1/AMPK has central roles in energy regulation and stress responses, and in humans, AMPK has roles in type 2 diabetes, obesity, and cancer. SNF1/AMPK is activated by phosphorylation, and the lab's current work focuses on control of this phosphorylation by upstream kinases and protein phosphatases. Their recent studies implicate multiple protein phosphatases in the yeast system, and future efforts will address whether the human counterparts of these phosphatases have roles in regulating AMPK.

Chang Lab

Fred Chang's lab 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 lab 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 lab 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

The David Figurski laboratory is studying 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 lab 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

The Max Gottesman 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

The Ivalyo Ivanov lab 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.

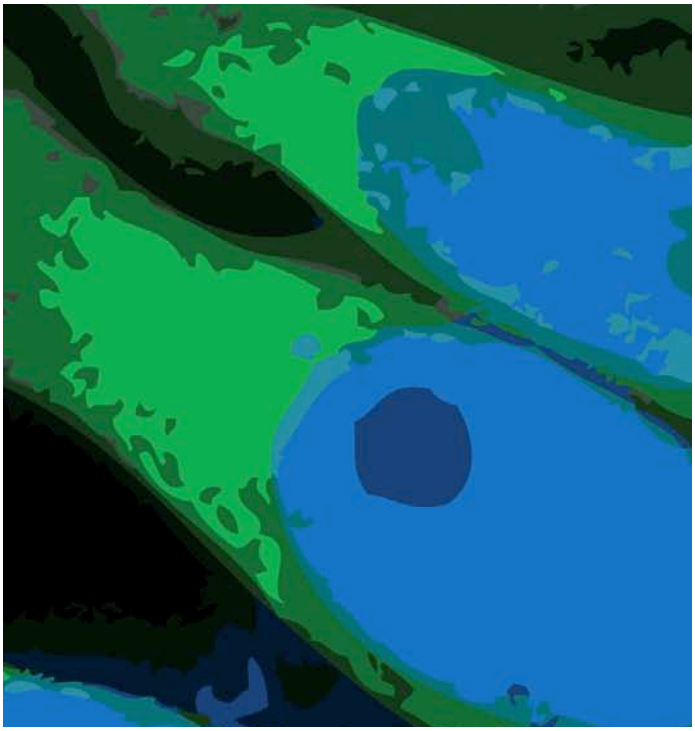
Klein Lab

Ulf Klein's lab 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 lab 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.



Ratner Lab

Adam Ratner's laboratory studies host-pathogen interactions, with a focus on bacterial colonization of mucosal surfaces. Recently, members of the laboratory have identified and characterized new pore-forming toxins from mucosal pathogens, including inerolysin from *Lactobacillus iners* and vaginolysin (VLY) from *Gardnerella vaginalis.* These proteins are members of a widespread family of Gram-positive toxins, the cholesterol-dependent cytolysins. VLY is of particular interest, as it is human-restricted and requires the GPI-anchored protein hCD59 on target cells for activity. Recently, the hCD59-transgenic mouse has been developed as a model for *G. vaginalis* and is being used to study the role of VLY in establishment and maintenance of colonization and in the initiation of innate immune responses at the mucosal surface. These studies have recently expanded to patient populations and are focused on the production of VLY and its relationship to inflammation during *G. vaginalis* colonization of humans. In the same study, members of the lab are evaluating a quantitative VLY ELISA as a new diagnostic tool for potential clinical use.

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.

Reizis Lab

The Boris Reizis lab 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

The Christian Schindler 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 lab 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.

Student News

Graduate student **Kanako Lewis** received the 2011 Richard C. Parker Graduate Student Award. Her research in the Reizis laboratory has focused on the genetic and functional analysis of dendritic cells (DCs), the key pathogen-sensing cell type in the immune system. She identified a novel functional subset of DCs in the spleen, and helped to define an essential role of plasmacytoid DCs in chronic viral infection.

The department established the Richard C. Parker Memorial Fund following Dr. Parker's death in 1986. This fund is used to sponsor, each year, a seminar by an outstanding scientist. The speaker is selected and hosted by the graduate students of the department, and spends the day talking with the students. This year, the students selected Professor Philippe Sansonetti as the 2011 Parker Award Speaker.

Eleni Mimitou, former student, received the 2011 Dean's Award for Excellence in Research for her doctoral research in the Symington laboratory. Her identification of the role of Sgs1 and Sae2 in a two-step mechanism of DNA double-strand break processing has increased our understanding of how cells maintain genomic stability. Eleni's work with Dr. Symington was recently published in both *Cell* and *EMBO Journal*.

The Dean's Award for Excellence in Research is awarded annually to the graduating Ph.D. student judged by a faculty-student committee to be most outstanding in his/her research accomplishment.

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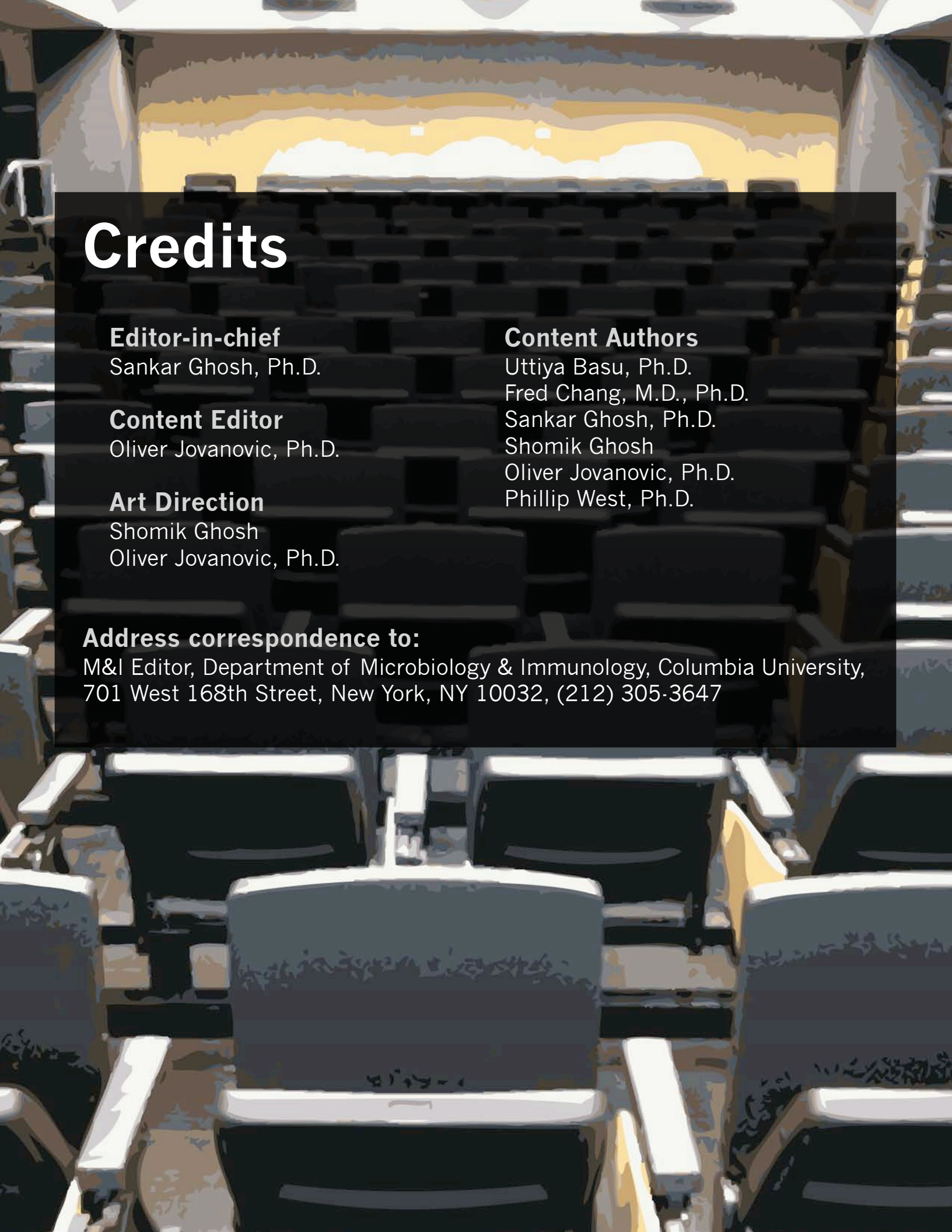
Events & Seminars

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, at which Dr. Ian Lipkin will be the keynote speaker. A full list of all events can be found on our website, www.microbiology.columbia.edu

Sep. 8-9	**M&I Retreat at Basking Ridge**
Sep. 21	**Roger Greenberg**
Sep. 28	**Michele Pagano**
Oct. 5	**Brett Finlay**
Oct. 12	**Mark Schlissel**
Oct. 19	**Seth Darst**
Oct. 26	**Barry Sleckman**
Nov. 2	**Stephen Smale**
Nov. 9	**Pippa Marrack**
Nov. 16	**Art Weiss**
Nov. 30	**Akiko Iwasaki**
Dec. 7	**Leo Lefrancois**



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