M&I

SUMMER 2013

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

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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**

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Improving, non-stop

Upgrading 168 St Station

What's happening?

MTA New York City Transit is upgrading the 168th Street and 181st Street stations on the 1. We are repairing the over-the-track brick arches, the historic terra cotta ceiling medallions, and the marble and mosaic wall panels; installing new reinforced cement ceiling panels; and improving guardrails on the cross-track bridges. We are also installing new granite floors on the platform and mezzanine levels, providing new platform lighting, replacing platform edges, installing Help Points, and making other structural and architectural station repairs.

Benefits 14,500 daily customers

- Repaired and reinforced brick arch ceilings
- Restored historic features and more appealing station environment
- Improved platform illumination and station communications

Cost

$66.7 million
(for both stations)

Completion

3rd Quarter 2015

We're working

- Brick arch, terra cotta
  marble and mosaic wa
- New granite floors, ce
  lighting, and platform e
- Help Point equipment
- Various structural and

Learn more about our capital program at mta.info/capital

Message from the Chair

I AM PLEASED to present the Summer 2013 Issue of M&I, the Department of Microbiology & Immunology newsletter.

In this issue, we have once again highlighted the science being carried out in the department, as well as different departmental activities. We have profiled research from the laboratories of Prof. Lorraine Symington, Prof. David Fidock and Prof. Donna Farber. Drs. Symington and Fidock are long time members of our department, but Dr. Donna Farber has just formally joined the department as a joint appointee. Dr. Farber came to Columbia in 2011 from the University of Maryland, and is also a member of the Columbia Center for Translational Immunology (CCTI), a cross-departmental initiative that emphasizes translation of basic immunological research to humans. This past year also saw the departure of one of our longest serving faculty members, Prof. David Figurski, who retired after 35 years of dedicated service. We celebrated his many accomplishments with a symposium and a wonderful dinner.

Our graduate program continues to flourish under the able supervision of David Fidock and Boris Reizis, and we have four outstanding new students this fall. Over the past year, with many of the rebuilding efforts having been completed, our goal has been to institute operational policies and programs that result in the department running smoothly. In this regard I would like to thank the very capable help provided by members of our departmental business office led by Edie Shumansky, including Carol, Marisol, Anna and Joan. Amir has helped run our two major equipment cores, namely the FACS and microscope facilities. Other individuals who have helped the department in numerous ways include my former assistant Elizabeth, Oliver and Suja. I would like to welcome my new assistant Carla, as well as Ronnette in the business office. This year, the editing and development of content of the newsletter was the work of Oliver and Suja, while the typesetting, formatting and graphics was as before the work of Oliver and Shomik.

We continue to be excited about the science that is happening in our department although we are, like others, highly concerned about the NIH budget and the impact that it is having on biomedical science in general. While it is unlikely that the budget constraints will disappear, we are hopeful that the political establishment in Washington will realize the incredible long-term value that NIH-funded science provides to the economy, and find the political courage to continue to fund basic biomedical research in the future.

I hope you will enjoy reading this newsletter and I would like to end by thanking all of you for your support and help.

Sankar Ghosh, Ph.D.

DR. LORRAINE SYMINGTON

Double Strand Breaks and Genomic Instability

GENOMIC INSTABILITY that can result from defective DNA double-strand break (DSB) repair mechanisms is a driving force behind tumorigenic transformation. DSBs are highly cytotoxic lesions that can occur during normal cellular processes, such as DNA replication, or following treatment of cells with DNA damaging agents. If DSBs are left unrepaired, or repaired inappropriately, they can trigger mutagenic events including chromosome loss, deletions, duplications, inversions and translocations. Indeed, mis-repair of programmed DSBs is a primary cause of lymphoid malignancies. Two main pathways have evolved to repair DSBs: homologous recombination (HR) and non-homologous end joining (NHEJ). HR relies on the presence of an undamaged homologous duplex, generally the sister chromatid, to serve as a template for repair of the broken chromosome and is generally considered to be error free. NHEJ directly ligates the DSB ends and can occur with high fidelity or be associated with small deletions or insertions at the junctions. Defects in

NHEJ are associated with severe combined immunodeficiency due to the important role of NHEJ in lymphocyte development, whereas compromised HR results in cancer susceptibility and infertility.

The Symington lab uses the budding yeast *Saccharomyces cerevisiae* as a model eukaryotic system to study how cells respond to and repair DSBs. One of the main areas of research in the lab is the mechanism used to process the ends of DSBs to generate long 3' single-strand DNA tails, a process referred to as end resection, which is the essential initial step for repair by HR. Previous studies from the Symington lab demonstrated that the conserved Mre11-Rad50-Xrs2/Nbs1 (MRX/N) complex, together with Sae2/CtIP, initiates end resection while more extensive processing of 5' strands requires the 5'-3' exonuclease, Exo1, or the combined activities of the Sgs1/BLM helicase and Dna2 endonuclease (Mimitou and Symington, 2008).

MRX and Sae2 can act directly to initiate resection by endonucleolytic cleavage of the 5' strand resulting in limited end processing, or act indirectly by recruiting Sgs1, Dna2 and Exo1 to DNA ends. Rad51 binds to the resulting ssDNA tails to initiate pairing and strand invasion with homologous duplex DNA. The 3' invading end from the broken chromosome is used to prime DNA synthesis, templated by the donor duplex, replacing the nucleotides lost by end resection.

Reconstitution of the Sgs1-Dna2 end resection mechanism *in vitro* revealed an essential role for replication protein A (RPA) to promote DNA unwinding by the Sgs1 helicase and to stimulate activity of the Dna2 endonuclease. However, evaluating the role of RPA for end resection is difficult due to the essential role of each subunit of the heterotrimeric RPA complex for DNA replication. To circumvent the lethality of RPA knockout strains, in our most recent work we employed a heat-inducible degron system that renders the Rfa1 protein temperature degradable (td) (Chen et al, 2013).

The RPA complex was rapidly degraded when a yeast strain harboring the td-RFA1 allele was grown at the restrictive temperature. We found that RPA depletion eliminated both the Sgs1-Dna2 and Exo1-dependent extensive resection pathways, but had no effect on the initiation of resection by MRX and Sae2. The Dna2 nuclease failed to localize to DSBs in the absence of RPA, consistent with the defect in end resection. In contrast, Exo1 was able to localize to DSBs without RPA suggesting the role of RPA in promoting Exo1-catalyzed end resection is at a later step. In addition, we discovered that the short single-stranded DNA tails formed in the absence of RPA were unstable due to 3' strand loss and the formation of fold-back hairpin structures. Thus, RPA is required to generate ssDNA, and also to protect ssDNA from degradation and inappropriate annealing that could lead to genome rearrangements.

References: Chen H, Lisby M and Symington LS (2013) RPA coordinates DNA end resection and prevents formation of DNA hairpins. ***Mol. Cell*** 50: 589-600.

Mimitou EP and Symington LS (2008) Sae2, Exo1 and Sgs1 collaborate in DNA double-strand break processing. ***Nature*** 455: 770-774.

DR. DAVID FIDOCK

Genome-editing an Etiologic Agent of Malaria

SEVERE MALARIA, caused by infection with the protozoan parasite *Plasmodium falciparum,* is responsible for over half a million deaths each year. Coordinated malaria control efforts that target the mosquito vector have made a significant impact on the incidence of the disease. Further advances have been achieved with improved access to artemisinin-based combination therapies. However, recent evidence of weakening efficacy of artemisinins in Southeast Asia suggests the parasite may be in the nascent stages of developing resistance to this critical drug.

Evaluating the molecular basis of drug resistance phenotypes, as well as interrogation of the roles of the >5,300 parasite genes in disease pathogenesis and parasite biology, requires the ability to modify the

parasite genome to generate gene knockouts, targeted integrants, and specific alleles of endogenous genes. Although the malaria parasite is genetically tractable, many molecular genetic approaches are laborious and time-consuming, requiring months to achieve stable integration, which can occur randomly in the genome rather than in a more targeted fashion. Clearly, there remains a distinct need for more specific approaches to move the field forward in this era of readily accessible genomic information that informs candidate drug-resistance loci.

Recent work in the Fidock lab has introduced revolutionary new tools of genome editing to the malarial research community. Partnering with researchers at Sangamo BioSciences, we sought to employ novel zinc-finger technology to specifically introduce targeted changes to the *Plasmodium* genome. This approach relies on the generation of unique DNA-binding domains that recognize specific sequences within the target genome. These domains are rationally designed based on well-characterized C2H2 zinc-finger protein scaffolds that are a hallmark of certain classes of transcription factors, and are fused to an endonuclease that introduces a double-strand break at the desired locus. This local perturbation to the DNA is then repaired via endogenous homology-directed repair pathways, and the presence of an exogenous DNA template that can contain a variety of useful alterations guides incorporation of specific changes at the target site.

As proof of principle, we first showed that we could generate an allelic replacement of an integrated heterologous marker. GFP that was stably integrated into a transgenic parasite line was targeted for deletion and replacement with RFP. This provided a readily quantifiable phenotype that demonstrated remarkable efficiency in a relatively short time frame. Having confirmed that genome editing could work in *Plasmodium,* we next sought to address a well-characterized drug-resistance phenotype by modifying *pfcrt,* the gene responsible for chloroquine resistance. By either complete allelic replacement, or more specifically, introducing only a single but critical nucleotide change in the genome of a drug sensitive parasite, we were able to confer resistance to chloroquine.

The ability to rapidly and precisely modify the genome of this important human pathogen opens up new possibilities to quickly assess potential drug resistance alleles and confirm causality associated with modifications that are detected in the field. Combined with next-generation sequencing efforts that identify these candidate loci, the field of parasite molecular genetics has entered an exciting new phase.

Reference: Straimer J, Lee MC, Lee AH, Zeitler B, Williams AE, Pearl JR, Zhang L, Rebar EJ, Gregory PD, Llinás M, Urnov FD and Fidock DA (2012) Site-specific genome editing in *Plasmodium falciparum* using engineered zinc-finger nucleases. ***Nature Methods*** 9: 993-998.

DR. DONNA L. FARBER

A Whole Body Analysis of Human T Lymphocytes

IMMUNE RESPONSES occur in diverse anatomical sites, including protective responses to pathogens and dysregulated immune responses in autoimmune and inflammatory diseases. As identified in mice, T cells control regional responses with different subsets localizing to distinct sites. Naïve T cells become activated by antigen in lymphoid tissue, differentiate to effector T cells which migrate to peripheral sites of inflammation, and can eventually persist as long-lived memory T cells which are maintained as heterogeneous subsets in lymphoid and mucosal tissue sites. Mouse models have further revealed that the differentiation of specific effector and memory subsets, and their migration and maintenance in diverse lymphoid and mucosal tissue sites is integral to protective immunity. However, in humans, our knowledge of T cell differentiation and maintenance derives almost exclusively from studies of peripheral blood, and little is known about how human immune responses function and are maintained in tissues.

In order to break new ground in the study of human immunology and develop effective vaccines and therapies that specifically target immune responses at the sites where they are needed, it is essential to move beyond conventional studies of human peripheral blood and study immune responses in tissues. The Farber laboratory has initiated a whole body analysis of human T cells in lymphoid and mucosal tissues obtained from organ donors with a healthy immune system in collaboration of the New York Organ Donor Network (NYODN), the organ procurement organization (OPO) for the greater New York metropolitan area. In a new study recently published in *Immunity,* the lab described a multi-dimensional analysis of T cells throughout the human body from 24 different donors aged 15 to 60 years. They found notable consistencies in the compartmentalization of T cell subsets between donors despite different causes of death, diverse lifestyle, and the known heterogeneity of the human population.

The results also revealed distinct compartmentalization of naïve, effector and memory CD4+ and CD8+ T cell subsets intrinsic to the tissue site that was remarkably consistent in diverse individuals. Memory CD4+ T cells were found to represent the majority subset in mucosal tissues and accumulated in lymphoid tissue throughout life. CD8+ T cell subsets, by contrast, were maintained as naïve cells in lymphoid compartments over decades, with memory CD8+ T cells mainly in mucosal sites and terminal effector cells confined to circulation. Importantly, memory T cells in all tissues specifically upregulated CD69 expression, a marker of T cell receptor (TCR)-mediated signaling, which distinguishes tissue-resident from circulating populations. Functionally, the majority of tissue-resident T cells were quiescent or IL-2-producing memory CD4+ T cells, followed by IFN-γ-producing memory CD8+ T cells, with IL-17 production confined to memory CD4+ T cells in mucosal compartments. Additional phenotypic distinctions in mucosal T cell subsets were found, specifically in upregulation of the integrin CD103 expression in CD8+ T cells in intestinal and lung tissues.

Together, these findings provide a novel assessment of T cell subset organization in the human body, and establish that the organization, differentiation and maintenance of human T cells in strikingly tissue-intrinsic. The findings also reveal that tissue-resident memory T cells are present in human lymphoid and mucosal sites, with mucosal tissue-resident memory T cell exhibiting tissue-specific properties. These results now set the stage for further investigation into maintenance, turnover and compartmentalization of CD4+ and CD8+ T cells and also for investigating T cell subset changes over time, in donors of different ages. Understanding the origin and identity of tissue-resident T cell populations can lead to therapies that target memory T cells to the specific sites of pathogen entry and persistence for protection. Ultimately, our approach to study human immune cells in tissue sites will open the door to fundamental studies on multiple aspects of human immunity, and will improve our ability to translate and optimize immunotherapies.

Reference: Sathaliyawala T, Kubota M, Yudanin N, Turner D, Camp P, Thome JJ, Bickham KL, Lerner H, Goldstein M, Sykes M, Kato T and Farber DL (2013) Distribution and compartmentalization of human circulating and tissue-resident memory T cell subsets. ***Immunity*** 38: 187-197.

Department News

Professor David Figurski, Long Term Member of Department, Retires

THE DEPARTMENT BIDS FAREWELL to Dr. David Figurski, who retires after 35 years as a faculty member of Microbiology & Immunology. Dr. Figurski joined the department in 1978 as an Assistant Professor, was promoted to Associate Professor in 1985, and became a full Professor in 1992. He also served as the Associate Dean of Graduate Students from 1997 to 2000.

Dr. Figurski's research focused on two major areas, promiscuous antibiotic-resistance plasmids and adherence in bacterial pathogens. The evolution, spread, and replication of antibiotic resistant plasmids in bacteria is a serious worldwide problem that threatens to undermine the treatment of bacterial infectious disease. His research in the IncP family of self-transmissible, highly promiscuous, antibiotic resistant plasmids revealed the existence of a novel plasmid regulon (the *kor* regulon) whose multiple operons encode a distinctive active partition system for DNA segregation and novel genes for plasmid maintenance in different hosts. His research in the Gram-negative bacterium *Aggregatibacter actinomycetemcomitans,* a dental pathogen, identified a cluster of *tad* (tight adherence) genes required for tight adherence to surfaces. Similar *tad*-like loci were subsequently found in the genome sequences of a wide variety of bacteria, including many significant pathogens, as well as Archaea, and appear important for colonization of a variety of environmental niches, including pathogenic ones.

Dr. Figurski has successfully guided numerous graduate students through careers in science, and has been an integral member of our teaching and research faculty. We wish Dr. Figurski all the best in his well-deserved retirement.

Four New Students Join Department

Lyla Youssef
Cornell University

Filip Cvetkovski
University of Heidelberg

Grace Nauman
Dartmouth University

Mariana de Almeida
University of Lisbon

Renowned Immunologist Joins Department

DR. STEPHEN EMERSON, M.D., PH.D., joined CUMC in 2012 as the Clyde and Helen Wu Professor of Immunology in Medicine, Professor of Microbiology & Immunology, and Director of the Herbert Irving Comprehensive Cancer Center. Dr. Emerson received his B.A. from Haverford College, and his M.Sc., Ph.D. and M.D. from Yale University. He has built an illustrious medical, academic, and administrative career over the past 2 decades, and joins Columbia after serving as President of his alma mater, Haverford College, from 2007-2012. Dr. Emerson's laboratory studies the transcriptional regulation of hematopoetic stem cell proliferation, self-renewal, and differentiation.

Department Welcomes Assistant Professor

DR. LEI DING, PH.D, joined CUMC as Assistant Professor of Microbiology & Immunology and Rehabilitation & Regenerative Medicine earlier this year. Dr. Ding received his B.A. from Peking University in Beijing and his Ph.D. from the University of Colorado at Boulder. Then, following his productive and successful postdoctoral training in Dr. Sean Morrison's Lab at UT Southwestern Medical Center, he was recruited to Columbia. Dr. Ding's work focuses on how signals from the microenvironment surrounding the hematopoietic stem cell (HSC) compartment contribute to regulation of HSC self-renewal, and how alterations in these signals contribute to diseases such as cancer and anemia.

Departmental Retreat

THE 2012 MICROBIOLOGY & IMMUNOLOGY annual retreat was held at the Dolce Basking Ridge Conference Center in Basking Ridge, N.J. on September 6th-7th. It featured research talks by faculty members, and a poster session presented by students and postdoctoral fellows. Laurie Dempsey of *Nature Immunology* and Bruce Koppelman of *Immunity* gave a special presentation detailing the manuscript review process and the role of a journal editor, followed by an informative Q&A session. During down time, attendees enjoyed numerous activities including swimming, playing basketball, going for walks, and impromptu pool games. The 2013 M&I retreat will be held at the Wyndham Hamilton Park Hotel & Conference Center in Florham Park, N.J. on September 9th-10th.

Roy Maute Wins Parker Award

THE RECIPIENT OF THE 2013 Richard C. Parker Graduate Student Award is Roy Maute. Roy Maute's research in Riccardo Dalla-Favera's laboratory explored novel mechanisms of small RNA signaling in human B cells, demonstrating that functional microRNAs can arise from cleavage of transfer RNAs. This work suggests a possible function for the thousands of microRNA-sized transfer RNA fragment that have been recently reported in many different biological systems. The award was presented on March 6, 2013 at the 27th Richard C. Parker Memorial Lecture, delivered by immunobiologist Ruslan Medzhitov, Investigator, Howard Hughes Medical Institute and David W. Wallace Professor of Immunobiology, Yale University.

Richard C. Parker Memorial Lecture

THE 27TH ANNUAL Richard C. Parker Memorial Lecture, "Host Defense Strategies" was delivered on March 6, 2013 by Dr. Ruslan Medzhitov, Ph.D., Investigator, Howard Hughes Medical Institute and David W. Wallace Professor of Immunobiology, Yale University. Dr. Medzhitov's research has helped develop a new paradigm of host-pathogen interactions in which the host organism protects itself from disease not only by detecting and eliminating invading pathogens, but also by tolerating pathogens, thereby reducing the inflammatory consequences of infection that could have a negative impact on host fitness.

Heidelberger-Kabat Lecture

THE 2013 HEIDELBERGER-KABAT LECTURE, "A General Mechanism for Modulating Immunoglobulin Effector Activity" was presented on June 11, 2013 by Dr. Jeffrey V. Ravetch, Theresa and Eugene M. Lang Professor and Head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology at Rockefeller University. Dr. Ravetch is well known for defining mechanisms of antibody-mediated effector responses and for establishing the importance of Fc receptor pathways as part of the immune response.

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.**

Alumni Spotlight

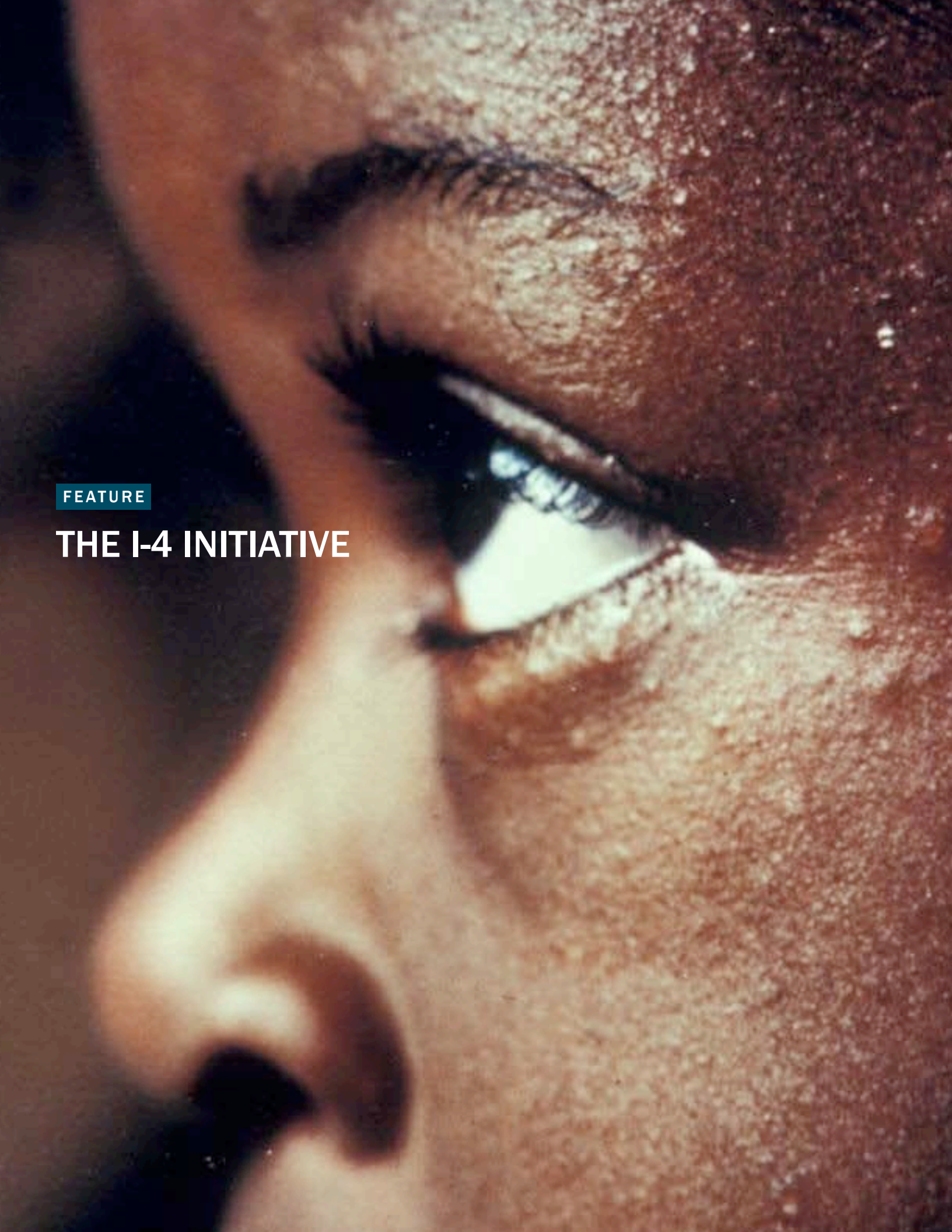
DR. CHRISTOS KYRATSOUS completed his doctorate in Microbiology studying Varicella Zoster virus in the laboratory of Saul Silverstein in 2009, for which Dr. Kyratsous received the 2009 Dean's Award for Excellence in Research. He went on to do postdoctoral work in the lab of Michele Pagano at New York University, where he worked as a Research Associate of the Howard Hughes Medical Institute. In 2011, Dr. Kyratsous joined Regeneron Pharmaceuticals, Inc. as a scientist, where he was promoted to the position of staff scientist in January of 2013.

Alumni Spotlight

DR. ANDREA NICOLAS completed her doctorate in Microbiology studying adenovirus in the lab of Hamish Young in 1995. She became a patent examiner, and went on to earn a J.D. from the Columbia University School of Law in 1998, where she was a Harlan Fiske Stone Scholar. Dr. Nicholas then joined Skadden, Arps, Slate, Meagher & Flom LLP, where she became a partner in 2008. Her scientific background has played a role at the firm in representing companies such as Omrix Biopharmaceutical, Inc. and Regeneron Pharmaceuticals, Inc. in I.P.O.s or stock offerings.

HIGHLIGHTS

I^4 + GRADUATE STUDENT LIFE + INNOVATION



FEATURE

THE I-4 INITIATIVE

THE MUCH ANTICIPATED Initiative in Infection, Immunity, and Inflammation (I-4) is underway! The Immunology and Infectious Disease faculty at CUMC and Dean Lee Goldman have begun to define the goals and fundraising requirements of the new initiative. After initial discussions, our immunology and infectious disease community has agreed upon the need for expansion in two rapidly growing fields of study. Specifically, I-4 will focus on improving our programs in human microbiome research and in vaccine and immunotherapeutic development.

The I-4 was created to provide a unified voice for immunology and infectious disease research across the University and to unite basic scientists with clinicians in order to address every aspect of major diseases. Furthermore, the initiative was intended to create infrastructure and resources that would benefit the entire community, thereby allowing us to recruit and build in a strategic manner. By defining the primary scientific goals of the initiative, the I-4 steering committee has taken the first step in the process towards strategic expansion.

The impact of the human microbiome on health and disease is a rapidly emerging field of study. This field is being accelerated by international efforts, such as the NIH Common Fund Human Microbiome Project (HMP), which aim to generate resources and publically available data sets that will allow for comprehensive characterization of the human microbiota in normal and disease states. In order to contribute to this current field of study, the I-4 proposes to establish a Microbiome Center. This center will enable and encourage the identification of commensal bacteria and the study of the impact of commensals on human health and disease. The I-4 hopes to recruit scientific leaders with expertise in microbiome research to head this new initiative and plans to revamp the educational program to enhance our microbiology curricula.

Another newly proposed focus of the I-4 is the translation of research in infection, immunity, and inflammation into therapeutic outcomes. In order to promote translational research, the I-4 would like to establish a Vaccine and Immunotherapeutics Center focused on the development of novel strategies to prevent and treat emerging and re-emerging diseases. In addition to recruiting faculty leaders and implementing new coursework in vaccine and therapeutic development, the I-4 is considering investment in a GMP Core facility, to enable drug design and scale-up.

Ultimately, creation of the I-4 is intended to integrate the disparate immunological research efforts at Columbia, resulting in a more collaborative environment and allowing for larger scale projects to be undertaken. In order to pursue the ambitious goals of the I-4, appropriate funding is required. Thus, fundraising for the newly defined scientific initiatives is the immediate goal of the I-4 and Dean Goldman. The resulting investments will likely advance the translational potential of the immunology and infectious disease research at CUMC, as well as further our ability to compete and contribute to the evolving scientific landscape that is the study of human health and disease.

FEATURE

Student Life

THE GRADUATE STUDENTS in the Department of Microbiology & Immunology invigorate our labs with the hard work and fresh perspectives that can only stem from enthusiastic young scientists. However, our students also find time in their busy work schedules to enjoy all that Columbia and New York City have to offer. There are two graduate student-run organizations at Columbia, the Graduate Student Organization (GSO) and the Graduate Student Advisory Council (GSAC), that provide a forum through which students can socialize, pursue outside interests, attend cultural events in the city, and importantly, address concerns about student life.

The GSO serves the graduate students in the biomedical science programs at the Columbia University Medical Center. The annually elected GSO board holds regular meetings, at which all students are

"The annually elected GSO board holds regular meetings, at which all students are welcome to enjoy a free dinner, to voice interests and concerns about graduate student life, and to help plan social events."

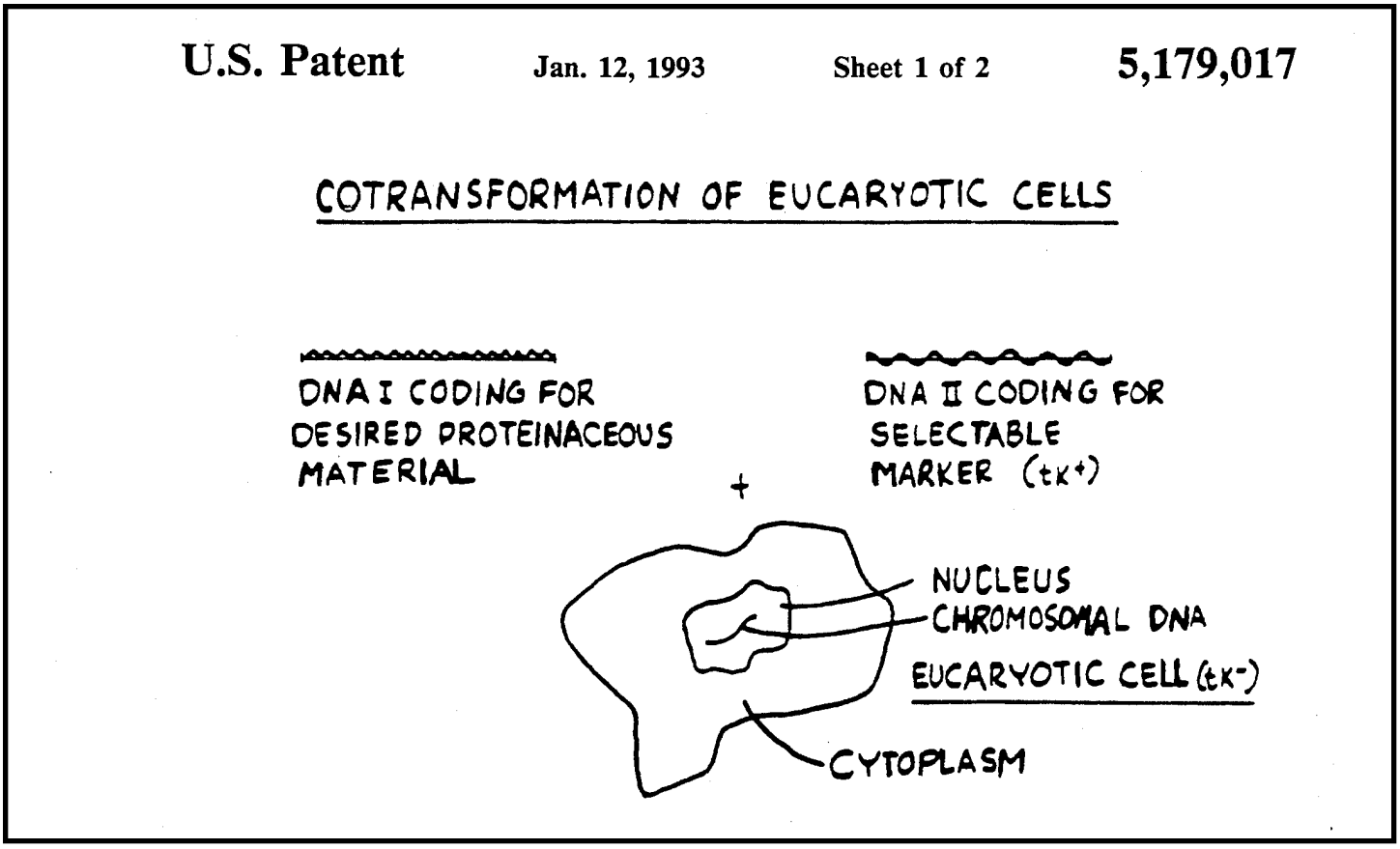
welcome to enjoy a free dinner, to voice interests and concerns about graduate student life, and to help plan social events. The board is currently made up of Co-Presidents Tulsi Patel and Olya Yarychkivska, Vice President Danielle Matsushima, Treasurer Lucja Grajkowska (who is a member of our own Department of Microbiology & Immunology), and the Social Committee, comprised of five other current students from various departments. These student-leaders plan events such as the weekly Friday gathering, known as Free Friday, where students wind-down with pizza, beverages, and good company in the Bard Hall garden or roof deck. Two popular events organized by the GSO last semester included trips to the interactive, *Sleep No More* show at The McKittrick Hotel and the *6th Annual Choice Eats* tasting extravaganza run by the Village Voice. Upcoming GSO plans for the summer include a subsidized trip to the beach, a group hike, and sale of discounted US Open tickets and AMC movie passes. The GSO board encourages all students to suggest activities of interest, and provides free entry for those students that plan an event.

In addition to providing current students with a social and cultural outlet, the GSO also helps with integration of the incoming graduate students into the student body. For example, during the graduate student recruitment weekends held in February of each year, the GSO plans an entire Saturday of events for our recruits, including typical NY-fare such a late morning brunch, a museum visit, and a night on the town. New and uninitiated students can learn more about the GSO and GSO-sponsored events through the gradtalk listserv. For those interested in running for the GSO board, elections will be held in the fall of 2013.

The GSAC is a Columbia-wide student government organization made up of student-elected representatives from the 62 Ph.D. programs and 26 M.A. programs housed in the Graduate School of Arts and Sciences (GSAS). Like the GSO, the GSAC organizes social and cultural events for the graduate students. However, the GSAC also serves to facilitate communication with university administrators to address students concerns such as housing, availability of study space, computer services, and health care and stipend issues. Notably, GSAC elects representatives from the GSAS to serve on a variety of important university committees, including the University Senate, which makes policy on a range of issues affecting the entire University community.

GSAC also publishes a weekly e-newsletter detailing upcoming social and academic events as well as news of interest to the graduate community. In addition, they have launched a new arts website, known as Arts4Grads, which notifies students of art and cultural opportunities around NYC, and enables students to purchase tickets to popular exhibits and shows at discounted prices. Students can become more involved in GSAC by serving as their elected departmental representative to the governing body or by running for office in the GSAC steering committee. For those interested students, our department is currently in need of a representative to the GSAC! All graduate students are encouraged to get involved and to make use of the many resources afforded by the GSO and the GSAC.

Innovation



HISTORICAL HIGHLIGHT

Inspiration from Past Innovators to the Innovators of Tomorrow

IN RECENT YEARS, "technology transfer" has become a major goal of academic institutions. The activities that compromise technology transfer, such as filing of patents, enforcement of licensing rights, and fostering of start-up companies, were traditionally activities based in the commercial sphere. However, this paradigm began to shift with the advent of the Bayh-Dole Act of 1980, which legislated that recipients of federal funding, for example universities, could patent and license inventions resulting from federally funded research. This law was intended to encourage the dissemination of academic research for commercial

use. As a result, patenting and licensing of new technologies emerged as a tool used by universities to invest in the R&D of clinically applicable discoveries. Columbia was one of the first universities to take up the government's challenge and implement a program to encourage commercialization of research, forming the office now known as Columbia Technology Ventures (CTV) in 1982. Moreover, researchers in the Department of Microbiology & Immunology have proven to be pioneers in the technology transfer sphere at Columbia University, claiming two of the most successful sets of patents in Columbia's history.

CTV has received 129 inventions from the Department of Microbiology & Immunology since 1983, when they began to track departmental contributions, and Microbiology & Immunology patents have generated over 30 license agreements. Two patent families in particular, the Co-transformation patents and the Chimeric Monoclonal Antibody patents, have been widely licensed and are behind many of the largest biotechnology therapies of the past two decades.

The Co-transformation patents are among the most lucrative and widely recognized biomedical patents in Columbia history. Even before the passage of the Bayh-Dole Act, at a time when patenting of biomedical technologies was uncommon, three scientists from Columbia University – Dr. Michael Wigler, Dr. Saul Silverstein, and Dr. Richard Axel – not only devised a novel technique, but had the forethought to patent their discovery. The patents were granted for the method of co-transformation. As a student in the Silverstein lab, Wigler, with the guidance of his mentor Dr. Silverstein, first introduced the thymidine kinase (tk) gene from the Herpes Simplex Virus genome into a mammalian cell line. This process may seem commonplace today, but Wigler and Silverstein were among the first to demonstrate expression of a functional protein by gene transfection in a eukaryotic cell system. Since cells lacking tk are unable to grow in HAT media, Wigler further demonstrated that culturing of the transfected cells in HAT media led to selection of cells that stably-expressed the tk gene over several hundred cell generations. His initial paper was published in *Cell* in 1977. Dr. Axel then contributed to the subsequent work by suggesting that co-transformation of a gene of interest along with a selectable gene, such as the HSV tk gene, could lead to stable expression of the gene of interest, for which there was no selection pressure. The resulting paper describing this revolutionary process of co-transformation was published in *Cell* in 1979. It was for this innovation, that Wigler, Silverstein, Axel, and a fourth innovator, Dr. James Roberts, submitted their first patent. Ultimately, Columbia University was granted five major patents for the co-transformation technique and related applications in 1983, 1987, 1993, and 2002.

Since the initial invention, co-transformation has become a widely used method that has contributed to the development of numerous commercial technologies. Silverstein recalls, somewhat ironically, that, "We actually thought it might be valuable, but we weren't sure." Genentech was the first company to license the technology, and then other biotech and pharmaceutical companies followed suit. Many products stemmed from the technology, but the most successful by far was Epogen, developed by Amgen. Epogen is a recombinantly produced human erythropoietin that is used to treat anemia associated

with chronic renal failure and chemotherapy. Among the many other important therapies that stemmed from the technology were two products developed by Genentech: Activase, a recombinant tissue plasminogen activator (tPa), is widely used to dissolve blood clots in heart attack patients, and Pulmozyme, a purified solution of human deoxyribonuclease I (rhDNase), is used to reduce viscosity in the lungs of cystic fibrosis patients.

The other major set of patents that stem from the Department of Microbiology & Immunology are for the development of chimeric antibodies, developed, in part, by a former faculty member, Sherie Morrison. For work done both at Columbia and while on sabbatical at Stanford University, Morrison is credited with being a co-inventor of a system to produce antibodies in cells and for developing a technique to create antibodies with both mouse and human components. In 1982, Morrison's lab developed a method to produce antibodies in lymphoid cells. They were able to identify lymphoid specific regulatory elements that controlled antibody expression and used this knowledge to create expression vectors to produce antibodies in cell culture. The primary goal was to make antibody fusion proteins with specific functional properties.

Monoclonal antibodies were used in the early 1980s for various applications, but were often produced in rodents, and were therefore immunogenic to other species. It was known that the constant region of antibodies had functions in complement binding, immunogenicity, and cell receptor binding. Thus, it was thought that a chimeric antibody containing a human constant region and a variable binding region specific for a particular ligand, as developed in a mouse cell system, could have clinical applications. These chimeric antibodies turned out to be better tolerated by the human immune system than rodent antibodies. Morrison and her colleagues attempted to patent the chimeric antibody technology in 1984, but the two patents were not issued until 1998 and 2001. This turned out to be advantageous since the patents ultimately went into effect at a time when the biotech and pharmaceutical industries were eager to adopt the technology.

The chimeric antibody technology has since been widely licensed and used by pharmaceutical companies to create various clinical products. For example, Centocor (now part of Johnson & Johnson) used the method to replace parts of a mouse antibody with human domains that recognize a cell adhesion molecule. The resulting drug is known as ReoPro and has been approved by the FDA to reduce clots and subsequent heart problems during heart surgeries. The Morrison patents have also lead to well-known products such as Remicade, a chimeric antibody against TNFα. Remicade was developed by researchers at Centocor and New York University (NYU) and is used for the treatment of Crohn's disease and rheumatoid arthritis.

In addition to the vast clinical applications of the Columbia-created technologies, an invaluable consequence of the patenting and licensing of the co-transformation and chimeric antibody production methods was the collection of licensing fees and royalties by the University. As with all patent revenue at Columbia, the significant revenue from these two sets of patents were divided to reward the inventors, to fund further research in the laboratories' of the inventors, and to be used for both the upholding of the patents and for general university expenses. It has been

reported by Jeffrey Kestler, associate general counsel of the Patent and Licensing Group at Columbia University, that the University's share of the licensing revenue from the co-transformation patent contributed to the establishment of various new programs, including the Department of Biomedical Engineering at the Fu School of Engineering, the J.P. Sulzberger Columbia Genome Center, and the Columbia University Earth Institute, among others.

The co-transformation and chimeric antibody patents also generated revenue for the University, the medical school and the Department of Microbiology & Immunology, which has supported decades of research and development. The patent money was used to establish four endowed professorships in the department and to set up a student fund for purposes such as purchasing laptop computers for incoming students. Funds were used to purchase computers for various labs, a departmental server, and departmental research software, such as Openlab and Volocity. Finally, the revenue was also used to fund the annual department retreat, which fosters collegiality and collaboration between the faculty, postdoctoral fellows, and students.

Despite our department's history of commercial success in translating laboratory discoveries to patents, it is important to remember that not all patenting and licensing attempts end with blockbuster victories. Patentability of a discovery is determined by how a technology is developed, when it is made public, and how it is protected during discussions with companies, that can sometimes cause even the best ideas to go unpatented or unlicensed. Commercializing intellectual property poses challenges, as well. According to the Association of University Technology Managers (AUTM), only 18% of invention disclosures turn into an active license, option, or startup. Of those licensed, less than one percent end up generating more than $1 million in licensing revenues annually. Even at Columbia, where gross tech transfer revenues have consistently been in the top five among U.S. universities, patents often take a long time to get licensed, and many don't get licensed at all. For example, the late Dr. Bernard Erlanger, a professor in our department, was a prolific inventor who was successful in obtaining over a dozen patents for innovations such as methods for screening anti-HIV compounds and novel treatment protocols for sickle cell disease. Of Dr. Erlanger's many inventions, one was licensed non-exclusively multiple times, and a second invention was recently licensed to a startup company, unfortunately only after Dr. Erlanger's passing.

Experience has proven that there is an element of luck in achieving commercial success. To maximize the chance of realizing the commercial potential of our work, Dr. Ofra Weinberger, Director at CTV, encourages the inventors among us to, "Submit invention reports to our office early and often, reach out to your licensing officer regularly, or email our office at techventures@columbia.edu to set up an appointment with a member of our team." Regardless of commercial outcome, however, the utility of working hard to create something of importance, be it a new technology or a better understanding of how a biological process works, should never be undervalued. As scientists, we proceed with the certainty that our work has significance and the belief that investment in our work will one day pay off, in one way or another.

HIGHLIGHT

Columbia Technology Ventures

So, you've invented something really great. Now what?

In order to transform your invention into a commercially successful product, you will need to work closely with Columbia Technology Ventures (CTV) to evaluate, develop, patent, and license your technology. This is an exciting process, which may ultimately yield a valuable application from your years of hard work. You may also receive great fame and fortune...or, at the very least, the appreciation of your fellow scientists!

The first step towards commercial success is to contact Columbia Technology Ventures and submit an Invention Report Form as early as possible, especially before public disclosure of your invention. Your invention will be assigned a Licensing Officer, who will coordinate the rest of the process. The information provided in your Invention Report Form, such as details about the invention, its conception, and its advantages over current technologies, will be used to assess patentability and commercial potential. Internal and external experts retained by CTV, including Columbia-affiliated patent lawyers, will perform this assessment.

If your invention is deemed patentable and commercially viable, Columbia will file for patent protection via the United States Patent and Trademark Office (USPTO). Patents often take 3 to 8 years to be approved ("issued") by the USPTO. If you are issued a patent for your invention, you will receive patent protection for 20 years starting on the date of the initial application.

Your technology has been patented! Now what?

CTV will begin marketing your invention as soon as the application is filed. Typical marketing channels include direct outreach to in-licensing teams within industry, introductions to CTV's contacts among venture and angel investors, posting on various intellectual property websites, and outbound email campaigns. At the same time, the Licensing Officer assigned to your invention will collaborate with you and other enabling partners to transform your inventions into investment-ready opportunities that will be desirable to potential business partners. The eventual goal is for your patented invention to be licensed to one or multiple worthy business partners, who will utilize your technology to make commercially applicable products and services.

As evidenced by CTV's annual gross licensing revenues (over $100 million), your patents can become very rewarding for you and the University. In general, the first $125,000 of revenue is shared as follows: 40% to the inventors; 20% to the inventor's labs; and the remainder to the University. Any revenue over $125,000 is split 20% to the inventors, 20% to their labs, and the remainder to the University, the Department, and the School.

The patenting and licensing process outlined by CTV is ultimately designed to ensure the best chance of marketplace success for your technology as well as to generate much-deserved revenue for you, your lab, your department, and the university for your innovative work. Good luck inventors!

Patent success at Columbia

Researchers in many different fields at Columbia University have created and patented technologies that have contributed to the development of many recognizable products that have transformed and enhanced our daily life.

Dimitris Anastassiou from the Department of Electrical Engineering has made significant contributions in the area of digital technology, and patented his work relating to video compression algorithms. This technology was considered essential for the development of the MPEG2 standard, a combination of video and audio data compression methods that facilitate storage and transmission of movies. Anastassiou's patent has been broadly licensed to manufacturers of digital video devices, and has lead to development of products and services such as Blu-ray Discs, DirectTV, and Dish Network, amongst others.

Ground-breaking research conducted by Columbia University professor Laszlo Z. Bito has revealed that prostaglandins, a family of chemicals produced by the body, given in extremely small doses, can lower ocular pressure—and thereby successfully treat glaucoma, a disease that plagues two million Americans with vision loss and causes 120,000 to go blind annually. Dr. Bito's discovery has led to the development of a synthetic prostaglandin, Latanoprost, which Pharmacia (now Pfizer) bought the rights to and used to create the drug Xalatan, a blockbuster treatment for glaucoma.

The commercial success of our patented work demonstrates the groundbreaking nature of the research happening here at Columbia. The advances that our scientists have made in the fields of biotechnology, medicine, digital technology, and computer graphics, amongst others, greatly enhance daily life in the public sphere. Furthermore, the patenting and licensing of these technologies allows the university and our scientists to further invest in the research and development that leads to such transformative technologies. We hope that these stories of past and ongoing successes inspire a new generation of inventor-scientists to dream big and one day better the world with their own innovative work.

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NOTES

New Labs

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 normal and pathologic 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 immuno-globulin loci in the development of Burkitt's lymphoma by analysis of the mechanisms regulating the expression of the normal c-myc gene as well as c-myc alleles structurally altered by chromosomal translocation in lymphoma cells.

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.

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.

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.

The Summer 2012 issue of M&I contains additional capsule descriptions of the research laboratories of the department's faculty. It is available online at: **http://www.microbiology.columbia.edu/resources/newsletter.html**


AMAZING
THINGS
ARE
HAPPENING
HERE

2013 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**

Sep. 25	**Nicholas Restifo**	*NIH/NCI*
Oct. 2	**Elizabeth Winzeler**	*UC San Diego*
Oct. 9	**Neil Hunter**	*UC Davis*
Oct. 16	**Didier Trono**	*Swiss I of T*
Oct. 23	**David Sibley**	*Washington U*
Oct. 30	**Beatrice Hahn**	*U Penn*
Nov. 6	**Kenneth Murphy**	*Washington U*
Nov. 13	**Alan Grossman**	*MIT*
Nov. 20	**Garry Nolan**	*Stanford U*
Dec. 4	**Maria Jasin**	*MSKCC*

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