

COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

Winter/Spring 2017

Space: the final frontier... at CUMC

Letter from the Chair

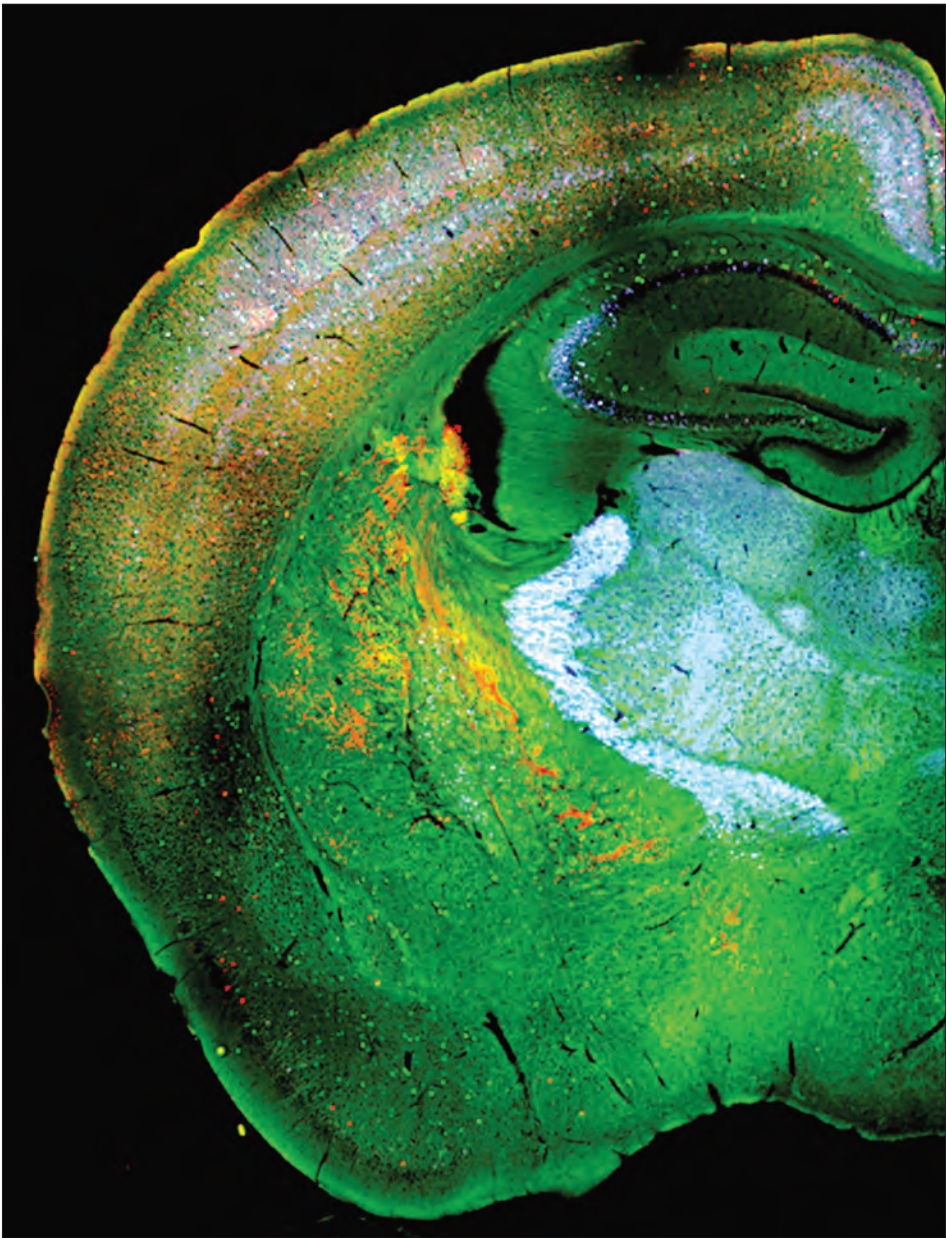


Growing up in the Midwest and spending the vast majority of my pathology faculty career at Washington University in Saint Louis and the University of Alabama at Birmingham (UAB), I developed a certain perspective on personal space needs and an appreciation for the relatively abundant clinical and research space available at those two institutions. Now, as a resident of Manhattan and Chair of the Department of Pathology and Cell Biology at Columbia University Medical Center, I frequently encounter spatial realities that challenge my previously held sensibilities. As an individual, I've adapted fairly quickly to less living space, crowded streets and packed subway cars. However, as the Chair of Pathology and Cell Biology, exploring the strange new world of CUMC space management presents a unique challenge, but one that I embrace with assistance from my departmental and institutional colleagues.

Several space related projects have recently gotten underway and several more are planned over the next few months. Humphreys Auditorium has been gutted and will soon be renovated for new offices and an expanded surgical pathology accession-

Continued on page 2

Studying the Developing Brain



Assembly of Inhibitory Microcircuitry in the Neocortex

See the article by Edmund Au, PhD on page 3

In This Issue

Writing for the Public.....	2	Promotions.....	8
New Faculty.....	3	Teaching.....	10
Annals of Administration	4-5	New Grants.....	11
Honors and Awards	6	In Memoriam.....	11
In Vivo.....	8	Anniversaries.....	12

From the Chair

(continued from page 1)

ing area. Todd Amphitheater has been upgraded and is now the main Department of Pathology and Cell Biology lecture hall. Plans to renovate the Fenoglio Library and nearby administrative and faculty offices are being reviewed. The Personalized Genomic Medicine (PGM) Laboratory, currently housed on the 17th floor of the Physicians and Surgeons Building (P&S), will be relocated to expanded space on the P&S 11th floor. The Precision Genetics Laboratory (PGL), a new joint venture between the Department of Pathology and Cell Biology and the Institute for Genomic Medicine, will be established and ultimately housed in the Hammer Building. I am optimistic that a significant expansion of the Frozen Section Room in Milstein Hospital will take place this year and that other improvements in clinical laboratory space will come to fruition in the near future.

Despite some unanticipated delays in the occupation of the Jerome L. Greene Science Center in the Mortimer B. Zuckerman Mind Brain and Behavior Institute, we have begun planning the renovations for laboratories that will become the future scientific homes for several new faculty recruits. Future projects must address upgrades to older laboratory facilities, administrative areas and faculty offices; space for core facilities; more efficient use of common space; additional temperature controlled server rooms for clinical and research needs; assessment of current and future microscopy needs; space for our growing residency and fellowship programs; and a more pro-active approach to laboratory space assignment that better aligns investigators' space allocations and needs with grant support. This priority list is not exhaustive and additional future projects are being contemplated to further enhance departmental facilities and capabilities. Meeting the space needs of our dynamic and growing department will not be easy, or cheap, but I am confident that by working together, we will be able to utilize the space available to us more efficiently and effectively.

Kevin A. Roth, M.D., Ph.D is also the Donald W. King, M.D. and Mary Elizabeth King, M.D. Professor of Pathology and Cell Biology; Pathologist-in-Chief, Columbia University Medical Center, and Editor-in-Chief The American Journal of Pathology

Writing for the Public

Science in an Age of Alternative Facts

Richard H. Kessin



Eppur si muove!
And yet it moves!
These are the words of Galileo, after torture by Pope Urban VIII and the Inquisition forced him to recant the idea

that the earth moves around the sun. Scripture said otherwise and the Pope had a vested interest in that fiction. Galileo was slammed into house arrest in 1633. Yet Eppur si muove survives as the defiant motto of those who support science and reason over power. Some of our graduate students at Columbia end their emails quoting Galileo, absorbing a little of his bravery over almost four hundred years.

When a government challenges a science, its first step is to demonize the scientists or the organization that supports them: They are against jobs; climate change is a hoax; why are they wasting our money? The second is to lock up scientific results that were in the public domain or ban further investigation. The third step is to cut funds and fire people.

Stalin banned Mendelian genetics because it did not allow for the inheritance of acquired characteristics—a concept that was necessary for the improvement of the new socialist man. The main villain was a charlatan named Trofim Lysenko who caused geneticists to die in the gulag, while others fled to the West. Science is a generational undertaking and Soviet science, especially biology and agriculture, never recovered. The United States was and remains the beneficiary of successive generations of Russian refugee scientists, engineers, and artists.

When Albert Einstein created the general theory of relativity, it was too clever for some German physicists, even after the first experimental proof emerged in 1919. Although Einstein was born in Germany, relativity was considered foreign and even a threat; German physics textbooks of the 1920s did not mention Einstein or relativity. The Nazis loved absolutism and relativity unnerved them. In 1933, Einstein's ideas were labeled Jewish physics and any discussion of relativity was banned. Einstein

and many other refugee physicists became Americans, built American physics and started the Manhattan project that created the first nuclear weapon.

There are many examples beyond these three but they have certain elements in common. The cases against these scientists started with a corruption of language. There is no Jewish physics. Science does not accept alternative facts or the ignorance and laziness called post-truth (the Oxford English Dictionary's 2016 word of the year). Aspiring autocrats are not constrained by decency or reasonable language—remember nasty woman, low energy and, (news to me) Meryl Streep and Hamilton are overrated. Language becomes Orwellian and truth and reason are no longer the default positions, as the University of Texas philosopher Kathleen Higgins pointed out in an article titled: Post-truth: a guide for the perplexed that appeared in Nature Magazine on Dec 1, 2016 (to be found on-line).

Once language is corrupted, scientific or other facts are dispensable; there is nothing to build on because post-truths and alternative facts are not solid, they are inventions of anger and convenience and allow no predictions. There are no scientific questions to be asked, say about vaccines or gun violence or why the oceans are rising. And no need. Raging autocrats know the answers.

The next step in the destruction of inquiry is to wreck the agencies that sponsor it. It just takes a few administrators to sequester the vast data of NOAA, the EPA or other agencies that is now available online for everyone's use. Will the carbon dioxide sensors on Mauna Loa be switched off? Will data from the buoys and satellites that measure ocean temperature, currents, and water levels become secret? Will the NSF be forbidden to fund research grants concerning the polar icecaps or the Greenland glaciers?

We are better off than Galileo and Russian geneticists—we have free newspapers, courts, and private foundations. The data from NOAA and the EPA have been downloaded to private servers.

Still, we could do worse than to channel Galileo's *And yet it moves*. Perhaps our motto should be: *Eppur cresce il mar. And yet the sea rises...*

From The Body Scientific | Tricorner News, The Lakeville Journal, Lakeville CT

New Faculty

Michael J. Lee, MD

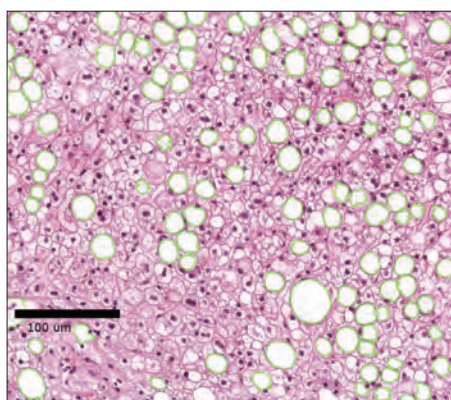
Assistant Professor of Pathology
and Cell Biology mjl2197@columbia.edu



Michael Lee earned his M.D. from Florida State University in 2009 and completed his anatomic and clinical pathology residency at Emory, followed by a gastrointestinal and liver pathology fellowship at UCLA. Before coming to Columbia, Michael was a faculty member at Baylor University Medical Center in Dallas, Texas.

Michael has previously studied different methods to assess liver steatosis with radiology, pathology and imaging algorithms. Since steatosis estimation by pathologists is prone to intra- and inter-observer variability, magnetic resonance imaging measurements, pathologist visual scoring, computerized techniques with a pixel count algorithm, and clinical parameters were compared to one another. This has resulted in more reliable methods (*see figure*).

Currently, Michael is studying the histopathologic features of Hepatitis C patients after they have successfully eradicated the virus. The liver pathology findings are not well characterized after patients are deemed to be clinically cured due to the advent of

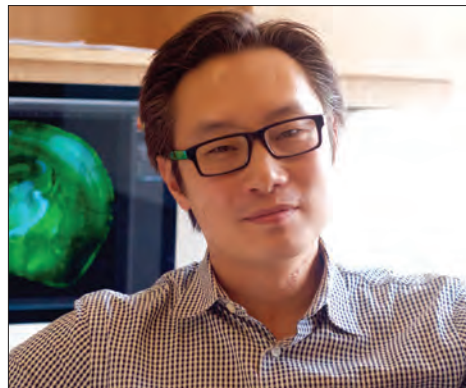


The green rims are an indication of liver steatosis.

Microcircuitry in the Neocortex

Edmund Au, PhD

Assistant Professor of Pathology and Cell Biology ea2515@cumc.columbia.edu
(continued from page 1)



Prior to joining the Department Dr. Au earned his PhD in neuroscience from the University of British Columbia and did his post-doc at the NYU-Langone Medical Center

In order to understand how the brain works, it is crucial to better understand its complexity and more specifically, how that complexity arises. One way to achieve this goal is to study complexity in terms of its core components: neuronal cell types and the rules that govern how individual cell types come together during development in the process of brain assembly.

The neocortex is the brain structure involved in higher-level executive function and decision-making. It is composed of two main cell classes: 1) long range principal cells that have stereotyped projections depending on the cortical layer in which they reside as well as 2) locally-projecting inhibitory interneurons distributed throughout the cortex. This second class of cell, cortical interneurons is perhaps the most diverse

new medications. He is also working with the Department of Radiology at CUMC to validate the Liver Imaging Reporting and Data System criteria for the diagnosis of hepatocellular carcinoma.

Michael Lee was born in Manhattan and grew up in Queens and Long Island before moving to South Florida. The transition and adjustment back to New York has been smooth since it feels like he has returned home.

neuronal population in the entire brain and plays a vital role in local information processing and the computational power of the brain as a whole.

My lab is interested in how different cortical interneuron subtypes arise, migrate into the cortex, and wire themselves into the cortex. We are also interested in how defects in specific interneuron subtypes can contribute to disease, especially mental illness. Our general approach is to start with undifferentiated stem cells that we convert into interneurons and then introduce them into embryonic mouse brain so that they can recapitulate normal development and maturation. This approach allows us the flexibility to *a priori* alter individual molecular components – gain-of-function as well as genetic loss-of-function by CRISPR – in order to study their downstream effects on interneuron microcircuit assembly.

Specifically, we are interested in understanding the molecular underpinnings of microcircuit assembly during three distinct phases developmentally: i) lineage specification that produces broad subclasses of interneurons; ii) arealization – interneurons arise from a distal progenitor region and through a poorly understood process, migrate to different regions of the cortex and settle throughout the cortical layers; iii) synaptic specificity – interneuron subtypes form characteristic synapses onto other cortical neurons in order to establish stereotyped microcircuits throughout the brain. We are also interested in how the failure to establish proper microcircuits can lead to neuropsychiatric disease.

Legend for the figure on page 1

A reporter mouse embryonic stem cell line (mES), *Dlx6a-Cre; Ai9* was differentiated into immature cortical interneurons. mES-derived interneurons were then transplanted in utero and allowed to undergo normal development in a wild-type host. Image shows a postnatal day 21 coronal section of host brain with mES-interneurons (red) populating host cortex. This section has been counterlabeled with two common interneuron subtype markers, parvalbumin (blue) and somatostatin (green).

New Faculty

Dominick Santoriello, M.D.

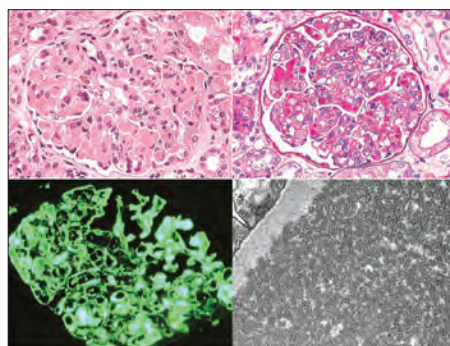
Assistant Professor of Pathology and
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I am a life-long New Yorker, and grew up on Long Island. I earned my M.D. from SUNY Downstate in Brooklyn in 2011 and completed my residency training in Anatomic Pathology at NYU Langone Medical Center in 2014. I then joined the Department of Pathology and Cell Biology at CUMC, where, in 2015, I completed a 1-year post-doctoral clinical fellowship in Renal Pathology under the tutelage of Dr. Vivette D'Agati. Currently, I am an Assistant Professor in the Division of Renal Pathology, where I spend the majority of my time involved in clinical activities.

As a renal pathologist, I work closely with nephrologists to integrate clinical, laboratory, and pathologic data in interpreting kidney biopsies. In doing so, I utilize 3 diagnostic modalities (light microscopy, immunofluorescence, and electron microscopy) to diagnose and classify patients' medical kidney disease which will, in turn, inform clinical decisions with respect to optimal therapy. Light microscopy is utilized to assess the pattern of kidney injury, which can affect the glomeruli, the tubules and interstitium, or the blood vessels. Often, the clinical history provides important clues as to where the main site of injury will be. For example, if the nephrologist tells me the patient is spilling protein or blood into the urine, I would expect to see damage to the glomerulus (the "filter"). Because many kidney diseases are immune-

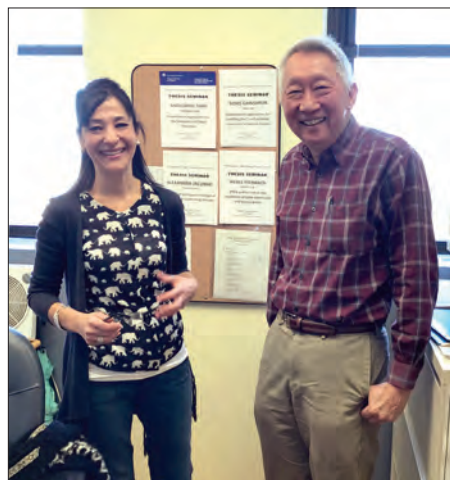
mediated, immunofluorescence microscopy is utilized to characterize the nature of the immune deposits present. Finally, electron microscopy allows us to assess the ultrastructure of the kidney.

My particular areas of clinical interest include infection-related glomerulonephritis, cryoglobulinemic glomerulonephritis, and kidney diseases in pregnancy. In addition to clinical work, I am actively involved in the medical education, of medical students, residents, and fellows. I also am actively involved in many professional societies, including the Renal Pathology Society and the American Society of Clinical Pathology.



What the pathologist sees: The image shows occlusion of glomerular capillary lumina by "immune thrombi" (panels 1 & 2), which stain most intensely for IgM and kappa by immunofluorescence (panel 3) and exhibit organized "annular-tubular" substructure by electron microscopy (panel 4). These findings are pathognomonic for type 2 cryoglobulinemia which, in this particular patient, was secondary to active HCV infection.

Zaia Sivo and Ron Liem, looking uncharacteristically relaxed. In the past months they have completed a major training grant for the Integrated Program in Cellular Molecular and Biomedical Studies, at which they were successful. They are now in the midst of graduate student recruitment.



Annals of Administration

Christopher Freeman, MS

Divisional Administrator
Personalized Genomic Medicine
cf2489@cumc.columbia.edu



Christopher Freeman joined our department in July 2011 as the Cancer Cytogenetics Supervisor. He spent five years in this position, and has recently taken on the role of Divisional Admin-

istrator in the Personalized Genomic Medicine (PGM) Laboratory.

Christopher completed his undergraduate studies at the University of Connecticut with a dual major in Diagnostic Genetic Sciences (DGS) and Molecular and Cellular Biology. He is an active Advisory Board Member of UConn's DGS program where he has held a seat for the last 3 years. After graduating, he went on to work in the private laboratory industry. After a few years in industry, Chris decided to pursue a Master's of Science Degree in Human Genetics at Tulane University Medical Center. Here he also worked as the Laboratory Supervisor in the Genetics Department.

After completing his Master's Degree, Christopher decided to follow his passion in the field of oncology and joined Columbia as the new Cancer Cytogenetics Supervisor where he worked for the next 5 years. A few years into this role, Chris had the opportunity to take on an additional role in the Personalized Genomic Medicine (PGM) Laboratory as Oncology Quality Assurance Manager. Here his passion for the rapidly advancing field of molecular genetics grew.

In September of 2016, Chris joined PGM full-time as the new Divisional Administrator. It is in this role that Chris hopes to have the biggest impact on advancing the field of genomics and personalized medicine.

Annals of Administration

Maurice Wiggins, Director of Human Resources and Academic Affairs, PH15-1564
mw2805@columbia.edu



Maurice joined Columbia University in 2011 and the Department of Pathology and Cell Biology in 2013. He rapidly applied his education, training and professional experiences to develop a thoughtful and effective plan for enhancing departmental Human Resource (HR) functions. He selected and recruited a talented HR team that under his leadership has streamlined and improved departmental HR operations.

Maurice has been instrumental in developing a department-wide commitment to professionalism and teamwork. He has served as coach, mentor and advisor to faculty and staff and has worked diligently to enhance departmental and interpersonal communications and to promote the implementation of HR policies and procedures.

Moving forward, Maurice will play a key strategic role in new departmental initiatives to create professional development opportunities for both faculty and staff. He will help develop and execute a comprehensive communication strategy for administrative programs that will improve employee engagement, satisfaction and career growth.

Outside of the department, Maurice serves as a Learning Academy facilitator for customer service based training and a trainer in the University's new Management Development Program. His advice on HR operations and management is sought by other departments and the University administration. He has led roundtable discussions with colleagues to develop best practices and shared management strategies.

CPR (*Columbia Pathology Reports*) sat down to interview Maurice Wiggins:

CPR: So, we hear you will be graduating in May from Columbia's School of International and Public Affairs (SIPA).

MW: Yes, with a master's degree in Executive Management and Non-profit Finance. It's a

mid-career program and you need ten years of experience. They choose 35 out of 500 applicants and it is very practical, not theoretical.

CPR: Congratulations. How long did that take?

MW: Since they let you do it on Saturdays while working and it's 45 credits or 15 classes, it took three years and I graduate this May. Happily, the University covers tuition.

CPR: Three years of Saturdays? That's a lot of Saturdays. Was it worth it?

MW: I loved it, really worth it. They have lots of programs and smart people. They all have similar experience and can be really creative.

CPR: Where were you before that and when did you come to Columbia?

MW: I'm originally from North Florida and went to Florida State University. I worked at Citibank and I had a job with the Jacksonville Jaguars with the press box staff and public outreach. After that I started working in Grants Administration at Florida State University. I had a stint at UCLA that was necessary because I was looking after my grandmother, but finally we moved to New York and in July 2011, Margaret Gibson convinced me to come to CUMC Central Administration. And then I came to Pathology and Cell Biology in 2013.

CPR: You quit an NFL job?

MW: Yeah, I thought Florida was a bit too slow. So were the Jaguars.

CPR: But life is not slow here?

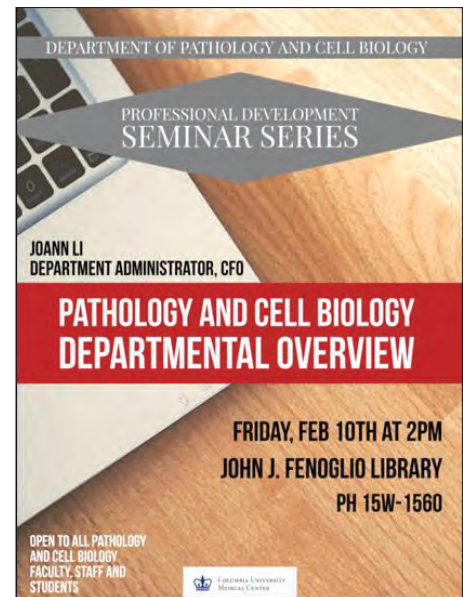
MW: Definitely not. I'm involved in a lot of projects, including performance assessments, cultural awareness changes, strategic planning. Also we have a nifty new staff development lecture series that is being launched. Also I get to know people; in Central HR the individuals were more remote and you did not get to deal with problems before they get out of hand.

CPR: So people could come to talk about SIPA?

MW: Sure, and any problems in Academic Affairs!

Professional Development Seminar Series

The Department of Pathology and Cell Biology Professional Development Seminar Series, which kicked off in February, 2017, is a training platform geared towards providing Faculty, Staff and Trainees with information in all areas of academia (research, education and clinical) and administration. Every month, speakers will be invited to give a 1 hour information session on a specific topic that is relevant to the operations and mission of the Department of Pathology and Cell Biology. If anyone would like to request that a specific topic be covered, please contact Tina Xue at tx2160@columbia.edu.



Honors and Awards

Congratulations to **Dr. Edmund Au**, a recipient of the 2017 Whitehall Foundation Award Grant! Dr. Au has won a Three Year Research Grant for his proposal “Identifying the Role of Wnt Signaling in Subpallial Neuronal Lineage Specification”.

The Foundation emphasizes the support of young scientists at the beginning of their careers and productive senior scientists who wish to move into new fields of interest.

See the article on Dr. Au elsewhere in this issue.

Drs. Charles Marboe, Ronald Liem and Joseph Schwartz have each been recently welcomed as the newest members of the Virginia Apgar Academy of Medical Educators. Apgar Academy is an active community of educators at P&S dedicated to promoting, rewarding, and supporting outstanding education for P&S medical students, residents, fellows, and faculty.



Associate Professor of Pathology and Cell Biology, **Dr. Eldad Hod**, was awarded Taub Institute MRI Platform seed grant funding to perform initial fMRI

and neurocognitive studies for his R01 funded study, “Red blood cells from iron-deficient donors: recovery and storage quality”.



And speaking of our formidable blood bankers, **Dr. Steven Spitalnik** has been Inducted into the National Blood Foundation (NBF) 2016 Hall of Fame. Steve has also

been awarded the 2017 Klaus Mayer Award in Laboratory Medicine.



Dr. Richard Francis, Asst. Professor of Pathology and Cell Biology (and yet another blood banker), has won Provost's Grant Program for Junior Faculty

Who Contribute to the Diversity of the University. Dr. Francis studies the pathophysiological consequences of oxidative stress that occurs during the refrigerated storage of red blood cells before transfusion.

Synthetic Biology Prize: The Newsletter has been notified by Dr. Harris Wang that a Columbia team, with contributions

from many departments and schools, won a Gold Medal at the The International Genetically Engineered Machine (iGEM) Foundation Jamboree in Boston. Over the summer of 2016 the team designed and engineered skin bacteria that can secrete a natural mosquito repellent compound and tested the system in cell-culture, mosquitos, and mouse models. This project involved an admirable integration of the various resources of the entire University, including our department.

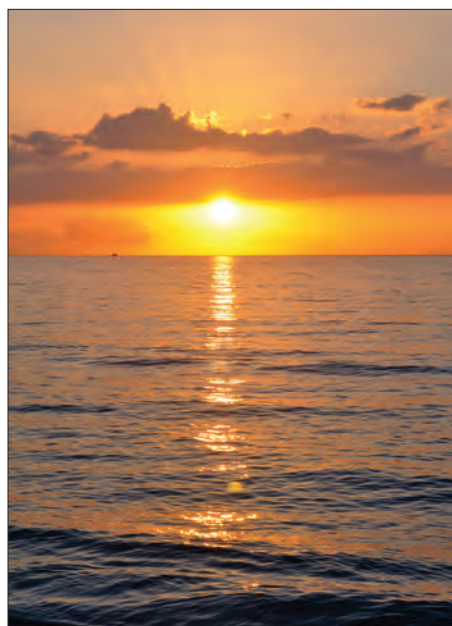


Dr. Antonia Sepulveda was the lead author and co-Chair representing the Association for Molecular Pathology for the Molecular Biomarkers for the Evaluation of Colorectal

Cancer Guideline, released in February 2017. The guideline is published by The Journal of Molecular Diagnostics, The American Journal of Clinical Pathology, Archives of Pathology and Laboratory Medicine, and Journal of Clinical Oncology.

<http://www.amp.org/committees/clinicalpractice/AMPclinicalpracticeguidelines/CRCMMGuideline.cfm>

Our Far Flung Photographers



Sunset in Negril, Jamaica by Richard Miller



Sunset in Buenos Aires, Argentina by Dr. Patricia Wasserman

Our Hospital Archipelago NYP/Lawrence Hospital in Bronxville

By Peter Hoffmann, MD

Hoffmann@lawrencehealth.org

Since 1909, Lawrence Hospital has served the health care needs of southern Westchester as a primary and secondary care provider. For those patients with complex and multispecialty health care needs, the tertiary medical centers of New York City always beckoned. But now New York Presbyterian/Lawrence Hospital can provide for many of those needs.

Since joining with Columbia University, New York-Presbyterian-Lawrence Hospital (or NYP-LH) has become a tertiary care facility for malignant neoplasms in all their stages. November of 2016 marked a turning point with the opening of the NYP-LH Cancer Center, which means that residents of Bronxville, Eastchester, Scarsdale, Yonkers, and Mount Vernon will no longer have to make the trip to Manhattan to receive personalized cancer treatment based upon predictive biomarkers specific to each patient's disease.

The NYP-LH laboratory, which operates under the oversight of Columbia's Department of Pathology and Cell Biology, now offers all the pathology and clinical laboratory resources of the University in a general

hospital setting. Dr. Peter Hoffmann, who trained as pathology resident and surgical pathology fellow at Columbia, directs the lab. He, along with his colleague Dr. Sergey Cherneykin, have noted a significant rise in cancer patients, who choose to remain at NYP-LH, where surgery, infusion, and radiotherapy are conveniently located one floor apart.

"It's the good mix," Dr. Hoffmann says, "The patients receive the advantage of convenience and expertise. They obtain the full breadth of specialized knowledge and skills provided by the entire Columbia pathology department.

Under this arrangement, consultations for challenging pathology slides remain just one courier ride away to a specialist of record, and recommendations for further studies rely on nothing more than a phone call. Work is in progress to fully integrate all clinical testing between the two institutions so that the back and forth flow is seamless. Then, there is tele-pathology, which looms on the not too distant horizon. The resources of an academic medical center have come to southern Westchester.



The NYP-Lawrence Pathology team at their annual holiday party

Department of Pathology & Cell Biology Website Project Update Winter 2017

By Tevra L. Francis

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2017 began with a fresh perspective and a new urgency to complete the Pathology and Cell Biology Website Project. After a successful website committee "pep rally" in the fall, the consensus was that in order to achieve a July 1st, 2017 launch date, we will need a more aggressive effort to update and create content for the new website. We decided that the most time-efficient strategy is to directly involve the faculty of the department in the creation of their laboratory, service line, and research area webpages. An "all hands on deck" push is what is required to make a Summer 2017 launch date a reality.

To do this, first the Core Planning Group hosted a full day of working group committee meetings to explain the new strategy, review site maps, and answer questions about content. Core Planning Group was then expanded with the addition of Director of Research Administration, Tina Xue and Application Support Specialist, Andy Wu to advance content development efforts in the Research and Diagnostic Services sections of the project. Then, a direct appeal to the faculty was made to encourage laboratory, research, and service line directors to submit their overview, faculty, and test menus (when applicable) by March 1st.

The overall goal is to serve our stakeholders with a comprehensive, user-friendly website will be achieved through the teamwork and cooperation of the entire department. We are working hard and looking forward to a Summer 2017 launch celebration!

Ideas and feedback are always encouraged, and can be sent to

PathWebMaster@columbia.edu.

In Vivo-Life in the PhD Programs

By Aiden Quinn
PhD Candidate

We have experienced a data explosion in human disease research that accompanied the so-called Genome Epoch and the rise of sequencing technology throughout the last 15 years. As the data produced by molecular biology and genetic experiments increases, interpretation of the results of these experiments becomes more complex from a conceptual standpoint and also from a technical one.



Graduate students in the Department of Pathology and Cell Biology are realizing not only the need for biologists to be well versed in the methods of bioinformatics but

also the synergy that comes from thinking about both the computational and wet lab aspects of a project. Sara Viragova, an Integrated CMBS student is one example. Sara studies the role of Sox transcription factors in breast cancer in Piero Dalarba's laboratory. Specifically, she is characterizing cell type heterogeneity in epithelial tissues and corresponding tumors.

Sara is building a foundation in bioinformatics and computational biology to understand more deeply the results of her experiments and to inform her experimental design. Over the past summer she participated in the single cell analysis course at Cold Spring Harbor Laboratories that focused on the technical approach to both generating and analyzing high throughput data from single cell experiments. Regarding her experience Sara said, "One of the main things I learned at CSH was the importance of cooperation between wet lab and computational scientists. It feels like often, a person in one group could work in a vacuum without really having an understanding of the work of a person in the other group."

Most of the graduate students working in the Department of Pathology and Cell Bi-

ology take some statistics courses that require the students to learn how to use R, a statistical programming language. However students in the department have increasingly been taking elective courses involving statistics and bioinformatics within Columbia and participating in external workshops such as those at the New York Academy of Sciences.



Chelsea Dieck, a graduate student in the laboratory of Adolfo Ferrando, wanted to go beyond what she learned in her required statistics training. Early in her graduate school career, she

took an interdisciplinary course on the genomics of gene regulation. Chelsea, who studies the role of NT5C2 mutations in relapsed Acute Lymphoblastic Leukemia, said that this training allowed her to better understand how to analyze and derive biologically important conclusions from genomic data.

Theses Defended

Gannie Tzoneva

Adolfo Ferrando lab - May 9, 2016

"The role of cytosolic 5' - nucleotidase II (NT5C2) in drug resistance and relapse of acute lymphoblastic leukemia"

Patricia Sheehan

Clarissa Waites lab - July 12, 2016

"Molecular Mechanisms of Synaptic Vesicle Degradation"

Wolfgang Pernice

Liza Pon lab - September 6, 2016

"Asymmetric Mitochondrial Inheritance and Retention in the Regulation of Aging in S. cerevisiae"

Yang Ou

Wei Gu lab - November 30, 2016

"Dissecting the role of p53-mediated metabolic regulation in tumor suppression"

Promotions

The Department is delighted to announce the following promotions to Associate Professor or Professor of Pathology and Cell Biology at CUMC:

Laura Pasqualucci, MD

Promoted from Associate Professor of Pathology and Cell Biology (in the Institute of Cancer Genetics) at CUMC to Professor of Pathology and Cell Biology (in the Institute of Cancer Genetics) at CUMC. Dr. Pasqualucci's work is concentrated on the genetic basis of B-cell malignancies.

Patricia Tiscornia-Wasserman, MD

Promoted from Associate Professor of Pathology and Cell Biology at CUMC to Professor of Pathology and Cell Biology at CUMC. Dr. Wasserman's interests involve all aspects of cytopathology, especially thyroid disorders, head and neck neoplasms, and cervical cancer diagnosis and management. Dr. Wasserman serves as the Director of Cytopathology. She is also an excellent photographer who regularly contributes photographs to our newsletter.

Reporting Significant Events

Readers may have noticed that the flat screen monitors's and the Website are being updated regularly. A new website is being prepared. We do not want the website, even in its current form, or the Newsletter: CPR – for Cell and Pathology Reports—to be static. We welcome advice and creative ideas on any subject that would improve the department, particularly on using social media or videos in our website or for CPR. If you have news of interest: lectures, thesis defenses, new discoveries, interesting images or other informative information, please send it to: PathNews@columbia.edu. A system will be created to make sure we archive (i.e. don't lose) these messages.

For special honors, either received by you or which our Department has conferred on others, please notify us so these awards can be acknowledged or forwarded to university-wide publications.

Spinal muscular atrophy: a success story from the bench to the bedside

Meaghan Van Alstyne

PhD Candidate researching the molecular mechanisms of motor neuron death in SMA in the Pellizzoni Lab

Integrated Program in Cellular, Molecular, and Biomedical Studies

Center for Motor Neuron Biology and Disease

Neurodegenerative diseases are debilitating conditions, yet few effective treatments are available. However, Spinal muscular atrophy (SMA), a hereditary disorder that results in the impairment of motor ability and muscle wasting, is now one notable exception. Since the genetic cause of SMA was first identified over twenty years ago, the work of many scientists delineating the biology behind the disease and developing courses of action for treatment, has recently culminated in the first ever FDA-approved treatment for this devastating disorder.

SMA is the leading genetic cause of infant death, with ~1 in every 50 individuals in the normal population being asymptomatic carriers for the disease mutation. While SMA is classified in several groups based on motor milestones reached and the age of disease onset, the most severe and most common form (Type I) affects infants within the first few months of life, resulting in the inability to sit unassisted and often leads to death within two years due to respiratory distress. SMA includes a wide range of clinical presentations with the mildest form being adult onset and patients having a normal lifespan. Children with intermediate severity can survive into adulthood, however they remain non-ambulatory and are subject to progressive weakness.

Identification of the SMA causing gene in 1995, opened the door for a deeper understanding of the underlying mechanisms of the disease. In SMA the loss of the survival

motor neuron 1 (SMN1) gene by deletion or mutation results in the characteristic death of lower motor neurons in the spinal cord (see figure), which serve to send signals to muscle and control movement, thus resulting in the neuromuscular disorder.

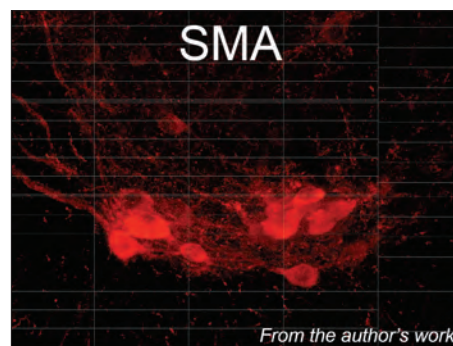
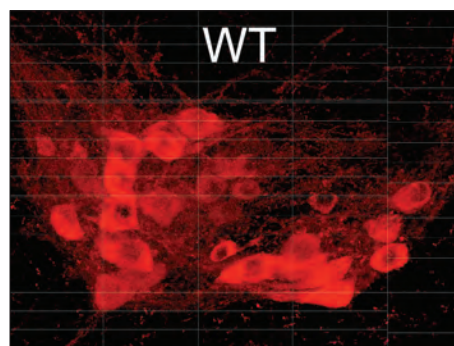
Functional studies of SMN led to the discovery of a novel macromolecular complex and a new biological activity in the assembly of RNA-protein complexes (previously thought to be driven by self-assembly) which carry out pre-mRNA splicing, a critical process for gene expression of eukaryotic cells. Given the fundamental role of SMN in RNA metabolism, it is not surprising that the protein is essential and its complete absence in experimental models leads to early embryonic lethality. In contrast, SMA patients retain a second, nearly identical copy of the gene called SMN2. However, due to a critical base pair difference between the SMN1 and SMN2 genes, 90% of transcripts from SMN2 are aberrantly spliced, and produce an unstable, rapidly degraded form of the protein that is unable to compensate for the loss of SMN1. All SMA patients have at least one gene copy of SMN2, however varying numbers of SMN2 copies are found in the patient population, accounting in part for the wide range of disease severity and indicating that increasing SMN would be a viable therapeutic approach.

Current SMN-targeted approaches for SMA treatment involve 1) replacing the

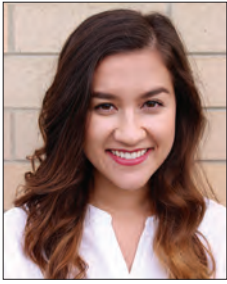
deleted or mutated SMN1 gene through gene therapy, or 2) correcting the processing of the SMN2 gene to increase production of functional SMN. The development of SMA mouse models that recapitulate the human disease has facilitated development and validation of these candidate therapeutic approaches, many of which have shown remarkable success in pre-clinical studies. One such therapy that has been translated from the bench into clinical trials, employs nusinersen, an antisense oligonucleotide produced by Ionis/Biogen that restores the proper splicing of SMN2 derived transcripts. Results from a phase 2 clinical trial have recently been published including patients recruited at Columbia University Irving Medical Center through the Spinal Muscular Atrophy Clinical Research Center headed by Darryl De Vivo, MD and Claudia Chiriboga, MD, MPH, one of four participating institutions. Remarkably, data from this study in Type I SMA patients demonstrated improved motor function, extended survival, and delayed need for respiratory support; however, long-term effects are yet to be fully evaluated. Moreover, a subsequent late stage trial was recently halted as it was deemed unethical to not provide treatment to control patients as a consequence of the clear benefits, further establishing efficacy. This past December the antisense molecule (renamed SPINRAZA) was granted FDA approval, the first of a newly approved treatment for SMA, and a groundbreaking advance in the field of neurodegeneration.

While the development of SPINRAZA is unprecedented, multiple other courses of treatments are being explored. One potential drawback of SPINRAZA is the requirement for recurrent injections directly into the spinal fluid through a lower spine puncture. In contrast, another approach aimed to increase SMN protein through replacement of the SMN1 gene, can be delivered in a single treatment. This gene therapy approach is being spearheaded by AveXis, and utilizes an adeno-associated virus to deliver the cDNA to cells in the body by either intrathecal or intravenous injection. A phase I trial is cur-

(continued on next page)



Immunostaining of motor neurons from a wild-type and a spinal muscular atrophy mouse model at a late disease stage demonstrating the loss of motor neurons. The molecular mechanisms underlying motor neuron death remain unknown.



Meaghan Van Alstyne

rently underway, and indications of improved motor skills and tolerability have resulted in breakthrough therapy designation by the FDA, with a pivotal trial planned to begin in 2017.

Another outstanding question in SMA therapeutics is the clinical importance of delivering treatments to peripheral tissues, outside of the spinal cord, which has yet to be fully evaluated in patients, and presents a possible caveat for approaches that do not deliver drug to these potentially important locations. A developing therapeutic approach utilizes small molecules that specifically target and correct SMN2 processing which are orally deliverable, thus enhancing SMN in all tissues. Several such compounds developed by Roche/PTC in collaboration with the SMA Foundation have progressed to early clinical trials. Novartis is developing compounds that act through similar mechanisms and are in the early stages of clinical testing. Since these compounds are orally bioavailable they not

only permit a more accessible mode of delivery, but also enable the targeting of tissues beyond the central nervous system.

With several SMN-targeted treatments demonstrating great promise, focus can now be placed on how to optimize such therapies. Studies in animal models indicate treatment is most effective when delivered before symptoms appear, and intervention loses efficacy when provided at later stages, emphasizing the importance of early diagnosis. With an FDA-approved drug now available, the implementation of universal newborn screening for SMA through genetic testing will likely be boosted and in the foreseeable future allow treatment of patients at pre-symptomatic stages. As a note of caution, while these treatments show efficacy in the improvement of motor function—a groundbreaking development in its own right—they still do not provide a complete cure and long-term outcomes remain undefined. Additionally, critical questions such as whether differential treatments will be required for the existing SMA patient population of varying disease severity at post-symptomatic stages have yet to be elucidated. In order to address these issues, several additional SMN-independent therapies are

under development for the treatment of SMA, which could potentially be used at post-symptomatic stages or in tandem with the SMN upregulation strategies discussed previously. Such combinatorial approaches are beginning to emerge and will require the continuing support of basic research of SMN biology and SMA pathology.

Uncovering novel targets for further therapies requires a deeper understanding of disease mechanisms at the molecular, cellular and system levels, much of which is only beginning to be revealed and may also further broaden our knowledge of aspects of neurodegeneration. Such investigation is ongoing in several labs dedicated to research in the field of SMA in the Motor Neuron Center and the Department of Pathology and Cell Biology at Columbia University Irving Medical Center, where I study the molecular mechanisms underlying motor neuron death in SMA, which remain largely unknown despite being a hallmark of the disease. While important questions such as this must be addressed and highlight how much more molecular understanding we have yet to gain, the development of pioneering effective therapies has provided unprecedented hope for a previously untreatable and encumbering disease.

Teaching: Internationalization of Medical Education at P&S



On December 5, 2016 P&S students and Pathology-Anatomy faculty video-conferenced with their international counterparts in Halle, Germany and Kyoto, Japan presenting reports to each other that resulted from several prior small group meetings. The aim of the project is to promote early internationalization in medical education via early peer-to-peer collaboration - starting in the Anatomy course that will hopefully extend throughout these students' careers. The project was initiated in the P&S Anatomy course and is now in its third year.

This year, 55 students from the US, Japan and Germany had video-conferenced and worked together on papers in small groups (n=11) for 6 weeks prior to the final paper presentation. Students from the different schools chose to work on topics such as medical education, health insurance, abortion and residency training, comparing and contrasting these topics in their different countries.

The picture shows the Columbia group gathered for the conference including the Clinical Gross Anatomy course director, Dr. Paulette Bernd (left) and P&S Anatomy faculty Dr. Anette Wu (right). Dr. Takeshi Sakurai (faculty at P&S and Kyoto University) represented Kyoto University, Japan and Professor Dr. Heike Kielstein represented Halle University, Germany. Participating Anatomy students from P&S and CDM classes of 2020 are Max Pensack, Artur Wysoczanski, Lilian McKinley, Shaheen Malick, Brandon Mogrovejo, Gabriel Garcia, Ngobitak Ndiwane, Vicky Ro, Michelle Chee, Taiwo Alonge (in picture). Students that are not shown in the picture and participated in the study are Andrew Heinrich, Ryan Blake and Jonathan Xu. In the background are screenshots of the German and Japanese students during the conference.

(The study was supported by a grant of the Virginia Apgar Academy of Medical Educators, Columbia University.)

New Grants: since June 2016

PI	Sponsor	Title
Teich, Andrew	National Institute on Aging/NIH/DHHS	An integrative analysis of DNA methylation, transcriptomic changes, and cognitive dysfunction in Alzheimer's disease
Haeusler, Rebecca	American Diabetes Association, Inc.	Hepatic insulin action and endothelial function
Sepulveda, Antonia	National Cancer Institute/NIH/DHHS	Genomics and Mechanisms of Esophageal Carcinogenesis
Wichterle, Hynek	Biogen Idec	Developing motor-neuron driven reporter induced pluripotent stem cells (iPSC) lines
Gershon, Michael	National Institute of Neurological Disorders and Stroke	Modeling enteric nervous system development and Hirschsprung's disease in human pluripotent stem cells
Canoll, Peter	National Institute of Neurological Disorders and Stroke	Mechanism of regulation of progenitor proliferation and transformation
Au, Edmund	Whitehall Foundation, Inc.	Investigating the role of Wnt Signaling in Subpallial Lineage Specification

In Memorium

Jakob Franke

by Richard Kessin

Jakob Franke, who ran the Kessin lab for almost thirty-five years, died suddenly on November 10, 2016. He was 75.



Courtesy New York-New Jersey Trail Conference

Jakob and Gely Franke came to the United States in 1968 to join the lab of Maurice Sussman at Brandeis where I was a graduate student. As it happened, we were both doing experiments that lasted late into the night and between samples, we bonded over a chessboard. Jakob and Gely soon became part of my family in New Hampshire. The Dutch, or more particularly the blunt-mannered Friesians, which Jakob proudly was, are flatlanders—they like soccer fields and skating. In New Hampshire, Jakob met serious mountains, which he loved. In the first year or two, he climbed a snowy Tuckerman's Ravine on Mt. Washington, which is as near to being a cliff as one can imagine without being one. There

were many lab winter camping trips, some bordering on crazy.

When I came back from a post-doctoral stay in England, I got a job offer from Harvard and asked Jakob if he would join me if I could get an NIH grant. He said yes, as did the NIH and for eight years we were at Harvard, where Jakob developed the first minimal medium for the amoeba *Dictyostelium discoideum* and purified the cAMP phosphodiesterase and its inhibitor protein that are critical to chemotaxis and development of these astonishing amoebae. He was a methodical worker who had all of the skills that I lacked, including patience.

In 1983 we moved to Columbia and just continued working. We cloned the complex genes for the cAMP phosphodiesterase and related proteins, studied their role in chemotaxis and development and then went on to studies of autophagy and infection by pathogens. The lab isolated the first cheater mutant—a cell line that resists a fate that leads to death and will only make spores, thus extending the use of *Dictyostelium* into evolutionary biology.

Jakob had extreme organizational talents and set about cataloguing all of the references to *Dictyostelium* and related social amoebae since 1867 and then started a strain

collection, which recovered the many stains created by the community. It is now based at Northwestern University. These efforts provided the basis for a book, *Dictyostelium: Evolution, Cell Biology and the Development of Multicellularity*, which remains the latest complete monograph in the field.

There were many graduate students, post-docs and technicians whom Jakob and Gely helped along the way. They have all gone on to fine careers in academia and industry.

Jakob is survived by his wife, Gely Franke, and two daughters, Ettaly Franke Jobses and Arva Franke Rogers and their son Conner. Jakob and Gely also have extensive family in the Netherlands. Both Ettaly and Arva attended Columbia University as undergraduates and Ettaly attended medical school at P&S. She is now a pediatrician practicing in Annapolis, Maryland. Arva became a veterinarian and has a practice in Oklahoma.

After retiring from Columbia University, Jakob remained tirelessly productive, building hiking trails with the NYNJ Trail Conference and rewriting his Field Guide to the Morris Canal of NJ (see nynjtc.org or canalsocietynj.org). A memorial service will be held May 2017 in Mahwah, NJ.

Anniversaries

The Newsletter has yet to solve the problem of proper recognition of long-serving members of the Department. That is primarily because there are so many of us. That speaks well to the atmosphere and stability of the Department of Pathology and Cell Biology. The list, five year increments, is shown below. Alas, there was no space for those who have served for 10 years.

(Carmen Amaros, Laboratory Technologist, reached her thirty-year milestone after the list was produced, so she gets an individual shout out.)

Name	Years of Service	Current Title
Stecher, Lee R.	50	Administrative Aide
Silvia, Elaine A.	40	Staff Associate
Pesce, Michael A.	40	Special Lecturer
Rotterdam, Heidrun	40	Special Lecturer
Dempster, David W.	35	Professor of Clinical
Johnson, Elnora	35	Director, Business Office
Hernandez-Rosa, Evelyn	35	Senior Research Worker
Delatorre, Ludwika E.	35	Senior Staff Associate
Krishna, Sindu	30	Senior Staff Associate
Shelanski, Michael L.	30	Senior Vice Dean/Name Professor
Chang, Chih-Chao	25	Assistant Professor at CUMC
Saqi, Anjali	25	Professor at CUMC
Faust, Phyllis L.	25	Associate Professor at CUMC
Boldogh, Istvan	25	Associate Research Scientist
Chalazonitis-Greene, Alcmene	25	Senior Research Scientist
Valladares-Silva, Sunilda	25	Manager, Histology
Ming, Ming	20	Staff Associate
Jiang, Hong Holly	20	Associate Research Scientist
Yu, Zhimin	20	Staff Associate
Acevedo Jr, Melvin	20	Laboratory Technologist
Vundavalli, Murty V.	20	Associate Professor at CUMC
Finan, Gina M.	15	Associate Research Scientist
Melikyan, Hranush	15	Senior Research Worker
Dohanich Jr., Peter P.	15	Laboratory Coordinator
Caicedo, James	15	Staff Associate
Jobanputra, Vaidehi	15	Associate Professor at CUMC
Vallee, Richard	15	Professor
Alobeid, Bachir	15	Professor at CUMC

A Note to Our Readers

Pathology and Cell Biology Reports (PCR) intends to inform all members of the Department about the work of each of our branches. These include Pathology and all of its divisions, Administration and all of their valuable functions, and also Cell Biology including neuroscience and cancer biology. We intend to publish the normal congratulations, retirements, and promotions, but also substantive short articles. We also publish photographs and artwork, scientific or otherwise, by our members. If you have an idea, please contact us at: PathNews@columbia.edu.

A Note on Publications

Our department is large and its members publish hundreds of papers a year in peer-reviewed journals. References can be found on the pages of individual faculty members. Every effort is made to keep these bibliographies current. For recent papers by Residents see:

<http://pathology.columbia.edu/education/residency/publications.shtml>

Our Diagnostic Services

The Department offers a very broad range of expertise and diagnostic services. We are available for consultation at the following sites.

Web: www.pathology.columbia.edu

Email: pathology@columbia.edu

Laboratory services: 1-800-653-8200/1-212-305-4840

Administrative Services: 1-212-305-7164

COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

Winter/Spring 2017

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The Columbia Pathology and Cell Biology Report is a publication of the Department of Pathology and Cell Biology at the Columbia University Medical Center.

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