COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT
Fall 2016

In This Issue

When the Pathologist Becomes the Patient

A Personal Journey: My Brain, Dearest

By Kurenai Tanji, MD, PhD

On December 21, 2012, which I later remembered was the last day of the world according to the Mayan calendar, I woke up as on any other morning and left home for work. It was a cloudy winter morning with a slight drizzle.

I did not make it to work, not even to the subway station. When I was crossing 123rd Street at Morningside Avenue with a green traffic light to get to the subway, I was struck by a car. I was knocked down and hit the ground with my left occiput. My brain was swung against the overlying cranium, and bounced back and forth. The results were classic coup and contra-coup brain injuries, or in neuropathological terms, a brain contusion associated with subdural/subarachnoidal haemorrhages in the left occipital and in the right frontal lobes. Accordingly, my destination of the day was not my office on the 15th Floor of the Presbyterian Hospital Building, but the emergency room of the nearest hospital (St. Luke's) and eventually the Neurological Intensive Care Unit (Neuro-ICU) of the

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The bold architecture of the Roy and Diana Vagelos Education Center; now accepting students. *Photo credit: Nic Lehoux*

Next Generation Tumor Banking: An evolving mission critical function

By Hanina Hibshoosh, MD
Director of the Tumor Bank,
Director of the Molecular Pathology Shared Resource of the Herbert Irving Comprehensive Cancer Center

The capacity to interrogate tissues and extract valuable information in a cost efficient manner makes biobanking operations critical to patient care and institutional success.

In traditional biobanking tumor/normal pairs were derived from surgical resections where excess tissue from mass forming lesions is frozen, either in the frozen section room or the gross room. Frozen tissues were used short-term for diagnostic purposes, but were banked long-term for research only. Tissue annotation relied primarily on pathology reports with limited additional data. Thus our tumor bank grew to contain 30,000 diverse tumors (70,000 blocks) collected over the past 25 years. It has been extraordinarily valuable in oncological research.

To address the needs of the precision medicine era, tissue acquisition has undergone

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Letter from the Chair

Aspects of Departmental Excellence: *The Measurable and The Intangible*

Dr. Kevin A. Roth, baseball fan

What makes an academic department great, and more specifically, how will we know if the Department of Pathology and Cell Biology has achieved "greatness"? As I enter my second year as chair of the department, I often contemplate the metrics of departmental success and wonder if the decisions I make and the priorities I set will maintain or enhance the department's national and international reputation. Some metrics are easy to quantitate….for example: numbers of faculty, graduate students, post-docs, clinical trainees, publications in high-impact journals, national academy members, and faculty honors; big numbers indicating a large and successful department (arguably, a "great" department). In particular, total NIH grant funding and departmental rank relative to others in the discipline are topics of intense conversation at gatherings of department chairs, are of significant interest to institutional leaders, and are used to measure both a chair's and department's performance.

On these metrics, we are succeeding. Our department receives approximately $25 million in annual NIH grant support, ranked sixth for NIH funding to departments of pathology in 2015, and is projected to be fifth in the 2016 rankings based on current NIH.gov award data. I am very proud of these accomplishments and the recognition that we receive for consistently being a top-five NIH funded department. However, NIH funding alone does not define us as great. For this distinction, success across multiple domains, including the clinical, teaching and training missions, must be achieved. Accurate performance metrics and relative rankings to other departments nationally

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From the Chair

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for these other activities are more difficult to obtain but based on semi-quantitative and qualitative data, I am confident that we are accomplishing excellent results.

As described in this and previous newsletters, our faculty members are consistently recognized locally and nationally for achievements as medical and graduate student educators. We are attracting many of the most academically gifted graduate students and residents in the country and their performance in the research laboratory and on clinical service is outstanding. For example, 100% of our residents over the past decade have passed the American Board of Pathology exam on their first attempt and our graduate students have received numerous local and national awards for research excellence. On the clinical front, we are expanding our residency program, developing a physician-scientist residency track and hiring additional faculty members across many clinical divisions to meet an increasing case volume. We now perform over 180,000 tests in Anatomic Pathology and approximately 20 million tests in Laboratory Medicine. We have excellent clinical subspecialty services, continue to grow our Personalized Genomic Medicine (PGM) Laboratory capabilities, and meet all of the clinical quality indicators jointly established with New York-Presbyterian Hospital (ranked sixth nationally in the U.S. News Honor Roll of Best Hospitals 2016-17).

Given the accomplishments described above, what more do we need to do to be a great department; or perhaps more accurately, how do we become even greater? In my opinion, the department will reach its zenith when we develop a deep sense of professionalism that permeates all faculty, staff, and students and our interactions with others. The goal is to be a department with a deep commitment to academics and patient care, one that supports professional career development of all its employees, that is able to improve itself through careful self-evaluation and constructive criticism from others, and finally, one that we are all proud to be part of. We will always have room for improvement but significant progress is being made towards the goal of being the greatest Department of Pathology and Cell Biology we can possibly become. I look forward to working with you to make it happen.

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

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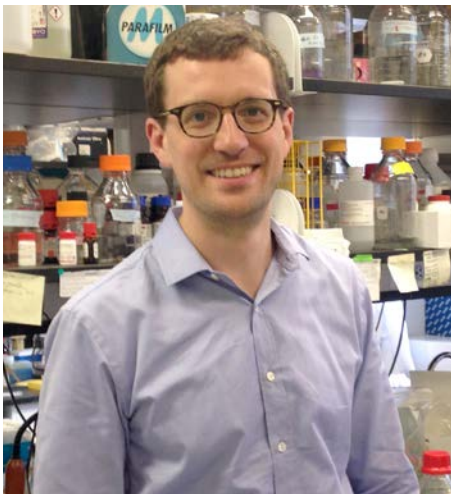
Andy Teich MD, PhD wins Beeson Award from The National Institute of Aging. Assumes co-leadership of the New York Brain Bank.



The Beeson award is named after Dr. Paul B. Beeson, who was the Chairman of Medicine at Emory and Yale Medical Schools, Nuffield Professor at Oxford University, and Professor and distinguished VA Physician at the University of Washington. He chaired the first Institute of Medicine study on "Aging and Medical Education" in 1978, and he was also an editor of the Cecil Textbook of Medicine.

The award that bears his name is intended to support clinically trained faculty members who seek additional research, career, and leadership skills essential for assuming a leadership role in the field of aging research. Andy writes that: "this award will facilitate research that focuses on Alzheimer's disease (AD) and neurodegenerative diseases of the aging brain, and integrate this study with my clinical role as a neuropathologist. I am coming off 2 years of a K08 grant that supported my career development, and in that time I have developed two research programs (one involving molecular drivers of neuronal degeneration in AD, and a second on defining the changes in gene expression that occur in normal pressure hydrocephalus). The Beeson award will fund continued work on these projects. The actual title of the grant is: *"An integrative analysis of DNA methylation, transcriptomic changes, and cognitive dysfunction in Alzheimer's disease"* In addition, I have recently assumed a leadership role at the New York Brain Bank, where I am Co-Director with Dr. Jean Paul Vonsattel, and this award is welcome help as I assume this responsibility.

NYP/Lawrence Hospital

The NYP/Lawrence Hospital in Bronxville has chosen ColumbiaDoctors and the Department of Pathology & Cell Biology to provide Medical Directorship for the Hospital's clinical and anatomic pathology services.

The Department conducted a national search for a Medical Director and is pleased to announce that Dr. Peter Hoffmann accepted the position and, since 9/1/16 has been working in his new role. Dr. Hoffmann trained in the Department of Pathology. Dr. Hoffmann will have the responsibility of oversight of the Anatomic and Clinical/Blood Bank Laboratory, Outreach Services and clinical program development.

Dr. Sergey Cherneykin also provides onsite pathology service. Drs. Hoffmann and Cherneykin have agreed to write more extensively about NYP/Lawrence Hospital in a future edition of the newsletter.

All Lawrence hospital faculty and their patients now have the advantage of Columbia's export pathologists, streamlined reporting directly into the patient's Electronic Health Record, rapid turnaround times, and ad hoc physician to physician consensus conferences.

A Personal Journey: My Brain, Dearest

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Milstein Building, Columbia University Irving Medical Center. The possibility of craniotomy for evacuation of intracranial blood was discussed, but, the bleeding stopped before forming a substantial mass, and the craniotomy was deemed unnecessary.

That was the first day of my long journey of the next three and a half years towards recovery. On Day 1, my brain started crying out, causing me severe headache with nausea and vertigo that I had never experienced in my whole life. My world was spinning around me every time I tried to move in bed. On Day 2, I was able to walk with help, but was quite ataxic. It appeared a miracle to me that I did not have any broken bones or torn ligaments. There was only a small incomplete skull fracture where my skull was forced to meet the icy-hard surface of 123rd Street.

Christmas was approaching, and my brother happened to be on route to New York from Tokyo for a vacation. As soon as his plane landed at JFK, he was summoned to the reception desk of the Milstein Building, where he was told of his sister's whereabouts. His first words were, "Neuro-ICU!! Is she still alive?" Later, he told me, as he was in the Milstein elevator to the Neuro-ICU, that he was thinking how to execute his family responsibility of bringing his sister's dead body with its crushed brain back to Japan.

On my discharge, alive, from the ICU on Christmas Eve, the chief ICU neurologist matter-of-factly delivered the news that my brain had another problem. An MRI incidentally found a 3cm-extra-axial tumor, most likely a meningioma, occupying the left cerebello-pontine(C-P) angle and the petrous cerebellum. "A meningioma in my brain, compressing the 7th and 8th cranial nerves, the brainstem and cerebellar roof?" I repeated his words to myself.

I do not remember how I reacted to his words. But, I do remember my profound, burning, undirected anger: why now or ever do I have to know and deal with this? I just wanted to get out of the ICU, out of the hospital, and forget everything: brain trauma, headache, meningioma or whatever else went on in my life. All I wanted was to go home and eat the Italian meatballs that my brother had bought in a nearby supermarket to celebrate our transformed, sister-brother-reunion, a unique type of Christmas Eve dinner.

How many brains with intracranial haemorrhage have I cut and examined in my 25 years as a neuropathologist? How many pathology reports of meningiomas have I signed out? The answer is "many". But, while doing so, did I ever consider the reality that a neuropathologist would have the same risk of contracting a brain injury or tumor as any other member of the human population, or that having one pathology in the brain does not preclude the possibility of having a second? No, I did not. As to my own meningioma, I wondered how many years it had taken to grow to be a 3cm-mass in a very narrow space like the C-P angle without warning neurological symptoms.

When a physician gets sick, especially with diseases of her own specialty, she seems to behave in a peculiar way. I was moved and inspired by a recent New York Times article by a distinguished neuroscientist at NIH, who bravely disclosed her own story of psychiatric symptoms caused by metastatic cancer to the front lobe of her brain. My heart ached, as another professional woman carrying a brain tumor, while reading her simple and straight-forward description about her altered professional and personal life after the brain metastasis. She wrote that she was indeed calm and objective, rather than panicky or emotional, to face the reality of disease progression, because our medical education trained us with an emphasis upon the analysis of "diseases." I agree with her about our medical training in general, but think that, when it comes to the personal event, it also acts as our own defence mechanism.

I am not certain how objective I was about my brain injury and tumor, while I tried to be calm. At least, I knew that screaming and crying was not going to help my situation. Retrospectively, however, my calmness was, at least in part, based on the illusion that the tumor would remain in its place until the day I died and that I would take it with me into my grave.

I lived with this denial and illusion for the next three years, while I suffered from existential post-traumatic headaches, which were becoming chronic and continuous until I began to experience additional positional vertigo, an undeniable vestibular sign caused by the compressed 8th cranial nerve by the tumor. Finally, in December 2015, I gave up on my own illusion and consented to a craniotomy. The surgery was performed in February 2016, three years and two months after my first brain injury, to be precise. My meningioma was completely removed by my most trusted neurosurgery colleagues, and I was left without any neurological deficit.

I admit that, in spite of being a physician, I was irrational in denying the presence of a growing tumor in my brain. At the same time, however, I come to realize an objective, analytical aspect in me as far as the concussion and my injured brain due to the accident are concerned. I noticed interesting phenomena, especially in the months immediately following the accident. First, the smell and taste of certain foods were altered, and I could taste only extremely salty or sweet food. Coffee did not smell like coffee, and chocolate did not taste like chocolate. It remains an unsolved neurological question why smell and taste changed, since my olfactory bulbs and facial nerves were not directly damaged by the injury. A colleague neurologist suggested the possibility that the subarachnoid blood may have tracked down the nerve sheath to irritate the nerves. The other interesting change, more shocking to me than the previous, was that my brain (temporarily, thank God!) experienced difficulty processing music. I am a great fan of classical music and opera, and together with my late husband, who was a neuroscientist and classical music scholar, had collected many CDs and videos of outstanding performances in classical music. After my brain injury, the music that I had enjoyed so much became just collections of fragmented sounds without any emotional, narrative content. I could hear the sounds or short segments of melody

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lines (therefore, it was not a mere auditory functional issue), but could not process them as integrated notes and chords. It took almost half a year for my brain to re-comprehend the elegant flow of music and find beauty within it. Neuroanatomically, our brains appear to have a center for processing music, located close to the language center called Broca's area, based upon the advancing neuro-functional imaging technology. However, "enjoying the music" is such a complex matter, as it involves not only auditory processing, but also emotional arousal, pleasant rhythmic entertainment and synchrony. This complex process requires the participation of the front-temporal circuit including the caudate nuclei, insula, and amygdala. That said, was my brain shaken so violently by the accident that this deep neuronal circuit was disrupted, at least temporally? I do not know the answer. I also have no explanation for, why, 3 months after the accident, I felt quite dizzy and nauseous and ended up leaving my seat at the middle of a performance, when gazing at the opera stage where approximately 40 singers in simple black-and-white shirts and trousers were moving around. Did this visual stimulus cause some kind of epileptic waves in my brain, even 3 months after "the Shake?" Dr. James Goldman, my division director back then, suggested that I write about my experience to Dr. Oliver Sacks, the famous neurologist and writer authoring "Musicophilia." Dr. Sacks died before I had the opportunity to contact him.

My brain surgery of February 2016 was followed by a period of so-called posterior fossa syndrome, post-operative aseptic meningitis, which brought me a new kind of headache. Initially, especially after post-operative high dose-steroid treatment, I was extremely emotional and disappointed with the never-ending headaches, which I had hoped so desperately would be gone after the operation. However, as time went on and the meningitis subsided, something in my brain (I call it 'wisdom of my middle-aged brain', although recent neuroscience may have a fancier term) told me that I was actually lucky for the surgery had granted me a chance at a new life. Now, having travelled my 3.5 year-journey after the first accident, I feel that I have become more insightful into human suffering associated with "diseases." My current, residual and continuous headache, called by my neurologist occipital neuralgia, is presumably caused by the damage to peripheral nerve branches in the subcutaneous and connective tissue of the head. Regardless of the name of my headache, life will continue with this brain of mine sending me a variety of signals. Whatever the future has in store for me and my brain, one thing I do feel — my brain is now more compassionate, more hopeful, and happier.

To end this essay, I would like to acknowledge that I would not have possibly been here today, might not have written what I did write, without the support during my most challenging years, physical or psychological, direct or indirect, from my personal and professional friends and colleagues in and beyond my beloved Department, and the excellent neurosurgical assessment and treatment by the team lead by Drs. Michael B. Sisti and Guy M. McKhann. My article is dedicated to all those people, to whom I owe my life.

Dr. Kurenai Tanji

Department of Pathology & Cell Biology Website Project Update - Fall 2016

By Tevra Francis

Closing in on the 6-month mark, the Pathology and Cell Biology Website project is still going strong. During this time, the Website Committee has been at work on several fronts. To date, faculty and staff have reorganized the site map, written and edited content, and participated in photography sessions. The Core Planning Group has had several meetings with Catherine Freeland, Associate Vice Dean of Marketing and Strategic Communications, whose web development department is currently working on a new format for the improved website. Updates about the Columbia University Profile System (CUPS) have been circulated among the Pathology and Cell Biology faculty. Please update your profiles online.

The goals of this project remain the same, to serve our stakeholders with a comprehensive, user-friendly website. "I have had the pleasure of revising the existing site along with the members of my group, to develop what we believe will be a Research Section filled with vibrant, scientific images and content that will keep the Research community both at Columbia and beyond intrigued with the work being done in this department," said Jennifer Fernandez of the Research Group.

Committee member Andy Wu said: "It has been a great experience to work with the different divisions within Pathology with whom I would normally not interact. The website still needs a lot of time and effort, but I am sure the finished project will turn out spectacularly." With hopes for a launch date in Spring/Summer 2017, a mid-project "pep rally" will be held in November that will allow each working group to report progress, discuss the next phase, and to thank everyone for their commitment.

We encourage ideas and feedback. Send them to PathWebMaster@columbia.edu.

Next Generation Tumor Banking: An evolving mission critical function

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remarkable change. One of these changes includes near real-time collection of samples to minimize cold ischemic time and to preserve viable tissues. To achieve this we have a patient-specific acquisition process that was developed with the Clinical Protocol Data Management office and our Tumor Bank. The protocol defines a patient's procedure location, the analytes to be collected, the manner of their processing, and their destination. The acquisition of tissues has expanded to a variety of locations beyond the operating rooms and the pathology gross room and now includes interventional radiology(IR), doctors' offices, and endoscopy units, among others. The expanded venues, particularly in IR, allow for capture of analytes including fresh and frozen tissue in addition to fixed tissue. The capture of tumors in IR settings allows for an expanded collection of metastatic tumors and radiographically defined lesions. One research effort, led by Dr. Gary Schwartz, supports a phase one drug-screening program, which is one of the first of its kind.

In traditional biobanking, as used for personalized genomic medicine, the tissue is frozen in a nonviable manner. Recently, we have expanded to freezing tissue for viability (performed by Dr. Mark Frattini) to enable future live-cell studies that include culture, cytogenetics, and drug testing.

The collection of fresh tissues not for banking but for immediate dispersal has markedly expanded and requires a near sterile approach and modification of our work flow in the operating rooms and elsewhere to avoid contamination of samples. Fresh tissue is increasingly being utilized for patient derived xenografting. Dr. Andrew Kung and Dr. Mahesh Mansukhani carry out research in pediatric precision medicine to support biological studies and preclinical therapeutic efforts. In addition our efforts support vaccine preparation by Dr. Ilya Trakht, and stem cell isolation and organoid culture by Dr. Michael Shen. Dr. Andrea Califano's N-1 Master Regulator/ pharmacogenomics program requires real time ex-vivo drug testing in tissue provided by our Shared Resource Center. We also provide isolated compartments of a tumor-like immune microenvironment for work by Dr. Swarnali Acharyya and Dr. Yvonne Saenger.

Acquisitions of various analytes under strict conditions (ischemic time less than one minute, freezing in liquid nitrogen to satisfy sponsors of phase-one trials (Dr. Schwartz, Dr. Carvajal and Dr. Rizvi) has markedly expanded. This capacity has been critical in allowing many patients to enroll in immune checkpoint inhibitors trials.

Quality assurance of captured material is being critically performed via real time imprint cytology assessment in non-surgical cases or frozen section diagnosis in mass lesions.

CLIA biobanking became a reality this year allowing for retrospective analysis in a clinical setting of captured tissues. This represents a critical shift that will pay dividends for many years to come.

Beyond these modifications is the enhanced annotation of banking material through the Database Shared Resource (DBSR) allowing for linkage to a robust clinical data set. Our "Next Generation Banking" program, which systematically analyses and processes banked tissue for H&E review, microdissection, DNA and RNA extraction and TMA construction produces an off-the-shelf robust research resource, reducing barriers to research in multiple organ systems.

All this is accomplished with the help of many constituents (clinicians, surgeons, oncologists, pathologists, residents, CPDM). First among them is our Banking Team (picture).

Key to success is the realization by all stake holders that banking is a mission critical function supporting our clinical, research and educational enterprise especially in the precision medicine era.

See our website http://www.hiccc.columbia.edu/research/sharedresources/molecular or give us a call at 212-305-1608 for more detailed explanations.

From left to right in photo: Junru "Andy" Zhu, Christopher Lufkin, Lysette Seegobin, Hanina Hibshoosh, Mohammad Ullah, Dajiang "Kevin" Sun.

The Mystery of Glioblastoma; three potentially useful drugs

By Markus D. Siegelin, MD, Dr. med.

Apeksha Rao, Markus Siegelin, Georg Karpel-Massler, Chang Shu

The prognosis for patients with Glioblastomas (GBM) is poor. We are trying to find novel treatments for GBM, the most common malignant primary brain tumor in adults. We have adopted several strategies that merge efficient and specific induction of apoptosis (the mechanism by which cells self-destruct) with alternative forms of cell death. Certain drugs, called BH3-mimetics (ABT263, ABT199 and ABT737) inhibit Bcl-2 and Bcl-xL, two anti-apoptotic proteins, at very low concentration. Mcl-1 is another member of the anti-apoptotic Bcl-2 family, but it is not inhibited by the ABT compounds. High levels of Mcl-1 are an obstacle to efficient induction of apoptosis by BH3-mimetics in malignant glial tumor cells. The idea is that if we can suppress Mcl-1, the ABT inducers of apoptosis should work much better.

In collaboration with researchers from the University of Ulm in Germany, we have shown that L-asparaginase, a compound that is a standard-of-care treatment for acute lymphoblastic leukemia, down-regulates protein levels of Mcl-1. It has an associated stabilizer, Usp9X, both of which in addition to Mcl-1 are up-regulated in GBMs and drive resistance to intrinsic and extrinsic apoptosis (1-2). Based on these molecular observations, we found that L-asparaginase potently enhanced the effects of ABT263 both in vitro and in vivo. Given that L-asparaginase is a FDA-approved drug and ABT-263 has reached clinical trials, it is possible to test the hypothesis that this drug combination will be effective against GBM in patients, an approach we are taking.

There is another route to GBM growth inhibition. IDH1 (isocitrate dehydrogenase) is an enzyme that is located in the cytosol of tumors, where it generates NADPH2 from NADP through oxidization of isocitrate. Low-grade gliomas, oligodendrogliomas and secondary GBMs commonly harbor a heterozygous mutation of IDH1 (R132H). The mutation leads to a metabolic alteration that causes certain intracellular changes that are therapeutically targetable. Because of its impact on prognosis, the IDH mutation has been included in the WHO classification scheme for CNS tumors. We have identified compounds that take advantage of the metabolic deregulations in IDH mutated tumors, leading to specific cell death induction. This may sound abstruse, but it works. To evaluate candidate compounds in clinical trials, we are elucidating the molecular mechanisms and testing these compounds in IDH-mutated murine models of glioma. We are performing these experiments in close collaboration with Dr. Peter Canoll (Director of Neuropathology) and Dr. Jeffrey N. Bruce (Department of Neurosurgery).

Another strategy aims at the identification of targets that cause synthetic lethality in the presence of mitochondrial matrix chaperone inhibitors, which are called Gamitrinibs and are in clinical development. Targeting a specialized chaperone network found in tumor cells, Gamitrinibs elicit a tumor cell specific cell death, thus limiting side effects. Our earlier work has demonstrated that these compounds cause a mitochondrial unfolded protein response with a global change in transcription and a subsequent significant suppression of NF-kB signaling. This treatment sensitizes a broad range of recalcitrant cancer cells to extrinsic apoptosis induction in vitro and in vivo. Through a high-throughput drug screen, we identified a novel synthetic lethal interaction between Gamitrinibs and the inhibition of a certain class of molecules that reside at the outer membrane of tumor mitochondria. With these three leads, we hope that our research provides part of the foundation necessary to move forward to clinical trials.

Photo by Dr. Patricia Tiscornia-Wasserman, from a collection entitled, "Reflections".

The research is currently supported by the recently awarded NIH NINDS grant R01NS095848, K08NS083732 and recently awarded BCURED Foundation grant. Former support was received from the American Association for Cancer Research, the American Brain Tumor Association and the Irving Cancer Center Pilot Award.

1. Karpel-Massler G, Ramani D, Shu C, Halatsch ME, Westhoff MA, Bruce JN, Canoll P, Siegelin MD. Metabolic reprogramming of glioblastoma cells by L-asparaginase sensitizes for apoptosis in vitro and in vivo. Oncotarget. 2016. doi: 10.18632/oncotarget.9257. PubMed PMID: 27172899.

2. Karpel-Massler G, Horst BA, Shu C, Chau L, Tsujiuchi T, Bruce JN, Canoll P, Greene LA, Angelastro JM, Siegelin MD. A Synthetic Cell-Penetrating Dominant-Negative ATF5 Peptide Exerts Anticancer Activity against a Broad Spectrum of Treatment-Resistant Cancers. Clinical cancer research : an official journal of the American Association for Cancer Research. 2016. doi: 10.1158/1078-0432.CCR-15-2827. PubMed PMID: 27126996.

ATF5 and glioblastoma treatment: past, present and future

By Lloyd Greene

Rarely, as a basic scientist, does one get the opportunity to contribute to an enterprise that might have therapeutic benefit. The story starts with our (the author and Jim Angelastro, then a research associate and now Associate Professor at UC Davis) interest in the role of the basic leucine-zipper transcription factor ATF5 in nervous system development. This interest soon led to the observations that ATF5 is highly expressed in glioblastomas (as well as other types of tumors) and that interfering with its' expression or activity rapidly causes the demise of tumor, but not of normal cells.

Heedless of the dictum that transcription factors are 'undruggable', Jim designed a cell penetrating dominant-negative form of ATF5. This peptide not only kills tumor cells in dishes, but also in mice and in the 1 dog tested so far. So far, it seems to be remarkably safe. Thanks to the efforts of the Columbia Technology Ventures office, our technology and advice have been embraced by Sapience Therapeutics, a biotechnology company that is presently focused on developing our dominant negative version of ATF5 for treatment of glioblastomas. If they are successful, which we should hopefully know within a few years, then there will be many heroes to thank, which I will be delighted to enumerate in detail on these pages.

Lloyd Greene, Alcmene Chalazonitis-Greene (center) and Dr. Taube Rothman, a long-time faculty member who has retired and taken up painting. Lloyd, Alcmene and Taube were at an exhibition of Taube's work (see background).

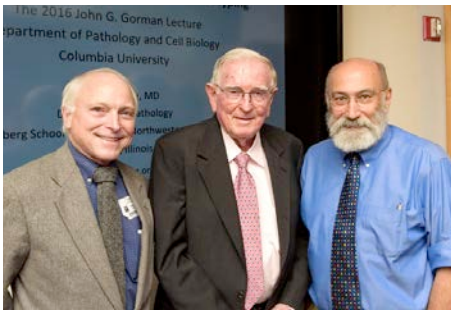
Laboratory Medicine

The Inaugural Dr. John G. Gorman Lecture

By Dr. Steven Spitalnik, Jim Rowell and Tevra L. Francis

This summer the Department of Pathology & Cell Biology at Columbia University Irving Medical Center established The Dr. John G. Gorman Lectureship for Excellence in Transfusion Medicine to honor our former colleague, Dr. Gorman. The Lectureship was created to celebrate the pioneering medical achievements originating at the College of Physicians & Surgeons and to advance educational opportunities for future generations of Pathologists at Columbia University.

This fall, we were honored to host Dr. John Gorman and several colleagues in Transfusion Medicine for the Inaugural Dr. John G. Gorman Lecture and Reception on September 23, 2016. Hosted by Dr. Steven Spitalnik and the Department of Pathology & Cell Biology, the event attracted attendees from Mt. Sinai, the New York Blood Center, and friends of Dr. Gorman, along with our own Columbia University/New York Presbyterian faculty and staff. The event's speaker, Dr. Glenn Ramsey, MD, is a Professor of Pathology at Northwestern University, and Director of the Transfusion Medicine Service Northwestern Memorial Hospital in Chicago, IL. Dr. Ramsey presented "From Type-and-Screen to Type-and-Gene: Everyday Uses of RBC Blood Group Genotyping", in the Fenoglio Library to faculty, staff, residents, fellows, and guests.



Pictured left to right:
Dr. Glenn Ramsey, Dr. John Gorman and Dr. Steve Spitalnik

Dr. John Gorman, M.D., was a Professor of Pathology in the College of Physicians & Surgeons at Columbia University and the Director of the Blood Bank at (what was then called) Presbyterian Hospital. At that time, Dr. Gorman, along with his Columbia colleague, Dr. Vincent Freda in the Department of Obstetrics & Gynecology, and their collaborator, Dr. William Pollack at Ortho Diagnostics, a Johnson & Johnson company, made one of the most important medical discoveries of our generation.

In particular, they discovered a method to prevent Rh isoimmunization and hemolytic disease of the newborn caused by the Rh blood group antigen (i.e., "Rh Disease"). Their concept, involving passive immunity, permitted protection of mothers from immunization by their fetus, via administration of anti-Rh antibodies to the mother. The initial Rh immune globulin (i.e., RhIg) product available for patient use was RhoGAM® Rho(D) Immune Globulin (human), developed and manufactured by Ortho Diagnostics, a Johnson & Johnson company. The work of these individuals, resulting in the availability of this commercial product, has saved thousands of lives of newborn babies and prevented enormous suffering among Rh-negative mothers and their children.

The Dr. John G. Gorman Lectureship program will continue to develop and host educational opportunities for years to come, hopefully with the help of philanthropic gifts and sponsorships.

Dr. John Gorman, Dr. Yvette Tanhehco, and members of the CUMC/NYP Transfusion Medicine staff.

Infection and its control: Looking at history in the archives of Norfolk, Connecticut

Richard Kessin

Nothing improves writing like explaining a scientific issue to interested people who last took a biology course decades ago. The format is 750 words, so that any word or paragraph that is not essential must be slashed. Adverbs all die, as do most adjectives and the passive voice. For six years I have been writing a column called The Body Scientific for The Lakeville Journal and its associated papers in Northwest CT. It is part of a mission to bring scientific thought to Northwest CT. I cover all manner of subjects but most columns recently have been about infection or disease. Some members of the Department have written guest columns. Contact me if you are interested. Think of it this way: there are 8000 potential readers, one excellent editor, two fact checkers, and no reviewers. What a relief! The article below was part of a five part series. Find the rest at: http://tricornernews.com/category/opinion-author/body-scientific

The Lakeville Journal in Lakeville CT. Janet Manko, Editor-in-Chief.

Recently I visited Linda Perkins, the town clerk of Norfolk, Conn. to do research on dangerous bacteria. Linda Perkins is not a scientist, but she has history on her side because her office meticulously maintains the records of births and deaths in Norfolk, back to the end of the 18th century.

There were 45 deaths in Norfolk from 1872 to 1874 in a population of 1,000 to 1,200. Of the 10 children who died, almost all were lost to infectious diseases — erysipelas (a strep infection), dysentery, pneumonia, meningitis, and typhoid fever in this small sample. In a few cases, the cause of death was not recorded (usually these were among the poor who did not have a physician). One young mother died of a burst uterus and her child died as well. Older people among the 45 died of pneumonia, peritonitis, measles and tuberculosis. It is not that Norfolk did not have physicians; it did, including the Welch family and particularly William H. Welch, P&S 1875, who went on to introduce modern medicine to the United States as a founder of The Johns Hopkins Medical School.

I chose the years 1872 to 1874 because the idea that bacteria caused infection had spread to the medical profession. Beginning in 1857, Louis Pasteur realized that microorganisms were the causes of fermentation, putrefaction, and infection. The first physician to take advantage of Pasteur's idea was the English surgeon Joseph Lister (yes, Listerine was named after him), who decided to sterilize all of his instruments, the patient's skin, the surgeons' hands and even the air circulating around the operating table. By 1865 he achieved a dramatic reduction in surgical infections and death among his patients, but these antisepsis practices did not find acceptance among surgeons for several decades and in the beginning, Lister was often mocked. Lister's methods might have saved the 25-year-old woman who died of a burst uterus — because it (and ether) made abdominal operations, including Caesarian sections, possible by avoiding infection of the mother.

What of the other 44 people who died from 1872 to 1874? Some of those infections might not have occurred if the germ theory of disease had been used in the practice of public health, as it had surgery. Water and milk, the sources of many infections, could have been tested for bacterial contamination. A famous report from the Public Health Service in 1909 listed more than 500 disease outbreaks traced to milk between 1880 and 1907. These included the case of a farmer who was a carrier of the agent of typhoid fever and contaminated all of his milk, starting a serious epidemic.

In 1910, New York City's Department of Health ruled that all milk delivered to the city had to be pasteurized and chilled. Its quality was also improved. No event in public health saved more young lives than this one. Deaths in New York from dysentery and other diseases fell dramatically after 1910. Most of the childhood deaths in Norfolk — two cases of typhoid fever, two cases of infant diarrhea, a case of dysentery, a child afflicted with meningitis and another with a strep infection all might have been avoided because of clean water, pasteurized milk, vaccines, and antibiotics. Death due to malnutrition would have been treated with healthy food. Nutritional and vitamin deficiencies were not widely recognized in 1872.

The adult deaths from peritonitis, TB and other bacteria would have been treatable. The measles victim, a young woman, would today have been vaccinated. Some adult deaths were due to heart disease, including a 16-year-old, possibly a consequence of rheumatic fever. There were people who died of accidents — one young man in a farm accident and one froze to death, possibly due to alcohol. Many people died in middle age and people who died in their early 70's (irritatingly) were listed on their death certificates as succumbing to old age.

I resurrect this history to begin a series on infection because recently we have had certain failures, reversions to 19th century risks — think measles and whooping cough epidemics and ghastly drug-resistant bacteria. The next column will describe the first vaccines and ask why they did not appear until about 1880.

Thanks to Janet Manko, Editor-in-Chief, The Lakeville Journal Company and her staff and to Linda Perkins, Norfolk town clerk.

Anniversaries and Retirements

Whenever I write this column, it strikes me that people tend to stay here for a long time. This must say something about our Department because our campus is not what you would call a low key, bucolic place. We have had one official retirement and that is longtime professor and anatomy teacher Ernie April. Ernie served as a dedicated teacher of Gross Anatomy for many years.

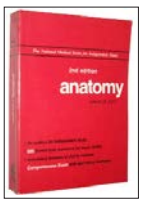
Dr. Ernie April with happy Gross Anatomy students

In the last issue Lee Stecher was leading the pack of longtime employees at 50 years. She is now at 51 and increasing her lead. Pathologists Jay Lefkowitch and Chuck Marboe, have been here for 36 years, but seem not to be aging. There are so many people in our department that after this, we will go in increments of five years. David Dempster, Elnora Johnson, Evelyn Hernandez-Rosa, and Ludwika Delatorre have survived 35 years. Krishna Sindu, Michael Shelanski and Carmen Amoros have each clocked 30 years.

Anjali Saqi (see other news about Anjali elsewhere in PCR) and Phyllis Faust have reached 25 years as has cell biologist Istvan Boldogh and neuroscientist Alcmene Chalazonitis-Greene. So have Sunilda Valladares-Silva and Phyllis Della-Latta.

Twenty Year veterans include Zhimin Yu, Melvin Acevedo Jr., Murty V. Vundavalli and Chang Shu.

There are seven members of the Department who have been here for 15 years and twenty for ten.



Dr. April's textbook of Anatomy

Promotions

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

Peter Canoll has been promoted to Professor, as has Michael Barry Stokes.

Vaidehi Jobanputra, Tilla Worgall and Fann Wu have been promoted to Associate Professor.

Ulrich Hengst has been promoted to Associate Professor with tenure.

Ulf Klein has also been promoted to Associate Professor with tenure.

Reporting Significant Events

Readers may have noticed that the flat screen TV'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@cumc.columbia.edu. A system will be created to make sure we archive (i.e. don't lose) these messages.

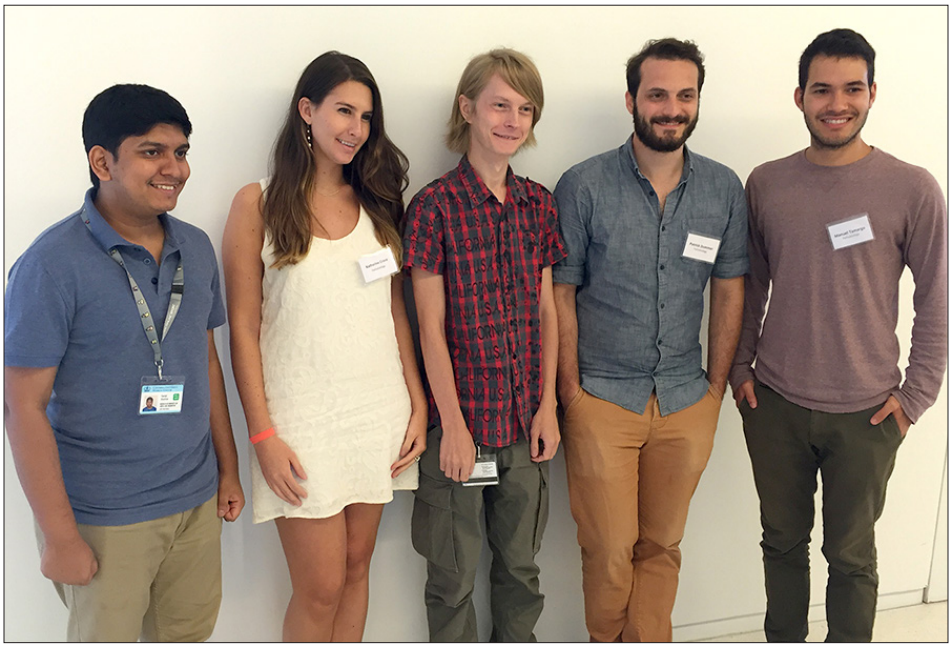
For special honors, either received by you or which our Department has conferred on others, please notify us so these awards can be acknowledged or forwarded to university wide publications.

Our Far-Flung Photographers

Photo by Dr. Patricia Tiscornia-Wasserman, from a collection entitled, "Reflections".

Brooklyn's Marine Park Salt Marsh by Mitchell Steinhardt son of Eric Steinhardt our Director of Pathology IT. Mitchell studied photograph at Long Island University and Empire State College.

The New Pathobiology and Molecular Medicine PhD Students



From left to right:

Sanjid Shahriar: Sanjid was born in Bangladesh and did his undergraduate work at the University of Toronto. He first came to Columbia for the Masters of Arts in Biotechnology and was a research assistant in Dr. Cory Abate-Shen's laboratory. After he received his MA, he joined Gil DiPaolo's laboratory as a research technician, where he worked for a year before joining the Pathobiology and Molecular Medicine Graduate program.

Katherine Croce: Katherine did her B.S. at Lehigh University. As an undergraduate, she did two summer internships in the Jessell laboratory. After graduation, she joined the Jessell lab as a research technician, where she worked for two years before joining the Pathobiology and Molecular Medicine Graduate Program this fall.

Vlad Korobeynikov: Vlad has a medical degree from the Novosibirsk State University in Russia (Siberia). During this time, he did three years of independent research in biochemistry and biophysics. In December 2014, after obtaining his MD, Vlad went to work as a Visiting Scientist at Fox Chase Cancer Center, where he did research in the laboratory of Dr. Erica Golemis before joining the Pathobiology and Molecular Medicine Program.

Patrick Dummer: Patrick did his undergraduate studies at St. John's College in Santa Fe, NM. He then joined the laboratory of Dr. David Kopp at the NiDDK, in 2009, first as a postbaccalaureate intramural research trainee, and then as a Research Fellow. He also joined the Postbac program at the University of Maryland, where he took additional courses.

Manuel Tamargo: Manuel received his BS in Biomedical Engineering from Columbia University School of Engineering and Applied Sciences this past spring. As an undergraduate, he did research in the laboratory of Dr. Cathy Mendelsohn. He also was a Research/Editorial Assistant in the Chemistry department under the supervision of Dr. Nina Berova.

Honors and Awards

CPR likes to recognize those who have received special awards.

We are pleased to note that Dr. Anjali Saqi and Dr. Vivette D'Agati were peer nominated and selected as Castle Connolly Top Doctors for 2 consecutive years.

Andy Teich MD, PhD has been awarded a Beeson Award from The National Institute of Aging. He has also been appointed as co-director of the New York Brain Bank. See the article elsewhere in this issue of CPR.

Dr. Stuart Weisberg will be the Shaffer-Wilk-Miller Fellow in Clinical Pathology for 2016-17

Dr. Carol Mason has shared the 2016 Antonio Champalimaud Vision Award with Dr. John Flanagan (Harvard Medical School), Dr. Christine Holt (Cambridge University) and Carla Shatz (Stanford). The award, from the Portugal based Champolimaud Foundation, recognizes contributions to vision research and vision saving efforts based in communities. The 2016 award went to Dr. Mason and the other researchers for work that has illuminated our understanding of the way in which our eyes send signals to the appropriate areas of the brain. The citation stated: "This work may offer hope of fighting vision disorders by means of neurological therapies." Carol is also a recent past president of the Society for Neuroscience.

Dr. Steven Spitalnik has been invited to give the Klaus Mayer lectureship at Memorial Sloan Kettering. This is the Department of Laboratory Medicine's premier named lectureship to honor the service of Klaus Mayer, M.D., and his distinguished leadership, promoting research, service, and teaching in Laboratory Medicine, Hematology and Transfusion Medicine at Memorial Sloan Kettering. This distinction is bestowed annually on a scientist and/or physician, who has demonstrated outstanding leadership and accomplishment, and whose work has had a significant impact on improving patient care.

Pathology Grad Students: Committed to Health Inside and Outside the Lab

By Aiden Quinn

It shouldn't be news to anyone that the graduate students of the Department of Pathology and Cell Biology are dedicated to unraveling the mechanisms of disease in the laboratory, but two students have taken that dedication to another level entirely. Jessi Neufeld (Ph.D. candidate in Pathobiology and Molecular Medicine) and Wolfgang Pernice, Ph.D. (Pathobiology and Molecular Medicine, 2016) are making an impact outside of the lab by raising nearly $13,000 for Cancer and Muscular Dystrophy research.

Jessi Neufeld is a fourth year Ph.D. candidate in Dr. Scott Small's laboratory who spends most of her time working on discovering biomarkers that will aid in the rapid development of novel therapies for Alzheimer's disease. Her project leverages proteomics and lipidomics to identify specific molecular signatures predictive of response to emerging therapies targeting endosomal trafficking pathways.

Having always been an athletic and health-conscious person, Jessi decided to challenge herself and run the NYC Marathon on November 6th this year. Seizing every opportunity to effect positive change, Jessi leveraged her run to raise $3,000 for the James Blake Foundation. For Jessi, the James Blake Foundation was an obvious choice to run for because 100% of the donations directly fund basic and translational cancer research, and Jessi understands first-hand, both the pervasive and devastating nature of cancer as well as the importance of funding to research labs.

The NYC Marathon is not the only event that Columbia Pathology graduate students are leveraging for the greater good this year. In his spare time, while he was preparing his thesis describing a novel mechanism of mitochondrial retention and the regulation of aging in yeast, Wolfgang Pernice, Ph.D. '16 of Dr. Liza Pon's laboratory, also organized a team that ran the NYC Triathlon this summer. In so doing he raised nearly $10,000 for Muscular Dystrophy research and patient care.

Wolfgang, who has Charcot-Marie-Tooth (CMT) himself, has been making significant contributions to advancing our understanding and management of CMT from both within and outside the laboratory. Together with the Motor Neuron Center here at Columbia, Wolfgang performed Whole-Exome sequencing on his family's DNA, which led to the identification of a novel genetic cause of CMT. Outside of lab, Wolfgang said about running the NYC Triathlon for the Muscular Dystrophy Association "There's no event that better underlines what Muscular Dystrophy takes away from its victims – their ability to walk, swim, use their hands, or even breathe – than a triathlon. In your face muscular dystrophy!" Wolfgang will tell this story himself in a future issue.

Summer PhD Theses Defended

Patricia Sheehan
Molecular Mechanisms
of Synaptic Vesicle Degradation
Laboratory of Dr. Clarissa Waites

Yajing Xie
Genetics of ABCA4-associated Diseases
and Retinitis Pigmentosa
Laboratory of Dr. Rando Allikmets

Gannie Tzoneva
The Role of Cytosolic 5'-nucleotidase II
(NT5C2) in Drug Resistance and Relapse
of Acute Lymphoblastic Leukemia
Laboratory of Dr. Adolfo Ferrando

Wolfgang Pernice
Asymetric Mitochondrial Inheritance
and Retention in the Regulation of Aging
in S. Cerevisiae
Laboratory of Dr. Liza Pon

Tina Xue Becomes Director of Research Administration

Ms. Tina Xue, MA, has joined the Department of Pathology and Cell Biology as the new Director for Research Administration. Tina is a newcomer to New York, having spent the last two years at the University of Toronto as the Director of Finance and Administration in the Faculty of Medicine. Prior to that, she worked as a Program Manager/Research Finance Manager at the Brigham and Women's Hospital/Harvard Medical School in the Center for Neurological Diseases. She has extensive experience in higher education administration and research management. Tina is a Certified Research Administrator with a Dual Honors Bachelor of Arts degree from the University of Toronto and a Master of Liberal Arts degree from Harvard University. Her leisure interests and hobbies include, good food, traveling, and pet sitting.

Research fund-raisers at the NYC triathlon

Nick Deveaux, Wolfgang Pernice and Arda Bozyigit

New Grants: *since June 2016*

PI	Sponsor	Title
Pellizzoni, Livio	National Institute of Neurological Disorders and Stroke/NIH/DHHS	SMN dysfunction in FUS-dependent ALS
Pon, Liza	National Institute on Aging/NIH/DHHS	The Role of Actin in Cellular Aging
Clark, Lorraine	National Institute of Neurological Disorders and Stroke/NIH/DHHS	Planning grant: Columbia-Yale-Bilkent Study: Genetic Study of Essential Tremor
Bartolini, Francesca	National Institute on Aging/NIH/DHHS	Pathogenic role for formin mediated microtubule stabilization pathways in Alzheimers disease
Spitalnik, Steven	National Heart, Lung, and Blood Institute/NIH/DHHS	Red blood cells from iron-deficient donors: recovery and storage quality
Siegelin, Markus	National Institute of Neurological Disorders and Stroke/NIH/DHHS	Dual Inhibition of Mitochondrial Matrix Chaperones and Anti-Apoptotic Bcl-2 Family Members for Glioblastoma Therapy
Siegelin, Markus	BCured	Induction of Synthetic Lethality in IDH1 Mutated Gliomas
Santa-Maria Perez, Ismael	National Institute of Neurological Disorders and Stroke/NIH/DHHS	MicroRNA modulation of tau expression and phosphorylation in tauopathy
McIntire, Laura Beth	Alzheimer's Association	Functional genetic CRISPR screen for prevention of synapse loss in AD
Monani, Umrao	Glut1 Deficiency Foundation	Defining the spatial and temporal requirement of the Glucose Transporter-1 in Glut1 deficiency syndrome
Andy Teich	National Institute on Aging	Integrative Study of Alzheimer Disease

The Residents at the Marboes'

The Alumni Dinner

New York Presbyterian/Columbia Society of the Alumni Annual Dinner, October 18, 2016 From left to right: Hermann Schubert, Mahesh Mansukhani, Alina Iuga, Andrew Teich, Sonya Purushothaman, Huimin Yang and Charles Marboe

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

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 Rich Kessin (rhk2@columbia.edu) or PathNews@cumc.columbia.edu.

In our next issue *(tentatively)*

Progress on the website.

A report from Wolfgang Pernice, Ph.D.

The usual categories and matter arising.

Space revovations.

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

COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

Fall 2016

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