

## From the Chairman

This issue of Pathology and Cell Biology Report comes at a time of many changes in the Department. The end of this academic year is marked by the retirement of Rick Ambron, Nicole Suciu-Foca, Heidi Rotterdam, and our editor, Rich Kessin. Each has contributed in his or her own way to the success of the department over the years. Rick was a master teacher of human anatomy as well as a significant contributor to our understanding of the neurobiology of pain. Nicole led our Immunogenetics Laboratory supporting the largest solid organ transplant program in the nation. She was a pioneering researcher in the area of transplantation immunology. This was actually Heidi's second pass through the Department. She was here briefly during training and then returned to provide expertise in surgical and GI pathology. She is the author of numerous papers and monographs in this area. Rich Kessin is a leading authority on the biology of the slime mold (more interesting than its name), the squash and lunch buddy of Carl Reyes and the founding editor of this newsletter. He will continue writing for The Lakeville Journal in Connecticut. Over 30 years, he has taught generations of medical and graduate students, served as the Dean of the Graduate School of this campus and helped implement the Basic Science Track of the new Scholarly Projects Program for medical students. Also leaving is Nino Sireci who served us as both a resident and faculty member. He is heading off into the world of consulting. All of these contributors will be missed.

After 17 years at Columbia, Ramon Parsons has left to become Chairman of the Department of Oncology at Mt. Sinai. Ramon is best known as the discoverer of PTEN and has been a key member of our department and graduate program over the years. We wish him the very best.

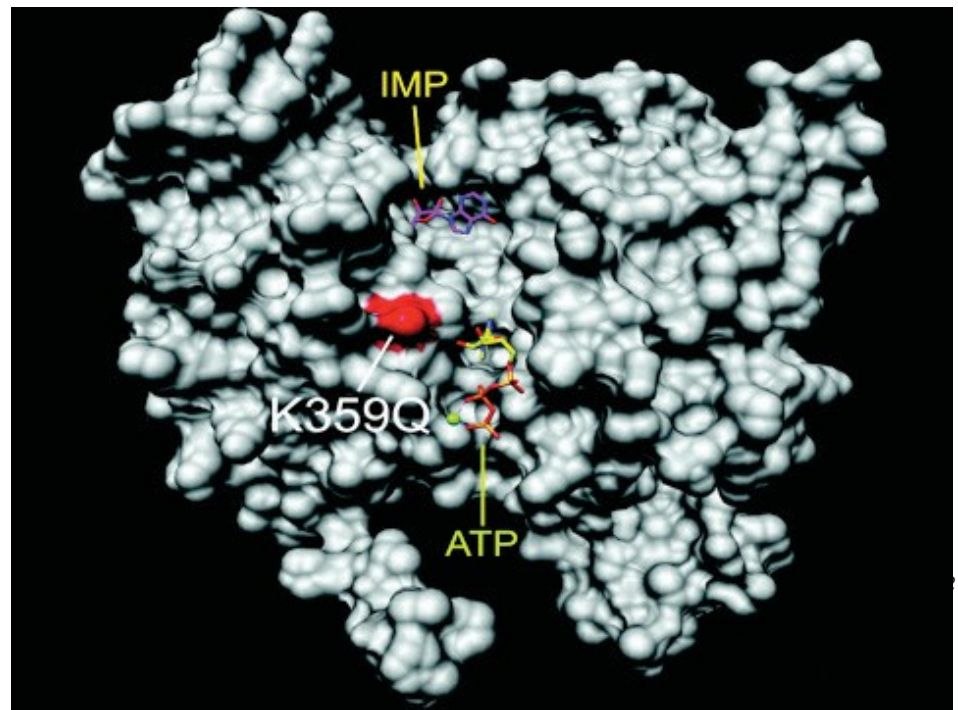
With Rich Kessin's departure we are seeking another editor for this newsletter and

*Continued on page 15*

This is the 10th issue of Pathology and Cell Biology Reports (PCR). Despite the difficult times, we have managed to improve our clinical and our basic science laboratories. The current issue highlights new faculty and their achievements. We describe new initiatives, new residents and new PhD students. We have had numerous awards, from our PhD students and our Residents to our junior and senior faculty. Despite the difficult times and the sequestration, we seem to be working well. In this issue we cover progress in all of our divisions and feature photos from some of our artists. Who knew we had them? We also take leave of Heidrun Rotterdam, Nicole Suciu-Foca, and Richard Kessin.

Those Sequestration, Keep Calm and Carry On, Talkin' Blues...

## A Mutation That Ruins Chemotherapy for Leukemia



Relapsed leukemias are characterized by a chemotherapy resistance phenotype and poor prognosis. The Ferrando lab has identified recurrent gain of function mutations in the NT5C2 nucleotidase gene as drivers of resistance to 6-mercaptapurine chemotherapy at relapse. The K359Q mutation in this structural model is shown in red. *Tzouneva et al. Nature Medicine 2013; 19:368-71.* There were a number of additional authors. Kudos to them, (see photo below).

*Continued on page 10*



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## In This Issue

Chair's Letter.....	1
Editor Departs .....	2
Advances in Administration.....	3
Research News.....	1, 4, 5, 6, 12
PhD Students .....	7
Retirements .....	2, 9, 13
Residents.....	13
Grants.....	14

## PCR Editor Returns to the Forest *By Joann Li*



*The former Pathology and Cell Biology Reports editor in Carter Notch, New Hampshire on a cold, cold day. Photo Credit: Dr. Gregg G. Gundersen, a wonderful colleague, no matter the temperature.*

**JL:** You're not really going back to the woods, are you?

**PCR:** Yes, actually. I am going to hike the Appalachian Trail in Connecticut and then later I'm going to climb Mt. Madison in my native New Hampshire. Also the Sierra with my daughter Jessica.

**JL:** Whatever for?

**PCR:** Call it the Wormhole Theory of Retirement. You have to go from one reality to another, painfully, and then everything will be OK. Besides I like to walk.

**JL:** Why Mt Madison? That's a big pile of rock.

**PCR:** True, but fifty years ago this summer

I was the mountaineering counselor at the Ogontz Mountain Camp for Girls in Lisbon, New Hampshire...

**JL:** Of course you were...

**PCR:** Yeah, I was and it was bizarre, but I took a dozen 14 year-old girls up onto the Presidential Range and we got fogged in. It was a little dicey, but we made it to Madison Hut, a bunkhouse run by the Appalachian Mountain Club, where I signed the ledger. I want to see if it's still there, fifty years later.

**JL:** Assuming you survive, what then?

**PCR:** I have a Newspaper column in Connecticut in which I try to explain science to the public. It appears in The Lakeville

Journal and the Winsted Journal. There are 9000 potential readers and no reviewers, except for a terrific editor. So far people seem to like the columns. I've written almost 30, sometimes with our junior faculty. The articles are on my page of the Pathology Website. There's everything from PCB's in the Housatonic to Alzheimer's disease. I'll keep that up and maybe expand it. I'll also be back from time to time to give lectures.

I'll see what else I can do for science education up in the NW corner of CT. In the winter we're going to the Baylor College of Medicine in Texas, where it's flat and warm. I'll work with Gad Shaulsky and Adam Kuspa, just to keep my hand in. They use my favorite organism, *Dictyostelium*, to study bacterial pathogenesis.

**JL:** Is there really a novel in the offing? Or is that a rumor?

**PCR:** There is. Stay tuned.

**JL:** Tell me it doesn't take place in a Pathology Department!

**PCR:** There's ambition, sex, disease, anxiety, intrigue and religion. How could it possibly take place in a Pathology Department?

**JL:** Have people read this putative novel?

**PCR:** They have. Scientists and non-scientists. They seemed to like it. Especially Carl Reyes and his family, one of whom is an actual novelist.

**JL:** But all friends of yours?

**PCR:** Mostly, but my friends are all very smart and have good taste.

**JL:** When do I get a copy?

**PCR:** Ah, that would be a Conflict of Interest. You manage my last sliver of funding, so you'll have to wait for it to appear on Amazon!



## Advances in Administration



Doreen Hebert is the Divisional Administrator for Anatomical Pathology under the leadership of Dr. Alain Borczuk and Dr. Glen Markowitz. In this capacity, she manages all of the AP operations which includes a team of nearly 100 employees and an operating budget in excess of \$16 million. She supports approximately 30 AP faculty and oversees the training of our residents and medical students in both Surgical and Autopsy Pathology all while ensuring the efficient and accurate processing of over 57,000 surgical specimens annually. Faced with this enormous responsibility and in keeping with her other role in Quality Operations and Management, Doreen and her colleagues instituted an advanced barcode and tracking system which improves patient safety. This is only one of the many initiatives that she has spearheaded to improve services for the Department and to ensure compliance with all of the regulatory agencies. She enjoys a well-executed policy and procedure and is a stickler for the abolition of under-sink storage. While she has a fondness for completely filled in temperature logs, her dislike for expired reagents is legendary.

Doreen started off as a biochemistry and biology major at the University of Hartford and holds a Master's degree from Quinnipiac University as a Pathologists' Assistant. She retains close ties with that program and its director. After a stint at the Albert Einstein College of Medicine, she was recruited in 1998 to support the obstetric and perinatal diagnostic services and to

manage the Division of Medical Pathology. Doreen particularly enjoyed her years of service of 1998 to 2003 as the manager of the autopsy service. Our institution performs 260-280 autopsies a year and is a 24 hour service. There are instances when autopsies must be organized within an hour and Doreen was charged with coordinating attendings and residents and timely reporting. Some cases were strange – the occasional drug mule, for example, that required coordination with the Medical Examiner's office. She became the Divisional Administrator of Anatomic Pathology in January 2012, although she still maintains an active role in the autopsy program. The hardest job, she says, is time management, partly because she is often interrupted by a call for autopsy training.

The Newsletter would like to recognize Doreen for her unique combination of skills, experience, commitment and many contributions to her colleagues and the Department of Pathology and Cell Biology.

## The Grant Office Angels



*Frances Antonetty*

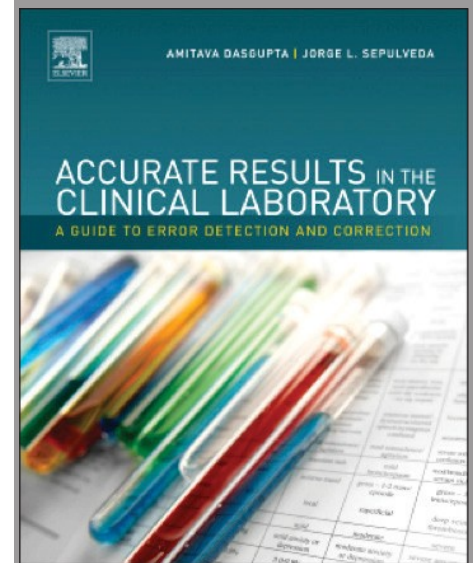
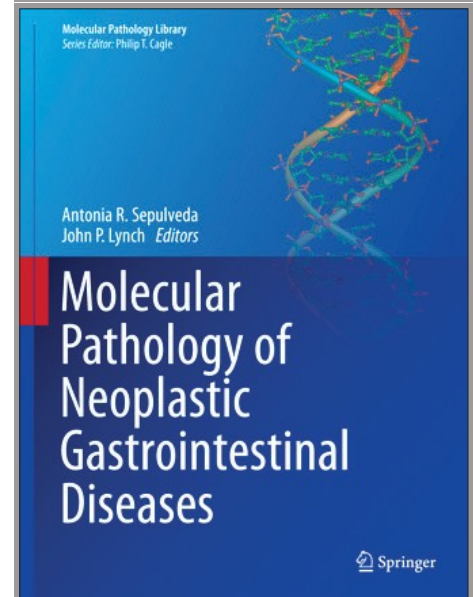
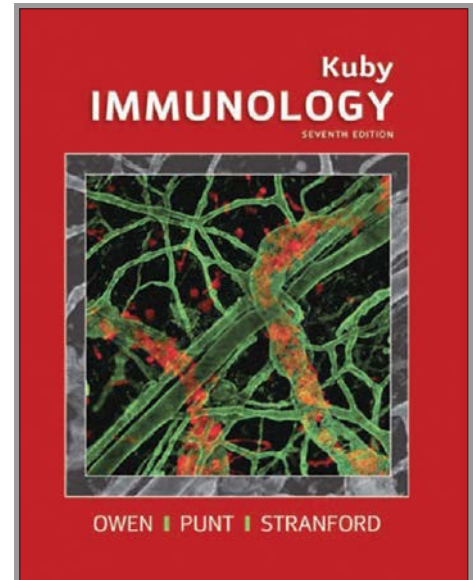


*Irene D'Silva*



*Josie Salcedo*

## New Books by Faculty





## Fighting Macular Swelling and Blindness *Carol Troy*



Diabetic macular edema is the leading cause of new blindness in the Western world. Current therapies include laser photocoagulation treatment and intravitreal injection of anti-VEGF compounds. Therapeutic limitations include the lack of defined molecular targets and convenient access to the retina. We show that specific inhibition of caspase-9 activity abrogates edema in models of cerebral ischemia. The retina is part of the central nervous system and we propose that caspase-9 is a molecular target in diabetic macular edema.

Edema is caused by a loss of vascular integrity, rather than death of endothelial cells and pericytes in the blood vessels (BV). The elimination of tight junctions between these cells allows extravasation of fluid from small capillary BVs. In our hands, a cell permeant caspase-9 inhibitor provides neuroprotection and concomitantly abolishes edema. This finding opens the question of whether caspase-9 activity is a direct cause of edema through the impairment of vascular integrity of small BVs. Our prior studies show that caspase-9 is activated during cerebral ischemia. Pathologically, cerebral ischemia leads to vasogenic edema, neuronal process loss, and neuronal death. We found that cerebral ischemia induces caspase-9 in small blood vessels. Pen1-XBIR3, our novel caspase-9 inhibitor, delivered directly to the parenchyma or by intranasal application prevented neuronal process loss and neuronal death. There was also substantial functional recovery at 3 weeks post-ischemia. Pen1-XBIR3 decreased extravasation of fluid after ischemia and also blocked the increase in expression of matrix metalloproteinase 9 (MMP-9), a protein implicated in the pathogenesis of vasogenic edema. We predict that diabetic macular edema is also mediated by caspase-9 activity and

that blocking caspase-9 activity will be a therapeutic intervention for this condition.

Access to the retina is regulated by the blood-retina barrier, similar to the blood-brain barrier. In our studies of cerebral ischemia, we linked our caspase-9 inhibitor to a cell permeant peptide, Penetratin1, to provide intracellular uptake in the cerebral parenchyma. For retinal delivery we have preliminary data showing that we can deliver a FITC-labeled Pen1-peptide by intravitreal injection or by application of eyedrops. We detect uptake of the peptide in the retina after either mode of delivery.

We now have established a target, caspase-9 activity, a therapeutic, Pen1-XBIR3 and a mode of delivery, topical or intravitreal. We are beginning work that is being funded by Novo Nordisk to establish the efficacy of Pen1-XBIR3 in rodent models of macular edema. The development of retinal disease will be followed *in vivo* using retinal imaging, including fluorescein angiography and optical coherence tomography; these *in vivo* measures will be used to follow patients with retinal disease. This will allow the results to be translated to a clinical setting.

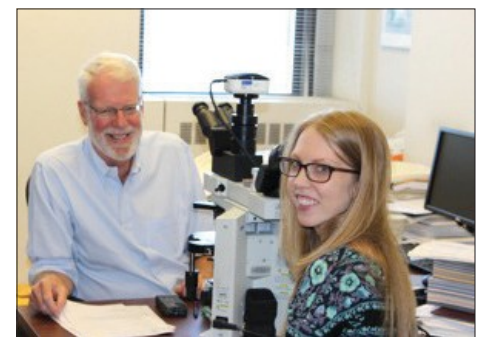
## Carol Ann Mason wins Stevens Triennial Prize



The Stevens Triennial Prize was established in 1891 by Alexander Hodgen Stevens, MD, a former president of P&S, and is awarded to an individual whose research is deemed to be the most meritorious.

The citation reads: "Carol Ann Mason, PhD, Professor of Pathology & Cellbiology, neuroscience, and ophthalmic science, for her research on cell-to-cell interactions in the developing brain, which has been recognized by her election to the Institute of Medicine and as president of the Society for Neuroscience". Heresheiswith Trustee Ken Forde, MD and Dean Goldman.

*Photo by Dr. Michael Shelanski*



*Dr. Charles Marboe and Amy Coffey, MD, PGY1 - A Teaching Moment*



*Mr. Antonio Barrucco - A Laughing Moment - even after 51 years in Pathology*



## Honors and Awards

**Dr. Paulette Bernd** has written a dissection manual with the help of Columbia medical and dental students. Their presentation of the manual at the AAMC Northeast Group on Educational Affairs won the “Excellence in Medical Education Award” in the Pre-Clinical Curriculum.



“Revamping Anatomy Education: Student-Authored Dissection Manual Significantly Improved Learning and Academic Performance.” The authors were **Dustin Tetzl**, **Justin Neira**, **Lily Grossmann** and **Jose Ramirez**. Lily is a student at SUNY Downstate.

**Dr. Steven Spitalnik** will be giving the Graham A. Jamieson Memorial Lectureship, American Red Cross in Rockville, MD. In September Steve will receive the Emily Cooley Award and Lectureship at the annual meeting of the American Association of Blood Banks in Denver.

**Dr. Michael M. Shelanski** received the Distinguished Service Award from the University of Chicago Division of Biological Sciences on June 7th. Mike is an alumnus of the University of Chicago.

(see photo on page 9)



Second year graduate student **Kristin Politi** has won a coveted NSF Predoctoral Award. She will do her PhD thesis with Professor Serge Prezboriski on ALS.



**Dr. Francesca Bartolini** has won a 2013 New Investigator Research Grant from the Alzheimer Association, for an application entitled: *Regulation of Mi-*

*crotubule Dynamics by Amyloid-Beta Peptide*



**Josh Cook**, a PhD student with Dr. Domenico Accili, received a travel award to attend the Annual Meeting of the Endocrine Society in San Francisco and deliver an oral presentation on his doctoral work. It's an unusual honor

for a graduate student. Josh was also a featured speaker at a recent meeting of the University's Board of Advisors, chaired by Dr. Roy Vagelos.

At the American Association for Cancer Research's (AACR) Annual Meeting in Washington, D.C. (April 6-10, 2013) **Markus D. Siegelin, MD** was named the 2013 recipient of the AACR-National Brain Tumor Society Career Development Award for Translational Brain Tumor Research. Markus has also received a second grant from the American Brain Tumor Association to investigate new, powerful anti-tumor treatments for glioblastoma multiforme (GBM) patients. See article by Dr. Siegelin elsewhere in the Newsletter.



Facing South-Photo by Charles Manley

### Dr. Jorge Sepulveda *Heart Failure and Cardiomyocyte Hypertrophy*



My research goals center on the molecular mechanisms of transcriptional regulation of cardiac myocyte phenotypes during cardiogenesis and during the pathologic cardiac hypertrophy (an increase in cell size) that leads to heart failure.

We have discovered a connection between events that stimulate hypertrophy and regulation of lipid synthesis. These events are mediated by sterol response element binding protein (SREBP) transcription factors. SREBP have 3 major isoforms, and we are beginning to understand their role in regulating metabolic responses such as glycolysis and de novo lipogenesis. SREBP2 and SREBP1a are isoforms involved in the mevalonate pathway that provides farnesyl intermediates for the activation of small G-proteins such as Ras and Rac, which are involved in cardiac cell growth and hypertrophy, as well as cholesterol synthesis. All SREBP isoforms can be found as ~120 kDa inactive precursors in the endoplasmic reticulum (ER) tightly bound to a protein called SCAP (SREBP Cleavage Activating Protein). SREBP's are activated by proteins that sense cholesterol levels. High cholesterol levels initiate a multi-step cascade whereby the SREBP is cleaved to produce a protein fragment that migrates to the nucleus and activates target genes.

We have created a mouse model to study the role of SREBP transcription factors in the heart. We can control the cascade that activates target genes. Our data suggest that

maintaining a tightly regulated balance of cholesterol levels in the myocytes is critical for optimal cardiac health. We are also examining human hearts from patients with heart failure, diabetes, and normal controls to detect changes in SREBP-dependent genes, including those involved in cholesterol and fatty acid metabolism. Our goals are to understand how the hypertrophic or failing heart interacts with systemic metabolic diseases, such as diabetes, with the aim of developing therapeutic interventions to improve the prognosis of heart failure.

In addition to my research goals, I am interested in efficient laboratory management and provision of user-friendly laboratory information and interpretation to optimize patient care. As a clinical laboratorian and research scientist, I am interested in translating scientific advances into practical and cost-effective clinical laboratory tests that improve patient care. In particular, we are developing state-of-the-art analytical and bioinformatic technologies to guide patient-specific diagnostic, prognostic and therapeutic interventions.



*Mahattanville Rising-Water color and gouache, part of a series on our neighborhood by Ruth Rooks, Swampscott, MA. [ruth@ruthrooks.com](mailto:ruth@ruthrooks.com)*



*Introducing Eric Gili Harik, born on May 30th, 2013 with his big brother. Sons of Dr. Lara Harik*

### Jennifer Punt, VMD, PhD



Dr. Jenni Punt, currently Professor of Biology at Haverford College, is joining Pathology and Cell Biology. Jenni is an immunologist and an expert in T-cell

development. She is one of the authors of a recent update of Kuby's Immunology text – see Books by Faculty Members. Jenni's current research focuses on a gene called Nur77 and its role in regulating the fate of developing blood cells, including thymocytes and hematopoietic stem cells. Jenni is also a master teacher and, beyond her research efforts at Columbia, she will take over the Basic Science Track of the Scholarly Projects Program that is now an integral part of the P&S curriculum. Rich Kessin handled the track in the inaugural year and is pleased at its success and to hand it over to Jenni. Jenni has also developed a prospective MD – MSc dual degree program for research oriented medical students, which she will run in collaboration with Dr. Jaime Rubin. Finally, she will make use of her experience in the undergraduate setting to enhance educational interactions between the medical and undergraduate campuses at Columbia.

### Harris Wang, PhD



Harris Wang has joined Columbia University Medical Center as an Assistant Professor in the Columbia Initiative in Systems Biology and the Department of Pathology and

Cell Biology. His research focuses on applying synthetic and systems biology approaches the formation, maintenance, and evolution of genomes within and across microbial populations. Using new methods in genome engineering, high-throughput DNA synthesis, next-generation sequencing and functional genomics, Harris studies how genomes in microbial communities evolve over time and across different environments. His goal is to use synthetic biology approaches to engineer



## Pathobiology and Molecular Medicine PhD Students

ecologies of microbial populations, such as those found in the gut and elsewhere in the human body, in ways that could improve human health. Harris is a recent recipient of the NIH Director's Early Independence Award to support research towards building strategies to effectively engineer and reprogram the human microbiome. His lab is identifying patterns of horizontal transfer by mobile genes, such as those causing antibiotic resistance and pathogenicity, and developing novel methods to control and limit their propagation in the gastrointestinal tract.

Harris earned double BS degrees in physics and applied mathematics and minored in biomedical engineering at the Massachusetts Institute of Technology. He completed his PhD in biophysics at Harvard University, where, as a graduate student in George Church's laboratory, he pioneered the Multiplex Automated Genome Engineering (MAGE) platform to accelerate the engineering and directed evolution of gene networks and genomes. This approach made it possible to generate synthetic organisms with novel properties including phage resistance, new genetic codes, and optimized metabolic networks. Most recently, he was a Wyss Technology Development Fellow at the Wyss Institute for Biologically Inspired Engineering and a Lecturer in the Department of Systems Biology at Harvard Medical School.

To learn more about research in the Wang lab, visit <http://wanglab.c2b2.columbia.edu>, and see a recent review in *Molecular Systems Biology* (doi:10.1038/msb.2012.66) surveying new techniques in genome-scale engineering for systems and synthetic biology.



Communities of *E. coli* cells that have been developed to produce lycopene, a pharmaceutical and nutritional supplement, through genome engineering.



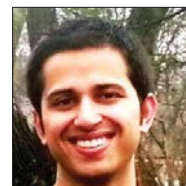
**Tiara Ahmad** was born in New York City, but grew up in Bandung, Indonesia. She graduated from Michigan State University, majoring in Biochemistry and Molecular Biology/Biotechnology. While at MSU she did undergraduate research on chloroplast division in the model plant *Arabidopsis thaliana*. She has also worked as an intern at Pfizer for one year. Tiara has a wide range of interests in research on the mechanisms of disease.



**Xiaoyi Qu** is a recent graduate from the University of Wisconsin, where she majored in Biology. She is originally from Beijing, where she attended a high school affiliated with Tsinghua University. At the University of Wisconsin, Xiaoyi did a senior honors thesis on the antitumor effect of anti-CD40 immunotherapy mediated by macrophages in a mouse model.



**Justin Hickman** graduated from the University of California at San Diego. Prior to his undergraduate studies, Justin had six years of service in the United States Air Force, where he specialized in munitions equipment maintenance and storage. After graduating from UCSD, Justin worked at Isis Pharmaceutical, where he conducted RNA-based drug discovery research for disease.



**Samik Upadhaya** grew up in Kathmandu, Nepal. He did his undergraduate studies at Central Michigan University, where he majored in Biochemistry. After graduating in 2011, he did his MS studies at Central Michigan University in Chemistry. His MS studies focused on preparing and characterizing fluorescent nanomolecules that may be used as biological markers in neurodegenerative disorders.

## Just Who Runs the Graduate Programs?



Zaia Sivo and Ron Liem



Vimla Aggarwal, MD, PhD  
Division of Personalized Genomic Medicine



## Our Far Flung Photographers – The Art of The Panorama



*Cuernos del Paine from Lago Perhoe, Patagonia, Chile Photograph by Michael M. Shelanski, MD, PhD*



*A View From The Bridge Photograph by Patricia G. Tiscornia-Wasserman, MD*

## Pathology and Cell Biology and The Lakeville Journal



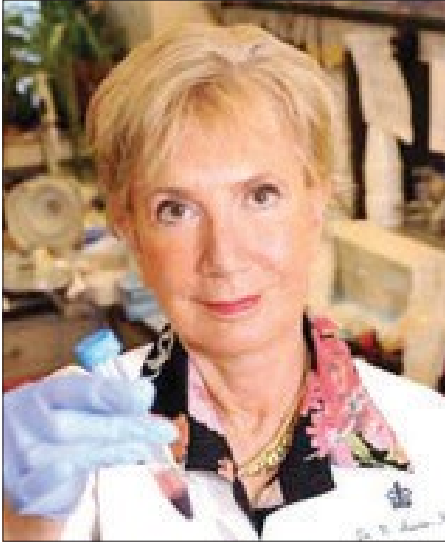
The Lakeville Journal is a small local newspaper in Lakeville CT for which Rich Kessin has been writing general science articles for an interested and literate readership – so far almost 30. The paper and its sister publications have a circulation of about 9000 readers. Except for an excellent editor, Janet Manko and a good copy editor, there are no reviewers – except the occasional letter writer. Guest writers fill in – Adam Ratner on infectious disease, for example. Previous columns covered PCB's in the Housatonic River, Chestnut blight, autism, flu vaccines and raw milk, which, by the way, tastes a lot better than skim. See <http://www.tricornernews.com>. Search for Kessin.

Recently, Janet Manko asked if we knew anything about neurodegenerative diseases here at Columbia. “A bit,” Rich replied. This has led to a series of columns on Alzheimer's disease, for which Rich teamed with neuropathologist Andrew Teich. These essays confront the problems of the field, scientific and ethical. A third column is in progress. Then the focus will shift to Parkinsonism. In the Fall, Ottavio Arrancio will give a public lecture that is being arranged by the Lakeville Journal.

Although Rich is beginning phased retirement, he will keep doing this column, which is formally called The Body Scientific. If you have ideas, let him know.



## Dr. Nicole Suci-Foca Has Retired



After over forty years in the Department of Pathology and Cell Biology, Professor Nicole Suci-Foca has retired. Dr. Suci-Foca received her undergraduate and graduate training from the University of Bucharest and earned a PhD in 1969. She subsequently did post-doctoral work at Sloan Kettering for two years before starting her career at P&S in 1971 as a Research Associate. She became an Assistant Professor in 1973 rising through the ranks to Full Professor in 1981. Since 1973, she has been the Director of the Immunogenetics Division of the Department of Pathology. Under her leadership, this Division has become a thriving entity of crucial importance to the Columbia's world-renowned transplant effort. Dr. Suci-Foca also established a research laboratory and made many contributions to immunology, particularly in allograft rejection as it relates to transplantation of pancreatic islet cells as a treatment for diabetes. Her work has been supported by multiple grants from the NIH and other agencies. She has also served on the National Institutes of Allergy and Infectious Diseases Study Section.

Dr. Suci-Foca began the American phase of her career with an Eleanor Roosevelt Fellowship for Cancer Research at Memorial Sloan-Kettering Cancer Institute from 1969-1971. Her laboratory has won numerous awards in the Transplantation and Histocompatibility field. Dr. Suci-Foca was the Vice President of the XVIII International Congress of the Transplan-

tation Society in 2000. In September, 2002 she was awarded the National Order 'For Merit' with the degree of Commander (Star of Romania) from the President of Romania for remarkable scientific contribution in the field of Immunology and Genetics. Later that year, she received the Distinguished Scientist Award from the American Society for Histocompatibility and Immunogenetics (ASHI).

Her laboratory has been highly productive and her research has resulted in some 350 publication over the years. While Dr. Suci-Foca is now happily retired in Rome, we are grateful Dr. Raphael Clynes has taken over as Director of the Immunogenetics Division.

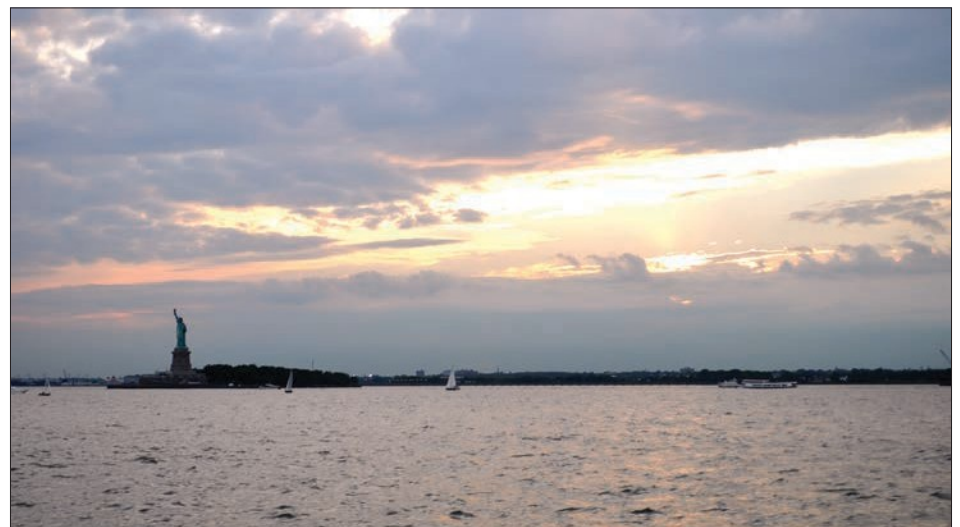
We salute Nicole Suci-Foca for a friendship and a career brilliantly accomplished.

## Dr. Shelanski Receives Distinguished Service Award From His Alma Mater, The University of Chicago



*Dr. Michael L. Shelanski with Kenneth S. Polonsky, MD, Executive Vice President for Medical Affairs, O Dean, Division of the Biological Sciences Dean, Pritzker School of Medicine Professor of Medicine and Holly J. Humphrey, MD, MACP, Ralph W. Gerard Professor in Medicine Dean for Medical Education*

## The Statue of Liberty: Open Again After Sandy



*Ms. Liberty at dusk. Photo by Richard Miller*

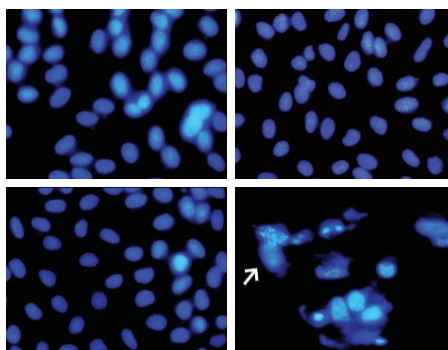
### A new type of drug that enters the brain and inhibits glioblastoma

By Markus D. Siegelin MD



Glioblastoma WHO IV (GBM) is the most common primary malignant brain tumor and has no curative treatment. Most patients succumb to their disease

within 24 months after initial diagnosis. We are exploring a novel drug, called CP-d/n-ATF5 that has shown promising anti-glioma activity in our model systems. CP stands for Cell Penetrating and d/n for dominant negative. This compound is unique in that it specifically targets an important molecule, called Activating transcription factor 5 (ATF5). High levels of ATF5 in glioma cells allows them to evade cell death. Glioblastoma cells are notoriously resistant to molecules that cause cell death. A single treatment with CP-d/n-ATF5 elicits potent anti-glioma activity in a mouse model of glioblastoma with an eradication of tumors 21 days after treat-



The drug CP-d/n-ATF5 causes cells to die in the presence of the drug TRAIL. The fragmented nuclei (arrow) indicate cell death. Hoechst stain.

ment. None of the tumors in this glioma model have recurred 6 months after the treatment period and there were no signs of toxicity or side effects, according to Dr. Jim Angelastro, a collaborator at UC-Davis. Based on these promising effects, we are exploring CP-d/n-ATF5 in combination with another promising drug, TNF-related apoptosis-inducing ligand (TRAIL) in order to establish an even more potent treatment for glioblastoma. Our data strongly suggest that CP-d/n-ATF5 overcomes TRAIL-resistance in a variety of

glioblastoma cells by enhancing the expression of TRAIL receptor 2 (DR5) on the surface of glioblastoma cells. We are dissecting the mechanisms by which CP-d/n-ATF5 exerts its anti-cancer activity and sensitizes glioblastoma cells to apoptosis caused by TRAIL. Using in vivo studies we will extend our combination treatment findings in a patient-relevant model system. Based on these findings and working with Dr. Lloyd Greene and other collaborators, we hope to lay the foundation for new and effective treatments for glioblastoma and will move toward clinical trials for this devastating cancer. The research is to be funded by the American Association of Cancer Research and the National Brain Tumor Society.

#### About Glioblastoma multiforme (GBM)

GBM is one of the most devastating forms of all cancer, with a dismal life expectancy after diagnosis of less than 15 months. GBM is also extremely complex, with some four known subtypes and multiple mutations per tumor. After initial resection and chemo/radiation treatment, it almost universally comes back, and when it does, it virtually always resists the original and standard of care treatment. Despite breakthroughs in understanding the tumor, no recent therapy has proven effective beyond just a few months. Thus, there is still more to learn about how the disease escapes anti-cancer drugs that often work even in other cancers with similar genomes, which is one of the main project focuses of DefeatGBM.

### A Mutation That Ruins Chemotherapy for Leukemia *continued from page 1*

Gannie Tzoneva is a third year graduate student in the Pathobiology and Molecular Medicine PhD Program. Gannie is also a participant in the Med-into-Grad Program. Gannie comes to us from South Africa, where she attended the University of Capetown. She is doing her graduate studies in the laboratory of Dr. Adolfo Ferrando. This is the result so far.

From left to right, (front row), Arianne Perez-Garcia, Teresa Palomero, Adolfo Ferrando (back row), Zachary Carpenter, Raul Rabadan, Hossein Khiabani, Gannie Tzoneva

Why are the men not smiling?





## New Residents



**Elizabeth Godbey – AP/CP**  
MD - Columbia University College of Physicians and Surgeons, 2013  
BS - The University of Georgia, Biology, Phi Beta Kappa, *summa cum laude*, 2009



**Simon Sung – AP**  
MD – Columbia University College of Physicians & Surgeons, 2013  
Post-baccalaureate pre-medicine – Rutgers University 2007  
Bachelor's in Music – Peabody Institute of Johns Hopkins University, Classic Guitar, 2006



**Daniel Green – CP**  
Resident in Pathology, AP/CP, Stanford University Hospital, 2012-13  
MD - Columbia University College of Physicians & Surgeons, AOA, 2012  
Doris Duke Clinical Research Fellowship, Department of Medicine, P&S, 2010-11  
BA – Northwestern University, Cognitive Science, *cum laude*, 2006



**Monica Paroder – AP/CP**  
MD – Albert Einstein College of Medicine, 2013  
PhD – Albert Einstein College of Medicine, Molecular Pharmacology, 2010  
BA – New York University, Biochemistry (major), Mathematics (minor), Phi Beta Kappa, *summa cum laude*, 2005



**Stuart Weisberg – AP/CP**  
Postdoctoral Research Fellow with Boris Reizis, PhD, Microbiology & Immunology, Columbia University College of Physicians and Surgeons, 2008-13  
Resident in Pediatrics, Columbia University, CHONY, 2007-8  
MD – Columbia University College of Physicians & Surgeons, 2007  
PhD – Columbia University Graduate School of Arts and Sciences, Molecular Biology, with distinction, 2005 BSc– Brown University, Neurobiology, 1997



**Maryam Shirazi – AP/CP**  
Post-doctoral Research Scientist with Vaidehi Jobanputra, PhD, Pathology and Cell Biology, Columbia University, 2010-13  
Post-doctoral Research Scientist with Salvatore DiMauro, MD, Neurology, Columbia University, 2009-2010  
M.Sc.D – Tehran University of Medical Sciences, Iran, 2006, Honours Certificate



**George Zanazzi – AP/NP**  
MD – Stony Brook University School of Medicine, 2013  
PhD – Stony Brook University School of Medicine, Neuroscience, 2010  
MS – Stony Brook University, Neuroscience, 2004  
Research technician with James L. Salzer, MD, PhD, New York University School of Medicine, Smilow Neuroscience Program, 1993-2002  
BS – Stanford University, Biological Sciences, 1993



*Midtown Under Clouds Photograph by Patricia G. Tiscornia-Wasserman, MD*

## Gastrointestinal Cancers: Molecular Basis and 21st Century Diagnostics

Antonia R. Sepulveda MD, PhD

Professor and Vice Chair for Translational Research

Director, Division of Gastrointestinal Pathology



Before starting Residency training I decided to join a particular species – the physician-scientist. By combining clinical diagnostic Anatomic Pathology, where I focused on the practice of Gastrointestinal Pathology, with a research program gave me the rudiments of a thrilling and rewarding career. It takes experience to manage the balance between the two (that being part of the interest of this career path), and I encourage younger pathologists to be to consider it! This combination has allowed me to become a gastrointestinal and molecular pathologist combining conventional morphology and novel molecular applications for tissue diagnosis. In this role, my clinical practice is centered on the diagnosis of digestive, pancreatic and biliary tract diseases with integration of molecular testing especially for personalized cancer therapies.

My research program is focused primarily on digestive organ cancers, addressing underlying molecular mechanisms, biomarkers for cancer risk, prediction of response to therapies and inherited cancers. I am specifically interested in developing and applying pathology-integrated cancer molecular testing taking advantage of genomic and epigenomic biomarkers for early cancer detection and personalized cancer management of digestive organ cancers. Our research follows two arms: one tackles the molecular

mechanisms and the other the evaluation of biomarkers of gastrointestinal carcinogenesis, spanning gastric, esophageal, colorectal and pancreas tumors.

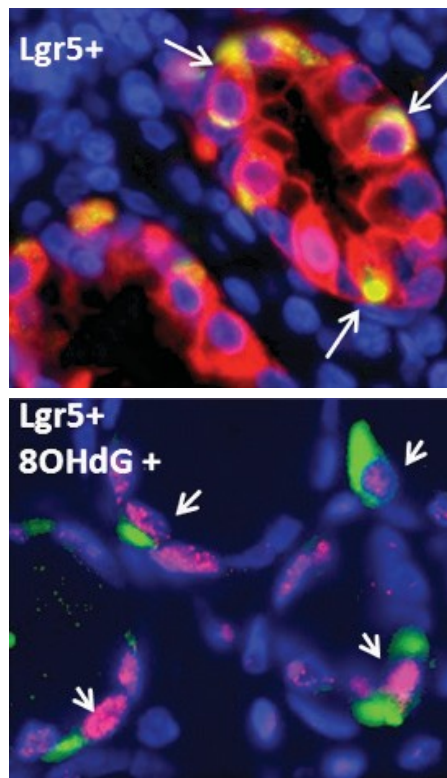
Research in our laboratory has unraveled molecular mechanisms underlying the association of *H. pylori* infection, development of intestinal metaplasia and gastric cancer. We were among the first to report an association of *H. pylori* infection and gastric tumors with deficient DNA mismatch repair and microsatellite instability (MSI). In subsequent studies we demonstrated that *H. pylori* induces significant alterations in DNA repair, involving gene expression and methylation changes, which underlie increased mutagenesis in gastric epithelial cells (published in *Helicobacter*, 2006), thus contributing to gastric cancer development. We have reported the role of CpG methylation in regulation of the DNA repair protein MGMT and DNA mismatch

repair protein MLH1 in gastric carcinogenesis and association with *H. pylori* infection (*Helicobacter*, 2006; *Gastroenterology*, 2010). We have shown that Lgr5-positive epithelial stem cells in gastric antrum are involved in the response to *H. pylori* infection and are susceptible to oxidative DNA damage that results from the *Helicobacter*-inflammatory milieu.

Our laboratory is moving on to translational applications of genomic and epigenomic biomarkers of cancers of the esophagus, stomach, colon, biliary tract and pancreas, for assessment of cancer risk of pre-neoplastic diseases in Barrett's esophagus, inflammatory bowel disease and gastritis and for personalized cancer treatment. We are evaluating genomic and epigenomic biomarkers to assess the risk of dysplasia and cancer in inflammatory bowel diseases (Ulcerative colitis and Crohn's disease).

We are using powerful genomic technologies such as next generation sequencing and highly sensitive and specific approaches for detection of rare events in the human genome to translate our research into testing methods that we hope will help manage and enhance the health of patients with digestive diseases that predispose to cancer.

### Our Webmaster Reminds You to Update Your Website!



DNA damage in gastric stem cells (Lgr5+) in *H. pylori*-positive patients with gastric cancer (*Digestive Diseases & Sciences*, 2013).



Ping Feng, our hardworking webmaster





*Dr. Patricia Tiscornia-Wasserman  
Cytopathologist and Amateur Photographer*

Dr. Patricia Tiscornia-Wasserman joined the Department in 2012 as Director of Cytopathology Services. Her research interests involve all aspects of cytopathology, especially thyroid disorders, head and neck neoplasms, and cervical cancer diagnosis and management.

Dr. Wasserman received her medical degree with Honors from the University of Buenos Aires School of Medicine in Argentina. Following her residency in Anatomic and Clinical Pathology, and fellowship in Cytopathology, at The Mount Sinai School of Medicine in New York, she joined Long Island Jewish Medical Center. She was the

Chief of the Division of Cytopathology at LIJMC, beginning in 1993. In 1999, she organized an independent Cytopathology fellowship-training program in the Department of Pathology and became the Director of the Cytopathology Fellowship at LIJMC. In 2009, she was named Senior Director of the Division of Cytopathology at North Shore-Long Island Jewish Health System and also began a joint appointment in the Department of Otolaryngology and Communicative Disorders at NSLIJHS.

Dr. Wasserman is actively involved in several professional societies, including College of American Pathologists, American Society of Cytopathology, International Academy of Cytology, Papanicolaou Society of Cytopathology and American Society for Colposcopy and Cervical Pathology. In addition to her many national roles she is also an Inspector and a Spokesperson for the College of American Pathologists. She is a CAP Advocate, having lobbied in Washington on behalf of Cytology issues.

Dr. Wasserman authored over sixty publications and abstracts and contributed to three book chapters. Space does not permit a full listing of her accomplishments – for that see the website, but the Newsletter is happy that Patricia is a devoted amateur photographer, whose images we have scattered throughout this Newsletter.

## Dr. Heidrun Rotterdam Retires After Nearly 40 Years at P&S!



Dr. Heidi Rotterdam became an Instructor of Pathology at Columbia in 1974 and she is now Professor of Clinical Pathology. During that 39 years, Heidi assumed many duties including Director of the Pathology Residency Program and Director of the GI Pathology Training Program. She has lectured to second year medical students on GI pathology for many years. She has been a teacher and friend to generations of Pathology Residents.

Beyond her duties to Columbia and our Department, Dr. Rotterdam has served as an outside case reviewer at NYU and given numerous invited lectures. She has published many case reports and papers.

Heidi received her MD from the University of Munich and then came to the United States. She received some of her early training from Raphael Lattes. One of her proudest possessions is a bronze bust of Arthur Purdy Stout that she rescued from oblivion. She is trying to find a home for it in the department. Heidi is the author of a short article on how women first entered Pathology at Columbia and how they have finally prospered. See the Departmental Website. Click on About Us!

## Cytology Division Spring Lunch



### The Cytology staff from top to bottom, left to right:

*Abel Gonzalez, MD, Dmitry Kaminsky, CT, Diane Hamela-Bena, MD, Betty Saleh, Justin Dizon, Eugene Sostre, CT, Teresa Wood, CT, Mark Ewalt, MD, Khadijah Newell, CT, Anjali Saqi, MD, Radica Persaud, June Grimes, Zoya Melnikov, CT, Nikosa Collins, CT*

## New Grants

PI	Agency	Title
Abeliovich, Asa	Merck & Co., Inc.	Characterization of human-induced neuronal (hiN) cells from Alzheimer's disease (AD) patients' skin
Abeliovich, Asa	National Institute of Neurological Disorders and Stroke/NIH/DHHS	Generation and integration of new CNS neurons by in vivo directed conversion
Abeliovich, Asa	National Institute on Aging/NIH/DHHS	Human Induced Neuronal Stem Cell Models of Familial Alzheimer's Disease
Clark, Lorraine	Parkinson's Disease Foundation	Parkinson's Disease Foundation (PDF) Research Center Grant 2012-2013
Crary, John	American Health Assistance Foundation	Role of microRNAs in tangle predominant Alzheimer's disease
Di Paolo, Gilbert	CHDI	Towards understanding Huntington's disease through lipidomic profiling
Gershon, Michael	Shire Pharmaceuticals	Prucalopride-mediated Neuroprotection and Neurogenesis in the Enteric Nervous System
Greene, Lloyd	Bumpus(William N and Bernice E) Foundation	Defeating insect-borne diseases using atomic resolution structure
Greene, Lloyd	National Institute of Neurological Disorders and Stroke/NIH/DHHS	Mechanisms of Dopamine Neuron Degeneration
Henderson, Christopher	Amyotrophic Lateral Sclerosis Association	Contribution of neurotensin to degeneration of vulnerable motor neurons in ALS
Henderson, Christopher	Johns Hopkins University	Generation and Characterization of Amylotrophic Lateral Sclerosis
Kim, Tae-Wan	American Health Assistance Foundation	Novel CNS transporter target in Alzheimer's disease
Liem, Ronald K	MDA	Characterization of a new mouse model for CMT2E
Liem, Ronald K	Charcot-Marie-Tooth Association	Generation of Cell Lines for CMT2E Drug Screening
Mason, Carol Ann	Fight for Sight, Inc.	Genes that regulate retinal ganglion cell identity
McCabe, Brian	Amyotrophic Lateral Sclerosis Association	Disruption of neuronal NF-kB signaling by TDP-43 and FUS/TLS mutations in familial ALS
Monani, Umrao	AADC Research Trust	Mouse model of Aromatic L_ amino acid decarboxylase deficiency
Monani, Umrao	ALADD Foundation	Toward a Mouse Model of Aromatic L_ amino Acid Decarboxylase Deficiency
Monani, Umrao	Pediatric Neurotransmitter Disease Association	Toward a mouse model of Aromatic L-amino acid decarboxylase deficiency
Monani, Umrao	SMA Europe	Identifying spinal muscular atrophy modifiers
Przedborski, Serge	Amyotrophic Lateral Sclerosis Association	Cell-based assays for the screening of neuroprotective small molecules for ALS
Przedborski, Serge	Parkinson's Disease Foundation	Localization of a-synuclein in mitochondrial -associated ER membranes (MAM)
Troy, Carol	NIH, NINDS RO1	Mechanisms and Treatment of CNS Edema
Troy, Carol	Novo Nordisk	A Novel Therapeutic for Diabetic Macular Edema
Vallee, Richard	National Institute of General Medical Sciences/NIH/DHHS	Mechanism of Action of Dynactin
Wichterle, Hynek	National Institute of Neurological	Motor neuron selector genes and the







*The Number 1 station at 125th Street-Water color and gouache.  
Part of a series on our neighborhood by Ruth Rooks, Swampscott, MA. ruth@ruthrooks.com*

## From the Chairman

*continued from page 1*

applications are being accepted. The only compensation is being “in the know” and a small amount of funds for expenses. All interested can line up outside my door. They will have the expert advice of our graphic designer, Richard Miller.

In spite of the “Sequester” and gridlock in Washington, the year has been a good one for us. Our clinical practice has grown at a rate of 15% for the third year in a row. We are slowly evolving toward a sub-specialty model in anatomic pathology and our laboratory medicine group continues to grow both its clinical and research efforts. Our basic research is thriving and new faculty members will be introduced in this newsletter as they arrive oncampus.

Summer is here and it is time to unwind, regroup and be ready for the coming year. My deepest thanks to all the members of the department – faculty, staff and students – who have made it possible for us to succeed.

*Michael Shelanski*

## Our Diagnostic Services

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

**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 on Publications

*The members of the department contributed approximately 260 peer reviewed publications in the years 2011-2012. The newsletter suggests that interested parties search the websites of the individual faculty members at <http://pathology.columbia.edu/>*

# COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

Volume 10, Issue 2  
Summer/Fall 2013

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Pathology and Cell Biology

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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.





COLUMBIA UNIVERSITY

*Department of Pathology  
and Cell Biology*

***Personalized Genomic Medicine***

The Laboratory of Personalized Genomic Medicine in the Department of Pathology and Cell Biology is a state-of-the-art clinical diagnostic laboratory that performs cutting-edge tests in the areas of genetics, oncology and molecular microbiology. The laboratory is accredited by CLIA, the College of American Pathologists (CAP) and the Clinical laboratory Evaluation Program (CLEP) of the New York State Department of Health.

We rapidly adapt scientific discoveries to develop clinically relevant diagnostic, prognostic and predictive assays to add to our ever-increasing test menu. Our division led by an experienced team of directors is committed to providing superior testing services and to make personalized medicine a reality for our physicians and their patients.

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