

# COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

Volume 1, Issue 2

Summer 2008

## From the Chairman



This is Emily. We show her because her family and our department have a link. Emily's mom had lost two previous pregnancies. Few people can understand the pain that such losses cause and while I could ask you to imagine such a situation, I'm sure that unless you have experienced it, you cannot. As Emily's Mom pointed out in a recent letter to the New York Times, it is important in such cases to perform an autopsy. When Emily's Mom had her first tragedy, our own Harsh Thaker was the pathologist. He was faced with a fetus with the unusual combination of cystic kidneys and a fatty liver. In trying to arrive at the correct diagnosis, Harsh considered, and then eliminated, several possibilities such as trisomy 13, autosomal recessive polycystic kidney disease, and Meckel syndrome. That left the possibility of a rarer metabolic disorder. Unfortunately, for the first fetus, no clear answer appeared – partly because there was no unfixed tissue to do biochemical analysis.

And then disaster struck again. The second fetus - this time observed earlier in preg-

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We are pleased to send the second issue of the Columbia Pathology and Cell Biology Report. The theme of this issue is our Department's ability to unite basic and clinical science. In this issue we have included more substantive material. You will learn about an interesting recent case of Hemoglobin H disease, as well as new methods to deploy microarray analysis for tumor identification. We continue to explain the clinical work and research going on in each of our three divisions. Finally, in this issue we are pleased to congratulate a number of our colleagues on their promotions, on their awards, on their new grants, and on their length of service.

## BIOLOGY AND PATHOLOGY UNITE!

ANATOMIC  
PATHOLOGY

CLINICAL  
PATHOLOGY

CELL AND  
MOLECULAR BIOLOGY

### Anatomic Pathology A Short Tour of the Renal Pathology Division

By Vivette D'Agati  
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The Renal Pathology Division of Anatomic Pathology at Columbia University, which was founded in 1973 by Dr. Conrad L. Pirani, has a rich history of subspecialization and integration with the Division of Nephrology. The laboratory has been administered by Division Director, Dr. Vivette D. D'Agati since 1984. Over the past two decades, the laboratory has grown enormously in clinical and research activities, with the addition of 3 more full-time attendings, Dr. Glen S. Markowitz in 1998, Dr. M. Barry Stokes in 2002, and Dr. Samih H. Nasr in 2005. Both Dr. Markowitz and Dr. Nasr received renal pathology fellowship training at Columbia; Dr. Stokes did his fellowship at University of Washington and was an attending at New York University prior to joining Columbia. The laboratory staff includes 8 technicians highly skilled in the processing of renal biopsies by light, immunofluorescence and electron microscopy, a secretary, and a transcriptionist.

The laboratory receives 3500 renal biopsies per year, including native and allograft biopsies, of which approximately 900 origi-

nate within Columbia Presbyterian Medical Center and 2600 are sent as wet tissue from over 350 nephrologists at academic and community-based medical centers within 12 states (spanning a broad geographic base that extends from Rhode Island to Florida, and as far west as Indiana). This clinical practice is one of the largest in

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COLUMBIA UNIVERSITY  
MEDICAL CENTER

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## Chairman's Letter

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nancy - also had cystic kidneys and a fatty liver. Everything was the same, except this time the clinicians and pathologists were ready. Harsh became a detective and after working through many possibilities he was able to make an informed guess. Because of the preparation he was able to obtain sufficient fetal blood to send samples to the biochemical genetics lab at Mayo Clinic. The answer came back that there were extremely high levels of C16-C18 acylcarnitines, indicating defective function of carnitine palmitoyl transferase (CPT) II. This is an enzyme that is located in the inner mitochondrial membrane and is involved in the transport of fatty acids into mitochondria. A deficiency of this enzyme results in defective fatty acid oxidation (explaining the fatty liver phenotype). CPTII deficiency usually presents in adults or young children but a rare perinatal lethal form has been described - as in this case.

Armed with the knowledge of this diagnosis, Wendy Chung of Clinical Genetics amplified the suspect gene by PCR sequenced it and showed that both parents were heterozygous for a two nucleotide deletion in the CPT-II gene. And there was now a genetic test.

Early in the third pregnancy a chorionic villus sampling was performed and sequencing of the CPT-II gene showed that the baby did not have two defective genes. Emily was born healthy, as you can see. Emily's Mom and Dad hope that the test can be used systematically and that screening for this rare condition can become standard.

I would like to congratulate Harsh and Wendy. This sort of persistence, knowledge and compassion is what our Department stands for. I would like to thank Emily's Mom and Dad for letting us tell this story. They are also particularly grateful to their genetic counselor Kathleen Berentsen.

Now if Emily were to go to medical school, she could graduate from The College of Physicians and Surgeons in, let's see - 2032.

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## Cell and Molecular Biology The Mitotic Check Point

By Richard Vallee, Director,  
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Arguably, the most important event in the life of the cell is mitosis, the process of cell division. The typical cell in the human body is the product of numerous cell division cycles. For some cells, divisions continue throughout life. This is a critical process for the cell to get right - no mistakes can be allowed in the equal segregation of chromosomes. Errors can be disastrous, in some cases leading to abnormal proliferation and cancer.

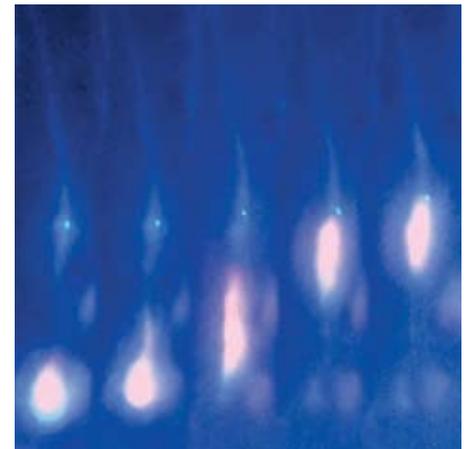
Consistent with the importance of mitosis, cells have evolved their most important quality-control mechanism, the mitotic, or mitotic spindle assembly "checkpoint." This mechanism is active during early mitosis, when chromosomes first become associated with the mitotic spindle. It remains in effect until all of the sister chromatid pairs are aligned in the center of the mitotic spindle to form an imaginary "metaphase plate." At the moment of alignment the checkpoint signal is switched off. It takes a few minutes before active checkpoint components degrade and disappear, and then the important business of chromosome separation - anaphase - begins.

The molecular nature of the mitotic checkpoint has been a subject of great interest for many years, and is the major interest of Dr. Yinghui Mao, who has recently joined the department as Assistant Professor. Dr. Mao works with dividing mammalian cells, but much of his work is carried out using cytoplasm prepared from eggs of the African horned toad *Xenopus laevis*. The eggs can be obtained in large quantity arrested in mitosis (specifically in metaphase II of meiosis). They are crushed rather than extracted to yield cytoplasmic preparations with properties close to those *in vivo*. Remarkably, mitotic spindles can be induced to form and chromosomes to segregate within these *in vitro*, test tube preparations. This makes it easy to add, subtract, and modify proteins of interest and look for effects on mitotic progression.

Using this system Dr. Mao has identified a series of protein interactions that are at

the heart of mitotic checkpoint control. He has found, in particular, that the protein kinase, BubR1, which resides at the mitotic kinetochore, is activated by a kinetochore "motor protein," CENP-E. This finding directly links the force-producing machinery for chromosome segregation to checkpoint control. Dr. Mao has recently identified a physical link between these proteins and the tumor suppressor protein APC (adenomatous polyposis coli), mutations in which are strongly associated with colon cancer. Mao believes that mutant APC may directly interfere with the all-important mitotic checkpoint, and leads to severe errors in chromosome segregation. Mao is hot on the trail of the detailed mechanism underlying these effects, which have important implications for understanding not only colon cancer but cancer progression in general.

## The Art of Cell Biology



Neural precursor cells migrating through the developing rat brain. The centrosome (find the green dot) moves well in advance of the nucleus, which then rapidly catches up. Mutations in the LIS1 gene interfere with this behavior, resulting in the smooth brain disease, lissencephaly. (From Jin-Wu Tsai and Richard B. Vallee)

## Lung adenocarcinoma- a new frontier in molecular pulmonary pathology.

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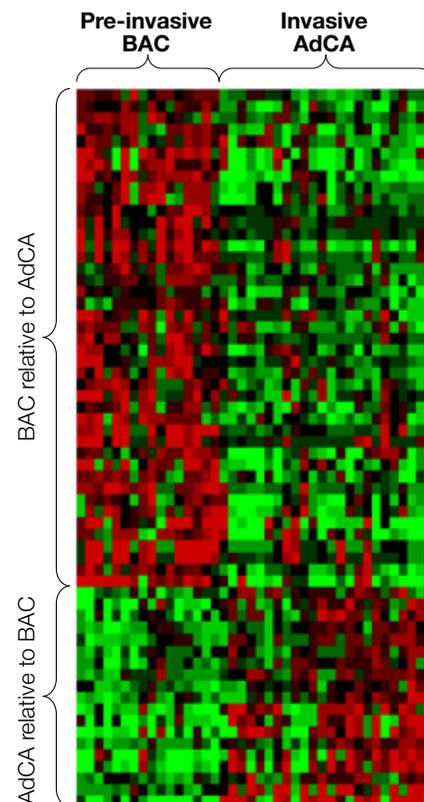
Clinically oriented research at Columbia University is helping to clarify pre-invasive and invasive subtypes of pulmonary adenocarcinoma, which are poorly understood. A recently funded collaboration between our laboratory in the Department of Pathology and Cell Biology and Dr. Charles Powell in the Division of Pulmonary Allergy and Critical Care Medicine has identified three distinct subgroups of adenocarcinoma - as well as a 42-gene molecular signature associated with prognosis. Laser capture micro-dissection of tumor cells as well as tumor associated stroma allows us to sample very small groups of cells. Microarray analysis of transcripts isolated from these small samples has yielded insights into the mechanism of invasiveness of these tumors. Microarray analysis of transcriptional activity has the power to tell us which genes are active in each of the subclasses of adenocarcinoma. The results are displayed as shown in the figure and constitute a fingerprint based on the relative expression levels of many genes.

The nascent division of thoracic pathology will continue to develop this type of advanced tumor analysis as well as providing the prior technology that is based on individual markers that have significance for cancer therapeutics (See the other Newsletter article on microarray analysis by Dr. Brynn Levy).

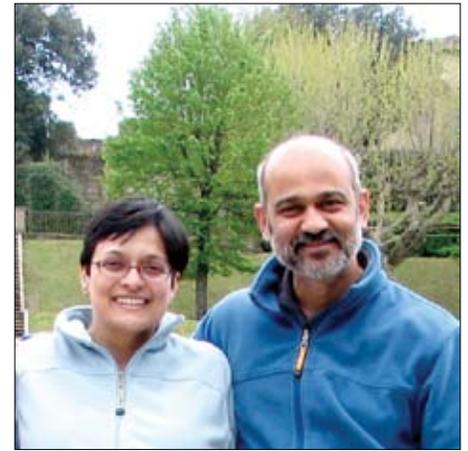
We also examine the expression of individual genes. Testing for epidermal growth factor expression and amplification as well as a search for k-Ras activating mutations has become part of a panel for lung adenocarcinoma work-up. Characterization of non-small-cell carcinomas using immunohistochemical markers to define adenocarcinoma and squamous cell carcinoma groups has become standard and guides the choice of modern molecular therapies, personalized to the status of the patient's tumor. Newer markers, including ERCC1 as both a prognostic marker and a marker for cisplatin resistance (a chemotherapeutic agent commonly use in non-small-cell lung cancer) have been validated and made available to oncologists at or own and at other institutions. The division of thoracic

pathology will continue to expand this type of testing with the goal of generating high throughput molecular information tailored to the patient's individual tumor.

These efforts are part of a wide expertise in thoracic transplantation pathology (Charles Marboe and Matthias Szabolcs), as well as interest in respiratory cytology and interstitial lung disease pathology (Anjali Saqi). Thoracic pathology at Columbia University is an active diagnostic and research division contributing to the future of surgical pathological and molecular diagnostics. For more information contact Alain Borczuk.



Microarray technology reveals genes that are up-regulated (in red) and down regulated (in green) for pre-invasive bronchioloalveolar carcinoma (on the left) and invasive mixed subtype adenocarcinoma (on the right). Each column is an individual tumor. Squares across represent individual genes expressed in one tumor type relative to the other.



### Ila and Harsh Head West

Ila Singh and Harsh Thaker are leaving us for the University of Utah. These two wonderful people have an unusual story. They met over a cadaver on the first day of medical school at the University of Bombay and have been inseparable ever since. Both took their Ph.Ds at Yale and then did post-docs at Stanford. They became residents in our department where they received their training and then became Assistant Professors. Ila is a virologist working on retroviruses and hepatitis C. Harsh's full name -Harshwardhan -means somebody who increases joy - and as The Chair's column in this issue points out, this is something he has certainly done. They will become Associate Professors at The University of Utah. Ila will continue her research and will be Associate Director of the retrovirus and hepatitis virus lab at ARUP - a reference lab that does complicated testing in pathology. Aria Thaker, 15, their daughter, is a wonderful singer, who will also have good opportunities in Salt Lake City. The entire Department wishes them *bon voyage* and at least some of us promise to visit. All that snow, you know.

### Shine Yun heads even farther west

Shine Yun is leaving us to take a position at the California Pacific Medical Center in San Francisco where he will be a staff pathologist. California Pacific Medical Center is a large hospital with 5 campuses. Shine went to the Medical College of Wisconsin, did his AP/CP residency with us and was a fellow in cytopathology at Penn before returning as an attending. Shine will marry his fiancé Iwei on June 21 and is happy to return to his family in San Francisco. Good luck and *bon voyage* Shine and Iwei.

# Clinical Pathology: From Genome to Gene Using Microarrays

By Brynne Levy

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Historical Perspectives in Clinical Cytogenetics: Chromosomes were first observed in plant material by Eduard Strasburger in 1875 and in animals by Walter Flemming in 1879-1889. The word chromosome derives from the Greek words chroma meaning colored and soma meaning body and was coined by W. Waldeyer in 1888. Given that the study of chromosomes began about 120 years ago, it is surprising that prior to 1956, the human chromosome number was believed to be 48. The reasons for this stem from the fact that prior to 1956, direct examination of chromosomes was a technically difficult procedure. In the 1950s, several technical advances were made that would bring cytogenetics out of the so called "Dark Ages" and launch it into a fast growing field with clinical diagnostic capabilities. These included [a] improvements in techniques for culturing tissues and cells *in vitro*, [b] the discovery of [i] mitogens (PHA) to push cell into active cell division, [ii] spindle poisons (colchicine) to produce metaphase arrest, [iii] hypotonic solution to spread out the chromosomes & reduce clumping and [iv] differential staining for unequivocal identification of each chromosome. The clinical nature of chromosomal abnormalities was first recognized by Lejeune who demonstrated that an extra copy of one of the smallest human chromosomes (# 21) was present in individuals with Down syndrome. By the early 1970's, the clinical consequences of aneuploidy and structural abnormalities were readily appreciated as a significant cause of human pathology and chromosome analysis became widely utilized in prenatal, postnatal and miscarriage specimens. The next major advance came in the late 70s and early 80s when the technique of fluorescence *in situ* hybridization (FISH) was developed by combining traditional cytogenetic and molecular techniques. The employment of FISH has been especially useful in [i] defining cytogenetically detected chromosomal material of ambiguous or unknown origin, [ii] detection of microdeletion or microduplication events associated with clinical disorders such as DiGeorge syndrome and [iii] rapidly determining

the ploidy for specific chromosomes at interphase, e.g. trisomy 21. In 1992, a one-step whole genome screening technique called comparative genomic hybridization (CGH) was developed. Although initially utilized as a cancer research tool, its utility in clinical cytogenetics was recognized by some investigators and this ultimately led to the development of array CGH technology which is now considered to be a major part of the "new cytogenetics".

The Clinical Implications of a Chromosome Abnormality: Constitutional chromosomal abnormalities are often associated with a spectrum of clinical abnormalities. The phenotypic consequences of the anomaly vary considerably and depend on the nature and chromosomal origin of the apparent imbalance, as well as precisely which genes are involved in the aberrant region. Additional molecular cytogenetic studies using various FISH approaches (traditional, multicolor and reverse FISH) and/or CGH are often necessary to characterize the chromosomal abnormality and provide more specific details regarding the nature of the aberrant genomic material. While these techniques provide more information than conventional cytogenetic methods, they are still relatively coarse in their assessment of the precise boundaries and nature of the region of imbalance, especially with respect to the gene content. In many cases, prognostic information is solely derived empirically by reviewing apparently similar cases in the literature.

The Microarray Era: Given that each FISH probe is on average 100-200Kb and the whole genome is comprised of 3 billion base-pairs, it is impossible to use conventional FISH probes to scan the entire genome in karyotypically normal patients suspected to have a microdeletions or microduplications. Array based methodologies allows for genome-wide screening at a resolution not achievable using cytogenetic methods. There are various types of array platforms. These include [i] BAC (Bacterial artificial chromosome) arrays which are primarily used to detect gains and losses of  $\geq 100\text{kb}$  and [ii] oligonucleotide microarrays that can potentially detect gains and losses in the range of  $\geq 1-100\text{kb}$ . These platforms typically employ either a targeted design which interrogates specific genomic regions of known clinical significance, eg. microdeletion syndromes or a whole

genome / tiled design that utilizes probes spread across the entire genome at various intervals. Clinical utilization of microarrays in people with mental retardation and birth defects has detected at least twice as many potentially pathogenic de novo copy-number imbalances as conventional cytogenetic analysis.

SNP Oligonucleotide Microarray Analysis (SOMA): In 2006, we partnered with Affymetrix to assess the utility of their high-density SNP oligonucleotide-based arrays (500K) for clinical cytogenetic analysis. I was drawn to SNP based technology for a number of reasons: In contrast to the CGH array approaches, in SOMA only one genomic sample is hybridized to the array, so copy number changes are identified by comparison with independent control hybridizations. With over half a million SNPs and a mean spacing of 5.8 kb, the 500K SNP array offered a comprehensive whole genome scan with the potential to detect partial aneuploidy far below the threshold of the maximum resolution of conventional cytogenetic analysis by G-banding ( $<4-7\text{Mb}$ ). Since deletions and duplications could be precisely defined by using the SNP positions on the genome browser, SOMA promised to be useful for the clinical interpretation of both visible and submicroscopic cytogenetic imbalances. SOMA also allows for precise definition of the boundaries and nature of the region of imbalance, including the gene content. Another advantage of using a SNP-based array lies in the concurrent availability of genotype information that would allow simultaneous DNA-based studies such as uniparental disomy (UPD), zygosity and maternal cell contamination. To validate the use of the Affymetrix 500k array for this purpose, we carried out a blinded study of specimens with known cytogenetic aberrations; including cryptic subtelomeric unbalanced rearrangements, as well as patients with diseases due to single gene abnormalities. In all cases, we reliably detected the chromosomal imbalances, with sizes ranging from single genes to several megabases. We have also used SOMA in a clinical setting to characterize more precisely the size and gene content of visible cytogenetic aberrations or those previously defined only by FISH. In a few instances, the cytogenetic aberration was far more complex than indicated by GTG banding. By this approach, we also uncovered a new

microdeletion syndrome involving patients with GLUT-1 deficiency. Other candidates for SOMA included patients with non-specific phenotypic abnormalities and normal or balanced karyotypes. In this manner, we unexpectedly discovered a 3.8Mb deletion in the long arm of chromosome 20 in a patient with a non-standard balanced 11-22 translocation. More recently, we have switched to the Affymetrix® GenomeWide Human SNP Array 6.0 where the median intermarker distance is less than 700 bases, giving the highest resolution of copy number detection currently available. We are part of a multicentre NIH clinical trial that is investigating the use of DNA microarrays for prenatal detection of chromosome imbalances.

In a separate project, Vaidehi Jobanputra, the recipient of a K12 award, will define the abnormal genomic regions in patients with known constitutional chromosome rearrangements detected either prenatally or postnatally. This information will be catalogued in a database together with detailed clinical information regarding the fetus or patient with these abnormalities, thus providing the basis for more precise genotype-phenotype correlations. This database will be instrumental for the development of guidelines for predicting outcome in future cases. Our use of SOMA has not been restricted to clinical diagnostics and multiple projects are ongoing using SOMA for interrogation of copy number imbalances in various cancer specimens including pre-invasive and invasive subtypes of pulmonary adenocarcinoma. These projects (see the article by Alain Borczuk in this issue of the Newsletter) illustrate our Department's philosophy which is to make the transition from basic to clinical science seamless.

## An Appreciation of May Parisien, MD

By Charles Marboe



May Parisien (née Plummer) received her B.S. from Sainte Rose de Lima, Port-au-Prince, Haiti, and her M.D., with honors, from the Faculty of Medicine, State University, Port-au-Prince. She served a year of residency in medicine at General Hospital, P-au-P and then came to the United States for an additional year of internship in medicine at Albert Einstein Medical Center in Philadelphia.

With this strong background in medical practice she embarked on a career in pathology spanning 37 wonderful and productive years. May trained at New York Medical College and Beth Israel Medical Center before coming to Columbia for a fellowship in bone pathology. She focused her specialization with a research fellowship at INSERM-234, Lyon, France studying metabolic bone disease and histomorphometry. She applied this training in research with an NIH RO1 award studying "Skeletal Homeostasis in Blacks and Whites" over four years; in the bone histomorphometry core funded by NIH for five years for a Specialized Center of Research in Osteoporosis; and for five years in an NIH funded study of "Primary Hyperparathyroidism." She was an active contributor to the medical literature with 35 peer-reviewed publications and 13 chapters and reviews. She frequently presented at national and international meetings.

In addition to being the pathologist responsible for diagnostic orthopaedic pathology at the medical center for some 30 years, May was an avid and enthusiastic teacher. She lectured extensively in post-graduate courses for orthopaedic surgeons

at Columbia and Helen Hayes Hospital/Regional Bone Center and at the New York Orthopaedic Hospital. She instructed residents in pathology and orthopaedic pathology in bone pathology.

May remains active in Haiti, serving as a Visiting Professor of Pathology at Université Notre-Dame, Haiti, from 2000, actively teaching and supporting clinical activities at the university. Her contributions to her native Haiti continue in her founding and service as President of RepresentAction, a group active in economic and medical aid in Haiti. She is a member of the Boards of the National Organization for the Advancement of Haitians (NOAH) and of PromoCapital, The Haitian-American Investment Bank, and is a founding member of The Alliance of Overseas Haitians. We wish May a happy and productive retirement and hope that she visits often.

## Incoming Fellows 2008



**Miles Levin, MD**

*Temple University*

Miles will be a Fellow in Hematopathology. Prior to Columbia he was a resident in Anatomic and Clinical Pathology at Montefiore Medical Center. He received his MD from Temple University. He is a member of the College of American Pathologists and other societies.



**Wendy Yang, MD**

*University of California-Davis*

Wendy received her MD from UC-Davis. She did an AP/CP Combined Residency Program at UCLA. Prior to that she was CEO of FreshGene, Inc, a biotech firm in Concord, California.

# Anatomic Pathology

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the United States and provides a valuable resource for fellowship training, clinical-pathologic studies and basic research using archival human renal tissue.

Major areas of research include pathomechanisms of focal segmental glomerulosclerosis, HIV-associated nephropathy, lupus nephritis, polycystic kidney disease and drug toxicities. The laboratory has advanced our understanding of podocyte dysregulation in the mediation of glomerulosclerosis. NIH-funded research is directed to mechanisms of podocyte toxicity and oxidative stress in the adriamycin mouse model of focal segmental glomerulosclerosis. For 10 years, the laboratory has been part of a program project grant investigating the role of direct HIV infection of the podocyte and tubular epithelium in HIV-associated nephropathy. The mechanisms of nef and vpr-induced podocyte proliferation and dedifferentiation are currently under study.

The Columbia renal pathology laboratory has described novel drug toxicities including the glomerular and tubular toxicities of the bisphosphonates, pamidronate and zoledronate. The group was the first to identify cigarette smoking as a cause of nodular glomerulosclerosis. In December, 2005, the Science section of the New York Times featured the laboratory's discovery of a form of chronic, irreversible renal toxicity resulting from exposure to oral sodium phosphate (OSP) bowel preps for colonoscopy. The clinical-pathologic characterization of this new entity, "phosphate nephropathy", by the Columbia team has led to increased physician awareness of this potential toxicity, an alert issued by the United States Food and Drug Administration in May, 2006 and a warning issued by the American Society of Colon and Rectal Surgeons and the American Society of Gastrointestinal Endoscopy. The manufacturers have responded by reducing the phosphate content of their OSP preps by approximately 20%.

The Columbia Renal Pathology Division has hosted several important international consensus conferences on the classification of renal diseases, including the first working group classification of focal segmen-

tal glomerulosclerosis, held at Columbia University (supported by the National Kidney Foundation of NY/NJ and the Kidney and Urology Foundation of America), (2000-2002) and the revised WHO classification of lupus nephritis held at Columbia University (sponsored by the International Society of Nephrology and the Renal Pathology Society), (2002).

The Renal Pathology Division runs an annual postgraduate course "Renal Biopsy in Medical Diseases of the Kidney", which is now in its 31st year. The 4-day course, which is given jointly with the Division of Nephrology, provides a comprehensive update of major diagnostic entities in nephropathology, with emphasis on clinical correlations and pathogenesis. The longest running CME course at Columbia University Medical Center, it is attended annually by approximately 250 registrants from over 30 countries.

The Division hosts a weekly in-house renal biopsy conference, which has been ranked by the nephrology fellows as their most valuable teaching conference in the medical center. Dr. Markowitz provides continued education to the many referring nephrologists throughout the tri-state area through a regular rotation of regional renal biopsy conferences. This year, Dr. D'Agati was elected "Teacher of the Year" by the second-year Columbia medical school class of 2010, and Dr. Markowitz was named "Distinguished Spring Lecturer".

The Columbia renal pathologists are invited regularly to lecture at annual meetings of the American Society of Nephrology (ASN), the United States and Canadian Academy of Pathology (USCAP), among others. Dr. D'Agati has given short courses on Glomerular Disease at the USCAP and the ASN and served as Chair of the USCAP Evening Specialty Conference in Renal Pathology. She is co-author of the AFIP fascicle on Non-Neoplastic Kidney Diseases. Dr. Markowitz lectured on phosphate nephropathy at the newsworthy 2007 ASN symposium on novel renal toxicities. Dr. Stokes has become a leading authority on subtypes of focal segmental glomerulosclerosis and their clinical-pathologic correlations. He has contributed an im-

portant chapter on the causes of nephrotic syndrome to a major, upcoming renal pathology textbook. Dr. Nasr has published extensively on patterns of glomerulonephritis related to infections and dysproteinemias. He presented his data on the newly recognized entity of IgA-dominant post-staphylococcal glomerulonephritis at the 2006 International Academy of Pathology meeting.

Dr. D'Agati currently serves on the Editorial Boards of the Journal of the American Society of Nephrology and Kidney International. Dr. Markowitz is an Associate Editor of Kidney International, where he oversees "The Renal Consult" column. Dr. D'Agati served as President of the Renal Pathology Society in 1996 and was awarded the society's "Jacob Churg Award" in 2000 for lifetime contributions.

## Publications

1. Nasr S.H., Markowitz G.S., Stokes M.B., Said S.M., Valeri A.M., D'Agati V.D.: Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. *Medicine* (Baltimore) 87: 21-32, 2008.
2. Stokes M.B., Valeri A.M., Markowitz G.S., D'Agati V.D.: Cellular Focal Segmental Glomerulosclerosis: A Distinct Clinical-Pathologic Variant. *Kidney Int* 70: 1783-1792, 2006.
3. Markowitz G.S., Radhakrishnan J., Stokes, M.B. D'Agati V.D.: Acute Phosphate Nephropathy Following Oral Sodium Phosphate Bowel Cleansing: An Under-recognized Cause of Chronic Renal Failure. *J Am Soc Nephrol* 16: 3389-3396, 2005.
4. D'Agati V.D. Podocyte Injury in Focal Segmental Glomerulosclerosis: Lessons from Animal Models. *Kidney Int* 73: 399-406, 2008.

## Faculty Promotions

### **Arthur P. Hays, M.D.**

*From:* Associate Professor of Clinical Pathology & Cell Biology  
*To:* Professor of Clinical Pathology & Cell Biology

### **Glen S. Markowitz, M.D.**

*From:* Associate Professor of Clinical Pathology & Cell Biology  
*To:* Professor of Clinical Pathology & Cell Biology

### **Brynn Levy, Ph.D.**

*From:* Assistant Professor of Clinical Pathology and Cell Biology  
*To:* Associate Professor of Clinical Pathology and Cell Biology

### **Alexander Kratz, M.D.**

*From:* Assistant Professor of Clinical Pathology and Cell Biology  
*To:* Associate Professor of Clinical Pathology and Cell Biology

### **Mathias Szabolcs, M.D.**

*From:* Associate Professor of Clinical Pathology and Cell Biology  
*To:* Professor of Clinical Pathology and Cell Biology

### **Tae-Wan Kim, Ph.D.**

*From:* Assistant Professor of Pathology and Cell Biology  
*To:* Associate Professor of Pathology and Cell Biology in the Taub Institute with Tenure.

## Our Predecessors



*Rudolf Virchow (1821-1902) one of the great founders of Pathology. He established that all cells come from pre-existing cells. He described leukemia and many other conditions. Virchow was a great humanitarian and liberal politician who vehemently opposed the authoritarian regime of Kaiser Wilhelm and Otto von Bismarck.*

## Anniversaries

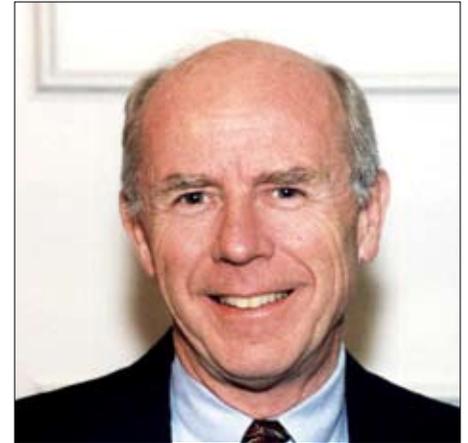


The Newsletter takes pleasure in acknowledging the people who have worked in the Department for many years. We are pleased to recognize **Eileen Erceg** who has been with the Department for 40 years now. Eileen came to us from the Missionary Sisters of the Sacred Heart via the Drake Business School. She was interviewed by former chairman Donald West King on May 5, 1968 and hired immediately. Dr. King still sends Eileen a poinsettia every Christmas. Initially an autopsy secretary, Eileen became the executive secretary for Dr. Conrad Pirani in Renal Pathology, then an administrative assistant, administrative coordinator and is currently Administrative Manager for Academic Appointments and Personnel. All of us have been helped by Eileen over the years. The Newsletter salutes her for many years of vital service.

In the next issue the Newsletter will highlight the career of Dr. Tuan Pham, who will reach his 40th anniversary at about that time. We recognize many individuals have had milestone anniversaries prior to the creation of this newsletter, while we do not have the space to list all past events; we plan to do our best to celebrate our milestones.

The Newsletter would like to recognize the long service of **Dr. Ralph M. Richart**, the longest serving member of the Department after Dr. Phil Brandt. Dr. Richart is a recipient of The Distinguished Service Award, The Medical Center's highest record of achievement.

Dr. Richart has been at Columbia for 45 years. In 1963 Dr. Richart was recruited to CPMC by Don McKay who had moved



from Harvard to Chair the Department of Pathology at Columbia several years earlier. Dr. Richart was appointed Director of the Division of Obstetrical & Gynecological Pathology and Cytology – a post he retained for the next 35 years when he was succeeded by Dr. Thomas Wright, the current Director of the Division.

For most of those 35 years the Division became known as a center for diagnostic excellence and training, and it attracted both pathology and clinical ob/gyn residents wanting to learn ob/gyn pathology. Rotations through the division were established with Harlem Hospital, Albert Einstein Medical Center, Roosevelt/St. Luke's Hospital Center, Holy Name Hospital, and North Shore Hospital among others. Teaching Columbia residents and those from around the tri-state area became an important Divisional function. At its peak, the program taught about 30 residents a year. In addition, the Division attracted research fellows from the United States and abroad – a number of whom stayed on as Associate Directors before moving on to head or join divisions of their own. Over one hundred fellows studied in the division during Dr. Richart's 35-year tenure, a record he regards as a pivotal legacy.

Dr. Richart has published 360 articles in peer-reviewed journals and co-written or edited 7 books. He has served on numerous editorial boards and gave endless numbers of lectures at home and abroad. He continues many of these activities as Emeritus Professor. All of us extend a hearty congratulations to Ralph Richart.

## Honors

Members of our department have received numerous awards for teaching and research since the last issue of The Newsletter.



**Dr. Letty Moss-Salentijn**, the Dr. Edwin S. Robinson Professor of Dentistry and Senior Associate Dean in the School of Dental and Oral Surgery received a Presidential Teaching Award at graduation. Letty has taught dental and other students with excellence and passion for many years and this award is richly deserved.

After 45 years of dedicated service, **Dr. Ralph M. Richart** has received The Distinguished Service Award from the College of Physicians and Surgeons. See the profile of Dr. Richart elsewhere in this issue.



**Dr. Ann-Judith Silverman** has won the Balmfolk Award for distinguished teaching in the pre-clinical years. Ann-Judith is the fourth of our faculty to win this award - previous winners include Taube Rothman, Joan Witkin, and Liza Pon.

We should be particularly pleased that the Class of 2010 has singled out members of the Department for special praise. Among the people receiving kudos were **Vivette D'Agati**, as Co-teacher of the Year, **Jay Lefkowitz** as Distinguished Fall Lecturer, **Glen Markowitz** as Distinguished Spring Lecturer, and **Kurenai Tanji**, and **Peter D. Canoll** as Outstanding Group Preceptors. Congratulations to all of you.

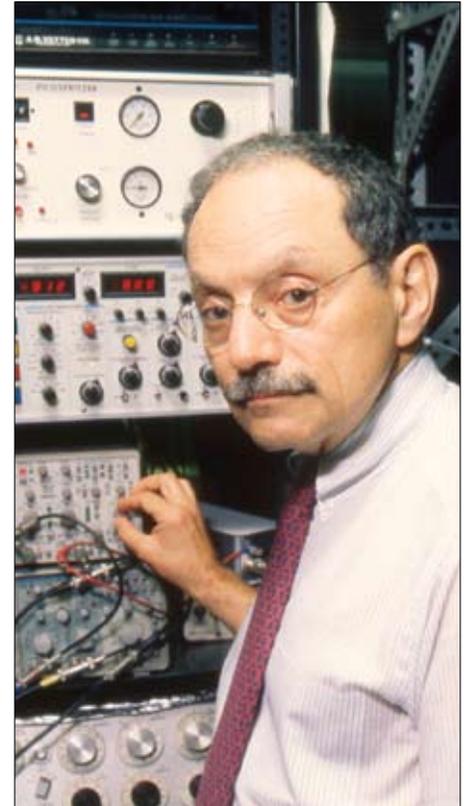


**Dr. Janet Sparrow** has received the Research to Prevent Blindness Senior Scientist Award. This award, which includes substantial laboratory support, goes to established scientists and is given on the basis of research accomplishments.

**Dr. Ottavio Arancio** has received the inaugural Margaret Cahn Research Award. Mrs. Margaret Cahn is a donor to the Zenith Society at the Alzheimer's Association and in recognition of her commitment to Alzheimer's research the Alzheimer Association has created this award in her honor. Ottavio was honored for his research on Alzheimer's disease over the last eight years.

**Dr. Robert Schlaberg**, one of our excellent Postdoctoral Residency Fellows, been selected to receive the Paul E. Strandjord Young Investigator Award from the Academy of Clinical Physicians and Scientists for 2008 for his work on the prevalence and distribution of XMRV, a novel retrovirus, in neoplastic and non-neoplastic human prostate tissues.

From the Ph.D program in Pathology and Cell Biology, **Ellen Ezratty** was the Convocation Speaker at the Graduation Ceremony for Ph.D students. Ellen had previously won The Harold Weintraub Graduate Student Award for work with Gregg G. Gundersen and has now run the table by winning the Dean's Award.



**Dr. Michael D. Gershon** received the 2008 Masters Award for Sustained Achievement in Digestive Science. The Award for Sustained Achievement in Digestive Sciences recognizes scientists and physicians who have made significant and sustained contributions to gastrointestinal disease research and who have been academic leaders as well.

Dr. Gershon has also been inducted as an AGA Fellow. Fellowship in the American Gastroenterological Association (AGAF) is an honor bestowed for superior professional achievement in practice and/or research in the field of gastroenterology.

# The Case of the Missing Genes: Hemoglobin H Disease

Patrice F. Spitalnik, M.D. (pfs2101@columbia.edu), Brie Stotler, M.D. (bs2277@columbia.edu), and Jeffrey S. Jhang, M.D. (jj222@columbia.edu).

## Clinical History

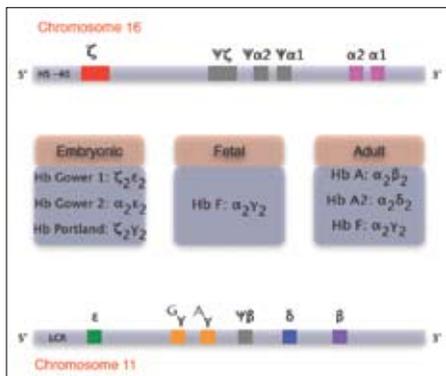
A 69 year old Southeast Asian man with a past medical history of gout, hypertension, chronic renal insufficiency, and fatigue presented to his primary care physician with a painful, swollen joint and was found on routine complete blood count to have anemia.

## Laboratory Studies

The routine blood count showed a severe microcytic, hypochromic anemia with a very low level of hemoglobin (8.8 g/dl), markedly reduced mean red cell volume (MCV 66.7 fl), and low mean cell hemoglobin (MCH 18.2 pg). This type of anemia is most commonly caused by either a genetic abnormality of hemoglobin synthesis or iron deficiency. Since the iron studies were normal in this patient, a genetic abnormality of hemoglobin was suspected.

## Normal Hemoglobin

Hemoglobin is a major red cell protein and the primary oxygen carrier in blood. Normal adult hemoglobin is composed of two  $\alpha$  and two  $\beta$  globin chains that combine to form hemoglobin A ( $\alpha_2\beta_2$ ). The minor adult hemoglobin fractions are hemoglobin F and hemoglobin A2 (Figure 1).

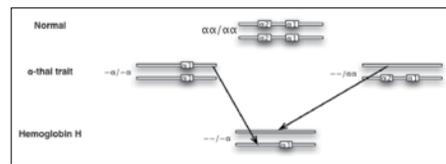


**Figure 1**  
The  $\alpha$  and  $\beta$  globin gene clusters are encoded on chromosomes 16 and 11, respectively. Alpha-like and  $\beta$ -like globin chains combine to form the various hemoglobins expressed during normal development.

## Thalassemias

Thalassemia is the most common genetic abnormality leading to a microcytic, hypochromic anemia. Alpha and  $\beta$  thalassemias are caused by deletions or mutations affecting one or more  $\alpha$  and/or  $\beta$  globin genes, leading to decreased or absent glo-

bin chain production (Figure 2). The loss of all four  $\alpha$  globin genes, Hemoglobin Bart's hydrops fetalis, is incompatible with life. Loss of one  $\alpha$ -globin gene is clinically and hematologically silent. Loss of two  $\alpha$ -globin genes either in cis (on the same chromosome;  $-/\alpha\alpha$ ) or in trans (one on each of the chromosomes;  $-\alpha/-\alpha$ ) produces a mild hypochromic, microcytic anemia.



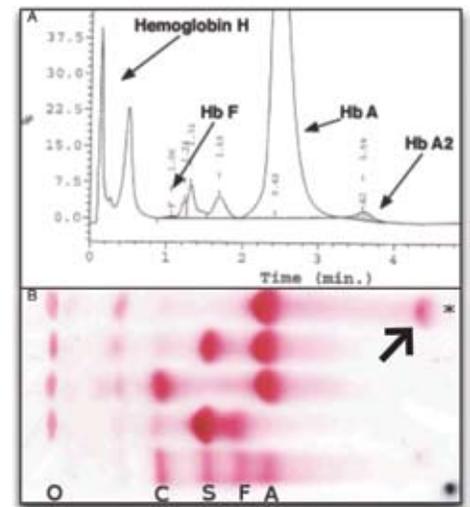
**Figure 2**  
This schematic diagram shows that there are normally four  $\alpha$  globin genes per person. Alpha thalassemia trait results from 2 gene deletions (either in cis or in trans). Hemoglobin H disease results from three  $\alpha$  globin gene deletions.

## Hemoglobin H Disease

When three  $\alpha$  globin genes are deleted, the imbalance of  $\alpha$  and  $\beta$  globin chain production leads to  $\beta$  globin chain tetramer formation (hemoglobin H) that precipitates and causes chronic hemolysis. This imbalance results in a severe hypochromic, microcytic anemia and splenomegaly. The clinical manifestations of hemoglobin H disease are variable and can be so mild, as in this patient that the abnormality is only found incidentally. Hb H disease is found mainly in Southeast Asia, the Middle East and the Mediterranean. It is particularly prevalent in Southeast Asia and Southern China.

## Diagnosing Hemoglobin H Disease

Evaluation for a hemoglobinopathy in this patient initially consisted of high performance liquid chromatography (HPLC), which showed the presence of normal amounts of hemoglobin A, A2 and F. However, an early double peak at a retention time of less than one minute (Figure 3), which is characteristic of hemoglobin H, prompted further evaluation with alkaline (cellulose acetate) hemoglobin electrophoresis. The electrophoresis revealed a very fast moving band representing 8% of the total hemoglobin, consistent with the presence of hemoglobin H and the absence of structural hemoglobin variants (Figure 3). A hemoglobin H inclusion body stain (brilliant cresyl blue) was also positive and



**Figure 3**  
(A) High Performance Liquid Chromatography (HPLC) shows hemoglobins A, A2, F, & the characteristic early double peak of hemoglobin H (B) Cellulose Acetate Electrophoresis (alkaline pH of 7.4) demonstrates hemoglobin H(\*) in the top lane. The control lane containing hemoglobins A, F, S, and C is shown at the bottom. Other hemoglobin variants are shown for comparison.

the hemoglobin H was shown to be unstable. Molecular testing by gap PCR confirmed that three out of four  $\alpha$  globin genes were deleted.

## Why is this important?

Diagnosing hemoglobin H disease is important because the presence of a hypochromic, microcytic anemia can lead to the misdiagnosis of iron deficiency. Empiric iron therapy can lead to iron overload because patients with hemoglobin H disease have increased iron absorption. This overload can lead to chronic liver and heart disease. In addition, diagnosing hemoglobin H disease and other  $\alpha$  thalassemias in high risk patients is necessary to prevent offspring from inheriting hemoglobin Bart's hydrops fetalis. The fetus is not viable and can put the mother's health at risk. Antenatal carrier screening programs for thalassemias have been very successful. Carrier screening programs in Sardinia and Cyprus have led to a significant decrease in the number of newborns with  $\beta$ -thalassemia major. Clinical laboratories play a critical role in prenatal screening for hemoglobinopathies. In addition to laboratory testing, the Special Hematology Laboratory at Columbia University Medical Center provides the expertise of three clinical pathologists in the interpretation of these results.

## Incoming Residents 2008



**Tatyana Gindin, MD, PhD**  
*Mount Sinai School of Medicine  
CP/Research*

Tatyana received her MD and PhD degrees from Mount Sinai where she specialized in biophysics. She is the author of a number of publications and is a member of the Biophysical Society and the International Society of Quantum Biology and Pharmacology.



**Paul Hosking, MD**  
*SUNY Buffalo School of Medicine AP/CP*  
Paul received his MD from from SUNY Buffalo and did research at Roswell Park. He is a member of the Gold Humanism Honor Society.



**Marcela Salomao, MD**  
*Universidada Estadual de Campinas, Brazil  
AP/CP*

Marcela did her MD in Brazil at the Universidadada Estadual de Campinas. She has completed five years of post-doctoral research at the New York Blood Center where she focused on erythrocyte membrane proteins.



**Nadejda Tsankova, MD, PhD**  
*University of Texas SW Medical School  
at Dallas AP/NP*

Nadejda received her MD from UT Southwestern Medical School in Dallas. She has done significant research on the mechanisms of psychiatric disorders with a number of publications to her credit. She is a member of the Society for Neuroscience.



**Jonas Heymann, MD**  
*College of Physicians & Surgeons AP/CP*  
Jonas received his MD degree from the College of Physicians and Surgeons where he did research in the Department of Radiation Oncology. He is the author of several research articles on radiotherapy.



**Stephen Lagana, MD**  
*University of Pittsburgh School of Medicine  
AP/CP* Stephen received his MD from the University of Pittsburgh School of Medicine. He has been interested in cardiac and circulatory issues and currently has an article in press in *Circulation*.



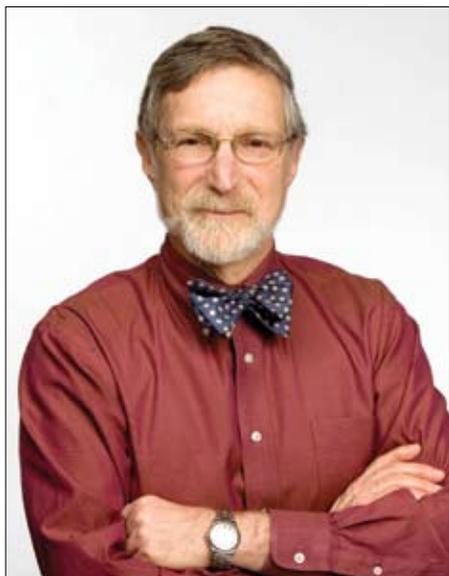
**Andrew Turk, MD**  
*College of Physicians & Surgeons AP/CP*  
Andrew received his MD from the College of Physicians and Surgeons. He has extensive research experience and is the author of several publications. He is particularly interested in HIV-related health care.



**Melanie Hawver, MD**  
*SUNY Syracuse College of Medicine AP/CP*  
Melanie received her MD from the State University of New York at Syracuse College of Medicine. She is a member of AOA and The American Society of Clinical Pathology.

# SECRET REVEALED!

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*Dr. Jakob Franke*



*Dr. Michael Shelanski*



*Lieutenant Carl Reyes*

The Newsletter's investigative reporters have uncovered a long hidden secret. There are two Michael Shelanskis. Or rather, there is one and he has a stunt double. Or, one could say there are two Jakob Frankes. The similarity between Jakob and Mike has long been noted, but what the Newsletter has uncovered is that this similarity has been exploited. When confronted with this discovery, the two men confessed and agreed to an interview:

**Columbia Pathology Reports:** Is it true that for certain meetings that Chairs are required to attend that Jakob went instead of you?

**MS:** Well, frankly, yes. Fortunately I am known as mild mannered and often I don't say much, so we just gave Jakob a bowtie and it was great. I had an hour off.

**CPR:** And how long has this gone on?

**MS:** Oh, years I suppose. We knew we had a good thing going when my daughter-in-law got into an elevator and said, "Hi Mike" to Jakob. Jakob and I especially enjoyed fooling the prior administration. Big meetings where I was supposed to attend and nod approval were particularly good. Jakob nods just like me and he had the

right to vote too, if they wanted a vote.

**JF:** There were some problems, though. I'm a little taller than Mike, so I sat as quickly as possible. And being Dutch I could never quite manage a Brooklyn accent, so I would just nod, clear my throat, and mouth the word laryngitis.

**MS:** There was that unfortunate time you voted to merge our department with Cornell's...

**JF:** I thought they said *Carmel*, which you have to agree would be nice.

**CPR:** So how was this arrangement discovered?

**JF:** The budget meeting, I think.

**MS:** Yeah, I think that was it. You couldn't even manage Eaten Budget Model with a Brooklyn accent?

**JF:** Can you pronounce Koninklijke Luchtvaart Maatschappij?

**MS:** No, usually I just say KLM.

**CPR:** So what happened in the budget meeting?

**MS:** It seems that our Departmental Administrator is a trained investigator.

**CPR:** Would that be former NYPD Lieutenant Carl Reyes?

**MS:** The same. After 21 years in the NYPD, some habits are hard to break. Also it was just a small meeting and I guess we were getting cocky.

**CPR:** So Carl recognized Jakob and objected to his being present instead of you?

**MS:** Yes, but not for the reason you might imagine. I think Carl was ready to go along, but then Jakob started to make suggestions. He is a notorious skinflint who can squeeze a nickel until the buffalo screams. That's how he kept Rich Kessin's lab afloat for 35 years. Carl, shall we say, wanted a little flexibility.

**CPR:** So now we will be seeing less of you because of all those meetings you have to go to?

**MS:** Sadly. And in December Jakob is retiring. But maybe you'll freelance? I need a stand-in for the Horwitz dinner.

## New Grants

Ottavio Arancio  
**Calpain Inhibitors Against  
Alzheimer's Disease**  
*U01 (NIH)*

Ottavio Arancio and Ariel Hidalgo  
**Mechanisms of Synaptic Dysfunction  
by Amyloid Peptides**  
*R01 (NIH, supplement)*

Alain C. Borczuk  
**Poor Prognosis Gene Expression  
Signatures Suggest Molecular Pathways  
of Mesothelioma Progression**  
*Mesothelioma Applied Research Foundation*

Gilbert Di Paolo and Belle Chang  
**Regulation of pip2 Metabolism  
in Nerve Terminals**  
*F31 Predoctoral Fellowship (NIH)*

Gilbert Di Paolo  
**Down Syndrome-Linked Synaptic  
Dysfunction and Cognitive Deficits**  
*The Irma T. Hirsch Trust*

Andrew J. Dwork  
**Neuropathology of White Matter  
in Schizophrenia**  
*Stanley Medical Research Institute  
and  
Myelin Pathology in Schizophrenia*  
*R01 (NIH)*

Lloyd A. Greene  
**Neurotrophic Factor Deprivation  
and Neuronal Cell Death**  
*R01 (NIH)*

Gregg G. Gundersen  
**Nucleocytoplasmic Interactions  
and Dynamics in Emery-dreifuss  
Muscular Dystrophy**  
*ROI (with Professor Howard Worman)*

Gregg G. Gundersen  
**Role of TorsinA in Cell Polarization.**  
*Dystonia Medical Research Foundation*

Harold Kaplan and Barbara Rabin Fastman  
**Knowledge Discovery:  
The Development of an Error/Solution  
Matrix to Improve Patient Safety.**  
*National Patient Safety Foundation*

Carol Mason  
**Local Translation and Transport of  
Mrna for the Guidance Receptor Ephb1:  
A Model for SMN Function**  
*Motor Neuron Center*

Livio Pellizoni with Dr. Brian McCabe  
*(Physiology)*  
**Defective Processing of a mRNAs  
Containing the Rare U12-Type Class  
of Introns**  
*Spinal Muscular Atrophy Foundation*

Hadassah Tamir  
*(with Dr. Victoria Arango, Psychiatry)*  
**5-HT1A Receptor: Antiapoptotic  
Transduction Pathways in Suicide Victims**  
*R01 (NIH)*

Ira Tabas  
**The Unfolded Protein Response  
in Sterol Cytotoxicity**  
*R01 (NIH)*

**Mechanisms of Atherogenesis  
in Insulin Resistance**  
*P01 HL087123 (NIH)*

Hynek Wichterle  
**SMN and Local Translation  
During the Formation of  
the Neuromuscular Junction**  
*Spinal Muscular Atrophy Foundation*

## Our Departmental 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](http://www.pathology.columbia.edu)

**Email:**  
[pathology@columbia.edu](mailto: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 2006-2008. 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 1, Issue 2  
Summer 2008

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