

COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

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From the Chairman

In the past 20 years the Department of Pathology has grown by the accession of some activities and contracted by “spinning off” others. For example, we have taken full responsibility for the laboratories at CUMC, incorporated the neurological molecular diagnostics laboratory and, most significantly, merged with the Department of Anatomy and Cell Biology to form the Department of Pathology and Cell Biology. On the other hand, our Division of Oncology has become the Institute for Cancer Genetics and, with the exception of academic appointments and close intellectual ties, functions independently of the department. In addition, we have a significant number of faculty members who have their primary appointments in other departments and joint or secondary appointments with us. Given the large size of our faculty, this web of cross-appointments can be confusing and I thought it might be valuable to devote this letter to clarifying some of these connections.

Faculty members with primary appointments in the Department of Pathology and Cell Biology can be divided into two groups – those for whom the Department assumes administrative and financial responsibility and those for whom responsibility is assumed by Institutes or Centers that cannot make independent academic appointments. In the former category are all physicians in the department with clinical appointments at Columbia University Medical Center/New York Presbyterian Hospital and the researchers housed on the 14th, 15th and 16th floors of the medical school building. In the latter category are the majority of researchers housed in the Taub Institute Laboratories on the 12th floor of the medical school, researchers in the Motor Neuron Center on the 4th and 5th floor of the medical school and researchers in the Institute of Cancer Genetics in the Herbert Irving Cancer Center building. This group totals over 70 full-time faculty members split about equally between those whose responsibilities are

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Since the last Newsletter in the Fall of 2009, the anxiety of the economic crisis has continued to recede – more slowly than we had hoped, but so far the trend is for improvement. For science and for people as dependent on the Federal Budget as we are, the news is perhaps slightly better. The NIH did not suffer in the President’s proposed budget – moving from \$31 billion to \$32 billion. As the following articles will show, we are doing well in our grant applications and our research and clinical efforts. Thanks to the hard work of a dedicated staff our grant and clinical revenues are keeping pace with inflation. This Newsletter describes improvements in our laboratories, the progress of various research efforts, the imaginative direction of our graduate programs, and the personal achievements of our students and faculty.

Blood Banked! Weightlifters Saved! Flu Fought! Not Bad.

ANATOMIC
PATHOLOGY

CLINICAL
PATHOLOGY

CELL AND
MOLECULAR BIOLOGY

New Neurons in Old Brains



Fiona Doetsch

It is an important milestone when a dogma is transcended. The theory of evolution supplanting the inheritance of acquired characteristics and Pasteur’s challenge to the theory of the spontaneous generation of life gave rise to microbiology. In chemistry, the theory of oxygen-based combustion eventually overthrew the theory of phlogiston secretion, and in physics the Copernican model transcended Ptolemaic cycles. Each year when new graduate students come, we should revisit our graveyard of ideas and confess honestly. “Ah, yes, everyone believed these once.” Examining fallen dogmas is more than an exercise in humility. If the Central Dogma of Molecular Biology had

been an article of faith, no one would have discovered reverse transcriptase or prions.

Below, Fiona Doetsch, Assistant Professor in the Departments of Pathology and Cell Biology, Neurology and Neuroscience and head of the Jerry and Emily Spiegel Laboratory for Cell Replacement Therapies, describes work from her laboratory on the identity and regulation of the stem cells for adult neurogenesis.

It has long been dogma that, of all cells in the body, neurons do not regenerate. However, it is now clear that stem cells residing in specialized niches in the brain of normal adult mammals, including humans, are constantly producing new neurons. More than a hundred thousand new neurons are born each day and undertake

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COLUMBIA UNIVERSITY
MEDICAL CENTER

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Our New Neurogenetics Laboratory



Members for the Laboratory: From left to right: Jiesheng Lu (Associate Research Scientist), Dr. Naini, Sindu Krishna (Senior Staff Associate) and Maryam Shirazi (Postdoctoral fellow).

We would like to welcome the CUMC Laboratory of Molecular Neurogenetics into the Molecular Diagnosis Section of the Department of Pathology and Cell Biology. The Laboratory Director is Dr. Ali Naini. The Laboratory performs molecular tests for mutations in mitochondrial DNA, depletion of mitochondrial DNA, mutations in nuclear DNA affecting mitochondrial function, and DNA analysis for glycogenoses and lipid disorders. In addition, the laboratory performs biochemical tests to evaluate respiratory chain enzymes, Coenzyme Q10, thymidine phosphorylase, glycogenoses, and lipid disorders. This diagnostic testing effort benefits from the expertise of Drs. Salvatore Dimauro and Michio Hirano, who are among the founders of the field of mitochondrial genetics. This effort depends upon the close collaboration of the nerve and muscle service of our Division of Neuropathology, which is led by Dr. Kurenai Tanji.

Dr. Naini has been at Columbia for 22 years. He was educated in Iran and left before 1979 to pursue a Ph.D in Clinical Biochemistry in London, after which he came to Columbia. Before molecular diagnostic efforts were unified in the Department of Pathology and Cell Biology, he worked in the Department of Neurology. His current plans are to expand its diagnostic capabilities into ALS, Parkinsonism, and other neurological disorders. Dr. Naini would like nothing

better than to assist our clinicians and basic scientists working on these diseases. He can be reached at abn2@columbia.edu.

The Laboratory of Molecular Neurogenetics is part of an effort to expand our capabilities in Molecular Pathology under the direction of Drs. Mahesh Mansukhanai and Steven Spitalnik. Readers of the Newsletter should consult previous issues articles about our clinical cytogenetics capabilities under the direction of Dr. Brynn Levy. All previous issues of the Newsletter are available on the Pathology and Cell Biology website: <http://pathology.columbia.edu>

A Prospect of Spring



For those of you depressed by an endless winter we offer this drawing by our designer Richard Miller and the reminder that daylight savings time returns on March 14th and the Yankees open against the Red Sox on April 4th.

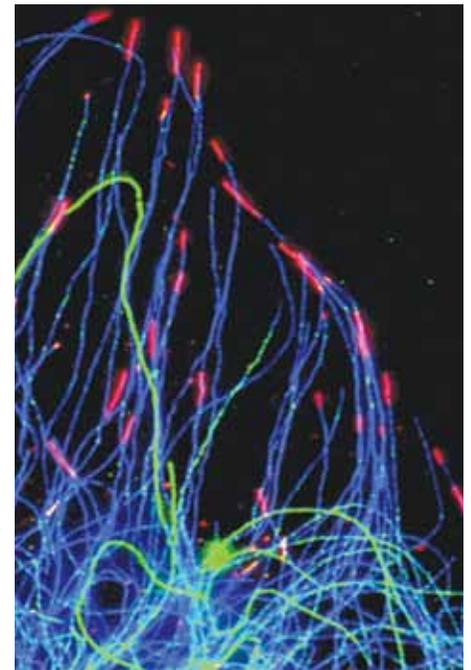
New Arrival



Peter Nagy, MD, PhD

Dr. Peter Nagy will arrive on March 1 as an Assistant Professor and Assistant Director of Molecular Diagnosis. Dr. Nagy will add to the Department's increasing efforts in molecular diagnosis. Dr. Nagy's interests lie in chromatin and epigenetics and the diagnostic potential of genome wide arrays. He is also studying how defects in transcriptional termination lead to certain neurological diseases. He comes to us from The University of Iowa.

The Art of Cell Biology



Microtubules and Rho GTPases in Cell Polarity and Cell Migration. Red segments show tubulin additions onto the ends of dynamic (blue) microtubules but not stable (green) microtubules, which are capped. -Courtesy of Gregg Gundersen

The Renovations on the Twelfth Floor of the Black Building

The 12th floor labs in the Black Building were a congested and dark place to work – a dark satanic mill of science. No longer. Thanks to support from the Taub Foundation, and Dean Goldman, the space is now open, completely redone and inviting. It will house researchers working on Neurodegeneration, including the laboratories of Asa Abeliovich, Carol Troy, Ulrich Hengst, Lorraine Clark, Richard Ambron and Peter Nagy. One of the pleasant discoveries of the construction was that the windows extended from just above the floor to ceiling but the lower halves had been blocked off. The new windows are all full length and the resulting light and views contribute immensely to the atmosphere. This is the second great improvement in space on the 12th floor coming soon after the adjacent space in the P&S building. Other improvements in Clinical areas are also scheduled.



Almost done. The new open laboratories on the 12th floor.

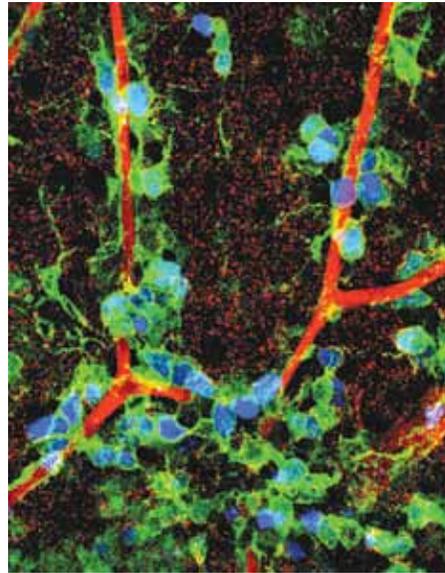


View of the George Washington Bridge from the new lab.

Website Revisions

The Departmental Website and all of its subcategories are being revised. The aesthetics and the usability of the site will be improved. All links will be tested and where necessary, changed. New units affiliated with the Department (for example, see Neurogenetics in this issue) will be incorporated. If your portion of the Pathology and Cell Biology website needs improvement, contact Rich Kessin at rhk2@columbia.edu.

The Birth of Neurons *continued from page 1*



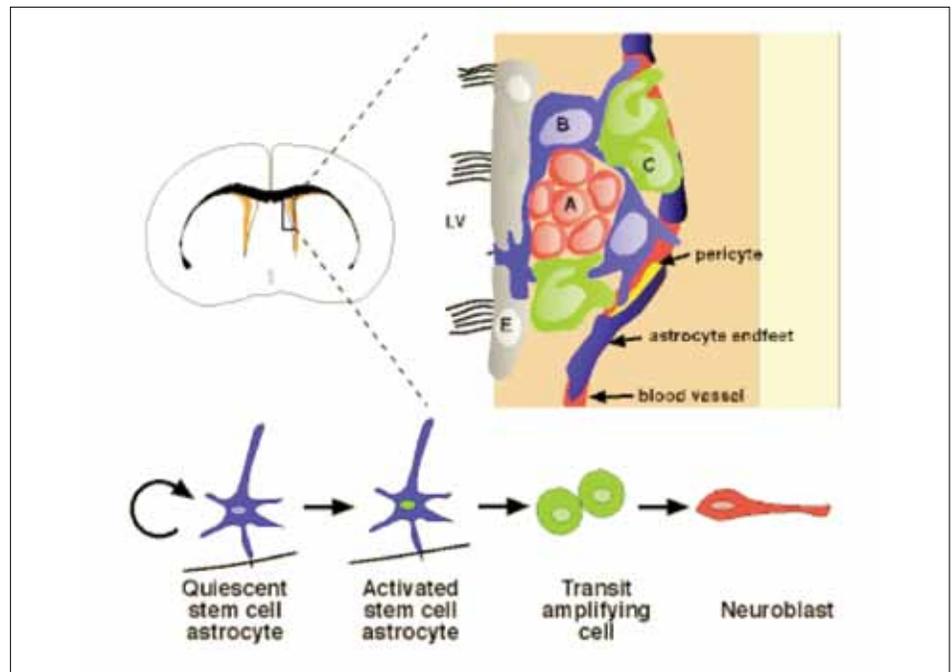
SVZ stem cell lineage and niche

a remarkable journey from their site of birth to distinct brain regions. In mice, new neurons are added to brain areas important for olfaction and for memory formation. Although the function of these new neurons is unknown, it is possible that they provide a novel mechanism for learning and memory formation.

The discovery that certain regions of the adult brain harbour stem cells has raised great excitement, both for its implications for brain plasticity and for the potential for brain repair. The adult brain contains two main cell types, neurons and glia. Neurons are the cells that allow us to think and move. Glial cells are the “glue” of the brain and have numerous functions, among them, providing support for neurons. In previous work, my colleagues and I showed that the stem cells in the adult mammalian brain are a subset of astrocytes, glial cells that were classically believed to derive from a lineage distinct from neurons. This finding overturned the concept of cell lineages in the brain and raised the exciting possibility that glial cells (or some of them) throughout the brain may also be latent stem cells. Work in my laboratory focuses on uncovering the biology of the brain’s own stem cells and the unique niche they inhabit that supports the formation of neurons throughout life.

The subventricular zone (SVZ) is the largest germinal region of the adult mam-

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Schema of coronal brain section of mouse brain showing SVZ in orange. Box is expanded at right to show SVZ cells, with the SVZ lineage below. Stem cell astrocytes (labeled B, blue) and transit amplifying C cells (C, green) often contact the vasculature at regions of blood vessels lacking astrocyte endfeet (dark blue) and pericyte coverage (yellow). Chains of neuroblasts (labeled A, red) shown here in cross-section, are less closely associated with the vasculature. Ependymal cells (E, gray), line the lateral ventricles. Quiescent stem cell astrocytes (Type B, blue) give rise to activated stem cell astrocytes (blue, green nucleus). They in turn give rise to transit amplifying cells (Type C, green), which generate neuroblasts destined for the olfactory bulb.

Bulking up with Anabolic Steroids Harms Kidneys

(adapted from press release on Columbia University Medical Center website)

Anabolic steroids may help athletes gain muscle mass and strength, but this bulking up comes at the risk of serious kidney damage, according to research published in the *Journal of the American Society of Nephrology*. The findings indicate that the habitual use of anabolic steroids has potential harmful effects on the kidneys that were not previously recognized.

“Anabolic steroid abuse is prevalent among both amateur and professional athletes. While these drugs are known to cause endocrine and liver dysfunction, until now their effects on the kidneys have not been appreciated,” says Vivette D’Agati, M.D.

The investigators studied a group of 10 bodybuilders who took anabolic steroids for years. All developed protein leakage into the urine and severe reductions in kidney function. Kidney biopsies revealed that the bodybuilders had developed focal segmental glomerulosclerosis, a type of scarring within the kidneys. This disease typically occurs when the kidneys are overworked. The kidney damage in the bodybuilders has similarities to that seen in morbidly obese patients, but appears to be even more severe.



Vivette D’Agati, M.D.

When the bodybuilders discontinued steroid use, their kidney abnormalities stabilized or improved, with the exception of one individual with advanced kidney disease who developed end-stage kidney failure requiring dialysis. The single patient who resumed steroid abuse developed a severe clinical relapse.

The researchers propose that extreme increases in muscle mass drive the kidneys to increase their filtration load, placing harm-



Weightlifter Patrick Antonecchia, prior to participating in the Columbia University Medical Center study. Credit: Strong and Fit For Life. (with permission)

ful levels of stress on these organs. Because the kidney injury following steroid abuse is more severe clinically and pathologically than that seen in morbidly obese patients with even higher body mass indices, it is also likely that anabolic steroids have direct toxic effects on the glomeruli, whose cells bear receptors for these agents.

Aside from increased lean body mass, the cohort of bodybuilders had additional factors that could exert stress on the glomeruli, the million capillary sieves per kidney required for the ultrafiltration of plasma to form urine.

Ingesting massive amounts of protein and other supplements to bulk up, a practice common among heavy weightlifters, causes an increase in renal blood flow and glomerular filtration rate by a variety of mechanisms. While this is an appropriate adaptive response to the increase in nitrogenous waste that is the byproduct of protein metabolism, chronic hyperfiltration from a high-protein diet may accelerate progression to glomerulosclerosis.

Six of the 10 patients also had elevated blood pressure or a history of hypertension at the time of renal biopsy. Systemic hy-

pertension as well as the extreme episodic elevations in blood pressure typically experienced during heavy weight lifting also may contribute to kidney injury.

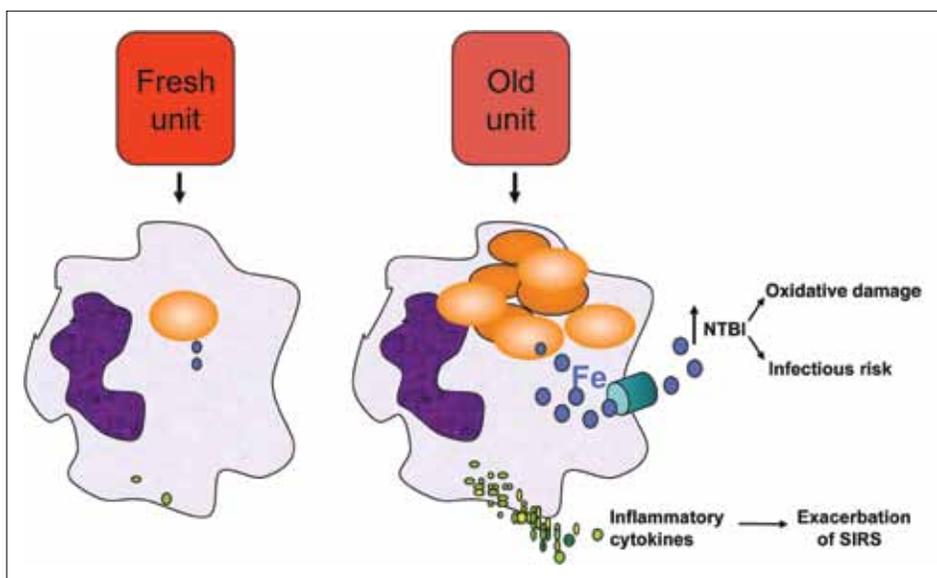
Because the major laboratory test that measures kidney function, the serum creatinine level, is influenced by the amount of muscle mass a patient has, kidney dysfunction can be difficult to identify in highly muscular athletes.

“Mild increases in creatinine may be overlooked as a normal physiologic response to increased lean body mass. Therefore, more sensitive tests to measure renal function and urinary protein are needed to detect the early stages of kidney disease in this population,” Dr. D’Agati said. “Because young athletes appear healthy and so few admit to use of anabolic steroids, this condition is likely to be under-recognized without more widespread screening of individuals at risk,” she added. “What looks healthy on the outside may be causing silent, progressive injury to the kidneys.”

The Columbia Renal Pathology team’s discovery was featured in the *New York Times Sports Section* on Dec. 10, 2009.

The Variability of Red Blood Cells

By Eldad Hod and Steven Spitalnik



A model to explain the deleterious effects of stored blood.

Over 15 million units of red blood cells are transfused each year in the United States, making RBC transfusion one of the most frequently prescribed therapies in the hospital setting. Dr. Steven Spitalnik's laboratory studies the side effects and toxicities resulting from administration of this unique "drug." In contrast to drugs or biologicals manufactured by the pharmaceutical industry, RBC units used for transfusion, which are derived from individual human volunteers, have substantial inherent variability. These differences can lead to potentially fatal consequences; for example, hemolytic transfusion reactions are caused by minor antigenic differences between the RBC donor and the transfusion recipient.

Over the past few years, the laboratory has developed mouse models of IgM-mediated and IgG-mediated hemolytic transfusion reactions using donor mice transgenic for human glycophorin A, a RBC membrane glycoprotein encoding the human M/N antigens. Using wild-type mice and knock-out mice as transfusion recipients, passively immunized with anti-human glycophorin A monoclonal antibodies, the laboratory began to understand the pathophysiological mechanisms underlying hemolytic transfusion reactions. These models also allow pre-clinical testing of novel therapies with the goal of treating or preventing these reactions in humans.

Other side effects of RBC transfusions may result from refrigerated storage of donor

units for up to 6 weeks prior to transfusion, which is in accord with FDA standards. This approach induces a complex "RBC storage lesion," which leads to decreased survival of transfused RBCs in the recipient. Recent epidemiological studies implicate prolonged RBC storage with multiple adverse effects in certain patients, including increased rates of infection, renal dysfunction, multi-organ failure, myocardial infarction, and death. To address these issues, the laboratory recently developed a mouse model of RBC storage that is similar to the current practice using human donors. Storing mouse RBCs in preservative solutions for up to 2 weeks yielded an average post-transfusion 24-hour RBC survival in mice of at least 75%, which meets FDA requirements. Transfusions of 2 week-stored, but not fresh, mouse RBCs induced a pro-inflammatory response in mice, with increased circulating levels of multiple cytokines (e.g. MCP-1, IL-6, IL-8, MIP-1, and TNF). Interestingly, this cytokine response is induced by transfusions of washed, 2 week-stored RBCs, but not by RBC-free supernatant, RBC lysate, or hemoglobin-free ghosts, all derived from 2 week-stored RBCs; this result suggests that delivery of membrane-bound RBC contents (presumably hemoglobin iron) is required for inducing inflammation. In addition, transfusions of 2 week-stored RBCs into mice injected with a sub-clinical dose of endotoxin produce a synergistic inflammatory effect with dramatic clinical signs

and symptoms. Finally, transfusions of 2 week-stored RBCs abruptly increase circulating levels of non-transferrin bound iron (NTBI); the resulting plasma enhances proliferation of a bacterial pathogen *in vitro*, an iron-specific effect. Taken together, these results support a novel "iron hypothesis" to explain the adverse effects seen after transfusion of stored RBCs (Figure 1).

The results from this mouse model formed the basis of a successful NIH R01 grant to initiate a human study to determine whether similar events occur after transfusion of stored RBCs. Thus, the laboratory is now truly "translational": using macrophage cell culture systems *in vitro* to improve fundamental understanding of the consequences of RBCs phagocytosis, using mouse models to elucidate the inflammatory pathways involved, and performing human studies to assess the applicability of these novel findings to clinical practice. In addi-



Drs. Eldad Hod and Steven Spitalnik

tion to involving members of the Spitalnik laboratory (Drs. Eldad Hod and Boguslaw Wojczyk), this work benefited by engaging multiple faculty members in the Department of Pathology and Cell Biology (Drs. Jay Lefkowitz, Vivette D'Agati, Joseph Schwartz, Jeffrey Jhang, Nicole Suci-Foca, Adriana Colovai, Alexander Kratz, Susan Whittier, and Phyllis Della-Latta) and the Department of Pediatrics (Drs. Gary Brittenham, Sujit Sheth, and Margaret Lee). Finally, these studies are part of a long-standing collaboration with Dr. James Zimring's laboratory in the Department of Pathology Laboratory Medicine at Emory University.

The Birth of Neurons *continued from page 3*

malian brain. The SVZ lies next to the cerebrospinal-fluid filled lateral ventricles in the brain, largely separated from the ventricles by a layer of ependymal cells. The SVZ is the source of neurons destined for the olfactory bulb. Stem cells in this region divide to generate neurons via rapidly dividing intermediate transit amplifying cells. The new neurons then migrate as long chains through the brain to reach the olfactory bulb.

A key question in the field of adult neural stem cells is why new neurons are made in some parts of the brain and not in others. We have recently found that blood vessels are a key aspect of the adult SVZ neural stem cell niche that supports life-long neurogenesis. Intriguingly, the blood vessels in the SVZ have unusual properties. They form a large planar structure that extends through the entire SVZ. Both stem cells and their transit amplifying progeny are found right next to blood vessels, both under normal conditions and during regeneration. Strikingly, they directly contact them at specialized sites that lack glial endfeet, a feature unique to this part of the brain. This suggested that the blood-brain-barrier, which prevents factors in the blood from entering the brain, may be altered in the SVZ. Indeed, small molecules can uniquely enter the SVZ stem cell niche directly from the circulation. Stem cells and their progeny therefore have privileged ac-

cess to a variety of signals from blood vessels: those mediated by direct contact as well as secreted signals from the cells that form blood vessels, and circulating factors in the blood.

Understanding the molecular pathways that control the maintenance and differentiation of *in vivo* stem cells is key to elucidating how a stem cell astrocyte turns into a neuron and eventually into harnessing the brain's own stem cells for brain repair. A major limitation in the neural stem cell field has been the lack of markers that distinguish between stem cell astrocytes and astrocytes in the rest of the brain. The identification of markers expressed by stem cell astrocytes would allow their purification directly from the brain without any culturing. This is especially important as culturing cells with growth factors alters their properties. We have recently developed a novel strategy to simultaneously purify stem cells and their daughter cells directly from the brain using fluorescence activated cell sorting. This is the first time that it has been possible to separate stem cell astrocytes from other brain astrocytes and allows us to test the functional properties and molecular signatures of each cell type. This powerful approach has allowed us to identify all of the genes expressed in each cell type and to compare stem cell astrocytes to other brain astrocytes. It

has also revealed that some stem cells are quiescent, lying dormant until needed.

The molecular regulation of neural stem cell self-renewal and differentiation are just beginning to be uncovered. microRNAs are small non-coding RNAs that are emerging as key regulators in a variety of systems. Most gene regulation occurs at the DNA level, with genes being made into RNA and then into protein. In animals, microRNAs largely act by blocking the production of protein at the mRNA to protein step. We have found that microRNAs (miRNAs) are key *in vivo* regulators of adult neurogenesis and uncovered a novel role for the brain-enriched miRNA, miR-124. miR-124 is important for controlling progenitor pool number and regulates the timing of progression along the SVZ stem cell lineage both under normal conditions and during regeneration. A key function of miR-124 is the down-regulation of the transcription factor Sox9, which is important for glial differentiation and stem cell self-renewal.

By uncovering the molecular pathways that regulate stem cells in the adult brain and the niche that supports neurogenesis, we hope to understand the function of adult neurogenesis, as well as illuminating steps towards harnessing endogenous stem cells for brain repair.

Pathologists at Play



Columbia and Einstein Pathology take to the slopes. No injuries reported.

Harsh and Ila find success in Utah!

Ila Singh and Harshwardhan Thaker, formerly in the Department of Pathology and Cell Biology, and now at the University of Utah, have recently had a significant paper published in the Proceedings of the National Academy of Sciences. They have found that a retrovirus, XMRV, has a significant correlation with prostate cancer. The title is: *XMRV is present in malignant prostatic epithelium and is associated with prostate cancer, especially high-grade tumors*. Your old colleagues extend their congratulations. Ila can be reached at ila.singh@path.utah.edu.

Honors and Awards

Dr. Paulette Bernd has received the coveted Golden Scissor Award from the P&S Class of 2013. The Award, Gross Anatomy's equivalent of the Golden Globes, was presented for superb teaching in the newly reorganized Gross Anatomy course. The scissors really are gold and they are beautifully, if minutely, engraved – Thank you Dr. Bernd, P&S class of 2013. Congratulations to Paulette!

Dr. Robert Winchester was just appointed chair of the Arthritis, Connective Tissue and Skin NIH study section. Dr. Winchester is also the Director of the Division of Rheumatology.

Eldad Hod, MD, working with Dr. Steve Spitalnik, received the Fenwal Transfusion Medicine Scholarship Award from the American Society of Blood Banks for the following paper: Harmful effects of erythrocyte transfusion after prolonged storage is mediated by iron (see accompanying article).

AND... in what may be a first, two PhD students in the Molecular Medicine and Pathobiology program, **Angela Yuanyuan Jia** and **David Alexander Silberstein MacLeod**, have announced their engagement.



Angela is working on her thesis with Professor Carlos Cordon-Cardo and David with Asa Abeliovich. As it turns out, David's father also got his PhD from us. The editor takes no position on whether or not marriage is an Honor or an Award, but this seems the right section to announce such a thing. The wedding will take place on Labor Day in Toronto and it promises to be most interesting.

New Grants

Asa Abeliovich

Autophagy and protein degradation in Parkinson's disease models
NINDS (R01)

IPS cell-derived neurons carrying an allelic series of CNTNAP2 structural mutations
NIMH

Peter Canoll

The role of white matter progenitors in glioma formation and progression
NINDS

Vivette Den D'agati

Pathology of the FSGS kidney
NIDDK

James Goldman

KAI1/CD82 regulates oligodendrocyte progenitor migration and differentiation-
NMSS (*fellowship*)

Lloyd Greene

Neurotrophic factor deprivation and neural cell death
NINDS

Gregg Gundersen

Regulation of microtubules by Rho GTPASES
NIGMS

Christopher Henderson

Generation and characterization of amyotrophic lateral sclerosis IPS cells
JH
Transcriptional control of target muscle innervation by facial motor neurons
NINDS

Brynn Levy

Array CGH analysis using DNA samples from the stillbirth collaborative research network (SCRN)
NICHD and Research triangle Institute

Ronald K. Liem

Identification of compounds to treat charcot-marie-tooth type 2E neuropathy
NINDS

Carol Ann Mason

Vision Sciences Training Grant
NEI

The role of ZIC genes in patterning the binocular projection
NEI

Livio Pellizzoni

Noncoding rna targets of the spinal muscular atrophy protein
NINDS

Regulation of SMN function in ribonucleoprotein assembly
MDA

Michael Shelanski

Faculty recruitment on the neurobiology of aging
NIA

Steven Spitalnik

Harmful effects of transfusion of older stored red cells: iron and inflammation
NHLBI

Mechanisms of effect of iron status and interventions on malaria and other infections
NICHD

Carol Troy

Downstream regulators of Beta-Amyloid induced neuronal death
NINDS

Richard Vallee

Molecular genetics of cytoplasmic dyein
NCRR

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

Email:

pathology@columbia.edu

Laboratory services:

1-800-653-8200/1-212-305-4840

Administrative Services:

1-212-305-7164

H1N1 at CUMC—an interview with Dr. Phyllis Della-Latta

Now that H1N1 vaccine is widely available and the first pandemic of the 21st century has been almost wrestled to the ground, Columbia Pathology Reports (*CPR*) decided to sit down with Director of the Clinical Microbiology Service, Dr. Phyllis Della-Latta, to ask how her lab dealt with the pandemic.

CPR: What was so unusual about the 2009 H1N1 influenza A virus?

PDL: First of all, it was the first flu pandemic that we experienced in 41 years. The genetic reassortment among swine, human and avian strains of influenza A was such that the rate of human transmission through droplet aerosols was very high. Globally, this strain spread from the first recognized cases in Mexico throughout the world within 2 months!

CPR: How did the 2009 H1N1 influenza A pandemic impact the Clinical Microbiology Lab?

PDL: Just as the Virology lab was recovering from the 2008-2009 seasonal flu season, the novel H1N1 hit NYC around April 23rd. We were the hardest hit US city during the first wave of the pandemic. Our hospital emergency preparedness team (EPT) and laboratory surge plans were immediately activated. The emergency departments were overflowing with patients with influenza-like illness (ILI) symptoms. The Clinical Microbiology Service was charged with crafting diagnostic test strategies to detect this novel virus. Conferences were held daily; the Microbiology Laboratory provided essential information regarding optimal specimen types, specimen collection methods, and transport containers as well as assays to be ordered and test interpretations to the influenza working team for dissemination through Infonet alerts.

CPR: Did new virology tests need to be introduced?

PDL: It became rapidly apparent as ILI cases increased logarithmically that a more sensitive molecular test to differentiate influenza A from influenza B and respiratory syncytial virus (RSV) had to be fast tracked into our test armamentarium in order to

provide an accurate lab diagnosis. The time-honored viral culture gold standard took far too long, exacerbating the potential to cause nosocomial transmission among employees and patients. We were faced with the challenge of instituting a new PCR nucleic acid amplification system, not only for detection of these viruses but also for subtyping influenza A to differentiate the Tamiflu susceptible 2009 pandemic fluA from Tamiflu resistant seasonal H1N1. Of overriding concern was the delivery of results in a clinically relevant timeframe. The process was very labor intensive and we are extremely proud of our entire Microbiology staff, particularly the Virology team for working long hours under the pressure of overwhelming specimen loads. Test algorithms needed to be crafted, explained and disseminated to the clinical staff. There was also updating of patient virology test results which were formatted into a chart, updated at least once a day and widely disseminated to the EPT and other appropriate personnel.

CPR: Were the Virology tests accurate in detecting the pandemic H1N1?

PDL: The Enzyme ImmunoAssays (EIA) routinely used to detect antigens present in influenza A, B and respiratory syncytial viruses provide results in minutes and have good sensitivity and specificity with seasonal flu. However the kit's performance in detecting the pandemic 2009 influenza A resulted in 60% sensitivity and 99% specificity. Therefore, false-positive results were not a concern, but the 40% false-negatives necessitated a sensitive confirmatory PCR test. PCR is more sensitive and provides results in hours, whereas the time-honored viral culture is labor intensive, less sensitive than PCR and takes days for results.

CPR: What was the major lesson learned?

PDL: We worked together as a team to deal with this crisis. A lesson learned by many was the need for state of the art technology and laboratory facilities. Timely detection of infectious pathogens leads to rapid diagnosis, appropriate treatment and improved patient management and outcomes. This axiom holds especially true during times of epidemics and pandemics. Clinical microbiologists are often the unsung heroes in the fight against the invisible enemy.

Chairman's Letter

Continued from page 1

primarily clinical and those whose activities are focused on research. All of these faculty members play an active role in our medical, graduate and post-graduate educational programs.

A second group of faculty members consists of those with primary appointments in other departments. Many of these people play an active role in graduate teaching in the department. They are all subject to Department of Pathology and Cell Biology review for tenure and promotions, but our department is not responsible for their space or for their salary support.

The faculty members in a third group are those who are located at affiliated hospitals. These major sites include the St. Lukes-Roosevelt Hospital Center, the Helen Hayes Hospital, Stamford Hospital and the Mary Imogene Bassett Hospital. The last of these, Bassett in Cooperstown, New York is involved in an exciting medical education program with Columbia in which a group of medical students will be admitted each year who will do their pre-clinical work at the medical school and then the majority of their clinical training in Cooperstown.

This list does not cover adjunct faculty members and people who have maintained an association with the department for years after they have ceased active work at Columbia.

Going forward we will continue to make joint appointments where it is in the interest of the department though these are likely to be fewer than in the past. It is no longer necessary for a member of a clinical department to have an appointment in a basic science appointment to be able to have graduate students. This was a major reason that many people sought joint appointments in the past.

I hope that this letter clarifies the various ways by which our faculty members participate in the department.

Michael Shelanski

Je ne suis pas leur mère! Zaia and the PhDs

Zaia Sivo, who administers both the Integrated Graduate Program in Cellular, Molecular and Biomedical Sciences and the newish Pathobiology and Molecular Medicine program has an enormous task. She has prepared the applications of hundreds of applicants, arranged 87 interviews, including travel (during a snowstorm, yet!) and begun what we are sure will be another excellent recruitment year. When she is not handling this onslaught during interview season, she manages the careers of all of our graduate students. If students take their qualifying exams on time and graduate a little earlier it is in great part due to Zaia. The rules are the rules, she tells a laggard student. And then, privately, after they have gone, she tells the rest of us, with faux exasperation, “Je ne suis pas leur mere - I’m not their mother”. But, in a way, thankfully, she is and we are not giving her back to her native Grenoble.



Zaia Sivo

A New Job for Emily Herzfeld

Emily has moved from IT to be the laboratory information Systems/CoPath Coordinator. She makes sure that all of our reports reach their correct destination. Emily will be spearheading our bar coding initiative for all specimens. She reports to Edward Kritchevski in Anatomic Pathology.

Our Predecessors

Two cousins in Breslau - 1876



Carl Weigert

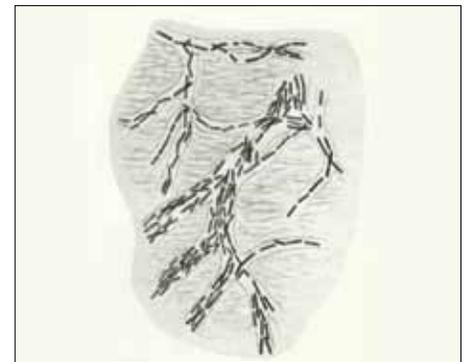
In the mid-1870’s Breslau in Silesia was the place for a pathologist to be-especially the laboratory of Julius Cohnheim. One of his students was Carl Weigert (1845-1904) who is, famous for the stains he developed, particularly for myelin. This was so important in the history of neuropathology that Alois Alzheimer praised him as “the master who created the tools for us.” His stains also served other vital purposes – they helped Robert Koch see bacteria in infected wounds and led to Koch’s seminal book *The Etiology of Traumatic Infective Diseases*. This book established once and for all that bacteria cause infection – a matter that was much debated and seriously doubted in 1876. (The Department possesses a translation.)



Paul Ehrlich

Also in the lab was Paul Ehrlich (1854-1915), only 22 in 1876, but a budding chemist and histologist whose techniques would

help Koch identify *Mycobacterium tuberculosis* in lung tissue. Ehrlich was Weigert’s first cousin. Ehrlich had a long career in therapeutics and after many contributions to immunology he devised the first chemotherapy for a bacterial disease – syphilis. He created the arsenical compound salvarsan. In 1908 he shared the Nobel Prize



Koch’s drawing of septicemia in the vessels of the rabbit kidney, a critical step in proving the germ theory of disease.

with Elie Metchnikoff. Ehrlich is considered the father of medicinal chemistry.

Koch, Ehrlich, Weigert, and Cohnheim met by chance. In May 1876, Koch, then a young health officer in Wollstein, not far from Breslau, wrote to Julius Cohn, one of the fathers of bacteriology, asking for an audience. Cohn had classified bacteria and established that they are stable species that do not capriciously change shape – something that was in doubt into the 1870s. He also found the first bacterial spores in *Bacillus subtilis*. Koch told Cohn that he had worked out the complete life cycle of the anthrax bacillus, proved that it caused anthrax and explained why it persisted in contaminated fields – the bacilli formed spores. Cohn invited him to Breslau, saw what he had done and immediately summoned Cohnheim, Weigert and Ehrlich. William Welch, P&S grad and founder of Johns Hopkins, was visiting Cohnheim’s lab at the time and he too was invited to see Koch’s slides. They were all convinced that finally there was a proof that bacteria could cause a disease and were not the result of a disease – also something that was still in doubt. The following decade saw the union of pathology and bacteriology, the isolation of numerous pathogens, and the establishment of the germ theory of disease. It was one of the most productive periods in the history of medicine.

New 'Med into Grad' Initiative Funded by the Howard Hughes Medical Institute

A new program that incorporates the knowledge and skills of medicine and pathobiology into graduate education has recently been funded by the Howard Hughes Medical Institute. The leadership of this initiative all have appointments in our department. Dr. Ron Liem is the Director of this new and exciting program and Drs. Steve Spitalnik and Howard Worman serve as Co-Directors. The program is a natural offshoot of the Graduate Programs in Molecular Basis of Health and Disease, which includes the Pathobiology and Molecular Medicine Program and follows from the course in "Mechanisms of Human Disease" that is run by Drs. Liem and Spitalnik. This course covers a number of diseases in depth, including patient interviews, histology, genetics, cell biology, physiology, pathology, and therapeutics. The course was taught by a team that included a large number of Pathology faculty members.

The new HHMI supported Med into Grad initiative will expand the course work related to human disease and will include a clinical program. Graduate students selected for the program will go on medical rounds, discuss cases with attending physicians, emphasizing differential diagnosis, diagnostic/treatment plan and underlying pathophysiology. They will also be assigned one or more mentors in medicine, pediatrics, neurology, psychiatry or pathology who are involved in the care of



Drs. Ron Liem and Steve Spitalnik wrote the HHMI grant. Dr. Liem is pictured. Dr. Spitalnik appears elsewhere in this issue.

patients, but with major effort in an active research program in laboratory or translational research on mechanisms of disease. Students will be fully supported by the HHMI grant during this year.

Students will be selected predominantly from the many excellent students currently enrolled in the Graduate Programs at Columbia University Medical Center based on their records and their interest in research related to the causes and treatments of diseases. The program should improve the understanding of medicine and pathobiology by Ph.D. students in the biomedical sciences. The goal is to increase the number of scientists who are prepared to undertake research that bridges the gap between basic biology and clinical medicine.

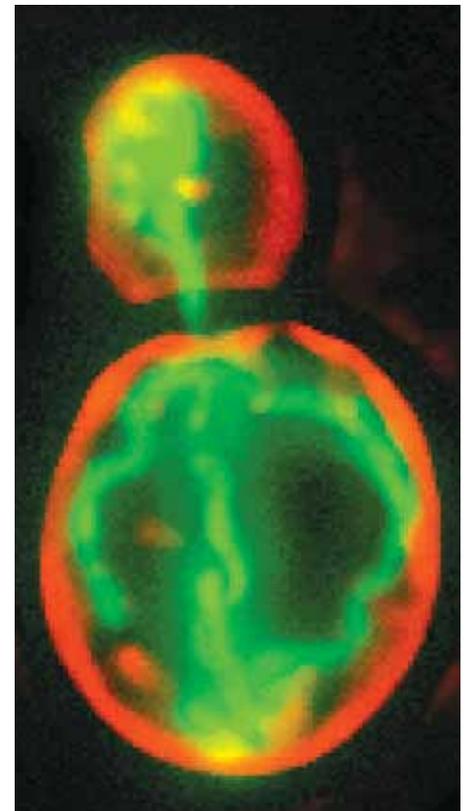


The First Year Class in Pathobiology and Molecular Medicine. From left to right: Jason Vevea, Kelvin Pau, Netonia Marshall, Preeti Putch and Shawn Jordan.

Anniversaries

We like to think that the Department promotes longevity. **Phil Brandt** and **Reba Mirsky Goodman** have been here for 50 years. Though retired, both are still working! **Ralph Richart**, also of the working retired, is only three years behind, having arrived in 1963. **Lee Stecher**, Surgical Pathology transcriptionist extraordinaire, came in 1966 and has been faithfully working for 44 years and **Dr. Karl Perzin** is close on her heels with 43 years of service. **Dr. Ernest April** celebrated 40 years of service this past July. **Mike Gershon** will celebrate 35 years in October – how many thousands of superb lectures have occurred in that time? **Aurica Foca-Rodi**, Senior Staff Associate in Immunogenetics and **Jay Lefkowitz** of liver fame are officially here for 30 years and **Jeanette Rodriguez** for 25. **Judy Burrell is retiring!** Judy currently provides administrative support to Dr. David Zegarelli in Oral Pathology. She has provided 26 years of service to the department. She assures the Newsletter that grandchildren will keep her busy.

The Art of Cell Biology



Mitochondria (green) are pulled into the bud during division in budding yeast—Courtesy of the Pon lab

Welcome to the Resident's Column in the Department of Pathology and Cell Biology newsletter. This is a chance to recognize the accomplishments of our department's residents in research and clinical work and to celebrate new and joyous events in their lives. It is also the place where current residents can update the department with news from the Anatomic and Clinical Pathology Residency Program at Columbia.

In addition to our clinical duties (grossing, autopsy, blood bank coverage, apheresis) and teaching responsibilities (1st year histology, 2nd year pathology, 4th year clinical pathology), many of our residents traditionally find time to engage in a variety of research projects, ranging from clinical to translational to basic science. Our strong annual presence at national meetings is a direct result of this tradition and this year, at least 7 residents will be presenting posters or platforms at the annual meeting of the United States and Canadian Academy of Pathology (USCAP). Impressively, three of these young investigators are from the second year class while the others come from later years. The meeting will be held in Washington, DC in mid-March so if you're planning on attending, stop by and check out our innovative research.

While USCAP is an anatomic pathology-oriented meeting, residents in clinical pathology will soon be submitting abstracts for the annual meeting of the Academy of Clinical Laboratory Physicians and Scientists (ACLPS) to be held in early June in Nashville, Tennessee. Our department is generally very successful in obtaining platforms/poster sessions at this meeting.

As we approach Match Day in March, when the department learns who has matched into our incoming first year class, we also begin to bid farewell to our senior residents. So what lies in ahead for graduates of our residency program?

First, we'll start by discussing our current stellar chiefs. Our AP-chief, Nike Beaubier, will be staying on at Columbia to complete a fellowship in Molecular Diagnostics and a Post-Doctoral fellowship in Dr. Shelanski's laboratory. Richard Francis (CP-chief) will be pursuing a fellowship in transfusion medicine, likely at the New York Blood Center. Finally, Jennifer Lambe, the AP/CP chief,

will be going on to a Surgical Oncology fellowship at Sloan Kettering Cancer Center.

Kalpana Deveraj (AP/CP) will stay on at Columbia as our GI fellow. David DeVinck (AP) will be moving on to a dermatopathology fellowship at Einstein's Montefiore hospital after completing his time as our surgical pathology fellow. Woojin YU (AP/CP), having completed his GI fellowship during his residency, will go on to doing full-time surgical pathology at Kiaser Permanente in the Bay Area of California. Finally, Erin Weeden (AP/CP) will be honoring her commitment to the US military and going into active duty in the US Air Force as a Staff Pathologist at Keesler Air Force Base in Mississippi. Congratulations to you all and we wish you the best in your continued training and future careers!

Finally, congratulations to our chief, Jennifer Lambe on the birth of her baby boy, Owen Lambe, on January 8th, 2010 at 8lbs 10oz.

The Residents' column will appear in future issues. It will provide updates on our residents and our program. Contact Anthony Sireci at ans2133@columbia.edu

Promotions

The following are recent promotions in the Department of Pathology & Cell Biology:

Michael B. Stokes, M.D. – Promoted to Associate Prof. of Clinical Pathology & Cell Biology

John Crapanzano, M.D. – Promoted to Associate Prof. of Clinical Pathology & Cell Biology

Bruce Wenig, M.D. - (St. Luke's -Roosevelt) Appointed Adjunct Prof. of Clin. Path & Cell Biology

Emilia Sordillo, M.D. - (St. Luke's - Roosevelt) Promoted to Associate Prof. of Clinical Medicine & Clinical Pathology & Cell Biology.

Joseph Schwartz, M.D., promoted to Associate Professor of Clinical Pathology & Cell Biology.

The Earthquake in Haiti

Many in the Department know that our own graduate student Roger Lefort lost both of his parents in the earthquake. Although the acute phase of the disaster has passed Haiti is still in need and we hope that the department's generosity continues. Roger's grandmother and other members of his family survived. Roger is a student of Michael Shelanski who is thankful to have Roger back and wishes to thank the Department for their support.

In Memoriam Alicia Cordon-Bouzan

The Department notes with sadness the passing of Alicia Cordon-Bouzan, a breast cancer survivor, to a rare lung disease on Oct 17, 2009. She was the wife of Carlos Cordon-Cardo, M.D., Ph.D., Vice Chairman of Pathology and Professor of Pathology and Urology. Mrs. Cordon-Bouzan is survived by her husband, her younger sister Cristina, and her children Carolina, age 16 and Daniel, age 9.

Mrs. Cordon-Bouzan served heroically in the service of many charities, including the Fresh Air Fund, The Administrative Board of the Society of Memorial Sloan-Kettering Cancer Center and the Sarcoma Foundation of America. She was a champion of those in need.

The Pathology Billing Staff



Back row, from left to right: Jose Nunez, Yamila Cason, Sherri Long, Laura Jeter, Wilbur Estrada, and Jose L. Corneille.
Front row: Darnella Harris, Estelsita Santiago, Melissa Carter, Neelwite Khan, Amell Solano, and Clarissa Cristian

Scientists and clinicians are absorbed in their immediate concerns and may not always realize that behind them is an administration that is dedicated to making their work possible – providing billing services, setting up accounts, attending to compliance and academic appointments, grants management, and dealing with the problems that arise when more than 300 people work together. Here, the Newsletter recognizes the efforts of some of our administrators.

A huge effort is required to ensure that we are properly compensated for the services we provide. We have a loyal staff of 13, led by Jose Corneille. This has been a tough year, with changes and new regulations in Medicare and Medicaid. Even private insurance is not a simple matter. The staff must contact primary and secondary insurers and sometimes bill the patient. The group has its own initiatives, one of which concentrates on reducing errors in the bill-

ing cycle, from patient registration to payment. Every day the staff negotiates with the hospital, with physicians and the public. Mr. Corneille is particularly proud of his team. Happily, our services and collections are keeping pace with inflation. We should note that faculty who have HIPAA privacy or billing compliance questions should contact Laura Jeter (*shown above*) at lj2184@columbia.edu.

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