COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

Volume 4, Issue 1 Spring 2011

From the Chair

The 9 months since the last newsletter have been challenging. We have had to plan for success in a world where reimbursement for medical care and government support for biomedical research have not increased and threaten to diminish. We have attempted to do this without layoffs. We have also attempted to provide bridge funding to investigators whose funding has decreased. Since the department does not have significant reserves and receives little philanthropic support, our only source for these funds is derived from the practice of pathology. The good news is that the bad news has not been as bad as we had predicted and that we have the luxury of breathing a bit easier and moving forward. I attribute this reprieve to the hard work of the clinical, academic, and administrative staff.

Many exciting things have happened over the year. We have opened our new accessioning area and started bar-code driven specimen tracking. The Immunogenetics Laboratory has moved to new modern laboratories on VC-15 and Molecular Diagnostics has been expanded on VC-15 as well. We have obtained our first "deep" sequencer, a Roche 454 GS Junior and installed in on P&S 14 under the direction of Peter Nagy. This expands the training possibilities in our newly accredited Molecular Genetic Pathology program headed by Mahesh Mansukhani. See articles in this Newsletter. Work is about to start on rebuilding PS 14-401 into modern Stem Cell research labs for Fiona Doetsch and Hynek Wichterle.

The Motor Neuron Center has joined the Department of Pathology and Cell Biology. Two of its members, Chris Henderson and Livio Pellizoni were already members of the Department, but we have now also gained Serge Przedborski, Umrao Monani, and George Mentis. The Motor Neuron Center is such an important addition that it will be covered thoroughly in a future Newsletter.

Two of our outstanding faculty members are moving on to new challenges. Shi Du Yan has assumed the Howard Mossberg

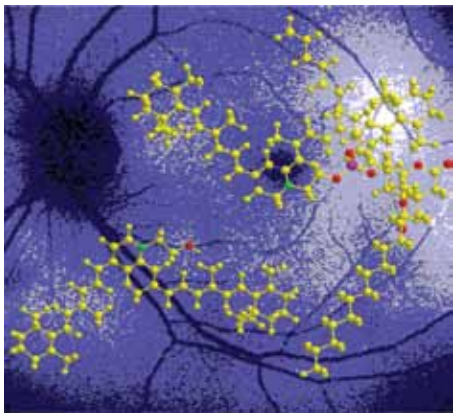
Continued on page 9

Well, we are a dogged lot. We just keep working. The Newsletter has been silent for a while, so we have more than the usual number of accomplishments to report and a number of congratulations to hand out. We have welcomed new classes of Residents and Fellows as well as a new class in our increasingly sought after Pathobiology and Molecular Medicine Ph.D program. Congratulations to Mahesh Mansukhani and his team for a new fellowship program in Molecular Genetic Pathology. Our grant applications are proceeding apace and the clinical side of Pathology and Cell Biology is working as hard as ever. On the administrative side our unsung (or not enough sung) staff is working hard to support our physicians and scientists and to keep our department productive and solvent. Our accession of samples is being streamlined and made much more efficient. There are almost 400 of us in Pathology and Cell Biology so we hope you learn something about what those other folks are doing.

Through Tough Times

ANATOMIC PATHOLOGY | CLINICAL PATHOLOGY | CELL AND MOLECULAR BIOLOGY

Why does the living retina glow? by Janet Sparrow, PhD



The natural autofluorescence of the retina originates from the bisretinoid compounds of retinal pigment epithelial lipofuscin. In the foreground of this artist's reconstruction are 3D structures of 2 of the bisretinoids, A2E and A2-DHP-PE.

The diagnosis of acquired and monogenic forms of retinal degeneration, including age-related macular degeneration (AMD) and some forms of retinitis pigmentosa, usually includes photographs of the retina obtained with a high energy blue 488 nm exciting light and confocal optics. The image obtained reveals an intrinsic retinal autofluorescence that is generated from the lipofuscin in retinal pigment epithelial (RPE) cells. In subjects with normal retinal status, fundus autofluorescence increases linearly with age, although there is individual variation.

While the lipofuscin of other non-dividing cells may originate from oxidative mechanisms, the lipofuscin of RPE cells is distinctive in that it is generated from random inadvertent reactions of vitamin A aldehyde (all-trans-retinal), the latter being produced upon photon absorption by the visual pigment chromophore 11-cis retinal. These bisretinoids form in the outer segments of the light absorbing photoreceptor cells; in a healthy retina they are kept to a minimum by daily shedding of packets of

Continued on page 2

COLUMBIA UNIVERSITY MEDICAL CENTER

In This Issue

Why does the living retina glow? *continued from page 1*

photoreceptor outer segment membrane. RPE cells ingest this membranous debris by phagocytosis. Consequently, the vitamin A aldehyde-adducts that will become the lipofuscin are deposited into the lysosomal compartment of the RPE where they appear to be refractory to enzyme degradation and thus accumulate with age.

Not surprisingly, given the relationship to the vitamin A chromophore of visual pigment, the formation of these bisretinoid lipofuscin fluorophores is light dependent. The efficiency with which the retinoid cycle replenishes the 11-cis chromophore of cone and rod visual pigment determines all-trans-retinal flux and thus is tightly coupled to the formation of lipofuscin bisretinoids. In addition, conditions that interfere with clearance of all-trans-retinal from the interior of outer segment discs result in accelerated formation of the bisretinoids. This is the case for some monogenic forms of retinal degeneration that have onset early in life and are associated with particularly enhanced fundus autofluorescence.

The bisretinoid composition of RPE lipofuscin is complex. Several of the constitutents have been identified and structurally characterized in the laboratory of Janet Sparrow. The best known of these compounds is A2E. The bisretinoids of lipofuscin (e.g. all-trans-retinal dimer, A2E) are also photoreactive compounds that upon photon absorbance generate singlet oxygen. Significantly, these bisretinoids then quench these reactive oxygen species, thereby becoming oxidized. By utilizing liquid chromatography coupled to electrospray ionization mass spectrometry together with tandem mass analysis, recent studies in the Sparrow laboratory have shown that bisretinoids of RPE lipofuscin undergo photocleavage at sites of singlet molecular oxygen addition to carbon-carbon double bonds. Among the mixture of aldehyde-bearing degradation products released is methylglyoxal, a low molecular weight reactive dicarbonyl with the capacity to form advanced glycation end (AGE) products. Methylglyoxal was previously known to be generated by carbohydrate and lipid oxidation; production from bisretinoid photocleavage is a previously unrecognized source. This reactive dicarbonyl can alter molecular structure and function by forming AGE-adducts with proteins. AGE-modification of proteins contributes to age-related inflammatory disease. Thus it is significant that AGE-modified proteins are detected in deposits called drusen that accumulate below RPE cells in vivo; drusen have been linked to AMD pathogenesis. These findings suggest an association between RPE lipofuscin photooxidation and drusen formation and are of additional interest given emerging genetic evidence of a role for complement dysregulation and inflammatory processes in AMD.

Kim SR, Jang Y, Sparrow JR. 2010. Photooxidation of RPE lipofuscin bisretinoids enhances fluorescence intensity. *Vision Res* 50:729-736.Wu Y, Yanase E, Feng X, Siegel

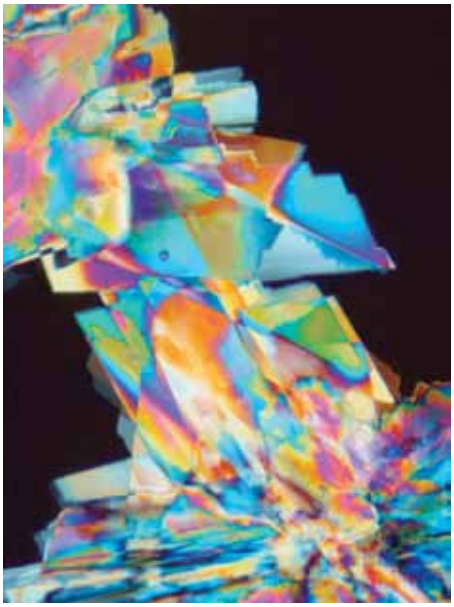
MM, Sparrow JR. 2010. Structural characterization of bisretinoid A2E photocleavage products and implications for age-related macular degeneration. *Proc Natl Acad Sci* 107:7275-7280

Our bridge at dusk

Promotions

Kurenai Tanji has been appointed the head of the Neuromuscular Pathology Service, replacing Dr. Arthur (Rusty) Hays, who is retiring. Dr. Tanji plans to expand the service and make it more broadly available.

The Art of Pathology



Cholesterol crystals from a bile duct aspirate under polarized light. The crystals are large, flat, rectangular or rhomboidal plates with notched corners and are positively birefringent. The presence of cholesterol crystals in bile is often associated with calculi – aka gall stones (x200).

Provided by John Crapanzano, MD, Associate Professor of Clinical Pathology

The Fatty Liver: An Expanding Problem

by Jay Lefkowitch, M.D.

A simple glance at the protuberant abdomens around you on the subway, or on the street makes it clear that we have become a nation of very large people. The WHO estimates that >1 billion adults worldwide are overweight, of whom 300 million are clinically obese (Body Mass Index >30 kg/m2). In the liver, obesity results in the accumulation of large vacuoles of excess triglyceride within hepatocytes, known as macrovesicular (large droplet) steatosis or, more simply, the fatty liver. Anatomic pathologists have long been familiar with the fatty liver because of its association with alcohol abuse, but obesity, diabetes and corticosteroid administration are other causes. Many obese individuals are also characterized as suffering from the metabolic syndrome if they have the combination of truncal obesity, type 2 diabetes mellitus, insulin resistance, dyslipidemia and hypertension. The entity known as NAFLD (nonalcoholic fatty liver disease) is considered the hepatic expression of metabolic syndrome. NAFLD encompasses not only macrovesicular steatosis, but also its major potential complications NASH (nonalcoholic steatohepatitis) and cirrhosis.

In the U.S., the most common cause of abnormal serum liver function tests for aminotransferases (AST and ALT, or aspartate aminotransferase and alanine aminotransferase), is fatty liver disease. For many individuals this type of abnormality is often first discovered on a routine blood test. Release of AST and ALT enzymes from hepatocytes occurs in the setting of macrovesicular steatosis because of oxidative stress on hepatocytes which results in lipid peroxidation, hepatocyte apoptosis, and the potential engagement of a host of inflammatory cells which produce damaging cytokines. What was for many decades thought to be only "simple" steatosis—with a benign clinical and pathologic outlook– may, in fact, over the long term be detrimental to the liver. In 1980, a landmark study by the chief liver pathologist of the Mayo Clinic, Jurgen Ludwig and colleagues, described alcoholic hepatitis-like changes in obese and/or diabetic subjects and coined the term NASH[1]. The possibility that obesity could result in

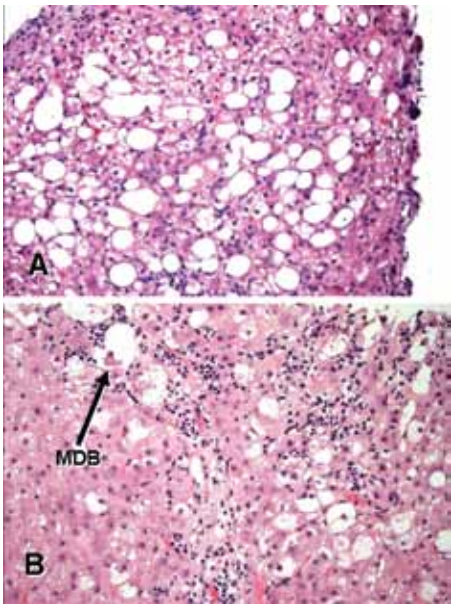


Figure 1 *Macrovesicular steatosis and steatohepatitis. A: Large droplet fat vacuoles are present in hepatocytes in this obese subject. B: The centrilobular region in a subject with NASH shows hepatocyte ballooning, intracellular Mallory-Denk bodies (MDB)— formerly known simply as "Mallory bodies", and moderate inflammation. (A&B: H&E stain).*

significant hepatic inflammation and fibrosis was thereby put on the map, and now 30 years later NAFLD and NASH have become a focus of clinical, epidemiologic, histopathologic and basic science investigations around the world. A practical corollary in anatomic pathology is that we are now seeing many more routine diagnostic liver specimens that show evidence of NAFLD and NASH.

What is the actual scope of the problem in the U.S.? A major recent publication by Williams and colleagues[2] assessed the prevalence of NAFLD and NASH (using ultrasound and liver biopsy) in 328 predominantly middle-aged adults recruited from the Brooke Army Medical Center. They found a prevalence of NAFLD of 46%, with NASH in 40 patients (12.2%). These statistics confirm and further emphasize older studies with similar data; NAFLD and NASH are significant clinicopathologic problems that are not going away any time soon. We currently understand the histologic spectrum of NAFLD and its sequelae[3] to be: macrovesicular steatosis→steatohepatitis→cirrhosis (Figs. 1 and 2), though this is not an obligatory pathway in all subjects with fatty livers. Unfortunately, hepatocellular carcinoma (HCC) may be the last port of call of this progression, though in a small number of individuals. NAFLD and

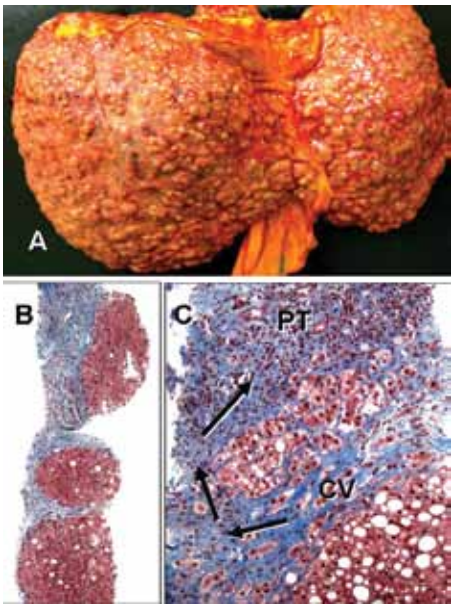


Figure 2 *Cirrhosis following NASH. A: Micronodular cirrhosis has developed, with regenerative nodules generally < 3 mm diameter surrounded by extensive grey fibrous scar tissue. B: Needle liver biopsy showing circumscribed fibrosis (blue) surrounding cirrhotic nodules with scattered fat vacuoles (Trichrome stain). C: Fibrosis in NASH predominates in centrilobular regions (CV) where activated perisinusoidal stellate cells produce a pericellular "chicken-wire" pattern of fibrosis. Progression to cirrhosis proceeds by bridging of fibrosis toward portal tracts (PT) as shown by the arrows. (Trichrome stain).*

NASH appear to also have a specific impact on the morphology of HCC. We recently described a histologic variant of HCC that we termed the "steatohepatitic-HCC" (SH-HCC) which recapitulates in the tumor most of the features seen in non-neoplastic NASH . Our study, led by senior pathology resident Dr. Marcela Salomao, found that the majority of the cirrhotic hepatitis C virus positive patients who had developed the SH-HCC variant tumors had risk factors for NAFLD and NASH. For more news on the fatty liver story, stay tuned!

References

1. Ludwig J, Viggiano TR, McGill DB, Oh BT. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto un-named disease. *Mayo Clin Proc* 1980; 55: 434-438.
2. Williams CD, Stengel J, ASike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology* 2011; 140: 124-131.
3. Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. *World J Gastroenterol* 2010; 16: 5286-5296.

Advances in Administration!

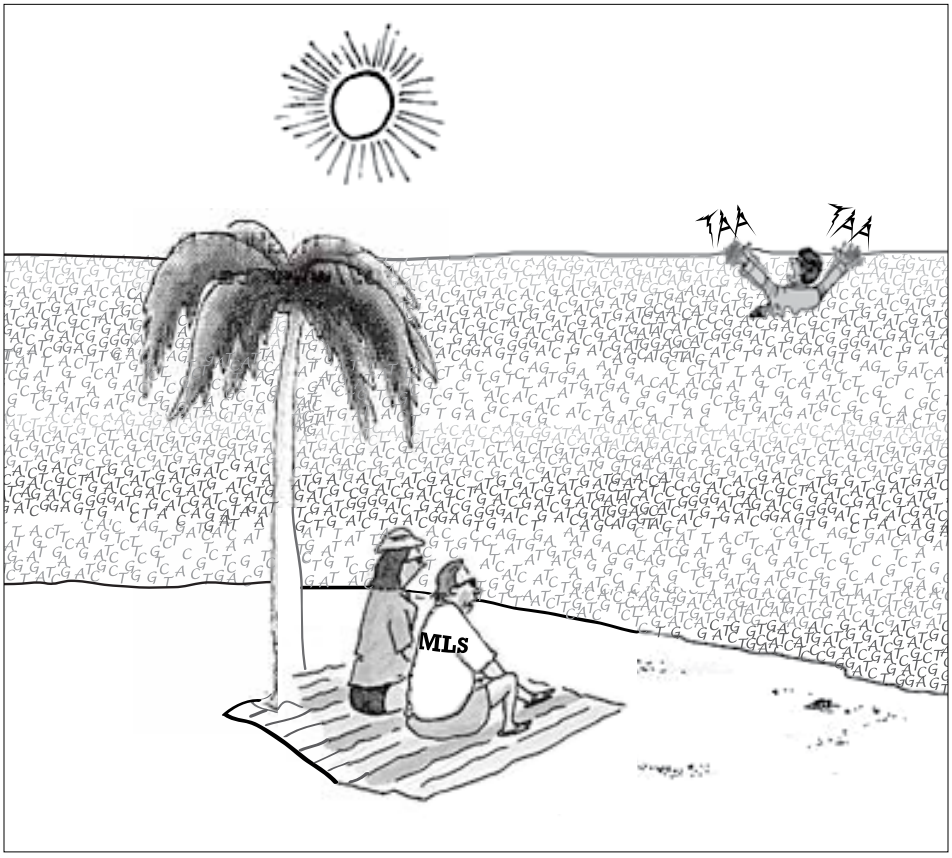
Edward Kritchevski, Emily Herzfeld, Michael Shelanski, Michelle Rosado, and Carl Reyes

The Department has successfully analyzed millions of samples, but the process by which we accept specimens is being extensively revised. First, there is to be a central accessioning facility in what used to be the back of Humphreys Auditorium (you could not hear back there anyway). The new facility is being built to house a centralized core facility for all clinical AP specimens. Until now, molecular, renal, muscle, neurogenetic, gynecological specimens and material for second opinion consults were all received or accessioned at different locations. It is inefficient and increases the possibility for error or delay.

In addition to a new central facility, we will begin bar-coding all samples. The process is called AB&T for (absolute bar-coding & tracking). All articles of histology and pathology work- flow will be tagged to insure the integrity of patient/specimen identity throughout the entire process. This is a primary patient safety measure that is soon to become a regulatory requirement. AB&T will also improve specimen tracking, productivity measurement, labeling, and retrieval of archival material.

The implementation of AB&T is a complex process that involves re-building the entire co-path infrastructure to support tracking/default printing. A lot of equipment needed to be installed; scanners, PCs and label printers. Perhaps more difficult – but of great importance - is that the implementation of AB&T will require a fundamental change in the workflow and lab "culture". Many people are participating, including Emily Herzfeld, Brent Powers, Michelle Rosado, and Edward Kritchevski.

Lost in The Sea of Data



Mahesh, I said, leave the data at home. But noooo...

Mr. Anthony Barrueco

Tony celebrates his twentieth year in the department. He is a source of constant good cheer. He can fix anything and has a superb knowledge of the New York Yankees.

Copenhagen *(the play)* comes to Pathology and Cell Biology *(no kidding)*

Ben Hopkins is a Ph.D student with Prof. Ramon Parsons, but before he came to graduate school, he was a divinity student at Yale, where he worked on problems of bioethics. When it came time to take the Responsible Conduct of Research course that every graduate student must take, Ben pleaded, on the basis of his divinity degree, that he should be excused. The course director, Dr. Richard Kessin said OK, but extracted a price. Ben would have to teach a small group session (required by the NIH) the following year, which is to say, last March.

Ben decided that the best discussion of scientific responsibility was the play Copenhagen by Michael Frayn. So we read the play - out loud – in the Pathology library. This is the story of a visit by Werner Heisenberg (then working for the Nazis) to his mentor, Niels Bohr, in the occupied Copenhagen of 1941. The readings were enthusiastic – as was the discussion. Ben provided the metaphysical background – a far cry from the standard science paper, but a relief, too. Heisenberg, the students pointed out, never seriously attempted a nuclear bomb, a fact not known in 1941. Bohr helped the American effort. Perhaps, some suggested, Bohr bore the greater responsibility for nuclear weapons. This thought prompted a discussion of the world situation in 1941. There were four serious, but entertaining hours. Ben will do it again this year.

Clinical Pathology

Ipsilateral spread or independent primaries?

by Mahesh Mansukhani, MD

A 59 year old woman, a former smoker with a 20 pack-year smoking history, presented with a 1.6 cm lung nodule with multiple ground glass opacities. Biopsy of large nodule showed an adenocarcinoma, and she underwent surgery, which showed two histologically adenocarcinomas in the lower lobe, one measuring 1.9 cm in greatest dimension and the other, 0.4 cm. In addition, there were multiple foci of atypical adenomatous hyperplasia.

KRAS mutation testing of the two tumors showed an Arginine to Valine change at codon 12 in one, and Arginine to Cysteine in codon 12 in the other. Both tumors were negative for EGFR exon 18-21 mutations and for ALK rearrangement. Real-time PCR amplification plots of the two tumors showed they were different.

Why is this important?

(both for this patient and for evaluating outcome in groups of patients?).

When a patient has two separate primary tumors in an organ, then the tumor with the highest stage determines the patient's prognosis. On the other hand, when two nodules of a tumor represent tumor spread within the organ, then the patient may be considered to have a higher stage tumor with a poorer prognosis. In this patient's case, proving that the patient has two separate tumors, the result means that this is a "T1" tumor and, in the absence of lymph node involvement or distant metasasis, her stage is "IA".

KRAS mutation is generally an early event in lung carcinogenesis, occurring at a higher rate in atypical adenomatous hyperplasia, a precursor of adenocarcinomas, than in adenocarcinomas themselves. Therefore, this is strong evidence that, in the case the patient has two independent primaries, rather than spread within the same lobe, means she has two T1 tumors, and because she did not have cancer spread to lymph nodes or elsewhere, hers is a stage 1A cancer. If the nodules were to represent the spread of the same tumor within the lobe then her tumor would be classified as T3 with clinical stage IIB .

Is this significant or just an academic issue?

Patients with stage I disease have a 60 to 80% five year survival rate; this declines to 40-50% for those with stage II disease. For patients with completely resected stage IA disease, there is no benefit from postoperative chemotherapy, whereas stage II patients seem to benefit from postoperative cisplatin-based adjuvant therapy.

Recognition that patients whose stage has been determined by the presence of a satellite nodule has resulted in lowering the T-stage designation of satellite nodules (From T4 to T3 for spread within the same lobe, and from M1 to T4 for spread within a different lobe on the same side; spread to the opposite site is still considered a metastasis). However, this does not address the issue of heterogeneity of "satellite nodules" when histological criteria alone are used. Some "satellite nodules" may represent true spread and others, two separate primary tumors with identical histology. This case illustrates that. Unfortunately, this only works when both tumors have different mutations, or one tumor has a mutation and the other not. Because only 20-30% of tumors have a KRAS mutation, the question of one or two primaries cannot be answered in most cases. There is a need for a more "global" analysis of the genomic changes of tumors to develop a "signature" of each individual tumor. Recent studies have shown that most tumors have many different mutations just because of genomic instability, with only a few mutations shared among different tumors. So in the future we should expect "whole genome" approaches to characterize individual tumors – not only for staging, but also to differentiate recurrences or metastases from new primaries, and to choose tailored treatment for individual patients. This is the future and the Department will be ready for it – our new fellowship program in Molecular Genetic Pathology is described elsewhere in these pages.

This case highlights the synergy between the different divisions in the Department. Anatomic and clinical pathology. The testing and applications highlighted in this article were made possible by ideas and organizational help from Dr. Alain Borczuk.

New Fellowship Program

A New Molecular Genetic Pathology Program approved by American Council of Graduate Medical Education

Nike Beaubier

The Newsletter is pleased to announce a new one year program focused on training of fellows with a background in either pathology or clinical genetics in diagnostic molecular pathology. The new fellowship program will be directed by Dr. Mahesh Mansukhani. With rotations in the main molecular pathology laboratory, the neurogenetics laboratory, clinical genetics (including genetic counseling), molecular microbiology, immunogenetics and molecular cytogenetics, the program will feature a thorough experience in the application of molecular methods to the management of genetic disease, infectious diseases, and cancer. Fellows with a pathology background will focus on clinical genetics and genetic counseling by attending pediatric and adult clinics that manage heritable disease, whereas fellows with a genetics background will gain experience in anatomic pathology through participation in hematopathology, autopsy and surgical pathology conferences, as well as review of cases tested in the lab. All fellows will participate in quality assurance, quality management and other administrative activities, and will also complete internal validation of a laboratory developed assay, from assay design through submission for NY State approval. Fellows will also participate in research programs under one of the many faculty members in the program. The first fellow, Nike Beaubier, starts on July 1.

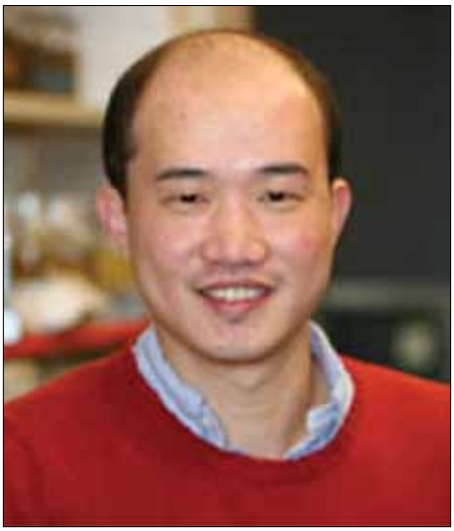
New Faculty

The Institute for Cancer Genetics

Ken Olive

The Olive laboratory performs preclinical therapeutics trials using genetically engineered mouse models of pancreatic cancer, a disease that claims over 35,000 people annually in the US. The core of our laboratory is based on a preclinical trials infrastructure called the "Mouse Hospital". This effort seeks to treat mice with pancreatic cancer in exactly the manner that human patients are treated. Tumor volumes are tracked and quantified using advanced small animal imaging technologies such as high resolution ultrasound and optical imaging, and mice are enrolled into randomized therapeutics trials. Pharmacokinetic and pharmacodynamic analyses, functional imaging, microscopy, biochemistry and molecular biology techniques are employed to assess drug mechanisms and understand relevant signaling pathways. Ultimately, successful therapies will be translated into the clinical setting through our collaborations with the Pancreas Center of Columbia University.

The next issue of
The Newsletter will profile new
Intitute of Cancer Genetics
and Pathology and Cell Biology
faculty member Shan Zha.



Bin Zheng

Our laboratory is deciphering the mechanisms of metabolic signaling in cancer, with special emphasis on melanoma, and translating these basic findings into potential personalized targeted therapies. The focus of our current research is on the LKB1-AMPK signaling pathway, which couples energy metabolism to cell growth, proliferation and survival. AMPK (AMP-activated protein kinase) is a Ser/Thr protein kinase that serves as a cellular energy sensor. The activity of AMPK is regulated by the AMP/ATP ratio and by upstream activating kinases, including the tumor suppressor LKB1. Metformin, one of the most prescribed drugs for treating type II diabetes, targets the LKB1-AMPK pathway and is being evaluated for the treatment of cancer in clinical trials. Understanding the complex LKB1-AMPK signaling circuitries underlying tumorigenesis will contribute to the development of effective therapeutic strategies.

The LKB1-AMPK pathway serves as an "energy brake" to suppress cell growth and proliferation under energy stress conditions. Cancer cells need to inactivate this pathway in order to gain a growth advantage over normal cells. We are studying various mechanisms by which the LKB1-AMPK "energy brake" is "overridden" in cancer.

New Grants

Peter Canoll and Steven Rosenfeld
Myosin II and Glioma Dispersion
NIH

Gilbert Di Paolo
Lipid imbalance and endosomal dysfunction in Down Syndrome - A lipidomic approach
Foundation Jerome Lejune – France

Lloyd Greene
1. The role of TRIB3 in neuronal apoptosis caused by NGF deprivation
National Institute On Aging
2. Mechanisms of dopamine neuron degeneration
National Institute of Neurological Disorders and Stroke

Christopher Henderson
1. Columbia Sma Project: Role Of Mmp-9 In Motor Neuron Susceptibility To "Sma"
Department of Defense
2. Collaborative Effort in Stem Cell Biology
Helmsley Foundation

Eldad Hod
Mechanisms underlying the harmful effects of stored red blood cell transfusions
National Heart, Lung, & Blood Institute

Tae-Wan Kim
1. Dissecting The Role Of Pi3k Family Members In A Biogenesis
Alzheimer's Association
2. Validation of a novel lipid phosphatase target in Alzheimer's Disease
NIH

Livio Pellizzoni
1.Columbia Sma Project: Role Of Mmp-9 In Motor Neuron Susceptibility To "Sma"
Department of Defense
2. A Functional Cell-Based Screen for Potential SMA Therapeutic Compounds
National Institute of Neurological Disorders and Stroke

Liza Pon
1. Mitochondrial Localization And Aging
Ellison Medical Foundation

Michael Shelanski
Dendritic Spine Alterations in HD Models
CHDI Foundation

Richard Vallee
Mechanism Of Action Of The Lissencephaly Gene Lis1
National Institute of Child Health & Human Development

The list does not include awards to faculty members in The Institute of Cancer Genetics

Honors and Awards

Brynn Levy has been appointed to an FDA panel that is charged with creating "standards for manufacturers seeking to bring assays for approval," and to ensure that array-based cytogenetic tests are "safe and effective".

Eldad Hod won the Fenwal award again this year (probably the only person winning twice in a row) and he will be presenting his paper at the American Association of Blood Banking meeting. *(See the last Newsletter for research details.)*

Ottavio Arancio has been featured discussing Alzheimer disease at BigThink.com. This is a series of illuminating discussions carried out by a prominent think tank. Ottavio has also been awarded the Edward N. and Della L. Thome Memorial Foundation Award. The Foundation was created in 2002 to advance the health of older adults through the support of direct service projects and medical research on diseases and disorders affecting older adults. In particular, this award funds Alzheimer's Disease Drug Discovery Research.

Riccardo Dalla-Favera has been elected to the Institute of Medicine of the National Academy of Sciences.

Shan Zha, MD, PhD, assistant professor of pathology & cell biology and pediatrics in the Institute for Cancer Genetics, has received a three-year scholar grant from the St. Baldrick's Foundation. The funding will help him continue research to understand the role of DNA repair in childhood leukemias.

Patrice Spitalnik received the outstanding teacher of the year award in a small group setting from the class of 2013. She was honored for her direction of the histology section of the basic science component and her enthusiastic and comprehensive presentations in the histology and pathology components of the basic science curriculum.

Jay Lefkowitch received the outstanding teacher of the year award in a small group setting from the class of 2013. He was recognized specifically for his well organized and beautifully illustrated pathology lab sections of the basic science curriculum and for the legendary Man in the Pan autopsy conferences.

Paulette Bernd has been named a distinguished lecturer of the year by the Class of 2013. This follows an equally impressive recognition last year.

Richard Kessin has become the Science Columnist for two good newspapers in northern Connecticut - The Lakeville Journal and the Winsted Journal. The column, called The Body Scientific, alternates between gee-whiz science and controversial science issues. It promotes evolution, vaccines, animal research, and other elements of the rational world. With nearly 10,000 potential readers, it is distressing that in one week he can reach more readers than ever read his scientific papers. On the other hand, there are no reviewers. He thanks his colleagues in the department for their helpful consultations.

Gloria Su was awarded with the AACR-Pancreatic Cancer Action Network Innovator Grant $200,000 total over 2 years. Drs. Jan Kitajewski and Carrie Shawber are co-PIs. Gloria also been serving as an Ad Hoc reviewer on the NCI Tumor Progression and Metastasis Study Section.

Anthony Sireci has been named the recipient of the Advanced Training Grant in General Elective sponsored by CAP Foundation.

Alcmene Chalazonitis has been asked to serve as a member of the Professional Development Committee and Committee on Women-in Neuroscience of the Society For Neuroscience. She also serves on the Scientific Achievement Awards committee.

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

Our Residents

The Residency Programs By Anthony N. Sireci, MD

The start of this academic year in July of 2010 saw the introduction of an impressive group of 6 new physicians to the residency training program in anatomic and clinical pathology and one dentist to the training program in anatomic and oral pathology. By way of introduction, we'll start with Shana Coley MD, PhD , our new AP-only resident who will complete 3 years of training in anatomic pathology. She comes to us from Emory University, having completed a PhD on the role of interferon-gamma in allotransplantation. There are four new AP/CP residents who will spend four years on microscopy and assay validation. In alphabetical order, the first is Susan Hsiao, MD, PhD, who hails from NYU and completed a PhD on role of telomeic proteins in genomic stability. Jennifer Oliver-Krasinski, MD, PhD, is from Penn and her PhD is on the role of pdx in prancreatic development. Elizabeth (Beth) McMillen, MD, is a graduate of the Humanities and Medicine Program at Mount Sinai School of Medicine and completed research projects in medical school on hepatocellular carcinoma and non-small cell lung cancer. Last but not least is James Mitchell, MD, a graduate of the University of Texas Medical Branch SOM. He has an undergraduate background in Chemistry and Mathematics from Austin. Our new AP/NP resident is Markus Siegelin, MD, who will complete 2 years of AP training before entering a fellowship in neuropathology. He graduated from the Johann-Wolfgang-Goethe-Universitat in Frankfurt, Germany and comes to us with previous research in new therapeutic targets in glioblastoma funded by the German Research Foundation at the University of Massachusetts. The department's new AP/OP (oral pathology) resident is Eugene Kim, DDS. He is a native to Columbia, having completed dental school here. He will compete 1.5 years of general AP training before moving on to specialized training in oral pathology. Please offer a warm welcome to the new residents if/when you see them in the halls.

The interview season is in full-swing and the program has seen a large number of very talented, high-quality and impressive applicants. We look forward to welcoming the new residents in July 2011.

We'd like to congratulate Shana Coley on her recent marriage in October, 2010 and wish her the best of luck!

Shana M. Coley, MD, PhD

MD: Emory University School of Medicine
PhD: Emory University. Immunology and Molecular Pathogenesis (thesis on Interferon-gamma and allotransplantation). President, Emory MD/PhD Student Organization.
BS: Auburn University, Microbiology, summa cum laude, National Honor Society, Phi Kappa Phi, Outstanding Student Award for Science and Math.

Elizabeth M. McMillen, MD

MD: Mount Sinai School of Medicine; Humanities and Medicine Program. (research: Scutellaria baicalensis effect on hepatocellular carcinoma cells; EGFR mutations and P-EGER expression in non-small cell lung cancer; medical school peer tutoring training curricula.)
BA: Harvard University, Classical Archaeology, magna cum laude, Vermeule Prize for excellence in Archaeological Scholarship, John Harvard Scholar, Hoopes Prize for senior thesis.

Susan J. Hsiao, MD, PhD

MD: New York University School of Medicine
PhD: New York University School of Medicine. Pathology (thesis on role of telomeric proteins tankyrase 1 and 2 in genomic stability)
BS: Cornell University, Biology, magna cum laude, Ho-Num-De-Kah Honor Society, Golden Key International Honor Society.

Markus D. Siegelin, MD

MD: Johann-Wolfgang-Goethe-Universitat, Frankfurt, Germany, summa cum laude, Rudi-Busse award for best MD thesis (cerebral ischemia)
Prior residency: Neuropathology (2 years). Ruprecht-Karls-University Heidelberg, Heidelberg, Germany. Young Investigator Award (glioblastoma research exploiting new therapeutic targets).
Current research funded by German Research Foundation (DFG) at University of Massachusetts, Department of Cancer Biology.

James M. Mitchell, MD

MD: University of Texas Medical Branch School of Medicine. Tutor in academic courses and medical Spanish; student representative to AAMC.
BA: Austin College, Sherman, Texas, Chemistry and Mathematics with minor in Asian Studies, magna cum laude, Phi Beta Kappa, Austin College Distinguished Achievement Scholarship, McKinney Education Foundation Achievement Scholarship

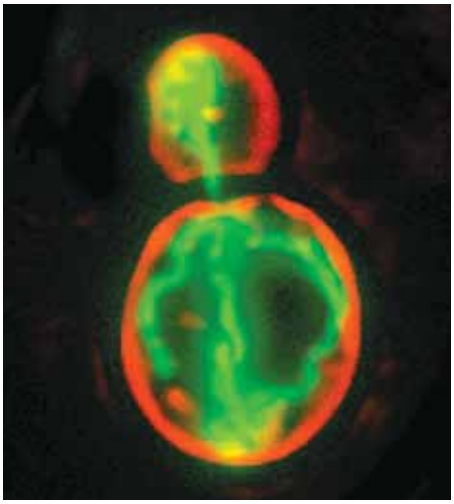
Jennifer M. Oliver-Krasinski, MD, PhD

MD: University of Pennsylvania School of Medicine. NIH-National Research Service Award. Boricua Latino Health Organization.
PhD: University of Pennsylvania School of Medicine, Institute of Diabetes Obesity and Metabolism (thesis on the role of pancreatic duodenal homeobox 1 (Pdx1) in the differentiation of pancreatic endocrine progenitor cells). Dept. Medicine Holmes Bench Research Award, Penn's single nominee to national Council of Graduate Schools dissertation award.
AB: Princeton University, Molecular Biology.

Eileen Erceg Retires after 42 Years

Well, 42 years is a long time but at that time our Eileen was a nun at the Missionary Sisters of the Sacred Heart. After deciding that teaching was not her future, Eileen was released from her Order by the Archbishop of Newark and she went to business school for a year. After a year at the Drake School of Business she came to Pathology thanks to the then Chair, Donald West King. She went through a number of administrative positions including executive secretary for Conrad Pirani in Renal Pathology. She finished her career as the Administrative Manager for Academic Appointments and Personnel. If your appointment went through and all the papers were in order and your check arrived – then you have Eileen to thank.

The Art of Cell Biology



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

Our Predecessors

Alonzo Clark and the Beginnings of American Pathology

The Newsletter staff is tracing the history of our department through its Chairs.

The first of these, as far as we can tell, was Alonzo Clark who took his degree from P&S in 1835, and then did the obligatory tour of Europe, particularly France and Germany. He learned percussion, the use of the microscope, and the stethoscope. In New York, at Bellevue, he confirmed these principles. American medicine in those days – with occasional exceptions – was not a vibrant enterprise and so it is not surprising that Dr. Clark, though the head of Pathology at P&S, published little. His claim to fame was not to invent new therapies, but to discontinue the useless inheritances of the past. For peritonitis he stopped bleeding and giving mercurials, then an almost universal treatment. He substituted opium.

Alonzo Clark taught physiology and pathology at the College of Physicians and Surgeons (1848-55). He held the Chair of Practice (in Pathology from 1855-1885 and from 1875 and until 1885 was simultaneously Dean of P&S.

There are records in the archives that he lent the medical school money and founded a scholarship-the first recipient of which was T. Mitchell Prudden. Dr. Prudden played an enormous role in introducing bacteriology and vaccines to New York and was also a Chair of our department. He was memorialized in a previous Newsletter (available at http://pathology.columbia.edu/)

Like most P&S physicians of the day, Dr Clark was a patrician New Englander. Dr. Clark was fond of aphorisms, *some* of which still make sense:

'The medical errors of one century constitute the popular faith of the next. "

"Every man 's disease is his personal property."

"You may know the intractability of a disease by its long list of remedies. "

"Symptoms which cannot be readily marshalled into line must be credited to the nerves."

'"There is no courtesy in science. "

From a Memoir to the New York Academy of Medicine 1925. Thanks to JoAnn Li for compiling the geneology of Pathology Chairs.

Chairman's Letter

Continued from page 1

Distinguished Professorship at the University of Kansas Medical Center. Shi Du was an important part of our Alzheimer's disease research program in the department and in the Taub Institute. Dr. Carlos Cordon-Cardo, Vice-Chairman for Translational Research will move to Mt. Sinai School of Medicine as Chairman of the Department of Pathology. Carlos has made many excellent contributions to the department over his years at Columbia. On behalf of the entire Department of Pathology and Cell Biology, I wish both Shi Du and Carlos many years of continued success and thank them for their contributions to our department.

In the coming year I intend to focus on the issue of career development for our junior faculty both on the clinical and on the research side. I have asked several of the senior faculty to join me in this effort and hope that it can clarify the expectations that we have of our Assistant Professors and the goals that they need to reach for promotion.

High throughput sequencing in clinical diagnosis
Peter Nagy, MD, PhD

The normally sane Dr. Nagy finishing the marathon.

Most familial diseases and syndromes are genetically heterogeneous and can result from mutations at multiple genetic loci. ALS, muscular dystrophies, cardiomyopathies, cardiac arrhythmias, mitochondrial disorders, metabolic syndromes and retinopathies are a few examples in which many genes must be rapidly sequenced in order to reach a diagnosis. The Sanger method, brilliant as it is, is slow and becomes prohibitively expensive as the number of genes to sequence increases. Currently available high throughput sequencing technologies make sequencing 10-40 genes in several patients simultaneously both technically feasible and financially viable. They also allow identification of rare mutations that arise in viral genomes during infection and determine responsiveness to specific drugs, as shown for HIV. We want to exploit the potential of this novel sequencing technology both for the purposes of clinical diagnosis and translational research and lay the foundation for the leadership of our department in the area of medical genetics in this new era of personalized medicine.

We have recently purchased a 454JR pyrosequencer machine capable of providing 40 Megabase of sequence in a single run. This is roughly the equivalent to the entire coding sequence of the human genome. This power will allow us to sequence the coding region of up to hundred genes at ten to fifty fold coverage or the mitochondrial genome at several thousand–fold coverage. The genic regions of interest will be selected using hybridization based technologies from Nimblegen. We expect that using this approach we will be able to provide fast reliable genetic diagnosis to patients who suffer from familial/genetic disorders from blood samples, obviating the need for surgical procedures and general anesthesia. We will initially focus our efforts in the area of neuromuscular disorders to support our clinical colleagues working towards the creation of a Neurogenetics Clinic at Columbia. However, once the methodology becomes routine, we hope to expand into all areas of genetic disease, including cancer.

The high throughput sequencing laboratory will be part of the Molecular Genetic Pathology Laboratory under the direction of Dr. Mansukhani and technical supervision of Dr. Nagy on the 15th floor of the Vanderbilt Clinic. We look forward to providing research training opportunities to all residents and fellows interested in genetic molecular pathology. To that end, Dr. Mansukhani will direct a new fellowship program in molecular diagnostics.

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/

Anniversaries

This is the Newsletter's tribute to perseverance and longevity: The winners are **Phil Brandt** and **Reba Mirsky Goodman** who have been here for (count 'em) fifty years each. See Phil's comments elsewhere in the Newsletter. **Michael Gershon** has been at Columbia for 35 years, although his service should probably be measured in brilliant lectures given to medical and dental students. It is a large, large number. **Aurica Foca-Rodi, Jay Lefkowitch**, and **Chuck Marboe** have achieved the thirty year mark. **Jeanette Rodriguez** has 25 years. **Edna Velez, Milagros Castillo, Ellen Greenbaum**, and **Mathias Szabocs** have survived 20 years. So have **Joann Li**, who came shortly after adolescence, **Liza Pon, Tony** *(what would we do without him)* **Barrueco**, and **Josefa Salcedo**. Actually, I think my list is a year old, so some of you may want to award yourselves an extra year. Feel free. In any case, the Department is grateful to you all.

The Art of Pathology

Immunohistochemical stain for gastrin of a gastric antral biopsy shows normal gastrin-producing endocrine cells (G cells) in the neck glands which are located at the interphase of foveolae (surface) and pyloric glands (deep).
Courtesy of Dr. Heidrun Rotterdam

In Memoriam
Dr. Herman Yee

The Department of Pathology notes with sorrow the passing of Dr. Herman Yee, Associate Professor of Pathology at New York University Medical Center (also Director of the Immunohistochemistry and Flow Cytometry Laboratories at Bellevue and incumbent to Chief of Service at Lincoln Hospital) on November 9, 2010. Herman is very fondly remembered from his Columbia Pathology residency days (and later) for his ebulliently sunny disposition and many accomplishments in Hematopathology. He will be greatly missed.

Dr. Yee was born 1959 in El Paso, Texas. In 1981 he completed his undergraduate degree in Chemistry at the University of Southern California, from which he also received his Ph.D. in Physical Chemistry in 1988. In 1990 he received his Doctor of Medicine and Master of Surgery from McGill University in Montreal. Following postdoctoral training in Anatomic Pathology at Columbia University Medical Center and in Hematopathology with Dr. Giorgio Inghirami at NYU School of Medicine, he joined the NYU Department of Pathology in 1996. He was scheduled to begin his tenure as Chief of Service at Lincoln Hospital in November 2010.

A message to us from Herman's wife, Ann Elizabeth Doniguian, MD (also a pathologist) said: "he loved his time as a resident at Columbia. When he became an Attending, he loved teaching, and really enjoyed helping medical students and residents. He was famous at NYU for his frozen section cutting abilities. He loved to keep things fun, and to find the humor in things. He also kept a wide range of interests, without the super narrow enclosed focus that we sometimes see today. I recently saw an article about convergence, and how fields of interest need to be wider in order to leave opportunity for the serendipitous finding. That is how he was all the time." Dr. Yee is survived by his wife Ann Elizabeth, their daughter Lily, his parents and a brother and sister.

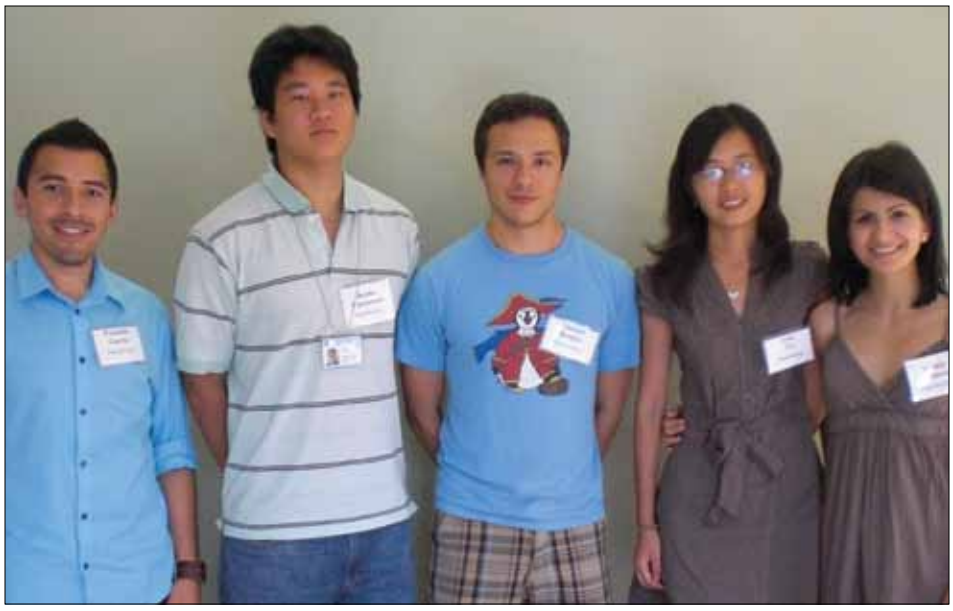
A memorial service to commemorate the life and work of Dr. Yee will be held on Wednesday, March 23, 2011, 4:30 p.m.-6:30 p.m. in the MSB Faculty Dining Room at NYU.

Joan Witkin Retires

Dr. Joan Witkin has retired from years of research and an important role in teaching histology and neuroscience to medical and dental students. Joan received her BA and MA in zoology from Mt. Holyoke College and her PhD in anthropology from Columbia. For many years she worked with Prof. Ann-Judith Silverman on the development, connectivity and plasticity of the Gonadotropin releasing hormone (GnRH) system. In 2004, Dr. Witkin won the coveted Balmfolk Award for teaching excellence. Earlier she and Glenda Garvey had won similar teaching awards from the College of Dental Medicine. Joan, characteristically modest, was most proud of being associated with the legendary Dr. Garvey.

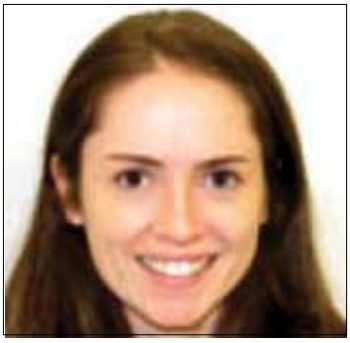
Thoughts of Spring

The Pathobiology and Molecular Medicine PhD students



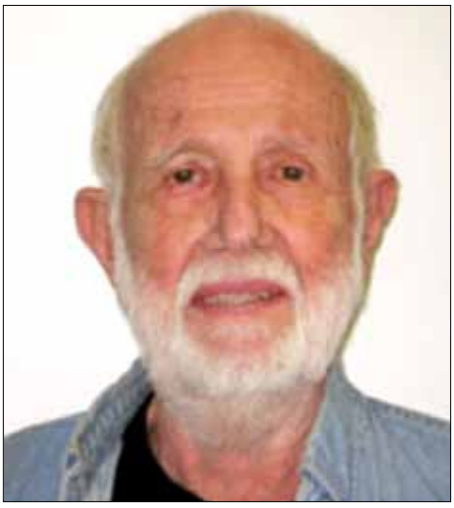
From left to right: Franklin Garcia, Kenta Yamamoto, Michael Badgley, Yang Ou and Gannie Tzoneva. Franklin comes to us from UC Irvine, Kenta from Brandeis, Michael from Harvard via the NIH, Yang from Beijing and Gannie from the University of Capetown.

The Pathobiology and Molecular Medicine Program and its offshoot, The Grad to Med program, which allows students to take clinically oriented courses, are doing exceptionally well. This year's students are enjoying their rather demanding classes. Applications for next year's class are up and the quality of the applicants is astonishing.



Kimberly Robinson and Kelly McGrath are MD/PhD students who have joined the Pathobiology and Molecular Medicine PhD program for their research years.

A note from Gross Anatomy staff member Professor Phil Brandt



Phil writes: *Last year I asked Jay Lefkowitch to take samples of the pathology we encounter in the Gross anatomy lab and to diagnose it. He was happy to do it. After analysis, we told the students what kind of tumor the body had. For the first time in my 50 years of teaching we learned the true diagnosis. In the past we just guessed or said we didn't know. That to me is wonderful. I want to note how integration of the Anatomy and Pathology Departments has improved teaching.*

The Newsletter salutes Phil's 50 years of teaching, research and general dedication!

COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

Volume 4, Issue 1
Spring 2011

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

If you have comments or questions, contact:
Dr. Richard H. Kessin
at 212.305.5653
Email: rhk2@columbia.edu