

From the Chairman



Since the last issue we have seen convulsions in the global economy and survived a Presidential election. By the time you read this I will have been able to get back to work after checking the poll results on an hourly basis. Since I am not the only one in the department who has been gripped by the election, I expect our productivity will increase by 50% in the months to come. In this issue we will update you on activities in Anatomic Pathology, Cell Biology, and in Microbiology. In Anatomic Pathology, Mahesh Mansukhani describes how microRNAs, only recently discovered, have become a new diagnostic tool. The malaria case presented by Susan Whittier will provide a segue into our nascent international presence in Gondar, Ethiopia with an article and pictures by Chuck Marboe. These were taken on the recent Alobeid-Marboe expedition to teach in Gondar. We hope to expand this relationship and invite residents, fellows and faculty who would be interested in taking part to get in touch with Chuck. The trip is long and the conditions far from opulent, but as they say in the Guide Michelin, the people and the culture of Ethiopia are “vaux le voyage”.

On the education front, Steve Spitalnik and Ron Liem will describe the new graduate course on the Pathology of Disease that has been a smashing success with 25 students enrolled. There has been a new alignment

We are pleased to send the third issue of the Columbia Pathology and Cell Biology Report. In this issue we continue with the amazing inroads of modern molecular analysis into diagnosis of subtly different forms of lung cancer. We also describe the astonishing abilities of our microbiologists and of a cell biologist whose work has not reached the clinic – yet. Readers will learn about our revamped Ph.D program and its new course and new students. Did you know that our people are helping in Ethiopia? They are. Believing with George Santayana that those who do not know history are doomed to repeat it, we continue with the section entitled Our Predecessors. This time we focus on the first chairman of our department, the extraordinary T. Mitchell Prudden. We are pleased to recognize the people who have received new grants and new honors. We salute Tuan Pham for forty years of service and prize-winning teaching. In addition, we recognize and thank some of the medical practices who use the services of our pathologists. We hope to engage them further.

MicroRNA! Malaria! Horses! Heroes!

ANATOMIC
PATHOLOGY

CLINICAL
PATHOLOGY

CELL AND
MOLECULAR BIOLOGY

Anatomic Pathology Micro RNAs and Cancer: New Test Approved

By Mahesh Mansukhani
(mm322@columbia.edu)

Micro RNAs, (miRs) a recently discovered group of small RNAs – the discoverers of which shared in this year’s Lasker’s awards – modulate cellular protein levels by regulating translation of target mRNAs. Requiring only partial complementarity to the target mRNA, one miR can modulate the levels of dozens of proteins, with profound effects on cellular phenotype - without always altering the levels of the target mRNAs. Only 20-25 nucleotides long, they are more stable than mRNAs in various specimens and thus excellent targets for diagnostic testing.

The restricted expression of various miRs in specific cell types allows their use to classify cancers or to identify the tissue of origin of cancers. Some cancers overexpress or fail to express specific miRs, which can be used as cancer markers. miRs are present in genomic regions of frequent gains

and losses in tumors, and could be both diagnostic and therapeutic targets in these settings. P53 loss causes loss of expression of miR34a, and this loss can be used as a

Continued on page 6



COLUMBIA UNIVERSITY
MEDICAL CENTER

Inside This Issue

| | |
|-------------------------------------|----|
| From the Chair..... | 1 |
| Anatomic Pathology..... | 1 |
| Cell & Molecular Biology..... | 2 |
| Clinical Pathology..... | 3 |
| Outreach to Ethiopia..... | 4 |
| New Graduate Program..... | 5 |
| New PhD Students..... | 5 |
| Promotions and Anniversaries..... | 7 |
| Notable Contributions..... | 8 |
| New P&S Curriculum..... | 8 |
| Our Predecessors..... | 9 |
| Our Departmental Administrator..... | 10 |
| CU Outreach Pathology Services..... | 11 |
| Paulette Bernd..... | 11 |
| New Grants..... | 12 |

Cell and Molecular Biology: Gil Di Paolo

By Richard Vallee, Director,
Division of Cell and Molecular Biology
(rv2025@columbia.edu)

Gil Di Paolo is a recent recruit to our department. He is from Switzerland, where he grew up as the son of Italian immigrants, and he is multilingual. His Ph.D. studies were on stathmin (aka Op18), a factor responsible for regulated disassembly of microtubules, so he had early mutual interests with several current department members. He then spent several very productive years with Pietro De Camilli, making considerable advances in our understanding of the role of phospholipids in synaptic vesicle trafficking. I asked him a few questions about his experiences at Columbia and his current work.

RV: *I understand you have a bit of a commute to get to work.*

GDP: Indeed, I live in the New Haven area. I have yet to find at Columbia an individual with a longer commute. Even Carol Mason's record has been pulverized. MetroNorth trains are not as reliable as Swiss trains, but when they do stop at the right station, they are convenient. A key was also to get a noise-cancelling headset to stop a whole range of human sounds.

RV: *Your lab is in its third location in three years. What do you think about this?*

GDP: We were happy to leave the first lab (P&S12-403, an old anatomy lab) because the smell, which was a combination of sewage, rodent - and possibly human - cadavers, as well as solvent, was dreadful. It probably scared away a few postdoc and student applicants. The ones who joined this first lab must have felt a bit trapped. The temporary move to ICRC was viewed as a relief for the 'survivors' and a Hilton-like experience, thanks to the pure air, the elegant lab design, and to the warm welcome we received from Riccardo and our floor neighbors. We have recently moved to the more pragmatic, and beautifully renovated 12th floor of P&S and, so far, the open lab space has been extremely well received by my co-workers. It requires more energy to set it up, but once established, it is highly functional and truly facilitates lateral interactions between the labs. The positive experience also stems

from the human and scientific qualities of all our neighbors. Considering the focus of our research, it is strategically important for us to be in the College of Physicians and Surgeons and specifically, on a Taub floor. We are happy to be stably anchored there and hopefully, will not have to look at blue prints for a while.

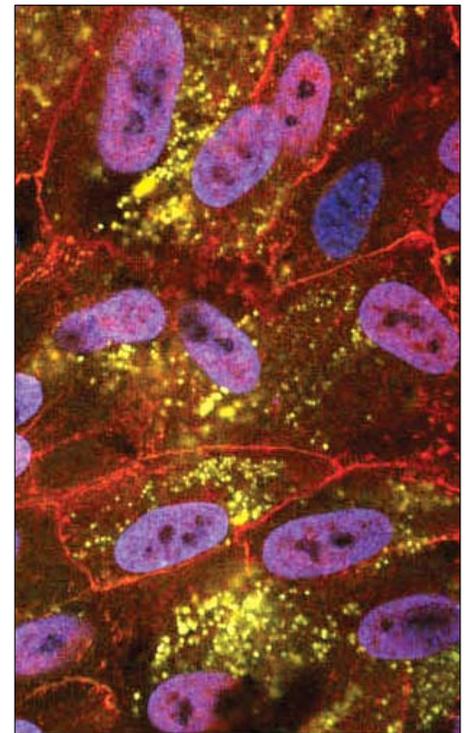
RV: *What's new in your research?*

GDP: As anticipated, it took a while to establish new research programs, but thanks to the quality of my coworkers, the cooperation of various funding sources, including NIH, and the precious interactions/ collaborations we have been having with our closest colleagues (e.g. Ottavio Arancio, Tae-Wan Kim and more recently, Scott Small), this endeavor was greatly facilitated. A significant fraction of my lab has been focusing on the role of phosphorylated lipids called phosphoinositides (e.g. PIP2) in neuronal and synaptic physiology and their relevance in such disorders as Down syndrome and Alzheimer's disease. We have recently published two studies. The first one connects the overexpression of the PIP2 phosphatase synaptojanin 1 to brain dysfunction in Down syndrome mouse models, whilst the second, a collaborative effort between our lab and those of Tae-Wan and Ottavio, shows that amyloid beta disrupts PIP2 metabolism and that this defect may be relevant to synaptic dysfunction in AD. The follow-up studies are promising and are part of an expanding research program in my lab focusing more broadly on the role of lipid dysregulation in Alzheimer's disease-linked synaptic dysfunction and neurobehavioral deficits.

The other part of my lab focuses on the role of the same lipids in the regulation of synaptic vesicle recycling and more generally, the endo-lysosomal pathway, including autophagy using biochemical and cell biological approaches in combination with mouse genetics. For instance, we have been interested in understanding how synaptojanin 1 is recruited to the synaptic plasma membrane at sites of endocytosis, where extensive PIP2 hydrolysis is believed to occur. Our studies on the synaptojanin knockout mouse have indicated that failure to hydrolyze PIP2 during the endocytic process slows down the recycling of synaptic vesicles and affects

the efficacy of neurotransmission. Current models emphasize the importance of the partnership between synaptojanin and endophilin in this process, based on a simple scenario, namely, that endophilin recruits synaptojanin to the plasma membrane to facilitate PIP2 hydrolysis. We have recently added a new dimension to the model involving the known effects of endophilin on membrane curvature. Using synthetic phospholipids we find that the increased membrane curvature affects the ability of synaptojanin 1 to promote PIP2 hydrolysis. Indeed, this process occurs with much faster kinetics on highly curved (i.e., synaptic/endocytic-like) membranes. Because endophilin drives membrane curvature, we now propose that endophilin generates and stabilizes curvature at sites of endocytosis, and then recruits synaptojanin and optimizes conditions for PIP2 hydrolysis. Curvature sensing by proteins is an emerging theme in the field of membrane traffic because this property may be key to understanding the mechanisms regulating protein sorting and more generally, membrane budding from all cellular organelles.

The Art of Cell Biology



A bisretinoid chromophore implicated in macular degeneration accumulates in lysosomes of retinal pigment epithelial cells.

Courtesy of Professor Janet Sparrow

Clinical Pathology: A Day in the Life of a Clinical Microbiologist...

By Susan Whittier, Ph.D (whittie@nyp.org)

A ten year old girl presented to one of our pediatric clinics with complaints of fever and lethargy. A test performed in the Clinical Microbiology lab provided a diagnosis that required immediate intervention. Phone calls to her home went unanswered. NYPD successfully dispatched officers to find her and bring her back for treatment. She was admitted directly to the pediatric ICU. Meanwhile, a 30 year man has been admitted to Milstein with diffuse pain and fever. He had recently been discharged from another institution where his symptoms were treated with pain medication. The continuance of his illness brought him to Columbia University Medical Center. Once again a test performed in microbiology provided his team of clinicians with a specific diagnosis and appropriate therapy was immediately instituted. What could these very different patients possibly have in common? They were both infected with *Plasmodium falciparum*, the parasite most often associated with fulminating malaria.

Our pediatric patient had recently returned from a two month visit to the Ivory Coast and her caregiver assured the clinician that she had adhered to the anti-malarial prophylactic regimen prescribed. Further investigation revealed she had run out of medicine during her last week abroad. Three weeks after her return to the United States, she presented to us with positive blood smears. Upon admission she was treated with quinidine and clindamycin and was then switched to malarone (atovaquone/proguanil). Her level of parasitemia decreased rapidly and by day 5 no plasmodial parasites could be found in her blood.

Our adult patient was a very different story. He has sickle cell disease and was admitted for pain management associated with vaso-occlusive-crisis. Over the course of his seven day admission he demonstrated low grade fevers. Once a recent travel history to the Ivory Coast was elucidated, blood smears were examined for parasites and malaria was diagnosed. He received malarone, but left the hospital AMA after 24 hours.

Malaria is a parasitic disease, which is endemic in many countries in various areas of the world. Each year it causes up to 3 mil-

lion deaths and close to 5 billion cases of clinical illness worldwide. The four human malaria species causing most infections are *P. falciparum*, *P. ovale*, *P. vivax* and *P. malariae*. *P. falciparum* is by far the most life threatening. This species produces up to 40,000 merozoites per day, which are then released from the liver into the bloodstream. Once the trophozoites develop in the red cell, the RBCs become “sticky” and adhere to endothelial cells, which interferes with clearance.

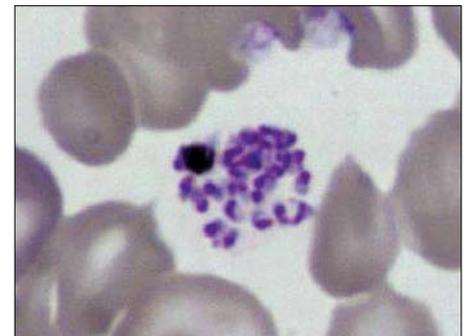
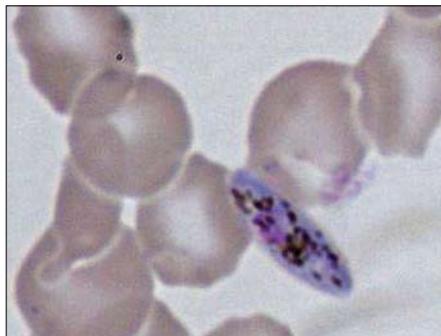
Malaria was first described more than 4,000 years ago and is a loose translation of the Italian expression for “bad air”. The initial discovery of the malarial parasite and its subsequent characterization has led to numerous Nobel prizes, including Ronald Ross who identified mosquitoes as the vector of transmission (1902), Camillo Golgi who defined the periodicities of the disease (1906), and Charles Louis Alphonse Laveran, who first noticed parasites in the blood of a patient suffering from malaria (1907). When the CDC was established in 1946, one of its first battles was the fight against malaria. In 1947, 15,000 U.S. malaria cases were reported. By 1950, only 2,000 cases were reported and by 1951, malaria was considered eradicated from the United States. Quite a success story!

Chloroquine resistance is so wide spread, that it is no longer considered first line therapy. Therapeutic regimens are complex, taking into account geographic exposure, plasmodial species, severity of disease, and age of the patient. Typically first line therapy includes malarone or quinine sulfate combined with clindamycin. Cur-

rently, there is no malaria vaccine approved for human use. This is due in part to the complexity of the plasmodial life cycle. Its antigens are constantly changing, which makes vaccine development a challenge. A vaccine remains an important research project in public health, since other methods of fighting malaria, including drugs, insecticides, and bed nets, have not succeeded in eliminating the disease.

Of interest, at least two genetic variations associated with human red blood cells have been demonstrated to convey varying degrees of protection against malaria. Individuals who have the sickle cell trait (heterozygotes for the abnormal hemoglobin gene HbS) are relatively protected against *P. falciparum* malaria. This protection is not absolute, but severe infections are avoided in 60 – 90% of carriers. Consequently, the sickle cell trait is frequently found in parts of Africa with the highest rates of malaria. Individuals who are negative for the Duffy blood group have red cells that are resistant to infection by *P. vivax*. Since the majority of Africans are Duffy negative, *P. vivax* is rare in Africa south of the Sahara, especially West Africa.

Our laboratory tools for the diagnosis of malaria remains the examination of thick and thin Giemsa-stained blood smears. At least 300 microscopic fields must be examined, on a series of bloods collected over time, in order to rule out infection. Positive smears must be critically observed for speciation and determination of per cent parasitemia. This calculation enables clinicians to monitor efficacy of treatment and determine whether transfusions will be necessary.



These thin prep Giemsa-stained blood smears from our adult malaria patient are atypical in that we see a *Plasmodium falciparum* gametocyte (left) and merozoites (right) rather than the trophozoite ring forms within the red blood cells.

Outreach to Ethiopia

By Chuck Marboe (ccm1@columbia.edu) and Bachir Alobeid (ba2024@columbia.edu)



Left to right:
Chuck Marboe, Teklu Bekele, and Bachir Alobeid at the Pathology Department Office in Gondar

In June, Charles Marboe, MD, and Bachir Alobeid, MD, traveled to Ethiopia to deliver lectures to third year medical students at the Gondar College of Medical Sciences. Teaching at the medical school is in English and, although providing 6 hours of instruction on topics in liver pathology generally outside their expertise, the sessions were well received by an attentive and enthusiastic class of 50 students. The visit was hosted by Teklu Bekele, MD, at the time the sole pathologist in the department, under the auspices of the Dean, Assefa Getachew, MD.

Gondar is one of three medical schools, in Ethiopia; the others are Addis Ababa University and Jimma University. The college at Gondar was established in 1954 as a Public Health College and Training Center by Ethiopia, WHO, UNICEF, and USAID. The guiding philosophy has been a team approach and community based teaching of health professionals. The college now has 4,100 students in medicine, public health, biomedical sciences, physiotherapy, anesthesia, optometry, nurse cataract surgery, ophthalmia, occupational health, surgery, and human nutrition. The College

has recently established a peer reviewed scientific journal (The Ethiopian Journal of Health and Biomedical Science). With a population of approximately 75 million,

an average age of 18 years, and a life expectancy of 49 years, the need for medical professionals is great.

We are planning further collaborations with Dr. Teklu at Gondar, the Department of Pathology in Addis Ababa and Black Lion Hospital (with the country's only pathology residency training program). Our efforts will employ computer-based learning and case studies. Anyone interested can contact Chuck Marboe or Mike Shelanski.

Gondar city was founded in 1636 by Emperor Fasiladas, had a population of 65,000 at the time of his death in 1667, and was the capital of Ethiopia for 250 years. The Royal Enclosure includes 3 castles, bathing pool, library and a lion house (no longer used). An additional tourist attraction is Debre Berhan Selassie Church whose ceiling is decorated with paintings of the winged heads of 80 Ethiopian cherubs. Gondar is at an altitude of 6,000 feet and is adjacent to the Simien mountains in northern Ethiopia. It is approximately 40 miles north of Lake Tana, the source of the Blue Nile. Gondar can be reached by plane, a short flight from Addis Ababa, or by bus, a journey taking many days.



View of Gondar from Gondor University with Simien Mountains in the background.

New Graduate Program, New Course, New Students!

By Steve Spitalnik (ss2479@columbia.edu) and Ron Liem (rkl2@columbia.edu)

The reorganization of the Graduate Programs at the Medical School has grouped the programs into five divisions. These include new Programs in Molecular Basis of Health and Disease, as well as Basic Cell and Molecular Biology, while continuing the Programs in Neurobiology and Behavior, Medical Informatics and the umbrella Integrated Program in Cellular Molecular and Biomedical Studies. The Pathobiology and Molecular Medicine Program is one of the Health and Disease Programs and is centered in our department. Furthermore, members of our department have leadership roles in the Cell Biology program, one of the Basic Cell and Molecular Biology Programs, the Integrated Program and the Neurobiology program. Our department also provides the leadership in the M.D.-Ph.D. program. The specific graduate programs that comprise the division of the Molecular Basis of Health and Disease provide unique perspectives from Pathobi-

ology, Pharmacology, Nutrition and Physiology. Applicants to these programs are reviewed by a joint admissions committee and take a common core curriculum that includes knowledge of the fundamentals of human disease and the underlying basic science research.

New and Unusual Course:

As part of our new mission in graduate education we have organized an unusual course (G6003) MECHANISMS IN HUMAN DISEASE (Fall 2008). This course analyzes several organ systems and a disease associated with each organ system. The course has four modules; each module will describe the basic physiology, nutritional status, health and anatomy of the organ system, the genetics, cell and biochemical mechanisms and pathologies associated with the disease, as well as basic pharmacology and therapeutics to treat the disease. Participants in the course include clinicians and basic scientists and

cover all the important aspects of each organ system and the disease associated with it. The course is unusual in that it includes patient interviews and goes so far as to discuss the ethical issues of treatment.

The modules are:

Hematopoietic System Sickle Cell disease:

Steven Spitalnik

Nervous System-Alzheimer's Disease:

Ron Liem and Asa Abeliovich

Pulmonary System-Cystic Fibrosis:

Steven Spitalnik

Cardiac System-Atherosclerosis:

Alan Tall and John Loike

There are 25 students in the class and so far it is a great success.

New PhD students

We have three new students in the pathobiology graduate programs and hope to have more next year. They are:



Gregory Minevich was born in what was then called Leningrad, Russia. He moved to the U.S. with his family and attended Boston University for his undergraduate studies. After obtaining a M.S. at the London School of Economics, Greg worked in software and web development, before deciding to go into biomedical sciences. He worked as a laboratory technician with Dr. Robert Winchester for five and a half years and also obtained an M.S. from Columbia's Biotechnology program before being admitted to the Pathobiology & Molecular Medicine graduate program.



Rosa deVries received her B.S. degree from the University of Utrecht in the Netherlands. She started studies on her M.D. degree at Groningen University and enrolled in a Master's program parallel to medical school. As part of her Master's studies, she came to Columbia to do a 7 month internship in the laboratory of Dr. David Sulzer. She quickly decided that she wanted to obtain a Ph.D. She is in the Pathobiology & Molecular Medicine graduate program.



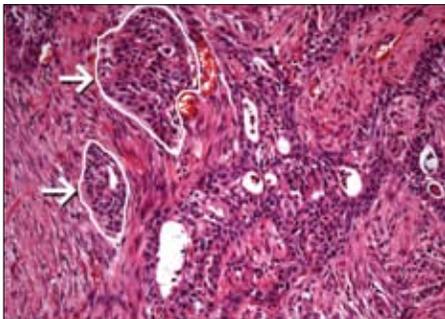
Yige Guo received his B.S. in Biological Sciences from the College of Life Sciences, Peking University. Following graduation, he did a short internship at the National Chengdu Center for Safety Evaluation of Drugs at the West China Hospital, before working as a laboratory technician in the Laboratory of Neuronal Differentiation and Neurodegenerative Disease at Peking University, where he did research on kinesin mediated vesicle transport. Based on his interest in mechanisms of disease, Yige decided to come to the U.S. for his Ph.D. studies and was admitted to the Pathobiology & Molecular Medicine graduate program.

Anatomic Pathology

Continued from page 1

marker of loss of p53 function (a critical cancer marker). Studies are also underway to use miRs for early detection of cancer.

At the CUMC molecular pathology laboratory we are validating clinical applications of miRs for diagnostics in partnership with Rosetta Genomics. Our first application has been the use of miR205 to identify squamous differentiation in non-small cell lung cancer (NSCLC). Before the advent of targeted therapies, only the distinction of non-small cell from small cell lung cancer was considered important, as all non-small cell lung cancers were treated in the same manner. With targeted therapies, there is an increasing need for subclassification of NSCLC, especially with an FDA black-box warning to exclude carcinomas of squamous histology from treatment with Avastin, because of increased risk of fatal bleeding.



Squamous or Adenocarcinoma? This tumor was identified as squamous with high confidence by the Lung-squamous miRdicator™ assay.

Using the Lung-squamous miRdicator™ assay, developed by Rosetta Genomics, we compared levels of miRs 205 and 21, and a “housekeeping” RNA, U6. After determining thresholds on a training set of 26 tumors – 12 squamous and 14 adenocarcinomas – we tested the assay on an additional 79 samples – without knowing the diagnosis of these tumors. We obtained results in 73 cases – a success rate of over 90% from paraffin embedded tissue. 23/24 squamous cases were identified as squamous, and 44/49 non-squamous cases were classified as such, for a sensitivity and specificity of 96% and 90% respectively. This result compares favorably with sensitivity and specificity of histological classifications submitted to cancer registries, with sensitivity for squamous histology ranging from 70-89% and specificity ranging from 87 to 96%. We have received approval from the New York

State Department of Health to offer this test clinically. Although this test does not obviate the need for careful histological evaluation of the tumor, it is a useful adjunct.

Another important distinction that is difficult to make by morphologic examination alone, is that of mesothelioma from metastatic carcinomas, whether in the pleura or the peritoneum. Pathologists currently use a combination of immunohistochemical markers – some relatively sensitive and/or specific for mesothelioma, and others expressed primarily by adenocarcinomas – to make this distinction. No one marker is absolutely sensitive or specific, and there can sometimes be differences in opinion, even among experts. Our partners have discovered that mesotheliomas show relatively greater expression of miR193a-3p, while various adenocarcinomas express miRs 122, 192 and/or 200c at higher levels. Again, using a scoring system based on an external training set we evaluated the performance of the Mesothelioma miRdicator™ assay on a set of 43 mesothelioma samples from 37 cases, and 86 adenocarcinoma samples from 72 cases. Using samples with at least 50% tumor, results were obtained for 39 mesothelioma samples from 35 cases, and 83 samples from 69 cases. Of these, 38 samples from 34 mesothelioma cases were classified as mesothelioma, and 82 samples from 68 adenocarcinoma cases were classified as adenocarcinoma, for a sensitivity of greater than 97% and a specificity of greater than 98%. Again, reproducibility was very high. We are in the process of completing our application to NY State Department of Health to allow us to offer this test clinically.

We are evaluating a miRNA-based assay to determine the tissue of origin of unknown carcinomas. We will use a combination of metastases and poorly differentiated primary tumors to evaluate the ability of this test to identify the tissue of origin of various carcinomas. A currently available test evaluates the expression of around 1500 mRNAs, require frozen tumor, and uses black-box algorithms. The test that we will evaluate will examine includes 34 miRs. It uses a multistep logistic regression algorithm and can be used on paraffin embedded samples, increasing its potential applicability. We anticipate that this test will add to the cancer diagnostic armamentarium of the pathologist.

Chairman's Letter

Continued from page 1

of graduate programs that makes such a course essential. The course is surprisingly broad and recently covered sickle cell anemia from the behavior of red blood cells to the sometimes poor treatment of its victims. We are pleased to introduce our new graduate students and hope to increase the class next year.

Rich Kessin takes us on a voyage of a different kind – into the history of our department and a surprising equine connection. A hundred or more years ago, P&S physicians and scientists were in the forefront of the establishment of disease treatments and in the sometimes difficult task of imposing public health measures on unwilling physicians and patients. Two P&S physicians (Welch and Halsted) were among the four that started the Johns Hopkins Medical School.

We have had a number of well-deserved promotions, as you will see below, and one extraordinary long-time faculty member, Dr. Tuan Pham has reached his 40th anniversary at Columbia. Tuan is an award winning teacher of Gross Anatomy. I am pleased that the Newsletter is introducing Dr. Paulette Bernd. Paulette has also won awards for teaching Gross Anatomy and she will assist us in the difficult task of bringing the course into the new curriculum.

I would like to invite the members of the department and of our wider public to submit suggestions about a topic you might like to have addressed in future Chairman's letters and in the Newsletter as a whole.

Well, let me add an addendum. The election is over. My hope is that a respect for science and its possibilities will be restored. My euphoria is such that I still have not been very efficient. Perhaps next week.

Mike Shelanski (mls7@columbia.edu)

Faculty Promotions

The Newsletter would like to congratulate the following Department members:



Mahesh Mansukhani, M.D. has been promoted from Assistant Professor of Clinical Pathology & Cell Biology to Associate Professor of Clinical Pathology & Cell Biology. Mahesh specializes in the pathology and mechanisms of cancer cell growth. See his article in this issue.



Phyllis Faust, M.D., Ph.D. has been promoted from Assistant Professor of Clinical Pathology & Cell Biology to Associate Professor of Clinical Pathology & Cell Biology. Phyllis specializes in the pathogenesis of CNS defects in peroxisomal disorders. She is an enthusiastic teacher of medical students.



Kurenai Tanji, M.D., Ph.D. has been promoted from Assistant Professor of Clinical Pathology & Cell Biology to Associate Professor of Clinical Pathology & Cell Biology. Kurenai specializes in neuromuscular pathology with a specific interest in mitochondrial encephalopathy. She started Columbia life as a post-doc in the department of neurology in 1991 intending to stay only 2 years. Columbia is now home.



Hanina Hibshoosh, M.D. from Associate Professor of Clinical Pathology to Professor of Clinical Pathology. Hanina specializes in the molecular pathology of breast cancer.

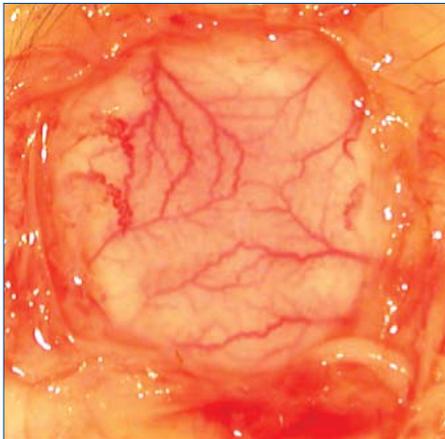
Anniversary



Dr. Tuan Pham is celebrating his 40th anniversary in our Department. Tuan (actually Tuan Duc Pham) left Hanoi for Saigon in 1954 and then emigrated from Vietnam to Austin, Texas in 1961 where he got his Bachelor's Degree in biology at St. Edward's University in 1963. After brief stints at the Alexian Brothers Hospital in Chicago and also a year in Strasbourg, France, He took an MS in Anatomy at Loyola Medical School in 1967. Coming to New York, he got a job at the old Delafield Hospital in 1968 and then, from 1972-75 did his Ph.D in Anatomy under Sarah Luce and Edward Dempsey – both of whom died while Tuan was in training. His training was taken over by Charlie Noback, who still survives. After post-doctoral fellowships with Vincent Butler and Bernie Erlanger, Tuan received a joint appointment in Pharmacology and Anatomy. At first teaching histology, Tuan has taught Gross Anatomy since 1986 and has received six Teacher of the Year Awards from the first year medical students. For some years, Tuan has been associated with the laboratory of Mike Gershon.

Perhaps his finest accomplishment is the success of his children – who are something of a Columbia dynasty. Daughter Kim received her MD and MPH in 1991 as did his son-in-law David Cone MD. His son, Philip, received an MD and a PhD in 1998 and his daughter-in-law, Andrea Nicolas, a Ph.D and an LL.D. Bach-Tuyet (aka Mrs. Pham) received her BS in nursing degree and M.S in nutrition, also from Columbia. There are a number of grandchildren headed you-know-where.

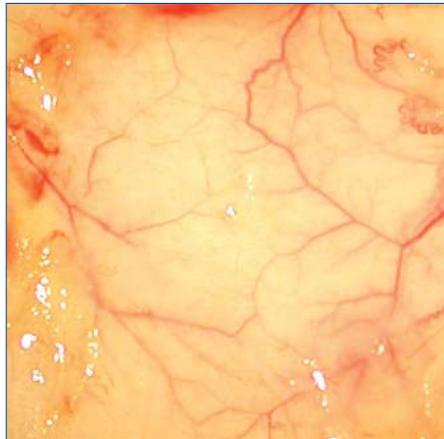
Notable Contributions



VEGF-A

Several papers from the department have excited the scientific community lately. Department members Hynek Wichterle, and Chris Henderson were part of a team of Columbia and Harvard scientists who caused a skin cell from an 82 year old patient with ALS to revert to a stem cell that could be expanded into a large population. They then developed ways to make these cells develop into neurons. These methods open new possibilities for the study of amyotrophic lateral sclerosis. See: *Science* 321, p1218 August 29, 2008.

The laboratory of Jan Kitajewski has discovered a new way to disrupt the blood flow to tumors that may become resistant to available anti-angiogenic drugs. Since the concept of anti-angiogenesis was introduced, efforts to shrink tumors by shutting off their blood supply have focused on blocking VEGF, a growth factor that tumors release to spur new blood vessel construction. VEGF inhibitors, such as Avastin, impede vessel construction and shrink tumors, sometimes extending the lives of patients. Even though all tumors require a blood supply, a VEGF blockage does not shrink all types of cancer. And those that do shrink can eventually become resistant to the blockage. Jan and a large team describe a new drug that disrupts a tumor's blood supply by blocking an entirely different target, an angiogenic receptor called Notch. Notch is required to construct normal arteries during development, but also plays a role in building blood vessels to growing tumors. After VEGF, it is considered the most popular target in anti-angiogenesis research. See: the June 15 issue of *Cancer Research*.



VEGF-A + Notch 1 decoy reduces angiogenesis

Finally, two former graduate students and their colleagues at Yale and Harvard have used a new technique to sequence the genome of the very troublesome pathogen *Acinetobacter baumannii*. Maintaining their friendship from graduate school days in the late Department of Anatomy and Cell Biology (now part of Pathology and Cell Biology), Michael D. Smith and Stefan Pukatzki rapidly sequenced and characterized the genome and identified a large number of potential antibiotic resistance genes. The sequence reveals an extraordinary ability to accept foreign DNA, which could account for the exceptional drug resistance. The sequenced isolate was frozen from days before widespread antibiotic use, but others have shown that now many of the antibiotic resistance genes have assembled in one locus causing huge problems. The complications in wounds from Iraq have given this organism the nickname Iraqibacter. Mike, Stefan and their colleagues mutated many of the new putative virulence genes and tested the mutants for virulence with new and elegant assays in *C. elegans* and *D. discoideum*. The former is a worm and the latter a soil amoeba and both are very useful in studies of bacterial pathogenesis. Mike was excellent on NOVA and on NPR. Excellent job, gentlemen. See: *Genes and Development* 21, 601-614, 2007

If you have published a paper that received independent commentary, contact the Newsletter and we will include you in future issues.

New P&S Curriculum for 2009

The next class of medical students will find a thoroughly renovated curriculum. As our department members are responsible for teaching for all four years of medical education the new curriculum will take some planning on our part. Traditionally we have had a two year block of courses in the preclinical years, but this will now be changed to 18 months. Students will have more patient contact earlier in their careers. In that 18 month period our department's teaching of Gross Anatomy and of Histology and Cell Biology will have to be adjusted. Dr. Paulette Bernd is already designing an appropriate Gross Anatomy course in cooperation with our existing staff (see the article about her elsewhere in this issue).

What now corresponds to the third year will be divided into 12 week blocks of clinical exposure interspersed with a week of classroom sessions. The idea is to create a classroom experience that is immediately valuable to the students in the initial clinical setting. An innovative aspect of the new curriculum concerns the fourth year when students will be allowed to concentrate on an academic project. Five areas of concentration have been defined – Research, Medical Education, International Health, Social Medicine, or Community Service. Our department, including its basic scientists can expect fourth year medical students to apply for research projects. That, however, is a few years off. The curriculum was last changed dramatically in the early 1990s and we are all eager to see the results of this new thinking.



"They're harmless when they're alone, but get a bunch of them together with a research grant and watch out."

Our Predecessors

Buy Me Some Horses!



T. Mitchell Prudden
and the fight against diphtheria

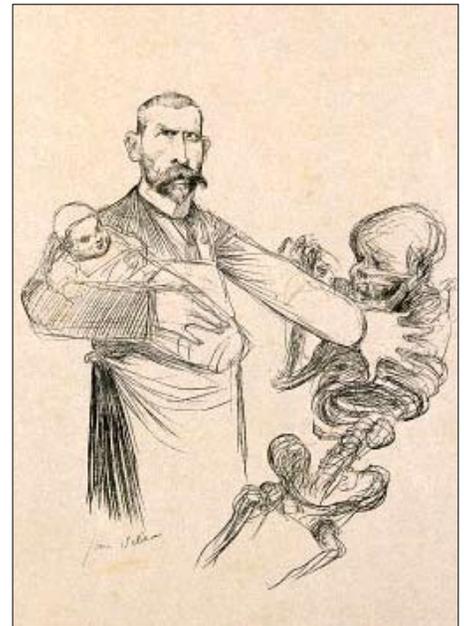
Just outside of The Alumni Auditorium, in that space where we often have receptions, there is a portrait of T. Mitchell Prudden. It is one of those old canvasses, commissioned by his students that we usually ignore. But Dr. Prudden should not be forgotten. He was a graduate of P&S and the first Chairman of the Pathology Department after it separated from the Department of Medicine in 1893. P&S became part of Columbia University in that year. He was one of those post Civil War medical graduates who, despairing of the quality of American medical schools, went to Europe. There he studied pathology and picked up the new science of bacteriology, which he brought back to a small laboratory funded by the P&S Alumni Association. That was in 1878. After returning to Germany in 1885 to take Robert Koch's course in microbiology, Prudden founded the first bacteriology course for medical students in New York and probably in America. In 1892, he was instrumental in introducing microbiology to the New York Board of Health – to screen for cholera and for diphtheria.

Diphtheria was ravaging the children of poor neighborhoods in New York and was very frequently lethal. When Emile Roux in

Paris created the first large scale diphtheria antitoxin by inoculating horses with diphtheria toxin – and showed that it controlled the disease if given early enough – Prudden petitioned the Board of Estimate for money to buy horses. They dithered - it was 1894 and Tammany Hall controlled the city. Patronage was their major concern, not the public welfare and men like Prudden resigned from the Board of Health. Undaunted, but furious, Prudden and his colleague Herman Biggs (one of the great names in American Public Health) bought their own horses in December of 1894 and made antitoxin. Politically adept, they launched a newspaper campaign in the *New York Herald* for public funding and eventually, they succeeded. The horse serum from Prudden and Biggs was the first rationale and effective treatment of an infectious disease in America. Prudden was one of the great forces for a national bureau of health. He felt that it should be staffed by experienced scientists and not “the flotsam and jetsam of the political ocean, from which too often strange, uncouth things are stranded in offices where malfeasance may mean death to some, disease to many”.

Readers may be interested in how this treatment came about at all. Diphtheria was a scourge that could kill all of the children in a family. The responsible bacillus was isolated by Loeffler and Klebs in 1884 from the artificial membrane that forms in the throats of diphtheria patients. We now know that *Corynebacterium diphtheriae* is a gram positive aerobic bacterium that secretes an exotoxin that ADP-ribosylates host EF-2, thus causing an inhibition of protein synthesis. Curiously, the toxin itself is produced only in those bacteria that harbor a particular lysogenic bacteriophage.

Beginning in 1888, Emile Roux and Alexandre Yersin, working at the new Pasteur Institute, showed that *C. diphtheriae* produced a soluble toxin. In 1890, Emil Behring and Carl Fraenkel in Germany show that an attenuated *C. diphtheriae* could cause immunity in guinea pigs. Behring and Kitasato also showed that serum itself would kill *C. diphtheriae* – the first description of a humoral response. At this point, a few small



Emile Roux, who created vaccines for anthrax, rabies and diphtheria.

trials had been done on sick children, but there was not enough serum. To solve that problem, Roux and his colleagues turned to horses, which they gradually immunized. This produced enough serum to immunize 300 children. The case fatality rate decreased from 45-55 percent to 24.5 percent. The earlier the serum was given to infected children the better the chance of success. That result was announced to great joy at a conference in Budapest in 1894. The cartoon of Roux shows the public's appreciation.

In the end, a vaccine was developed for healthy children. First, the toxin reacted with the specific antibody was used as a vaccine and later the toxin was inactivated with formalin to create toxoid. That vaccine, begun in the early 1930s, reduced the incidence of the disease to almost zero in the countries that used it. Diphtheria survives in underserved parts of the world. The vaccination we received as children probably no longer protects us. Readers who wish to know more should consult *Childhood's Deadly Scourge-The campaign to control diphtheria in New York City-1880-1930* by Evelyn Hammonds. This excellent book reveals the large role that P&S physicians and scientists played at that time.

Rich Kessin (rhk2@columbia.edu)

Our Departmental Administrator (and how we got him)

Many of you were struck by the photo of NYPD Lt. Carl J. Reyes that appeared in our last issue. Since Carl is our Departmental Administrator, the Newsletter thought that readers might be interested in how a man goes from walking a beat in Canarsie to administering a Department of Pathology and Cell Biology. Mr. Reyes agreed to an interview with Columbia Pathology and Cell Biology reports (CPR):

CPR: *When did you join the NYPD?*

CJR: I joined in March of 1969 – I was already married with two kids and one on the way. For the first four and a half years I was a beat cop in Canarsie – that would be the 69th precinct. Except for a few moments, it was pretty quiet. At night I went to Brooklyn College. With three kids and overtime it took me a while, but I graduated in 1978, with a major in sociology and minor in economics.

CPR: *When was your first promotion?*

CJR: Well I was promoted to Sergeant in 1979, even though I passed the test in 1973. Those were the years of the city's fiscal crisis and everything suffered – including promotions. I made Lieutenant in 1982 and worked for a while in the Bureau of Audits and Accounts.

CPR: *Why did you stay a cop?*

CJR: Frankly, I liked being a cop. You had to deal with people and not let things get out of hand. It's good training for everything.

CPR: *Would you mind telling us your scariest moment?*

CJR: Sure. One day, early in my career, we got a call that a couple of guys with shotguns were robbing a bar in Canarsie. It was a very sunny day and as my partner and I entered the darkened bar with guns drawn we realized we couldn't see a thing. Had the perps still been on the scene, we might not be having this interview. Fortunately they had fled, leaving the vics locked in a bathroom. For the record, in 21 years on the force, I never did fire my gun.

CPR: *So then you left the NYPD and went to Harvard?*

CJR: Right, in 1985. What an experience! One day I was chasing bad guys over fences and the next I was drinking sherry. They called it attitude adjustment hour at Harvard. I received a Mayoral Scholarship to the Kennedy School of Government (thank you, Mayor Koch) and got an MPA in Public Administration. I had never heard people like Robert Reich before – the future Secretary of Labor. What an organized and informative speaker. I loved it.

CPR: *And what happened when you came back?*

CJR: I returned as commanding officer of the Police Quartermaster Section until 1990 when I retired from the police after 21 years to join NYC/EMS. I ran all of the EMS support services, administration, and finance until Mayor Guiliani merged it into the Fire Department.

CPR: *What could the NYPD and EMS possibly have in common with the Department of Pathology and Cell Biology?*

CJR: More than you think. People are people and everyone has to work together. We have budgets to prepare and there are a thousand details that are required to run a department – or a precinct- or an ambulance service. Fortunately, I don't have to

arrest the faculty or the staff or carry them out on stretchers – at least not yet.

CPR: *So it would be safe to say that an irate faculty member ranting in your office about a missing account number or a hitch with a grant would not cause your blood pressure to rise?*

CJR (laughing): Nope. But some have tried. One of the charms of our faculty is that most of them don't carry shotguns.

CPR: *The crack investigative reporters of the Newsletter have noticed that sartorially speaking, you far outpace the other members of the Department. How did this come about?*

CJR: Well, if you spend 21 years in uniform, life gets to be a bit monochromatic – the only color is blue. So yes, I do like a nice suit. My wife likes it too.

CPR: *C'mon! Hugo Boss suits? Gerry Garcia ties? One of the Newsletter staff plays squash with you. Reportedly, your headband always matches your shorts, your shirt, and your underwear.*

CJR: All true. I confess. I'm a cop and I have to pass inspection every morning. Besides, as they teach you in the police academy – appearance is everything.



Carl Reyes now...



and then.

Columbia University Outreach Pathology Services

Columbia University Pathologists was formed by the Pathology faculty of Columbia University to offer expert diagnostic pathology and cytology services to patients and physicians both at the Medical Center in New York City and – as part of an outreach program – to community-based doctors in the Metropolitan area. This outreach program enables non-Columbia physicians and patients to take advantage of the specialized training and skills of the diagnostic surgical pathologists which were previously unavailable to them.

Because the Columbia University Pathologists are actively involved in cutting edge basic and clinical research and actively participate with CUMC clinicians in patient care decisions, they are uniquely able to assist practicing, community based clinicians who want to discuss their diagnoses, issues of patient management, or the latest research and its relevance to their patient's care through direct consultation.

Some of the Practices We Serve

We would like to thank the following practices:

ACE – Ambulatory Center for Endoscopy
Cityscape OB GYN
Kips Bay OB GYN
Rockland Urology Associates, PC
SoHo OB GYN,
Suburban Endoscopy
Drs. Mark and Elliot Fagelman
Dr. Steven Batash.

We appreciate the confidence of these fine physicians and hope to serve them and their patients. We would like to thank Ken Findlay, Marketing Representative for his efforts.

We Invite You To Join Us

Pathologists in the Columbia University Pathologists group would be pleased to serve your practice and to provide world-class diagnostic and consultative services.



Dr. Charles Goldberg of Suburban Endoscopy

We accept and are par with most regional third-party carriers, provide all supplies, specimen handling, and state-of-the-art reporting. Call us at 800 653-8200 or reach us at <http://pathology.columbia.edu/>

Paulette Bernd Joins in Gross Anatomy Teaching

A many of you may know, since the merger of the Department of Pathology with the Department of Anatomy and Cell Biology, we have been responsible for a much larger fraction of medical student teaching – including, of course, Gross Anatomy. This is a course in revision and so it was with particular delight that the new Department of Pathology and Cell Biology welcomes Dr. Paulette Bernd, an award winning teacher whose previous career has been at Downstate Medical Center.

Paulette joined the Department of Pathology and Cell Biology this past September. At the State University of New York, Downstate Medical Center, she was Distinguished Teaching Professor of Anatomy and Cell Biology. Paulette got an A.B. degree in Biology from Colgate University in 1975 and a Ph.D. in Anatomy from Columbia University in 1980. Her thesis work was done with Dr. Michael Gershon and the project involved the mechanisms of serotonin storage in the thyroid gland. Paulette then did a postdoctoral fellowship in the laboratory of Dr. Lloyd Greene at New York University from 1980 to 1982 (at



which time Dr. Shelanski was Chairman of Pharmacology), where she began studying the role of neurotrophins in development.

In 1982 Paulette became an Assistant Professor in the Department of Anatomy at Mount Sinai School of Medicine and

moved to SUNY Downstate in 1987. Paulette has continued to work on neurotrophins, investigating their role in the development of dorsal root, sympathetic, cochlear and vestibular ganglia, as well as the heart. She is looking forward to doing research again with Lloyd Greene.

At SUNY Downstate Paulette was the Gross Anatomy Course Director for almost 20 years. She will take on this role at Columbia beginning with the 2009/2010 academic year. Her challenge is to re-create the Gross Anatomy Course to fit into the new, shorter, basic science curriculum. Paulette plans to compensate for the loss in time by having the students alternate dissection, thereby sharing in the work. Students who are not dissecting will participate in small group clinical correlation sessions incorporating surface anatomy, radiology, cross sectional images, ultrasound, case-based learning etc. It is her intention that the revised course will retain the clinical relevance of the current course yet fit into the shorter time frame and stress active learning. Paulette's office is in PH1574B.

New Grants

Asa Abeliovich
MicroRNA Regulation of a Synuclein as a Drug Target
Michael J. Fox Foundation

Gilbert Di Paolo
Role of PIP2 Metabolism Imbalance in Down Syndrome
National Institute of Child Health and Human Development

Gilbert Di Paolo
Genetic Modulation of PIP2 in AD Mouse Models: Effect on Cognitive Decline
Alzheimer's Association

Carol Troy
Downstream Regulators of Beta-amyloid Induced Neuronal Death
National Institute of Neurological Diseases and Stroke

Richard Vallee
Characterization of the Molecular and Cellular Function of the Dynein-Interacting Protein NudC
American Heart Association

Steven Spitalnik/Eldad Hod
Characterizing and developing a model of the humoral immune response to ABO-incompatible renal transplantation
CAP Foundation Fellowship

Ed Laufer
Regulation of Adrenocortical Aldosterone Producing Cell Homeostasis and Regeneration
American Heart Association

Christopher Henderson
Neuroprotective Small Molecules for the Treatment of Amyotrophic Lateral Sclerosis
DDEF

Nicole Suciu-Foca
Suppression of Islet Allograft Rejection by Treatment with ILT3-FC
Juvenile Diabetes Foundation

Patricia Ducey
Regulation of Beta Cell Proliferation by Osteocalcin
Juvenile Diabetes Foundation

Thomas Carr Wright
Analyses of HPV Infections and HPV-associated Diseases in Black African Women
Gates Foundation

Michael Shelanski
Caspase-2 as a Target for the Treatment of Alzheimer's Disease
Wallace Foundation

Gloria H. Su
The Role of ALK4/ACVR1B in Pancreatic Tumorigenesis
National Cancer Institute

and

Novel Mutation Analysis Methods for PIK3CA in Clinical Application
Irving Institute for Clinical and Translational Research, Columbia University (Irving Scholar)

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

A Note on Publications

The members of the department contributed approximately 260 peer reviewed publications in the years 2006-2008. The newsletter suggests that interested parties search the websites of the individual faculty members at <http://pathology.columbia.edu/>

COLUMBIA PATHOLOGY AND CELL BIOLOGY REPORT

Volume 1, Issue 3
Fall/Winter 2008

Chairman
Dr. Michael L. Shelanski
Delafield Professor of Pathology
Pathology and Cell Biology

Editor
Dr. Richard H. Kessin
Professor
Pathology and Cell Biology

Design and production
Richard V. Miller
Center for Biomedical Communications

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

<http://pathology.columbia.edu/>