

From the Chair

Once again the newsletter has been delayed because of my slothfulness. I offer little excuse other than, as you will see in this issue, this is a time of change in the Department of Pathology and Cell Biology. With the New Year, we will see the departure of my Executive Assistant Cindy Kitzinger. Carl Reyes is stepping down as Departmental Administrator and Joanne Li is moving into his role. Fortunately, Carl will remain in the department for a year in a part-time role directing our never-ending series of construction projects. This has been a year of triumphs, not least of all the award the NIH Director's New Innovator Award to Julie Canman and the election of Carol Mason to the Institute of Medicine of the National Academy of Sciences. We have been saddened by the untimely loss of David Colman, Director of the Montreal Neurological Institute and a former faculty member of our department.

Many changes are underway. Hynek Wichterle and Fiona Doetsch are moving to new stem cell research labs on the 14th floor in January of 2012. The leadership of our immunogenetics laboratory is passing from its founding Director, Nicole Suci-Foca to Raphael Clynes, Associate Professor of Pathology and Cell Biology. We have just opened our new Molecular Diagnostics and Personalized Medicine Laboratory on the 17th floor of P&S and are delighted to announce that Dr. Mahesh Mansukhani will serve as overall director of this effort with the assistance of Peter Nagy, Brynn Levy, Ali Naini and Lorraine Clark. These laboratories contain state of the art apparatus for all aspect of molecular diagnostics including 454 and Illumina deep sequencing platforms.

As I have written before, the economic environment on both the research and clinical side is challenging. Thanks to the tremendous efforts of our faculty and our administrative staff, we have been able to grow and prosper in spite of these challenges. As we go into 2012, I am confident we will continue to move forward on all fronts.

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This issue of the Pathology and Cell Biology Report is our 7th. We are diverging from the normal format that includes sections for the three major divisions of the Department – Anatomic Pathology, Clinical Pathology, and Cell and Molecular Biology. Our series on important scientists and pathologists who preceded us, will also return in the next issue. In this issue we highlight the exciting efforts of the Motor Neuron Center, which has joined forces with Pathology and Cell Biology. This group has been organized to tackle the most vexing neurological diseases. It is directed by Drs. Chris Henderson, Serge Przedborski, and Darryl De Vivo. We also welcome new faculty, new residents, new students, and Ph.D students who have joined the very successful med to grad program. Do you remember the microscopes that we used to use in histology? They are now being used in women's health clinics in Rwanda and Peru. As always, we have an all too brief salute to some of our administrators – in this case the Business Office. We note anniversaries, honors, and happy news about the success of grant applications. Finally, we mourn the passing in May of our colleague and friend David Colman.

The Motor Neuron Center Bonds with Pathology and Cell Biology

Spinal muscular atrophy—a tale of two genes, SMN1 and SMN2

By Umrao Monani (um2105@columbia.edu)



Of the 6000 or so single gene disorders known to afflict humans, spinal muscular atrophy (SMA) stands apart for several reasons. First, it is the most common inherited cause of infantile death. With a carrier frequency of about 1 in 40, the incidence of SMA approaches that of more widely recognized diseases such as cystic fibrosis and muscular dystrophy. Second, it is among a group of disorders that mostly affect a single cell-type, but trace their origins to genes whose functions are ubiquitously required. In the case of SMA, the cell most profoundly affected is the spinal motor

neuron. Other neurons including those that control higher brain functions are apparently unscathed. The selective vulnerability of spinal motor neurons, which make direct contact with muscle, leads inevitably to paralysis. The result is an intact mind entrapped within an impaired body, an especially wrenching prospect in the case of a growing child.

Perhaps the most fascinating aspect of SMA is its underlying genetics that involve

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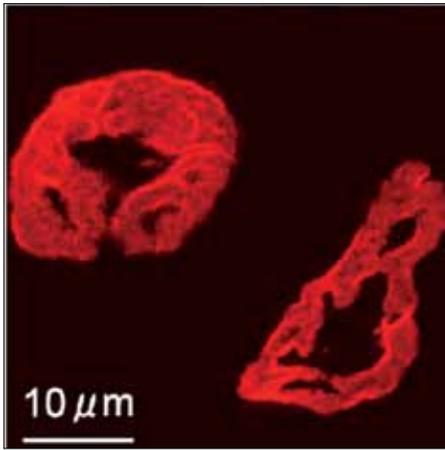


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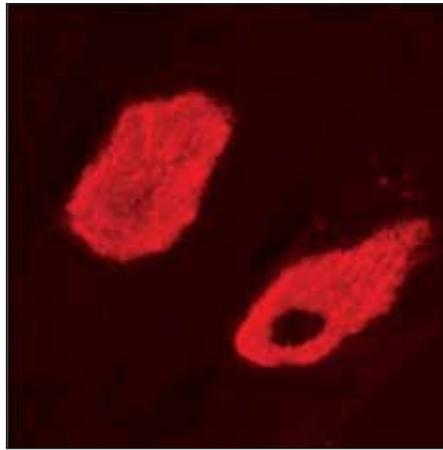
Spinal muscular atrophy *(continued from page 1)*



Impaired development of the neuromuscular synapses in SMA lead to plaque-like motor endplates instead of “pretzels” seen in wild-type individuals.

two virtually identical Survival of Motor Neuron genes, SMN1 and SMN2. Despite their identity, differing by a single nucleotide in a 35,000bp sequence of DNA, only one of them, SMN1 is the SMA gene. Yet, it is SMN2, the copy gene that has garnered most of the attention primarily because it is always present in patients and therefore serves as the substrate for future treatments. These factors are among just a few that have brought together investigators from diverse backgrounds to the Motor Neuron Center at Columbia to unravel the biology of SMA. They include Drs. Pellizzoni, Henderson and Przedborski who use cell models to study the disease and Drs. McCabe and Mentis who use fly and mouse models to investigate how motor circuitry is affected in SMA. The expertise of the basic scientists is complemented by our colleagues at the SMA Clinic headed by Drs. De Vivo and Chiriboga.

My laboratory uses mouse models to understand the molecular basis of SMA. However, since rodents, indeed all non-human species harbor only an SMN1 gene, the mice must first be “humanized” transgenically with SMN2. Such mice, when deleted for their SMN1 gene, develop a severe neuromuscular phenotype, recapitulating the essential characteristics of the human disease. Using SMA mice, we have addressed questions about the natural history of the disease, the tissue and temporal requirements for SMN, the protein deficient in SMA and, for the first time, novel genetic determinants of the disease. Thus, whereas the human disease was commonly described as a motor neuron degenerative disease based on autopsies



of spinal cord tissue, a careful analysis of the mice demonstrated that the disease really begins by arresting the development of the neuromuscular synapse. Accordingly, the synapses fail to mature into the normal “pretzel” shapes, remaining instead as premature “plaques” (Fig. 1). This phenomenon is driven to a large extent by the absence of SMN in nerves since selectively depleting the protein in motor neurons also causes disease. Nevertheless, restoring SMN to the nerves and other cell types of SMA mice even after the development of severe muscle weakness can effect remarkable phenotypic rescue, raising a great deal of optimism about the treatment of symptomatic patients. Our work has shown that SMN is not just therapeutic in SMA, but also protects against the toxic effects of mutations linked to Lou Gehrig’s disease. While the precise mechanism(s) underlying the protection is unclear, the availability of the mice allows us to continue to probe the beneficial effects of SMN and the

pathways that lead from a deficiency of the protein to motor neuron dysfunction and disease. Indeed, proof-of-concept studies in the mice have already resulted in the design of a clinical trial that involves anti-sense oligonucleotides capable of promoting the expression of the SMN protein from SMN2. The trial, spearheaded by investigators at Columbia and Isis Pharmaceuticals with funding from the SMA Foundation, is expected to begin late this year or early 2012. The outcome of the study is eagerly awaited and the endeavor illustrates, at its best, how discoveries at the bench can turn into real therapies for human patients.

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The Hudson River on a stormy day taken from the Medical Center by Richard V. Miller.

An Interview with the Directors of the Motor Neuron Center



The Motor Neuron Center co-directors: Drs. Christopher Henderson, Darryl De Vivo and Serge Przedborski are in the foreground. In the background are Dr. Lewis Rowland and former Dean Gerald Fischbach, who were instrumental in setting up the center.

Pathology and Cell Biology Report (CPR) recently sat down with the three directors of the Motor Neuron Center, Drs. Chris Henderson, Darryl De Vivo, and Serge Przedborski to discuss the Center and its goals. An article on spinal muscular atrophy (SMA) by MNC member Umrao Monani appears in this issue.

CPR: Why do you think that the time is right for progress on neurological diseases that have proved intractable for so long?

SP: I think that the time is at hand because of our increased knowledge of motor neurons and their development and of the molecular basis of diseases that selectively affect motor neurons including SMA and amyotrophic lateral sclerosis (ALS). The problem has been to develop faithful animal models of these diseases, to understand the underlying disease mechanism and to deliver therapies to the affected cells in the spinal cord.

CPR: What advantages does the MNC have?

SP: First, we embrace the translational spirit. We delight in basic research using fruit flies that has recently provided us with clues for treatments and we are equally at home with human clinical trials. We have faculty that cover a broad range of expertise and they are in close proximity. It is also important to us to be housed

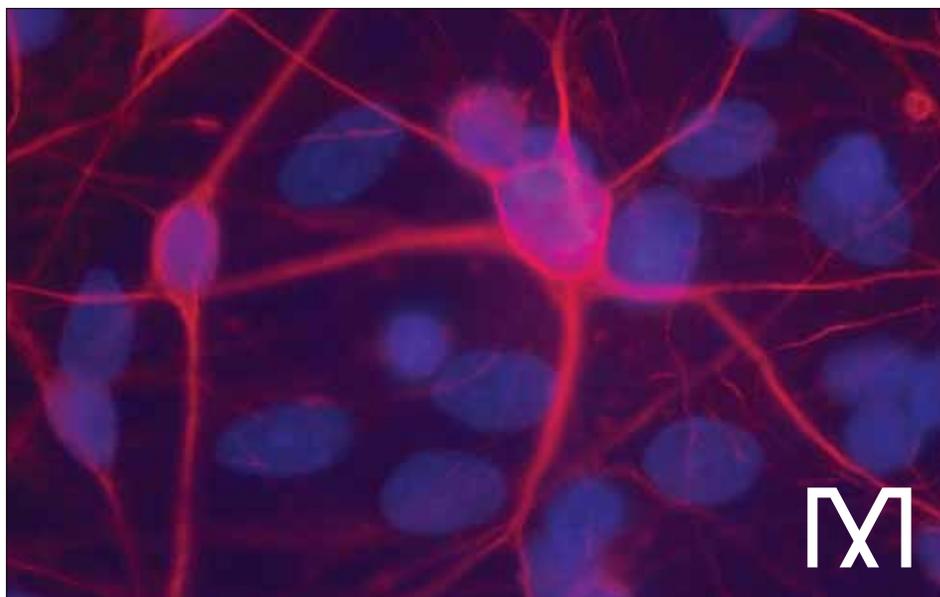
in Pathology and Cell Biology, with its rich clinical and basic science expertise, and to have a membership from 12 other departments, including notably the Department of Neurology. Pathology and Cell Biology is also home to the Pathobiology and Molecular Medicine graduate program and the Howard Hughes-funded Med-to-Grad program, which informs Ph.D students about clinical problems and this has been very useful to us and, I hope, to the students. I should mention the support provided by the Department's administrators.

CH: There is direct benefit from our scale

of operation – there are over 40 laboratories associated with the MNC. Nearly twenty of these work on ALS and 15 on SMA so there is a lot of cross-fertilization. We are the biggest aggregate of researchers on motor neuron diseases worldwide. This range of expertise has been a magnet for recruiting excellent faculty and students. It would not have been possible without support from committed private donors who believed in the project from well before the establishment of the Center and also provide a partnership with families who are dealing with these diseases. Key support for the MNC has been provided from the start by the Spinal Muscular Atrophy Foundation and the Leonard and Claire Tow Charitable Trust, and our work on human stem cells is supported by Project A.L.S.

CPR: Have we advanced to clinical trials?

DDV: Yes! There are currently three trials for SMA – one is on the role of exercise in ameliorating the condition. Surprisingly little is known. The second derives from a study of the neuronal circuitry underlying SMA in the fruit fly by Brian McCabe. It involves a potassium channel blocker. Finally we are awaiting final approval for a molecular treatment for SMA that involves collaboration with a company called ISIS which employs an antisense molecule for the defective SMN gene. We are the lead agency in a study that will involve researchers at Harvard, the University of Pennsylvania and the University of Texas Southwestern. We hope to begin enrolling patients in December or shortly afterward.



Renal Pathology Course Still Going Strong

The 34th annual CME course “Renal Biopsy in Medical Diseases of the Kidney”, directed by Vivette D’Agati of Renal Pathology, was held from Aug 3-6, 2011. Attended by 230 nephrologists and pathologists from 34 states and 23 foreign countries, including representatives from 6 continents, the course was highly successful, with 94% of attendees rating the quality and organization as “excellent”. The course features a world-renowned faculty, including Columbia’s Gerald Appel, Glen Markowitz and Barry Stokes. The course has become a medical center tradition. Founded in 1977 by Dr. Conrad Pirani and run by Dr. D’Agati since 1984, it is the oldest running CME course in the history of Columbia University Medical Center. It provides in-depth review and updates on parenchymal diseases of the kidney as seen through the window of renal biopsy, with emphasis on structural-functional and clinical-pathologic correlations. The course is unique among nephrology courses for its emphasis on renal pathology and disease mechanisms. An annual state-of-the-art lecture is given in Dr. Pirani’s honor. This year’s Conrad Pirani lecturer was Dr. Terry Cook of Imperial College, London, who spoke on complement dysregulation in glomerulonephritis.



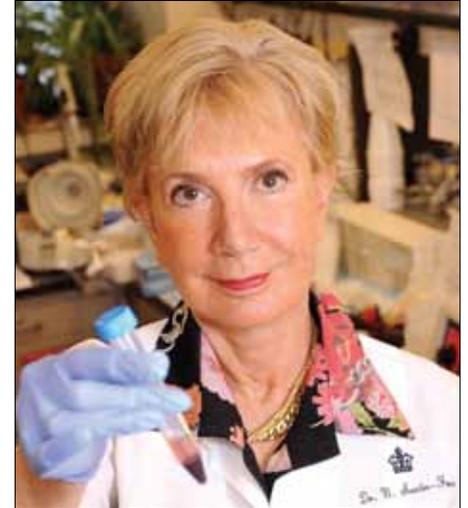
Anniversaries

According to Ms. Nontrel Carwell, the Administrative Coordinator of Pathology Human Resources, there are 338 employees of the Department of Pathology and Cell Biology. The list Nontrel provided also tells us that 68 have been here 20 years or more. Lee Stecher, at 45 years, is the current record holder. The Newsletter cannot list 68, so here, in five year increments are some of our long serving colleagues: **At 20 years**, we have, Robin L. Miller, Teresita Austria Frank, Chih-Chao Chang, Phyllis L. Faust, Anjali Saqi, Istvan Boldogh, Malgorzata Simm, Frances Antonetty, Sunilda Valadares-Silva, Josette A. Archin, Alcmene Chalazonitis-Greene.

At 25 years: Mintsai Liu and Eric Koonming Ho. **At 30 years:** Elnora Johnson, (See *Elnora’s Business Office group elsewhere in this issue*). Heidrun Rotterdam and Elaine A. Silvia have been here for 35 years.

Nicole Suci-Foca

40 years and more: Nicole Suci-Foca has been at this address for 40 years and is beaten only by Ernie April (42) and the aforementioned Lee Stecher.



Annals of Administration

The Business Office Staff



From left to right: Carmen Caraballo, William L. Schaaf, Marybelle Deleon, Rene Deknatel, Jeanette Rodriguez, Dorian Dufore, Monserrate Santiago, Elnora (Ellie) Johnson, Moises Olivares.

The Business Office staff provides financial services to support the Administrative, Clinical, Educational and Research operations of the Department. We are here to help you find your way through the ever-changing bureaucratic procedures inherent to procurement, accounts payable, accounts receivable, and account management. Besides being a fairly cheerful, pleasant, and nurturing group, the staff of the Business Office collectively possess at least 90 years of experience in financial service at Columbia University. This experience is going to be important because the University’s financial systems are about to change. Ellie and her staff will be here for all of us during this happy transition.

Gross Anatomy Memorial Service

By Paulette Bernd, PhD

Professor of Clinical Pathology & Cell Biology
Director, Clinical Gross Anatomy

A memorial service was conducted on April 13th, 2011 for the individuals who donated their bodies to Columbia for use in the Gross Anatomy course. It was organized and conducted by the first year medical and dental students. This long-standing tradition was instituted by Dr. Ernie April over thirty years ago. For the first time, however, the families of the donors were invited to the service and seven families attended. The program included musical offerings played by our talented students, as well as remarks by the faculty, students and family members. Students and faculty

alike were touched by the poignant memories of the families' loved ones. In addition to bringing closure, this service helped students connect with individuals to whom they are grateful.



Paulette Bernd is the Gross Anatomy course director

Say it Ain't So! Cindy Kitzinger to Retire



Cindy Kitzinger, longtime executive assistant to Chair Mike Shelanski, is calling it quits at the end of December. Cindy has served the Department and all of its members

with calm consideration for eleven and a half years. Asked what she is planning to do, she reminded the Newsletter reporters that she has four grandchildren – Katie and Libby and also Rina and Nate who will keep her busy. As respite, Cindy plans to travel – first, to South America. Send us photos. We will miss you, but we are glad you will be having a good time.

Chairman's Letter

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As a final word, I would like to extend my personal thanks to Rich Kessin who has made this newsletter a reality and kept it from being too serious.

Pathology Case Report

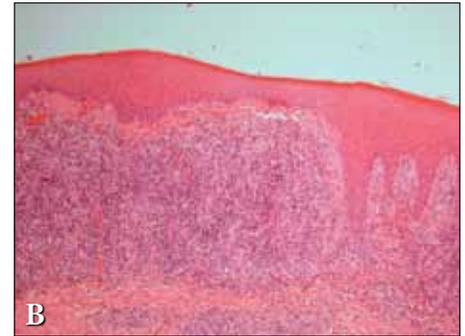
An Odd Source of Contact Stomatitis

Angela J. Yoon, DDS, and Elizabeth Philipone, DMD



The Oral and Maxillofacial Pathology biopsy service at NewYork Presbyterian Hospital (NYPH) was founded by David J. Zegarelli, DDS in 1972. It has grown in volume, accepting specimens primarily from the tri-state region, and has become an integral part of the Department of Pathology and Cell Biology. Currently there are three oral pathologists, headed by Dr. Zegarelli. They include Angela J. Yoon, DDS, and Elizabeth Philipone, DMD. Together they carry out daily tasks of surgical sign-outs, student teaching, research and clinical practice involved in the diagnosis and treatment of mucosal lesions.

In one such case, a healthy 22-year-old man presented with an asymptomatic 2 by 2.5 cm well-delineated, bilaterally symmetrical erythematous, nonblanching lesion of the palate (Panel A). No systemic symptoms were noted. The lesion persisted after a 2-week course of topical corticosteroid treatment. A subsequent incisional



biopsy revealed a non-specific interface mucositis, which was negative for fungal microbes (Panel B). On the follow-up visit, the patient mentioned the use of cinnamon flavored breath freshener strips for the past 2 years. At this point our clinical impression was that of a contact stomatitis from an artificial cinnamon flavoring agent contained within the strip. Cinnamon oil in chewing gum, candy, toothpaste, mouthwash and many other products can cause a contact stomatitis manifesting as a diffuse or localized, erythematous lesion with or without whitish hyperkeratotic areas. The patient discontinued the use of breath freshener strips for 6-weeks with a complete resolution of the lesion.

For a more serious case from our Oral Pathology Service, please see the Pathology and Cell Biology website at: <http://pathology.columbia.edu/>. The departmental website will soon feature a Case of the Month that will be edited by Dr. Helen Remotti.

Carol Mason to IOM!



The Newsletter takes great pleasure in announcing that Dr. Carol Mason is one of 65 distinguished scientists or physicians who have been elected to the Institute of Medicine of the National Academy

of Sciences. The Institute of Medicine is an independent, nonprofit organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public. Congratulations to Carol.

Promotions

Bachir Alobeid, MD has been promoted to Professor of Clinical Pathology, as has Govind Bhagat, MBBS. Peter Canoll, MD, PhD to Associate Professor and Lorraine Clark, PhD has advanced to Associate Professor of Clinical Pathology. Fiona Doetsch, PhD has been promoted to Associate Professor, with tenure.

Ali Naini, PhD and Patrice Spitalnik, MD have been promoted to Associate Professor of Clinical Pathology. Kurenai Tanji, MD is now Associate Professor of Clinical Pathology (in Neurology).

The Med to Grad Program



New students in the Med into Grad Program are chosen from several PhD programs. From the left: Mike Badgley (Pathology), Liz Millings (Nutrition), Eliezer Stavsky (Neuroscience), Moneek Madra (Nutrition), Dana Alessi (foreground, Cell, Molecular and Biophysical Studies, CMBS), Netonia Marshall (Pathology), Liz Nagle (CMBS), Franklin Marshall (Pathology), Ambar Grijalva (Nutrition), and Annina DeLeo, (CMBS).

The Med into Grad program is a new program at CUMC that is designed to incorporate an understanding of the principles of medicine and disease into the education of Ph.D. researchers. The program is supported by the Howard Hughes Medical Institute and the CTSA at Columbia and is directed by department members Drs. Ronald Liem, Steven Spitalnik, Howard Worman, and Patrice Spitalnik.

Students in the program take a one year course in the “Mechanisms of Human Disease,” which describes the pathophysiology of organ systems and their roles in disease. In addition to intensive reading and discussion of the pathologies associated with a disease and their molecular basis, students meet patients and their caregivers. This is a new experience for Ph.D. students, who do not usually see the effects of a disease on another person.

During the year that they are part of the Med into Grad Program students go on rounds with Attending Physicians in Medicine, and are assigned a clinical mentor in their areas of research. They attend clinic or rounds with their clinical mentors twice a month. The Program Directors meet with the students twice a month and the students take turns presenting cases that they have observed. The program is now in its second year and has been enthusiastically reviewed by the students who have finished the program and by the faculty who enjoy teaching in it.

New Pathobiology and Molecular Medicine PhD Students



From the left: Chang Liu, comes from Tsinghua University; Kristin Politi graduated from Franklin and Marshall College. Wolfgang Pernice, though a native of Germany graduated from Imperial College, London. Joshua Cook is a Columbia MD/PhD student. Jennifer Crowe comes to us from Haverford College and Patricia Sheehan from Skidmore College.

In Memoriam

Dr. David Colman



David and Liz Colman, in a moment of celebration.

David Colman died in late May. His accomplishments were exceeded only by his humanity. At the time of his death, Dave was the head of the Montreal Neurological Institute where he had a major role in maintaining that famous institution. He had a productive career with many publications and a devoted collection of friends and students. For those of us who knew him in his years in The Departments of Anatomy and Cell Biology and Pathology, he was a scientist, a conversationalist, and a friend beyond measure. His students loved him and still do. We called him Dave the Dude, a tribute to a certain un-definable style. The Department salutes his memory, as do his students from that time: Susan Staugaitis, MD/PhD, Michele Sinoway, PhD, ChingWen Yang, PhD, Joe Doyle, PhD, Donatella D’Urso, PhD, Bernadette Alinquant, PhD, Serge Timsit, MD, Kazuo Kitagawa, MD and Mika Yoshida, MD/PhD. Our thoughts go out to Elizabeth and their daughters Monica and Miranda.

Richard Kessin

New Faculty



Shan Zha, MD, PhD

Assistant Professor of Pathology and Pediatrics

In the Zha Lab, my colleagues and I are interested in how mammalian cells, especially developing lymphocytes handle DNA double strand breaks to suppress oncogenic translocations. DNA double strand breaks are the most severe form of DNA damage. In particular, lymphocyte development requires ordered assembly and subsequent modification of the antigen receptor genes through two programmed DNA double strand break repair events - V(D)J recombination and class switch recombination. The breaks during V(D)J recombination and Class switch recombination are initiated by lymphocyte-specific proteins, the repair of these breaks depends ubiquitously expressed DNA damage response factor (e.g ATM kinase and its substrates) and the Non-Homologous End Joining (NHEJ) pathway. Mistakes in resolving those programmed DNA double strand breaks often lead to large chromosome rearrangements such as translocation, gene amplification and deletions, which are the hallmarks of lymphoma and leukemia. Accordingly human patients with mutations of genes among the ATM mediated DNA damage response pathway or the NHEJ pathway are often immune deficient and are predisposed to lymphoid malignancy. Somatic mutation of ATM and its downstream factors are also found in a large number of human lymphoid malignancies. In our laboratory, we develop and characterize mouse models with defects in key DNA repair and response factors to delineate the functional interaction between DNA dam-

age response factors and the NHEJ pathway and to better understand the etiology of human diseases – especially primary immunodeficiencies and lymphoid malignancies, associated with these mutations. In addition to the mechanistic studies, the animal models we developed also provide useful platforms for pre-clinical studies.



Clarissa L. Waites, PhD

Assistant Professor of Pathology and Cell Biology

My laboratory studies molecular mechanisms underlying the formation, function, and stability of excitatory synapses in the central nervous system. Our focus is on ubiquitination, a post-translational modification that targets proteins for degradation and also regulates their intracellular trafficking and binding interactions. We have recently discovered that local imbalances in synaptic protein ubiquitination can trigger a massive degradative response within the entire neuron, leading to synapse degeneration and eventual cell death. We are currently investigating whether such a mechanism could contribute to the etiology of neurodegenerative diseases such as Alzheimer's. Our other major area of study is how protein ubiquitination regulates normal synaptic function. In particular, we are investigating its role in neurotransmitter release from the presynaptic compartment, and in the trafficking of neurotransmitter receptors in the postsynaptic compartment. Our long-term goal is to facilitate the development of treatments for neurodevelopmental and neurodegenerative disorders that are linked to defective synaptic ubiquitination, including Angelman syndrome and Parkinson's disease.

Honors and Awards

Dr. Karl Perzin received the Outstanding Teacher Award

Over five decades at Columbia, Dr. Karl Perzin has earned a reputation as an outstanding diagnostician and researcher. It is, however, his abilities as a teacher which the residents, past and current, wish to celebrate by naming our Outstanding Teacher in Anatomic Pathology Award in his honor. This award, given annually, will now be the Karl Perzin Award.

Dr. John Crary and **Dr. Andrew Teich** have been selected as the winners of the 2011 Louis V. Gerstner, Jr. Scholars Program award. Designed to support physician-scientists in their goal of bringing new treatments to patients, the initiative selected its first winners in 2008.

Qing Fan, Assistant Professor of Pharmacology and Pathology and Cell Biology has won the McKnight Scholar Award

Michael D. Gershon was elected a member of the American Clinical and Climatological Association (ACCA). In other good news Mike and Anne Gershon were awarded a grant from NIH to study VZV in the enteric nervous system: pathogenesis and consequences. This is a very long standing and happy collaboration.

Ira Tabas, MD, PhD was awarded the 2011 Alumni Research Achievement Award, Washington University School of Medicine

Dr. Anjali Saqi received the "The Dr. Karl Perzin Anatomic Pathology Faculty Teaching Award."

Dr. Adrianna Colovai received the 2011 Joseph G. Fink Laboratory Medicine Faculty Teaching Award.

Dr. Ali Naini, after many years in the Department of Neurology, has been appointed to the Department of Pathology and Cell Biology, where he is in charge of many of our molecular diagnostic tests.

Dr. Julie Canman has received the coveted NIH Director's New Innovator Award. The title of the grant is "IR-LAMP: Optogenetic technology to spatially manipulate protein function *in vivo*". See article on back cover.

Our New Residents



Anne Koehne de Gonzalez, MD

Anne received her MD from the University of Maryland School of Medicine where she carried out research on the epidemiology of bacterial colonization of ICU patients. She received her BA from Cornell University in Linguistics and Cognitive Science.



Hemant Varma, MBBS, PhD

Hemant received his MBBS from the All-India Institute of Medical Sciences. He received his PhD from Michigan State University in Biochemistry and Molecular Biology. He was a post-doctoral scientist at MIT where he worked with Brent Stockwell on the discovery of small molecules that prevent neurodegeneration in Huntington's disease models.



Allison Mautone, MD

Allison received her MD from the University of Medicine & Dentistry of New Jersey-New Jersey Medical School. Her research interest was in osteogenic differentiation of mesenchymal stem cells. She received her BS from the University of Virginia in Biomedical Engineering.



Paul Rosenstiel, MD, PhD

Paul received both PhD and MD degrees from the Mount Sinai School of Medicine. His thesis subject was in the Role of HIV-1 Vpr in the tubular epithelial cell pathogenesis of HIV nephropathy. He received his BS degree from Duke University where he studied Biomedical Engineering.



Fresia Pareja Zea, MD, PhD

Fresia received her MD from the Universidad Catolica de Santa Maria, Peru. She received her PhD from the Weizmann Institute of Science in Molecular and Cellular Biology. Her thesis was on the role of deubiquitinating enzymes in the EGF signaling pathway in breast cancer.



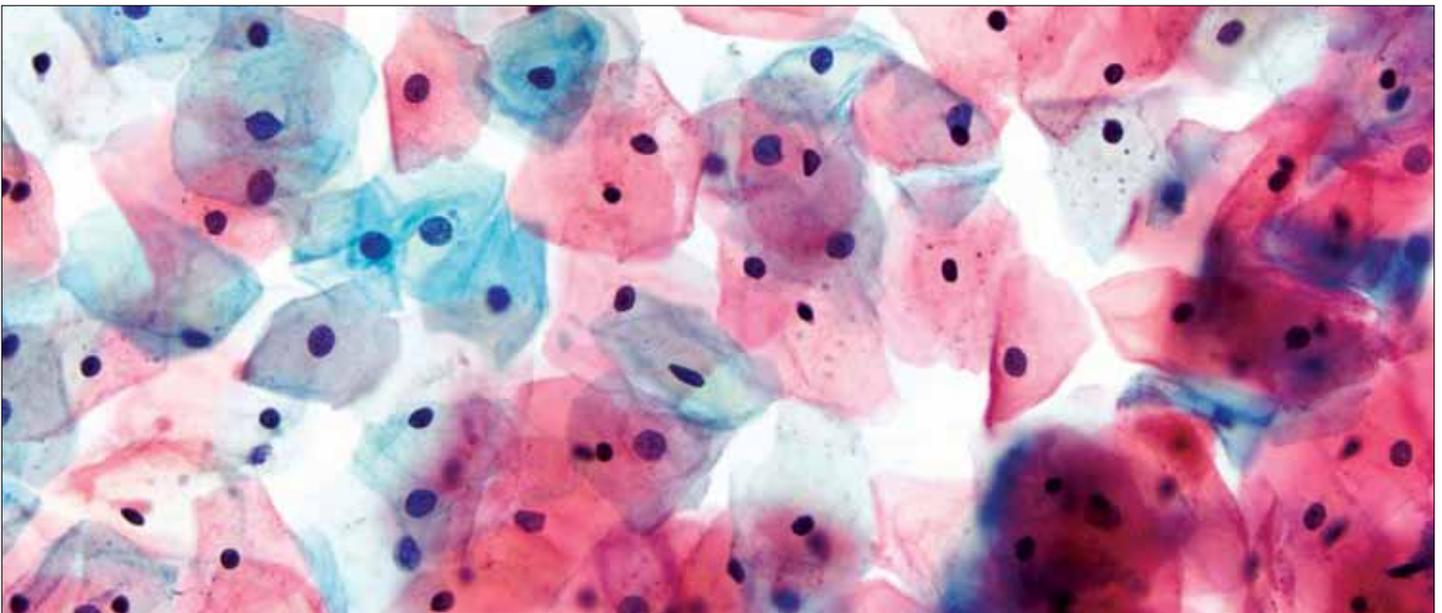
Patricia Marie Raciti, MD

Patricia received her MD from New York Medical College. She received her BA from Harvard University where her major was History & Literature. Her research interests include leptin regulation of neuroendocrine function. She was once a financial analyst in Morgan Stanley's Strategy and Execution Group.



David Thomas Terrano, MD, PhD

David received his MD from the University of Arkansas. He also received his PhD from Arkansas where his thesis was: Identification of Cdk1/cyclin b as the Vinblastine Activated Bcl-xL Kinase. He received his BA degree from the College of Wooster, Wooster, Ohio, where he studied biochemistry. He has also worked at The University of Chicago where he pursued an interest in mouse models of Alzheimer's disease.



Squamous cells from a Pap smear, courtesy of Anjali Saqi, MD. See article on page 10.

Our New Fellows



Tatyana Gindin, MD, PhD (Hematopathology). Tatyana received her MD and PhD degrees from the Mount Sinai School of Medicine. Her research interest was the *Allosteric regulation of blood coagulation factor VII*. She did her CP Residency at The New York Presbyterian Hospital, Columbia University Medical Center.



Shafinaz Hussein MD (Hematopathology) Shafinaz received her MD from New York Medical College and did her AP/CP Residency at The New York Presbyterian Hospital, Columbia University Medical Center.



Stephen Lagana, MD (Surgical Pathology and Gastrointestinal and Liver Pathology) Stephen did his MD at the University of Pittsburgh School of Medicine and his AP Residency at The New York Presbyterian Hospital, Columbia University Medical Center.



David Pisapia, MD (Neuropathology). David completed his MD at Weill Cornell Medical College and did his AP Residency at The New York Presbyterian Hospital, Weill Cornell Campus.



Shree Sharma, MD (Renal Pathology) Shree did his MD at the All India Institute of Medical Sciences, New Delhi, India. He completed his AP/CP Residency at The University of Arkansas for Medical Sciences



Denisa Slova, MD (Surgical Pathology). Denisa completed her MD at the Faculty of Medicine, Tirana University in Albania and did her AP/CP Residency at St. Luke's-Roosevelt Hospital Center in New York.



Marcela Salomao MD (Surgical Pathology and Gastrointestinal and Liver Pathology). Marcela did her MD at the State University of Campinas in Brazil and did her AP Residency at The New York Presbyterian Hospital, Columbia University Medical Center.

Homage to the Lens



As lovers of fine optics and photography, Pathology and Cell Biology Reports thought you would like to see Saturn eclipsing the sun taken by the orbiting Cassini spacecraft. The night side of Saturn is partly lit by light reflected from its own ring system. The rings appear dark when silhouetted against Saturn, but bright when viewed away from Saturn, slightly scattering sunlight in this exaggerated color image. Saturn's rings light up so much that new rings were discovered. Seen in spectacular detail, is Saturn's outermost E ring, created by the newly discovered ice-fountains of the moon Enceladus. The ice-fountains of Enceladus sound like science fiction but they are real. There is a small dot at about 10 o'clock. This is the Earth. Courtesy of the Cassini Imaging Team.

Pathologists and Microscopes Support Women's Health

Years ago Columbia University invested in excellent Nikon microscopes that we used to teach histology to dental and medical students. Times move on, to the chagrin of some of us, and the microscopes have been replaced by computers. The microscopes are quite good and in excellent condition, so we have wondered what to do with them. They have found a number of interesting homes but two of the best were found by Dr. Anjali Saqi in Rwanda and Dr. Ellen Greenebaum in Peru. Both are dedicated to issues of women's health.

In Rwanda, the Kibagabaga Hospital specializes in fistula repair – a terrible condition that arises from prolonged childbirth without medical attention. The efforts of the hospital are supported by The International Organization for Women and Development, Inc. whose efforts have now expanded beyond fistula repair. Find out about the extraordinary efforts of this organization at: <http://www.iowd.org/>. Dr. Saqi recently spent a week in Kigali at the King Faisal Hospital where she developed templates for surgical pathology and cytology reports.



Technician Paul Gasana, Director of Kibagabaga Hospital, Dr. Christian Ntzmira, and IOWD Dr. Josh Holden of CUMC ObGyn. Delivering the microscope brought by Pathologist Dr. Anjali Saqi to Kibagabaga Hospital.

In June, Dr. Ellen Greenebaum took another of our microscopes to Cusco, Peru where there is a serious medical problem. In the splendor of the Andes Mountains, there is a sinister disease. It is cervical cancer- a lethal condition that is entirely preventable. Peruvian women, particularly those who live in the isolated mountain regions have one of the highest rates of cervical cancer in the world. Although culturally rich, many women lack the financial means and geographic access to preventive healthcare enjoyed by others in more developed nations.



Nurse Anesthetist Rebekah, Dr. Yonas, Dr. Yong, Dr. Anjali Saqi, Dr. Dave and Nurse Anesthetist, Kathryn. (people go by first names).

CerviCusco was created to advance cervical cancer prevention with the goal of reducing the morbidity and mortality of cervical neoplasia in Peruvian women. The organization has built a culturally sensitive, comprehensive cervical cancer prevention program at which Dr. Greenebaum volunteered. CerviCusco provides high quality screening, diagnostic and therapeutic medical services, unique expertise and has resources to ensure that even impoverished women receive care. The



Reading Pap smears at CerviCusco.

modern medical center employs trained Peruvian medical personnel to maintain a sustained, permanent medical presence in the region. Foreign medical providers enhance the care delivered at CerviCusco, by educating the public and medical community about cervical cancer prevention and advance the scientific discovery process through INS-approved clinical studies. See <http://www.cervicusco.org>.

People who are interested in aiding either of these efforts should contact Dr. Saqi or Dr. Greenebaum.



Ellen Greenebaum (left) and colleague at Machu Picchu

New Grants

Asa Abeliovich

Collaborative Effort in Stem Cell Biology
Leona M. and Harry B. Helmsley Charitable Trust
(with The Salk Institute)

Peter Canoll

Predicting and Controlling Glioma Recurrence: The Role of Heterogeneity and Microenvironment
James S. McDonnell Foundation

Raphael Clynes

1. Role of Immunity in Efficacy of Chemotherapy Plus Trastuzumab
National Cancer Institute

2. Epigenetic events underlying Type I diabetes

National Institute of Diabetes and Digestive and Kidney Diseases

3. Epigenetic Biomarkers of Type 1 Diabetes Progression
Juvenile Diabetes Research Foundation International

4. Pathogenic Role of Islet Cell Autoantibodies in Type I Diabetes
National Institute of Diabetes and Digestive and Kidney Diseases

5. Role of Islet Cell Antibodies in Autoimmune Diabetes
Juvenile Diabetes Research Foundation International

Vivette D'Agati

1. Pathogenesis of HIV Associated Nephropathy
NIDDK in collaboration with Baylor College of Medicine

2. The New York CKD Biomarker Discovery Program
NIDDK in collaboration with Mt. Sinai School of Medicine

Gilbert Di Paolo

The Study of Phosphatidic Acid and Phospholipase D in Membrane Trafficking
NIGMS

Fiona Doetsch

1. Mechanisms and significance of stem cell fate plasticity in the adult hippocampus
New York State Research Foundation for Mental Hygiene

2. Cerebrospinal fluid regulation of adult neural stem cells

New York State Department of Health

3. Perivascular niche for adult neural stem cells

National Institute of Neurological Disorders and Stroke

Karen Duff

1. Profiling Pathologically Normal ApoE Variants to Identify Pathways for AD
NINDS

2. Autophagic Function in Tau Clearance: Biochemical and Therapeutic Implications
NINDS

3. "Spatio temporal relationship of pathology and functional decline with tauopathy"
NINDS

Gregg Gundersen

1. The Nucleocytoskeleton in Progeria and Aging

National Institute of Child Health & Human Development

2. Role of Nucleo-cytoskeleton Interactions in Cell Migration
National Institute of General Medical Sciences

Christopher Henderson

1. "Columbia SMA Project: Role of MMP-9 in Motor Neuron Susceptibility to "SMA"
Department of The Army, Army Medical Research and Materiel Command

2. P2 ALS Initiative **Project A.L.S.**

3. Collaborative Effort in Stem Cell Biology
Leona M. and Harry B. Helmsley Charitable Trust
(with the Salk Institute)

4. High-Throughput Screening and Chemistry Shared Facility
SYSTEM

Tae-Wan Kim

Screening for AD Therapeutics Based on a Novel Lipid Phosphatase Target
National Institute on Aging

Brian McCabe

Deciphering the Genetics of Synapse Development by Whole Genome Sequencing
National Institute of Neurological Disorders and Stroke

George Mentis

1. SMA as a progressive synaptic disease
Families of Spinal Muscular Atrophy

2. The Loss of Proprioception As a Mechanism Underlying the SMA Phenotype
Department of The Army, Army Medical Research and Materiel Command

Umrao Monani

1. Determining Developmental/Temporal

Requirements of The SMN Protein
Muscular Dystrophy Association

2. Investigating the Temporal Requirements of the SMN Protein
SMA Europe

Livio Pellizzoni

1. Therapy for Spinal Muscular Atrophy
National Institute of Child Health & Human Development
(in collaboration with The Ohio State University)

2. Columbia SMA Project: Identification of Genetic Modifiers of SMN Expression and Function
Department of The Army, Army Medical Research and Materiel Command

Liza Pon

Mitochondrial-Cytoskeletal Interactions and Aging
National Institute of General Medical Sciences

Serge Przedborski

1. Pre-Clinical Testing of New Hydroxybutyrate Analogues
Department of The Army, Army Medical Research and Materiel Command

2. Pre-clinical testing of necrostatin as a potential small molecule for the treatment of ALS
National Institute of Neurological Disorders and Stroke

3. PINK1 Role in Mitophagy
Thomas Hartman Foundation for Parkinson's Research, Inc.

4. P2 ALS Initiative
Project A.L.S.

Michael Shelanski

National Alzheimer's Coordinating Center (NACC) Year 13
National Institute on Aging
(with University of Washington)

Richard Vallee

1. Targeting of Cytoplasmic Dynein to the Nuclear Envelope During Brain Development
National Institute of Child Health & Human Development

Hynek Wichterle

1. P2ALS Initiative
Project A.L.S.

2. Collaborative Effort in Stem Cell Biology
Leona M. and Harry B. Helmsley Charitable Trust
(with the Salk Institute)

Julie Canman Awarded Director's New Innovator Award



Julie C. Canman, PhD, Assistant Professor in the Pathology and Cell Biology department, has been awarded a 2011 Director's New Innovator Award from the NIH. This grant will provide \$1.5 million

in funding over five years. The funding will be used to develop novel infrared laser-based optigenetic technology to manipulate protein function at precisely defined moments and positions during a complex cellular behavior while simultaneously monitoring the kinetic effects on that behavior. Proper temporal and spatial molecular regulation is critical for the accuracy of complex cellular behaviors such as cell division, cell migration, and polarity establishment. Localization of a given protein to the centrosomes vs. within the nucleus, for instance, presents an entirely different molecular niche and potentially different function for that protein. The Canman lab will develop this technology to understand how protein localization to distinct sub-cellular structures contributes to accurate cell division, a process fundamental to the development and homeostasis of all multi-cellular organisms. Once developed, this technology will be applicable to any cellular or developmental process accessible to light microscopy, such as studies on cell adhesion, cell migration, neuronal signaling/path-finding, or programmed cell death.

Notable Paper

In an important paper, the Abeliovich laboratory has succeeded in converting fibroblasts of Alzheimer and normal subjects to dopaminergic neurons. The Abstract speaks for itself:

Directed conversion of Alzheimer's disease patient skin fibroblasts into functional neurons.

Qiang L, Fujita R, Yamashita T, Angulo S, Rhinn H, Rhee D, Doege C, Chau L, Aubry L, Vanti WB, Moreno H, Abeliovich A.

Cell. 2011 Aug 5;146(3):359-71.

Departments of Pathology & Cell Biology, and Neurology and Taub Institute, Columbia University, New York, NY 10032, USA.

Directed conversion of mature human cells, as from fibroblasts to neurons, is of potential clinical utility for neurological disease modeling as well as cell therapeutics. Here, we describe the efficient generation of human-induced neuronal (hiN) cells from adult skin fibroblasts of unaffected individuals and Alzheimer's patients, using virally transduced transcription regulators and extrinsic support factors. hiN cells from unaffected individuals display morphological, electrophysiological, and gene expression profiles that typify glutamatergic forebrain neurons and are competent to integrate functionally into the rodent CNS. hiN cells from familial Alzheimer disease (FAD) patients

with presenilin-1 or -2 mutations exhibit altered processing and localization of amyloid precursor protein (APP) and increased production of A β , relative to the source patient fibroblasts or hiN cells from unaffected individuals. Together, our findings demonstrate directed conversion of human fibroblasts to a neuronal phenotype and reveal cell type-selective pathology in hiN cells derived from FAD patients.

Our Diagnostic Services

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

Web:

www.pathology.columbia.edu

Email:

pathology@columbia.edu

Laboratory services:

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

Administrative Services:

1-212-305-7164

A Note on Publications

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

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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

CUMC IT

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

Senior Associate Proofreaders

Ms. Cindy Kitzinger

Ms. Casey Schadie

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If you have comments or questions, contact:

Dr. Richard H. Kessin

at 212.305.5653

Email: rhk2@columbia.edu