

FSM Research Newsletter

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Feinberg School of Medicine Office for Research
Northwestern University

GOLDMAN LABORATORY CONTINUES GROUNDBREAKING PROGERIA RESEARCH

Robert Goldman, PhD, the Stephen Walter Ranson Professor and chair of the Department of Cell and Molecular Biology is well known for his pioneering research into the structure and function of the nuclear lamins, one subgroup of the large family of intermediate filament proteins. Recently an ever-increasing number of mutations in the gene encoding one of these proteins, nuclear lamin A, have been identified as causative factors in a wide range of human diseases. Quite remarkably, the latest tally shows that there are more than 300 mutations in the lamin A gene leading to a wide range of diseases including muscular dystrophies, cardiomyopathies, lipodystrophies, and premature aging diseases such as Hutchinson-Gilford Progeria Syndrome, or simply progeria. Progeria is a rare aging disease of children that affects about 1 in 4 million. At birth, children with the disease appear normal. However, their growth soon slows, and children with progeria show signs of accelerated aging, such as hair loss, wrinkled skin, loss of body fat, and osteoporosis. A 10-year-old child with progeria typically looks like an 80-year-old adult. The disease also leads to atherosclerosis and death at an average age of 14 due to strokes and heart attacks.

Dr. Goldman and his coinvestigators have previously reported on

experiments that show that progeria mutations in the lamin A gene interfere with key regulators of gene expression and of the cell cycle. Their first study discovered that the most common progeria-linked mutant lamin A protein, known as progerin, alters the organization of regions of chromosomes that are critically important in regulating gene expression. A second study revealed that mutant lamin A proteins turned up in the wrong place—too tightly linked to the membranes of the nuclear envelope—which disrupted their functions during cell division and other stages of the cell

cycle. The localization failure of mutated lamin A proteins would severely compromise the ability of progeria cells to engage in normal DNA replication, a probable factor in their premature senescence.

Now, Dr. Goldman and researchers at Feinberg, the Institute of Human Genetics in Munich, and the Laboratory of Supramolecular Biophysics in Hokkaido, Japan have reported research that provides new insights into the mechanisms responsible for lamin functions. The study, "The A- and B-Type Nuclear Lamin Networks: Microdomains Involved in Chromatin Organization and Transcription," was published in the December 15 issue of *Genes and Development*. In this article, Dr. Goldman and his colleagues explain that the nuclear lamins normally function in the regulation of transcription and epigenetic modifications of chromatin. However, they note that the mechanisms responsible for these lamin functions are poorly understood. Their research demonstrates that A- and B-type lamins form separate but interacting stable meshworks in the lamina and have different mobilities in the nucleoplasm as determined by fluorescence correlation spectroscopy. They showed that silencing lamin B1 expression dramatically increases the lamina meshwork size and the mobility of nucleoplasmic lamin A. The results of this study suggest that the A-type lamins are preferentially associated with gene-rich regions of chromosomes. This was demonstrated by the introduction of a novel method for the laser-based microdissection of small regions of nuclei enriched in lamin A and determining their specific chromosome content. Based upon their recent findings the Goldman group concludes that in normal cells, the meshworks of A-type and B-type lamins provide functionally different microenvironments whose coordinated activities finely tune the regulation of gene expression. Dr. Goldman and his co-investigators believe these findings could have important implications for understanding progeria and a host of other laminopathies.



Robert Goldman, PhD

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It is noteworthy, too, that Dr. Goldman's pioneering studies on nuclear lamins have been useful in developing clinical trials that offer hope to families of children with progeria. Dr. Goldman and others have shown that the posttranslational

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MEET TANYA SIMUNI, MD



*Associate Professor, Neurology
Director, Parkinson's Disease and Movement Disorders Center*

What Are Your Research Interests?

My research centers on finding pharmacologic therapies that are useful in caring for patients with movement disorders. In particular, my work focuses on finding treatment options that are effective for patients at different stages of Parkinson's Disease. I also collaborate on a number of

studies with my colleagues at Feinberg and at the Rehabilitation Institute of Chicago (RIC). For example, at RIC, I am collaborating on studies exploring non-pharmacologic therapies, like physical therapy for gait and balance, for patients with Parkinson's Disease.

What Are You Working on Now?

I am the principal investigator of a new study, which just received funding from the Michael J. Fox Foundation for Parkinson's Research. It is a pilot phase II double-blind, placebo-controlled clinical trial, which is aimed at determining safety, dosage, and relative efficacy of the drug, isradipine, in patients with early-stage Parkinson's Disease. This study represents the translational project based on the work done by D. James Surmeier, PhD, the Nathan Smith Davis Professor and chair of physiology, demonstrating that the drug isradipine, an FDA-approved antihypertensive agent, is neuroprotective in animal models of parkinsonism.

The study will recruit 100 patients with early Parkinson's Disease, from 17 centers nationwide, who are not yet taking any medications to treat their symptoms. They will be assigned to one of four treatment groups: 5 mg, 10 mg, 20 mg, or placebo. They will be followed for 12 months. The safety of each dose of isradipine will be evaluated first based on the number of patients able to complete the study on their original dosage amount, and the rate and severity of side effects. If all dosages are tolerable, the dosage that is most effective will be selected based on the comparison of the rate of progression of Parkinson's symptoms in each group over the 12 months of the study. The tolerable dosage that is deemed most

effective will then be used in future studies to determine if isradipine slows the progression of Parkinson's Disease.

What Are the Goals of This Research?

At this time, there are no treatment modalities that have been proved to stop or slow the progression of Parkinson's Disease. Having a drug that significantly slows the progression of the disease would greatly broaden the therapeutic window for treatments aimed at lessening the symptoms in the early stage of disease, thus improving the quality of our patients' lives. As a clinician, I am keenly aware of the importance of finding better ways to treat the disease early and effectively.

Why Did You Choose Northwestern?

I came to Northwestern in 2000 to be the director of the Parkinson's Disease and Movement Disorders Center, and I can now say it was the most exciting and fulfilling decision I ever made. Today, the center cares for approximately 1,500 patients, including those with Parkinson's Disease and other movement disorders, including dystonia, tremor, tic disorders, and myoclonus, to name a few. This is a wonderful program because it coordinates all of the care and services our patients and their families need: physical, occupational and speech therapy, social work, etc, and the full range of resources available at Northwestern, including RIC, for example. Of course, research, such as the work we have done investigating isradipine and multiple other clinical trials, raises the level of care, too, allowing us to offer our patients hope. In caring for patients with Parkinson's Disease, our clinical and research efforts are both well recognized. The Parkinson's Disease and Movement Disorders Center is a National Parkinson's Disease Foundation Center of Excellence, and collaborating with the the Udall Center of Excellence for Parkinson's Disease Research that is directed by Dr. Surmeier.

What Are the Challenges You Face?

As a clinician and researcher, I face the challenges of combining a busy clinical practice with the demands of research. But this is exciting, too, and allows me the rewards of seeing our research efforts translated into better care.

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processing of lamin A is required for its normal functions in nuclei. One of these changes involves farnesylation of the C-terminal CAAX box, an important step in the targeting of lamin A to the membrane of the nucleus. Under normal conditions this farnesylation site is removed to form mature lamin A so that it is properly incorporated into the nuclear lamina. However the mutant protein, progerin, becomes permanently farnesylated and so appears to be the major causative factor in this disease. This basic knowledge has led to the rapid implementation of a drug trial employing a farnesyl transferase inhibitor, lonafarnib. Since the mutation in the gene (LMNA) causing progeria was only discovered in 2003, this represents an unusually rapid transition from the lab bench to the bedside and demonstrates the enormous importance of basic biomedical research. Had the information produced by the Goldman lab and several others worldwide not been available when the disease gene was discovered, implementation of drug trials would have been delayed by many years, perhaps even decades.

SPONSORED AWARDS

**Raymond Bergan, MD**

Director, Experimental Therapeutics
Robert H. Lurie Comprehensive Cancer Center

Project title: Genistein-Mediated Regulation of Prostate Cancer Cell Motility
Sponsor: National Cancer Institute

The ability to therapeutically inhibit metastasis represents a long sought-after goal. The project has shown for the first time that transformation to a metastatic phenotype can be halted in prostate cells in man by the natural product, genistein. The goals of this R01 are to advance the understanding of the molecular regulation of metastatic transformation in human prostate cancer, to characterize the molecular pharmacology of therapeutically targeting regulatory pathways, and to assess both these factors in vitro and in murine xenograft models.

[Click here for a list of recent FSM sponsored awards](#)

**Linda Teplin, PhD**

Professor of Psychiatry

Project title: Assessing ADM Disorders Among Juvenile Detainees
Sponsor: Department of Justice, Office of Juvenile Justice and Delinquency Prevention, cofunding from the Centers for Disease Control and Prevention

This grant cofunds the Northwestern Juvenile Project, the first large scale, longitudinal study of health needs and outcomes of delinquent youth. For this study, Dr. Teplin's team tracks and reinterviews 1,829 participants, recruited when they were first arrested and detained between 1995 and 1998, when they were aged 10-18 years. Participants are now in their mid-twenties to early thirties. This epidemiologic study examines psychiatric disorders, patterns of service utilization, HIV/AIDS risk behaviors, mortality, and other health outcomes.

The Northwestern Juvenile Project is funded by a consortium of federal agencies and private foundations. In addition to the funding described above, the project recently received two five-year grants from the National Institute of Drug Abuse (one cofunded by the National Institute on Alcohol Abuse and Alcoholism) to study how patterns of drug abuse and incarceration affect HIV/AIDS risk and infection in emerging adulthood and young adulthood.

**A. Vania Apkarian**

Professor of Physiology

Project title: Cortical Pathophysiology of Pain
Sponsor: National Institute of Neurological Disorders and Stroke

Chronic back pain is a major health problem and there is little understanding of its underlying mechanisms. We have shown that many brain properties are different in chronic back pain patients in contrast to healthy controls. Here we examine these brain biomarkers as we track subjects transitioning from subacute back pain to either pain resolution or to chronic pain, over an 18-month monitoring period, and contrast these outcomes to healthy controls and to more chronic back pain patients. We also plan to build models for predicting chronic pain based on brain parameters measured in the subacute stage.

ANIMAL RESEARCH CORNER



The CCM veterinary staff has recently identified pinworms (*Aspicularis tetraaptera*) in a group of imported mice in the Evanston-quarantine facility. Because of space constraints, these animals shared a cubicle with other investigators' mice, and cages of the latter were released from quarantine and transferred to the Lurie barrier facility. Because of possible cross-contamination, released animals that were housed in the same cubicles as pinworm-positive mice are considered "pinworm-suspect" and are being treated prophylactically. Investigators who had mice in quarantine in conjunction with the pinworm-positive animals have been individually notified.

Pinworms reside in the cecum and colon of mice. Infections in mice are usually subclinical in immunocompetent mice; however, in severe infestations, clinical signs include rough hair coat, decreased growth rates, constipation, decreased intestinal motility, rectal prolapse, and possibly altered immune responses.

Transmission occurs through the transfer of eggs that are excreted in the feces. The eggs are very light and may be carried on air currents as well as transferred via fomites such as clothing, paper or



Pinworm egg

experimental manipulanda. The eggs are extremely difficult to eradicate as they are resistant to heat, chemical, and desiccation and may remain viable in the environment for extended periods of



Pinworm (*Aspicularis tetraaptera*)

time. The most effective methods of eradication include environmental decontamination, treatment of animals with deworming agents, or rederivation of animals.

If you have animals housed in a pinworm positive or suspect location, we strongly urge you to follow posted precautions. Any questions regarding pinworms may be directed to either Dr. Nicolette Zielinski-Mozny at n-zielinski-mozny@northwestern.edu or Dr. Tracy Gluckman at t-gluckman@northwetsern.edu.

STUDENT PROFILE: BLAYNE AMIR SAYED



*MSTP
Class of 2008*

Where is your hometown?

I grew up most of my life in Richmond, Virginia but my family moved to Charlottesville, Virginia in 2002, so that has been

home for the last few years. If you've never been there, it's worth a visit—an artsy college town tucked into the foothills of the Blue Ridge Mountains.

Where did you go for your undergraduate degree?

I went to the University of Virginia where I majored in religious studies with a concentration in Islam. I briefly contemplated pursuing my PhD in that field, but I eventually decided that esoteric basic science research was more interesting to me than esoteric study of the ineffable religious experience— but just barely.

What are your research interests?

In the long run, I'm interested in studying how particular pathogens are able to modify or suppress the immune response in order to better colonize the host and establish chronic infection.

What exciting projects are you working on?

My research focuses on understanding how mast cells influence adaptive immune responses. In particular, I am examining the role of mast cells in modulating pathogenic T cell responses in EAE (experimental autoimmune encephalomyelitis), the mouse model of the human autoimmune demyelinating disease multiple sclerosis (MS). Mast cells are awfully fascinating. They are positioned at important sites throughout the body that have direct contact with the external environment and thus are among the first responders in infection settings. They also express a wide variety of immunomodulatory molecules that can direct the adaptive immune response.

My work has shown that mast cells play an essential role in facilitating the entry of autoreactive T cells into the central nervous system, allowing these T cells to orchestrate the destructive inflammatory response that characterizes MS. Mast cells are a fairly well known entity, pharmacologically speaking,

due to their well established and crucial contribution to allergic disease, so a better understanding of how they control the inflammatory response in autoimmune disease may have some real crossover potential for human treatment.

What attracted you to the MSTP program?

Some would call it indecision, but I had an interest in both research and medicine, so the MST program seemed like a natural fit.

What has been the best (or worst) experience so far?

Graduate school has been a very rewarding, though at times frustrating, experience. Generally the most meaningful experiences come when you're able to synthesize background knowledge and new data to craft new hypotheses and experiments. Of course, these experiments don't always work and the data is often hard to interpret, thus the frustration. But self-directed learning is never easy and the payoff is acquiring the skills necessary to be a successful independent researcher.

How would you describe the faculty at FSM?

The majority of faculty members with whom I've interacted at FSM are accessible and engaging. I've needed help with various projects and decision-making processes in my years here, and there have been quite a few folks who have been very helpful to me in those regards. Foremost amongst them is my advisor, Dr. Melissa Brown.

What do you like to do for fun?

My wife and I have a toddler, so she's about all the fun that we can handle right now. We do take advantage of all that Chicago has to offer during the warmer months and are often out and about at various music and cultural festivals. We also work with several community organizations active in various peace and justice movements. Finally, we love to travel and a trip to Morocco is in the works for this spring.

What are your plans for after graduation?

Most likely I will pursue a residency in internal medicine and then a fellowship, perhaps in infectious disease. Ideally I'd like to pursue another "STP" opportunity, namely a Physician Scientist Training Program (PSTP), which would allow me to combine my residency and fellowship and facilitate the transition into a tenure track academic position.

WELCOME NEW FACULTY

Alexander Stegh joins as assistant professor of neurology. He holds a PhD in cell biology and biochemistry from the German Cancer Research Center in Heidelberg, Germany. Prior to joining FSM, he worked as an instructor in medicine in the Department of Medical Oncology at the Dana-Farber Cancer Institute of Harvard Medical School.

CHANGES IN THE RESEARCH OFFICE



The Feinberg School's office for research has recently undergone a few changes. Catie Hor, who has served as executive administrative assistant to Dr. Rex Chisholm, has been promoted to the position of manager for finance and administration in the office for research. In this role, she is responsible for the office's financial transactions, business activities, and administrative operations (budgeting, account transactions, payroll, human resources, etc). She is now charged with overseeing the annual budget for FSM research core facilities and the FSM graduate programs IGP and MSTP). She will continue to act as managing editor of the FSM Research Newsletter. "I am excited to play a part in the development and execution of strategic efforts designed to enhance the research infrastructure," she says. "I admire Dr. Chisholm's vision and passion for research, and I enjoy Feinberg's diverse and supportive environment." Catie, who has a BA in Economics from the University of Chicago, worked at the University of Chicago Hospital and the Graduate School of Business at University of Chicago before joining FSM in 2006.



Replacing Catie Hor as administrative assistant is another University of Chicago graduate, Kristin Jacobsen. Kristin is new to Feinberg, having worked for the last eight years in the world of finance and real estate development. "I was looking for an environment that would provide educational opportunities and stimulation," she says. "I am delighted to be part of such a prestigious institution and to support the important work of research." Though her degree is in English literature, Kristin admits to being interested in many things, including movies, the violin, singing, traveling, bird watching, and writing.

VISIT the new and improved
FSM Office for Research Home Page:

<http://www.feinberg.northwestern.edu/research/>

- Read regularly updated FSM research news
- Search for research-related lectures, seminars, and events
- Find resources and useful links to support the needs of FSM faculty, staff and students
- Submit news, events, comments and suggestions



WHAT'S IN THE NEWS?

New record set for research grants at Northwestern
Chicago Sun-Times – January 3
http://www.suntimes.com/news/education/1360618_w-northwestern-research-grants-010309.article

Northwestern University's sponsored research award volume climbed to \$438.8 million this year, the highest in the University's history and a 5 percent increase over last year's record-breaking \$416.4 million.

The larger dollar volume of awards in fiscal year 2008 was fueled by a 10 percent increase (\$28.7 million) from federal agencies, with the largest portion from National Institutes of Health (NIH) grants, according to a release from the university.

The Feinberg School of Medicine received \$268.7 million, accounting for more than 61 percent of the University's total. Feinberg's awards represented a 14 percent increase over 2007, following a 17 percent increase a year earlier. The majority of the research support came from the NIH, the release said.

Walking Is Good for Blocked Leg Arteries
U.S. News & World Report - January 13
<http://health.usnews.com/articles/health/healthday/2009/01/13/walking-is-good-for-blocked-leg-arteries.html>

Anyone looking for proof that a planned program of walking is good for people with the leg blood-vessel blockage called peripheral arterial disease (PAD) should check the results of a new U.S. government-funded study.

The study of 156 people with PAD—many of whom didn't have the pain that is the classic symptom of artery blockage—showed that regular six-minute walks on a treadmill improved their endurance and quality of life.

While walking is a standard recommendation for people with PAD, the study was different in two ways, said study lead author Dr. Mary M. McDermott, an associate professor of medicine at Northwestern University's Feinberg School of Medicine in Chicago.

New Mouse Model Found for Allergy
United Press International – January 13
http://www.upi.com/Science_News/2009/01/13/New_mouse_model_found_for_allergy/UPI-68181231874523/

Researchers in Chicago say they have developed a new way to get mice to mimic symptoms of humans having an allergic reaction to peanuts.

Peanut allergies affect many people, particularly young children, so finding an animal model that mimics a severe reaction will help scientists develop better treatment strategies, said Paul Bryce, who led the mouse model team at the Feinberg School of Medicine at Northwestern University.

Look for weekly event announcements and funding opportunities in your email.

UPCOMING EVENTS

Community-Engaged Research Seminar Series

"School Based Health Care Programs"

Speaker: Dr. Virginia Bishop

Date: Wednesday, January 28, 2009

Time: 11 a.m. - noon

Location: 303 E. Chicago Ave., Ward 5-230 – CHI

Contact: NUCATS Community-Engaged Research Center - Michelle Melin-Rogovin, 312-503-5050 or m-melin-rogovin@northwestern.edu

More Info: http://www.nucats.northwestern.edu/centers/cerc/seminars_and_events.html

Allergy-Immunology Research Conference

"Mechanisms of Particulate Matter Induced Inflammation"

Speaker: Dr. Scott Budinger

Date: Friday, January 30, 2009

Time: Noon - 1 p.m.

Location: 676 N. St. Clair St., Room 14018A – CHI

Contact: Division of Allergy/Immunology - Kathleen Harris, 312-503-8095 or k-e-harris@northwestern.edu

Feinberg Cardiovascular Research Institute Seminar Series

"Signaling and Signal Transduction in Cardiac Sarcomeres"

Speaker: John Solaro, PhD, Distinguished University professor and head of Physiology and Biophysics, University of Illinois at Chicago

Date: Thursday, February 5, 2009

Time: 8 - 9:30 a.m.

Location: 303 E. Superior St., Lurie Building, Baldwin Auditorium – CHI

Contact: Feinberg Cardiovascular Research Institute - Donna Ray, 312-503-2296 or dlr635@northwestern.edu

IHS Seminar Series

"Making Medical Decisions"

Speaker: Alan Schwartz, PhD, associate professor and director of Research, Department of Medical Education, research associate professor, Department of Pediatrics, University of Illinois at Chicago

Date: Thursday, February 5, 2009

Time: Noon - 1:00 p.m.

Location: 340 E. Superior St., Weiboldt Hall, Room 421 – CHI

Contact: Institute for Healthcare Studies, Allan Doeksen, 312-695-4903 or a-doeksen@northwestern.edu

Event organizers are encouraged to submit calendar items on

[Plan-it Purple](http://www.feinberg.northwestern.edu/research/calendar/). For more events, visit www.feinberg.northwestern.edu/research/calendar/.

SAVE THE DATE!

5th Annual Lewis Landsberg Research Day

Thursday, April 2, 2009

303 E. Superior St.

Lurie Medical Research Center

Ryan Atrium & Hughes Auditorium

Chicago Campus

Stay tuned for more info!

FUNDING OPPORTUNITIES

LIMITED FUNDING OPPORTUNITY: Packard Fellowships for Science and Engineering Program

David and Lucile Packard Foundation

http://www.packard.org/assets/files/conservation%20and%20science/2009_Fellowships_Guidelines_Final.pdf

Internal LOI deadline: 2/1/2009

Internal proposal deadline: 2/8/2009

Amount: \$875,000. Sixteen recipients will receive individual grants of \$875,000 distributed over five years. Of the \$175,000 paid each year, \$17,500 is available to the university as compensation for administrative costs.

Synopsis: The intent of the fellowship program is to provide support for unusually creative researchers early in their careers; faculty members who are well established and well funded are less likely to receive the award. It is further the intent of the foundation to emphasize support for innovative individual research that involves the fellows, their students, and junior colleagues, rather than extensions or components of large-scale, ongoing research programs.

LIMITED FUNDING OPPORTUNITY: NIH/NCRR Shared Instrumentation Grant Program (S10)

National Institutes of Health (NIH), National Center for Research Resources (NCRR)

<http://grants.nih.gov/grants/guide/pa-files/PAR-09-028.html>

Internal LOI deadline: 2/8/2009

Internal proposal deadline: 3/23/2009

Amount: The NCRR intends to commit approximately \$43 million in FY2010 to fund approximately 125 new awards. The minimum award is \$100,000; the maximum award is \$500,000.

Synopsis: The objective of the program is to make available to institutions expensive research instruments that can only be justified on a shared-use basis and for which meritorious research projects are described.

For more funding opportunities, visit:

www.feinberg.northwestern.edu/research/funding-opportunities/

We want to hear from you!

Your feedback and suggestions are always welcomed!

Feinberg School of Medicine Office for Research

E-mail: fsm-research@northwestern.edu

Phone: 312-503-1499 Fax: 312-503-2790

www.feinberg.northwestern.edu/research/