Feinberg Study Reveals Unique Ways Capillaries Clear Blockages

Researchers at the Feinberg School of Medicine have discovered that capillaries have a unique method of expelling debris, such as blood clots, cholesterol, or calcium plaque, which blocks the flow of essential nutrients to brain cells. The capillaries spit out the blockage by growing a membrane that envelopes the obstruction and then pushes it out of the small blood vessel.

The National Institute on Aging-funded study, led by senior author and principal investigator Jaime Grutzendler, MD, assistant professor in the Ken and Ruth Davee Department of Neurology and the Department of Physiology, was recently published in the Nature article, “Embolus Extravasation is an Alternative Mechanism for Cerebral Microvascular Recanalization.”

“The blockage of microvessels in various organs occurs frequently throughout life, with the cumulative effect often leading to organ damage,” Grutzendler says. “Our research uncovered the physiological mechanism that efficiently eliminates virtually any type of material blocking these small blood vessels.”

Experts have long understood how large blood vessels clear blockages: blood pressure pushes against the clot and may eventually break it down and flush it away, or clot busting enzymes rush to the scene to dissolve a blockage. But very little was previously known about the clearance of debris in capillaries.

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This study found that enzymes and blood pressure lack efficiency in clearing capillary blockages within the critical 24- to 48-hour period. Those mechanisms only work half the time, and only when blood clots are involved. Other types of debris, particularly cholesterol, which is difficult to dissolve, are not affected.

“We needed to find out what happens to the blood vessels that aren’t cleared — whether they die or are taken over by some other mechanism,” says Grutzendler.

To find out, the team developed a new research strategy that created micro-clots, tagged them with red fluorescence, and infused them into the carotid arteries of mice. Using a multiphoton microscope, the team examined the brains of live mice at various time intervals as clots traveled into the capillaries.

“This innovative imaging strategy allowed us to discover previously unknown mechanisms that are important to a variety of brain disease processes,” says Grutzendler.

These high-resolution images revealed that the blood vessel cells next to the blockage grew a membrane that completely enveloped the debris. Then the original wall of the blood vessel opened up and spit the debris into the brain tissue, rendering it harmless. The envelope covering the clot became the new vessel wall. This resulted in complete restoration of blood flow and salvaging of the tiny vessel and surrounding brain cells.

The scientists also discovered that it didn’t happen in humans. But, we still have to prove it,” he says.

Determining the importance of salvaging blood vessels and other cells in an organ like the brain could reap major benefits for patients suffering from age-related diseases such as vascular dementia and stroke.

“We would like to immediately begin testing pharmacological compounds in order to further our understanding,” he says. “By accelerating the process of clearing blockages, new therapies may be realized.”

The study’s collaborators include then Northwestern undergraduate students and co-first authors Carson K. Lam, BS ’06, now a third-year medical student at Feinberg, and Taehwan Yoo, BA ‘07, now a medical student at the University of Michigan. These students were joined by Bennett Hiner, MS, a post-baccalaureate research fellow, and Zhiqiang Liu, MD, a research associate — both from the neurology department.

“We engaged these students in high-risk experiments, and these major findings were the outcome of their efforts,” says Grutzendler. “The results indicate the potential for early immersion in biomedical research.”

For more information about his research, contact Jaime Grutzendler: grutz@northwestern.edu or (312) 503-5298.

Jaime Grutzendler, MD

“The slowdown may be a factor in age-related cognitive decline and may partly explain why elderly patients who get strokes do not recover as well as younger patients.”

- Dr. Jaime Grutzendler

Want to learn more about Dr. Grutzendler’s research? Attend the Feinberg Cardiovascular Research Institute seminar on January 20, 2011, to hear Grutzendler present “Of Pipes and Blood Vessels: Unclog or Perish.” The event will be held in the Baldwin Auditorium, Lurie Medical Research Center, from 8 to 9:30 a.m.

Visit the Feinberg Cardiovascular Research Institute web site for more information on the seminar.
Since joining the Northwestern University Feinberg School of Medicine faculty in 1966, her colleagues and students have recognized Paula Stern, PhD, professor and vice chair of molecular pharmacology and biological chemistry, as an exceptional educator and researcher. She received two Feinberg educational awards: the George H. Joost Outstanding Teacher Award and the Dean’s Award for Teaching Excellence. She was also lauded as a Distinguished Woman in Medicine and Science by the Women Faculty Organization. Additionally, the American Society for Bone and Mineral Research, Stern’s professional affiliation, named one of its esteemed honors after her. The annual Paula Stern Achievement Award recognizes a woman who has made significant scientific achievements in the bone field and who has promoted the professional development and advancement of women in this area.

FSM Researcher recently caught up with Stern to learn about her research and current projects.

**Q&A**

**What are your research interests?**

I am interested in bone cell biology. I focus on the mechanisms of bone formation and resorption, including the actions of hormones, cytokines, physical forces, pharmacological agents, and disease processes. Ultimately, I am interested in understanding the mechanisms of bone diseases and identifying potential new therapeutic targets.

**How did you become interested in this area?**

It was an odd transition. My PhD research in pharmacology focused on effects of hepatotoxic agents. I was intrigued by the role that the endocrine environment played, so I did post-doctoral training in endocrine research. I joined a laboratory that was doing groundbreaking work on hormone effects in bone. This was a relatively new area, especially therapeutically. At that time, osteoporosis was considered an inevitable consequence of aging. Bone research has continued to be exciting, and over the years has led me to learn more about rheumatology, immunology, nephrology, cancer, cardiology, and neuroscience, as these areas impact bone.

**How does your research advance medical science and knowledge?**

The research of my laboratory, along with studies from clinical collaborators, has allowed us to address and answer diverse questions regarding bone disease. In very early work, we developed a bioassay for the active form of vitamin D. This enabled us to understand why some patients with sarcoidosis develop hypercalcemia and address other questions related to vitamin D and calcium metabolism. Another area of interest has been thyroid–bone interactions. Our research identified the role of thyroid hormone target genes, growth factors, and cytokines involved in these effects. In other studies, we identified a factor mediating bone effects of prostate cancer metastases. We are currently studying the differential mechanisms of estrogen and androgen in males and females. Our long term research has been on parathyroid hormone, which has both anabolic and catabolic effects on bone. The different G protein-mediated signaling pathways activated by parathyroid hormone and the genes that are affected by these parathyroid hormone effects are being investigated in our current research. Recently, an accepted manuscript on that topic, co-authored by Jun Wang, PhD, research assistant professor of molecular pharmacology and biological chemistry, Annette Gilchrist, PhD, adjunct assistant professor of molecular pharmacology and biological chemistry, and me was designated a “must-read” by Faculty of 1000, which was exciting.

**How is your research funded?**

Since I came to Northwestern, our major funding has been a grant from the National Institutes of Health (NIH), “Effects of Hormones on Signal Transduction in Bone.” We have also benefitted from other funding sources. For example, some of the thyroid hormone research was supported by a Howard Hughes fellowship to a
New Dixon Translational Research Grant Awards Announced

Northwestern Memorial Foundation, the charitable arm of Northwestern Memorial HealthCare, and the NUCATS Institute are pleased to announce the Dixon Translational Research Grant awardees for FY11. The grants are awarded to Northwestern investigators for innovative multi-disciplinary clinical and translational research collaborations that accelerate the identification and implementation of new treatments to improve human health.

“These grants are an invaluable catalyst for clinical and translational research across Northwestern’s research enterprise,” said Chuck Watts, MD, chief medical officer and senior vice president of Medical Affairs, Northwestern Memorial Hospital. “We’re proud of all the investigators in this round and drew our winners from a highly competitive field of projects.”

A list of awardees follows:

Priority Research Initiative Award

• Douglas Losordo, MD, director, Feinberg Cardiovascular Research Institute and Eileen M. Foell Professor of Heart Research, will research enhancing progenitor cell function using bioactive peptide amphiphiles to improve outcomes associated with critical limb ischemia (CLI), a severe manifestation of peripheral artery disease (PAD) that can necessitate partial or complete amputation of the affected limb (usually a leg).

Innovation Awards

• Navdeep Chandel, PhD, associate professor, Department of Medicine, Pulmonary Division, will pursue research targeting SOD1 for treatment of lung cancer, specifically testing efficacy of ATN-224, an orally available small molecule that inhibits SOD1, which is required to convert superoxide to hydrogen peroxide.

• Vincent Cryns, MD, associate professor, Department of Medicine, Endocrinology Division, will examine the potential for dual anti-angiogenic and cytotoxic nanostructures as a novel breast cancer therapy.

• Francesca Facco, MD, assistant professor Department of Obstetrics and Gynecology, will study the correlation between sleep-disordered breathing and preeclampsia in high-risk women.

• Andrew Naidech, MD, MSPH, associate professor, Department of Neurology, will pursue research on cerebral infarction after intracerebral hemorrhage, a deadly form of stroke with no FDA-approved treatment.

Young Investigator Awards

• Jeffrey Allen, MD, assistant professor, Department of Neurology, will examine dosage and tolerability of alpha-lipoic acid in patients at risk for neuropathy.

• Malek El Muayed, MD, MSCI, instructor, Department of Medicine, Endocrinology Division, will study the mechanism by which cadmium impairs beta cell function without inducing global cell toxicity.

• Brian Layden, MD, PhD, instructor, Department of Medicine, Endocrinology Division, will examine role of short chain fatty acids and their receptors in human islets to identify the pathways that mediate the response of islets to insulin resistance.

• Marc Slutzky, MD, PhD, assistant professor in Ken and Ruth Davee Department of Neurology/Physiology and Physical Medicine and Rehabilitation, will evaluate the potential for a myoelectric-computer interface in stroke rehabilitation. Myoelectric-computer interfaces contain the potential to revolutionize rehabilitative medicine by improving function in patients with neurological deficits from disorders such as stroke, multiple sclerosis, spinal cord injury, or dystonia.

Pilot grant awardees are supported in part by NIH grant UL1 RR025741 from the National Center for Research Resources. For more information on NUCATS pilot funding opportunities or opportunities across Northwestern, please contact Jim Bray at j-bray@northwestern.edu.

Core Fact

The Cell Imaging Facility is pleased to announce a new service for poster printing!

Our new HP z6100ps is a large scale printer for photo quality poster printing. Posters can be printed for display at meetings, recruitment, and site visits. Posters are printed on glossy, photographic stock paper (with a 60” width) in CMYK.

Information on printing can be found on our site.
Welcome New Faculty

Eva Gottwein, PhD, joins as assistant professor in microbiology-immunology. Gottwein was most recently a postdoctoral research associate in the Department of Molecular Genetics and Microbiology at Duke University Medical Center, where she received the Duke Comprehensive Cancer Center Robert M. and Barbara R. Bell Award for exceptional abilities in cancer research and the Duke Comprehensive Cancer Center Young Investigator Award in 2008. Before Duke, she completed her doctorate degree in the Department of Virology at Heidelberg University in Germany. Gottwein’s research interests include the role of viral and cellular miRNAs in cancer and virus replication and Kaposi’s Sarcoma associated herpesvirus (KSHV) biology and KSHV-related malignancies.

Sameer Ansari, MD, PhD, joins as assistant professor in radiology, Ken and Ruth Davey Department of Neurology, and neurological surgery. Ansari was most recently assistant professor and director, neurointerventional service in the departments of radiology, neurology, and surgery at the University of Chicago Medical Center. Ansari’s research interests include the effect of cell cycle and signaling transduction factors on viral transportation and replication in the central nervous system (especially HIV and JCV), gene transduction into central nervous system cells using different strategies (especially viral vectors and siRNA), and molecular imaging and therapeutics. He is also interested in the safety and efficacy of coated coils in the embolization of intracranial aneurysms, the role of intracranial stents in the treatment of distal cervical and intracranial dissections, and molecular pathogenesis and imaging of neurovascular disease, specifically endothelialization and inflammation.

Seminar: Team Science and Collaborative Funding Opportunities

Researchers address complex public health, social, technological, and environmental problems through cross-disciplinary scientific pursuit. Such challenges require long-term, cross-disciplinary, sustainable collaborations (i.e., team science). However, team science efforts are not easily supported by the same funding approaches and mechanisms as individual investigator-driven research. They require a different strategy.

Chicago campus date: Tuesday, December 14
Time: Noon to 1:00 p.m.
Location: Hughes Auditorium, Lurie Medical Research Center, 303 E. Superior St., Chicago

Alternative date: A session will also take place in Evanston on December 13

Presented by: Holly Falk-Krzesinski, PhD
Research Assistant Professor
Director, Research Team Support & Development, NUCATS Institute

Participants will learn about:
• Key differences between developing and funding team science vs. individual research
• Collaborative research funding opportunities available from federal agencies and foundations
• Special requirements for collaborative grant/contract proposals

Co-sponsored by:
NUCATS
Clinical and Translational Sciences Institute
NURAP
Northwestern University Research Assistance Program
A new resource, “Collaboration and Team Science: A Field Guide”, is now available online. Written by L. Michelle Bennett, Howard Gadlin, and Samantha Levine-Finley, all from the NIH, the guide “is intended for anyone who is currently participating on or leading a research team, considering becoming involved in a research team, or contemplating building a research team.”

NIH director Francis S. Collins issued a statement regarding the potential creation of a new institute focusing on substance use, abuse, and addiction research. The institute would integrate research portfolios from the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and other NIH institutes and centers. Collins said, “the formation of a single, new institute devoted to such research makes scientific sense and would enhance efforts to address [our society’s] substance abuse and addiction problems.” A task force is expected to present recommendations for the new institute in the summer of 2011.

The NIH opened an online forum to answer questions from those considering applying for the new Early Independence Awards. The Funding Opportunity Announcement can be found here.

Drs. David Armstrong, chief of the Review Branch, and Mike Sesma, a program officer with the National Institute of Mental Health, explain how to use feedback from your summary statement and program officer in “Thinking About Resubmitting.”

NIH on Twitter

Feinberg researchers can stay in touch with NIH on their mobile devices and personal computers via Twitter, a popular microblogging service.

- Users can follow “NIH For Funding” (twitter.com/nihforfunding) to receive regular updates on grant application extensions and deadlines, new funding opportunity announcements, and more.
- “NIH for Health” (twitter.com/nihforhealth) shares news, research discoveries, and event announcements with the general public and the health and science community.

Researchers who would like additional information about using Twitter or selecting applications for devices can contact the Office of Communications at n-mladic@northwestern.edu.

The Feinberg Twitter feed is available at twitter.com/NUFeinbergMed.

Richard Pope, MD, Chief, Division of Medicine-Rheumatology and Mabel Greene Myers Professor of Medicine-Rheumatology

Project title: “Genetic Predictors of Response to Anti-TNF Therapy in Rheumatoid Arthritis”

Sponsor: National Institutes of Health Pharmacogenomics Research Network

Long-term outcomes in patients with rheumatoid arthritis (RA) is highly dependent upon aggressive pharmacological control of inflammation early in the disease course. Despite the importance of selecting the optimal medication soon after disease onset, there is no clinical or biomarker predictor of drug treatment response. This research will uncover genetic variants that can predict whether a patient will respond to a class of drugs for RA (anti-TNF therapy).

The first aim of this research is generating and analyzing genome-wide association study (GWAS) data on approximately 1,200 RA patients to search for common variants that predict response to anti-TNF therapy. The second aim is to use Northwestern’s electronic medical records (EMRs), in conjunction with our collaborators at Partners HealthCare and Vanderbilt University, to define treatment response, and conduct a replication GWAS on approximately 1,200 additional RA patients treated with anti-TNF therapy.

Robert Plenge at Harvard Medical School is leading the multi-site study. The Feinberg team is actively involved in correctly identifying patients with RA via physician’s review of the chart. The data will then be compared to an algorithm developed at Partners to determine whether an RA diagnosis can be made correctly without a physician’s review of the chart. Finally, we will develop a system to identify responders and non-responders to anti-TNF therapy and these patients will be examined to determine the genetic basis for response.
New Clinical Trial: Lifestyle Interventions and Independence for Elders (LIFE) Study

**Investigator:** Mary McDermott, MD, Professor in Medicine - General Medicine and Preventive Medicine

**Sponsor:** National Institute on Aging; National Heart, Lung, and Blood Institute

**Collaborators:** University of Florida, Yale University, University of Pittsburgh, Wake Forest University, Stanford University, Pennington Biomedical Research Center, and Tufts University

Little is known about whether specific interventions can help prevent major mobility disability, defined as the inability to walk a quarter of a mile, or four blocks, in older men and women. For older adults, staving off disability could help them maintain their physical independence and enhance the quality of their later years.

Based on promising results from a pilot study among 424 sedentary older adults who were randomized to a physical activity intervention or a successful aging health education intervention, a Phase 3 multi-center randomized controlled trial — the largest ever conducted on physical activity in older adults — is being conducted to compare a moderate-intensity physical activity program to a successful aging health education program in 1,600 sedentary older adults who are followed for an average of 2.7 years.

The primary aim is to assess the long-term effects of the proposed interventions on the primary outcome of major mobility disability.

Secondary aims focus on assessing the relative effects of the interventions on the following outcomes: cognitive function; serious fall injuries; persistent mobility disability; the combined outcome of major mobility disability or death; disability in activities of daily living; and cardiovascular and pulmonary events. The cost-effectiveness of the intervention will also be assessed.

Tertiary aims relate to assessing the relative effects of the interventions on (a) the combined outcome of mild cognitive impairment or dementia and (b) physical performance within pre-specified subgroups defined on the basis of race, gender and baseline physical performance.

The proposed trial will provide definitive evidence regarding whether lifestyle modification interventions are effective and practical for preventing major mobility disability. Eight sites around the country participate in the LIFE Study, including Northwestern University.

To learn more about Northwestern’s participation in the LIFE Study, visit the Department of Medicine’s web site Northwestern researchers, coordinators, postdocs, or students can contact Rex Graff with questions about the study at (312) 503-6447 or rgraff@northwestern.edu.

Potential subjects can learn more by visiting www.theLIFEstudy.org/enroll or by calling the Northwestern recruitment line at (312) 503-5223.

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*Stern, continued from pg. 3*

Feinberg medical student, Bill Huang, which enabled him to spend a year in my laboratory. The prostate cancer work started through a pilot project grant from the NIH-funded Northwestern University Specialized Program of Research Excellence. Our investigation of gonadal hormones was funded by a Pioneer Award from the Northwestern University Institute for Women’s Health Research. The ability to generate preliminary results and publications through these pilot grants is invaluable.

**What do you enjoy about teaching/mentoring young scientists in the lab?**

Young scientists with diverse backgrounds bring new ways of thinking, new ideas, and new interests to the laboratory. It is a delightful experience to design experiments together, look at results, and discuss further plans. It is an important, positive stimulus for students to see their results published. I have been fortunate to have also had a number of talented and enthusiastic young post-docs and visiting scientists from Japan, Austria, and Hungary join our group over the years. In addition to the research activities, learning about these countries and cultures has been exciting and broadening. Keeping in touch with former trainees is like having an extended family.
Research in the News

WFLD-TB (Chicago) November 11
Dr. Phyllis Zee was interviewed about her sleep research.

Medical Daily November 11
Calcium could prevent Parkinson’s Disease
Dr. Jaime Guzman’s research was featured.

WBEZ-FM (NPR Chicago) November 10
WGN-TV (Chicago) November 10
Chicago Tribune November 9
Chicago Sun-Times November 9
Dr. Jane Hall was interviewed about the National Children’s Study.

Nature November 10
Motor disorder could have stress-fighting solution
Dr. James Surmeier’s research was featured.

Chicago Sun-Times November 9
Don’t blame getting older for all of your body’s woes
Drs. Sandra Weintraub and Phyllis Zee were quoted.

Newsweek November 8, 2010
Preserving Parenthood
Dr. Teresa Woodruff was featured.

“Weekend Edition” NPR November 6
Dr. Phyllis Zee was interviewed.

MSN.com November 6
Check yourself!
Dr. Shannon Galvin was quoted.

New York Times November 4
After a study, healthy changes
Dr. Romana Hasnain-Wynia was quoted.

Men’s Fitness November 3
Not sleeping well? Start working out
Dr. Phyllis Zee was quoted.

Crain’s Chicago Business October 30
40 under 40: Shad Thaxton
Shad Thaxton was named one of Chicago’s 40 under 40.

High-Impact Factor Research October 2010


More headlines
Funding Opportunities

**NINDS Institutional Center Core Grants to Support Neuroscience Research (P30)**

More information

Submission Deadline: January 25, 2011
Upper Amount: $2,500,000

Synopsis: The purpose of this program is to advance the National Institute of Neurological Disorders and Stroke (NINDS) mission to promote understanding and treatment of neurological disorders by providing core research facilities that are not otherwise available. This support, by providing more accessible resources, is expected to assure a greater productivity than would be possible from the separate projects.

NINDS Center Core Grants will support centralized resources and facilities shared by investigators with existing NINDS-funded research projects. Each center will be composed of one or more research cores which will enrich the effectiveness of ongoing research and promote new research directions. A Center Core Grant will support individual neuroscience research projects by providing necessary resources and performing required services that would be difficult or impractical to provide in individual labs.

**Resource Program Grants in Bioinformatics (P41)**

More information

Submission Deadline: January 25, 2011
Upper Amount: $8,750,000

Synopsis: This Funding Opportunity Announcement announces grants supporting the continued operation, enhancement, and dissemination of databases or software tools that are unique, and of major importance to research using animal models of embryonic developmental processes. The NICHD Biomedical Informatics Resource Program grant will support ongoing research, maintenance, and enhancement, of the tool or resource, user training and services, and wide dissemination of the tool or resource. To qualify for support, bioinformatics resources - software, algorithms, or knowledge resources - must be of demonstrable value toward advancing research utilizing animal model systems in the biomedical sciences and must also be of particular importance to those seeking to understand the biological basis of human and animal development and the etiology of structural birth defects.

View more funding opportunities

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**Featured Events**

**d13** Pathology Research Conference
“Kidney Cancer Genomics” presented by Teh, Bin Tean, MD, distinguished scientific investigator, Van Andel Institute

Date: December 13 Noon to 1 p.m.
Location: Ward building, Rm. 3-015
303 E. Chicago Ave. (Chicago campus)
Contact: a-rafe@northwestern.edu
More information

**d16** Microbiology-Immunology Seminars
“Nanoscopic Imaging of Biomolecules and Cells” presented by Xiaowei Zhuang, PhD. Howard Hughes Medical Institute Investigator, professor of Chemistry and Chemical Biology and Physics

Date: December 16 Noon to 1 p.m.
Location: Lurie Medical Research Center
Hughes Auditorium
303 E. Superior St. (Chicago campus)
Contact: john-marko@northwestern.edu
More information

**d17** Commercialization Clinic
Presented by INVO and NUCATS

Date: December 17 8:45 a.m. to Noon
Location: Ford Motor Company Engineering Design Center, Unilever Conference Room
1233 Sheridan Rd. (Evanston campus)
Contact: m-melar@northwestern.edu
More information

**Feinberg Cardiovascular Research Institute Seminar**

PROMIS: Patient Reported Outcome Measurement Information System in Relation to Cardiovascular Research, presented by David Cellai, PhD, chair and professor, Department of Medical Social Sciences at Feinberg

Date: January 6 8 to 9:30 a.m.
Location: Lurie Medical Research Center
Baldwin Auditorium
303 E. Superior St. (Chicago campus)
Contact: dlr635@northwestern.edu
More information

More events
Event organizers are encouraged to submit calendar items on Plan-It Purple for consideration. Please contact the Research Office with further questions.