Animal Model Developed by Feinberg Researchers Holds Potential to Unlock Therapeutic Advances for ALS

Amytrophic lateral sclerosis (ALS), also referred to as Lou Gehrig’s Disease, is a disease of the nerve cells in the brain and spinal cord that control voluntary muscle movement. While the basis of the disease is not fully understood, it is believed to be triggered by both genetic and environmental factors, like cellular stresses including oxidative damage. ALS overlaps with a subset of a group of common neurodegenerative disorders named TDP-43 proteinopathy. The disease weakens and eventually destroys motor neurons that are essential for movement, causing a progressive loss of functionality — most often taking the life of those inflicted within three to five years of diagnosis.

“ALS is a devastating neurodegenerative disorder,” says Jane Wu, MD, PhD, Charles Louis Mix Professor of Neurology in the Northwestern University Feinberg School of Medicine Department of Neurology, and member of the Robert H. Lurie Comprehensive Cancer Center and Center for Genetic Medicine. "Patients initially experience muscle weakness and later become paralyzed; ultimately, loss of respiratory function is the cause of death.”

Wu studies the molecular and cellular mechanisms underlying the TDP-43 proteinopathy, a group of diseases characterized by the presence of inclusion bodies in the affected brain regions containing TDP-43, a protein that has multiple functions in regulating gene expression. Members of the Wu laboratory aspire to develop new diagnostic tools and innovative therapeutic approaches that delay or stop the advancement of neurodegenerative diseases such as TDP-43.
proteinopathy, including a subset of frontotemporal lobar dementia (FTLD) and ALS. By constructing a powerful transgenic animal model, they have taken a step forward toward that goal.

Principal investigator Wu, along with first author Yan Li, PhD, formerly a research assistant professor of neurology at Feinberg (now a professor at Chinese Academy of Science in Beijing), recently published an article, "A Drosophila model for TDP-43 proteinopathy," in the journal Proceedings of the National Academy of Sciences of the United States of America (PNAS). Its findings detail how genetically modified Drosophila (transgenic fruit flies expressing human TDP-43) show many of the features of ALS.

It was Wu’s daughter, Elizabeth Rao — now an undergraduate student at Yale University — who initiated this research project in the Wu lab. Rao was inspired while attending a Les Turner ALS Foundation event with her mother; she had also spent two summers at Stanford University performing research using fluorescent confocal microscopy to examine transgenic flies, so she was familiar with the model. Rao prompted her mother to study ALS and suggested the research animal model. Subsequently, other members of the Wu team joined the project. While no animal models had previously been used to study ALS, Wu says there are distinct benefits of using a fly model versus other animal models, like a mouse model, for example.

“We can express a human protein easily in a fly, yet flies have shorter life cycles, are easier to maintain, are more cost effective, and have powerful genetics, so the research process is much faster,” Wu says. “We can easily express a human protein in flies selectively in a subset of target cell populations, for example motor neurons, at specific time windows. Also, Drosophila is well studied and has been widely used to model other genetic diseases.”

Wu adds this is a model that displays a wide range of neuropathological, biochemical, and functional features of a human TDP-43 proteinopathy. She and her team have shown that motor neuron defects can be detected early in the larval stage in transgenic flies expressing human TDP-43.

“We can see critical features of ALS in the flies and have found that the swelling of the motor neurons and their axons (which hold the TDP-43) is a sign of the disease,” Wu explains. “That means this model may help us to detect ALS earlier in humans.”

The study also found that the overexpression of TDP-43 caused progressive death of the motor neurons (a sign of ALS) and a dramatic destruction of the brain function (a sign of FTLD) — central nervous system changes and functional deficits similar to those observed in patients affected by TDP-43 proteinopathy.

As a result of the study, Wu and her team recently began using the transgenic fly model to not only further investigate mechanisms underlying the TDP-43 proteinopathy, but also to screen for drugs that potentially slow down or block disease progression.

“We have begun to screen both chemical compounds and genes that can modify disease progression,” says Wu. “Developing drugs that even simply postpone the onset of the disease or slow down disease progression will be of great help to patients.”

Wu has teamed up with other investigators in the field of neuroscience. These national and international research collaborations, Wu says, maximize testing opportunities, expertise, and resources, and will help speed up the discovery of new drugs to treat and possibly cure ALS. Wu believes that this fly model has the potential to elicit treatment discoveries for other neurodegenerative diseases.

For more information about her research findings, contact Jane Wu: jane-wu@northwestern.edu or (312) 503-0684.
Anne Marie Singh, MD, joins Children’s Memorial Hospital as attending physician, allergy and immunology, and as assistant professor of pediatrics at Feinberg. She was previously a clinical assistant professor at the University of Wisconsin-Madison and received her Doctor of Medicine degree at Albert Einstein College of Medicine of Yeshiva University in New York.

Mark Mandel, PhD, joins as assistant professor, microbiology-immunology. He most recently completed his post-doctoral fellowship at the University of Wisconsin-Madison, and previously completed his doctorate degree at Princeton University. He is the founder and curator of the Vibrio fischeri genomics website, www.wfdna.org. The goal of Mandel’s research is to understand the molecular basis by which animals and their natural microbiota form specific, reproducible interactions.
Animal Corner

Recently the Center for Comparative Medicine (CCM) has noted incidences of needles and syringes being disposed in the regular trash canisters in animal holding rooms. This presents a huge safety hazard for CCM personnel who are responsible for emptying trash containers. Already, one CCM staff member suffered a needle stick when emptying the trash due to improperly disposed needles. We would like to prevent future injuries.

Please make sure sharps are never thrown in the regular garbage. Sharps can easily puncture plastic garbage bags and cause injury when personnel are handling the bags. In addition, the syringe/needle could contain drugs or hazardous substances that upon exposure could put that person at risk for illness. Sharps containers are located in most CCM animal holding and procedure rooms.

The Office for Research Safety has guidelines for labs for disposing of needles and syringes. They are as follows:

- Syringes used with hazardous agents shall have needle-locking or equivalent tips to assure that the needles cannot separate during use.
- Do not recap needles after use. Recapping of needles potentially contaminated with human blood, blood products, or other potentially infectious materials is prohibited.
- Syringes, needles, or scalpels shall be disposed of immediately after use in sealable, puncture-resistant, disposable containers that are leakproof on the sides and bottom. The containers shall be appropriately labeled as to the chemical or biological hazard. Sharps containers shall be easily accessible to personnel in the immediate area of use.

If you have any questions or would like more information, please visit the Office for Research Safety web site at http://www.research.northwestern.edu/ors/.
With a doctorate degree in social policy and master’s degrees in social work, public health, and learning sciences, it’s no surprise that Michael S. Wolf, PhD, MPH, MA, associate professor of medicine and associate division chief, research in the Feinberg School of Medicine Division of General Internal Medicine, and associate professor of learning sciences in the Northwestern University School of Education and Policy, focuses his research efforts in areas such as health literacy, adult learning, health promotion, and medication safety.

FSM Researcher recently caught up with Dr. Wolf to learn about his current projects. He will be soon continue his work from the University of Liverpool, as he was recently awarded a prestigious J. William Fulbright Foreign Scholarship that grants him the opportunity to move abroad and collaborate with investigators from academic and public health institutions across the United Kingdom.

**What are your research interests?**

Our program studies learning in the context of healthcare, which requires a focus on individual abilities and health system demands. We conduct cognitive epidemiological research investigating the skills one must possess to promote, protect, and manage health. This line of inquiry is at the heart of the emerging field of “health literacy” research, defined as an individual’s capacity to obtain, process, and understand health information and make informed decisions.

Likewise, several of our funded projects attempt to simplify the user-interface of healthcare. Working with colleagues from Cornell, Emory, Harvard, and Louisiana State, I lead a clinical trial testing a universal medication schedule to standardize how prescription drug label instructions are written. We believe that clearer, explicit guidance on how to use medicine can improve a patient’s ability to consolidate and self-administer complex drug regimens.

Similarly, we have leveraged the electronic health record to impart clinic protocols that engage patients in providing more complete medication lists, standardizing prescribing practices of physicians, and generating plain language print information for patients newly prescribed medicines that explain its safe use.

In yet another clinical trial, we are testing how best to implement a low-literacy diabetes self-management strategy in safety net clinics.

**What research projects are you currently pursuing?**

The health literacy field has mostly addressed the health implications of poor reading and numeracy skills. Along with my colleague Stacy Cooper Bailey, our program is now extending our work to address language barriers as well. We just received a research grant from the Agency for Healthcare Research and Quality (AHRQ) to address better drug labeling for Spanish-speaking, diabetic patients. The California Endowment also funded our program to translate a standard set of prescription instructions and precautions for pharmacy practice in Russian, Chinese, Korean, Vietnamese, and Spanish.

The most challenging research project I lead to date is referred to as LitCog, funded by the National Institute on Aging. We are recruiting 1,100 older adults from Northwestern and community-based practices and administering a comprehensive cognitive battery, while also having them perform numerous common health tasks (e.g., dose out multiple drug regimens, read health forms, recall information from a medical encounter, learn from a health education video, navigate a web site, etc.). Improving our under-
standing of what the actual health literacy barriers are will better inform future interventions aimed at restructuring health tasks, as well as better identify those who may be at greater risk for poor self-management.

We recently requested further NIH support to track participants for the next five years as a cohort study, so we may examine how health literacy skills decline over time and explore ways to maintain self-care skills.

**What is the ultimate goal of your research?**

I want to help patients and families understand their role and responsibilities in managing their health, while simultaneously reducing the unnecessary confusion within the healthcare system.

Our program reflects an applied research agenda with the potential to make direct impacts on personal health and healthcare in the foreseeable future. Whether our target is community health centers, pharmacies, schools, or primary care practices at Northwestern, the focus has always been on improving the accessibility of healthcare services to those most vulnerable and underserved.

**What brought you to Northwestern?**

I originally came here for the Institute for Healthcare Studies post-doctoral fellowship, where I was fortunate to meet wonderful faculty that helped to shape my current career. However, what kept me at Northwestern was a stroke of good fortune (that is, for me). One of my personal heroes early in my career happens to be my current division chief, David Baker. As I was prepping myself to be on the job market at the end of my fellowship, a colleague of mine at Emory introduced me to Dr. Baker via email, who at the time was senior faculty at Case Western in Cleveland. I drove out to meet him and to be considered for a faculty position there. I didn’t know he was coming to Northwestern when I interviewed, but once he contacted me with the news, I happily stayed and have never looked back.

**What are some of the challenges you face?**

In this line of research, there are challenges in every direction. Many of the past successes in health education and behavior interventions have demonstrated only short-term gains. Ironically, what is often most exciting about several of our active projects is what we are learning from the difficulties experienced during implementation. The objective is to best understand the root causes of failure, then identify the most sustainable manner to modify healthcare and promote patient compliance.

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Wolf, also member of the Robert H. Lurie Comprehensive Cancer Center, serves as director of the medical school’s Health Literacy and Learning Program, is on the editorial board of Patient Education and Counseling, and is a reviewer of numerous professional journals, including American Journal of Public Health, Journal of the American Medical Association, and Social Science and Medicine. Wolf is also an active contributor to national organizations such as the Food and Drug Administration, Joint Commission, and Agency for Healthcare Research and Quality.

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**Lewis Landsberg Research Day Winners 2010**

Research Day 2010 featured more than 150 participants in the poster session. Amidst a sea of activity in the Lurie Building, winners were selected by a panel of judges representing clinical research, basic science, and the Women’s Faculty Organization.

Top prizes in the poster session were awarded to the following:

**Basic Science**

*1st Prize:* Mario Shields, MPhil  
*2nd Prize:* Aigerim Bizhanova, MS  
*3rd Prize:* Cynthia Danielson, BS

**Clinical Research**

*1st Prize:* Arlene Hankinson, MD, MS  
*2nd Prize:* Norrina Allen, PhD  
*3rd Prize:* Rayna Sweis, MD

**Women’s Faculty Organization**

Min Xu, MD, PhD,  
Gildasio de Oliveria, Jr., MD

A full listing of all abstracts can be found on the Research Day 2010 [web site](http://www.fsmtoday.org).
Staff Profile: Maureen Mwangi, Program Coordinator,
Feinberg School of Medicine Research Office

How long have you been at Northwestern?
I started working at Northwestern in April 2009, so it’s been exactly one year.

Where are you from?
I’m a local; I pretty much have always lived on the North side of Chicago.

What’s your educational background?
I have a Bachelor of Arts degree from Columbia College Chicago and a Bachelor of Science degree from DeVry University.

What is your role in the Research Office?
I assist the executive director for research and manager for finance and administration.

In this role I provide assistance in administering research space management, serving as liaison to Feinberg faculty and staff, Facilities Management, and other designated personnel regarding research space issues. I also oversee the update and maintenance of the annual SIMS survey for the Feinberg Research Office. In addition, I compile, maintain, and distribute lists of weekly funding opportunities and event announcements, coordinate efforts for limitation submissions, and provide general administrative support for the research office. I served as the lead planner for this year’s Research Day.

What’s a typical day like for you?
A typical day is a lot of e-mail correspondence—setting up meetings and fielding phone calls regarding the Research Office, which mostly involves working with department administrators regarding space related issues. I also spend a lot of time looking for new funding opportunities for investigators and compiling event announcements. Parts of my job vary from day to day so it’s interesting; no one day is ever alike.

Why did you choose to work here?
I previously worked in a medical institution and really wanted to get into academia. Being from Chicago, I had heard a lot about Northwestern, and I knew people who worked here. They all had really great things to say, so it seemed like the most natural choice for me.

What do you like about your job?
I like working here because there is an opportunity to learn many different things; it’s amazing to see the kind of research that is taking place. My job also exposes me to the various departments at Feinberg, and so I get to meet a lot of great people.

What are your favorite books or movies?
I love to read fiction and non-fiction books from great mysteries to autobiographies. I also love watching movies; I can pretty much watch anything as long as it holds my interest, from old black and white westerns to documentaries, thrillers, and of course the mushy girlie movies. I also love the arts and enjoy visiting museums and art shows. I love to travel and try to take advantage when the opportunity presents itself.

What do you like to do outside of work?
Besides my hobbies, whenever I get a chance I like to volunteer at the Living Room Café in Woodlawn. It serves meals restaurant-style and also provides support to individuals who are homeless or low-income and assists them with attaining skills to succeed in the workforce and become self-sufficient.

I also like to spend time chasing around my 14-month-old nephew for my workout.

Top Honors

Dr. Franck Mauvais-Jarvis, elected to the American Society for Clinical Investigation in recognition of his contribution to the characterization of ketosis-prone diabetic syndromes and the discovery of estrogen receptor for extranuclear actions in pancreatic islet survival.

Dr. Michael Wolf, awarded a J. William Fulbright Foreign Scholarship to the United Kingdom (UK) sponsored by the United States Department of State, Bureau of Educational and Cultural Affairs.

The Feinberg School of Medicine, ranked 18th for research in the 2011 U.S. News & World Report (from 19th in 2010).
Student Profile: Brian Emmer
Integrated Graduate Program (IGP) in the Life Sciences

Where is your hometown?
Muskegon, Mich.

Where did you complete your undergraduate degree?
I completed my undergraduate degree at the University of Michigan.

What are your research interests?
Generally speaking, I am interested in the molecular processes underlying disease pathogenesis. My research to date has focused on infectious diseases. First, in college, I studied the mechanism of action of antiviral drugs against human cytomegalovirus. For my graduate thesis research, I studied the African trypanosome, a parasite endemic to sub-Saharan Africa. Human infection causes African sleeping sickness, a disease that is exorbitantly fatal if untreated. Trypanosomes also pose a major barrier to economic development in these areas, as they can also infect cattle to cause nagana, thus rendering vast regions untenable for livestock.

What exciting projects are you working on?
The main focus of my thesis research is the pathway by which trypanosomes sort proteins to specific membrane domains. Trypanosomes swim through their environment by virtue of a single motile flagellum. These finger-like projections are found on cells of eukaryotic organisms ranging from trypanosomes all the way to humans. Yet in no organism do we truly understand how it is that the cell targets proteins and lipids to the flagellar membrane instead of other membranes.

For the family of calcium-binding proteins I studied, I found that a particular lipid modification, palmitoylation, was critical to this process. I went on to perform a genetic screen that identified the single enzyme mediating this process. I then discovered the localization of this enzyme within the cell, as well as the entire cellular complement of proteins that shared this lipid modification. Taken together, these results indicate a role for palmitoylation in flagellar targeting that is critical to trypanosome biology, and likely conserved in all organisms from trypanosomes to humans.

What attracted you to the IGP program?
I came to Northwestern because of the strength of the medical school as well as the abundance of top-notch research.

What has been your best experience at Feinberg?
I’ve enjoyed my entire time at Northwestern. After the first two years of medical school, I went into the lab for four years. While research has its share of trials and tribulations, there is nothing quite like diving headfirst into a field of research to attempt to solve unanswered questions. To participate in fundamental discoveries of clinically relevant biology is a privilege.

Probably my single best experience, though, has been my third year of medical school, during which we leave the classroom to go into the hospital and rotate through the various branches of medicine. It’s an incredible opportunity to learn clinical medicine while sampling all of the various fields, whether it be seeing patients in an office-based primary care clinic, taking care of the sickest patients in the ICU, helping to deliver a baby on obstetrics, or scrubbing in to the OR on surgery.

What do you do for fun?
I enjoy spending time with my wife, who came here from Michigan with me and works as a first grade teacher for Chicago Public Schools.

We enjoy going out to the many great restaurants in the city, meeting up with our friends, or just spending a quiet night at home together. Chicago has been a great home for the past seven years!

What are your plans for after graduation?
I am just now beginning the process of applying for residency programs. I intend to go into "fast-track" program that combines an internal medicine residency with a fellowship in a subspecialty. I am considering infectious disease, hematology-oncology, and cardiology. Eventually my goal is to become a physician-scientist, splitting my time between patient care and running my own basic science laboratory.

Core Fact
Are you aware that Feinberg now has a human embryonic and induced pluripotent stem cell facility? The Core can provide plated cells ready for your experiments or teach you to culture them yourself.

Interested? Please contact Ljuba Lyass (l-lyass@northwestern.edu).
Cajal‐Retzius cells in the postnatal hippocampus remain almost unexplored. In fact, contrary to the diffuse false notion that Cajal‐Retzius cells are a transient cellular population that completely disappears soon after birth, they actually persist in the adult hippocampus. Surprisingly, despite having already been described a century ago by the founder of modern neuroscience, Ramon y Cajal, and having been more recently discovered to play a critical role in the development of cortical layers, the conventional electrophysiological and network properties of Cajal‐Retzius cells in the postnatal hippocampus remain almost unexplored. In fact, contrary to the diffuse false notion that Cajal‐Retzius cells are a transient cellular population that completely disappears soon after birth, they actually persist in the adult hippocampus.

Suffice it to say that the direct effect produced by Cajal‐Retzius cells on their postsynaptic targets has never been recorded. Thus, it still remains unclear what neurotransmitter they use. Furthermore, recent studies have discovered that Cajal‐Retzius cells express a specific chemokine membrane receptor (CXCR4), highlighting the potential role of these neurons as cellular mediators of chemokine actions in physiological and/or pathological conditions such as epilepsy and neuroinflammation. However, both the functional impact of CXCR4 activation on Cajal‐Retzius cells and its consequences for the network remain unknown.

This project is taking advantage of GFP‐labeled transgenic animals that allow the unequivocal identification of CXCR4‐expressing Cajal‐Retzius cells for electrophysiological recordings in vitro. We are combining sophisticated anatomical and electrophysiological techniques such as electron microscopy and paired whole‐cell recordings from anatomically connected neurons to answer several key questions such as what type of synapse is made by these cells, what postsynaptic effect is produced by their neurotransmitter, and what impact CXCR4 activation has on their own electrical activity and on the activity of the hippocampal network in various models of epilepsy in vitro. All these answers will be important for a deeper cell type‐specific understanding of hippocampal functions in physiological and pathological states.

### Research in the News

**Chicago Sun‐Times** March 19
*Polycystic ovary syndrome study seeks participants*
Dr. Andrea Dunaif’s research was featured.

**CNN, Paging Dr. Gupta** March 22
*Nanotech cancer treatment shown to work in humans*
Dr. Gayle Woloschak was quoted.

**Chicago Tonight** March 23
Dr. Abel Kho discussed a new grant and electronic health records.

**Associated Press** March 28
*Chicago doctor named to presidential AIDS council*
Dr. Patricia Garcia was featured.

**Associated Press** March 29
*Illinois Health Registry seeks more women participants*
The Institute for Women’s Health Research was featured.

**NPR Los Angeles** March 29
Dr. Linda Van Horn discussed nutrition.

**U.S. News & World Report** March 29
*Can this test be saved? Improving on PSA for prostate cancer*
Dr. William Catalona was quoted.

**Chicago Tribune** March 30
*Northwestern study shows promise for treating rheumatoid arthritis*
Dr. Harris Perlman’s research was featured.

**New York Times** April 2
*Two comebacks unlike any other*
Dr. Alice Dreger was quoted on Tiger Woods’ return.

**Los Angeles Times** April 7
*The gender line*
Dr. Martha Gulati was quoted on women’s heart disease.

For more headlines, visit: [www.feinberg.northwestern.edu/](http://www.feinberg.northwestern.edu/)
Funding Opportunities

Collaborations with National Centers for Biomedical Computing (R01)
Submission deadline: June 5, 2010
Upper Amount: $2.5 million

Synopsis: This Funding Opportunity Announcement (FOA) is for projects from individual investigators or small groups to collaborate with the NIH Roadmap for Medical Research National Centers for Biomedical Computing (NCBCs). The intention of the collaborating projects is to engage researchers across the nation in building an excellent biomedical computing environment, using the computational tools and biological and behavioral application drivers of the funded NCBCs as foundation stones.

Edward N. and Della L. Thome Memorial Foundation, Bank of America N.A., Trustee, Awards Program in Alzheimer's Disease Drug Discovery Research
http://www.hria.org/tmfservices/thomead.html
Submission deadline: June 15, 2010
Upper Amount: $750,000

Synopsis: The goal of the Awards Program is to support innovative drug discovery research that will lead to improved therapies for individuals suffering from Alzheimer’s disease.

Examples of funding areas include the design, synthesis, and development of target compounds or the modification of existing compounds to improve drug effectiveness and safety as well as other approaches within the field of medicinal chemistry. Researchers dedicated to the validation and testing of target compounds, small molecule therapies, nanotechnologies, or similar techniques are also encouraged to apply.

Basic research or new target discovery, genetic studies, biomarker research, neuroimaging, and clinical studies are currently outside the scope of this program. Investigators in postdoctoral positions are strongly encouraged to apply.

For more events, visit:
www.feinberg.northwestern.edu/research/calendar/
Event organizers are encouraged to submit calendar items on Plan-it Purple.

Your feedback and suggestions are always welcome.
Contact the Feinberg School of Medicine
Office for Research:
kristin-jacobsen@northwestern.edu or n-mladic@northwestern.edu
Phone: (312) 503-3129  Fax: (312) 503-2790

On the Web: www.feinberg.northwestern.edu/research/