

FSM Research Newsletter

June 2008

Feinberg School of Medicine Office for Research
Northwestern University

HAPO STUDY REVEALS MATERNAL HYPERGLYCEMIA ASSOCIATED WITH PREGNANCY COMPLICATIONS

Feinberg School Researchers at the Helm of International Study

Feinberg School of Medicine researchers have played a lead role in an international study that shows an association between maternal hyperglycemia and the risk of pregnancy complications. Boyd Metzger, MD, the Tom D. Spies Professor of Metabolism and Nutrition at the Feinberg School, is the principal investigator for the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, which explored the association between maternal hyperglycemia less than that in diabetes mellitus and adverse pregnancy outcomes. The results of this study have now been reported in "Hyperglycemia and Adverse Pregnancy Outcomes," in the May 8 issue of *The New England Journal of Medicine*. Dr. Metzger led a team of investigators that also includes the Feinberg School's Alan R. Dyer, PhD, Professor, Department of Preventive Medicine, principal

investigator of the HAPO Data Coordinating Center, and Lynn P. Lowe, PhD, Research Assistant Professor, Department of Preventive Medicine, Project Manager for the HAPO Study. Sharon Dooley, MD, Professor of Obstetrics-Gynecology, was principal investigator of the Clinical Center that enrolled participants at the Northwestern site of the HAPO study.

The HAPO study report notes that though overt diabetes mellitus during pregnancy is associated with significantly increased risk of adverse prenatal outcomes, the risks associated with hyperglycemia less severe than diagnostic diabetes have been uncertain. There are no uniform international standards for the ascertainment and diagnosis of gestational diabetes mellitus. In addition, the extent to which adverse outcomes associated with gestational diabetes mellitus may be explained by confounders such as obesity or advanced maternal age is unclear. This study was conducted in an effort to clarify the risks of adverse outcomes associated with various degrees of maternal hyperglycemia less severe than in overt diabetes mellitus.

A total of 23,316 pregnant women, from 15 centers in nine countries, participated in and completed the HAPO study. The women, none of whom had received treatment for diabetes before the current pregnancy, underwent a standard glucose tolerance test, with the use of a 75-g dose of glucose, between 24 and 32 weeks of gestation (the target time of testing was 28 weeks). Height, weight and blood pressure were measured at the test visit. Data concerning maternal alcohol use, history of diabetes and hypertension among first-degree family members, and demographic characteristics were collected by means of a standardized questionnaire. Data were blinded if the fasting plasma glucose level was 105 mg/dL or less and the two-hour plasma glucose level was 200 mg/dL or less. Primary outcomes

were birth weight above the 90th percentile for gestational age, primary cesarean delivery, clinically diagnosed neonatal hypoglycemia, and cord blood serum C-peptide level above the 90th percentile. Secondary outcomes were delivery before 37 weeks of gestation, shoulder dysplasia or birth injury, need for intensive neonatal care, hyperbilirubinemia, and preeclampsia.

The researchers calculated adjusted odds ratios of adverse pregnancy outcomes associated with an increase in the fasting plasma glucose level of 1 SD (6.9 mg/dL), an increase in the one-hour plasma glucose level of 1 SD (30.9 mg/dL), and an increase in the two-hour plasma glucose level of 1 SD (23.5 mg/dL). For birth weight above the 90th percentile, the odds ratios were 1.38, 1.46, and 1.38, respectively; for cord-blood serum C-peptide level above the 90th percentile, 1.55, 1.46, and 1.37; for primary cesarean delivery, 1.11, 1.10, and 1.08; and for neonatal hypoglycemia, 1.08, 1.13 and 1.10. Significant associations were also observed for secondary outcomes.

These results indicate that women with high blood sugar not diagnostic of diabetes face an increased risk of complications. "We found strong independent associations between the mother's blood sugar levels during oral glucose tolerance tests at 28 weeks of gestation and pregnancy outcomes," says Dr. Metzger. "But because the relationship between the mother's blood glucose level and risk tend to be continuous, it is not immediately obvious where the risk reaches the point where treatments should begin." Dr. Metzger notes that the results of the HAPO study will be discussed at the annual meeting of the American Diabetes Association, held in early June.

"Those of us who care for pregnant women are grateful for the HAPO study and its implications on the role of hyperglycemia," says Dr. Dooley. "We will be watching with interest to see if new guidelines for clinical care emerge from this important study."



Boyd Metzger, MD, principal investigator for the HAPO study.

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MEET MICHAEL ABECASSIS, MD, MBA



The J. Roscoe Miller Distinguished Professor of Surgery and Microbiology/ Immunology, Director of Transplantation and Dean for Clinical Affairs, Feinberg School of Medicine

What are your research interests?

My research efforts focus on improving the success of organ transplantation. I am involved in a number of studies. I am a principal investigator and member of the Steering Committee of the National

Institutes of Health Adult-to-Adult Living Donor Liver Transplantation (A2ALL) Cohort Study. This is a seven-year study that involves nine of the United States' top liver transplant centers, including Northwestern. This study aims to provide data that will help us inform the process of living donor liver transplantation. The research team is comparing outcomes of living donor transplants with those of patients who received livers from deceased donors as well as assessing all potential complications in the living donors. Also, several ancillary projects within A2ALL include an assessment of the success of living donor liver transplants in patients with hepatocellular carcinoma, hepatitis C and in liver regeneration. I also serve as the principal investigator and member of the Steering Committee for another NIH-funded study called Clinical Trials in Organ Transplantation (CTOT), which investigates the molecular biomarkers in the blood and urine that predict and accurately diagnose rejection and ischemia/reperfusion injury of transplanted organs. Through three national consortia of transplant centers, Northwestern participates in several studies within CTOT that include functional genomics as well as observational and interventional studies in kidney, liver and heart transplant recipients. Finally, I am a principal investigator in another NIH-funded study through the Immune Tolerance Network (ITN). We are investigating the withdrawal of immunosuppressive (anti-rejection) agents in liver transplant recipients in an attempt to elucidate the mechanistic details of immune tolerance in this patient population. This is an exciting area of investigation that has truly been the holy grail of transplantation research – the ability to transplant organs without a need for lifetime immunosuppression.

One of the sequellae of immunosuppression is the development of opportunistic infections such as cytomegalovirus (CMV) infection. CMV is a herpes virus that is present in the majority of adults and can establish a lifelong latent infection. In transplant recipients, reactivation of the virus is frequently observed, and despite effective anti-viral prophylaxis can be associated with serious morbidity and, occasionally, mortality. My laboratory is looking at the molecular mechanisms by which CMV establishes latent infection and reactivates from latency. This research uses a mouse model. Mice are infected with murine CMV and we are using ChIP assays to investigate potential epigenetic mechanisms of transcriptional silencing, including DNA methylation and histone modification. Also, we have postulated that reactivation is triggered by the inflammatory response in the transplanted organ

resulting from both ischemia/reperfusion injury and the allo-immune response. The inflammatory cytokine TNF and the transcription factor NFκB are particular targets of this investigation and more recently we have focused our attention on Toll-like receptors (TLRs) and other transcription factors. Kidneys transplanted in mice are analyzed for RNA expression and activation of transcription factors known to be involved in regulating both cellular and viral gene expression. Transgenic and knock-out mice are used to test the requirement of cytokines and TLRs in CMV reactivation focusing primarily on the regulation of the CMV Immediate Early gene promoter/enhancer region. We are currently creating viral mutants that lack specific binding sites for specific transcription factors in this promoter/enhancer region to test the hypothesis that these transcription factors are required for reactivation. My hope is that this research will lead to strategies for developing molecular approaches that can knock down the triggers viral gene expression and thus prevent reactivation and its associated sequellae.

What is the ultimate goal of your research?

The goal of my research efforts is to increase both access to transplantation as well as success rates. Our program is a national leader in living donor transplantation in an attempt to improve access to transplantation given the shortage of organs from deceased donors. With liver transplantation in particular, we are increasingly focused on establishing its role as a life-saving option for many people with end-stage liver disease who may not have access to livers from deceased donors. At the same time, it is clear that although current results are excellent, we can do better. This involves being able to treat rejection earlier, avoiding the sequellae of immunosuppression such as infections, and ultimately avoiding immunosuppression altogether. I am hopeful that we can achieve these goals in my lifetime.

What brought you to the Feinberg School of Medicine?

I came to Northwestern in 1992 because I envisioned a great opportunity to fulfill these goals. It turns out that my instincts were right. The commitment to clinical excellence at Northwestern, combined with an environment of collaboration and a palpable enthusiasm for this type of program have made the Feinberg School of Medicine an exciting place for all of us involved in the challenging field of organ transplantation. I want to highlight the fact that transplantation is a team sport. The advances we have made at Northwestern, both in adult and pediatric transplantation, would not be possible without the commitment, dedication and support of the leadership of this institution and the many individuals involved. I am looking forward to many more achievements in this field that will be made possible only through the unwavering support we have experienced.

SPONSORED AWARDS

**Anis Contractor, PhD**

Assistant Professor, Department of Physiology

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

Project Title: Kainate Receptor Signaling at Excitatory Synapses
 Sponsor: National Institute of Neurological Disorders and Stroke
 Budget Period: 4/1/08 – 3/31/09
 Amount: \$302,000

Kainate receptors are glutamate-gated neurotransmitter receptors that are critical to synaptic signaling and cellular excitability in the central nervous system. Pathophysiological activation of these receptors has been linked to several important neurological conditions including chronic pain, neuroinflammatory demyelinating diseases, and temporal lobe epilepsy. The goals of this study are to delineate the actions of kainate receptors at synapses and to comprehensively uncover their roles in modulating neuronal excitability, thus providing further validation of these receptors as potential therapeutic targets.

**Anne Rowley, MD**

Professor of Pediatrics and of Microbiology-Immunology

Project Title: The Pathogenesis of Kawasaki Disease
 Sponsor: National Heart, Lung, and Blood Institute
 Budget Period: 3/11/08 – 2/28/09
 Amount: \$411,583

Kawasaki Disease (KD), the most common cause of acquired heart disease in children in developed nations, is an acute vasculitis of young children that can result in coronary artery aneurysms, myocardial infarction and sudden death; the etiology is unknown but is likely infectious. This project extends further work by the Rowley lab demonstrating the presence of cytoplasmic inclusion bodies in acute KD bronchial epithelium that are targeted by the acute KD IgA immune response. The goals of the proposal are to identify the tissues in which inclusion bodies form in acute KD and to search for microbial elements in these tissues, to identify the nucleic acid and protein contents of KD cytoplasmic inclusion bodies, and to determine whether dysregulation of the TNF superfamily contributes to KD vasculopathy.

**Karla Satchell, PhD**

Assistant Professor of Microbiology-Immunology

Project Title: Genetic and Biochemical Study of V. Cholerae RTX Toxin
 Sponsor: National Institute of Allergy and Infectious Diseases
 Budget Period: 4/1/08 – 3/31/09
 Amount: \$377,500

The bacterial pathogen *Vibrio cholerae*, the etiological agent of the diarrheal disease cholera, secretes a novel toxin that is the founding member of new toxin family, the Multifunctional-Autoprocessing RTX toxins. The MARTX toxin of *V. cholerae* contributes to infection in mice and may be an important factor for persistent intestinal colonization both in cholera patients and non-symptomatic carriers. This study pursues the biochemical mechanism of action of this toxin. Completion of this research will impact not only our understanding of cholera pathogenesis, but also the function of other uncharacterized toxins produced by other human pathogens that share the unique enzymatic activities carried by this toxin.

**William Schnaper, MD**

Professor of Pediatrics

Project Title: Adaptor Molecules in TGF-beta Signaling
 Sponsor: National Institute of Diabetes, Digestive and Kidney Diseases
 Budget Period: 4/1/08 – 3/31/09
 Amount: \$299,939

Transforming growth factor (TGF)- β is a cytokine with many different and sometimes conflicting effects on cell function. Because canonical TGF- β signal transduction occurs through a relatively straightforward signaling pathway involving the Smad family of proteins, additional regulatory mechanisms must account for the variability and selectivity of the cell response. This project focuses primarily on understanding one such mechanism, involving a TGF- β receptor adaptor protein called Smad anchor for receptor activation (SARA). Preliminary data suggest not only that SARA regulates specific responses to TGF- β , but also potential roles for SARA in regulating cell phenotype and receptor trafficking.

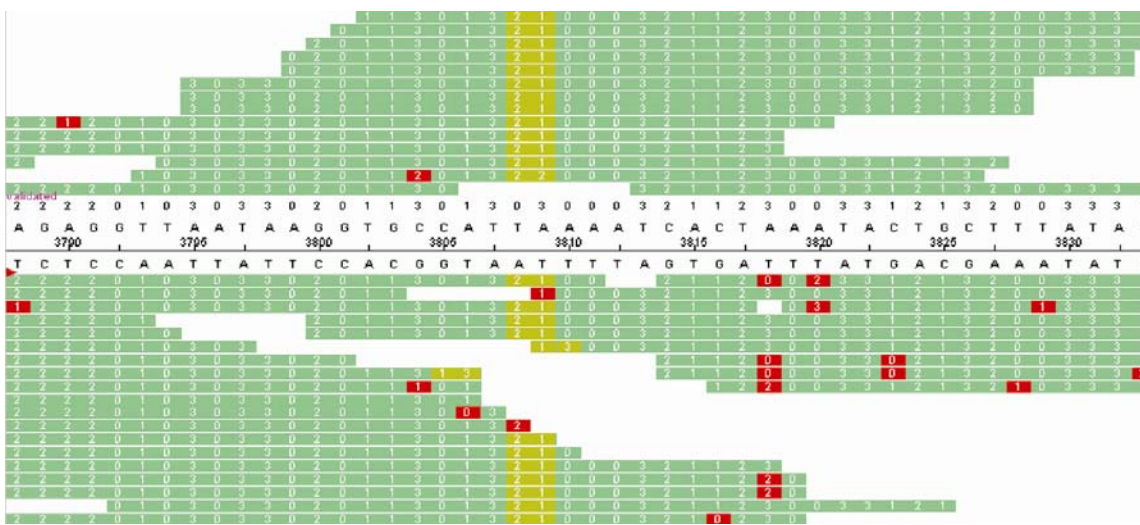
GENOMICS CORE FACILITY

The Genomics Core Facility at the Center for Genetic Medicine provides a wide range of high quality services to the investigators at the Feinberg School of Medicine, the Robert H. Lurie Comprehensive Cancer Center (RHLCCC), Northwestern University and external researchers. Services include low, medium and high density SNP analysis; high and low density gene expression profiling, high throughput DNA extraction and DNA sequencing. In addition, the Genomics Core helps maintain a high level of knowledge amongst Northwestern University and Chicagoland area investigators by sponsoring educational talks and seminars to introduce and update new technologies. Ensuring that the facility remains at the forefront of DNA sequencing technology, the Genomics Core recently unveiled two new instruments:

The new **SOLiD System, a next generation sequencer**, from Applied Biosystems was acquired through a generous donation

from Northwestern trustee and Feinberg School benefactor, Ms. Ann Lurie. The SOLiD System is a genetic analysis platform that enables massively parallel sequencing of clonally amplified DNA fragments linked to beads. The sequencing methodology is based on sequential ligation with dye-labeled oligonucleotides. The system is a "short reader," meaning it can read between 25 and 35 bases at a time and sequence up to nine gigabases per run. The applications include Targeted Resequencing, Gene Expression, MicroRNA Discovery, Chromatin Immuno-precipitation (ChIP-Seq) and Whole Genome Sequencing. The Genomics Core will dedicate a technician to run and

A snapshot of sequencing reads aligned in the SOLiD™ Alignment Browser (SAB).



ANIMAL RESEARCH CORNER



Northwestern University is preparing for its triennial visit from the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International which will occur June 23-26. AAALAC is a voluntary accreditation program run by renowned professionals in the laboratory animal field. Every three years, each institution must submit a Program Description that describes every aspect of the animal care and use program including IACUC processes, animal and veterinary care, facilities, training and occupational health. If you would like to view a copy of the Program Description, please contact Dr. Lisa Forman at l-forman@northwestern.edu.

When the site visitors arrive, they assess the program based on the *Guide for the Care and Use of Laboratory Animals*, which is the industry standard for laboratory animal care. By meeting the recommendations in the Guide and maintaining full AAALAC accreditation, the institution is committing itself to the highest standards of humane care and use of lab animals. This is extremely important for both the researcher and the institution when applying for funding from agencies such as the National Institutes of Health (NIH) and the National Science Foundation (NSF).

The site visitors will certainly select and visit a number of laboratories. Please be mindful of the type of questions you might be asked. The approach the site visitors will take is best compared to that described in our PAM (Post Approval Monitoring) Program. For more information about the PAM Program, please visit the CCM website at <http://www.research.northwestern.edu/ccm/> and view the PAM section on the home page. We expect to hear back from AAALAC in mid-fall regarding our accreditation status. If you have any questions or would like more information, please contact Dr. Lisa Forman at the email address above.

maintain the new sequencer to ensure the timeliness and quality of service. It also plans to hire a data manager and a bioinformaticist to offer high-level analysis. The system will be available for use by the end of this summer.

The facility has also acquired a **Beckman ArrayPlex NX automated workstation**, purchased with grant funds awarded by the vice president for research's Shared Facilities Program. The workstation will automate the setup of sequencing reactions which will increase productivity.



Beckman ArrayPlex NX automated workstation

The Genomics Core operates under the guidance of facility director, Nadereh Jafari, PhD, five research technicians and a program assistant. Visit the facility website at www.medschool.northwestern.edu/cgm/genomics/ for more information on services and upcoming seminars.

POSTDOC PROFILE: MILAN JOKSIMOVIA



Milan placed first for the basic science award at the Fourth Annual Lewis Landsberg Research Day with his project titled, *Neurogenic potential of the rostral floor plate*.

Could you briefly describe your project?

The work presented in my poster focuses on developmental genetics of the midbrain floor plate and one of its key derivatives - dopamine neurons. A motivation for detailing the embryonic development of dopamine neurons is the exciting potential for stem cell-based therapeutics of

Parkinson's disease. Central to understanding the genetic basis of Parkinson's disease and formulation of effective therapeutics, is a clear grasp of the developmental molecules and processes governing the birth, specification, migration and survival of midbrain dopamine neurons.

In our study, using *Sonic hedgehog (Shh)* as a driver for lineage analysis, we showed that the midbrain floor plate was neurogenically active producing dopamine neurons, in contrast to the neurogenically inert hindbrain floor plate. Further, a conditional deletion of *beta-catenin*, a component of canonical Wnt signaling, resulted in diminished dopaminergic neurogenesis while an early removal of *Shh* remarkably unleashed the latent neurogenic

potential of the prospective hindbrain floor plate, resulting in the production of dopamine-like neurons. These studies demonstrated, *in vivo*, how the dynamic interplay of canonical Wnt signaling and Shh may orchestrate floor plate neurogenesis and a production of dopamine neurons. This work was performed in the laboratory of Dr. Raj Awatramani.

Why did you select FSM?

I chose FSM because of a high quality research at this institution. In addition, I wanted to continue working on cell fate specification during development of the central nervous system that I initially started at Iowa State University working on *Hox* genes. So, despite other offers, I decided to join Dr. Raj Awatramani's laboratory in spring 2006.

How would you describe the faculty at FSM?

The faculty at FSM is outstanding that is consistent with, again, a high quality research at this institution including excellent scientific communication and interaction among the FSM scientists.

What are your plans for the future?

As expected for postdoc future plans, I would like eventually to start either my own lab or a lab together with my wife (a stem cell biologist, currently a postdoc in Martha Bohn's lab at Children's Memorial Research Center) to jointly pursue basic/translational science research.

STAFF PROFILE: JULIE SCHLESINGER



Director of Administration and Research
Department of Surgery

Julie will be celebrating her thirteenth year at FSM in August. She is an avid traveler and enjoy stamp collecting from all over the world. So far, she has visited about 35 countries!

Where are you from?

I was born in Chicago, but went to college and graduate school on the West Coast. I spent about 20 years in California before returning to the Midwest.

What's your background?

I have a Bachelor's degree in Mandarin Chinese and French languages and an MBA in International Business, Chinese business emphasis. I have worked in the telecommunications, aviation and property management industries, but much prefer the academic environment.

What is a typical work day like for you?

One of the things I really like about my job is that no day is truly "typical". With 14 divisions, I usually work on a variety of things each day that are both research and non-research related. In addition to all things research, I am responsible for other NU operational areas such as payroll and AR/AP for the Department of Surgery.

What do you like about your job?

I find it very rewarding to facilitate the ground breaking research going on in our Department particularly in the areas of cancer, diabetes, stem cell, living donor transplant, and nanotechnology.

What do you do in your spare time?

I am renovating a home built in 1900 in the Bronzeville area and have been working on it for the past several years.

STAY IN TOUCH by visiting the new and improved FSM Office for Research Home Page:

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



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- Search for research-related lectures, seminars, and events
- Access archive of monthly FSM Research newsletters
- Find resources to support the needs of FSM faculty, staff and students
- Submit feedback using the 'Comments and Suggestions Form'

IN THE NEWS

Couples, get naked for your health

Los Angeles Times—May 20th

Original Article: http://latimesblogs.latimes.com/booster_shots/2008/05/couples-get-nak.html

"Melanoma can appear in places where the sun never shined," says Dr. June K. Robinson, dermatologist and lead author of the study. "There's a fear of lying there naked and vulnerable when someone you care about is seeing you in not the most flattering light."

Researchers at Northwestern University's Feinberg School of Medicine recruited 130 survivors of melanoma, the most serious form of skin cancer. All the participants were married or had a life partner, but for half the group, only the patient was trained in skin self-examination. Participants in the second group learned the examination techniques with their partners.

FUNDING OPPORTUNITIES

National Center for Minority Health and Health Disparities Centers of Excellence (Limited Submission)

<http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-08-004.html>

National Institutes of Health (NIH)

NU Submission Deadline: 6/23/08

Contact: Alden Chang @ alden-chang@northwestern.edu

NEH Summer Stipends Program (Limited Submission)

<http://www.neh.gov/grants/guidelines/stipends.html>

National Endowment for the Humanities

Internal Letters of Intent: 6/27/08

NU Submission Deadline: 7/11/2008

Contact: Alden Chang @ alden-chang@northwestern.edu

Beckman Young Investigators Program (Limited Submission)

<http://www.beckman-foundation.com/byi.html>

Arnold and Mabel Beckman Foundation

Internal Letters of Intent: 6/27/08

NU Submission Deadline: 8/1/2008

Contact: Alden Chang @ alden-chang@northwestern.edu

Clinical Scientist Awards in Translational Research (Limited Submission)

http://www.bwfund.org/programs/translational/clinical_scientists_main.html

Burroughs Wellcome Fund

Internal Letters of Intent: 6/27/08

NU Submission Deadline: 8/1/2008

Contact: Alden Chang @ alden-chang@northwestern.edu

NIH Predoctoral Training at the Interface of the Behavioral and Biomedical Sciences (T32) (Limited Submission)

<http://grants.nih.gov/grants/guide/pa-files/PAR-06-503.html>

National Institutes of Health (NIH)

Internal Letters of Intent: 6/27/08

NU Submission Deadline: 8/1/2008

Contact: Alden Chang @ alden-chang@northwestern.edu

For more funding opportunities, visit:

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

UPCOMING EVENTS

Epstein-Barr Virus--The Epithelial Cell Connection

Lindsey Hutt-Fletcher, PhD

Tuesday, June 24th, 2008

12:00 PM - 1:00 PM

Baldwin Auditorium, Lurie Medical Research Building

Sponsored by Department of Microbiology-Immunology

Grants.gov Proposal Submission Training Opportunities

Wednesday, June 25th, 9:00AM – 11:00AM

Thursday, June 26th, 9:00AM – 11:00AM

Joseph Schaffner Library, 2nd Floor, Wieboldt Hall

Chicago Campus

Monday, June 30th, 3:00PM – 5:00PM

Wednesday, July 2nd, 3:00PM – 5:00PM

Library PC Classroom, University Library IT Computer Lab Lower Level,

Rm. B183, Evanston Campus

To RSVP, contact: David Hull at d-hull2@northwestern.edu

Sponsored by the Office for Sponsored Research

The CBC/IGSB Workshop:

High-Throughput Cellular Screening

Tuesday, July 8th

The Gordon Center for Integrative Sciences,

University of Chicago

929 E. 57th Street, Chicago, Illinois

Cost for the workshop is \$25.

Application deadline for the workshop is 5:00 pm, July 1st.

For more information, visit:

<http://www.chicagobiomedicalconsortium.org>

Sponsored by the Chicago Biomedical Consortium (CBC) and the

Institute for Genomics & Systems Biology (IGSB)

Event organizers are encouraged to submit calendar items on

[Plan-it Purple](#). For more events, visit

www.feinberg.northwestern.edu/research/calendar/.

Share your news with us!

Your feedback and suggestions are always welcomed!

Feinberg School of Medicine Office for Research

Email: fsm-research@northwestern.edu

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

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