

C.S. MOTT CENTER FOR HUMAN GROWTH AND DEVELOPMENT
Annual Report 2012

Narrative Summary

Robert Sokol, M.D. – Director

Introduction

Our efforts have been directed towards maintaining a preeminent position in Reproductive Sciences and Perinatal Research. We continue to build new areas to enhance the program in Reproductive Systems Biology consistent with the strategic vision of the School of Medicine and the University. All things considered - Top of mind for 2012 was to renew the Contract for Services in Support of the Perinatal Research Branch; the PRB occupies about a quarter of Mott net square footage and contributes massively to the perinatal research literature and to the total external grant support of WSU.

Where We Are

During 2012, the Mott Internal Advisory Committee continued to be chaired by Dr. Joseph Dunbar, Associate Vice President for Research; and the External Advisory Committee also continues to be chaired by Dr. Gloria Heppner, Associate Vice President for Research. Both the chairs and their committees continue to contribute immensely to the Mott's operation and development.

A first floor patient oriented Clinical Research Center was created as part of our commitment to translational research. This area is now fully operational, and has many on-going or soon to be on-going clinical research projects. These include --

- Human Skeletal Muscle Proteome and Phosphoproteome in Obesity and Type 2 Diabetes (College of Pharmacy and Health Sciences, Zhengping Yi - PI);
- Asthma Phenotypes in the Inner City (HFHS, Edward M. Zoratti - PI);
- A Biomarker-Based Pilot Study of Cockroach Sublingual Immunotherapy in Cockroach Sensitive Children with Asthma and/or Perennial Allergic Rhinitis (HFHS, Edward M. Zoratti - PI);
- The Role of Epigenetics in Inner City Asthma (HFHS);
- Registry for Asthma Characterization and Recruitment (HFHS, Edward M. Zoratti - PI);
- Preventative Omalizumab or Step-Up Therapy for Severe Fall Exacerbations (HFHS, Edward M. Zoratti - PI);
- Perceived Fairness and Biological Stress Reactivity (Family Medicine and Public Health, Todd Lucas - PI);
- A Phase 3/4, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Adult Subjects of Black Race with Systemic Lupus Erythematosus (SLE) (Internal Medicine, Josephine P. Dhar - PI);
- Phase I, Safety and Immunogenicity of Gardasil in Systemic Lupus Erythematosus (Internal Medicine, Josephine P. Dhar - PI);
- A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab as Maintenance Therapy in Subjects Requiring High Dose Corticosteroids for Active Non-Infectious Intermediate-, Posterior-, or Pan-uveitis – VISUAL I (Ophthalmology, James Puklin - PI); and
- Effects of Testosterone on Threat-and Reward-Related Neural Function (Psychiatry and Behavioral Neurosciences; Justin M Carre - PI).

NIH Site Visit

Some additional building renovation prepared the Mott Center for the NICHD/NIH PRB (Perinatology Research Branch) site visit. This included modernizing the lobby to the standards set by the PRB and building out additional Applied Genomics Technology Center (AGTC) space to house the new HiSeq 2500 as well as to provide a common research - clinical translation area. The visit was highly successful, very likely enhancing our proposal to retain the Perinatology Research Branch at Wayne State. The cost was about \$1.3 million, but assured that the Mott remains at the forefront of Next Generation Sequencing technology.

Graduate Program

The Department's doctoral program is housed in Physiology and noted as a concentration in Reproductive Sciences. The Reproductive Science concentration represents an integrated Ph.D. program incorporating the teaching, research, and physical resources of two departments, Obstetrics/Gynecology and Physiology. Program specific courses are taught by Ob/Gyn teaching faculty and dissertation research is performed in our departmental basic science laboratories at the Mott Center. The program presently offers 10 courses totaling 25 credit hours which cover a range of topics in the Reproductive Sciences field; in 2012, PSL 7690 was offered in the fall semester. In addition, the program's emphasis on bioinformatics was expanded by cross-listing 2 curriculum courses from the new Bioinformatics & Computational Biology Concentration offered by the Department of Computer Science and Center for Molecular Medicine and Genetics. This program had also been expanded for individuals with Medical Degrees to earn their Ph.D.s through the Reproductive Sciences Concentration. This effort is directed primarily at our young M.D.s currently participating in clinical fellowships in Maternal Fetal Medicine (MFM), Reproductive Endocrinology and Infertility (REI), and Gynecologic Oncology, as well as Research Fellows in the Perinatology Research Branch (PRB). Juan Gonzalez, M.D. has completed his course work and will shortly present his dissertation plan. Jimmy Belotte, M.D., is in his first year, and Rani Fritz, D.O., will soon be entering the program. Currently, 7 full-time students are enrolled amongst the 12 active research faculty.

One student graduated in 2012 bringing the total of 6 students that have now completed the program. These students are --

- Jill A. Slater (Mentor: Daniel A. Rappolee, Ph.D.), "Hyperosmotic Stress Enzyme Signaling Modulates Oct4, Nanog, and Rex1 Expression and Induces Prioritized Differentiation of Murine Embryonic Stem Cells" in Fall 2012;
- Sichang (Steven) Zhou (Mentor: Daniel A. Rappolee, Ph.D.), "Cell Lineage Choice during Differentiation of Trophoblast Stem Cells (TSC) is Dependent on Oxygen Levels, and Mediated by Stress Enzyme Pathways and Mitochondrial Function" in Fall 2011;
- Jennell White-Jackson (Mentor: Ghassan Saed, Ph.D.), "A Potential Role for Innate Immunity in the Pathogenesis of Post-Operative Adhesions" in Fall 2011;
- Dhiman Maitra (Mentor: Husam Abu-Soud, Ph.D.), "Destruction of Biological Tetrapyrrole Macrocycles by Hypochlorous Acid and Its Scavenging by Lycopene" in Fall 2011;
- Tiffini Gibson (Mentor: Carol A. Brenner, Ph.D.), "The Impact of the Mitochondrial DNA Genome on Skeletal Muscle and Preimplantation Development in the Rhesus Macaque" in Fall 2009; and
- Catherine DuPont (Mentor: Carol A. Brenner, Ph.D.), "Incidence and Mechanisms of Chromosomal Anomalies during Early Development of Rhesus Macaques" in Fall 2008.

There are another 2 who have green lights from their committees to defend their thesis in the next few months. These students are: Nicole Fletcher-King (Mentor: Ghassan Saed, Ph.D.) and Juan Gonzalez, M.D. (Mentor: Roberto Romero, M.D.). Dr. Dhiman Maitra, as mentioned above and who was working in Dr. Husam Abu-Soud's laboratory as a Postdoctoral fellow, presented an oral poster presentation at the

Experimental Biology 2012 meeting in San Diego, CA. Poster presentation entitled, "The Reaction of HOCl and Cyanocobalamin."

Seminar Series and Journal Clubs

In 2012, the Mott Center continued to have one on-going seminar series and two journal clubs. The faculty member "Brown Bag" seminar series continues. The Reproductive Biology Journal Club has joined Chromatin, Computers and Reproduction as an independent offering.

Collaborative Research and New Research Directions

The Mott Center continues to broaden collaboration by increasing interdisciplinary and multidisciplinary research in areas that include genomics, bioinformatics, perinatal epidemiology, reproductive sciences, and genetics. Partnership with the PRB continues and extends to other centers and departments within Wayne State University, e.g., the Center for Molecular Medicine and Genetics, Department of Clinical and Translational Sciences, and the Merrill Palmer Skillman Institute.

Perinatology Research Initiative

As part of the Perinatology Research Initiative for Year 2012, two new junior faculty were hired. The Mott Center welcomed Assistant Professors Kang Chen, Ph.D., trained at the Weill Cornell Medical College and Nardhy Lopez-Gomez, Ph.D., who trained at the University of Adelaide. Dr. Chen's research is focused on immunology, pathology, and laboratory medicine complementing Dr. Lopez-Gomez's research that focuses on the physiology of parturition and reproductive immunology.

Additional Pending New Faculty

Aliccia Bollig-Fischer, Ph.D., Assistant Professor will also join the Mott Center as a faculty member through the Department of Oncology. Dr. Bollig-Fischer's research interests focus on discovering cancer subtype-specific oncogenic signaling pathways important to cancer progression and resistance to targeted therapies.

Faculty Recruitment

Sorin Draghici, Ph.D., received a joint appointment to the Department of Obstetrics and Gynecology, as the Robert J. Sokol, M.D. Bioinformatics Endowed Chair in support of the PRB and DCaTS Bioinformatics Programs. His research is focused on computational biology, systems biology, and machine learning applications in life science.

Francesca Luca, Ph.D., Center for Molecular Medicine and Genetics, also received a joint appointment to the Department of Obstetrics and Gynecology. Her primary research interest is focused on combining functional and population genomic approaches to understand the genetic basis of variation in complex phenotypes (see <http://lucalab.wayne.edu> for more information).

Additional faculty recruitment was chaired by Dr. Randy Armant, and we are looking forward to Sascha Drewlo, Ph.D. (University of Toronto) joining the Department at the Mott Center just after the first of the year. Dr. Drewlo's research interests focuses on molecular mechanisms of placenta related pregnancy disorders and the development of *in vitro* models of disease and intervention strategies.

DCaTS (Department of Clinical and Translational Science)

The Mott Center continues to host this new department that was founded by and now chaired by Dr. Robert J. Sokol, Director of the Mott Center. DCaTS administers the Clinical Research Center on the first floor of the Mott. This unit supports clinical trials and has CRO functions serving the entire University and

other organizations, such as the Henry Ford Health System. On-going work continues so that this department will be fully operational when it transitions to its new space in the Multidisciplinary Biomedical Research Building.

Scientific Programs

Mott Center Scientific Retreat

Over the past few years, the Mott Center has held a yearly scientific retreat. This encompasses faculty and invited guests including select faculty from other departments within WSU and outside of WSU. All fellows, students, and laboratory personnel are encouraged to attend. The purpose of the retreat is to foster interdisciplinary collaboration, thereby initiating new research projects. The scientific retreat for this year was held at the Detroit Yacht Club on Belle Isle. There were 40 attendees and 13 presentations, two by invited guest speakers. At this retreat, Paulo Rinaudo, M.D., Ph.D., University of California – San Francisco, CA served as external reviewer commenting on a job well done.

MARTS (Michigan Alliance for Reproductive Technologies and Science) Symposium

The Michigan Alliance for Reproductive Technologies and Science was created approximately 4 years ago. This is a consortium effort between MSU, U-M, and WSU to accelerate growth of the reproductive sciences in Michigan. It is focused to enhance the communication and collaboration among researchers, clinicians, and educators. The alliance fosters a supportive environment for basic research, technological development, translational studies, and clinical implementation. Wayne State University, and specifically, the C.S. Mott Center on behalf of the Department of Obstetrics and Gynecology, hosted the 2012 event. It was organized by two graduate students, Graham Johnson and Nicole Fletcher-King and the lead office administrative assistant, Dawn Cochrane. This was supported by the Department of Obstetrics and Gynecology – WSU; Office of the Vice President for Research – WSU; School of Medicine – WSU; Abcam; Detroit R&D; Ferring Pharmaceuticals; Denville Scientific; Genomatix; Sigma Aldrich; ThermoFisher; and Fisher Scientific, with approximately 119 individuals in attendance. The full day MARTS Symposium program included two guest keynote speakers, Paulo Rinaudo, M.D., Ph.D., University of California – San Francisco, CA who presented the clinical research keynote address, “Long Term Health Effect of Preimplantation Embryo Culture” and; Michael K. Skinner, Ph.D., Washington State University, Pullman, WA who presented the basic research keynote, “Environmentally Induced Epigenetic Transgenerational Inheritance or Reproductive Disease: Ancestral Ghosts in Your Genome”.

Honors/Awards/Highlights

The Mott Center investigators were very active this past year and were recognized by a number of rewards or events in the Year 2012. Some highlights, honors, awards, and events are as follows:

- Dr. Doug Ruden was awarded an R21 grant entitled, “Effects of Lead on Neuronal Differentiation in Human Embryonic Stem Cells.” Funding agency: NIEHS/NIH.
- Drs. Stephen Krawetz and Michael Diamond were awarded an NIH Supplement grant entitled, “SPERM: Selection of Paternal Elements of RNA Messenger.” Funding agency: Yale University; Subcontract from NIH.
- Drs. D. Randall Armant and Michael Diamond were awarded an R21 grant entitled, “Genetic Analysis of Human First Trimester Trophoblast in Ongoing Pregnancies.” Funding agency: NICHD/NIH.
- Dr. Husam Abu-Soud was awarded funding for his research entitled, “Role of Myeloperoxidase in the Etiology of Sickle Cell Disease.” Funding agency: DMC (Detroit Medical Center, Detroit, MI).
- Dr. Kang Chen was awarded a postdoctoral competition grant from WSU’s Office of the Vice President for Research.

- Dr. Husam Abu-Soud will be bringing in the winner of the Fulbright Senior Scholar Award for the academic year 2012-2013. The winner is Dr. Iyad Ali, Najah University, Nablus, Jerusalem, Israel and will work on his research entitled, "Vitamin B12 Enhances the Growth and Metastasis of Ovarian Cancer."
- Dr. Stephen Krawetz welcomed Visiting Scholars from India and Spain.
- Dr. Aliccia Bollig-Fischer received an American Cancer Society – Institutional Research Grant to help fund her research. The research project is entitled, "Characterization of 5-Hydroxymethyl-Cytosine in Breast Cancer."
- Dr. Stephen Krawetz presented his research entitled, "The Secret Life of Sperm from Chromatin to Expression" at the ISABR 2012 IV International Symposium on Animal Biology of Reproduction, Sao Paolo, Brazil.

Future Plans -

WHERE WE ARE GOING? A Systems Biology Program

Over the past few years, we have undertaken an initiative to move the Mott Center back into the forefront of reproductive research and are moving ahead with a program centered in genomics and computational biology. We have envisioned this to span genomics, proteomics, and metabolomics to physiological function and its clinical application. This initiative is only possible because of the continued support of the School of Medicine, the Office of the Vice President for Research, and the Provost. Just as important to this effort are our partners in the Karmanos Cancer Center, the Center for Molecular Medicine and Genetics, the Department of Computer Sciences, and Computer and Information Technology.

Finally, while we didn't have a signed contract in hand at the first of the year, we'd been informed that we would be awarded the Contract in Support of the PRB!!