

# Geisinger Clinic - Weis Center for Research

## Annual Progress Report: 2008 Formula Grant

### Reporting Period

July 1, 2010 – December 31, 2010

### Formula Grant Overview

The Geisinger Clinic - Weis Center for Research received \$95,564 in formula funds for the grant award period January 1, 2009 through December 31, 2010. Accomplishments for the reporting period are described below.

### Research Project 1: Project Title and Purpose

*Genomics of Pregnancy-Related Complications* - Complications related to pregnancy are difficult to predict in advance, need better treatments, and are major causes of death or disability from pregnancy and/or delivery. Pregnancy-related complications include pre-eclampsia (high blood pressure and fluid retention caused by pregnancy) and pre-term or premature labor. Previous studies have shown that family history is a major risk factor for these complications, which indicates that they are influenced by inherited genetic factors. The goal of this study is to assemble a collection of blood and DNA samples from pregnant women and to use these in studies to identify genetic factors related to pre-eclampsia and pre-term labor. This information can then be used in follow-up studies to elucidate the biological factors associated with these conditions and to develop improved methods to diagnose and treat them.

### Duration of Project

1/1/2009 - 12/31/2010

### Project Overview

The goal of this project is to initiate genomic-based studies of complications related to pregnancy, specifically pre-eclampsia and pre-term labor. These studies will be carried out within the Geisinger Clinic, which provides an excellent platform for genomic medicine research. Geisinger is an integrated health care system providing care to a large, stable patient population in north-central and northeastern Pennsylvania, utilizing an advanced electronic medical record system. The project has two short-term goals. The first is to create a collection of blood and DNA samples from women receiving obstetrical care at Geisinger Medical Center; the samples will be linked to a broad and deep set of clinical data enabled by Geisinger's robust health IT infrastructure. The second aim is to use these samples as substrates for genomic analyses, in order to identify individual genetic variants that are associated with these pregnancy-related complications. In this initial project, we will attempt to establish the association of candidate genetic variants called single nucleotide polymorphisms (SNPs) with pre-eclampsia or

pre-term labor. A case-control genetic association approach will be used. SNPs to be tested will be selected from those previously reported to be associated with these complications or SNPs selected on the basis of their proximity to genes suspected to be involved in the disorders based on their biological functions. An attractive feature of this project is that the bank of biological samples to be created and associated clinical data can be used not only for the pilot studies outlined, but also for numerous future studies that apply genomics technologies to these problems.

### **Principal Investigator**

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### **Other Participating Researchers**

Glenn Gerhard, MD, Eric Bieber, MD, James Betoni, DO - employed by Geisinger Clinic

### **Expected Research Outcomes and Benefits**

Pre-term labor and pre-eclampsia are relatively common but serious complications of pregnancy. Current methods to predict these conditions in advance or to treat them are inadequate. There is good evidence that both conditions are influenced by genetic factors, although the mechanisms by which this occurs are poorly understood. We propose to apply genomic approaches to identify genetic variants that are associated with these pregnancy-related complications. Identifying genetic variants that are associated with these disorders will have several benefits. They can be used to develop markers for blood-based tests that identify individuals with elevated risk of these conditions. One benefit of this information would be closer monitoring of high risk individuals and application of existing therapies at an early stage when they are most beneficial. Knowledge of genetic variants associated with these disorders could also provide new insights into the disease mechanisms, for example by identifying previously unknown molecules or molecular pathways that are critical. Such information can be used to develop novel therapies that are more effective than those currently available.

### **Summary of Research Completed**

#### Aim 1 – Create a collection of biological samples to study the genomics of pregnancy-related complications:

Substantial effort was directed to continue to enroll eligible subjects into the research study and to create a repository of blood, serum, DNA and tissue samples that can be used to study the molecular and genetic basis of pregnancy-related complications.

Enrollment of eligible patients who made outpatient visits to the Women's Health Clinic at Geisinger Medical Center continued. Eligible patients were invited to participate in the study

during an outpatient visit and assisted through the informed consent process by a research assistant stationed in the Women's Clinic. During this 6 month project period an additional 520 subjects were consented via this route and agreed to provide blood samples for research. Of these, approximately 75 (~15%) have a documented history of preeclampsia; the remainder includes mostly women with non-complicated deliveries who can serve as controls for genomic studies. The research samples are banked in the Geisinger Clinic Genomics Core in the Weis Center for Research. Blood samples are used to isolate genomic DNA using a Qiagen biorobotics instrument. Serum samples are stored as frozen aliquots.

We also enrolled patients who are admitted to the Labor and Delivery unit at Geisinger Medical Center with preeclampsia or for a non-complicated delivery. Thirty-nine women were enrolled via this route during the 6 month reporting period. In addition to collecting blood samples for research, in some cases, samples of placental tissue for research use are also obtained. These are dissected and portions are preserved in RNA-later (as a source of RNA for expression studies), or paraformaldehyde (for anatomical and immunohistochemical studies), or frozen (for proteomic studies). During the current reporting period 22 placentas were processed and banked for research use. We also collected research blood and serum samples from 7 women with preeclamptic deliveries the day following their delivery. Since we also have research blood and serum samples from these women before their delivery, this enables us to study molecular changes that are associated with preeclampsia and its resolution.

In some cases we also obtained blood samples from the babies of preeclamptic deliveries and their fathers. There is evidence that babies of fathers with a history of preeclampsia are at increased risk for preeclampsia. Having DNA from the fathers provides a window to study the genetic basis of this risk. It has also been suggested that a genetic interaction between the mother and the baby influences the risk of preeclampsia, for example a genetic incompatibility between the mother and the fetus. Finally, several recent genome sequencing studies demonstrate the value of DNA sequence data from both parents and a child in interpreting genomic sequence data.

To augment subject recruitment, especially of trios (mother, baby, father) from preeclamptic deliveries, we added a retrospective enrollment arm. Eligible patients were identified by querying the Geisinger electronic medical record database. Potential subjects were contacted by letter with a follow-up phone call by a member of the study team.

For prospective enrollment separate consent for the baby was provided by the mother; blood was collected via the umbilical cord after the delivery was completed. Consenting fathers provided blood and serum samples for research by venipuncture. For retrospective recruitment, DNA samples were obtained using saliva collection kits. During the reporting period a total of 51 additional mother/father/baby trios were consented to participate and provide blood and/or DNA samples for research.

#### Aim 2 – investigate the association of genomic variants with preeclampsia:

During the current reporting period we continued our analysis of microRNA expression in preeclampsia using array-based high-throughput techniques. MicroRNAs are known to control the expression of other genes and might therefore be important in disease processes. RNA

isolated from placental tissue was labeled and hybridized to Affymetrix miRNA arrays that contain probes for human miRNAs and other small non-coding RNAs. Data from the first 6 samples (3 cases and 3 controls) was analyzed. These data identify 104 miRNAs and other non-coding RNAs that show statistically significant differences in steady state levels between preeclamptic and control tissue. Analysis of an additional 6 samples was underway but not completed by the end of the reporting period.