# UCSD Group Developing POC Technology to Detect Dangerous Pregnancy Complications

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***Premium***

NEW YORK (GenomeWeb) – A team of researchers at the University of California, San Diego is developing technology to noninvasively detect both protein and microRNA biomarkers that can signal potential complications in pregnancy impacting maternal and fetal morbidity and mortality.

The project was recently granted two years of funding for proof-of-concept studies from the National Institute of Child Health and Human Development, with the first year's award totaling $235,729. The researchers are also collaborating with Sera Prognostics, which will provide insights into biomarker selection gleaned from its mass spec studies and literature analyses.

The core technology of the project uses magnetic nanosensors to perform simultaneous multianalyte immunoassay and miRNA detection in a single cartridge.

The overall test system is being designed for point-of-care testing to pick up dysregulated biomarkers in maternal blood samples which may indicate placental dysfunction and predict pregnancy complications, such as preterm birth, preeclampsia, or fetal growth restriction.

The magnetic nanosensor technology has been in use for at least a decade, but this is the first time it is being applied to combined protein and miRNA detection, and the first application involving biomarkers of pregnancy complication, said Louise Laurent, the director of perinatal research for the UCSD department of reproductive medicine.

Laurent's colleagues at UCSD, Drew Hall and Yu-Hwa Lo, are spearheading the biosensor and instrument development.

Instead of using an optical-based method, as one would commonly use in ELISA or other immunoassay sensors, the technology uses magnetic probes and sensors. Such a system "has a fundamentally cleaner sensing environment," Hall said, because, while most biological samples have some optical background, "they have zero magnetic background."

Using the magnetic sensing leads to the benefit of being able to do wash-free assays, Laurent said, whereas optical methods usually require washing because unbound fluorophores contribute to background signal.

By switching from a fluorophore or colorimetric label to a magnetic nanoparticle, the overall sensor can also be extremely sensitive. Hall has been studying it for biosensing for more than a decade, and co-authored a

description of the biosensor technology in a 2009 *Nature Medicine* article. The magnetic sensors are also essentially the same as those found in hard disk drives, Hall said, so the technology is well characterized.

Along with his colleague, Shan Wang, who published in 2009 on a magnetic nanosensor chip for tumor antigen detection, as previously described, Hall has also published work describing a reusable peptide nanosensor microarray enabling precise detection of autoantibodies, and recently described circuit architecture that would enable 64-sensor magnetic arrays to be read out in four seconds.

One of the key advantages to the technology is the multiplexing abilities, Hall said. "It is very easy to array the sensors," he said, down to a spacing of about 100 microns. Also, magnetic particles tethered over one sensor are not "seen" by any of the other sensors because magnetic signal falls off at a rate inversely proportional to the distance cubed. The sample volume can also be very small because the reaction occurs all in one chamber, as opposed to different wells in an ELISA.

While there are a few companies working on developing diagnostics using magnetic nanosensors, Hall said none is yet commercialized to his knowledge.

The miRNA assay is also PCR-free and uses the same detection method, Hall said.

Lo, a professor of electrical and computer engineering, said the device the team plans to make is for *in vitro* diagnostics use, and that it can be applied to other conditions as well, with the cost and speed of the device tailored for use in the point-of-care environment, he said.

"We integrate both types of assay seamlessly in the cartridge format, but eventually the chip can be separate, almost like an integrated circuit concept," Lo said. The microfluidic device and biosensors will be put into the cartridge, and made disposable, and share the same electronic readout mechanism. "That streamlines the process and simplifies the back-end signal processing," Lo added.

Furthermore, Lo said his group has experience commercializing assays and biomedical instruments through spinout companies.

Meanwhile, Laurent and her lab at UCSD have been pioneering the biomarker discovery. Earlier this year they presented at the Society for Maternal-Fetal Medicine on work performing small RNA sequencing on extracellular RNA from maternal serum collected between 17-28 weeks' gestation in which the group identified candidate biomarker miRNAs in maternal serum for placental dysfunction. The newly funded work will focus on a novel set of 21 miRNAs.

Currently, the only miRNA assays commercially available are for liquid biopsy and are PCR- or sequencing-based, Laurent said, so a nanosensor-based test will be unique in that respect.

The extracellular microRNA biomarkers will be used to diagnose and predict pregnancy disorders, and will be merged with known and emerging protein biomarkers. "The idea is to have a combined panel for a given complication, such as preterm labor or preeclampsia," she said.

Currently, clinicians caring for pregnant women use protein-based assays. But despite an ongoing search for ideal panels of protein biomarkers, it turns out that, for these types of diagnoses, none is very satisfactory, Laurent said.

"The sensitivity and specificity of the existing biomarkers is not good enough," Laurent said. "Our overall premise is that cases that may not be well identified by protein may be more accurately identified by microRNAs, and vice versa," she added, so leveraging both types of analyte should increase the assay performance.

Preterm birth and preeclampsia share a prevalence of between about 5 and 10 percent of the pregnant population. These two complications can overlap in some cases, with preeclampsia causing some cases of preterm birth while other cases are spontaneous. Fetal growth restriction is another example of a pregnancy complication which can be present with preeclampsia, or independent of it, and is also a big cause of illness in babies, Laurent said.

There are also other, less prevalent complications that Laurent and others are looking at, such as placenta accreta that can lead to maternal hemorrhage.

Laurent's lab looked at prospective cohorts of pregnant women to correlate these dangerous outcomes with blood-based biomarkers. Sera Prognostics does a mixed approach, Laurent said, doing some discovery as well as targeted studies after combing the scientific literature for analytes associated with complications and using their targeted proteomics approach to look at the candidates.

For this project, Laurent said her group will interact with Sera to prioritize targets and focus on a couple of the targets that Sera has discovered as predictive biomarkers for preterm birth. Sera is also supported by the Bill and Melinda Gates Foundation to identify technologies that would work in low-resource settings, she said, and will be sharing some of their antibodies developed in that research for ELISA-based assays with Laurent's team.

Potentially, a panel of markers could impact patient care in the future, Laurent said. For example, with preterm birth, currently physicians assess risk from a patient history, with things like prior preterm birth or lifestyle habits impacting likelihood of early labor. Even combined, however, these risk factors are not great predictors of a preterm birth outcome, Laurent said.

"What we have now is not good," she said, but a more effective screening test could be used to refer people for higher surveillance, or possibly for newer preventative therapies currently in development. Furthermore, being able to provide test results during an office visit would hopefully eliminate delays in treatment.

Future efforts will focus on developing the point-of-care hardware and commercialization, but for now the group will emphasize developing the assays and will also work to define the way the different analytes change over the course of gestation.

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