2nd Annual National Academies Keck *Futures Initiative* Conference

Designing Nanostructures at the Interface between Biomedical and Physical Systems

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Build a Glucose Sensor to Circulate (Implant) in vivo in Humans and Regulate Insulin
Focus Group Summary

Summary written by:
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Focus group members:
- Ananth Annapragada, Associate Professor, Department of Bioinformatics, University of Texas Health Science Center at Houston
- Andres Garcia, Associate Professor, Department of Mechanical Engineering, Georgia Institute of Technology
- Eleni Kousvelari, Acting Director, Center for Biotechnology & Innovation, National Institute of Dental and Craniofacial Research
- Greg Lanza, Assistant Professor of Medicine, Department of Medicine and Biomedical Engineering, Adjunct Assistant Professor of Biomedical Eng., Washington University Medical Center
- Peter Ma, Associate Professor, School of Dentistry, University of Michigan
- G. Ramanath, Associate Professor, Department of Materials Science and Engineering, Rensselaer Polytechnic Institute
- Robert Raphael, Law Assistant Professor, Department of Bioengineering, Rice University
- Dave Roessner, Evaluation Consultant, The National Academies Keck *Futures Initiative*
- Judith Stein, Chief Technologist-Emerging Technologies, Department of Polymer and Specialty Materials, GE Global Research
- John V. Stone, Applied Anthropologist, Institute for Food and Agricultural Standards, Michigan State University
- Jonathan Stroud, Graduate Student, Science Writing Program, University of Southern California

Summary:
Focus Group 6 at the 2nd Annual National Academies Keck *Futures Initiative* Conference was initially charged with "Building a glucose sensor to circulate (implant) in vivo in humans and regulate insulin."

Instead, they determined and ranked the most viable options for glucose sensing and insulin delivery in the near future, using the scientific, social, and ethical implications of those treatments as a framework for consideration. They then presented their results to the general assembly of the *Futures Initiatives* conference.

The group was 1 of 10 such focus groups at the conference. The purpose of these focus groups was twofold: first, to facilitate future interdisciplinary research by developing ties between scientists from diverse fields of interest; and second, to solve potentially revolutionary problems using nano- or microtechnology and a wealth of expertise.

They did this by introducing individuals from diverse science-related backgrounds and giving them a challenging nano- or microscience-related problem, which they then attempted to solve over the five focus group sessions.

The idea was novel and admittedly untested, said Dave Roessner, an evaluation consultant for the National Academies Keck *Futures Initiative*. "It's an experiment," he said. "I'm fascinated with watching the process."

Over the course of the four-day conference, the group met in 5-1/2-hour sessions.

The Group 6 members first introduced themselves one by one, summarizing their diverse areas of expertise, which ranged from applied anthropology to tissue engineering.

The members included Ananth Annapragada, an associate professor at the University of Texas Health Science Center at Houston; Andres Garcia, an associate professor at the Georgia Institute of Technology; Eleni Kousvelari, the acting director of the National Institute of Dental and Craniofacial Research; Greg Lanza, an assistant professor of medicine and adjunct assistant professor of biomedical engineering at Washington University Medical Center; Peter Ma, an associate professor at the University of Michigan; G. Ramanath, an associate professor at Rensselaer Polytechnic Institute; Robert Raphael, an assistant professor at Rice University; Judith Stein, the chief technologist for emerging technologies at GE Global Research; John V. Stone, an applied anthropologist at Michigan State University; and Roessner.

Initially, the group appointed Annapragada the leader, and then asked Lanza, a member of the conference planning committee, to explain the types of diabetes, current treatments and problems facing physicians.

“Diabetes is a complicated disease fundamentally associated with a lack of insulin, the hormone that helps regulate blood sugar,” he said.

“Diabetes mellitus has two distinct varieties: diabetes type I is an autoimmune disease found in younger patients, while diabetes type II occurs as a result of obesity and hypertension and normally develops in older patients,” he said.

In type II, the body’s cells build up a resistance to insulin, and the pancreas’ islet cells, which secrete the hormone, must work harder, producing more insulin to assist in the uptake of glucose by the cells.

Complications arising from diabetes involve blindness, renal disease, neuropathy, cardiovascular problems, stroke, and heart attack. “Hypervascularization in the eye can also lead to blindness,” he said. Furthermore, hypoglycemia leads to the metabolism of fatty acids into ketones, which results in acidic blood.

“Obviously there are a lot of issues that can still be resolved, especially with type II diabetes,” Garcia said. “The potential threats are enormous.”

Diabetes can be treated by exercise and diet control, but often more action is required. Currently, managing diabetes normally involves sensing the levels of glucose in vivo by drawing a small amount of blood through the skin, normally with a small needle, or a “finger-stick.”

“Then, once reliable and regular sensing occurs, an adequate level of insulin must be injected into the patient’s blood stream,” Lanza said.

There are many different types of insulin on the market, including short- and long-lasting versions. However, in almost all cases, the insulin must be injected intramuscularly multiple times a day.

After Lanza finished explaining diabetes, its treatments, and its complications, the group decided to abandon the original focus of building a circulating glucose sensor.

Many group members did not have the background to develop a novel micro- or nanotechnology approach to address the problem, according to group members.

“Instead, we chose a different path,” Roessner said.

The group decided to focus on current technologies and experimental approaches to the problem and to use their interdisciplinary expertise to attempt to gauge which technology has the highest chance of success. The group also highlighted the major barriers to more effective insulin regulation. Key to the discussions was that the group framed their process around the potential social and ethical considerations, rather than incorporating such considerations at the end of the process.

“(Some of) these systems have been around for decades,” Annapragada said. “We turned them around and looked at it from a consumer’s point of view.”

What emerged was a list of different techniques currently being used to address the problem.

The most common means, according to Lanza, is a regular finger-stick coupled with intramuscular insulin injections. But the pain, regular injections, and the chance of human error make this treatment option imperfect.

Some patients wear an external, programmable insulin-pump that doses them before meals, but users must still routinely monitor their glucose levels. In addition, the pumps, which often contain an implanted needle for insulin delivery, can become infected.

Nancy Moteiro-Riviere, a professor who had worked with glucose-sensing technology, described a glucose-sensing watch she helped develop at North Carolina State University.

She said the “GlucoWatch” used reverse-iontophoresis to pull glucose out of the skin transcutaneously. In addition, the watch stored the information and even told time.

The group then looked at an SMSI implantable sensor. The sensor, which is currently undergoing clinical trials, uses radio frequencies to broadcast glucose information to a receiver worn outside the body, has a 6 to 12 month shelf life, and is the size of a small, thin pill.

Lanza also described an ingestible gastrointestinal mucosal patch that adheres to the GI and loads the blood with insulin, as well as an aerosol form of insulin that is inhaled.

He discussed experimental stem cell implants and islet cell implants, and explained that currently, insulin-producing islet cell implants are only viable for 60 days on average.

“Control is the problem,” Lanza said. “The goal is to try to keep the glycemic control as tight as possible.” Otherwise, he said, people quickly become hypoglycemic, growing faint and syncopated.

The group decided that monitoring glucose levels was the first step to solving the problem.

They decided to focus on an ideal glucose-sensing device, and asked each member to brainstorm their own solution to the glucose-sensing problems. The group then reconvened and members presented their ideas.

Roessner suggested a tiny implantable sensor capable of transmitting reliable glucose data to receptors outside the body, not unlike the SMSI glucose sensor, only smaller, more reliable, and with a longer device lifetime.

Kousvelari proposed an intra-dental implant residing in a false tooth, an idea Stone seconded and expanded on. “You could include a port to pump insulin in,” he said.

Then Garcia suggested a contact lens that has the ability to fluoresce in response to the concentration of glucose.

Ma proposed a gum with the ability to sense glucose levels in saliva; he also suggested a tissue-engineered cell-based system.

Next, Annapragada suggested inhaled particles that contained a compound that would break down and release insulin when the concentration of glucose in the lungs (a symptom of diabetes) rose.

Raphael had two ideas: First, a liposome that contained a glucose-binding protein and an MLCS channel, which would respond to mechanical stresses and then, when the glucose bound to the liposome, would release insulin; and second, non-invasive optical imaging that would send lasers through the skin and detect the level of glucose.

Ramanath put forward an earring or tattoo receiver with a chip made from conducting polymers, and that used frequency to monitor glucose levels through sweat, body heat, and intravenous fluids.

Lanza's idea was an external skin patch that could sense glucose through the skin.

Group members then voted for their first and second favored approach to the problem. Once the votes were tallied, the group picked the three with the most votes, deeming them the most viable.

An implantable micro- or nanosensor was the most popular solution, followed by tissue engineering implants and an external glucose sensor.

Then the group drafted a list of criteria which they believe a sensing apparatus would need to meet to be ideal. The group then prioritized attributes that were necessary to ensure that the objectives would be met.

The list of attributes included sensitive and reliable output, real-time output, an interrogation capability, device lifetime, device size, the expected inflammatory or immune response, convenience of implantability, recoverability, power source, cost-effectiveness, programmability, and the measure of fail-safe assurance.

These factors were all given a rating: either easiest to overcome, moderate to overcome, or hardest to overcome. The group then constructed a color-coded chart that helped visualize the differences between the three distinct approaches.

The group discussed the social and ethical implications of each approach, weighing the pros and cons of each. The group decided the general public would be far more receptive to an external glucose sensor, making it a much more marketable approach. They then presented their results to the conference.

When asked how they felt about the focus group sessions, some members felt the level of expertise was lacking, but said that the broad set of backgrounds helped the group consider a wide range of implications.

"We voted on limited expertise, but it almost doesn't matter," Roessner said. "The interchange and exchange that went on was superb."

Group members said that, while they did not believe the group developed any novel ideas, they thought the interdisciplinary nature of the discussion was enriching and significant. "We spent a lot of time debating the social and ethical implications of this technology," Annapragada said.

Stone agreed. "I don't know how useful what we came up with will be," he said. "But it was an interesting process."