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Virtual rat project earns $13 million grant for Medical College

International team to build a model to study physiology, genes, causal factors of dysfunction and disease

By Mark Johnson and Kathleen Gallagher of the Journal Sentinel

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In a project with broad implications for drug development and basic biology, the Medical College of Wisconsir has won a $13 million federal grant to lead an international team in building a revolutionary computer model of a rat's inner workings.

The five-year grant, one of the largest awarded to the Medical College in recent years, is significant because the rat has become one of the most common stand-ins for the human body in scientific experiments.

Humans and rats share about 90% of their genes, including most known disease genes, and even the specific sequences of these genes are approximately 85% identical, according to Aron Geurts, an assistant professor of physiology at the Medical College and a member of the team working on the project. Scientists know how to translate data from rats to humans to measure blood flow and kidney and liver function.

"The rat is probably the most common experimental animal model used to test drug reactions," said William Jusko, a professor of pharmaceutical sciences at the State University of New York, Buffalo who served on the National Institutes of Health committee that reviewed the Medical College proposal.

"It's easy to study large numbers of them when you have to, and a great deal (of their physiology) applies to the physiology of humans."

And yet, familiar as the rat is to modern science, little exists to show the complex interplay of genes, proteins, anatomy, organ systems and environmental factors.

"The grand vision here is to understand how dysfunction and disease emerge from multiple causal factors," said Dan Beard, professor of physiology at the Medical College and leader of the Virtual Physiological Rat project. Among other uses, the computer model will allow researchers to simulate a rat's cardiovascular system, from the way blood flows to the electrical properties of the heart muscles.

Beard's collaborators on the project include scientists from the University of Wisconsin-Madison, King's College London, University of Auckland in New Zealand, Norwegian University of Life Sciences, University of Washington, North Carolina State University and University of California, San Diego.

The grant will designate the Medical College as a National Center for Systems Biology and establish an annual scientific conference drawing some 50 to 100 researchers from around the world to discuss the virtua rat project and its applications. European scientists have been at work on a similar project, the Virtual Physiological Human, but Beard said there appears to be nothing comparable for other model organisms, such as monkeys and zebra fish.

Answering questions

Because scientists are prohibited from genetically engineering or experimenting on humans, the virtual rat model allows them to address fundamental questions they cannot answer directly with a human model.

The model won't replace the use of rats in the lab, but will allow researchers to better design experiments, testing them first on computers before adjusting or even discarding them. By pre-running experiments, researchers can save time and money and sacrifice fewer rats.

In essence, the computer model will help scientists build their experiments the same way Boeing builds its airplanes, said Jay Bayne, executive director of the Milwaukee Institute, a nonprofit group that is providing high-performance computing and related support for the project. Boeing, he said, builds its planes with computer modeling and flies them in virtual space before manufacturing begins.

"To the degree that the rat model is accurate enough, it shortens the experiment time frame, allows you to do a lot more experiments and lowers the cost considerably for pre-compound drug testing," Bayne said. "Because the rat's biology is similar to ours, it's a significant step forward."

The computer model of the rat will be constructed based on information already known about the rodent, but also on direct observation of a dozen or so different strains of rats being raised at the Medical College. Scientists will also develop so-called knockouts, rats in which a crucial gene is eliminated, or knocked out, in order to assess its role.

For example, researchers are interested in a gene that appears to be important in controlling the rat's metabolism.

"We're looking at knocking that gene out or making mutations to see the effect on the whole body and on cardiovascular function," Beard said.

Another possible use of the computer model would involve examining how a heart muscle cell gets energy to drive the pumping of the heart; this could help researchers determine whether deteriorating energy levels drive heart failure or are the just a result of it.

In Madison, UW cardiovascular and stem cell researcher Timothy J. Kamp will collect data on the electrical properties of heart muscle cells in various rat strains, information that will help to build and test the computer model.

Physiology and math

James B. Bassingthwaighte, a professor of bioengineering and radiology at the University of Washington, another of the Medical College partners on the project, said the model will describe rat physiology in mathematical terms. Numbers offer scientists a window into what happens when the rat's system functions normally and when it faces various stresses. Bassingthwaighte explained the concept this way:

"If you're doing your family budget, how do you understand it? One way is that you put it on a spreadsheet, all of the numbers, so you know the mortgage, the interest rates, the amount for groceries.

"Well, the body is doing the same thing. It has to produce energy and it uses energy. That's what metabolism is all about. When something happens to the family budget - the car gets in a wreck - how does the budget respond to that? The same thing happens in the body. If you have high blood pressure, the heart has to work harder. If that stress is maintained too long, why does the heart go into failure?"

Beard said the computer model will be a work in progress, constantly evolving as new information about rat physiology emerges. He and his colleagues on the project intend to make the model available to other researchers.

"This is an example of modern medical science where you develop collaborations that are worldwide," Bassingthwaighte said. "That way, you have people with a very high level of expertise. That's what Dan Beard has done."

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