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## Geneticist Gets Roadmap Grant

JHU team will examine proteins' interactions in systems

*By Joanna Downer*

*Johns Hopkins Medicine*

A team of researchers from Johns Hopkins has received a five-year \$17 million grant under the National Institutes of Health's Roadmap for Medical Research to develop new technologies to comprehensively examine proteins' interactions in systems ranging from yeast to human cells.

The grant is one of the first two awarded as part of the NIH's plan to support in-depth study of cells' complex biological interactions from the perspective of proteins rather than genes. Many people are by now familiar with genes, which carry the blueprint for proteins. But as scientists develop tools to figure out on very large scales how proteins interact, these workhorses of cells will be making headlines more often.

"These tools will give us a completely new way of looking at complex biological processes, allowing us to actually watch them in action," says NIH Director Elias A. Zerhouni. "As the centers refine the technologies, these valuable resources will be made available to hundreds of investigators across the country who are working in every disease area."

Leader of the Hopkins project is Jef Boeke, professor of [molecular biology and genetics](#) and director of the HighThroughput Biology Center, a brand-new component of the Institute for Basic Biomedical Sciences at Johns Hopkins. "We're going to develop several key technologies to look at proteins and their interactions, to measure proteins' modifications and see how those change over time," Boeke explains. "In the request for applications, the NIH said they wanted to support really new ways of looking at proteins, and we're certainly doing that."

Boeke himself uses genes to study protein function and the components of various biological pathways, mostly using single-celled yeast as an instructive model organism. Through techniques developed in his laboratory, scientists can quickly identify pairs of genes that, when missing at the same time, cause the organism to die. The knowledge gained from these "synthetic lethal" screens isn't just genetic, he says.

"The key is that the yeast die because the two genes' proteins weren't available to interact with one another," Boeke says. "From the results of these studies — for which we use a special type of "barcode" microarrays that provides a list of yeast mutants present, much like a supermarket scanner detects your purchases — we can put together maps of proteins that interact with one another and then use those maps as a starting point to probe the interactions."

A simple example might be some critical complex that is ideally formed by three proteins but that

can work well enough if at least two of the three are present — knock out two in a synthetic lethal screen, and the organism dies. But much harder to figure out is the web of proteins that represent different steps along a number of interacting biological pathways.

To try to tackle these difficult "big picture" problems in biology, the team of researchers will develop technologies in genomics, proteomics, mass spectrometry and microarray techniques and sort, analyze and process the information using cutting-edge computational biology. With colleagues at the Wistar Institute and the University of Wisconsin, Madison, they'll use the new tools to build maps of protein networks and clarify how different modifications of proteins, particularly of histones, affect the proteins' activities.

In one sense, histone proteins act as scaffolding on which cells' chromosomes are arranged for compact storage. But they also play a more active role, helping open chromosomes at particular times and places so that specific genes can be "read" and their instructions used to make proteins. Attaching and removing modifying groups is thought to be a major controller of histones' gene-revealing activities, but much about the processes involved is unknown.

So, in addition to figuring out which proteins interact with which other proteins, the team will develop ways to detect the modifications present on proteins such as histones and to track how they change with time, with cell function or in response to different triggers — say a drug or a chemical.

Those efforts will largely rely on advances in mass spectrometry, which, in general, uses subtle differences in the proteins' masses to separate and identify them, and computational biology, which would organize and analyze the information gained from all these experiments.

"The computational side is very important, and we have experts on the project who can build pictures of protein networks and track very complex changes in these networks, such as changes in the amount of the protein present or which pathways are active," Boeke says. "But what's been missing are good tools to see how the proteins themselves change over time — not just how much is there, but how the proteins are 'decorated.' We hope to create those tools."

These "decorations" are small groups of particular atoms, and their modification of proteins, particularly of a building block called lysine, is very common. The research team will be examining lysine because it is modified by a variety of groups: methyl groups, acetyl groups, ubiquitin and a molecule called SUMO.

The NIH awarded another grant in the National Technology Centers for Networks and Pathways program to the Burnham Institute in California. The research team there will be developing and applying technologies to determine the network of genes, proteins and biological signals responsible for breaking down proteins, a process called proteolysis.

Technologies developed through the two funded projects will be useful in future disease research. Improper histone modification is likely to contribute to diseases like cancers whose incidence increases as people age. Faulty proteolysis, the process studied by the California team, probably contributes to a number of neurologic diseases, such as Alzheimer's, which are characterized in part by a buildup of abnormal proteins that then cause cell death.

The NIH Roadmap is a series of far-reaching initiatives designed to transform the nation's medical research capabilities and speed the movement of research discoveries from the bench to the bedside. The TCNP program is administered by the NIH's National Center for Research Resources.

Leaders in the Hopkins TCNP project, Networks and Pathways of Lysine Modification, are Boeke, Heng Zhu, Joel Bader, Akhilesh Pandey, Bob Cotter, Phil Cole, Patrick Onyango, Andrew Feinberg, Cecile Pickart, Andre Levchenko and Jonathan Pevsner, all affiliated with Johns Hopkins; Shelley Berger, of the Wistar Institute; and Jorge Escalante-Semerena, of the University of Wisconsin, Madison.

● [GO TO OCTOBER 19, 2004 TABLE OF CONTENTS.](#)

● [GO TO THE GAZETTE FRONT PAGE.](#)

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