At the Next Frontier of Biological Research:
A New Center for Genomics and Proteomics at Yale

[Note: This is an expanded version of the article that appears in the *Bulletin of the Connecticut Academy of Science and Engineering*, Vol. 18,2, Summer 2003]

In a small cinderblock room, on the seventh floor of the Klein Biology Tower on Yale's Science Hill, a robot known as a microarrayer slides its arm back and forth on a long bar. With a whir, the arm drops towards a plastic rectangle. The rectangle contains a grid of 384 tiny wells, each of which can hold a unique sample of DNA.

The robot picks up a drop of each sample, by dipping a 'pin' in each well. These $375 pins look like furniture nails, but they are in fact made of a steel alloy, and they are precisely machined so that each one has a flat tip 70 microns in diameter. The tip of each one has a minute slot in which the DNA is gathered.

The robot moves again. It blots off excess DNA onto a glass plate, and then it deposits its samples onto a specially prepared slide.

The microarrayer is a key piece of equipment. It's used to help analyze DNA, proteins, and other molecules. It speeds up the research process. It's able to swiftly place thousands of molecules at precise locations on a single slide, so that researchers can analyze all of them at one time.

At Yale, A New Center for Genomics and Proteomics

It's this kind of research that will be fostered by Yale's new Center for Genomics and Proteomics, which was announced in the spring of 2002. More than just identifying the genes that make up an organism, the Center will focus on determining the meaning of those genes, and of the proteins that are associated with them. It will study the way these molecules function, the way they interact with each other. It will look at what they do, and how to control them. In fact, these emerging fields enable researchers to study organisms at one of their most basic levels.

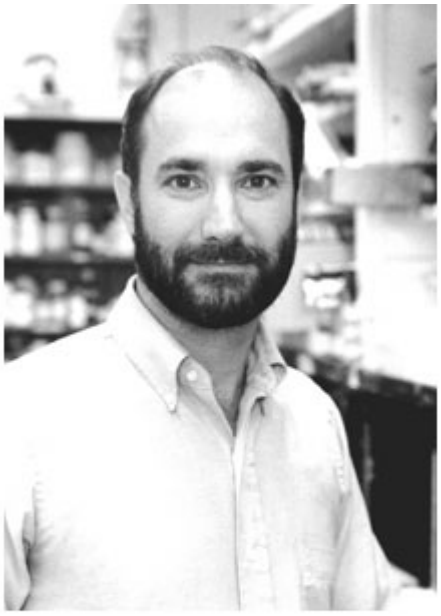
"This very new and very exciting area is the next frontier, the next direction for biological research," says Susan Hockfield, Yale provost and the William Edward Gilbert Professor of Neurobiology. "It represents a set of technologies and an approach that will become increasingly part of the standard repertoire in any of the molecular biologically inclined laboratories."

Yale expects to invest over $200 million in the Center, to add new facilities and renovate existing ones. It will also invest an additional $23 million to bring in new faculty, and to develop programs in these areas. The Center will allow researchers at Yale to take advantage of emerging technologies.

The fields of genomics and proteomics have advanced rapidly over the past few years. "The traditional method," explains Michael Snyder, Chair of Molecular, Cellular, and Developmental Biology, and the Center's director, "was to study one gene, or a few genes, at a time."

Now, though, with complete DNA sequences — known as genomes — identified for whole organisms, and with the new techniques that are available to study them, researchers can work on thousands of genes at once.

"In order to do this, though, things have scaled up," says Snyder. And that is why Yale's Center has become necessary. This work takes expensive equipment: microarrayers, mass spectrometers, and more, and the Center will make these easier for researchers to obtain. It takes new technologies, some of which are still being developed. Part of the Center's goal will be to help generate the technology that's still needed. And, often, it takes more than one laboratory. Here, too, the Center will help, by bringing researchers together.



Michael Snyder, Chair of Molecular, Cellular, and Developmental Biology, and Director of the Yale Center for Genomics and Proteomics.

"These are collaborative efforts," says Snyder. "No one group has the expertise to pull off some of these projects. You'll need bioinformatics, as well as basic experimentalists in order to accomplish some of these goals." The Center, he says, has emerged in part as a response to the changes in the field.

Many Yale researchers have already begun to utilize these techniques, Snyder notes, but the Center will provide an infrastructure to make it easier for them. "We'll have a core of infrastructure and expertise that anybody can tap into," he says. About 40 to 50 faculty members have already expressed interest, he says, and he expects that number to grow.

A 'Center Without Walls'

The Center should have participation from faculty throughout the university. Yale is using "a bit of a different approach," than most other campuses, says Hockfield. A lot of universities have approached this, she says, by creating freestanding structures that are, in a sense, separated from the rest of the campus.

But at Yale, she explains, the Center has been configured as a "Center Without Walls." Rather than being housed in a particular building, the center will, in essence, be located everywhere that researchers are using these technologies.

"By doing this," Hockfield notes, "not only do we capture the enthusiasm and interest and potential of those who are currently working in this area, but we leave it open for other people, as their research evolves to a place where they want to make use of these technologies."

In addition to making it easier for the Center to grow, the Center without Walls concept encourages cross-campus collaboration. "It brings together faculty from the biological and chemical sciences in the arts and sciences with the scientists in the medical school," she says.

Snyder agrees. "There are even more researchers in the medical school than there are on Science Hill," he says. "There will be a lot of participants from there."

The Center will, Hockfield believes, help bring the many researchers in this field together. In the past, she says, it's been difficult, even for those on campus, to appreciate how large the effort in genomics and proteomics is. The Center, she says, "creates a kind of synergy. It identifies a group of people who have shared interests and shared technologies, and it brings them together for their research."

From Functional Genomics to Bioinformatics

The Center will be organized, explains Snyder, into four core areas: functional genomics, which focuses on analyzing what tasks each specific gene performs; chemical genomics, which looks at the way small molecules interact with genes and proteins; medical genomics, which slants toward medical applications, and bioinformatics, which uses computer technology to make sense out of all information generated in the lab.

One goal, says Snyder, is not only to do cutting edge research in these areas, but also to stimulate the development of new technologies that will allow the research to advance even farther.

Because the field is so new, even data management capabilities are still being designed. The high-throughput processes now used in genomics generate such vast amounts of data that even being able to store it is not trivial, says Snyder. And developing the ability to analyze it — finding patterns, correlating sequences of RNA and

DNA, tracking pathways and interactions — will be key to understanding and using all this information effectively. The Center will be active in this key area, as well.

Powerful Practical Implications

The work being encouraged by the Center has powerful practical implications: it could lead to treatments for a multiplicity of human ills. With a microarrayer, for example, researchers can determine which molecules activate particular genes: once the various genes are spotted onto a slide, a bath of molecules can be placed on top of them. The researchers can then detect the genes to which the molecules bind.

That's useful for knowing how to turn on a particular gene, or even how to prevent that gene from working: pharmaceuticals often do their job by binding to a particular protein in a way that prevents the protein from attaching to, and therefore activating, a specific gene.

Determining how genes react could be very useful in prescribing medication. Statins, for example, which are used to lower cholesterol, work far more effectively on some people than on others. "You'd like to know why some people are good responders and some aren't," Snyder says. It may be possible, he explains, to figure out the genetic basis for these individual reactions.

But researchers don't even have to test a gene or protein with another molecule to figure out how to manage it. They can learn much about, say, how a protein works, by taking a look at its shape — although solving protein structure, says Snyder, is still a slow process.

Still, it's intriguing. "If you can see the 3-D structure of a protein's active site, you can see what molecules might fit in there, and design an inhibitor. It's extremely powerful for drug discovery, because the most potent inhibitors always target the active site," Snyder explains.

In fact, simply identifying the molecules, without even knowing what they do, can yield benefits. They can be used, for example, for diagnosis. "This kind of idea is currently being done with DNA microarrays," says Snyder. Each type of cancer, he explains, has its own DNA 'signature'; with each type, a specific set of genes is activated. In particular, researchers are interested in using a cancer's DNA signature to predict its outcome. "Some people get benign tumors, some get metastic tumors. There's a lot of interest in trying to see how these two types of cancer differ in the kinds of genes that are expressed."

Proteins, he says, would be even more useful for this type of diagnosis, because they can found in the blood — much easier to obtain than a piece of an organ. "The goal is to profile serum, find differences, and find signatures." Maybe, he says, you have to look at 50 proteins, which, taken together, can give you a good idea of how a disease will progress. Each one might indicate a 30% chance of a particular outcome, which by itself isn't terribly useful. "But if you have 50 of these things, all of which say you have a 30% chance, well, when you add it all up, then the probability goes way up."

Snyder emphasizes that this work is still in the beginning stages, but ultimately, it could be extremely useful in deciding how best to treat a cancer.

"These days," he points out, "when you remove a tumor, everybody gets chemotherapy." But chemo can cause its own set of problems. If proteins in the blood could be used to predict the likely course of the disease, then chemo could be given only when it was necessary, instead of all the time.

"With most drugs," says Snyder, "we don't know how they work. That's probably rather alarming to most people, and it is getting less and less that way. Now, we know quite a few, but I think that's still true of the majority [of drugs.] What you'd like to do is know what they bind to, to figure out how they work. You'd like to know why they give weird side effects. You'd like to know what they're binding to that you'd prefer they didn't bind to."

In addition to fostering research, says Snyder, the Center will help train researchers and it will provide exposure to these technologies for people at all levels. In addition to courses at both the undergraduate and graduate levels, the Center will provide training for individual researchers. It will offer symposia and workshops, and will encourage collaborative research. Local high school students will be invited in.

Yale is also very interested in building collaborations with industry, says Hockfield. The Center, she says, "has allowed us to talk to funding sources and potential corporate partners in a very different way that we could before."

A First Round of Pilot Grants

The Center recently awarded its first round of pilot grants. Out of 37 proposals, seven were selected, and given a total of $300,000 in funding. "We chose those that seemed most likely to grow into their own larger scale genomic program," said Sherman Weissman, Sterling Professor of Medicine and Genetics at the Yale School of Medicine, and the Center's co-director. These projects, Weissman explains, "represent either extending genomics to different organisms, or totally different aspects of broad scale analysis."

Indeed, in addition to further developing techniques that will help in the genomic and proteomic analysis of such model organisms as arabidopsis plants and fruit flies, the pilot grants will fund a project that will profile phospholipids — the fats that help form cell membranes — in different functional states.

"That seemed like the most novel, in terms of approaching new areas," says Weissman.

"These grants," says Hockfield, "in a sense, accomplished two of our very main goals." Because each proposal, she says, had to come from more than a single scientist, these grants encouraged researchers to join together in collaborative work.

And, importantly, they're expected to help bring in more external funding. The Center's seed money will help advance these projects so that they'll be better positioned to obtain grants from government and other organizations.

The Center's goals are far-ranging and ambitious, admits Snyder. But he believes that they can be achieved. "There's so much interest in this whole area," he says. Already, the Center has accomplished much: its activities range from the new grants, to holding monthly meetings that foster interactions among its participants, to sponsoring a DNA day at the Peabody Museum.

The Center's biggest contribution, says Snyder, will be in "promoting the development and access of these advanced technologies, at all levels." That's broad, he says. "But that's really what it's going to do."— *Karen Miller, science writer*

[Karen Miller is a freelance science writer based in northeastern Connecticut. Her articles have appeared in *Northeast Magazine* and on the Science@NASA website. She is a regular contributor to the Academy's *Bulletin*.]

Return to Bulletin of the Academy of Science and Engineering, Vol. 18,2