Moving from drugs to medicine

By following a systems approach, researchers and clinicians move toward predicting and preventing disease.

BY RANDALL C. WILLIS

"The elucidation of the human genome was the last step of obligate reductionist biology."

With that simple statement in his keynote address at the recent Bio-IT World Congress in Boston, George Poste, director of the Arizona BioDesign Institute, established the challenge being presented to scientists involved in multiple facets of the drug discovery and health care industries. No longer do researchers have the luxury of focusing on their own little corner of the biological universe. Rather, they must stand back from their experiments and look at human health from a broader perspective.

A four-step program

According to David Altschuler, professor of genetics and medicine at Harvard Medical School and Massachusetts General Hospital, this challenge can be divided into four basic steps, which he outlined in his talk at the conference:

1. define the functional elements of the human genome,
2. determine which genes or pathways are altered in the disease state,
3. discover inherited sequence patterns contributing to disease, and
4. apply genomics information to improve clinical practices.

To address the first issue, Altschuler calls on scientists to use comparative genomics to move beyond the gene coding sequences and look for signs of evolutionary conservation. He worries, however, that the genomes of two or three organisms might not be enough to complete the task. Furthermore, concomitant with the sequencing of a wider array of genomes comes a requisite explosion in the amount of data through which researchers have to delve.

"We already think that we are inundated with data," Arvinda Chakravarti, computational biologist and director of the McKusick-Nathans Institute of Genetic Medicine, told attendees. "But given what is coming down the road, we probably only know 1% of the information that we will know in five years."

Given this coming deluge, Chakravarti suggests that research organizations become more involved in what he calls a "wet–dry" cycle of science, whereby times of heavy genomic experimentation are offset by periods of mathematical or statistical modeling to identify gene functions. Poste agrees with Chakravarti, arguing that one of the "grand challenges" of computational biology will be to develop predictive simulations of gene regulation and genetic networks, with the goal of moving our understanding of disease processes from genotype to phenotype.

PHOTO: ARIZONA BIODESIGN INSTITUTE

Poste

Mounting methods

The second step in the process, according to Altschuler, is being addressed by methods, such as microarray analysis and proteomics initiatives, which allow researchers to identify molecules involved in the manifestation of disease and markers that can be used to classify patients into treatment subgroups. But even in this phase of the effort, it is important to understand not just what has gone wrong, but how.

"I don't think it's very interesting to say that something is a kinase," Altschuler commented. "It's like taking a part of your car and saying that it's a screw. It is accurate, but it really doesn't tell you much."

Rather than simply knowing that a gene has been down-regulated or that a particular protein has been mutated, it is necessary for researchers to understand the biomedical implications of these changes. Among the questions this raises: How does the alteration affect cellular metabolism? Or endocrine response? Or a patient's reaction to specific drugs?

To address the third issue, projects such as the HapMap are allowing researchers to look for patterns of sequence inheritance in people suffering from various diseases. For example, Chakravarti described his efforts using haplotype mapping to identify a genetic variant of *RET*, a gene that codes for a receptor tyrosine kinase associated with the human gastrointestinal disorder Hirschsprung's disease. With no previously identified disease-related coding sequence mutations, he explained, the role of *RET* might have been overlooked.

A systemic approach

Ultimately, however, the success of any of these efforts will come in their impacts on disease treatments and patient outcomes. Because clinical phenotypes result from the complex interaction of genotype, patient behavior, environment, and chance, Altschuler argues that it will be critical for clinicians and genomic scientists to form a partnership to facilitate the design and execution of relevant clinical trials.

According to Poste, biology and medicine are in a period of transition, becoming information-based sciences. As the principal technology drivers of molecular medicine, he argues, genomics and informatics offer prospects for improved disease diagnosis and treatment and the potential to move medicine toward prediction and prevention.

In other words, Poste believes that with a systems biology approach, we will see a gradual move from drugs as product to medicine as policy. ■

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