



Feature Articles

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Systems Biology Alters Drug Development Omics Tools Revitalize Field, but Deciphering High-throughput Data Is Still a Major Obstacle

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Research and development costs by pharmaceutical companies rose to an estimated \$55.2 billion in 2006, with costs to develop a biologic drug reaching \$1.2 billion. The potential of the Human Genome Project has yet to be fully realized, but many companies are starting to embrace systems biology as a way to integrate various omics technologies, potentially leading to new ways of understanding diseases that could yield cheaper therapeutics. CHI's "Beyond Genome 2007," held recently, featured a session that discussed systems biology and some companies' latest developments.

Genstruct (www.genstruct.com) has developed a platform to build Causal System™ molecular models of disease and drug action. "Drugs work by eliciting changes in the networks and pathways in cells, tissues, and organs where they have their effect," said Keith Elliston, Ph.D., president and CEO. "We map those out— it's like building a road map for each individual drug. By looking at the pathways the drug activates and regulates we can begin comparing individual drugs."

The company combines data from various sources, for example, high-throughput genomic, proteomic, and metabolomic data to create cause-and-effect disease models. It applies artificial intelligence tools to look at all the predicted and observed relationships between the data and puts it into the context of a complex system.

"This allows us to arrive at a real solution that can impact the clinical development of compounds. The end result is development and evaluation of hypotheses about mechanisms, markers, and effects that can be directly tested against additional large-scale experimental data or through subsequent validation experiments," noted Dr. Elliston.

There has been success with this approach; the company has collaborated on 30 commercial programs to date with pharmaceutical partners including **Pfizer** and **GlaxoSmithKline**. It is currently building an integrative oncology program, taking targeted cancer drugs and determining how they exert their effect through regulating the signal pathways, according to Dr. Elliston.

Since systems biology is a different approach to drug development, there is a high burden of proof, Dr. Elliston noted. "When you enter the clinical development arena, it's more difficult to innovate and to have influence with these types of new technologies. We've made good progress, but it's hard to show immediate impact."

Disease models combining extensive transcription profiling of global gene expression along with computational methods are being developed by researchers at the Institute for Systems Biology (ISB; www.systemsbiology.org). "The new technologies have dramatically changed the kinds of data we can look at, and therefore the inferences we can make about what's going on in the cells and organs," reported David Galas, Ph.D., professor, ISB, and vp and CSO, Battelle Memorial Institute.

Applications in Human Disease

"We have been able to identify a number of processes or networks involved in pathogenic processes of the brain," explained Dr. Galas. "These are complex; each network has 20 to 30 proteins, which are all connected. We've just

begun the analysis, but this is leading to a way of understanding exactly how complex networks, fundamental to the functioning of organisms, are related to disease processes.”

Complex diagnostics will have to be developed in order to understand disease processes in clinical situations, noted Dr. Galas. An example of this is his group’s discovery that the prions produced proteins that appeared in the blood and corresponded to changes in the brain.

“We’re just beginning to figure out how to do all this. More sensitive and reliable methods to detect proteins in the blood are needed to move things forward. Other than mass spectrometry, the only major way to identify proteins experimentally is using antibodies, and that’s pretty crude and not really scalable,” said Dr. Galas.

Working in collaboration with **Unilever**, researchers at **Entelos** (www.entelos.com) developed a skin sensitization model, Entelos® Skin Sensitization PhysioLab®, to support a future change in how companies in the consumer-product industry will make safety assessments of products. This is based on a EU ruling, effective in 2013, that says new products will not be approved if they have any animal testing of ingredients.

“The idea was to put together an in silico approach to replace current animal tests,” explained Christina Friedrich, Ph.D., associate director, in silico R&D development.

The first generation of the model was based on replicating the current gold standard assay for skin sensitization, the LLNA (local lymph node assay). In this assay, the test product is applied to a mouse’s ear over three days, and on the fifth day, the mouse is sacrificed and the lymph nodes examined for proliferation of T cells.

“We were able to input certain chemical properties and reproduce downstream outcomes such as the number of T cells in the lymph nodes. Next, we looked at the individual pathways in biology to discover the key drivers for the sensitization response. The idea with this type of approach is the development of truly predictive assays at the earlier stages,” said Dr. Friedrich. Unilever now has this model in-house and is moving ahead with its own program to develop these assays.

What makes Entelos’ approach unique, according to Dr. Friedrich, is the company’s top-down method, which synthesizes quantitative data from thousands of peer-reviewed papers into a single framework. “Our model doesn’t contain every piece of biology ever known in a subject, but what it does do is get you to something usable much faster than a more standard bottom-up approach,” explained Dr. Friedrich. The company uses a mathematical method to quantitatively describe the relationship between various biological entities over time, making simulations and predictions possible.

Dr. Friedrich added that some current challenges include getting the right kinds of data to calibrate and validate models and explaining the modeling process. “What we’re proposing is a different way of doing business, and that can be a real challenge.”

Systems from Raw Data

Gene Network Sciences (www.gnsbiotech.com) has a platform that enables it to model systems directly from raw molecular and genomic data combined with clinical response measurements. The methodology involves a combination of reverse engineering and forward simulation of models.

The first, reverse engineering, involves learning directly from raw data that predicts how key molecules work together to causally impact disease and response to therapy. The second part is a way to test the models and generate new predictions through specific perturbations. An example would be to predict which genes, when up- or down-regulated, would improve clinical outcome for a patient. This generates new hypotheses that can be directly tested experimentally.

“This is only possible today through advances in the omics technology, which enable us to observe what the system is doing on the molecular level, combined with massive computational power, which enables us to algorithmically learn what the system is doing,” said Iya Khalil, Ph.D., evp.

Advantages to the company’s approach include speed (super computers enable predictions within a few days),

unbiased knowledge (from raw data), and the ability to generate new hypotheses that go beyond the data itself, reported Dr. Khalil.

A recent collaboration with **Johnson & Johnson** involved different drugs hitting the erb-B pathway and understanding what those drugs were doing mechanistically. “We were able to learn how the drugs worked directly from the data, and this gave the customer insight on the key genes and markers the drugs were hitting,” added Dr. Khalil. “This gave them a set of predictions to validate in the lab.

“This is the paradigm that in silico modeling in biology needs to take to be effective. It’s not about modeling all the data in the world; it’s the strong interplay between the question you ask of the system and the experiment you design and then creating the model around that and getting to the next level and predictions that allow you to make the next set of decisions,” explained Dr. Khalil.

Focusing on Predictive Medicine

As a closing speaker, Stephen Naylor, Ph.D., CEO and chairman of **Predictive Physiology & Medicine** (PPM; www.ppmone.com), noted that the problems that existed five to six years ago still exist today. “Trying to make sense of high-throughput population study data was a sizable obstacle in terms of biological questions being asked and is still front and center.”

Many companies moved away from a systems approach because they didn’t have the right tools and couldn’t answer relatively simple biological questions, Dr. Naylor explained. “There’s a lot of effort going into sophisticated text- and knowledge-mining tools. I think there has been some tremendous work as these tools have been developed, but show me where there’s been some significant development in terms of our understanding of disease causation or treatment.”

Part of the problem, not just with systems biology, but with science in general, Dr. Naylor explained, is the hype of omics technology. “Everyone got caught up in the hyperbole and ridiculous expectations that were being set. Somewhere along the way people lost sight of the fact that science is dictated by asking significant questions and then trying to solve them.”

PPM is focusing on personalized medicine. The company has developed a platform, NetFit, with multiple entry points. “I call it a multifactorial platform where you can come in on the back end and use a whole suite of text-mining tools that help drive the question one is asking about the personal health of a person.”

Patients have blood samples taken and these are sent to PPM for analysis. The idea is an analysis of overall health and wellness. “You’ll get a report on cardiovascular disease risk, diabetes risk, etc. We’ve developed a series of algorithms where we can make a reasonable prediction based on looking at markers. We take massive amounts of information that already exists and integrate it so we can make health predictions,” noted Dr. Naylor. PPM is hoping to analyze its first patient samples within the next six months.