Bio-IT World

# Patience, Persistence, and Payoff

*Genstruct counts on perseverance for systems biology success.*

**By John Russell**

**May 12, 2008** | Many reasonable-sounding explanations are offered for the systems biology (SB) community's lack of traction: 1) the technologies weren't (aren't) really ready; 2) not enough biology was (is) known for predictive technologies to work very well; 3) desperate pharma jilted platforms for compounds; 4) collaborators wouldn't share meaningful IP; 5) personnel shuffling inside pharma has made maintaining influence problematic.

Genstruct CEO Keith Elliston is familiar with the list and doesn't agree with many of them. He is, however, a realist. A pioneer in using computational approaches to infer mechanistic hypotheses from large experimental data sets, Genstruct's bread and butter is hypothesis generation. In the past, most engagements lasted two to four months - Genstruct has done 30 or so such projects - and contrary to Elliston's original expectations, none grew into a sustained collaboration or produced the glittering IP that excites the financial world.

"When you're working in a process that has many different contributions, how do you measure the value of one particular contribution?" says Elliston. "When you have a compound, then you've got a piece of something tangible and you say, well, I developed the compound, so therefore this is my piece. When you define a hypothesis for a marker, or a mechanism, how does somebody value that? It's not a discrete entity, in many cases it's not a physical entity, and so getting real value for it is really tough. That's the reason we're actually looking at products."

Like most of its peers, Genstruct is adopting a hybrid business model that blends fee-for-service projects and R&D collaborations with internal drug and biomarker development. Recently, the company hired Michelle Gordon-Savenor to grow the consulting and alliance business. She had been alliance manager at Millennium Pharmaceuticals. Genstruct also recruited another former Millennium researcher, Christian Reich, to run internal R&D.

Genstruct's original premise in 2002 was to create a computational platform that could model biology and disease by describing systems and their components in terms of state (on, off, increased, decreased, no change).

The notion was that this would permit the technology to make biology "computable" to tease out mechanisms of action for compounds. But success in the lab and on projects for clients hasn't yet translated into clear business success. Several SB companies have begun using their platforms to reposition jettisoned compounds as a new strategy. Elliston is less sanguine about that approach. Others are investigating non-biomedical markets - biofuels and cosmetics, for example - and Elliston agrees

there may be worthwhile opportunities elsewhere. But the most promising opportunity for Genstruct, he says, is in biomarkers generally, and diagnostic biomarkers specifically.

"In seven biomarker programs we've done with one partner, we've identified 134 mechanistic biomarkers," he says. "So our goal is to go from doing hypotheses very well to doing molecules. Rather than doing therapeutics, which I think is a long, tough road and fraught with risk, we want to do molecular diagnostics, and to do them where we have now the key intellectual property, such biomarkers for breast cancer, for lung and neck cancer, etc."

To help guide the shift, Elliston is building a business advisory board featuring ex-pharmaceutical senior execs, people from diagnostics, and representatives from the payer side of the business. We think cancer is certainly the first area for us."

**New Strategy**

Elliston believes Genstruct's new strategy maps nicely against what the market will support. The kinks have been worked out of the technology, overhead has been deliberately kept low to reduce financial pressure, and confidence is growing in Genstruct's technology.

Last month, after five years of doing short-term projects with Genstruct, Pfizer struck a corporate-wide agreement that sets standard terms for working with Genstruct. It's not IP-sharing, but it is a vote of confidence in Genstruct technology. Individual Pfizer groups can now engage Genstruct quickly and easily.

To use Elliston's analogy, the Genstruct approach is a little like the National Transportation Safety Board's efforts to reconstruct why an airplane crashed by sifting through debris and reviewing flight conditions. He says this is different from trying to predict whether a crash will occur before takeoff, which he still thinks is difficult. It can, however, produce insight that leads to improved airplane design or better flight rules and traffic management to prevent crashes in the future.

Customers bring their experimental data to Genstruct to learn what their drug did, to whom, and why. The emphasis is on seeking mechanistic hypotheses. To accomplish this, Genstruct has built what it calls a Knowledge Assembly database of biological relationships, culled from literature and other work on rodent and human biology. This doesn't sound so different from what other pathway and disease modelers do. The key difference, says Elliston, is the conversion of the data into Genstruct's proprietary "computable" format and use of its causal modeling engine to produce hypotheses.

"In the pathway world," he says, "you have a network that's composed of simple nodes of proteins and complex connections. We've turned that paradigm completely around to be able to reason or compute on these networks. Our world has very rich nodes and very simple connections."

An example of a rich node? Consider protein X and its kinase activity. "The kinase activity, in fact, is distinct from the concentration, from the transcription, from other key attributes of that particular protein. We can relate that to other proteins through a series of cause-and-effect relationships. So this is a logical chain," says Elliston.

Each entity (e.g., protein) also has a "state" (up, down, no change) based on its interactions with other entities. In Lego-like fashion, they can be placed into networks a priori based on known biology and then have the client data "painted on" the nodes to produce a result. Similarly, a causal network could be "inferred" from customer-supplied data using Genstruct's causal modeling engine. In all cases, the nature of the system forces a "result," even if the result is no change or no connection.

"You do what we call a state change analysis. We analyze this data to figure out, did the state of transcription of X change or not? Did it change tenfold or fivefold or twofold? It doesn't matter to me. Did it change? What are my criteria for that? The beauty of how this works is, as long as I have signal in the system, I'll converge on something in the network. We've done a lot of experiments. If I don't have signal here, there's no convergence," explains Elliston.

Computing these "states" is fairly straightforward. Genstruct produces results generally in two to three months without exotic hardware. The "result" can be a family of mechanistic hypotheses, each scored for probability. These hypotheses, of course, must be tested in the lab. The system can also identify biomarkers associated with active networks.

Talking about the database, Elliston says it is "not particularly mind-boggling. The latest numbers on human [data show that] we have about 75,000 entities and about 300,000 relationships amongst them... There are about 15,000 known and demonstrated transcripts in the human genome. We have upstream causal relationships for 11,000 of those. If you look at protein phosphorylation, we have 20,000 sites. There's estimated to be about 60,000 sites."

One recurring criticism of database-informed approaches is that not enough biology is known for these systems to work well. Elliston scoffs at this idea. Far from the original estimates of 100,000 or more human genes, "we can build a human being with trillions of individual cells out of about 15,000 to 20,000 genes that we actively use," he says. "That tells us something about the way biology works. Many people say we only know 5 percent of what's going on biologically. I think we know much more than that if you take a look at the modularity and conservation of biology." Besides, says Elliston, Pfizer would have dumped Genstruct long ago if it weren't producing value.

Other notable current collaborators include GlaxoSmithKline, Dana Farber Cancer Institute, Stanford University, and the Institute for Systems Biology, as well as alliances with Ariadne, Jubilant BioSys, and Spotfire.

**Validated Approach**

Elliston says Genstruct has been operating at break even in recent years, and predicts the new strategy will double 2007 revenues. Bringing biomarkers to market, even through partnerships, will take some time. But Elliston is confident the Genstruct platform can create a high volume of candidates, and he says Genstruct will be happy to own a piece, say 10 to 20 percent, "of a large number of candidates." Meanwhile the consulting and R&D collaboration businesses will foot the operations bill.

Validation remains a missing competency, and the Genstruct CEO says he'd consider acquiring validation capacity to speed up the process. Pharma collaborators have validation capacity, but often not the urgency to do them quickly. If Genstruct did acquire wet lab capabilities, they would be focused on validation activities.

Reflecting on the challenges of selling technology to the biopharma industry, Elliston recalls the travails of the financial services industry. "In the '70s and '80s, there were huge problems with credit card fraud. A company called Fair Isaac came up with ways of using artificial intelligence to detect fraud. They initially tried to sell the technology to people and nobody would buy it. So they said, 'Well, wait a minute. You send us your transaction data, we'll look through it, and we'll tell you which transactions are fraudulent.' They started doing that business, and pretty soon everybody was sending them their data, and over 90 percent of credit card fraud detection was done by their technology... I think that's the way this has to be done.