Biocomputation Startups:

Where Does Value Lie?

BY KATHARINE MILLER

When discussing biocomputation startups, there's one thing people agree on: These days, they don't generate much excitement among venture capitalists.

"In the 1990s, there were a series of bioinformatics companies founded that did not succeed," says **Fred Dotzler**, managing partner of **DeNovo Ventures**, a healthcare investment firm. "Now money for these types of companies is thinner."

Why the pessimism? Simply this: There are a limited number of potential biopharma (biotech and pharmaceutical industry) customers for bioinformatics platforms, and many of those already have a suite of informatics products. Anything an outsider develops will have to be extremely promising and technically compatible with installed systems for these companies to make the change.

Nevertheless, many in the field are still trying to make a go of it by selling software platforms, tools, and services to biopharma. The pharmaceutical industry, they say, desperately needs to change how it does business. Estimates vary, but many say it costs more than a billion dollars to bring a new drug to market. Moreover, the failure rate of new drugs is extremely high, and drug safety problems are often discovered after millions have already been spent. Biocomputation, the argument goes, offers one possible way to discover new drug targets, determine drug toxicity sooner, and efficiently hasten the development of safe and effective drugs.

Colin Hill
CEO, president, chairman and co-founder of Gene Network Sciences (GNS)
Colin Hill had been doing research in theoretical physics and chaos theory in non-living systems for some time when he was drawn into applying those ideas to biological systems. He saw that the mathematical modeling of a complex many-component system wasn't really happening in the drug development world. "If one could master the source code of a living system," he says, "that would give us a huge capability to discover the underlying biological mechanisms of drug efficacy and toxicity." GNS was born of Hill's convictions.

Protein Mechanics □ Intelligenetics □ Molecular Applications Group □ Molecular Mining □ Physiome □ Rosetta Inpharmatics □ Molecular Designs □ GeneSpring □ Entelos □ Gene Network Systems □ Ingenuity □ 23AndMe □ Pathwork Diagnostics □

According to **Colin Hill**, CEO and co-founder of a systems biology company called **Gene Network Sciences (GNS)**, "At the end of the day I have to be bullish for this field, whether academic or commercial, because I don't see a way out of the pharmaceutical crisis without a better ability to discover drug mechanisms and ultimately predict efficacy and toxicity better than the industry does now." Companies such as GNS, **Entelos** and **Ingenuity,** discussed below, are betting their hopes on their ability to help the industry move forward more efficiently.

Other startup entrepreneurs, however, see greater promise in designing biocomputational products that are essential to clinical care and repeatedly needed. "I've always felt that given a chance to sell razor blades or a razor, I'd far rather sell razor blades," says **Glenda Anderson**, founder and chief technology officer at **Pathwork Diagnostics**.

A bioinformatics software platform is like a razor, she says, it's needed, but doesn't need replacing very often. Pathwork Diagnostics, by contrast, has created a razor blade—something that costs little to produce and is repeatedly needed. It's a bioinformatics tool that analyzes gene expression data to determine the likely source of cancerous tumors of unknown primary. They will charge for each biopsy result they analyze.

Anderson predicts this startup model is the wave of the future: "Biocomputational startups probably will start to look more like medical product startups with a heavy biocomputational component," she says. She points to **XDx** as another company following this model. And **23AndMe** (also discussed below) is a new company that hopes to market genetic information to the consumer—another razor blade.

The challenge for people looking to start new biocomputation companies, Anderson says, is figuring out which research ideas are commercially viable. "There's a real void here that I find quite exciting," she says. "Some of the best ideas in this field might be fantastic science, but might not translate into products that could fuel a successful startup. That's our opportunity and challenge."

Selling to Biopharma? Link to a Drug or Go without VC

According to Hill, a surge of funding for biocomputation startups in 2000 gave entrepreneurs the mistaken impression that a business could succeed just by generating data and related tools. GNS itself was funded in that wave.

> "If you just want to make a lot of money, go to Wall Street. Or create the next YouTube," says Colin Hill. "The ultimate test in our field is affecting disease in a living human.... it's much more difficult than just developing technology."

"VCs want companies that are going to have a good-size market with good revenue possibilities," says Alex Bangs. "If your market is to sell to a small part of the pharmaceutical industry, then you have a small number of customers with potentially varying budgets."

"I think it gave us a somewhat slanted view of where value was going to lie for computational systems biology," says Hill. "Normally, the real currency of the industry is around a drug."

GNS survived by making sure drugs were their central focus. The company's strategy is to create models on the fly from data about specific drugs in the pharmaceutical development pipeline. They have developed a unique tool that can quickly—in hours or days—uncover how a drug is working and predict which patient populations will benefit. For example, GNS helped Johnson and Johnson discover the mechanism of action for a multi-kinase inhibitor being developed to treat cancer.

"If we're right, this will become one of the key value drivers for the whole pharmaceutical industry. If we're wrong then we'll be one more platform technology company to come and go from the stage of pharmaceutical drug discovery and development," Hill says

These days, GNS works for pharmaceutical companies on a fee-for-service basis. But, he says, "A lot of investors would say you really need to take it all the way downstream to a drug to extract maximum value from breakthrough technology."

The potential revenue from making drugs is apparent to **Entelos** as well, says **Alex Bangs**, the company's co-founder and chief technology officer. A few years ago, for example, Entelos used its bioinformatics tools to help Organon, a pharmaceutical company, identify new drug targets for rheumatoid arthritis. A co-development agreement gives Entelos a piece of those drugs going forward.

But, like GNS, the bulk of Entelos' business still revolves around fee-for-service. The company's core product is computer simulation of chronic diseases in virtual patients. They build the models and collaborate with pharmaceutical companies along all points of the drug discovery, testing, and trial process. One of their challenges as a business is to explain the full range of their tools' potential. "A tool that works in discovery and clinical is unusual," Bangs says. "It's hard for people to wrap their arms around."

Bangs says their products have proven extremely valuable in telling pharmaceutical companies when a compound is likely to fail in the marketplace. "We've had people stop those programs and spend their money in a different way," he says. "And when we get a result that suggests something's going to work, we can explain why, suggest measures to confirm what we're seeing and recommend when to take those measures to get the best result. It's very much a scientific conversation, not a black box."

Entelos is no longer a startup. The company went public last April in the

(continues on page 11)

Alex Bangs
Co-founder and chief technology officer at Entelos
While working at a management consulting company in the early 1990s, Bangs helped his cohorts develop software tools in support of modeling work for pharmaceutical companies. His contribution: the creation of a software architecture that supported the development and analysis of large scale physiology models and virtual patients. By 1996, they saw that the tools had commercial potential. That's when five partners started Entelos. In 2006, the company went public.

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THE OPEN SOURCE BUSINESS MODEL

Warren DeLano, PhD
Principal, DeLano Scientific, LLC

"Scientists don't want black boxes in their software," says **Warren DeLano**, principal of **DeLano Scientific**. "They need to know how the thing works." So DeLano believes in making software that's open source rather than proprietary.

When he created PyMOL, an open source molecular visualization tool, DeLano hoped it would prove useful to many researchers and that, like other open source projects, it would benefit from an influx of good ideas, new features and code that would make it a self-sustaining project. The first part of that vision became a reality: PyMOL has proven quite useful. DeLano estimates that a quarter of all macromolecular crystal structure images published in the scientific literature today are created using PyMOL. But the software did not become independently self-sustaining. PyMOL's users aren't necessarily software engineers, says DeLano—they don't typically contribute code back to the project. Hence the need for a company—DeLano Scientific—to fulfill that role.

Four years into it, DeLano says the company can definitely support one salary, and will likely soon support two. "A business person would be trying to maximize profit by restricting the intellectual property and doling it out only for a high license fee," he says, "But because PyMOL is open source and it's important to me that it remains as such, we have to find other ways to grow revenue."

The open source nature of the software gives DeLano little leverage to charge high fees. He relies on negotiated relationships in which the clients recognize that, because they aren't contributing code back to the project, they should contribute some money instead—in the form of a subscription. For big customers, DeLano provides more individual interaction and support.

His is not the first company created to support open source software. RedHat serves that purpose for Linux users. And MySQL has a similar model. "Open source software is widely used, which translates into a very large impact on society from open source. But it's not a profit center like proprietary software has been for companies like Microsoft, Oracle, Apple and SAP."

And although he's a big proponent of open source software, he says that companies making proprietary software for biologists are starting to succeed by creating programs that act more like open source, with open architectures. "**Accelrys'** model is a very open-architecture, pluggable system," he says. "You can hook your code into these networks of capabilities which are visible and open. It's all proprietary architecture, but it's open in so many ways that a lot of flexibility is there."

As for DeLano Scientific, "On the continuum of open source to proprietary, we're somewhere in the middle," says DeLano. "You can get free versions, but you can get more value if you buy your subscription." He hopes to grow the business, but that's not the driving factor. "We're already achieving the kind of impact I wanted to achieve."

"What's unlikely to happen is to solely pursue the science and serendipitously have business opportunities and revenue drop in your lap," says Ramon Felciano.

(continued from page 9)

Alternative Investment Market (AIM)—a good market for small-cap technology companies that can show they have a revenue stream and growth opportunities, says Bangs. He says their success springs from three things: a technology that's proven to be of value to their customers in a short time frame; financial discipline over the last ten years; and maintaining focus on a few applications rather than expanding too rapidly.

Ingenuity Systems, Inc. is another company that strives to make drug discovery more efficient for biopharma. "It was not enough to provide a tool that would only be used by informaticians," says **Ramon Felciano, PhD**, founder and chief technology officer at InGenuity Systems, Inc. "At the end of the day, they are typically part of a larger team with a goal to discover a new drug, to understand its safety, to validate a lead. So really focusing on those more fundamental scientific and business goals I think helped us stay on track."

After eight years in business, Ingenuity's initial business idea is still working for them. They help researchers put high-throughput experimental results into the context of what is already known about a disease or cell. With the advent of high-throughput experimentation, "existing methods for understanding experimental data didn't scale well to the volume of data being generated," says Felciano. "We wanted to see if we could bridge that gap."

So Ingenuity created a large-scale platform with, at its core, a set of biomedical ontologies and a knowledge-base representing what is known about biology. "The "so what" of the data is hard to find because it's buried in research documents, figures, tables, PowerPoint slides and other non-structured repositories," says Felciano. But that's the information Ingenuity has gathered together. And they've made it available to their customers through the company's flagship product, Ingenuity Pathways Analysis: Researchers upload a dataset and run analytic algorithms to build de novo pathways linking their data and Ingenuity's knowledge base.

Industry, government and academic researchers use the knowledge base to identify or validate a new drug target or understand how a drug functions, including its toxic side effects. "We're trying to accelerate and improve the quality of scientific results that scientist users can produce," Felciano says. "We think we're doing well when they can get their work done more quickly and at a higher level of quality—better and faster."

The company now employs 85 to 90 people, not counting the part-time researchers around the world who help

Ramon Felciano, PhD
Chief technology officer & chief architect, InGenuity Systems, Inc.
Felciano and fellow Stanford students decided to start Ingenuity Systems in 1998 after they won an entrepreneurial competition held by the Business Association of Stanford Engineering Students (BASES). "Winning the competition was a threshold for us," says Felciano. Afterward, they received calls from VCs and did another round of conversations with researchers and industry people. "A lot of our initial understanding of the problem and the solution appeared to be valid. So we decided to give it a shot."

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Michael Sherman
Former CEO of Protein Mechanics, Now the chief software architect for Simbios, A National Center for Biomedical Computing at Stanford.

In 2000, Michael Sherman and his partner raised about four million dollars for their new company—Protein Mechanics—in one day. Their proposal: to apply their mastery of mechanical engineering and computer science to biological simulations. They started out developing software without much of a business model in mind. But, he says, the venture capitalists eventually wanted them to make drugs. Sherman saw that his company's chance of making a good drug was low. If he were to do it again, Sherman would do what he had done previously: start a sustainable business to sell useful software and make money, without relying on VCs. Although he currently works in academia, Sherman says he may eventually head back to the business world. "Academia is great because you can sit and think and do the right thing, but it has the character that basically nothing's at stake. Businesses are kind of cool because a lot of things matter, which makes it exciting. It can be a disaster too, but that's part of making it exciting."

Genomic Health □ Genstruct □ Optimata □ Cognia □ Myriad Genetics □ **Protein Mechanics**

"Be very cautious when taking money from venture capitalists because you might find your goals don't align well later," says Michael Sherman.

keep the knowledge base up to date. And, according to Felciano, Ingenuity's revenue and number of users are growing, as is their publication record. Over the last two to three years, the number of scientific publications citing Ingenuity's platform has grown 250-300 percent. "It's a great trajectory that we're looking at and a validation that we're doing well."

Hill, Felciano and Bangs all recognize that, nowadays, VC support for businesses like theirs is rare. As Bangs puts it, "VCs want companies that are going to have a good-size market with good revenue possibilities. If your market is to sell to a small part of the pharmaceutical industry, then you have a small number of customers with potentially varying budgets." So Bangs suggests an alternative to VC: the small business route. "Do it the old-fashioned way. Put a second mortgage on your home, get SBIR money, bank loans, and grow the business slowly. That's what you have to do in the current environment."

Michael Sherman learned that lesson the hard way. His company—**Protein Mechanics**—also saw its start in 2000 when "venture capital was flowing a little too freely." The company developed software to simulate proteins, but after a few years, their investors wanted them to make drugs. "We didn't know anything about drugs," he says, so the company sold at a fire sale in 2004.

His advice to scientists contemplating a startup: "Be very cautious when taking money from venture capitalists because you might find your goals don't align well later." And he agrees with Bangs' recommendation: go with the small business model. "The fact that Protein Mechanics isn't around anymore is a minor thing for the venture capitalists because they figure they invest in ten companies and nine might fail. But it's a big deal to me. I'd have rather built a sustainable company, but that wasn't interesting to the people who funded it."

Felciano, by contrast, has had a good experience with Ingenuity's VCs. But, he notes, "Good partners—whether VCs or others—can help you succeed, and bad ones can become major obstacles." Despite being a scientist himself, he's a realist about business. "If you want to purely drive the science there are better places to do that," he says. "What's unlikely to happen is to solely pursue the science and serendipitously have business opportunities and revenue drop in your lap."

The Razor Blade

In recent years, some biocomputation startups have drawn VC attention not by selling software to biopharma, but by masquerading as diagnostic, proteomic, or genomics companies. To Anderson of **Pathwork Diagnostics**, this is clearly the way to go. "A well-designed biocomputation product could be the ultimate razor blade. It just needs a little invention," she says.

According to Anderson, funding for bioinformatics platforms is virtually nonexistent from this point on. It's a lesson she learned from initially naming her company Pathwork *Informatics*. No one would fund it. "There are a lot of decent platforms out there. The world doesn't need a new one," she says. "However, applications that are anchored to solving a clinical problem and that map out a path to revenue and products are something else."

Coming up with a commercial product from good science is not always easy.

"The challenges start with how to frame a problem in such a way that research can discover an answer," says Anderson, "And then how do you layer it back into something that can be produced in a reasonably cost-effective way and delivered and sold to clinicians. There are many challenges in taking an idea into the actual practice, but that's what our business is about. If it were easy it wouldn't be so much fun."

Anderson has built her career around this kind of thinking. "What I've been really fascinated with my whole life is how you craft products that are successful along with a business model that's successful as well," she says.

Now, after three years in business, Pathwork Diagnostics has its first product before the FDA. It addresses a common problem in cancer recurrence: Often, clinicians cannot determine where the cancer started in the body. So, Pathwork's Tissue of Origin Test answers this problem by analyzing gene expression data from tumor biopsies. With the analytic report in hand, a physician can better determine how to treat such cancers.

But this is just the beginning, says Anderson. "The Holy Grail in oncology diagnostics is predicting treatment response. Our real intent is to develop a platform that could answer that question." The Tissue of Origin test positions the company to do just that, she says. "This is what makes our business model compelling and what helps pull us over the hump in terms of funding."

Pathwork Diagnostics is not alone in taking this approach. XDx, founded in 2000, offers a test to determine the likelihood that a heart transplant will be rejected. "XDx's analytics are their razor

"A well-designed biocomputation product could be the ultimate razor blade. It just needs a little invention," says Glenda Anderson.

Glenda Anderson

Founder and chief technology officer, Pathwork Diagnostics

After spending nearly twenty years leading research and development organizations for healthcare manufacturers, Glenda Anderson decided in 2001 to take a closer look at bioinformatics. "It was clear that biocomputation would form the basis for new medical products over the next 20-30 years," she says. And she thought her engineering degree in computer modeling and experience taking ideas from technology or science into a clinical application and a product would be helpful in building such a business. "Biocomputation is a field that lends itself to asking questions about how to put a business model and product together to create real value." In 2003, Pathwork was born, and the company's first product is now before the FDA.

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Valerie Daggett, PhD,
Future founder of Dynameomics
Professor of medicinal chemistry at the University of Washington

A few years ago, Valerie Daggett registered the domain name for dynameomics.com. "I've been getting ready to do this for a while," she says of the venture she has yet to launch. "This is the work we've been doing for the last 15 years or longer. I want to see it come to fruition."

GeneSpring ◻ Entelos ◻ Gene Network Systems Ingenuity ◻ 23AndMe ◻ Pathwork Diagnostics DeLano Scientific ◻ Dynameomics ◻ Celera ◻ Accelr ◻ Bioimagene ◻ XDX ◻ Genomic Health ◻ Genstruct Optimata ◻ Inforsense ◻ Cognia ◻ Myriad Genetics Protein Mechanics ◻ Intelligenetics ◻ Molecul

blade," says Anderson. "And they can command a high price for each potential transplant recipient they evaluate because the cost of failure is so high."

Genomics startups with a heavy biocomputation focus are also gaining some momentum according to Dotzler. A number of companies offer to analyze DNA from a blood sample or cheek swab to trace a customer's genealogy or give advice about disease susceptibility. One new company, **23andMe**, launched in 2006, hopes to take that analysis further. As new gene association studies appear in the literature, they gather the results together into a database. "There's an exciting flood of information about gene/disease associations," says **Brian Naughton, PhD**, one of the company's core team. Making sense of it is not a trivial task, he says. But he and fellow team member **Serge Saxonov, PhD**, both recent graduates of Stanford's Biomedical Informatics program (BMI), say they have the skills to do it.

This year, the company hopes to release its first product, which will require a saliva sample rather than a blood sample or a cheek swab. It will analyze the customer's entire genome looking for SNPs—the single nucleotide polymorphisms that distinguish individuals from one another; some SNPs are also associated with disease. "Most people are curious about their genetics—their families, their ancestry and their health—but have nowhere to go to learn about it," says Naughton. "We want to fill that niche."

Venturing Out of Academia

Startups often blossom directly from academic research. The very first biocomputation startup—**Intelligenetics**—began that way, says **Doug Brutlag, PhD**, professor of biochemistry and medicine at Stanford. He was part of that launch, which began in the late 1970s. After sequencing methods had been developed, he says, Stanford researchers put all the accumulating data and software on a computer and made it accessible over phone lines—before the Internet really took off. "We wanted to show people how useful it was so we made it freely available to biologists and everybody started using it." But, says Brutlag, "I didn't think it was appropriate to support biologists from an academic environment. Support is better provided by commercial entities." Moreover, he says, in this area it's very important to do technology transfer. "If you just publish your work and don't provide support for it, then people

Making open source code available through an academic web site can lead to frustration, says Valerie Daggett. "People in your lab become unpaid consultants responding to every call and email that comes in about how to use the software. I don't want to do that to my research program."

SUPPORTING TECHNOLOGY TRANSFER: THE STANFORD WAY

Stanford opens up channels for getting technologies out to the real world in three important ways. First, it allows faculty to consult up to 1 day per week (20 percent of their time). Second, it has a very proactive office of technology licensing that identifies potentially useful technologies in the lab—even if faculty aren't aware of it—and then files patents and markets these to companies that may want to productize them. And third, it has a corporate affiliates program that allows industry to provide funds—e.g., fellowships—to departments. In return, the affiliates get preferential access to workshops and students (for recruitment).

This approach to commercializing technology has produced Google, Yahoo, recombinant DNA, and the Yamaha synthesizer, to name a few, and has been a model for other universities to follow.

won't use it." So Intelligenetics was born—and it lasted about 13 years.

Nowadays, says Brutlag, things are different. With the development of the Internet, he does much of his technology transfer himself. "We make software tools freely available to not-for-profit institutions and allow for-profit companies to license them from Stanford University," he says.

But **Valerie Daggett, PhD**, professor of medicinal chemistry at the University of Washington, says making open source code available through a web site can lead to frustration. "People in your lab become unpaid consultants responding to every call and email that comes in about how to use the software. I don't want to do that to my research program." Moreover, she says, users of her protein dynamics simulation software really do need help. "These are very complicated simulations to setup and run, and biologists don't necessarily have the equipment or the skills to do it." The result: the academic software provider gets blamed for mistakes made by the users.

So Daggett is contemplating a new startup. She calls it **Dynameomics**. "It's very hard in academia to take your work to the next level and see it transition out of the computer lab and into an application that people will use," she says, but the technology transfer office at the University of Washington is helping out.

Daggett's lab has created the biggest database of protein simulations in the world. With upwards of 2500 protein simulations it becomes prohibitive to host the work (20 terabytes and counting) from an academic lab. This Spring, Daggett's group plans to take an early step toward commercialization when they launched dynameomics.org. The dot-com site will come later. The dot-org site will give people free access to simulations representing the top 30 folds (structures) of proteins known from the Protein Data Bank (PDB). These represent 50 percent of all known structures. From the web site, biologists will see the simulations; the structures generated by the simulations; movies of how the protein moves over time; and metadata (analyses of the simulations).

At some point, Daggett expects to take orders for simulations of specific proteins not represented in the set. Although dynameomics.com will offer much more, Daggett says, it's still unclear whether the product will be a software modeling package or drug design services or both. Several software companies and VCs have shown interest in both options, she says.

Either way, the dynamic aspect of proteins is really underutilized thus far and Daggett hopes to make it available to industry. "By basing functional analysis of proteins on static structures we're missing a good deal of the picture." And because there are loads of proteins and a lot of interesting biomedical targets that exert their actions through changing protein conformation, she thinks her protein dynamics simulation tools are a product people will need for some time to come. But until she settles on a product, it's not entirely clear whether she's commercializing a razor or a razor blade—she hopes it's the latter.

STICKING WITH IT

Regardless of the product being sold, says Hill, biocomputation startups require perseverance. "It's not an industry that typically gives quick payoffs," he notes. "Unlike pure technology companies, we don't have to just make some widget and sell it and be a huge success. ... The ultimate test in our field is affecting disease in a living human. ... It's much more difficult than just developing technology." So, he says, you have to do it for the right reasons. "If you just want to make a lot of money, go to Wall Street. Or create the next YouTube."

Hill himself was following his scientific interest when he started GNS seven years ago: He wanted to discover how living systems work in a fundamental way. "Having that goal collide with some serious unmet and burning needs in a very practical and very lucrative industry (pharmaceutical development and biotech) is what made me do this. The fact I could do both—have my cake and eat it too—that was too good to pass up." □