

BioCentury

Strategy

No middle ground

By Steve Edelson
Senior Writer

In April 2001 — after the genomics bubble had burst — Perlegen Sciences Inc. spun out of Affymetrix Inc. and raised \$100 million to read and analyze 50 human genomes. The company essentially disappeared for almost two years and resurfaced in late 2002 with a flurry of genotyping deals with pharma companies, mainly for studying the genetic factors that underlie drug response.

Again, Perlegen submerged and about two years later announced another series of partnerships, four of them so far in 2004. This time, however, the company's drug response partnerships foreshadow the next steps in developing its business: in-licensing compounds and using its platform for therapeutic development.

To do so, Perlegen is going straight from genotyping to clinical development — the company has no plans to add discovery or preclinical capabilities.

To make the value chain leap, Perlegen needs renewable sources of compounds. The company's strategy is to in-license failed pharma therapeutics that, in theory, had a competitive advantage versus marketed drugs.

Chain leaping

On its face, Perlegen's business strategy is a paradox. The company wants to take a technology that occupies one of the earliest links of the value chain and apply it to the opposite end without adding anything in between. But the company believes it has done a thorough enough job on the genotyping end that its whole genome sequencing platform will enable it to pursue the drug development end.

With more than 1.5 million SNPs in hand, Perlegen argues that it will be able to find therapeutic diamonds in the rough — compounds that have failed in clinical trials because of adverse events or lack of efficacy. The company believes it can put these compounds back on the clinical track by identifying the genetic component of the drug response. Perlegen thus expects to find the genetic fingerprint of patients who would respond favorably to these compounds.

"We developed a database of SNPs and finished that project in August 2002," said Philip Sussman, vice president of business

development. "Through a sample of 50 human genomes at single base resolution, we identified 1.5 million differences. Those are the spots in the genome that we interrogate today when we do genotyping. We did this using enhanced versions of Affymetrix's microarray technology, including some technology that has been exclusively licensed to Perlegen."

By doing this upfront work, Perlegen believes it now has an advantage versus other companies using pharmacogenetics for drug discovery. The company maintains that its database contains many times more genomes than its competitors.

As a result, Perlegen expects that its whole genome data will be more predictive than a single SNP or group of SNPs. As an example, CEO Brad Margus said that a version of a given SNP could increase a patient's risk of having an adverse event to a compound by a few percent. "An increase of a few percent isn't useful," he argued. "If you look at the whole genome, you can get enough genetic variation to actually be predictive, and perhaps show a 20-fold increase in the risk of an adverse event."

The company also argues that content breeds speed. "The key is that because of our genotyping work, we don't have to look at every base going forward — just the 1.5 million SNPs," said Sussman. "We can ignore 99.95% of the genome because it doesn't change from person to person."

In fact, the company expects that the actual number of SNPs involved in a given disease will be about 50 that are dispersed throughout the genome. "There are routine ways to test for a smaller number of SNPs," said Margus. "The problem for others is finding the fifty SNPs for which to test. Others may find five, which makes for a nice pub-

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— CEO Brad Margus

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lication but probably doesn't do squat in the clinic."

In addition to SNP identification, Perlegen has been quietly gathering a collection of patient samples. "The key with patient samples is getting very accurately defined phenotypes and complete medical histories," said Sussman. "We know exactly what we're getting because we've chosen the investigator first — people who are experts in their area and are involved in laying out the criteria that define the samples."

Perlegen has disclosed that it has patient samples for metabolic syndrome. In addition, the company said it has samples in other indications but is not disclosing specifics. Nevertheless, Perlegen may have given a hint in February when it appointed Eric Topol to its scientific advisory board. Topol is chief academic officer of the Cleveland Clinic Foundation and will advise the company on its myocardial infarction (MI) program, which aims to discover the genetic causes of heart attacks.

The deals

Perlegen said that its databases are suited to leaping across the value chain because they have utility at the chain's opposite ends: target identification and clinical trials.

In the area of target ID, the goal is to identify the genetic variants that are associated with disease.

"This is not just target identification," said Sussman. "It is a way of prioritizing existing molecular targets to choose those that have an association with disease. For example, a pharmaceutical company may have 100 potential molecular targets in a particular discovery program. This is an additional tool — with expression analysis, model systems and functional genomics — to narrow down the number of targets."

In the area of clinical trials, the company expects that its technology can be used to salvage compounds, picking patient populations to enter trials.

Perlegen's two deals with Pfizer Inc. in January serve to illustrate the applicability of the company's technology at the two ends of the value chain. In one deal, Perlegen is identifying the genetic basis of metabolic syndrome. In the other, it is looking at patient responses to depression drugs.

The metabolic syndrome deal comes at the early end. "We view metabolic syndrome as a type of disease composed of many diseases — obesity, diabetes, high cholesterol — that typically are addressed one by one," said Sussman. "What we're

Perlegen deals

Company	Year	Notes
AstraZeneca	2004	Research: Genotype SNPs in patient samples to discover genetic markers associated with heart attacks
Bristol-Myers	2002	Development: Use Perlegen's whole genome association technologies and SNP portfolio to identify markers for patient responses to medications from BMY
Eli Lilly	2002	Development: Use Perlegen's whole genome association technologies and collection of SNPs to identify genetic markers
Galileo Genomics	2004	Research: Develop a Quebec Linkage Disequilibrium Map (QLDM) of about 40,000 SNPs that represent genetic sharing in the Quebec founder population
GlaxoSmithKline	2002	Development: Use Perlegen's whole genome SNP scanning to identify genetic markers of drug response
Pfizer	2004	Development: Genotype SNPs in clinical samples to identify genetic markers associated with drug response for depression
Pfizer	2004	Research: Genotype SNPs in patient samples to discover genetic markers associated with metabolic syndrome
Pfizer	2003	Research: Identify genes and genetic loci associated with cardiovascular disease
Unilever	2003	Research: Use Perlegen's whole genome association

doing with Pfizer is finding a genetic basis for those patients that develop metabolic syndrome in order to develop treatments for the syndrome as a whole."

On the downstream end of the value chain, Perlegen and PFE (New York, N.Y.) are genotyping SNPs in clinical samples to identify genetic markers associated with drug response for depression.

In addition to this deal, Perlegen has drug response partnerships with Bristol-Myers Squibb Co. (BMY, Princeton, N.J.) and GlaxoSmithKline plc (LSE:GSK; GSK, London, U.K.) — both in undisclosed areas. The BMY deal is a pharmacogenomics collaboration looking at samples from patients who have been treated with an undisclosed BMY drug. (see "Perlegen Deals").

Building a business

Instead of exclusively dedicating itself to its partners' value chains, Perlegen said its drug response partnerships foreshadow the next steps in developing its business: licensing compounds and using its platform for therapeutic development.

"We're migrating from being an agent to a principal," said Margus. "We want to actively pursue opportunities where we can apply our technology to compounds that we in-license from others."

The company sees a broad — and

growing — universe of compounds for which partnering opportunities may exist. "You read and hear all the time about compounds that have hit obstacles after being exposed to a few hundred people," said Sussman.

While Perlegen has not brought in a compound for internal work, it has a three-person clinical group headed by Mark McCamish, who joined the company last September from Amgen Inc. (AMGN, Thousand Oaks, Calif.). "Right now, they're mostly looking at other companies' trials," Sussman said.

"The most straightforward application of our technology would be for products that missed their efficacy endpoint but have an indication of working in subsets of patients," said Sussman. "If there's a wide range of responses to a therapeutic, we should find subsets of patients who are more likely to respond."

However, Perlegen will be making its pitch for failed or shelved pharma compounds in competition with companies that are coming at the retasking problem from a different direction. Some, such as Vanda Pharmaceuticals Inc. (Princeton, N.J.), are looking to pick up Phase II failures that might have utility in indications narrower than or different from those in which they were tested.

Perlegen thinks it will be looking for

Long jumper

Perlegen's deals reflect the company's assertion that its whole genome association data-bases have utility at opposite ends of the value chain. The company has no plans to add the middle links.

Research		Development	
Target identification	Target validation; Lead generation; Lead optimization	Preclinical/ Pharmacology	Clinical trials
Activity: Genetics (e.g. SNPs and haplotypes)	NA	NA	Activity: Pharmacogenetics
Deals: 2 w/ Pfizer, Unilever, AstraZeneca, Galileo	NA	NA	Deals: Pfizer, GlaxoSmithKline, Bristol-Myers, Eli Lilly

different compounds. "We're not going for compounds that will be rescued by formulation or delivery," said Margus. "We just want the failures — the ones that aren't worth anything unless you can determine who will respond."

The company said it will seek compounds from failed trials where patient samples were collected, or compounds that address diseases where it is possible to collect such samples.

Sussman noted that more and more companies have moved to collect, archive and save such data. "I don't know the percentage of trials in which this is done, but it is growing," he said. "Companies have it more and more as standard policy."

In terms of IP that stems from patient sample genotyping, Perlegen expects there will be different scenarios for in-licensed compounds and its partnerships. In its deals where Perlegen is studying genetic factors related to response to a partner's therapeutic, the partner has exclusive rights to use data for clinical trials of the compound.

Perlegen said that other uses of the data are shared, such as the use of an identified genetic marker to discover new disease targets. For in-licensed compounds, Perlegen said it will own resulting data.

Practical matters

The company would not quantitate the failed drug space, but Sussman noted that "the supply gets replenished each year. There's an increasing amount of compounds that enter the clinic each year, and consequently more and more compounds are terminated."

Indeed, Sussman expects that "the issue is not the number of opportunities. Instead, it will be the willingness of pharma companies to take a terminated program and put it in our hands."

Perlegen thus will need to find an audience in pharma that recognizes the value in out-licensing shelved compounds. "One could argue that we should be talking to CFOs instead of clinical people," said Margus. "CFOs might have the most interest in getting value from their assets. We hope our existing partnerships will show that we can rescue some drugs that have failed."

Perlegen's selling proposition will be the homework it did via its SNP identification efforts. "The reason for a pharma company to put a compound in our hands is because they can't do what we do, which is identifying the genetic basis of a drug response through an intensive examination of the genomes of treated patients," Sussman said.

Although it is possible that pharma companies will simply contract out the association studies and keep their compound once Perlegen expresses interest, Sussman said this is an unlikely scenario. "Once a pharma company hits an obstacle with a compound, it's hard to revise a program. They move on and reallocate resources and disassemble infrastructure related to the program."

In selecting compounds, Perlegen will look for therapeutics that have a potential commercial advantage. Standard parameters the company will examine include a compound's dosing frequency and route of administration versus marketed compounds.

"We've backed away from licensing opportunities where we assessed a compound and decided that, if it makes it to market, it wouldn't be better than what's out there today," said Sussman.

For example, said Margus, "if we take in a compound that causes QTc prolongation and are able to screen patients who would have this adverse event with a one-time test, a doctor won't want to bother with the

test if the compound is no better than what's already on the market."

In its partnerships, pharma companies with diagnostic divisions tend to retain ownership of diagnostic rights. In other cases, Perlegen said it holds the diagnostic rights. For compounds that it develops internally, Perlegen plans to seek partners for developing such tests. "Any compound approved for a patient population identified via pharmacogenetics will need a diagnostic, but we're not a diagnostics company," said Sussman.

Proof of concept

Perlegen would not disclose any financial metrics, but the company has raised \$130 million since inception and thus probably has some time to turn its model into reality. Still, short of obtaining regulatory approval for a rescued compound, the outside world will be looking for some proof of concept in the interim.

Later this year, Perlegen hopes to bolster its case by publishing results on the use of whole genome association studies to identify markers for drug response.

According to Perlegen, the good news is that if it shows a correlation between drug response and side effects, it will also have proof of principle that its technology can correlate drug response and efficacy. "You only need to show one — it's the same basic science," said Sussman.

In the meantime, Perlegen said its internal product development efforts will not cause it to cut back its partnerships. "The technology is scalable, so we're able to expand as needed to do the association studies we need to do for partners or for ourselves," said Sussman.

The company has about 100 employees, divided among about 45 molecular biologists, geneticists and lab assistants, another 35 people involved in IT/bioinformatics, and about 20 management, sales and administrative personnel.

"It takes four months for us to deliver genotyping data from the time we receive samples," said Margus. "Capacity for deals and internal efforts won't be a factor."

Within 12 months, Perlegen hopes to complete another financing, which Margus said could be either public or private. At that time, he said, the company hopes "to have in-licensed drugs and to have demonstrated with partners that for a given drug, we can find the markers that predict response. With both in hand, the financing should be easy and friendly."