Published in

START-UP

Windhover's Review of Emerging Medical Ventures

WINDHOVER INFORMATION INC
windhover.com

JUNE 2000

Volume 5
Number 6

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Cytokinetics:

A Platform Case Study for the Next Decade

The flood of genomics data has raised the bar for what Big Pharma considers scientifically enabling.

By Jeffrey Dvorin

- Cytokinetics' plan to become a drug discovery company and ASP depends on an innovative technology platform, consisting of a program that targets the cell's cytoskeletal structure to develop novel therapeutics, and one in cellular bioinformatics, designed to unlock the lead optimization bottleneck by automating cell biology.
- The company has impressive talent and investors, along with some promising early validation of its technology.
- But it has yet to sign up any pharmaceutical company partners or customers. And it is selling to a skeptical industry that over the last decade has bought into a number of new technologies offering partial solutions to inefficiencies in the drug discovery process, without improving productivity in terms of generating pharmacologically acceptable lead compounds.
- Thus, the question facing Cytokinetics is how much will Big Pharma pay for potential discovery breakthrough technologies, and will it be enough for the biotech to validate their science. It's also a question likely to confront other emerging platform companies as they increasingly find themselves the sole entrants in their fields, and in the position of having to create their own markets.

Last March, in a *START-UP* profile, the management of **Cytokinetics Inc.** spoke of leading the way in what they hoped would become a hot new technological platform for drug discovery. Competition would come, they predicted—indeed, they said that additional players would help to establish the field, which brings together cell biology and informatics, in the eyes of potential pharmaceutical partners. But Cytokinetic's talent (which includes several highly respected cell biologists), intellectual property, and execution, they argued, would give it an edge as competitors emerged.

Their investors would help, too. The company's first round raised $5.3 million from high profile investors like the late Robert Swanson, founder and former CEO of **Roche**'s **Genentech Inc.** and The Mayfield Fund. The company added a further $20 million last September in a round led by International Biomedicine Holdings and Paul Allen's Vulcan Ventures. Those investors were undoubtedly attracted by a business plan which paired a potentially lucrative service business based, in part, around a proprietary understanding of the cytoskeleton, with an operation focused on finding drugs to modulate cytoskeletal targets, potentially useful in treating cancer and many other diseases. With the biotech financing market then in shambles, the strategy promised a way to fund the company without undue dependence on a fickle investment community.

Nearly a year and a half later, the good news is that Cytokinetics is arguably the frontrunner in cellular bioinformatics-based drug discovery and some compounds in *in vivo* testing for cancer. On the other hand, it has yet to receive the sort of validation that a pharmaceutical collaboration might bring. And the company remains virtually alone among start-ups in championing its technology, which has its skeptics. Being the only salesman in a territory has its advantages; but pioneering a sale when drug companies have spent the last half-decade buying discovery technologies which have done little to meet their near-term needs for actual drug candidates is now more difficult.

The company is thus at something of a crossroads—and represents an interesting case-study-in-progress of the new entrant in biotechnology. In the first place, new platform companies are more likely to be alone in their fields, therefore more likely to have to create their own markets. Five

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years ago, the venture community was alive to competition: the first combinatorial chemistry company, for example, was quickly followed by the formation of half-a-dozen others. The same held true for high-throughput screening, gene chips, even gene databases.

Meanwhile, Cytokinetics' plan depends in part on its ability to attract drug company interest and funding for its informatics platform which will in turn help support the funding for its drug discovery and development ambitions. And there is little question that the cellular bioinformatics solutions it is offering provide important, albeit partial, answers to drug discovery problems. The question is how much is a product-hungry pharmaceutical industry willing to pay for new technologies that are largely unproven, address only a relatively small part of their discovery needs, and which they have never encountered from other technology purveyors? And for companies like Cytokinetics: will it be enough for them to develop and validate their science?

Trailblazing

Cytokinetics is attempting to blaze trails on two drug discovery fronts. First, it is probably the only company that is looking to develop drugs by exploiting the cytoskeleton—a diverse multi-protein framework that performs fundamental roles in the various aspects of cell mechanics. And it is also one of only a handful of biotechs attempting to build a technology platform around the nascent, loosely defined area of cellular bioinformatics.

The cytoskeleton has traditionally been viewed as the cell's internal scaffolding. Some researchers have likened its properties to those of the geodesic domes designed by R. Buckminster Fuller. Fuller's dome design is based on the principle of tensegrity (tensional integrity) by which structures establish shape and strength by combining elements that resist compression with a network of other elements that are strong under tension. In cells, the former are represented by microtubules and the latter by actin microfilaments and intermediate filaments.

But in recent years, it has become clear that the cytoskeleton does far more than simply provide architectural support for the cell. It is, in fact, a framework for organizing many critical cellular processes, including signal transduction, cell division, intracellular transport, cell motility, and muscle contraction. This enhanced understanding of the cytoskeleton's significance led James Sabry, MD, PhD, a **University of California, San Francisco** faculty member, to join with three prominent cell biologists—Ron Vale, PhD (**University of California, Berkeley**), Larry Goldstein, PhD (**University of California, San Diego**), and James Spudich, PhD (**Stanford University School of Medicine**)—to found Cytokinetics in May 1998. Sabry now serves as the company's CEO and president, while the other three founders sit on the scientific advisory board.

Sabry uses the analogy of a city map to explain the dynamic role of the cytoskeleton in cell function. It serves, he says, as a cellular highway system for getting the right proteins to the right place at the right time. It is, however, a plan which changes constantly as the dynamic cytoskeleton modifies and restructures itself in response to environmental cues.

The major structural proteins of the cytoskeleton are tubulin, actin, and intermediate filaments. These proteins join to form polymers of variable length—known as microtubules, micro filaments, and intermediate filaments—which mediate nearly all aspects of intracellular transport and cellular movement, thus serving as the cellular highways. Most importantly, these filaments interact with a group of important and function-specific motor proteins, including kinesins, dyneins, and myosins. These mechanochemical enzyme superfamilies transport various forms of cellular cargo along filaments, and they organize filaments. The cytoskeleton also contains groups of non-motor filament binding proteins that regulate it and its motors so that the whole framework carries out a specific function.

A good example of the cytoskeleton's role in the cell's organizational activities, says Sabry, involves the phase of cell division known as mitosis. "Once the cell has committed itself to entering the mitotic state, in response to a signaling event, there is an orchestrated expression and coordination of a series of cytoskeletal motor proteins that cause the DNA to line up in the center of the cell and then move to the edges of the cell in a precise way. It is the organization—not just the movements—that is carried out by these specific cytoskeletal proteins."

Those proteins are implicated in the pathogenesis of many diseases, according to Sabry, who says that Cytokinetics will focus on four broad classes of proteins comprising approximately 1,200 human genes: the previously mentioned filaments and motor proteins, plus "remodeling proteins" which are involved in processes ranging from wound healing to the invasion of cancer cells into tissues, and filament binding proteins that organize filaments into functional arrays. Although targeting cytoskeletal proteins may eventually prove applicable to a wide range of therapeutic areas, the company is focusing on cancer, cardiovascular, and fungal diseases—with cancer the primary area of interest.

A Better Taxol

Sabry notes that some current cancer therapies provide partial proof of concept for exploiting the cytoskeleton for pharmaceutical purposes. *Taxol* (paclitaxel), vincristine, and estramustine all attack cancer by targeting tubulin, which is a cytoskeletal protein and the major structural

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START-UP
Windhover's Review of Emerging Medical Ventures

component of the mitotic spindle (a transient structure responsible for separating chromosomes during cell division). Modulating tubulin function disrupts mitosis and triggers apoptosis. The problem is that tubulin is an ubiquitous protein; interfering with its function in cancer cells therefore inevitably results in serious side effects. "The mechanisms of action of drugs like *Taxol*," says Sabry, "may involve the cytoskeleton, but they were discovered essentially by happenstance and not as the result of any systematic understanding of the cytoskeleton."

Cytokinetics, Sabry argues, has an answer in the form of molecular targets possessing highly specific functions and expression patterns. Sabry says that this specificity should lead to the development of cancer drugs that do not cause the undesirable effects of drugs that target the microtubule component of the mitotic spindle.

While a number of researchers are working with cytoskeletal targets, particularly kinesin inhibitors, there appears to be no other company exclusively focusing on the cytoskeleton for drug discovery. In the March 1999 *START-UP* interview, Sabry said that the lack of competition was not surprising since it had been unclear until very recently that the cytoskeleton's role in cellular mechanics was significant enough to serve as the basis for building a new business.

To date, the cytoskeleton-focused approach seems to be paying off. Cytokinetics is currently concentrating its efforts on developing inhibitors of mitotic kinesins, motor proteins that, using ATP as a fuel source, move along the microtubule highways of the cytoskeleton and play a crucial role in mitotic cell division. Perturbing mitotic kinesins leads to arrest of the cell cycle in the mitotic state, resulting in cell death, but without hurting the microtubule. The mitotic kinesin program has yielded nine validated mitotic kinesin targets to date, and identified an additional 23 novel kinesins. Sabry predicts an IND filing sometime next year for a small-molecule pharmaceutical compound which has "beaten Taxol" in mouse models.

That preliminary success notwithstanding, Cytokinetics hasn't yet found the drug company partners that it is looking for. Robert Blum, Cytokinetics' VP of business development, says that he is in advanced discussions with a number of large pharmaceutical companies regarding potential collaborations in this area, and that he is "very encouraged" by the feedback that he has received." But he's taking nothing for granted and has been talking with private investors about substantial, probably private, funding that would allow Cytokinetics to go it alone "if we don't get the very aggressive type of deal that we're looking for."

The Virtual Bench Top

Not that Cytokinetics is placing all of its bets on the discovery program. Indeed, from its earliest days, the company's plans included a business in cellular bioinformatics that would provide a separate revenue stream and synergies with its discovery efforts.

A growing number of biotech companies are building discovery platforms designed to relieve the bottleneck created by the wealth of data and information generated by technological advances in genomics, proteomics, high-throughput screening, and combinatorial chemistry. Some, like **Rigel Pharmaceuticals Inc.**, **Arcaris Inc.**, and **PPD Inc.**'s **PPD Discovery** see opportunities in streamlining the validation of the wealth of targets yielded through genomics research. (*See "Validated Target Discovery: Letting Nature Do The Work,"* START-UP, *June 1999.*) Cytokinetics and perhaps one or two other companies are attempting to address the logjam at the lead creation stage by essentially automating the biological study of compounds.

The idea is that while combinatorial chemistry and high-throughput screening have greatly increased the efficiency of hit identification, the next step of sorting through those hits to find the compounds most likely to have appropriate properties has not kept pace. Lead optimization, the argument goes, now generally involves slow, largely manual bench top biological research—including secondary screens, studies of the relationship between structure and activity of the compounds, and cellular toxicity measurements.

Cytokinetics' solution is its *Cytometrix* series of database products, which Robert Blum describes as a "marriage of cell biology and information technologies." *Cytometrix* combines high-throughput fluidic automation, high-resolution microscopy, image analysis, and bioinformatics to quantify cellular responses to the introduction of a chemical compound or genetic alteration. The system provides readouts on changes in cell shape, motility, cell cycle, protein trafficking, apoptosis, and a variety of other cellular functions. The result, says Sabry, are high-throughput, cell-based profiles that fingerprint the phenotypes of diverse molecular mechanisms of drug action. Particularly important are changes measured in the cytoskeleton—indeed, *Cytometrix* has played an important role in screening hits for the company's own cytoskeleton-based oncology work.

Cytometrix is designed to be a high-throughput secondary screen that, according to Blum, prioritizes compounds identified as hits in biochemical screens to help drug companies decide which are worth "the substantial investment in medicinal chemistry and *in vivo* characterization." Says Sabry, "We want to help companies prioritize which ones to take forward, and perhaps identify those that are going to fail sooner."

High-throughput screening companies like **Aurora Biosciences Corp.**, according to Blum, "are really using the cell to report a single dimensional output; that's not cell biology. Cell biology

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START-UP
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June 2000

looks at things in an integrated context." Cytokinetics, he argues, is measuring many parameters at the same time, and when you can do that, you can make great leaps forward in terms of being able to make interpretive and predictive statements.

It's Still Biology

To James Sabry, the value of automating cell biology for purposes of drug discovery is a matter of common sense. There is, he says, a growing awareness among pharmaceutical and biotech companies that "the actual quantification of cell shape and morphology, and the intracellular localization of proteins and cellular organelles, can be extremely valuable" for drug discovery. "This is not surprising: it's what cell biology has been for the last 10-20 years. All that Cytokinetics is doing," he continues, "is putting an informatics structure behind it. We're taking cell biology as it's practiced in the lab in a slow, qualitative way, and we're measuring it using automated cell handling and fluorescent markers—combined with advanced process engineering and image analysis software algorithms—that are easy to see and easy to quantify. What we've done is replace the human with a digital camera and computer programs."

Rigel's EVP, CSO and co-founder, Donald Payan, MD, expresses considerable enthusiasm for high-content assays, predicting that "it's where we're headed." Visual bioinformatics, he observes, is undergoing a "sea change," with essentially static images being replaced by dynamic measurements of cellular function.

Rigel's target validation technology involves introducing into a cell of interest (i.e. one displaying a phenotype of the disease process), a protein or peptide probe from a random library and observing whether or not the probe causes a desired change in cell behavior, such as stopping a cancer cell from dividing.

Payan says that technologies such as those offered by **Cellomics Inc.** or Cytokinetics could be very useful in measuring changes in cell function during that target validation process (the technologies of both companies are designed for use in target validation as well as screening). Rigel, he adds, is using high-content screening in its small-molecule screening program.

Two Flavors

Cytometrix will be commercialized in two forms. The first to be launched, according to Blum, will be an application service provider (ASP) business that will provide profiling of compounds provided by pharmaceutical companies. The second is a line of predictive databases (*Knowledgebase*) in different therapeutic areas to which access will be offered on a non-exclusive subscription basis.

Blum says that this latter offering is several years from hitting the market as a standalone offering and will require considerable internal effort to build to the point where it will be robust enough to sell as a separate product. Among other things, the company will probably try to cut deals that will allow them to screen client libraries, retaining some data for its databases, in return for early access to the system. But once the database is ready to go, says Blum, it will give the company a unique technology that should be a solid revenue producer. "The difference between [Cytokinetics' data] and genomics data," he says, "is that that ours isn't making its way into public databases in the same way. The content of the database will be a function of how we go about constructing and operating a system, what we measure, how we measure it, when we measure, and it will be proprietary to Cytokinetics."

The Company is currently conducting market research on the first version of *Cytometrix*' ASP, which will focus on oncology. Blum says that he is talking with the leading multi-national companies and asking them "what types of biologies they would like to see us measuring and which cell lines they rely on most: we'll engineer those cell lines into the platform." By summer, he thinks that the company will launch an early access program; those first clients will help to shape the final product development. Cytokinetics also hopes to enlist leading gene expression companies to determine whether there's a synergistic benefit to combining the two information sets.

A Cellular Counterpart to Genomics and Proteomics

The company perhaps first identified with the term "cellular bioinformatics" is Cellomics, which takes its name from the discipline that it hopes will join genomics and proteomics in shaping the future of drug discovery.

At least on the face of it, Cellomics appears to be approaching the automation of cell biology in much the same way as is Cytokinetics. Company materials (in a quiet period before its IPO, Cellomics' management couldn't talk to *START-UP*) refer to industrializing cell biology through the automated study of a multitude of cell functions, including morphology changes, cellular differentiation, motility, and cytoskeletal changes. Cellomics is also building a database of cellular information to be used as a predictive tool for better decisionmaking, and plans to use that database to eventually create a virtual digital cell which maps the network of cellular components and their interactions. According to Cellomics' SEC filing: "Just as the proliferation of automated DNA

Published in
START-UP
Windhover's Review of Emerging Medical Ventures

sequencing instruments led to a dramatic increase in the generation of vast amounts of genomics data and information, we believe that the automation of high-content screening systems will lead to a dramatic increase in cell-based data and information, thereby improving the productivity of the drug discovery process."

One key distinction between Cytokinetics and Cellomics is the way in which the two companies intend to make money. Cellomics wants to sell customized assays and instrumentation to drug companies. For example, its *ArrayScan II* product is a high-content screening instrument that combines fluorescent reagents, optical detection systems, and informatics to analyze drug effects on multiple intracellular targets and pathways. In addition, Cellomics sells customized reagent kits, called *HitKits*, which include combinations of cells, multi-color fluorescence-based reagents and other consumables, such as validated microplates.

Like Cytokinetics, the Cellomics database is still a work in progress which it plans to make available on a subscription basis. It is also developing a *CellChip* system that will combine high-throughput and high-content screening on the same miniaturized platform.

The SEC filing contains the following cautionary note: "The market for high-content screening, informatics, and cellular bioinformatics is new and undefined, and the use of these technologies by pharmaceutical and biotechnology companies and academic and government laboratories is currently very limited." It goes on to say that "because our initial products have been in operation for only a limited period of time, their ease of use and commercial value have not been fully established." Still, Cellomics does have sales—1999 revenues were $3.4 million, up from $2.3 million the previous year. It also has partnerships for the development of specific fluorescent assays using the *ArrayScan*. Those include deals with **Johnson & Johnson** (receptor internalization assay); **Merck & Co. Inc.** (two-color assay to follow the activation of a transcription factor as it is translocated from the cytoplasm to the nucleus) and **Warner-Lambert Co.**

Perhaps as a way of hedging their bets on the high-content screening/cellular bioinformatics front, Cellomics entered into a strategic partnership with **Carl Zeiss** which makes it responsible for the exclusive North American sales and marketing of Zeiss' ultra high-throughput screening system and related products. While the agreement also calls for Zeiss to be the exclusive manufacturer of an *ArrayScan Kinetics WorkStation* and *ArrayScan Kinetics* reader, the marketing rights to the high-throughput screening system gives Cellomics a source of income independent from the newer technology.

Timing Is Everything

Cytokinetics is thus still essentially alone both in terms of its cytoskeletal focus and its ASP cellular bioinformatics model. Stefan Ryser, a partner with International Biomedicines Management Inc. who sits on Cytokinetics' board of directors, felt the company's "originality of approach" made it a good investment—albeit one with a different kind of risk profile. Sabry acknowledges that, "both the business model and the technology… are unique and untested." He adds, however, that "the fact that we have a compound that is now beating *Taxol* in animal models and is going into the clinic next year against a cytoskeletal target, plus the fact that a number of companies have expressed an interest in gaining access to *Cytometrix*, means that the outputs of the company are attractive and valuable."

Nonetheless, leading the way in technological innovation can be a two-edged sword. A truly paradigm-shifting approach obviously has the potential to bring tremendous value. On the other hand, it raises a different set of risks. Like all start-ups, Cytokinetics faces the possibility of scientific failure—*Cytometrix* may not yield particularly useful information; its cytoskeletal targets may prove problematic; its compounds could simply fail in testing. But it also faces market risk: with no company having already sold what it's trying to sell, Cytokinetics has to educate a customer base from scratch. And the pharmaceutical industry is not exactly renowned for its rapid adoption of new technologies.

Paul Negulescu, vice president of discovery biology at Aurora Biosciences, for one, questions just how many pharmaceutical companies are ready to buy into either offering. To him, it's a matter of timing and where the technologies fit in the discovery process. "As scientists, we're very much at the tinker toy stage in terms of understanding all the connections inside cells and between cells inside an organism," says Negulescu. "It will take awhile before we understand how all those networks are working inside the cell. Even then you'll find skeptics who will say, 'what's going on inside a cultured cell is just the first step. It's really how cells work *in vivo* and with each other that we're fundamentally interested in, in terms of human physiology and disease pathology.'"

Negulescu doesn't doubt that cellular bioinformatics will help researchers. Academic groups, he says benefit "greatly from the improvements in the imaging technologies and the use of fluorescent labels to track movements of proteins inside a cell." But, he goes on to say, "that's very early in the process from a standpoint of what pharmaceutical companies are interested in." With Cytokinetics compiling data to validate their technology, it may be able to find buyers, according to Negulescu. The issue, he says, then becomes how much buyers will pay for it and whether it will make for a "big business or a little business."

And there's the matter of getting an industry notoriously slow when it comes to embracing new

Published in
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Windhover's Review of Emerging Medical Ventures

technologies to change the way it looks at cell biology. Pharma companies, argues Negulescu, "are more comfortable with the kind of approach we're taking at Aurora, in which you design an assay for a defined molecular target in a cell, and you use the assay to screen a lot of compounds." Negulescu notes that he and his colleagues at Aurora "have always been tempted to go deeper inside the cell and provide more information, but we backed off because we felt that it would overload our customer. The last thing they want are more questions—more things to track down and follow through." Companies like Cytokinetics, he says, must find a way to simplify the information that they deliver. "I don't know how they do it, but that's their challenge and it's why we've been directing our business to simplify cell exploration with assays that pretty much give you a yes-no answer about your target or drug." Sometimes, offers Negulescu, "getting more complicated is not necessarily going in the right direction."

Indeed, one problem for cellular bioinformatics companies is simply explaining what they are selling. One long-time health care VC professes: "It's one of the few areas where I don't know what people are talking about." To the extent that companies like Cytokinetics are talking about predictive cell phenotype profiles that help to refine hits, he doesn't see it as a distinct business space. "It's really slicing and dicing down to a sub-, sub-, sub-space of high-throughput screening."

The complexity of the type of information being gathered by Cytokinetics also raises the issue of standardization of assay methods and compatibility with data and information gathered by their customers. "When you're trying to compare data sets that are based on very different kinds of experiments, it can be difficult from an informatics standpoint to make sense of the data you're getting," says Negulescu. A "big challenge for those pursuing cellular bioinformatics," he says, "is how to integrate the data that they're getting with the data that pharmaceutical companies view as important decisionmaking information for their drug discovery and development processes." Robert Blum responds that the *Cytometrix* platform is not just a "sub-space" of biochemical screening. Instead, he argues, Cytometrix not only provides cellular information sooner in the pharmaceutical discovery effort but also eliminates many of the off-target surprises that await the downstream characterization of compounds that have only been evaluated against isolated proteins in biochemical screens.

Further, Negulescu suggests that companies like Cellomics and Cytokinetics face more competition than they might care to admit from screening companies like Aurora, noting that high-throughput screening "is really becoming high-content as well." He points to Aurora's ion channel technology for measuring the electrical activity of cells. "That technology allows us to measure action potentials that are the integrated activity of all ion channels in the cell membrane—and which can number over 20 in the case of a heart cell. So when we're using our technology to study a heart cell we're measuring the activity of 20 genes; if you want to extrapolate that to those genes that regulate the expression of or modulate the activity of those ion channels, you're probably talking about over 100 genes. But, says Negulescu, "we're getting one readout which is the physiological readout that everyone's interested in: what does the electrical pattern of activity look like in that cell. And we do it in a high-throughput way."

A Truly Predictive Model?

For some, it's more than just the pharmaceutical industry's reticence to accept new technologies that poses problems for companies looking to commercialize cellular bioinformatics. There are those researchers who believe that the technology is nowhere near developed enough to offer a robust predictive model.

Mark Velleca, senior director of research at **Cellular Genomics Inc.**, says that the biology of the cell is a "system of enormous variability" that simply doesn't lend itself to virtual modeling. "The amount of amplification and redundancy that is built into biological systems makes them extremely difficult to model, let alone predict; just look at the results from knockout mice." Moreover, he argues, the current state of knowledge is not close to that needed to create a database with significant predictive powers. Building the databases, he acknowledges, is a useful exercise that will add to our understanding of cell behavior. But for purposes of drug discovery, what he's seen in the way of cellular bioinformatics "doesn't add much to high-throughput screening."

Velleca's colleague, director of bioinformatics, Andy Whitney, agrees and says that "while modeling of specific cellular processes may help design experiments, nothing in the foreseeable future will be able to replace a well-planned and executed 'wet' experiment or assay." Cellomics' goal of creating a virtual cell, he thinks, is a long way off.

Honing In On Proteins

Already, the strategic challenges facing *Cytometrix* have caused one of its competitors to change direction. Founded in 1998, **Automated Cell Inc.** started out with a technology, if not a business plan, that sounded remarkably like that of Cytokinetics' *Cytometrix* platform. The company advertised its *CytoWorks* system as a "platform for round-the-clock automated investigation of cellular processes" that employs such tools as digital imaging and processing, artificial intelligence,

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and advanced bioinformatics to "deliver in-depth, dynamic cell biology information." At that time, Automated Cell was using its technology to explore the cell biology of human hematopoietc stem cells for use in bone marrow transplant therapeutics. Unlike Cytokinetics, Automated Cell indicated its intent to derive revenues only from the sale of its services to pharmaceutical companies; it was not looking to build its own drug discovery infrastructure.

A year later, the service model and *CytoWorks* remain, but the company's focus has changed. According to president, CEO, and co-founder, Raymond K. Houck, Automated Cell is now concentrating its efforts on building a technology platform to study protein function for purposes of target validation in small-molecule discovery and for therapeutic protein development.

Houck says that the early emphasis on a broad study of cell biology reflected the background of the company's scientific founder and chairman of its scientific advisory board, Joel S. Greenberger. Greenberger, who chairs the Department of Radiation Oncology at the **University of Pittsburgh Medical School**, has done extensive research in the areas of stem cell and bone marrow stromal cell technology.

The movement from a more general cell biology orientation to the current emphasis on protein function, according to Houck, stemmed from an examination of the market opportunities that led company management to conclude that there was a potential niche for them in the protein field. Houck emphasizes that multi-dimensional analysis of cell function and bioinformatics remain a foundation for the company in examining protein function—it's just that the company is using those technologies for a more directed purpose.

"It goes back to a question that one Pharma executive posed to me: 'Ray, don't tell me the five things you can do for me, tell me the one thing you can do for me.' And from my perspective that one thing had better be something that's really important to him."

That the "one thing" for Automated Cell is protein function also moves the company into a space in which others have partially paved the way. While it may be offering a novel approach—with its cellular bioinformatics package—it can be compared, as Houck suggests, to a number of companies providing protein function information, including **Deltagen Inc.**, **Atugen AG**, and **Oxford Glycosciences PLC.**

Making The Price Right

Sabry is perfectly willing to acknowledge the risks his business runs. "We don't have anywhere near the level of knowledge or sophistication to accurately predict the biological response to a drug," he says. "But what I'm talking about is really the beginning of creating technologies that will allow you to begin to address those issues. We don't say that we have all the information about what a compound does to a cell, but we do have a lot more than you'd get by looking at what the compound does to a single protein, which is really where the industry is right now."

And Cytokinetics is prepared to deal with corporate reluctance to adopt new technologies. As an ASP, "we can offer *Cytometrix* in a very inexpensive way, because we keep the technology in our shop. They send us small amounts of compound and we give them back the information. The cost to them is minimal because cost to us is minimal." He contrasts his future ASP with Aurora, which must transfer expensive equipment to the customer. The lower pricing, he argues, also means less red tape to cut through in order to make a sale, because the decisionmaking can be made at the scientist or group director level, rather than requiring an OK from the top.

While Cytokinetics may not earn much for each transaction, Robert Blum believes that it can generate a healthy revenue flow from a loyal customer base. "Companies like **MDS Panlabs Inc.** [which provides discovery research services], don't make a lot on a per transaction basis, but are able to generate a healthy revenue stream from repeat business."

Cytometrix' bottom-line appeal to pharma companies, says Sabry is that it can increase productivity at a time when roughly one out of five thousand compounds makes it to the clinic. *Cytometrix*, he argues, is a technology designed to result in "real world productivity gains that we can articulate, and that's something very difficult for the genomics industry to do now." Sequencing the human genome is very important, but the translation of it into market value is a long way off.

Convincing a Skeptical Pharma

Cytokinetics' idea of boosting drug discovery productivity by targeting the cell's cytoskeletal structure and by automating cell biology is a tantalizing one. And the apparent progress of its anti-cancer program provides some validation for the company's approach. But there remains the question of when, and what price, Big Pharma will pay for the technology.

Drug companies, points out Paul Negulescu, "are inundated with new technologies—you really have to stand out to get their attention." Indeed, genomics has done more than re-shape how drug discovery is carried out today; it has raised the bar for what is considered to be scientifically enabling. The problem is that the flood of gene data, in fact, increases drug discovery time and risk by increasing the number of targets one needs to validate and then the number of screening and chemistry projects required to find real drug leads for modulating these targets.

Cytokinetics' screening technology helps with parts of both these major problems, but solves neither completely. It helps determine which compounds among many are likely candidates for further

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chemistry optimization, but it doesn't speed up the process of creating a worthwhile drug lead itself (the purview of such small-molecule focused start-ups as **Sunesis Pharmaceuticals Inc.**, **Advanced Medicine Inc.**, and **Triad Therapeutics Inc.**—see "*Triad Therapeutics*," START-UP, *June 2000*). It can help researchers uncover new ramifications of perturbing targets, but it does not ultimately reveal the function of a new target.

The 1990s have seen a flood of companies offering partial solutions to the problems and opportunities created by new technologies. Combinatorial chemistry, for example, appeared just when manual chemistry methods were being overwhelmed by the need to screen new targets with new sources of diversity. But combinatorial chemistry has helped only incrementally, as it's turned out: it provides merely hits, leaving most of the high-risk, lengthy medicinal chemistry process to be helped by others. It could even be argued that combinatorial chemistry has increased the costs of medicinal chemistry by creating more high-risk projects to be completed. Combinatorial chemistry can create leads for dozens of targets, but—granted one even knows the value of the targets—how likely is it to actually turn these hits into pharmacologically acceptable lead compounds?

Drug company customers, that have already bought any number of partial solutions, are increasingly skeptical of new ones. To pay real money for them, they need to be convinced that, as Negulescu puts it, they're buying big slices of cake, if not the whole thing. "They just don't have time to adopt 15 technologies a year," he adds, "so they're going to choose the ones that will affect their programs across as broad a range of therapeutic areas as possible." That means they're first going to look at their current technologies to see if a solution can't be fashioned from what they've already bought into—increasing the content level of high-throughput screening, for example, rather than buying in a new high-content screening system.

But Cytokinetics' management has clearly perceived the challenges they face and planned accordingly. They've created separate drug discovery and bioinformatics businesses that have the potential to generate both near- and long-term revenues; they've priced *Cytometrix* with a mind to attracting early users; and they are preparing the company to handle at least some of the development chores if Big Pharma drug companies aren't willing to pay enough for the compounds coming out of the drug discovery program.

And, in emphasizing the potential productivity gains to be realized through its technologies, Cytokinetics certainly has the right message for its audience. Now they have to make themselves heard above the din created by the plenitude of other companies offering their own solutions for breaking through the discovery logjam.

Comments?

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Published in
START-UP
Windhover's Review of Emerging Medical Ventures

Cytokinetics: A Platform Case Study for the Next Decade

June 2000