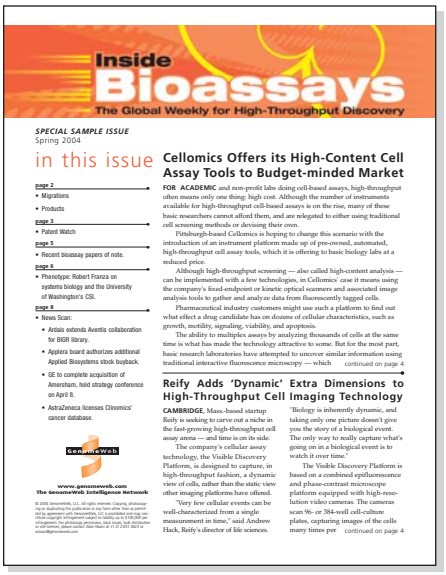
Inside Bioassays
The Global Weekly for High-Throughput Discovery



Inside Bioassays
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SPECIAL SAMPLE ISSUE
Spring 2004

in this issue

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Cellomics Offers its High-Content Cell Assay Tools to Budget-minded Market

FOR ACADEMIC and non-profit labs doing cell-based assays, high-throughput often means only one thing: high cost. Although the number of instruments available for high-throughput cell-based assays is on the rise, many of these basic researchers cannot afford them, and are relegated to either using traditional cell screening methods or devising their own.

Pittsburgh-based Cellomics is hoping to change this scenario with the introduction of an instrument platform made up of pre-owned, automated, high-throughput cell assay tools, which it is offering to basic biology labs at a reduced price.

Although high-throughput screening — also called high-content analysis — can be implemented with a few technologies, in Cellomics' case it means using the company's fixed-endpoint or kinetic optical scanners and associated image analysis tools to gather and analyze data from fluorescently tagged cells.

Pharmaceutical industry customers might use such a platform to find out what effect a drug candidate has on dozens of cellular characteristics, such as growth, motility, signaling, viability, and apoptosis.

The ability to multiplex assays by analyzing thousands of cells at the same time is what has made the technology attractive to some. But for the most part, basic research laboratories have attempted to uncover similar information using traditional interactive fluorescence microscopy — which continued on page 4

Reify Adds 'Dynamic' Extra Dimensions to High-Throughput Cell Imaging Technology

CAMBRIDGE, Mass.-based startup Reify is seeking to carve out a niche in the fast-growing high-throughput cell assay arena — and time is on its side.

The company's cellular assay technology, the Visible Discovery Platform, is designed to capture, in high-throughput fashion, a dynamic view of cells, rather than the static view other imaging platforms have offered.

"Very few cellular events can be well-characterized from a single measurement in time," said Andrew Hack, Reify's director of life sciences. "Biology is inherently dynamic, and taking only one picture doesn't give you the story of a biological event. The only way to really capture what's going on in a biological event is to watch it over time."

The Visible Discovery Platform is based on a combined epifluorescence and phase-contrast microscope platform equipped with high-resolution video cameras. The cameras scan 96- or 384-well cell-culture plates, capturing images of the cells many times per continued on page 4

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Inside Bioassays
The Global Weekly for High-Throughput Discovery

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June 8, 2004

in this issue

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Now on Its Own, Pharmacopeia Drug Discovery to "Ramp up" Internal Efforts

APPROXIMATELY one month after its spin off from parent company Accelrys, Pharmacopeia Drug Discovery finds itself shaping a new business strategy that focuses on increasing R&D spending to support both collaborative and internal drug discovery.

In addition, company officials told *Inside Bioassays* last week that "at least 50 percent" of its assay platforms and services are cell-based as opposed to biochemical-based, and that percentage should continue to grow as PDD leverages proprietary techniques such as episomal transfection agents and assay miniaturization technology.

PDD, which completed its spin off from Accelrys (formerly Pharmacopeia) in early May, will now trade as an independent company on Nasdaq under the ticker symbol "PCOP." The newly anointed Accelrys, meanwhile, has moved forward as a separate scientific software company. On May 20, it officially changed its name from Pharmacopeia, and is currently traded on Nasdaq under the symbol "ACCL." (See *BioInform, 5/10/2004*, *Inside Bioassays*' sister publication, for more details.)

Pharmacopeia has forged partnerships with several major pharmaceutical companies over the past few years, and has successfully guided four compounds to clinical trials with those partners. While the new PDD will continue this work of bringing lead compounds to the doorstep of

continued on page 3

Molecular Devices Redesigns and Launches FLIPR Fluorescence Scanner for 1,536-Well Plates

MOLECULAR DEVICES last week launched a new generation of its fluorometric imaging plate reader system for automated cell-based kinetic assays, known as FLIPR. The new version, FLIPR Tetra, reduces assay volume, increases throughput, and will soon expand the range of assays compared to its predecessor, FLIPR^3, according to the company.

FLIPR "has been redesigned from the ground up," said Stephen Oldfield, Molecular Devices' vice president of worldwide marketing.

Oldfield said the most important improvement over FLIPR^3, which was introduced three years ago, is likely the instrument's ability to run automated fluorescence-based fast kinetic assays in 1,536-well plates instead of just 96-well or 384-well plates, thus reducing the cost for consumables. With the old instrument, this "was theoretically possible but practically difficult," he said, whereas FLIPR Tetra is designed for this application.

The new instrument is unique in that it

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MIGRATIONS

Ingenium Research has named **Jamie Oliver** chief operations officer and head of development.

Oliver has served for seven years as vice president of clinical development for public and private biotechnology companies, Ingenium said. Most recently, he was the associate director of medical affairs with **ClinTrials Research** (now **Inveresk**), where he served as the medical monitor for numerous national and international clinical studies. Prior to this, Oliver directed the research operations of a large non-profit hemodialysis corporation, Ingenium said.

MultiCell Technologies announced last week that **Stephen Mon Wei Chang** has joined the company's scientific advisory board.

Chang currently serves as the CEO of **Astral Therapeutics**. He was the chief science officer and vice president of **Canji/Schering Plough Research Institute** from 1998 to 2004. From 1995 to 1997, he served as director of research for **Chiron Viagene** and **Chiron**, and prior to this he was the director of viral and genetic therapeutics and senior principal scientist for **Viagene**, MultiCell said.

Chang earned his PhD in biological chemistry, molecular biology, and biochemistry from the **University of California, Irvine**.

BioTrove has appointed **Alan Barber** chief financial officer, the company said last week.

Barber joins BioTrove from **Omnisonics Medical Technologies**, where he served as CFO. Barber has also previously served as the CFO at **Innovation Chain**, **MyWay.com**, **Medical Foods**, and **Ergo Science**. He is a CPA and has a BS in accounting from **Florida State University**.

Charles River Laboratories said last week that **Linda McGoldrick** has been elected to its Board of Directors.

McGoldrick is currently the chairman of **Financial Health Associates International**, which she founded in 1985. From 2001 to 2003, she served as senior vice president and national development director for healthcare and life sciences industry practices at **Marsh-MMC**. She has also been a board member and international operations and marketing director for **Veos**, according to Charles River Laboratories.

McGoldrick earned an MBA from the **Wharton School of Business** and an MSW in healthcare from the **University of Pennsylvania**.

ChromaVision Medical Systems, which provides automated cell-imaging systems for pathology, diagnostics, and drug discovery, announced last week that **D. Craig Allred** has been named a consulting pathologist and charter member of ChromaVision's new medical advisory board.

Allred is currently a professor and director of pathology at the **Breast Care Center, Baylor College of Medicine**. He holds an MD from the **University of Utah**, and is a former resident in anatomic pathology and fellow in immunopathology at the **University of Connecticut Health Center**.

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Genoptix, Human Genome Sciences, Cytokinetics, Stanford Win Patents

Genoptix has received US Patent No. 6,744,038, "Methods of separating particles using an optical gradient." According to the abstract, the patent describes apparatus and methods "for interacting light with particles, including but not limited to biological matter such as cells, in unique and highly useful ways."

Called optophoresis, the technology consists of subjecting particles to various optical forces, especially optical gradient forces, and more particularly moving optical gradient forces, so as to obtain useful results, the abstract states. In biology, the technology represents a practical approach to probing the inner workings of a living cell, preferably without any dyes, labels, or other markers.

In addition, the invention includes methods for separating particles in a medium where the particles have differing dielectric constants by providing a medium having a dielectric constant between the dielectric constants of the particles, subjecting the particles in the medium to an optical gradient field, and separating the particles, according to the abstract.

Human Genome Sciences has received US Patent No. 6,743,625, "Death domain containing receptor 5." The invention relates to novel death domain-containing receptor-5 (DR5) proteins which are members of the tumor necrosis factor (TNF) receptor family, and have now been shown to bind TRAIL, the patent abstract states. In particular, isolated nucleic acid molecules are provided encoding the human DR5 proteins. DR5 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of DR5 activity, the abstract states.

Cytokinetics has received US Patent No. 6,743,599, "Compositions and assays utilizing ADP or phosphate for detecting protein modulators." The patent describes methods which identify candidate agents as binding to a protein or as a modulator of the binding characteristics or biological activity of a protein, its abstract states. Generally, the methods involve the use of ADP or phosphate. The assays can be used in a high-throughput system to obviate the cumbersome steps of using gels or radioactive materials, the abstract states.

The **Board of Trustees of Stanford University** has received US Patent No. 6,743,583, "Identification of drugs and drug targets by detection of the stress response."

According to the patent's abstract, the invention features methods of high-throughput screening of candidate drug agents and rapid identification of drug targets by examining induction of the stress response in a host cell, e.g., the stress response in wild-type host cells and/or in host cells that differ in target gene product dosage (e.g., host cells that have two copies of a drug target gene product-encoding sequence to one copy).

In general, induction of the stress response in wild-type host cells indicates that a candidate agent has activity of the drug, the abstract states, and induction of a relatively lower or undetectable stress response in a host cell comprising an alteration in gene product dosage indicates that the host cell is drug-sensitive and is altered in a gene product that plays a role in resistance to the drug.

Pharmacopeia ...

continued from page 1

pharma partners, it will also greatly increase efforts to cultivate drug candidates through an internal drug discovery program.

"It's a two-pronged business strategy," said Simon Tomlinson, PDD's senior vice president for business development, "the first element being to continue with what has been very successful for us, which is collaborative drug discovery. The second is to ramp up what in the past has been a very modest effort for us, which is internal drug discovery."

Tomlinson characterized PDD's collaborative strategy as being from "target through to development," where the company offers assay development and miniaturization; "almost any kind of screen with any kind of readout"; and screening against its own or a collaborator's compound library.

"Then we take the hits or actives that we discover in screening, and then launch discovery, medicinal chemistry … and *in vitro* pharmacology campaigns to develop what we and others term 'development candidates,'" Tomlinson said. At this stage, a drug is ready for ADME/Tox screening, animal testing, and clinical trials, and this "is increasingly our preferred hand-off point in drug discovery," he added.

In terms of internal drug development, Tomlinson said that PDD has a "nice, healthy revenue position," with a "modest burn of $46 million that we're going to be

able to invest more in doing internal discovery." This initiative will be characterized by technologies and capabilities similar to those employed in the company's collaborative drug discovery program, with the hopes of "advancing compounds to at least development candidate" stage.

"That development candidate we would potentially seek to … outlicense," Tomlinson said. "Depending on what the economics of doing that look like, we may invest in taking the compounds forward, but almost certainly outsourcing the *in vivo* work required at that point."

When asked what potential therapeutic areas PDD would consider for internal drug discovery, Tomlinson said that the company is "just in the process of looking at this. It's an internal discussion that we're really involved in right now."

CELL-BASED TOOLS

According to David Dunn, PDD's assistant director of drug discovery, a majority of the company's tools have been thoroughly validated for a cell-based approach. This is particularly important because "at least 50 percent of its assays are cell-based as opposed to biochemical," he said.

"In terms of the growth of cell-based screening … it's fair to say we've seen a doubling in the amount of cell-based screening as well as … utilization of assays for lead optimization over the past five years," Dunn said.

"In terms of capabilities, we have a lot of capabilities that our collaborators have in this area," he added. "We have the capability of doing all the cellular-type work that our customers ask us to do — the basic set of tools. In addition to that, we have some unique tools and capabilities," he added.

Perhaps one of the most important of these tools, according to Dunn, is PDD's episomal transfection technology for expressing particular receptors or other types of proteins in cells. This technique, which is relatively new, is now becoming more widespread, according to Dunn, but PDD "has been using it for the last five years and has a lot of internal expertise" in the area.

Dunn said that the composition of the cDNA episomal constructs allows them to replicate autonomously in the cell — meaning DNA integration of the genes is not necessary for expression. What that translates into is the ability to generate cell lines that express receptors in "two to three weeks, as opposed to months for standard transfection," he said. In addition, he said that scientists "can generate these clones with high expression levels."

Another specific strength for cell-based screens that Dunn cited is the instrumentation for assay miniaturization. Specifically, he said that Pharmacopeia was one of the first to use 1,536-well-plate screening (the company now uses Corning ultra-low-volume microplates), and that the company makes the BlueBird micro-drop liquid dispenser to enable such assays.

"The most challenging process in doing ultra-high-throughput screening in sub-microliter liquid volumes is liquid handling," Dunn said. The BlueBird, he said, can deliver volumes down to 100 nL. Such small volumes are crucial in any screening campaign because of the desire to conserve reagents and drug candidates, but particularly in cell-based screens, in which live, transfected cells are an extremely valuable resource.

Lastly, Dunn alluded to a variety of read-out instruments — most of which are CCD-based and many of which Pharmacopeia helped develop early on in its existence.

It remains to be seen how successful PDD will be in internal drug discovery, but the company certainly has the appropriate tools in place: In addition to its assay platforms, Tomlinson said that the company has a "very large collection of proprietary drug-like small molecules — about seven-and-a-half million compounds, which we synthesized using our combinatorial approach to chemistry."

But for now, the company will have to sustain itself on revenues generated from pharma collaborations that were established by Pharmacopeia.

So far, it has helped bring four compounds to clinical trials with three pharma partners: A drug targeting p38 kinase for rheumatoid arthritis with Bristol-Myers Squibb; a drug for an undisclosed indication with Daiichi; and two compounds with Schering-Plough for respiratory and inflammatory indications. Each of these has clinical milestone and possible royalty payoffs, but each is only in Phase I trials.

In addition, though, Tomlinson said that the company has major new collaborations in the works, but declined to disclose with whom and for what indications.

The company is also busying itself with finding a permanent CEO and president. Joseph Mollica, who was president, chairman, and CEO of Pharmacopeia prior to the spin-off and name change, is currently the acting CEO and president of PDD. According to Tomlinson, this situation works fine for now.

"I'm not close to the situation myself," Tomlinson said. "But we don't feel any particular pressure — it's not like we have an empty chair. We've got [Joe], who knows our business inside-out, running the show. As he will continue on as chairman of the board, there will be a very smooth transition, we think, to the new CEO."

—BB

Molecular Devices ...

continued from page 1

combines a pipetting system with an optical system for simultaneous readout. "Clearly there are other machines that can pipette 1,536 [well plates] … but they don't do it on an optical bench so you can make simultaneous measurements," Oldfield said.

Smaller assays require fewer cells and drug compounds, thus reducing cost. According to Oldfield, pharmaceutical customers said their consumable budgets will remain flat in coming years, "so the ability to miniaturize all the way to 1,536 will allow them to screen more while staying within a similar cost structure."

The new pipetting system, which uses an elastomeric technology for contact-based liquid transfer, can dispense between 0.5 and 3 microliters of liquid. Typical assays on a 1,536-well plate have a volume of only three microliters, Oldfield said.

Furthermore, FLIPR Tetra, which uses banks of light emitting diodes instead of a laser, will soon have an expanded range of wavelengths compared to its predecessor, thus increasing the number of dyes its can use. These will include, for example, Invitrogen's Voltage Sensor Probe dye for measuring membrane potentials, Oldfield said.

Additional wavelengths will be added before the end of the year, he said, and can be installed on FLIPR Tetra instruments shipped before then. They will enable researchers to reduce interference by taking measurements at wavelengths that are different from those of naturally fluorescent compounds. Furthermore, the new instrument can measure two wavelengths in one assay, a capability required for ratiometric measurements to determine absolute concentrations. "Before, it was not easy to do two," he said.

In addition, the new instrument, contrary to FLPR^3, is small enough to fit through a doorway, needs no cooling water, and only requires standard power. "It looks like a refrigerator—you just wheel it into the lab," said Oldfield. Users can also change the fluidics easily, switching from 384-well plates to 1,536-well plates, for example. All this, the company hopes, will make it more palatable for users at small pharmaceutical or biotech firms.

"Clearly there are other machines that can pipette 1,536 [well plates] ... but they don't do it on an optical bench so you can make simultaneous measurements."

Molecular Devices did not provide a list price for the new instrument, but it hovers around that for a standard version of the previous model, depending on the configuration, Oldfield said. While a 96-well plate configuration for assay development will cost less than FLPR^3, the price for the fully automated industrial-level 1,536-well screening configuration will be "a bit more."

Beta testers for FLIPR Tetra included Jenny Stables at GlaxoSmithKline in the UK and Michela Stucchi at Axxam in Milan, Italy, who both presented data obtained with the new system at Molecular Devices' user meeting in Berkeley, Calif., last week. In addition, MD presented data from Roche Palo Alto, another beta tester, at the meeting. These companies' data will soon be available on MD's website, according to Oldfield.

Since the first FLIPR came out in 1997, Molecular Devices has installed more than 400 systems at sites of more than 150 customers, most of them pharmaceutical and biotech companies, according to Oldfield. However, a few academic centers have obtained an instrument through sponsorship from a pharma company: AstraZeneca, for example, sponsored a machine at Griffith University in Queensland, Australia, which is being used to screen natural products, especially those derived from the rainforest, he said.

According to Oldfield, FLIPR's main competitors are the FDSS 6000 from Hamamatsu, and PerkinElmer's ImageTrak system. The FDSS 6000 fluorescence drug screening system is "an imaging-based plate reader for cellular assays, assay development, and high-throughput screening," according to Hamamatsu's website. Features include an internal robot, injectors for 96- or 384-well plates, red or UV dyes that are excited by a Xe lamp, a non-confocal system, multi-dispensers, a two-CCD camera design, kinetic readout, and a cell reservoir, according to the product literature.

(For further information on PerkinElmer's ImageTrak, see *Inside Bioassays, 5/18/04.*)

Oldfield claimed, however, that FLIPR dominates the market in such a way that the calcium, membrane potential, and other assays users typically run on the instrument have become known as "FLIPR assays."

The company has had several orders for the new instrument already and will ship the first machines before the end of the month, Oldfield said.

— *JK*

Recent Cell-Based Assay Papers of Note

Journal	Title	Author
Analytical Biochemistry, 2004 Apr 1; 327(1): 14-22	Use of moving optical gradient fields for analysis of apoptotic cellular responses in a chronic myeloid leukemia cell model	Forster AH, Wang MM, Butler WF, Chachisvilis M, Chung TD, Esener SC, Hall JM, Kibar O, Lykstad K, Marchand PJ, Mercer EM, Pestana LM, Sur S, Tu E, Yang R, Zhang H, Kariv I
Analytical Biochemistry, 2004 Apr 1; 327(1): 74-81	State-dependent inhibition of L-type calcium channels: cell-based assay in high-throughput format	Xia M, Imredy JP, Koblan KS, Bennett P, Connolly TM
Analytical Biochemistry, 2004 Jun 1; 329(1): 28-34	Cell-based screen of HMG-CoA reductase inhibitors and expression regulators using LC-MS	Gerber R, Ryan JD, Clark DS
Analytical Chemistry, 2004 May 15; 76(10): 2902-9	Living bacterial cell array for genotoxin monitoring	Kuang Y, Biran I, Walt DR
Biochemical Pharmacology, 2004 May 15; 67(10): 1897-905	A cell-based system to identify and characterize the molecular mechanism of drug-metabolizing enzyme (DME) modulators	Miao W, Hu L, Kandouz M, Hamilton D, Batist G
Biosensors and Bioelectronics, 2004 Jun 15; 19(11): 1529-35	A low-volume platform for cell-respirometric screening based on quenched-luminescence oxygen sensing	Alderman J, Hynes J, Floyd SM, Kruger J, O'Connor R, Papkovsky DB
BMC Biotechnology, 2004 Mar 19; 4(1): 5	Cell-based assay for the detection of chemically induced cellular stress by immortalized untransformed transgenic hepatocytes	Sacco MG, Amicone L, Cato EM, Filippini D, Vezzoni P, Tripodi M
Drug Discovery Today, 2004 Apr 15; 9(8): 358-65	The evolution of microarrayed compound screening (review)	Hoever M, Zbinden P
Expert Reviews in Molecular Diagnostics, 2004 May; 4(3): 403-11	Use of the BRET 7TM receptor/beta-arrestin assay in drug discovery and screening (review)	Heding A
Immunology, 2004 Apr; 111(4): 422-9	Dendritic cell-based assays, but not mannosylation of antigen, improves detection of T-cell responses to proinsulin in type 1 diabetes	Narendran P, Elsegood K, Leech NJ, Macindoe WM, Boons GJ, Dayan CM
Investigational New Drugs, 2004 Aug; 22(3): 253-62	A novel mammalian cell-based approach for the discovery of anticancer drugs with reduced cytotoxicity on non-dividing cells	Gonzalez-Nicolini V, Fux C, Fussenegger M
Journal of Biochemical and Biophysical Methods, 2004 Jun 30; 59(3): 229-39	Miniaturization and validation of a cell-based assay for screening of Ca(2+) channel	Tammela P, Vuorela P
Journal of Biomolecular Screening, 2004 Apr; 9(3): 186-95	Miniaturization of whole live cell-based GPCR assays using microdispensing and detection systems	Kornienko O, Lacson R, Kunapuli P, Schneeweis J, Hoffman I, Smith T, Alberts M, Inglese J, Strulovici B
Lab Chip, 2004 Apr; 4(2): 148-51. Epub 2004 Jan 16	Cell immersion and cell dipping in microfluidic devices	Seger U, Gawad S, Johann R, Bertsch A, Renaud P
Methods, 2004 Apr; 32(4): 381-8	A cDNA library functional screening strategy based on fluorescent protein complementation assays to identify novel components of signaling pathways	Remy I, Michnick SW
Toxicological Sciences, 2004 Jun; 79(2): 214-223. Epub 2004 Mar 10	Use and application of stem cells in toxicology (review)	Davila JC, Cezar GG, Thiede M, Strom S, Miki T, Trosko J

MIT's Anne Carpenter Discusses HT Microscopy, Cellular Arrays

ANNE CARPENTER is an up-and-coming cell biology researcher in David Sabatini's laboratory at MIT's Whitehead Institute for Biomedical Research, and is a member of MIT's campus-wide Computational and Systems Biology Initiative. She is not only working with RNA interference, transfected cell microarrays, and high-throughput microscopy, but is also designing new automated imaging software. Last week, Carpenter took a few moments to discuss her work and ideas about systems biology with *Inside Bioassays*.

AT A GLANCE

NAME: Anne Carpenter

Postdoc, Whitehead Institute for Biomedical Research, MIT

Photo by Kelly Sullivan

BACKGROUND:

PhD, Cell Biology, University of Illinois, Urbana-Champaign — 2003

BS, Biology, Purdue University

Regarding your work in automated imaging and cellular arrays: How did you become interested in these areas?

The automated imaging started in graduate school when the work that I was doing required basically staring at samples for hours on the microscope, trying to decide if there was a difference between two different samples — the control and real sample. And it was so frustrating to look at the samples for such a long time and not really be able to come to a complete conclusion and to have it be very subjective. I wanted to be more quantitative, and I wanted to have more objective, unbiased results, so that led me to start collecting images — still by hand — but to develop some very rudimentary software to measure the things that I was looking at, which at the time was chromatin structure. And so once I saw how much the automated image analysis improved the results — suddenly we had objective, quantitative results coming from images — I became really excited about collecting images faster. So that led us to automate a microscope that we had in the lab. It had a motorized stage already, so we just programmed it so it would collect images automatically. So once that was set up, we were suddenly able to [do certain things]. I think my first project in grad school I spent two months, at least four hours a day, collecting images by hand, and it was so incredibly tedious. Once I got the automated microscope set up, in a week I collected more data than I had collected my entire graduate career up until that point, and it was able to be analyzed automatically, as well. So just the incredible increase in throughput made me see the power of this technology, and become interested in it as a career.

[Regarding] the cell arrays, I had read the original paper published by the Sabatini lab, which was a *Nature* paper (*Nature*, 2001 May 3; 411(6833): 107-10), and I just thought it was terribly clever. I didn't think about whether it was going to be relevant for me, in particular, but I just thought it was a really clever idea and set it aside early in grad school as something that I might be more interested in, so when it came time to look for postdocs, that was one of the labs that I considered joining.

Are these two techniques different means to the same end?

They're actually extraordinarily complementary technologies. Cell arrays are useful for looking at thousands of samples on a single microscope slide. So you can look at those samples just by eye, if you have a really obvious phenotype — say you're looking for increased staining of a certain protein — you can look at the arrays at a very low magnification and see bright spots where you have a hit from your screen. But with automated imaging, if you go to higher resolution and record images and analyze them, as well, you have much more ability to look at interesting phenotypes — either subtle phenotypes that you wouldn't be able to see just looking at the array by eye, or phenotypes that are just not feasible to see from the bird's-eye view. So it's looking at localization of proteins, looking at changes in protein levels, and all kinds of similar things.

Would you characterize the microscopy as being more high-content and the arrays as being higher throughput?

That's not wrong, but it's not how I would put it. Automated imaging does allow you to do high-content assays, and the cell arrays you can look at in either high-content or high-throughput mode, depending on how you want to look at them.

Is one more suited to a particular application or type of screen than another?

No, I think that really you get the most power if you use them both. I think automated imaging just makes cell arrays that much more applicable to a lot of different

phenotypes, whereas without automated imaging, the work would just be so tedious to look at high-resolution images by eye that it wouldn't be feasible.

David Sabatini, who is well-known in the RNAi field, heads your lab. How do either of these applications fall in with RNAi?

We're so fortunate that RNAi has become really reliable and feasible over these past few years, because it's a perfect complement, again, to these cell arrays. So previously, in the initial publication, the cellular arrays allowed us to look at overexpression of genes in different spots on a cell microarray. But with RNAi we can now do loss-of-function experiments, and so it brings the power of a traditional genetic approach to mammalian cell types and to *Drosophila* cells in culture, and allows you to do essentially genetics in cell culture.

All of this work falls under the umbrella of systems biology, at least according to the lab's website. That's a term that is getting thrown around a lot lately, but different people seem to have different definitions. How do you characterize it, and how do you think the concept will affect biological research in the future?

Well, the traditional biology approach has been to choose a gene of interest, and to perform a variety of assays on it. You might look to see: Does my gene of interest produce a protein that binds to this other protein? Does it localize in a certain place? Does it perform a certain enzymatic function? And so you choose a gene and perform a variety of assays.

What these new high-throughput approaches allow us to do, and this falls under the umbrella of systems biology, is instead of choosing one gene and performing all these assays, we can study the entire genome — every single gene — and perform the same kinds of assays. So this approach allows you to not only confirm whether your gene of interest is involved in some particular function, but it allows you to go ahead and screen the entire genome while you're at it. The conceptual approach is not really different from traditional biology; it's just a matter of being able to answer a particular question about all the genes in the genome instead of just one. So with that information, it allows for an unbiased screening of genes, so we are uncovering things that we would not have figured out just tracking down genes and performing assays in a linear manner.

As far as impact on the future of biology, I think that a lot of academic labs will be transitioning to doing these high-throughput screens [for] anything that can be converted to high-throughput format: If an experiment is worth doing once, it's worth doing 6,000 times for yeast, or 14,000 times for *Drosophila*. So I think we'll be seeing this transition occur more and more in academic labs, and as such, we'll probably start getting surprises as approaches become less biased towards candidate genes.

Did you develop this new automated microscopy platform or software for it? Are there any plans for commercialization of any of these technologies?

Automated microscopes are very readily available these days, so pretty much from any microscope company you can buy an automated microscope off the shelf, and it will come with some sort of software to control the hardware, at least, and maybe do some rudimentary image analysis, as well. There are also commercial companies that have produced systems that are geared more towards pharmaceutical companies, that are more in a box format, and already set up for high-throughput experiments. So that covers all the automated microscopes. The one that we bought in graduate school just required programming the hardware to collect images in the way that we wanted to, so it was published in a paper, but it was not necessarily commercially viable.

The cell arrays were, as I said, originally published in that *Nature* paper, and are being used by academics in many different laboratories, and if companies are using them, they license the technology through the Whitehead Institute. That was developed in the Sabatini laboratory before I arrived.

And the software for automated imaging has really been the bottleneck so far, especially from the academic perspective. Software was developed primarily for pharmaceutical applications, for very simple readouts; for example, looking for cell lethalities, such as counting cells, or just looking for changes in localization between the nucleus and cytoplasm — very simple outputs. There hasn't been software that's as flexible and useable for academics, especially, but even for pharmaceutical companies wanting to do something more interesting or complicated. So we saw that need when I joined the lab a year ago, and my project has been writing this software to fill that need. It's called Cell Profiler, and when it's published, we will make it available to academics for free, and will just charge a nominal fee to commercial users, just to [provide] the technical support for the software.

Would you care to comment on any of the specific microscopy or imaging platforms that you use in the laboratory? Do you favor any specific vendors?

Not really. The only things I can comment on would not be positive [laughs], so I think we'd better just leave that lie.

PHYLONIX WINS NIH GRANT FOR ZEBRAFISH ASSAYS

Phylonix of Cambridge, Mass., said last week that it has received a $993,463 Phase II SBIR grant from the National Cancer Institute to develop zebrafish apoptosis assays for drug screening.

According to an official company statement, Phylonix will be using dye-based assays to identify apoptotic cells in living zebrafish embryos, and will incorporate an automated liquid-handling workstation and microplate reader for high-throughput applications. A goal of the assays would be to aid in the development of compounds to modulate apoptosis, which plays an important part in diseases such as cancer, heart disease, stroke, AIDS, autoimmunity, and degenerative diseases, the company said.

Although embryos have previously been used as an alternative to cell-based assays, they have primarily been invertebrate embryos. Zebrafish physiology is more closely related to that of humans, making assay results more relevant to the development of human drugs, the company said.

Phylonix also said that zebrafish embryos have several additional advantages in screening assays, such as their small size, transparency, ability to reproduce quickly, and ease of maintenance. In addition, the company expects each assay to cost less than $100.

XCELLSYZ LICENSES CELL LINES TO BOEHRINGER INGELHEIM

Xcellsyz said yesterday that will license immortalized human skeletal cells to Boehringer Ingelheim for "evaluation and drug discovery research," according to an official company statement. Financial terms of the deal were not disclosed.

The specific cell lines that the company will be licensing are produced using a proprietary technology that allows cells to proliferate while maintaining the ability to revert back to their original phenotypes, the company said.

The company, based in Newcastle, UK, is focused on developing drugs for diabetes and obesity using cell-based technology. It also licenses cell lines and assay services to pharmaceutical companies for target discovery and validation, toxicity testing, and drug metabolism studies.

PROLYSIS COLLABORATES WITH ESSENTIAL SCIENCE ON ANTIBIOTIC SCREENING

Prolysis of Oxford, UK, announced yesterday that it is collaborating with Essential Science to commercialize Prolysis' platform for bacterial cell-based screening of antibiotic compounds.

Essential Science will provide business development support to Prolysis with the goal of establishing relationships in the areas of "library screening, in-licensing of development candidates, out-licensing of Prolysis' technologies, and development of new applications," the companies said. Financial terms of the deal were not disclosed.

Prolysis' technology is based on the work of Jeff Errington, a professor at the Sir William Dunn School of Pathology at the University of Oxford. The company said it has developed five proprietary whole-cell bacterial assays that target critical pathways to ensure therapeutics can enter the cell.

CHEMBRIDGE LABORATORIES REACHES MILESTONE IN EISAI DRUG DISCOVERY DEAL

ChemBridge Research Laboratories of San Diego said last week that it has achieved a milestone in its drug discovery collaboration with Eisai.

The goal of the collaboration, which the companies established in April 2002 and amended in Dec. 2003, is to discover compounds against an undisclosed G-protein coupled receptor. The nomination of the milestone results in CRL providing further support by facilitating the optimization of lead molecules, the company said. Further financial details were not disclosed.

TRIMERIS AND ARRAY BIOPHARMA EXTEND DRUG DISCOVERY AGREEMENT

Trimeris of Durham, N.C., and Array BioPharma, of Boulder, Col., said last week that they have renewed an agreement to discover small molecule entry inhibitors directed against HIV.

As part of the renewed agreement, which was originally established in August 2001, Trimeris will screen compounds created by Array for HIV entry inhibitor targets. Array will receive research funding, milestone payments, and royalties based on the success of the program, the companies said.

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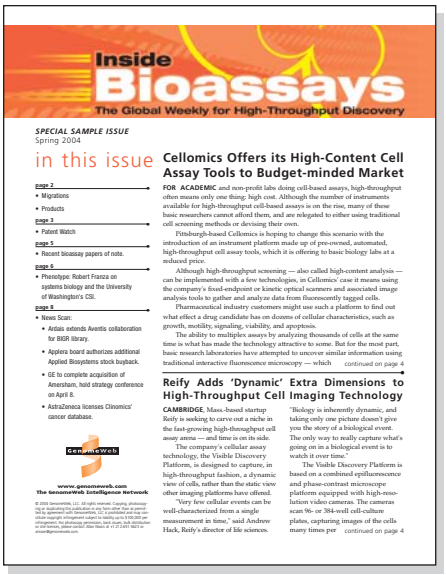

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Cellomics Offers its High-Content Cell Assay Tools to Budget-minded Market

FOR ACADEMIC and non-profit labs doing cell-based assays, high-throughput often means only one thing: high cost. Although the number of instruments available for high-throughput cell-based assays is on the rise, many of these basic researchers cannot afford them, and are relegated to either using traditional cell screening methods or devising their own.

Pittsburgh-based Cellomics is hoping to change this scenario with the introduction of an instrument platform made up of pre-owned, automated, high-throughput cell assay tools, which it is offering to basic biology labs at a reduced price.

Although high-throughput screening — also called high-content analysis — can be implemented with a few technologies, in Cellomics' case it means using the company's fixed-endpoint or kinetic optical scanners and associated image analysis tools to gather and analyze data from fluorescently tagged cells.

Pharmaceutical industry customers might use such a platform to find out what effect a drug candidate has on dozens of cellular characteristics, such as growth, motility, signaling, viability, and apoptosis.

The ability to multiplex assays by analyzing thousands of cells at the same time is what has made the technology attractive to some. But for the most part, basic research laboratories have attempted to uncover similar information using traditional interactive fluorescence microscopy — which continued on page 4

Reify Adds 'Dynamic' Extra Dimensions to High-Throughput Cell Imaging Technology

CAMBRIDGE, Mass.-based startup Reify is seeking to carve out a niche in the fast-growing high-throughput cell assay arena — and time is on its side.

The company's cellular assay technology, the Visible Discovery Platform, is designed to capture, in high-throughput fashion, a dynamic view of cells, rather than the static view other imaging platforms have offered.

"Very few cellular events can be well-characterized from a single measurement in time," said Andrew Hack, Reify's director of life sciences. "Biology is inherently dynamic, and taking only one picture doesn't give you the story of a biological event. The only way to really capture what's going on in a biological event is to watch it over time."

The Visible Discovery Platform is based on a combined epifluorescence and phase-contrast microscope platform equipped with high-resolution video cameras. The cameras scan 96- or 384-well cell-culture plates, capturing images of the cells many times per continued on page 4

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