Inside Bioassays
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Armed with $3.5M Stash, Vala Sciences to Sell Cellular Imaging Software, Reagents

WITH approximately $3.5 million from NIH grants and private investors under its belt, La Jolla, Calif.-based biotech startup Vala Sciences debuted last week as a provider of reagents and software for conducting image-based cell assays for drug screening and cell biology research.

Jeffrey Price, an associate professor at the La Jolla-based Burnham Institute and adjunct professor of bioengineering at the University of California, San Diego, is one of Vala's co-founders, and will serve as chairman and CEO.

Vala's other co-founder is Edward Hunter, who will be a director and chief technology officer at the company.

Price told *Inside Bioassays* last week that the bulk of its start-up cash — about $2.5 million — comes from NIH Small Business Innovation Research grants; one for assay development, and one for cell image-based software analysis development. Vala also received $100,000 from the California Technology Investment Partnership Program, and the remainder from undisclosed angel investors.

Price and Hunter together founded high-throughput imaging company Q3DM in 1998, and developed the EIDAQ 100 high-throughput microscopy system as its flagship product. Beckman Coulter acquired Q3DM in December 2003, and subsequently modified the core instrument into its own cellular analysis system, the CellLab IC 100. Coincidentally, Beckman Coulter announced the official launch of the IC 100 just one day prior to

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SUNY-Buffalo Researchers to Commercialize Novel Biochip to Measure Cell-Volume Changes

RESEARCHERS from the State University of New York at Buffalo have developed a novel microfabricated biochip that combines an electrical sensor and microfluidics to conduct non-invasive cellular screening based on changes in cell volume.

The researchers, whose work was published online Jan. 22 as an *Analytical Chemistry* "ASAP" article, now hope to commercialize the technology through SUNY Buffalo's technology-transfer office for possible applications in high-throughput drug screening, basic laboratory research, clinical testing, and environmental biosensing.

If commercialized, the product may fill a need for an inexpensive, disposable, and miniaturized cell-based assay method for conducting high-throughput screening of small-molecule compounds.

The technology is based on a concept called cell-volume cytometry. As the researchers describe in their paper, a wide body of research has provided evidence that changes in a cell's volume

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MIGRATIONS

Ann Reynolds has joined the board of directors of **Invitrogen**, the company said this week.

Until 2002, she was the president of the **University of Alabama at Birmingham**. Prior to that, she was the chancellor of the **City University of New York**, and before that, chancellor of the **California State University** system. Reynolds holds a PhD and a master's degree in zoology from the **University of Iowa**, and a bachelor's degree in biology from **Emporia State University** in Kansas.

MultiCell Technologies said last week that it has appointed **Stephen Chang** as president.

Chang is currently the CEO of **Astral Therapeutics**. He is also president of **CURES (Californians United for Research, Economic Development, and Saving Lives)**, a safe-research advocacy coalition. Chang is also a board member for life sciences organization **Biocom**. He has served as chief science officer and vice president for **Canji/Schering Plough Research Institute** from 1998 to 2004. He has also held director-level positions at **Chiron** and **Viagene**. Chang earned a PhD in biological chemistry, molecular biology, and biochemistry from the **University of California, Irvine**.

MultiCell also announced last week that it has appointed **Anthony Cataldo** as the non-executive co-chairman of the board. Cataldo is currently the chairman of **Brand-Partners Group**. He has also served as executive chairman of **Calypte Biomedical**, and has been employed by **Senetek**.

Carl Barrett will become global head of oncology biomarkers at the **Novartis Institutes for BioMedical Research** in Cambridge, Mass. He used to lead the division of basic sciences and the center for cancer research at the **National Cancer Institute**.

PRODUCTS

Sigma-Aldrich has announced the commercialization of the **TargeTron Gene Knockout System**. TargeTron provides a robust and simple method for site-specific disruption of DNA sequences within a host cell genome, Sigma-Aldrich said. The technology exploits the retrohoming ability of group II introns in order to "target" the exact position of gene disruption, the company said. The technology was developed by **Alan Lambowitz** from the **University of Texas at Austin**, and licensed from **Ingex**, Sigma-Aldrich said.

Celliance, a wholly owned subsidiary of **Serologicals**, has announced the introduction of **Hybri-CYTE**, a serum-free cell culture supplement designed and optimized for use in hybridoma cell culture. The supplement has been proven to work with mouse-, rat-, and rabbit-derived cell lines, Celliance said.

Peakdale Molecular has launched its fourth **Peakexplorer GPCR library**, featuring more than 1,100 compounds specifically designed, synthesized, and characterized for screening against GPCR targets. This latest library has been created through the assessment of seven chemotypes intended to target GPCRs, Peakdale said.

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Tosk, Duke, NYU, and MIT Are Among Recent US Patent Recipients

Tosk has been awarded **US Patent No. 6,855,504**, "*In vivo* high-throughput toxicology screening method."

Patrick Fogarty is the inventor listed on the patent.

According to its abstract, the patent protects a high-throughput toxicology screening method, in which at least 10 different compound compositions are tested simultaneously. Each compound composition is tested by contacting it with a plurality — for example, from about 10 to 1000 — of non-mammalian multi-cellular organisms, and determining the effect of the compound composition on the organisms, the abstract states. The multi-cellular organisms employed in the subject methods are small, have differentiated tissues and organs, and have a rapid generation time. The subject high-throughput screening methods find use in a variety of applications, and are particularly suited for use in the toxicology screening of libraries of compounds, such as libraries of combinatorially produced compounds, the abstract states.

Duke University has been awarded **US Patent No. 6,855,550**, "Expression of G-protein coupled receptors in yeast."

Inventors listed on the patent are **Klim King**, **Henrik Dohlman**, **Marc Caron**, and **Robert Lefkowitz**.

According to its abstract, the patent protects a transformed yeast cell containing a first heterologous DNA sequence that codes for a mammalian G-protein coupled receptor, and a second heterologous DNA sequence that codes for a mammalian G-protein a-subunit. The first and second heterologous DNA sequences are capable of expression in the cell, but the cell is incapable of expressing an endogenous G-protein a-subunit. The cells are useful for screening compounds that affect the rate of dissociation of G-protein subunits in a cell, the abstract states. The patent also protects a novel DNA expression vector useful for making cells as described above. The vector contains a first segment comprising at least a fragment of the extreme amino-terminal coding sequence of a yeast G-protein coupled receptor. A second segment is positioned downstream from the first segment (and in correct reading frame therewith), with the second segment comprising a DNA sequence encoding a heterologous G-protein coupled receptor, the abstract states.

Massachusetts Institute of Technology has been awarded **US Patent No. 6,855,551**, "Biological applications of quantum dots."

Inventors listed on the patent are **Moungi Bawendi**, **Vikram Sundar**, and **Frederic Mikulec**.

According to its abstract, the patent protects a composition comprising fluorescent semiconductor nanocrystals associated to a compound, wherein the nanocrystals have a characteristic spectral emission; said spectral emission is tunable to a desired wavelength by controlling the size of the nanocrystal; and said emission provides information about a biological state or event.

New York University has been awarded **US Patent No. 6,855,807**, "Heterodimeric opioid G-protein coupled receptors."

Inventors listed on the patent are **Lakshmi Devi** and **Bryen Jordan**.

According to its abstract, the patent protects opioid receptors that form functional heterodimers with each other and with other G-protein coupled receptors, such as dopamine receptors, adrenergic receptors, or chemokine receptors. These receptors can be exploited for high-throughput screening of compounds to identify heterodimer opioid receptor modulators (agonists and antagonists). The patent also protects the identification of novel heterodimer receptor ligands and synergistic compositions, which can provide strategies for analgesia, narcotic addiction, hypertension, HIV infection, and immune system function, the abstract states.

Vala Sciences ...

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Vala's announced founding. (see sidebar, p. 5).

A large percentage — about 75 percent, Beckman Coulter rep Mark Cheetham told *Inside Bioassays* in December — of Q3DM's former employees were integrated into Beckman Coulter. However, a few employees — most of whom helped develop CytoShop, the IC 100's current image-analysis software — did not join Beckman, and have now joined Vala Sciences as part of its software development team.

Price said that Vala has designed an image-analysis software package completely different from CytoShop, and has its own patents pending. The first release of the software is "essentially done," Price said, and will be ready to ship within the next few weeks.

"As a first release, of course, we'll be looking to expand it as we go," Price said. "We took a few years to develop our first release on the instrument-based system at Q3DM, and we took six to nine months to develop the first release of this software. So we have the background of what we consider to be cutting-edge cell-image based assay software."

Vala's software will utilize proprietary image-analysis algorithms to extract key features from fluorescence images of cells — a capability that is no different from

most high-content image-analysis software on the market. But what sets Vala's software apart from CytoShop — and it hopes from the rest of the market space — is that it is intended to be compatible with any fluorescence microscope or high-throughput cellular imaging system, and across multiple computer operating systems.

"When you design something for multiple operating systems and multiple computers, its architecture is fundamentally different," Price said. "Of course, we are going to use our experience from building [CytoShop] to build our [software]. We want to add things that basically reduce the number of clicks, and generate measurements easier and easier.

"There is still some technological challenge to using these instruments and software … but we want to drive that by making at least a set of software tools that anybody can access," Price added. "Researchers [may] use an instrument in a core facility, because maybe it's too expensive for [them] to have in their lab at — then they can still pull the images back and have a way to analyze them with our software. I think [we can] make those tools available for large companies that are selling instruments as well."

Vala may be entering a market rife with opportunity — the word at recent conferences such as Cambridge Healthtech Institute's High-Content Analysis meeting is that the physical hardware right now is pretty good, but image analysis is still a stumbling block.

Most high-throughput imaging systems on the market have their own image-analysis software, most of which are designed to interface only with their accompanying instruments. Although many researchers may be content with the capabilities of these packages, just as many desire some degree of flexibility. In addition, more and more companies' instruments now have an open architecture that allow them to be used with more than one type of user-supplied software.

High-content screening pioneer Cellomics has begun to recognize this trend, as it has made a recent effort to integrate its image-analysis software with other companies' imaging platforms. The Pittsburgh-based company announced last year that it was working with GE Healthcare to design an interface between its vHCS Discovery Toolbox and GE's IN Cell Analyzer instruments — although this was more at the "data-mining" level, and not the initial image-analysis level, John Sutton, a vice president of product management at GE Healthcare, told *Inside Bioassays* last July (see *Inside Bioassays, 7/6/2004*).

Judy Masucci, Cellomics' director of marketing, said last week that Cellomics is in the process of opening its HCS software to other platforms, as well.

As for direct competition, German software firm Definiens is also marketing image-analysis software for cell-based assays, called Cellenger, that it said is based on cognitive object-recognition, and is intended to be applied across several instrumentation platforms (see *Inside Bioassays, 12/14/2004*).

In addition, Whitehead Institute researchers led by Anne Carpenter are developing an open-source cell-based image-analysis software package called CellProfiler, which is currently undergoing beta-testing, and may be available this spring, according to *BioInform*, a sister publication to *Inside Bioassays*.

CELL IMAGE-BASED REAGENTS

The other prong of Vala's business model is reagents for image-based cellular assays, which the company intends to market — at least at first — coupled with related software for specific types of assays.

"We'll look at both the development and marketing of software that works with particular reagents, and those will be sold both as packages and independently, depending on how people want to use them," Price said. "We found that it's best to develop the software tools to work on a particular application, and to validate them and make sure they work properly, and with the performance that you're looking for.

"One of the challenges of this industry is that when you change the cells, dye, or compound, even small changes can alter the appearances of the image, and therefore the measurement," he added. "It's very important to develop the two together, and for people to understand in what context the measurements work"

At the outset, Vala will be using some assay reagents that are in the public domain, as well as in-licensing key reagents, Price said. But in many cases, he said that Vala will work with its customers to tailor software and reagent kits to a particular problem that they want to solve.

Vala already has four such collaborations in place — with the Chemical Genomics Research Consortium of the Gulf Coast Consortia and the Burnham Institute, for cellular assays in several areas; La Jolla-based RegeneMed, for 3D drug-toxicity assays in engineered liver tissue; and the University of Florida, for high-throughput genomic assays.

Price said that Vala has begun to explore partnerships with instrument manufacturers — though he declined to disclose which ones — to validate its software and reagents on their imaging systems, adding that he felt it was important that Vala's software not be linked to any one platform.

Vala's first reagent kit is for assaying PKC-alpha activity in 96-well plates, and is available via the company's website at a list price of $325. The initial software package is available for one-year license periods at a price of $795 for academic users, and $4,595 for commercial users. The website indicates that these prices are available for a limited time.

Price said that the software and reagents will be the company's main source of revenue for the time being,

but that Vala may offer assay services to customers "as the need arises." He also said that Vala "does not have any hard plans" to seek additional VC funding at this point, but likely will in the future.

Perhaps the most difficult challenge Vala faced at start-up was naming the company. Price told *Inside Bioassays* that a vala is a female seer, or soothsayer, from ancient Norse mythology.

"After having the name Quantitative 3-Dimensional Microscopy rolled into the name Q3DM — the tech guys kind of liked it, but the rest of the world thought it was unapproachable," Price explained. "So we wanted something kind of generic that didn't have a direct connection technologically. We were thinking of the imaging as a look into the future, in some sense."

— *BB*

BECKMAN COULTER 'OFFICIALLY' LAUNCHES IMAGING CYTOMETER FOR HIGH-THROUGHPUT CELLULAR ASSAYS

BECKMAN Coulter last week launched its first major product into the image-based cellular analysis market, the Cell Lab IC 100 Image Cytometer.

As reported by *Inside Bioassays*, the IC 100 has been on the market since at least December, when Beckman Coulter was showing off the final version of the instrument — having incorporated early-user feedback — at the American Society for Cell Biology Meeting in Washington, DC (see *Inside Bioassays, 12/14/2004*).

The formal announcement of the product's availability coincidentally came one day prior to a press release announcing the official launch of cell image-based software and reagent firm Vala Science, the founders of which, Jeffrey Price and Edward Hunter, also founded Q3DM, a biotech start-up that Beckman Coulter acquired in late 2003.

The original template for the IC 100 was Q3DM's EIDAQ high-throughput microscopy system, which, at the time of the Q3DM acquisition, essentially comprised a confocal microscope and an assortment of CCD cameras that enabled an auto-focus feedback loop for fast, automated cellular imaging. Since then, Beckman has transformed the instrument into an imaging "box" about the size of a copy machine.

"It is very nice to see the technology that we developed get disseminated by a company with that kind of global distribution channel," said Price, who besides being the president and CEO of Vala Sciences, also retains a consultancy relationship with Beckman Coulter.

The software for the IC 100, called CytoShop, was also developed by Q3DM scientists, chiefly Hunter. Although it has been tweaked to a small degree so far, Casey Laris, who is a product manager for the IC 100 and former Q3DM employee, told *Inside Bioassays* last week that the biggest changes are yet to come.

"We're spending a lot of effort on software," Laris said. "It's going to be stable from the perspective of user data — we're keeping everything backward-compatible, so there will be no transition cost as we upgrade the pieces.

"Also, we have an automation component coming within the next 30 days that will allow it to integrate with other Beckman automation components," Laris added.

Finally, Laris said that Beckman will be expanding CytoShop's "open plug-in architecture," which will allow researchers to have a choice of developing their own image-analysis algorithms, or relying on those designed by Beckman Coulter.

"We want to understand things on a cell-by-cell basis, and there are some strange-shaped cells out there," Laris said. "We're actively writing new algorithms to measure those, but sometimes pharmaceutical companies don't want it known in general how they do things, and sometimes academics want to play in their sandbox and not wait for companies to build it for them."

Another new feature related to the IC 100 that Beckman Coulter has launched since December is a bead reagent for imaging assays that the company has licensed from an undisclosed vendor.

"That's part of the reason we waited for launch — because we wanted to get reagents for that up and running," Laris said. "We've pushed it through some pretty heavy validation on our systems to make it work a little bit better for imaging."

Laris declined to provide a current list price for the IC 100, but in December, Mark Cheetham, Beckman's North American product manager for cytometry products, said that the list price for the basic instrument is about $260,000. The IC 100 is currently available only in North America, Beckman Coulter said.

— *BB*

SUNY-Buffalo ...

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reflect its response to a variety of perturbations, including excitability, metabolism, apoptosis, necrosis, neurotransmitters, toxins, and cell division and growth.

According to Susan Hua, corresponding author on the paper and an assistant professor of mechanical and aerospace engineering at SUNY-Buffalo, one cellular characteristic that has a particular correlation with cell volume is ion channel activity, which gives the chip potential as a drug-screening tool.

Hua said that a cell typically uses ion channels — including those for calcium, potassium, and sodium — to regulate its volume. Therefore, if scientists can measure minute changes in cell volume, it can be correlated to ion channels opening and closing.

Ion channels, particularly those that regulate changes in cellular calcium levels, are believed to be one of the most important drug targets in pharmaceutical science. Many methods exist to monitor changes in cellular calcium levels, but most of them require fluorescent dyes and optical-based methods to measure them. Perhaps the most well-known example of this is Molecular Devices' FLIPR assay, which is widely regarded as a "go-to" assay for measuring calcium flux.

Researchers have known for a while that cell volume can act as an indicator of ion channel activity, but according to the authors, no one has really devised a simple, straightforward method to measure changes in cell volume, such that it could be a useful tool for drug screening.

"Maybe people have tried to use cell volume to screen cells — we don't know," Hua said. "People have typically used a calcium indicator, but the reason they haven't used cell volume is because they haven't found a convenient way to do so."

The SUNY-Buffalo researchers devised a way to measure cell volume changes by monitoring changes in electrical impedance. The closest thing on the market is Beckman Coulter's Coulter counter. This technology — which was not created as a drug-screening tool — uses electrical impedance to measure the sizes of cells in flow. In addition, simple cell sorters have been used to quantify cell size, but are not robust enough to be used as screening tools.

"I only know of the Coulter counter and scattering from cell sorters as screening tools [using this method]," said Frederick Sachs, a co-author on the paper, and a professor of physiology and biophysics at the SUNY-Buffalo School of Medicine and Biomedical Sciences. "The Coulter counter requires suspended cells and is slow. The cell sorter is not very precise or fast, and doesn't provide kinetic information."

The SUNY-Buffalo researchers believe that their device — which, if commercialized, would be the first of its kind on the market — has three major advantages over fluorescent-based ion-channel assays or Coulter counter assays: It is inexpensive and disposable because the chip is composed of only silicon, electrodes, and a simple glass cover slip; it is completely non-invasive, since nothing needs to be added to the cell to make measurements; and it can be used for adherent cells or cells in suspension.

The experimental chip used by the researchers was fabricated on silicon with a microfluidic channel 15 microns deep and 1.5 millimeters wide, and connected to a fluid inlet and an outlet port. This channel contained two chambers, one the same height as the channel and used to measure cell volume, and the other deeper and used as a calibrating chamber.

Thin-film platinum electrodes in each chamber form a four-point probe for measuring the chamber resistance, the paper states. For adherent cells, the cells were grown on a glass coverslip, and then inverted on top of the measuring chip so the cells faced the chamber. For suspended cells, the cell suspension was simply added to the channels, and measurements were taken when the flow of cells stopped.

An active current source provided a microampere to the two outer electrodes, and the two inner electrodes were measured using a homemade instrumentation amplifier. Then, by adding various test compounds to the microfluidics channels, the researchers were able to detect how they affected cell volume.

"The cell's membrane is not conductive," Hua explained. "And the cells are put in the chamber with conductive saline solution. Since the cell takes up part of the area in the chamber, when it swells or shrinks the conductivity between the two electrodes changes."

The researchers used the chip to detect volume changes in a monolayer of astrocytes responding to an anisotonic stimulus; the sensitivity of suspended *E. coli* strains to antibiotics; and the changes in volume of various cells in response to a natural peptide found in spider venom. All of their measurements were made in 15 to 20 minutes, and the researchers believe that by tweaking certain parameters, it can be done in about five minutes.

The researchers envision the chip being used in high-throughput screening, and have begun to manufacture chips with multiple channels for highly parallel studies, Hua said.

"High-throughput screening would involve parallel sensors with different compounds added to each channel," Sachs added. "The assay would not need other cell-based assays, but later in the screen, more specific assays, such as electrophysiology, would be useful to remove some of the other feedback within the cell. By using hetero-expression systems with overexpression of the target, the volume assay can be made more specific."

Because the chip can be used with bacterial cells as well as mammalian cells, the researchers think that it may also be useful as an environmental biosensor, or in biodefense applications. Hua said that they have already contacted the US Department of Defense to gauge its interest.

A further extension of the chips' ability to measure volume changes in bacterial cells might be on-the-spot clinical antibiotic screening, the researchers said.

Hua said that patent on the chip is pending, and that the researchers are working with the SUNY-Buffalo tech-transfer office to commercialize the chip. She said that several pharmaceutical companies have contacted them about the technology, although she declined to say who they are. According to Hua and Sachs, the group will likely seek to license the technology out, as opposed to spinning off a company from the university.

— *BB*

NCGC's Jim Inglese on Small-Molecule Cell-Based Screening at the NIH

WHEN the NIH founded its Chemical Genomics Center in June of last year, it was entering somewhat uncharted territory — industrial-scale screening of small molecules, *a la* pharmaceutical industry. Where better to pluck staff from than the ranks of the pharmaceutical industry itself? Jim Inglese was one of those hires, and he brought nearly 10 years of small-molecule screening experience at leading drug-discovery and pharmaceutical companies with him. He now serves as director of biomolecular screening and profiling at NCGC, and as such, is responsible for aiding in the organization's infrastructure and staffing its laboratories. Inglese took some time last week to discuss with *Inside Bioassays* the evolution of his career, as well as the evolution of cell-based small-molecule screening.

AT A GLANCE

NAME: Jim Inglese

Director, Biomolecular Screening and Profiling, NIH Chemical Genomics Center (NCGC); Editor-in-Chief, *Assay and Drug Development Technology*

BACKGROUND:

Senior research fellow, Merck Research Laboratories — 1999-2004

Senior research fellow, Pharmacopeia — 1995-1999

Postdoc, Howard Hughes Medical Institute, Duke University — 1989-1994

PhD, organic chemistry, Pennsylvania State University — 1989

BS, chemistry, Rensselaer Polytechnic Institute — 1984

How did you develop an interest in screening small-molecule biomodulators?

When I was younger, I always had a fascination with chemistry, and subsequently this was my major as an undergraduate at Rensselaer Polytechnic Institute. As a senior at RPI, I had taken whatever graduate-level courses in advanced synthetic organic chemistry were available. During this time, Professor Jim Coward, now at the University of Michigan, had given me the opportunity to do an undergraduate thesis project in his lab. The project was to synthesize an analog of MTX, a cancer chemotherapeutic, where a gamma glutamyl hydrogen was replaced by fluorine. This subtle chemical alteration affected the electronic characteristic of MTX's gamma carboxylate, thus altering its ability to be modified by an enzyme in the cell responsible for potentiating some of the toxic side effects of MTX. This began my interest in how molecules interacted with biological systems, and so I initiated my PhD studies in bioorganic chemistry, where I studied both synthetic chemistry and enzymology in the laboratory of Professor Stephen Benkovic at Penn State University. After that I trained as a post-doctoral fellow in Professor Bob Lefkowtiz's lab at Duke, where I developed an understanding of signal transduction and how to use the tools of molecular biology. Still retaining a passion for chemistry, I ventured off to a small Princeton, (NJ)-based biotech called Pharmacopeia where I was able to work directly with chemists making large combinatorial chemical libraries encoding members with rule-of-five properties. I lead a group that was responsible for screening these libraries against targets of interest to the company. It was at Pharmacopeia that I first began screening for small-molecule biomodulators.

Parallel to your career, small-molecule screening itself has seemingly evolved to the point where the NIH is now heavily involved. How did this develop?

Three facts led us here: First, the Human Genome Project has provided an abundance of targets to screen; the current number of human genes is around 25,000. This can be equated to about one million human proteins encoded by the genome, once the gene products undergo post-transcriptional and post-translational modifications; second, the advent of commercial compound suppliers and combinatorial chemistry has provided hundreds of thousands of high-quality compounds to screen; and third, the advances in assay, screening, and robotics technologies have provided the capacity to screen those large numbers of compounds. From NHGRI's perspective, development of small-molecule research tools is critical, because they are able to alter function at the protein level, rather than mRNAs — siRNA, antisense, overexpression — or at the gene and locus level, as with knock-out mice. One of the lessons from human and other genome sequences is that complexity is not conferred by simple gene number, but rather the complexity of gene regulation, splicing, and protein functions — for example, multifunctional proteins, post-translational modifications, *et cetera*. To understand this complexity, research tools that perturb biology at the level of the effector of the phenotype — in other words, the protein — are needed.

The NCGC is expected to be at the cutting edge of small-molecule screening. Last year, it signed a large contract with Kalypsys for its screening technology. What made NCGC settle on this?

We needed very high capacity given our remit to do

screens for the entire research community, and to cover as much of the genome as possible. Kalypsys offered this throughput, precision of liquid handling, miniaturization, and low operating costs.

Obviously there is a lot of non-robotics work done still. What other types of major technologies is NCGC currently exploring?

We are positioning the center to screen assay formats and conduct follow-up studies not suitable for the Kalypsys system. To this end, we have invested in nanoliter liquid-handling technology from Aurora Discovery, which will allow us to generate compound titrations using minimal amounts of compound — again, to keep reagent costs low. To complement our plan to generate concentration response curves for all compounds screened, we have obtained state-of-the-art [GeneData] software for analyzing and visualizing HTS data and large numbers of concentration response curves in a way that will allow us to quickly make decisions on how to proceed with the next step in our biomodulator discovery process. For capturing assay protocol development information we have invested in another package, [Teranode Design Suite], which operates off a model-based paradigm allowing all of our assay optimization data to be stored in a database and retrieved, analyzed, and used for subsequent optimization designs. In my previous environments this data went primarily into lab notebooks or Excel files scattered about a common hard drive with no useful way to mine or search — this is something that I do not want to repeat at the NCGC.

What types of assay or instrumentation technologies are on your wish list — whether they exist or not?

Subcellular imaging to enable phenotypic screening is an area we plan to pursue. Given our interest in exploring the "dark matter" of the genome — that is, the many gene products of unknown function — phenotypic assays present one avenue to study this area. However, I am waiting for the field to mature further before bringing in a microscope-based analyzer. Some of the products I am interested in seeing evolved here include the ability of these systems to make rapid kinetic readings from a stimulus-driven cellular event, such as ion-channel activation. This would require the ability to perform rapid and low-volume liquid additions to the cell population during the image acquisition. Further, the manipulation and data reduction of image files generated from these systems is not optimal, nor are the 1,536-well microtiter plates currently available. To bridge the gap here, we have included a laser-scanning imager [from TTP Labtech] on our robotic platform that will permit population distribution analysis of cells or particles in the well of a microtiter plate. You can think of this as a "static" fluorescence-activated cell sorting instrument. This is in contrast to the population-averaged output one obtains from standard plate readers. Another technology that we would like is ligand- or function-independent assays and detection systems that, for example, might permit detection of small molecule-protein binding or thermal signatures of cellular metabolic or signaling states. Advanced low-volume calorimety technologies are of great interest, too, but have not yet proven feasible to us. We also would like to see primary and mixed cell culture techniques applicable to high-throughput screening, to permit screening in systems that better approximate physiological settings, and to potentially reduce variability in compound behavior due to subtle changes in assay conditions. Perhaps stem cells offer an opportunity here. And lastly, we need robust and flexible analysis tools to analyze multiparameter assay readouts — for example, image-based screens.

How much of what NCGC does is cell-based?

Anywhere from 50 to 70 percent of our assays are expected to be based on a cellular system. Initially, this means reporter gene and population analysis using laser-scanning imaging, which is essentially a means to obtain similar data that one obtains from a FACS analysis.

Doesn't the term "chemical genomics" imply cellular analysis?

Not at all. Though the term chemical genomics is used in many different ways, we use the term to simply describe the use of small molecules as research tools to understand basic biology. This can be done in cell-free systems, cellular reporter systems, cellular phenotypic systems, or even organismal systems — anything that will fit into a multiwell plate. Some use the term "chemical genomics" to describe the study of the effects of small molecules on gene expression genome-wide — for example, by microarray analysis of mRNA from treated cells — this may be what you're thinking of, but it is not how we use the term.

What are some other tangential interests of yours? You started a journal …

Yes, like you, I am interested in journalism. I founded and edit a journal called *Assay and Drug Development Technologies*, to report on integrated advances in science and engineering directed toward drug discovery. Progress in drug discovery and development is limited by a fluctuating gap that exists between science and technology, and I felt that those working in fields such as biology, chemistry, computer science, biophysics, and instrument engineering needed a platform that allowed cross-fertilization within these areas. The journal has been rather successful and appears to be well received.

SEROLOGICALS' UPSTATE UNIT INKS FOUR DRUG-SCREENING AGREEMENTS

Serologicals' Upstate Group last week said it has signed agreements to provide drug-screening services to Array Biopharma and three pharmaceutical companies.

The drug makers will use Upstate's KinaseProfiler service to help them determine the selectivity and specificity of candidate compounds, the company said.

The names of the three drug makers or financial details of the transactions were not disclosed.

Upstate is a wholly owned subsidiary of Serologicals, which acquired the firm in a $205 million cash-and-stock purchase in September 2004.

NOVASITE TO USE ORIGENE'S CDNA COLLECTION

OriGene said last week that Novasite Pharmaceuticals has licensed subscription access to its TrueClone collection of 24,000 full-length human cDNAs, suitable for transfection and high-throughput functional analyses.

"The OriGene TrueClone collection will complement our endogenously expressed receptor cell lines and jumpstart our programs to screen families of GPCRs for allosteric modulators," Juan Ballesteros, chief scientific officer for Novasite, said in a statement.

Financial terms of the deal were not disclosed.

BIOFOCUS LAUNCHES HT ION CHANNEL SCREENING SERVICE

BioFocus, based in Chesterford Research Park, UK, has launched an ion channel screening service, the company said last week at the Screening Europe conference in Geneva, Switzerland.

The service will be based on atomic spectroscopy, and will allow pharmaceutical companies to pre-screen their libraries against defined cell lines, and identify promising compounds to take forward into more time-consuming electrophysiological studies, BioFocus said.

If required, BioFocus can also undertake selectivity profiling against a panel of key indicators, the company said.

CELLULAR GENOMICS HITS MILESTONE IN SERONO KINASE DRUG-DISCOVERY DEAL

Cellular Genomics said last week that it has completed a performance milestone in its joint kinase drug discovery program with Serono.

Under the alliance, Cellular Genomics has been applying its chemical genetics Analog Sensitivity Kinase technology to a number of target kinases selected by Serono.

The milestone relates to the successful development of Chemical Genomics' *in vivo* models for kinase drug discovery, and has entitled the company to an undisclosed performance payment, it said.

CALIPER Q4 NET REVENUES UP 12 PERCENT; LOSS NARROWS 65 PERCENT

Caliper Life Sciences last week reported a 12-percent increase in revenues for its fourth quarter, ending Dec. 31, while its net loss narrowed 65 percent, the company said.

Caliper had total revenues of $24 million for the period, up from $21 million for the same quarter last year. The company's net loss was $7 million, compared to $20 million in the year-ago period. Caliper said it absorbed a $3.6 million non-cash charge in the quarter for closing the second of its three facilities in Mountain View, Calif. The company said it took the charge because of a "low probability of obtaining sublease income" from the facilities.

The company reported R&D costs of $4.7 million, compared to $7.6 million in its fourth quarter of 2003, and cash and cash equivalents of $9.4 million, and short-term marketable securities of $40 million.

Caliper said it expects first-quarter revenues of $17 million to $19 million, and to reach the operating cash-flow breakeven point in the fourth quarter of 2005.

