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JUNE 2008 • VOL. 7, NO. 5

23andMe's **Linda Avey** really wants to know:

'Who Are You?'

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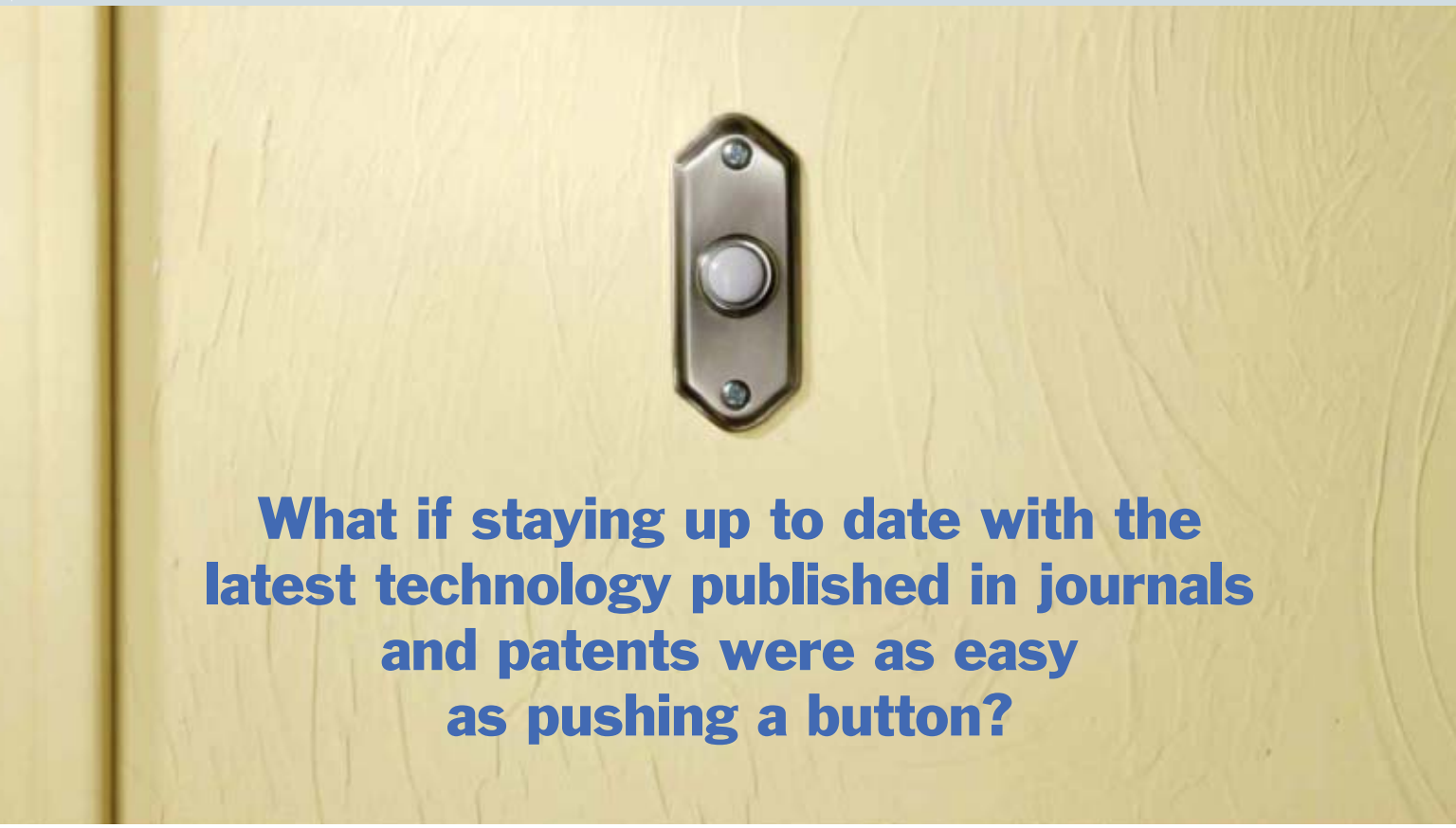

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Will Healthcare IT Trends Standardize?

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Adaptive Designs in the Real World

Despite potential advantages, pharma is taking a cautious approach to adaptive designs, resulting in a slow but sure restyling of the research enterprise. 24

Cover photo by Mark Gabrenya

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First Base

The Buzz at Bio-IT World

KEVIN DAVIES

There was a buzz and energy on the floor at this year's Bio-IT World Conference & Expo that hasn't been in evidence for several years.

So, what else did you expect me to say?! I heard it from lots of people after the show. This year's event, superbly orchestrated by CHI's Cindy Crowninshield and her talented team, gave credence to the notion that the challenges and opportunities in corralling life sciences data are spurring new tools and solutions, and that these three days in Boston are the perfect place to share ideas and innovations.

It was apparent in the scores of people attending a pre-conference workshop organized by BioTeam on next-generation sequencing data management and in the 1,500 people who walked the show floor over two days, taking in 75 exhibitors, including a first-time appearance by Google, and a rich array of new product launches (see p. 14). It was apparent in the increased attendance in five parallel conference tracks (see p. 12), and in the more than 220 guests who attended our Best Practices Awards dinner, surpassing our expectations, and the quality of the entries and winners (see p.next month's issue). Last but not least, it was clear in the enthusiastic and instantaneous response to a plenary panel discussion on personal genomics (see p. 11), which could become a regular event at the show.

MARK GABRENYA

Chris Dagdigian makes his point.

The IT Insider

One of the undisputed highlights of this year's meeting was the presentation by BioTeam's Chris Dagdigian. We first met Dagdigian in 2002, building the data center for an institute at Harvard (See, "Hooking Up Harvard's Genomic Research Center," *Bio•IT World*, July 2002). That meeting led to a productive ongoing affiliation between *Bio•IT World* and BioTeam, our regular "Inside the Box" contributors. "Dags" doesn't write much these days, however—he's too much in demand.

Dagdigian warned the audience that he had 60 slides to deliver in 30 minutes, which did not necessarily bode well. But his sharp, authoritative delivery of IT trends, based on the past year of building data centers and IT infrastructures for a host of academic and industry clients, ranked with anything presented at the show. Ten of Dags' take-home highlights include:

10. In the "CPU Wars," it's "back to benchmarking in 2008." AMD might have had the edge, but "it's more difficult to make the Intel/AMD decision."
9. "Clever cooling" designs include in-row chilling units and sealed data centers, but the most innovative is the overhead cooling design at the Cornell Liebert XDO, in a midtown Manhattan skyscraper.
8. Multicores have "wiped out the small-scale cluster market." The power of medium-sized cluster now resides on a desktop. This represents "a big change in our business… No more small clusters!"
7. Storage vendors are putting too much emphasis on "bells and whistles," instead of speed and scalability.
6. Backups remain the "single biggest nightmare." Storage is easy, but backup is not. Generally avoid tape, but disk-to-disk is fine for some environments.
5. Storage virtualization — jumping on the bandwagon now, but still don't want to pay for it.
4. Grid computing is "more hassle than it's worth."
3. The "terrifying trend" of terabyte-generating instruments. "We now have individual instruments producing multi-terabytes of data… [Do we] put a [Sun] Thumper in the wet lab?!" Small labs will need 40TB storage at a minimum. "The people selling these instruments are not exactly straightforward about the IT requirements!"
2. Data triage—throwing away primary data is anathema to research scientists and will be an adjustment.
1. Cloud computing is "the coolest trend" Dagdigian sees in the field. Amazon's S3 storage cloud, as an example, "is not hype —it's worked out wonderfully!" with easy data movement at reasonable cost. Dagdigian and many of his colleagues are independently using the cloud for various projects.

If you missed this year's show, we invite you to visit www.bio-itworld.com, where we and Cambridge Healthtech Media Group proudly present webcasts (with slides) of all three outstanding keynote talks and the personal genomics panel.

SAVE THE DATE: Next year's Bio-IT World Expo will be held in Boston on April 27-29, 2009.

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MARK GABRENYA

Reynders believes computers are essential to accelerating intuition.

Accelerating Intuition

Reynders IDs the big challenges for informatics.

BY CATHERINE VARMAZIS

BOSTON—Both integration and convergence will have profound implications for informatics and the future of personalized medicine, said John Reynders in his keynote at the Bio-IT World Conference & Expo.

Reynders, VP, CIO at Johnson & Johnson (J&J), said the "insane" amount of data being generated in the life sciences, and its heterogeneity require new ways of working with people. Reynders identified four layers of convergence that are occurring or have yet to happen: converge the data; converge information semantically; converge people; and converge knowledge to lead to reasoning capability.

Converge the Data

The first convergence layer involves the capture, processing, filtering, and management of data. Massive amounts of data create storage challenges that can leave researchers "data-rich but information-poor." Hierarchical approaches to data storage are needed because, "we can't keep all the data all the time." Such approaches involve not just technology solutions but also business models. For example, if you temporarily need a petabyte of storage, do you have the option to lease it? This concept goes by various terms, but "cloud computing" is the latest buzzword. Reynders argued that we must find ways to temporarily store vast amounts of data, mine it, extract what we need, and then "drain the pool" and start over.

Find Meaningful Connections

Data exponentials are growing in two dimensions—size and scale—as well as in terms of heterogeneity, said Reynders. The challenge facing biomedical scientists is how to converge all this data semantically and find meaningful connections between different kinds of data. Traditional means of finding semantic relationship in text data include latent semantic indexing (LSI) and natural language processing (NLP). While useful, Reynders said such tools do not serve the desired purpose, as we're now storing all kinds of data, including text, compounds, and genetic data.

Ontologies are promising platforms for forming semantic relationshipss, he said, but only get you so far. "Not only do we have an immense amount of data, but the data is very heterogeneous."

"Some of the algorithms that are needed for this very heterogeneous data integration, which typically go beyond ontology to a very large graph-type problem, are very relevant to our challenges," he said. "It's not enough that we can navigate in one of these domains because you cannot find those connections if you're only looking at one class of information."

Open Innovation

Reynders' third layer of convergence is that of converging people. "Where is the MySpace for scientists? Or that *in silico* watering hole where clinicians can share their ideas?" he asked. J&J, for example, has built the LINK (Leverage INternal Knowledge) expert locator system to enable collaboration among 14,000 enrollees across far-flung J&J subsidiaries. NineSigma lets seekers post RFPs and solvers bid against them. Your Encore is a space for retired scientists and engineers who want to get back to solving problems. Online IP markets such as yet2.com help innovators who have great ideas navigate all the steps of locking down their IP.

"More and more often, innovation will be coming from outside the organization," he said, "so paying close attention to how these open innovation models are evolving is going to be very critical to all of us."

Reasoning Layer: Accelerate Intuition

It was surprising to hear Reynders assert that one bottleneck in convergence is the human brain. Yet Reynders predicted that doctors and clinicians of the future will need the very best digital reasoning capacity available to help them sort through immense amounts of heterogeneous information to find the needle in the haystack. That reasoning layer will be the final layer, he said. It involves connecting information and forming neural circuitry between concepts that can be traversed by any kind of reasoning platform.

"We can't even start to think about the next layer until this capacity has been formed," Reynders concluded. "This kind of convergence in the future—Ah, it gets exciting." •

Predicting Patient Response

Vertex CEO champions modeling in drug development.

BY ALLISON PROFFITT

BOSTON—Joshua Boger, founder, president and CEO of Vertex Pharmaceuticals, opened the first full day of talks at the 2008 Bio-IT World Conference and Expo with three fascinating vignettes showcasing the use of information technology across commercialization, research, and development. Boger believes that information is being underutilized in a variety of ways, and there is still much opportunity to use information to "be more efficient and more effective in what we do."

In research, Boger emphasized that the best metric of success is "un-coerced adoption." As an example, he cited Vertex' electronic lab notebook (ELN) implementation. The key to successful ELN adoption was bringing in users from the very beginning. "We brought the community together and created a project that was owned by all the users," he said. After four months, across three sites and two continents, Boger said Vertex had 100% adoption.

MARK GABRENYA

Boger see IT's real payoff in drug development; that's where the money is.

Adoption is key for IT in commercialization as well—adoption of health informatics to increase the efficiency of the health care system. He envisioned an informatics-driven environment to help patients life healthier lives.

"You can be in the supermarket and use [a health informatics device] to scan a bar code, the bar code can look up the information on a Doritos package and tell you that, 'No, you idiot, you can't eat Doritos. They're not in your diet plan,'" Boger joked. "Information technology can speak to the whole patient, not just one part of the patient."

The Most Fertile Field

But the real prize, Boger believes, is in development. "A lot of IT effort is spent and has been spent in research," he said. "There's still a lot to do in the analysis of information, the presenting of data, the mining of various experimental databases, human genome, etc. This is all important work. But I would argue that the most fertile field for information technology is actually in development... As Willie Sutton said when he was asked why he robs banks, 'That's where the money is.'"

Boger's most exciting illustration was Vertex' recent work on the Hepatitis C virus (HCV). Hepatitis C infections are often fatal, with current treatment regimens (which typically last a year) less than 50% effective in curing patients. "This is a virus that mutates extremely rapidly, much faster than HIV, which sounds kind of scary," says Boger. Finding a therapy effective on the both the wild type and mutated species of HCV was crucial.

After designing a molecule called Telaprevir that disables one of the proteins essential for viral replication, Boger's team built a systems biology model of hepatitis C dynamics in patients, modeling all of the different species of HCV and adding data from hundreds of patients in the process. That model "consists of something like 1,700 differential equations, runs on a desktop computer, and actually starts to model and predict every single patient response," said Boger.

"The viral object modeling is driving development—continuously being confirmed by flooding more information into the virus model—and continues to drive our cellular design, even making some predictions that help in the regulatory pathway."

The model revealed that the mutant species of the virus were constantly present, and provided an explanation for why the virus would return even when the viral load was undetectable. The model also predicted that if Telaprevir could knock out the wild type of the virus quickly, follow-up with the current drugs could remove the remaining mutant species, successfully curing the disease.

"The model predicted that," said Boger. "The clinical data actually backs it up." But the model predicted more than just a successful treatment. "After 12 weeks with Telaprefir, the direct antiviral, it knocks the wild type down. It's done everything that it's going to do and having it on board in the patient longer than that actually doesn't lead to any advantage," explained Boger. The model suggested that a shorter duration of treatment would suffice; that patients needed less of the drug.

"That's a very controversial prediction... We confirmed it in the clinic to both our satisfaction and to the satisfaction of the FDA, who allowed us to configure out phase III trials with that presumption," Boger said. "We actually saved ourselves the $30 or $40 million, because at that point we believed the model."

"It's very exciting for the patients," said Boger. "This was a case where the virologic modeling started literally on the first day of clinical trials, and has driven and reinforced decision-making through the entire clinical trials process." •

23andWe

Avey proposes a new genomics paradigm.

MARK GABRENYA

Avey sees a bright future for personal genomics and the research it will enable.

BY KEVIN DAVIES

BOSTON—While the celebrity quotient in the audience for the final Bio-IT World Expo keynote might not have matched some of the events Linda Avey has attended in recent months, she didn't seem perturbed. "I feel like you guys are my peeps!" said Avey, co-founder along with Anne Wojcicki (wife of Google's Sergey Brin) of personal genomics phenomenon 23andMe. "This is the group I grew up with."

Avey reviewed 23andMe's web-based, direct-to-consumer genome service and the company's broader mission. 23andMe is about "how can we learn more about each other and about ourselves and build upon this information for yourself." For $999, 23andMe takes an individual's DNA sample and offers information on ancestry and genetic predispositions. A person's maternal lineage can be traced via mitochondrial haplotypes from the maternal lineage, and paternal ancestry via the Y chromosome. Said Avey: "When you go to a bar, the pickup line could change from, 'What's your sign?' to 'What's your haplogroup?'

Avey credited ex-Stanford geneticist Joanna Mountain with doing "a wonderful job of building out all the information in these maps." Avey's own mitochondrial haplogroup is H3, which she shares with about 70 "connections" on the site.

A new feature at 23andMe.com is ancestry painting. Avey showed a genome representation of an anonymous African American male, with chromosome segments colored navy for European ancestry, green for African. The donor was "64% European and only 33% African. One could maybe argue that this is what Barack Obama looks like." Added Avey, "I would have shown you mine, but it's really boring—all solid blue."

Gene Journal

The 23andMe "Gene Journal" provides personalized genetic information on various conditions that can impact a person's health. Initially containing just 14 topics, the list of traits has grown quickly to 60 with new entries added monthly.

Like other personal genomics companies, 23andMe applies a vetting process to validate published gene associations. "People like to paint 23andMe as the more fun and frivolous company, but we very seriously take the science of what are the genetic discoveries coming out of the research community," Avey said.

Avey cited a 2007 gene association on "avoidance of errors", which although published in the prestigious *Science*

The IT in Genetics

Many members of the 23andMe engineering team hail from Ebay, My Space, and the like. For a company that needed everything to happen "in web time," traditional IT and database infrastructures weren't going to work. "We have to show the whole genome," said Avey. "We have to compare one person to many people, all in the time it takes to load a web page."

Rather than put each SNP in a cell in a database, "They put all of our SNPs basically in a bag," Avey said. In addition to traditional MySQL relational databases, 23andMe also uses "a proprietary file system–based genotype storage and custom indexing."

Security is another key concern. "All of the data we have [are] encrypted... even the encryption keys are encrypted, so there's been almost a paranoia within the company." The main genotype data are stored separately from the web analytics. "We're very sensitive that these are real people, and we keep this information very secure and private, even within our own science team."

23andMe's web services use a LAMP stack (Linux, Apache, MySQL and Perl/Python), which Avey liked in part because "it's mostly all free."

magazine, only merited 1 star (out of four) by 23andMe's in-house experts. "We feel like it's almost the responsibility of 23andMe to put the caveats around this study," said Avey. "The study size was probably very small, and it just didn't hit all the criteria we've developed," she said. When she hears customers dismissing an association because it only received a 1-star rating, she says, "that's exactly what we want."

For type 2 diabetes (T2D), 23andMe currently screens nine genes to assess a person's relative risk of the disease (which has a major environmental component), and graphically displays the risk adjustment contributed by each gene. These risks can change depending on the individual's ethnicity. "23andMe really wants to add more diversity to the studies that are being done," said Avey. "Unfortunately, a lot of the work is done in Caucasian populations... We really want to try to change that, and make this applicable to all populations."

Despite the flurry of recent genome associations, Avey cautioned: "We think it's too early for this information that we're sharing with people to take it in to a point where they're doing too many things that are actionable." Said Avey, "It's really, really early for us to be making these big leaps of faith into what are the clinical endpoints for this information." Many more genes will be uncovered for T2D and other common conditions, she predicted.

23 Diseases

23andMe sees huge opportunities in social networking, not just for individuals wishing to share information a la Facebook, MySpace, and YouTube, but, "We're interested in taking this phenomenon and moving it more into the research space. We see this happening in Health 2.0," citing new resources such as PatientsLikeMe and Sermo that nurture networks for patients and doctors alike.

"We're calling the next phenomenon Research 2.0," said Avey. She foresees cancer survivors and adverse event patients sharing information online, looking for people with similar experiences, perhaps displaying badges on their Facebook pages when they contribute to future medical publications. Imagine, "if we can take these data back to the pharmaceutical industry, and say, 'Here's what we're seeing, what are you guys going to do about this?'"

Through all this, Avey said 23andMe intends to retain the perspective of the consumer. "We're really representing them. We're here as caretakers of their data. The data belongs to them, it doesn't belong to us." Part of that goal is to launch a research project called "23 Diseases—areas we intend to do research in. We'll create cohorts, we'll bring people in." The greater mission, said Avey, could be called, "23andWe. Let us know what you'd like to study and we'll get started!" •

MARK GABRENYA

Personalized genomics champions, sceptics. L to R: Linda Avey, Dietrich Stephan, George Church, Jeff Drazen, Fred Ledley, and John Halamka

The Genome Out of the Bottle

Industry pioneers discuss the pros and cons.

BY KEVIN DAVIES

BOSTON—Avey's keynote was followed by a formidable group of personal genomics experts in a plenary panel, including **Dietrich Stephan** (co-founder, Navigenics); **George Church** (Harvard Medical School); **Jeff Drazen** (editor-in-chief, *New England Journal Medicine*); **Fred Ledley** (Bentley College); **John Halamka** (CIO, Harvard Medical School); and **Linda Avey** (23andMe).

Stephan spoke of the looming health care crisis, and the need to maximize individual wellness and focus on prevention. "We refuse to test for quantitative traits, minors who can't give informed consent, family units because of high non-paternity rate, ancestry testing because of blowback." To wait a generation before offering personalized information "would be unconscionable."

Church is both an advisor to 23andMe and co-founder of Knome, which is offering full-genome sequencing to a few well-heeled customers. He's also expanding the Personal Genome Project, looking for 100,000 volunteers. "We're definitely keeping an eye on all of these companies," added Avey. "We're all about the consumer, what they're willing to spend for this information."

Will consumers use this information to change their lifestyle? Drazen recalled an asthma patient with serious cat allergies whose wife noted that she'd been married for 6 months, but she'd had the cats for 10 years. "What they did based on that information is very difficult to know," said Drazen. "There's potential promise but we're a long way from utility... We don't want to come across like we don't care about this... we have to show that it works. I'm from Missouri, show me!"

Halamka is a volunteer in Church's Personal Genome Project, and one of his challenges is to turn medical data into a semantically operable format and make them readable and computable.

Avey struck a conciliatory note on the question of regulation. "We all want to protect consumers," she said, and is talking to FDA, the CDC, and state legislators. 23andMe did not initially seek CLIA certification because, "We don't claim this to be a clinically relevant test yet, it's genetic information, it's not a test... Coming out and saying we were CLIA-certified was going to be disingenuous to our customers." That policy recently changed.

Drazen picked up the theme of a recent commentary in the *New England Journal*, raising concerns about consumer privacy, data security, and the "commercial personal interface." Fifteen years ago, big pharma was considered ethical. "The stakes getting big... I'm basically a futurist, but I want it to help everybody, not just help somebody get rich."

Church, playing devil's advocate, envisioned a ruse in which a synthetic saliva could be combined with whole-genome amplification, and Drazen raised the possibility that insurance companies could collect patient saliva samples and submit them for analysis without consent.

"Having crisp, well-understood privacy policies is really a prerequisite to having bigger and better technology to share data," said Halamka. •

Expo Conference Calls

From predictive modeling to personalized medicine.

BOSTON—Data warehouse architect **David Jordan** of the **Lineberger Comprehensive Cancer Center** at the University of North Carolina, Chapel Hill discussed how to design a bioinformatics data warehouse with Pentaho, which UNC selected to coalesce its tumor data. Despite the $250,000–$300,000 price tag, the project gathered information dispersed in numerous databases, while including separate silos for every tumor. The UNC team developed a "primitive ontology tool" to manage and map differing vocabularies for a uniform database. The prototype launched last fall, focusing on breast and lung clinical data, a tumor registry, and microarray data.

Les Jordan, technology strategist in **Microsoft's** life science unit said Microsoft is keen on jumping into the world of open source with renewed gusto. "We want to play nice in the sandbox," he said. As part of this trajectory, Jordan's team hopes to take data and "move it seamlessly," irrespective of platform. He talked about a life science "eco system," a catchall term for silos of information and single points of integration—including research, development and manufacturing. A major unsolved problem is duplications.

Predictive Science

Marco Ramoni, co-director of bioinformatics, **Harvard-Partners Center for Genetics and Genomics**, presented predictive models developed for assessing disease risks, such as the chance of stroke in patients with sickle cell anemia. Using a Bayesian network, Ramoni's team set up tables based on genotypes to assess such risks, for example, the odds of a stroke within five years. The network scheme was extended to look at the general population, investigating myriad candidate genes. As Ramoni told *Bio•IT World*, "If you use one gene at a time, not all the genes together, you don't get the predictive accuracy that you get by looking at everything together."

Vadim Sapiro, the **J. Craig Venter Institute's** VP for IT, discussed grid computing and related storage capabilities developed to offset IT problems impeding genetic research. The institute's sophisticated grid design includes APIs for less-sophisticated users, as well as standard applications for programmers. One example of their efforts is the workflow for The Institute for Genetic Research (http://tigr-workflow.sourceforge.net), which has pipelines to support discrete processes that can be executed either sequentially or in parallel.

More on the Web

For webcasts of the 2008 Bio-IT World Conference & Expo keynotes and the plenary panel, please visit www.bio-itworld.com/lswebcasts.aspx

Frank Brown, **Accelrys**' CSO, discussed the company's use of scientific business intelligence to drive decisions. He illustrated Accelrys' vision of scientific business intelligence with a pyramid topped by a "wisdom report," followed by "knowledge conclusion," "information results," and "data measurements." The bottom of the pyramid represents the most basic information, but then "as you go up the pyramid, analysis and aggregation are applied to refine the many data points into knowledge."

Semantic Web

Maurice Manning (**Lilly Singapore Centre for Drug Discovery**) described a system of cataloging and integrating information from a variety of sources to allow researchers to perform more powerful searches and gain better access to data. Rather than manually compiling information from the literature, internal data, and publicly-available databases, the center uses what Manning called "semantic integration." This system involves developing an ontology of various terms used in these data sources and exploring the data with software that understands the terms and their relationships. In this way, users can perform complex searches across many databases or browse data on a certain topic. Manning noted that the center's approach to semantic integration was more efficient and simpler than the standard approach.

Elgar Pichler, of Discovery Information at **AstraZeneca R&D** Boston, discussed a "protein thesaurus" that would also use semantic data. The system is open source, which could prevent companies from having to duplicate efforts to create such a thesaurus. Much of the data is extracted from the scientific literature, but Pichler encouraged the audience to support the semantic markup of data. "If you can, put me and other text miners out of business," he said.

Data Visualization

Michael Liebman, senior institute fellow and executive director of the **Windber Research Institute** discussed novel visualization techniques including linear distance plots, which can be used to represent a 3-D protein structure as a scatter plot. Liebman explained that no single view of a 3-D protein representation can show a protein's entire structure, whereas a linear distance plot is not affected by rotation. He also discussed a unique family tree structure that was organized by time rather than generation, so events such as the influenza pandemic of 1918 and the polio vaccine could be included. Finally, he discussed a technology that was originally intended to distinguish live warheads from dummy ones. It is now being repurposed to differentiate cancerous from benign breast masses.

Jean Peccoud, at the **Virginia Bioinformatics Institute** at Virginia Tech, presented GenoCAD, a web-based application for building genetic constructs from a set of pre-made "parts." The program was developed as a proof-of-concept over the past year, and the GenoCAD website says that the technology "will make the computer assisted design and fabrication of genetic systems a reality within a five-year time frame." •

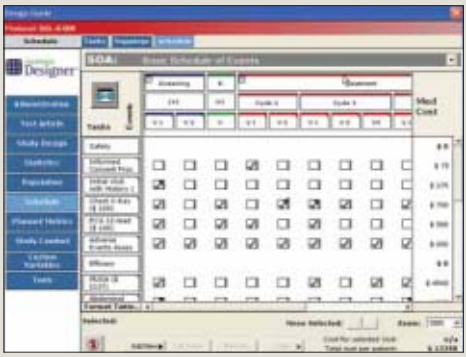
Reported by Laurie Wiegler, Ryan DeBeasi

The 2008 Best of Show competition broke all previous records with 32 new products competing in four categories. The excellent entries spanned electronic notebooks, servers, eClinical technologies, and life science applications. Peruse all the entries to see if you agree with our esteemed judges. **A.P.**

BEST OF SHOW: eClinical

Electronically Linking Disparate Systems

Medidata Designer, an automated clinical protocol authoring tool, was originally designed to provide electronic guidance and management for protocol design, facilitating trial design quality and consistency. Version 2.4 broadened the tool significantly to become the initial step in electronically linking disparate clinical systems by capturing trial elements as complex structured data specifications that could drive setup of downstream eClinicial trial systems. As the first and only CDISC ODM-certified application for protocol authoring, Version 2.4 creates "extensible" clinical documents whose content is captured and structured as an XML data model that can be reused and interpreted by systems such as EDC, data analysis, and submission systems. Designer has been featured as



the front-end technology that initiates downstream propagation of study metadata to create a consistent structure for the entire eClinical trial.

Product: Medidata Designer
Company: Medidata
Available: Now
For More Information: www.mdsol.com

Collaborative Controlled Programming

Waban Statistical Computing Environment (Waban SCE) is a modular system based on Waban Software's proprietary metadata driven clinical data repository (Waban CDR). Waban CDR/SCE provides a controlled and integrated Clinical Data Repository /Statistical Computing Environment that facilitates data management, statistical programming, analyses, and reporting in compliance with 21 CFR Part 11 regulatory guidelines. The system provides a common platform that supports CDISC standards such as SDTM and ADaM and supports creating submission-ready Define.xml or Define.pdf for inclusion in an eCTD electronic submission.

Product: Statistical Computing Environment
Company: Waban Software
Available: Now
For More Information: www.wabansoftware.com

Semantic Architecture for Visualization

CoMotion Trials is visual decision support software that allows dynamic collaborative visualization of integrated clinical trial data. This highly configurable application combines business intelligence with state-of-the-art visualization capabilities. Data from flat files, databases, and data warehouses are mapped via XML into a unique data repository whose architecture is designed for on-demand, low-bandwidth access and real-time collaboration. A semantic information architecture ties metadata concepts together, allowing previously unrelated concepts to be linked and combined in visualizations.

Product: CoMotion Trials
Company: Viz General Dynamics C4 Systems
Available: Now
For More Information: www.gdviz.com

DATATRAK's eClinical 5.0 utilizes three-tier distributed client/server architecture. Partitioning the application enables rapid design and development of the system. Multi-tier architecture also makes it simpler to scale the system across multiple processors on different machines, ensuring numerous users can access the system without affecting performance.

More Information: www.datatrak.net

The InforSense Translational Research Solution (TRS) provides a powerful and flexible framework to integrate and analyze clinical, patient specimen, and experimental data for translational research. The solution enables different user groups to integrate data and construct analysis workflows that can then be deployed to a wider scientific audience.

More Information: www.inforsense.com/solutions/translational_research

Phase Forward's Central Designer is a stand-alone study design environment that helps life sciences companies streamline the trial design process and reduce the time it takes to deploy a study to electronic data capture (EDC).

More Information: www.phaseforward.com

BEST OF SHOW: IT Infrastructure

Pay-As-You-Grow Storage

By combining Isilon's OneFS operating system software with the latest advances in industry-standard hardware, Isilon delivers modular, pay-as-you-grow, enterprise-class clustered storage systems that deliver unprecedented storage scalability and performance, and dramatically reduce the cost and complexity of managing storage growth—empowering enterprises to achieve unprecedented levels of innovation and business agility. Isilon's X-Series clustered storage systems deliver the industry's first and only storage system to scale to greater than 1.6 Petabytes of capacity and provide performance of 10 Gigabytes per second in a single file system and single volume—achieving

100X the scalability and 20X the performance of traditional SAN and NAS storage systems.

Product: X-Series Clustered Storage
Company: Isilon
Available: Now
For More Information: www.isilon.com

Maximize the Utility of Your Information

SciTegic Enterprise Server (SES) is a powerful data processing platform that streamlines the integration and analysis of vast quantities of information. SES and its graphical client, SciTegic Pipeline Pilot (SPP), help you maximize the utility of your information resources through enterprise-scale data flow control and powerful mining capabilities. Additionally, using the same graphical interface, SES can be used to create and execute multi-step, short-running web applications, allowing users to parameterize data processing routines through simple, customized interfaces. SES is the successor to the Pipeline Pilot platform, and is specifically designed to meet critical requirements of the research informatics professional: an agile development environment, fast and secure deployment, minimal maintenance costs, and application extensibility.

Product: SciTegic Enterprise Server v 7.0
Company: Accelrys
Available: Now
For More Information: http://accelrys.com/products/scitegic

Scalability, Speed, and Ease of Management

Univa's Grid MP is the leading product for building distributed computing environments from non-dedicated resources to deliver increased high-performance computing (HPC) power. With production installations at hundreds of customers including 9 of the top 10 Global Pharmas, Grid MP reduces costs and improves productivity by harnessing unused compute cycles to create desktop compute grids. No other commercial technology is engineered to operate across thousands of disparate, globally-dispersed devices. Grid MP's proven scalability, speed of application enablement, and ease of management are among the top features cited by satisfied customers worldwide.

Product: Grid MP 5.5
Company: Univa UD
Available: Now
For More Information: wwwunivaud.com

The Netezza Performance Server (NPS) family of enterprise-class streaming analytic appliances is designed specifically for high-performance, terascale analytics. The NPS system architecturally integrates relational database, server and storage in one compact, power-efficient unit.

More Information:
www.netezza.com

Tom Sawyer Perspectives facilitates rapid application development in a graphical environment. Perspectives is designed to reduce the time required to develop visualization applications while helping users discover new patterns, unknown relationships, and hidden dependencies in your data.

More Information:
www.tomsawyer.com/tsp/tsp.java.php

AMD's Quad-Core AMD Opteron processors provide extraordinary performance and efficiency in a consistent thermal envelope, thanks to a native core design. The product provides a seamless transition to quad-core computing from AMD's Dual-Core AMD Opteron (DDR2) processors.

More Information:
www.amd.com/quadcore

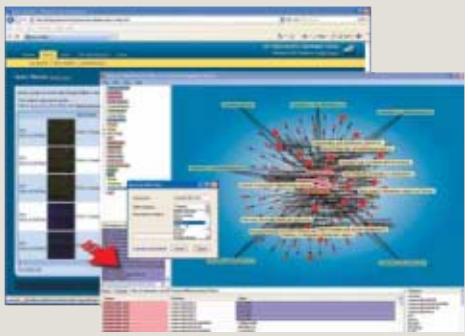
The Dell Latitude Tablet XT is the thinnest and one of the lightest 12.1-inch convertible tablets available. It is also the brightest in its category with an optional 400 nit daylight viewing panel. It is the industry's only sub-four-pound convertible tablet with pen and capacitive touch capability.

More Information:
www.dell.com/lifesciences

BEST OF SHOW: Life Science Informatics Platforms

Desktop Ontology Management

The Sentient Suite of software integrates data, applications, databases, and instruments into one secure and compliant interoperable environment. The Sentient Knowledge Explorer module, released in February, is a desktop application for ontology management, semantic data integration and knowledge visualisation. It includes a proprietary RDF-based Knowledge Base, tools for Cross-Ontology Mapping and for mapping of data to ontologies, SPARQL Query, an integrated Thesaurus Manager for data classes and relationships and other features, such as network complexity reduction tools and the ability to handle and merge data from different semantic standards from files or directly via URIs into a common ontology.



Product: Sentient Suite of Software, Knowledge Explorer
Company: IO Informatics
Available: Now
For More Information: www.io-informatics.com

The Biologist's ELN

Collaborative Electronic Research Framework (CERF) is a lab notebook designed by biologists for biologists. CERF 2.7.1 addresses feedback from over 30 commercial installations and focuses on the user experience and increased flexibility and interactivity. The update adds the new Science Desktop suite of integrated applications that includes a Semantic Spreadsheet application, Bibliography Management, Semantic Image Annotation tool, and the Automation Client for data collection and management services.

Product: CERF v 2.7.1
Company: Rescentris
Available: Now
For More Information: www.rescentris.com

Wireless Inventory

Progeny LIMS is a sample inventory management software capable of tracking any type of sample. Support is included for both 1-D and 2-D barcodes as well as wireless handheld devices. A full chain of custody is available within the software to determine any action taken on a single sample. The database included with this product is completely customizable, and custom workflows are supported. Built-in security allows users to control access to specific samples, as well as read and write access to data fields on samples. Every action performed on a sample by a user is auditable.

Product: Progeny LIMS
Company: Progeny Software
Available: Now
For More Information: www.progenygenetics.com

Genomics Lab System

Geneus is a genomics lab and data management system that integrates clinical data from hospital information management systems, electronic medical records, and clinical trial systems; manages specimens through DNA and RNA extraction protocols; provides robotics and instrument integration and automation; and pipelines data into sophisticated algorithms for knowledge discovery. Geneus is built on the Omix platform.

Product: Geneus
Company: GenoLogics
Available: Now
For more information: www.genologics.com

Core LIMS is a web-based, customizable LIMS available via 3 modes of delivery to match user requirements and budget including: LIMS Appliances, LIMS Hosting, and Enterprise LIMS.
More Information: www.coreLIMS.com

GenomeQuest is a web-based, sequence informatics platform for managing and mining sequence data. Users can exploit genomic information resources including the DrugBank Pro database.
More Information: www.genomequest.com

The Infosys Technologies Scientist WorkBench is an architectural approach, based on SOA and web services that addresses needs in biomarker based identification, structure based drug design, and other areas.
More Information: www.infosys.com

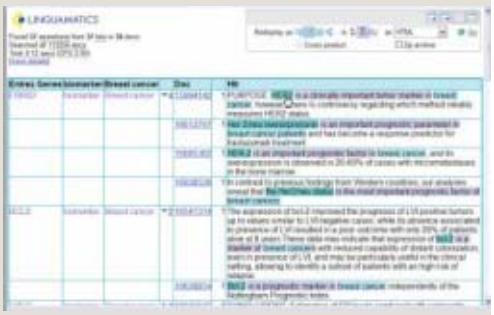
eNovator from KineMatik is web-based solution combining an electronic lab notebook, project and program management, quality management system, and a training management system.
More Information: www.kinematik.com

Symyx Notebook is a single, enterprise electronic lab notebook that replaces discipline-specific notebooks and consolidates experimental data from multiple disciplines.
More Information: www.symyx.com

CLC bio's Enterprise Suite is a fully integrated 3-tier client/server/database solution, merged into one single bioinformatics platform.
More Information: www.clcbio.com

BEST OF SHOW: Life Science Informatics Applications

Language-Based Search



I2E v 3.0 provides a high performance natural language processing (NLP)-based knowledge discovery platform that rapidly reveals high quality, facts and relationships from text. I2E combines four key capabilities: agile NLP-based querying; search engine approach; intuitive reporting; and domain knowledge plug-in. I2E features a client-server architecture built using industry-standard Java and C for use by single users, project teams, and in enterprise-wide deployments. Organizations control source content, definition of queries, and results output.

Product: I2E v 3.0
Company: Linguamatics
Available: Now
For more information: www.linguamatics.com

Playstation Algorithm

eHiTS Lightning is the first life sciences application delivered on the very powerful, yet inexpensive PS3 Playstation. eHiTS delivers a docking algorithm which performs an exhaustive, systematic, flexible docking pose search. The algorithm enumerates all feasible docking poses that are sufficiently different from each other and match both steric and chemical feature complementarity constraints. The algorithm divides the 3D structure of the ligand into rigid fragments and flexible chains and docks the rigid fragments independently into the receptor site. A novel graph matching algorithm rapidly enumerates all compatible fragment pose combinations.

Product: eHiTS Lightning
Company: SimBioSys
Available: Now
For more information: www.bimbiosys.ca

Next-Gen Sequencing on the Desktop

SeqMan Genome Assembler (SMGA) sequence analysis software permits users to assemble and work with multiple next-generation sequencing platforms on a desktop computer. The software can assemble data obtained from 454 and Illumina along with traditional Sanger data. Templated or de novo assemblies of up to 12 Mb in size can be performed on either Windows (XP or Vista) or Mac (OS X 10.4 or Leopard) systems. Minimums requirements are a 64-bit processor, 1.5 GB RAM, and 3 GB available hard drive space. Additional RAM and storage capability on a computer permits users to work with larger projects faster. SeqMan Genome Assembler can be used on either Windows or Mac operating systems.

Product: SeqMan Genome Assembler
Company: DNASTAR
Available: Now
For more information: www.dnastar.com

CLC bio's CLC Genomics Workbench includes high performance computing accelerated assembly of next-gen sequencing data, and support for a number of downstream analyses and work-tasks, such as reference assembly of genomes, de novo assembly of genomes, and SNP detection using advanced statistical models.
More information: www.clcbio.com

The BioTeam's WIKILims is a system for integration of next-generation sequencer (and other equipment) data into a wiki-based database. It is a user friendly, scalable database that doesn't require up front schema design and can be accessed via APIs. Automatic version control adapts well to continuously evolving requirements
More information: www.bioteam.net

ChemNavigator's iResearch Library tracks over 46.7 million chemical products ranging from drug-like compounds for testing in molecular screening to synthetic building blocks for use in chemical synthesis. Customers can purchase existing chemical samples for testing and identify new sources of chemistry.
More information: www.chemnavigator.com

GeneGo's MetaRodent is based on a manually-curated database of mouse and rat-specific biological interactions. It enables direct comparison of disease states and drug action in humans and rodents, facilitating the appropriate interpretation of experimental data for potential pharmacological and toxicological effects in man.
More information: www.genego.com

The Google Search Appliance provides universal search for life sciences organizations, which provides the ability to search all enterprise content including intranets, file shares, databases, real-time business data, and content management systems through one simple search box.
More information: www.google.com/enterprise/gsa/index/html

LabVantage's Sapphire BioBanking Solution with Integrative Analytics equips organizations with a comprehensive solution for enterprise operational workflow and data management; global data access and visualization; analytics-driven decision support; and laboratory informatics backbone.
More information: www.labvantage.com

Now and Future Sequencing Stories

Companies unveil next gen sequencers and data.

BY KEVIN DAVIES

SAN DIEGO—At the latest CHI next-generation sequencing meeting*, the focus was split between the ever-improving performance of current next-gen platforms, and the prospects for the future.

Patrice Milos, Helicos Biosciences' CSO opened the meeting by noting that the company's recent paper in *Science*—on the single-molecule sequencing of the M13 virus—was "proof of principle" work using old chemistry that was actually completed 18 months ago. The latest technology boasts the addition of reversible terminators and improved template density to one molecule per square micron. Moreover, a new strategy is being developed to extend the sequence reads using a "controlled dark fill" of unlabeled nucleotides, then extending the sequence for another 24 "quads." This technique could enable paired reads for larger DNA fragments up to 8-10 kilobases.

Abizar Lakdawalla (**Illumina** senior product manager) surprised some in the audience by informing them that their current Genome Analyzers (GAs) were now designated "classic," with new upgrades being designated GAII. Subsequently, representatives from genome sequencing centers at Baylor; the Broad, Venter, and Joint Genome Institutes; and Washington University in St. Louis, all said they were upgrading to GAIIs. The GAII can generate 3 Gigabases using paired-end reads, with individual read lengths poised to increase from 35 to 50 bp. By this summer, Lakdawalla said that base calling with be done in real time.

The daily output of the GAII is 750 million bases, with 80% of the individual reads having no errors. The GA is being applied to many applications, including the "killer app" of epigenomics. Lakdawalla also said that Illumina's "$100,000 genome" HapMap sample, performed by David Bentley's U.K. group in six weeks last Christmas, consisted of 27 runs and 70 gigabases (GB) of data. Since then, an additional 48 GB has been generated from 13 more runs. "The data will be in the public domain very soon," he said. Lakdawalla noted that some 250 GA systems have been installed so far, but significantly, it's the smaller non-genome centers driving much of the demand.

Todd Arnold (**Roche 454** director molecular biology) also revealed platform enhancements to the GS FLX arriving later this year. The GS FLX "Next-Gen" will boost sequence output fivefold (to 500 Mb/day) and increase individual read lengths up to about 400 bases. Technical enhancements include increased microwell density, reduced chemical crosstalk/background, and new paired-end strategies.

User Issues

Representatives from five leading genome centers shared their experiences on the next-gene pipeline and workflow front. At **Baylor College of Medicine**, **Donna Muszny** said the institute is running ten GS FLX instruments, producing 42 GB/month. There are also two Illumina GAs, and two SOLiDs (Applied Bio later announced they were shipping another six instruments to Baylor). Muszny said there were of course technical problems—blocked valves, leaky connectors, and some software issues, solved by moving the analysis offline. While 454 remains the workhorse for high-quality draft genome assemblies, it is supplemented by Sanger, Illumina, and SOLiD data.

Andrew Barry noted that the **Broad Institute** was taking delivery of its first Polonator (See, "PacBio Sparks Florida Fireworks," *Bio•IT World*, March 2008). "Spring has sprung in Boston, and members are very anxious to polonate," he joked, though he later admitted, seeing as the institute has 20 GA instruments, that it was a kind of "toy for technology development." At the **Joint Genome Institute**, **Daniel Rohksar** relies on two GS FLX machines and a pair of Illumina GAs for mostly microbial and plant genome sequencing. The highly repetitive nature of genomes, such as maize, puts a premium on read length for plant genetic analysis.

At **Washington University**, **Vincent Magrini** and colleagues use a dozen Illumina GAs, five 454s, and 1 SOLiD (with more en route). His team has estimated the cost of human genome assemblies using various platforms, but despite recent five-figure claims, still produces

Will single-molecule sequencing systems eventually replace the original next-gen platforms from the likes of 454 and Illumina?

"I don't think the single molecule is the Holy Grail, I think the $1000 genome is the Holy Grail! If the single molecule gets you there, great, if it doesn't, there are other ways forward potentially... We started off as a single molecule company [Solexa] way before. It's kind of a safety in numbers issue for us. If you have many copies of a molecule, your data quality improves substantially. There's no penalty in time per se. The big benefit of the single molecule [approach] is you save the time for the amplification process. Our cluster prep takes around five hours, so you're not saving a lot of time doing a single molecule, but you get all the benefits of a statistical average [in our approach], and the cost of reagents goes down, because you don't need super high purity reagents... There might be breakthroughs in the future which hopefully the phenomenal Illumina engineers will be solving. But right now, I think we're pretty comfortable with what we have."

Abizar Lakdawalla, Illumina

*CHI's Next Generation Sequencing Case Studies and Applications; San Diego, April 23-24, 2008.

GINA Passes Both Houses

AMERICAN SOCIETY OF HUMAN GENETICS

GINA panelists (L to R: Rep. Robert Andrews (D-NJ); Rep. Louise Slaughter (D-NY); Sen. Edward Kennedy (D-Mass.); Dr. Francis Collins (NHGRI/NIH); Rep. Judy Biggert (R-IL); Rep. Anna Eschoo (D-Calif.)) discussed the genetic information nondiscrimination act's importance in a press conference after it passed in both the House (414-1) and the Senate (95-0).

figures in the $280-600,000 range. **Applied Bio**, meanwhile, claimed to have internal results producing 17 GB mappable sequence on its SOLiD 2.0 systems, which launched last month. Beta testers have reportedly achieved similar outputs.

Future Technologies and Applications

While **Stephen Turner** (CSO, **Pacific Biosciences**) presented stunning early data on the zero-mode waveguide platform that he predicts will produce the 15-minute human genome in five years (See, "PacBio Sparks Florida Fireworks," *Bio•IT World*, March 2008), there was also considerable interest in the presentation from **William Glover**, president of **ZS Genetics**. Using transmission electron microscopy, Glover can visualize single linearized molecules of DNA, in a process he likened to "untangling spaghetti." Whereas natural DNA is invisible under transmission electron microscopy, heavy atoms (such as iodine and bromine) can be substituted in each base to render DNA strands visible and provide reads that could potentially run to 5 kilobases or more. Some of Glover's photographic data did, he admitted, resemble the tire tracks of a lunar lander, but it was possible to be persuaded that he was presenting stretched out ladders of DNA.

Many impressive applications were presented, including **Roger Maslen** (**Venter Institute**) discussing single-cell DNA sequencing. **Steve Kingsmore** (**NCGR**) presented mutation data on mesothelioma patients, and digital gene expression studies on schizophrenia, in collaboration with **Gary Schroth**'s group at **Illumina**. These studies have identified candidate genes that are differentially expressed in patients that were not picked up using Affymetrix chips. In some cases, these genes show association and/or gene variants correlating with the disease.

Nicholas Schork (**Scripps Genomic Medicine**) discussed the "GWAS (genome-wide association studies) craze," which he said has limitations. His group is exploring GWAS strategies at the DNA sequencing level, although he admits it would be computationally demanding. (A one-hour sequence-level GWAS study in humans would need 10-8 processors!) Schork also said the Cancer Genome Atlas project "is destined for failure" unless a suitable pipeline to make sense of the data is put in place.

Also in San Diego were representatives from several interested parties, including Complete Genomics, Invitrogen, and Oxford NanoLabs, some of whom might have something to present by the time of CHI's next next-generation meeting, this September in Providence, RI. •

HP ACQUISITION

HP will acquire **EDS** for approximately $13.9 billion, or $25 per share. The transaction is expected to close in the second half of calendar year 2008 and to more than double HP's services revenue. HP intends to establish a new business group, to be branded EDS—an HP company, which will be headquartered at EDS's existing offices in Texas.

TB GRANT

The **Texas A&M Health Science Center Research Foundation** received a Bill & Melinda Gates Foundation grant to study more effective treatments for tuberculosis. **Caliper**'s IVIS Spectrum imaging solution has been chosen to facilitate the research.

NONCODING RNA ACTIVITY

Invitrogen, using RNA samples from **BioServe**, identified noncoding RNAs that were differentially expressed in healthy and diseased tissues. miRNAs were found to be either up or down regulated in tumor versus healthy tissue. The findings were validated with quantitative PCR.

SUPERCOMPUTING AGREEMENT

Intel and **Cray** have joined forces to dramatically advance the state of supercomputing. The two companies signed a comprehensive multi-year agreement to advance high-performance computing using Intel processors, Cray server systems, and new technologies in the future.

CLONE VALIDATION

Sigma-Aldrich has joined phase two of the **RNAi Consortium** to validate clones from Sigma-Aldrich's MISSION shRNA library. The validated clones will be available to Sigma-Aldrich customers. The Consortium, led by the **Broad Institute**, hopes to eventually include 300,000 precloned lentiviral-based shRNA vector constructs targeting the human and mouse genomes.

Computational Biology

GNS: From SNPs to Outcomes

Colin Hill is gunning to turn raw data into key SNP discoveries.

Personal and consumer genomics are boiling right now. Yet sifting through the data flood and connecting the dots in ways that accurately predict single nucleotide polymorphisms (SNPs)-to-outcomes remains a huge challenge. Gene Network Sciences CEO Colin Hill says flatly, "GNS is gunning to be the first group that really breaks this open, by having a scalable, supercomputer-driven automated platform that can turn that raw data into discoveries of the key SNPs driving the outcomes."

To hit that target, GNS is pushing ahead (See, "GNS Charts Unknown Biology," Bio•IT World, October 2006). Hill recently hired Boston University biosimulation pioneer James Collins, as chief science officer. GNS has also expanded its reverse-engineering/forward simulation platform to accommodate DNA sequence data, in addition to traditional molecular data. Hill says the company doesn't need more money, partners, or computational power simply to put the platform to work to prove its power.

Bio•IT World *executive editor John Russell spoke with Hill about GNS' progress and its ambitious plans.*

MARK GABRENYA

Bio•IT World: How is GNS different today than it was a year and a half ago?

Hill: The technology's become a lot more robust, more scalable. We've gone through rewrites of the code to make it more robust. It's the same platform—reverse engineering, forward simulations is the core technology of the company—but it's become faster, stronger. There are a greater number of interaction forms, which are really the building blocks that describe interactions between components, between drugs and genes, between genes and other genes, between proteins and outcomes, clinical variables.

Is GNS attacking different questions than before?

A key focus area for the company is going from "SNPs to outcomes." We weren't as focused on DNA sequence information [before]. We hired somebody who's driving that effort. We're also driving a lot of our own discovery and we've found some partnerships with academic groups such as the Moffitt Cancer Center in Florida and the Weill Cornell Medical School in New York. That's enabling us to go after some of our own discoveries in addition to the big pharma and biotech collaborations.

But this SNP-to-outcome problem is a really big one. With all the progress that groups like Steve Turner's company [Pacific Biosciences] is making and other groups like deCODE or 23andMe, the data [are] going to be there. We have a lot of information on the variations that make us all different and determine our disease progression and response to therapeutics. But we have a big problem determining which of the three million genetic variations are causative of the outcomes. That's a very difficult computational problem that nobody has solved...

Can you build causal relationships from SNP data *a priori* without reference to the literature?

Yes—under certain conditions, depending on the information you have about inheritance and other information such as gene expression together with genomic variation and outcomes. Eric Schadt leads a group at Merck [Rosetta], and they've been gunning for this problem for some time and have certainly made some breakthroughs related to metabolic disease. GNS is gunning to be the first group that really breaks this open, by having a scalable, supercomputer-driven automated platform that can turn that raw data into discoveries of the key SNPs driving the outcomes.

Are you trying to fund platform development through R&D collaborations, while the real goal is to generate, capture, and commercialize biological IP?

You're mainly right. We're not planning to become a drug company. We understand where our expertise is. We think we're the best in the world at data-driven computation in this sphere. We have no desire to try to bring on capabilities that are well outside of that, [such as] medicinal chemistry...

Everybody agrees the drug discovery industry has to change. Pharma's in the toilet with Wall Street and everybody's calling for gloom and doom and such. Everyone agrees there needs to be new tools to advance the state of the art. The pharma companies know this better than

anybody. However, companies that have breakthrough technologies still have a hard time commercializing those technologies and capturing some of the upside from them. From an investor's point of view a lot of these platform companies have not performed well...

Are systems biology companies naïve to think they are going to change the drug game in a significant way in a five year window?

No. I don't think so. I honestly think it's the technology. I think many of the approaches that dominated the early days of systems biology were off the mark. People will look back some years from now and say those approaches couldn't have worked. There was too much unknown about biology, it was too complex, and there wasn't enough data. I'm referring to approaches based on literature as the starting point, whether it's assembling that information together into databases so you can visualize your molecular profiling data in this context or it's doing the simulation models based on literature information. I think those approaches have inherent limitations.

I've said to many people that for a number of years GNS was misguided. [Our] approach of trying to model all of the known pathways involving cancer cell biology had its merits, certainly as an academic effort, and had some use in the commercial setting, but I think it was limited.

We first need to discover what are the key molecules driving disease progression. We have to discover what the key molecules are driving drug response, both from efficacy and the safety perspective. There's been some recent papers from the Cancer Genome Anatomy Project and [Bert] Vogelstein's group at Johns Hopkins showing a huge amount of heterogeneity in human tumors: lung cancer, breast cancer. Assuming we believe those results, this is telling us that something is misguided about the view that there is this canonical uber-model that controls disease progression and is going to be common to everybody.

If that's true, what does it mean for the GNS value proposition?

... The value proposition for our partners, whether pharma partners or academic clinics, is we now have the tool. It scales with the power of IBM's largest supercomputers that allows us to take in data from a variety of sources, heterogeneous data, and actually discover the causal regulatory models connecting either genetic perturbation or drug perturbation to the molecular entities, be they genes or proteins or metabolites, and the clinical outcomes that they're driving.

Is most of GNS's current work in discovery or the comparison of compounds?

That's a very good question. I want to say it's about half and half; there is a good mix at this point and across a variety of data types. Like I said, we're doing our first set of projects in genomics being sequence versus molecular profiling. The team is now operating at a different level of test in terms of the number of projects they can execute on simultaneously. It's putting the platform we've been investing in to the test.

This is what we were practicing for and developing and investing in for all these years and we're starting to see it really pay off. I mean the scalability of this approach goes well beyond whatever you can do manually. Part of the beauty of this approach is it is automated. You have to do some statistical analysis of the data ahead of time. You have to understand the experimental design. Often we work with a collaborator to design the experiments in the first place. But once the data is in the right form, the process of reverse engineering the models and then doing the simulations to discover the key molecules driving outcomes, that part's pretty fast.

More Online
For the full transcript, visit www.bio-itworld.com.

Is biopharma more or less enthusiastic about this approach today?

More enthusiastic, but it's a sober enthusiasm. It's more specific about solving problems. For example, combo therapies in cancer. This is something that a lot of companies need to solve. They can't run enough clinical trials to explore all the combinations with standard of care therapies with their new targeted cancer drug. So here's an area where this kind of approach has a clear win, from single drugs applied at multiple doses in your biological system. We have a platform that can combine those drugs in two-way combinations or three-way combinations and determine the most synergistic combinations and the dose ratios needed to get to those results.

Who are some big commercial collaborators?

I can cite Pfizer and CombinatoRx. The academic partners are also important and are becoming more commercially focused these days, that's clear. You see more and more partnerships between big pharma and these groups... The big focuses, in terms of our internal discovery, are oncology, naturally, metabolic disease, meaning diabetes, Types I and II, and Alzheimer's.

Milestones for the next 12 to 18 months?

SNPs-to-outcomes across a few different therapeutic areas—that's what we're gunning for, really being able to relate SNPs to change and changes to outcomes. Essentially be able to do in an automated fashion in weeks or months what Eric Schadt at the Rosetta/Merck group did over the course of a couple years. Number two is combo therapies and oncology, to be the first to take a single drug, multiple dose, data sets and explore very quickly billions and trillions of drug and dose combinations of cancer drugs and discover the most efficacious combinations and the corresponding markers that indicate the patients that will have the strongest response.

That's all I care about. We are doubled down on our investments in technology. We are out there buying up data, partnering to get data, and the things that were clear bottlenecks to GNS a year and a half ago, two years ago, they're not there anymore. Could we do more with more money? Absolutely. We'd love to blow this out in a bigger way and I think the issue I'll be dealing with over the next year, 18 months, will be when is the time to possibly pull the trigger and accelerate. It's a bet. If we're right—and this is the way forward—this will yield discoveries at a pace and a scale that have never been seen before. •

Computational Development

A Virtual Pharma Organization

With private funding and Duke's help, Roses focuses on discovery and development.

2006 FILE PHOTO/MARK GABRENYA

Last year, Allen Roses left his position as senior vice president, pharmacogenetics, at GlaxoSmithKline to return to Duke University Medical Center, where he is director of the Duke Drug Discovery Institute (and Jefferson-Pilot Professor of Neurobiology and Genetics and a member of the Duke Institute for Genome Sciences and Policy). Ricki Lewis caught up with Roses, who keynoted Bio-IT World Expo in 2006 (See, "Personalized Medicine's Rosy Picture," Bio•IT World, May 2006), to review pharma's approach to genome-wide screening, his new freedoms back in academia, and the latest on pharmacogenomics and Alzheimer's research.

Bio•IT World: How is the pharmaceutical industry using genome-wide association studies (GWAS)?

Roses: Genome wide screening for pharma will be most important in confirming candidate gene variants that differentiate patients with efficacy, using the particular end-points of the clinical trial. This is most important at the critical proof-of-concept (POC) step. Let's say a molecule has made it through preclinical safety and first time in humans. The first efficacy indication would come from a small Phase IIA trial, then a larger Phase IIB proof of efficacy trial. During these smaller trials, an extensive list of polymorphisms from candidate genes, immunological genes and HLA antigens would be tested for possible associations. At this early stage, genome wide screening—and correction for the number of tests performed—would not be productive. The candidate list is small and more focused. The efficacy PGX experiment is designed to compare patients who met the proposed clinical endpoints against patients who did not. In this way early hypotheses could be incorporated into Phase III registration studies and, if re-confirmed, provide more information for targeting therapy.

How do genome-wide scans compare with a candidate gene approach?

Genome wide screening may be particularly useful early for identifying safety signals. We've initiated side-effect or adverse event (AE) experiments with candidate gene panels. We were able to show, in several clinical trial programs, that genome wide methods can later be helpful to confirm candidate genes and to recognize regions of the genome where additional candidate genes associated with AEs might lie. This takes at least 15 to 30 individuals who had experienced the AE. Genome-wide screens are better used to confirm candidate gene associations, or in a hypothesis-generating mode, or if nothing comes up with a particular candidate gene screen. This is also useful for drug surveillance, but the process of surveillance should actually start during development clinical trials.

Should GWAS be built into clinical trials prospectively, or analyzed retrospectively?

It is important that the data supporting a hypothesis are built into the clinical protocol for a predictive test. By funding the association with an AE, or with efficacy during a trial, regulators classify studies as "exploratory of hypothesis generating" versus hypothesis testing. The latter is preferred, so that the "generating" experiment can also be used for registration instead of mandating another repeat study. As development continues, each successive clinical trial can be used to confirm positive signals and sequentially eliminate false positive signals.

GWAS is most important in generating associated variants for use as a companion diagnostic. The experiments must be performed during development from a company's point of view. It can make the difference between a targeted therapy versus a borderline or negative efficacy result when only a few patients get excellent responses. Companion diagnostics should be timed with registration by the FDA, so that targeted therapy differentiation can be considered for pricing and, more importantly, reimbursement.

How did the situation with Iressa, which FDA cleared for marketing in 2003, highlight the value of genotyping?

Timing is key. Iressa [AstraZeneca's small cell lung cancer drug] was labeled as a second- or third-line therapy because the efficacy response rate was low across all comers. After marketing, several academic research groups observed that a few specific patients showed remarkably good improvement. Had that been studied before registration, efficacy would have been easier to demonstrate, albeit in a small subgroup. The company could have sought registration as a targeted therapy for cancer patients carrying specific mutations. The finding changed the

risk/benefit picture for a definable group of patients. Post-marketing is too late to change the commercial proposition. The end result was to take a small market and make it smaller, without increasing the price for a truly targeted therapy. If the company had that data during development, they could have registered the drug as a targeted therapy—with similar considerations of cost and pricing as with orphan drugs.

Won't genotyping limit market size by stratifying patients?
Large studies can hide subgroups who respond in a particular, genetically determined way. A question in industry is why genotype, restricting the market, when you can get the whole market? Iressa works well in some people. You barely get an average signature if you look at many patients, but get a very strong signal in a small identifiable subset of them. That's enough for a company to do well if it has developed a companion diagnostic and had it in the label. There was FDA Guidance for Industry in April 2008, providing definitions to be used in upcoming additional guidance documents for pharmacogenetics and pharmacogenomics. Interestingly, the April 2008 document also came with a "black box" on page one suggesting that variance from the suggested guidelines comes with some additional risk for approvals.

Can you give an example of how a pharmacogenetic approach improved the safety profile of a particular drug?
The Abacavir story [4-5% HIV patients taking the reverse transcriptase inhibitor develop hypersensitivity] has had a major impact on the ability to regulate safety, putting a focus on pharmacovigilance, and not requiring whole genome data. If you can select appropriate candidate genes for safety experiments (including some knowledge of the drug's mechanism), the candidate strategy works…

The general impact is that pharmacogenetics enables us to make drugs safer. Abacavir isn't the only example that has happened, just the first with a prospective clinical trial for measuring the predictive value of the test. Similar data have been developed for two other GlaxoSmithKline drugs [including Tranilast]…

Why was the pharma industry slow to embrace pharmacogenetics, given that discussions about sequencing the human genome began in the late 1980s?
Pharma has reacted to the period of time when the sequencing of the human genome was hyped and hyped (by NIH, Celera, and grant or investment seekers) about what miracles were just around the corner. They all acted as if they had broken a bubble, but the bubble was artificial. Even if the whole genome became known, we wouldn't know what to do with the information. Pharma and the venture marketplace viewed the lack of immediate effects from the genome project as part of that hyperbole. In the meantime, GlaxoSmithKline, for example, recognized the importance that pharmacogenetics could have and invested in the experiments important to a pharmaceutical pipeline. Early followers are now engaged to achieve a competitive advantage while creating drugs that can be predicted to be safe for most people.

You're best known for the Apolipoprotein E (APOE) story in Alzheimer's disease (AD). To what extent has APOE's role in the disease been validated?
We originally found the association with *APOE4* [the most serious version of a gene linked to Alzheimer's] in familial as well as sporadic cases in 1992—the age of onset of Alzheimer disease changes as a result of this genotype. We looked at tissues from homozygotes for *APOE4* and found that they had a lot more amyloid than homozygotes for *APOE3*. That was a phenotypic association.

Now we have a mechanism that explains what goes wrong in neuronal cells that allows the AD phenotype to emerge over time. There is a 10 to 15 year difference between *APOE4/4* individuals and *APOE3/3* individuals in what gradually progresses over time. But companies lose interest, because anything more that we learn about AD genes would not result in a new drug for another ten years. That is why I've returned to Duke, with private funding, to discover and develop a drug or drugs in a virtual pharmaceutical company...

Can you describe the new Alzheimer's gene your group recently discovered?
Nice try! It is proprietary for now. But our discovery of a second gene still needs to be confirmed. The results will be published. It may take up to two years to confirm the data but, in the meantime, we are developing a screening assay. If the data are not confirmed, we've wasted time, but if they are, and we find what we think we will, we'll be two years ahead.

Can you explain the surprising findings about *APOE4* in the rosiglitazone treatment trials for Alzheimer's disease?
The operative word in your question is "surprising." We have predicted that result [the drug was not efficacious for the whole population, subsequent analyses revealed that people who did not have an APOE4 allele improved with all three experimental doses in the study protocol]. [There's] an article in Forbes from April 4, "Attacking Alzheimer's". It begins: "The drug industry has bet heavily on one theory about the disease. What if that theory is wrong?" Well, I have thought it was wrong for almost 20 years. People in the Alzheimer's field are wrapped tight around amyloid as the cause, and are apparently "surprised" by the clinical trial. Amyloid and *APOE* are in fact interconnected with amyloid being a downstream consequence of *APOE*-induced mitochondrial toxicity, secondary to different rates for *APOE3* and *APOE4*.

Should the *APOE4* association be used to develop a predictive test for Alzheimer's?
My concentration is to develop a preventive therapy. If rosiglitazone works in patients with Alzheimer's and makes them a bit better, then the next opportunity is a prevention study attacking the same mechanism. It is a very interesting economic problem, from a company's point of view. The patent life for rosiglitazone will be over soon. It is now up to others in academia and the Alzheimer's community to find a way to focus on a prevention trial, perhaps at a low dose. One of the institute's goals is to organize a prevention trial. Another alternative might be to incentivize companies for continuing expensive Phase IV preventive trials. •

Feature

ADAPTIVE DESIGNS in the REAL WORLD

Despite potential advantages, pharma is taking a cautious approach to adaptive designs, resulting in a slow but sure restyling of the research enterprise. By Deborah Borfitz

Among the broad array of statistical methodologies being piloted in clinical research, none draw as much hope and consternation than adaptive designs that involve interim data analysis. (See, "Real-Time Trials," *Bio•IT World*, June 2006).

The potential of this approach is promulgated by vendors including Cytel and Tessella, which sell the accommodating software, together with a handful of evangelists within big pharma. Virtually unknown, however, is how these adaptive clinical trials (ACTs) play out in the real world and the overall tenor of regulatory agencies on the matter.

Aside from debate about the promise of ACTs in reducing development timelines and costs by utilizing actionable information sooner, much of the dialogue occurs behind closed doors. The FDA, which has been promising guidance on ACTs for more than a year, is currently handling novel designs on a "case by case basis" to give the agency "experience and definitions that will be useful for later advice," states Crystal Rice, spokesperson for the FDA's Center for Drug Evaluation and Research. The FDA does not track the number of adaptively designed protocols it evaluates, but "most all of the medical areas are receiving some protocols that have some aspect of the novel adaptive design associated with them."

Generically, an ACT describes an assortment of statistical approaches, including widely accepted designs such as "early stopping" and "dose-finding," says Donald Berry, head of the division of quantitative sciences and chairman of the department of biostatistics at the University of Texas MD Anderson Cancer Center. (Berry is also an independent adaptive design consultant.) Seamless trials, notably oncology studies that combine phases I and II, are also fairly common. Given the problems pharmaceutical companies have had in accurately establishing dosage, the FDA actively encourages adaptive approaches in early phase trials.

But in later stage ACTs, Berry says the FDA worries about the intrusion of bias and the inability to accurately read a treatment's false positive rate. "Almost all of [the ACTs] I've done," says Berry, "occurred before the confirmatory aspect kicked in." The exceptions were a few seamless phase II/III trials.

European Attitude

The European Medicines Agency (EMEA) appears more comfortable with seamless ACTs than the FDA. Last December, the EMEA helped organize a workshop focused on adaptive phase III designs. Robert Hemmings, a member of EMEA's Scientific Advice Working Party, reports that the number of adaptively designed phase III trials is growing so quickly that the agency has "stopped counting." The EMEA received 15-20 scientific advice applications in the prior two years across a variety of therapeutic indications and the "vast majority" were confirmatory studies and, more specifically, seamless phase II/III combinations incorporating dose selection, sample size re-estimation or both. Approximately 50% were single pivotal studies.

Among the adaptations deemed "problematic" by the EMEA, Hemmings says, are those that adjust the randomization ratio, resulting in a possible shift in popu-

lation recruited. The primary endpoint also needs to reflect patient benefit and be "independent" of interim data. The reasons for not endorsing several proposals for an adaptive design strategy included "lack of acceptable rationale, totality of evidence likely to be inadequate (due to early stopping), Type I error (false positives) not adequately controlled, concerns over dissemination of interim information, and inadequate pre-specification of intention to adapt.

The FDA comfort level with ACTs tends to be division-dependent, says Berry. "Usually, the FDA wants you to draw a line in the sand [regarding] when you switch from phase II to III and will only count data after that switch." But with rare conditions, such as a spinal cord injury, or in an area of high unmet medical need, such as a treatment for pancreatic cancer, the agency is more apt to "lower the bar."

There's not much expertise in the "adaptive" business, says Berry. The FDA doesn't know what to suggest. But absence of guidance on ACTs is not a key holdup in the adoption of adaptive designs.

It is, however, making companies almost universally mute on the topic. A half dozen companies that have publicly acknowledged doing ACTs declined to be interviewed about the particulars of any of their seamless, later-phase trials, citing bad timing (in one case, conflict with a study's upcoming publication in the medical literature) and general discomfort in talking about cost savings of the approach. Normally talkative technology vendors have also been unusually quiet, hoping not to raise further the anxiety level of their clients.

For self-teaching purposes—and to please regulators—some sponsors have opted to do "inferentially seamless" trials that transition into traditional confirmatory trials once dosage is firmly established, says Berry. MD Anderson, together with the FDA and the National Cancer Institute, is eyeing the potential of adaptive designs targeting biomarker-defined populations. The idea is to look at the benefit of different therapies and combinations of therapies based on patients' genetic makeup.

From the regulators' standpoint, the overriding concern about ACTs seems to be who has access to information during interim analysis, says Trevor Mundel, global director of the immunology and infectious disease for Novartis Pharmaceuticals. Companies need an independent data monitoring committee (DMC), "probably outside the company," and an independent statistician to do evaluations. The regulatory worry is whether a company will live up to the guarantee of data integrity implied by a DMC. "It was easier for us to go to regulators the second time…based on what was done in the past."

The fear is that information leakage will potentially skew trial results as well as incite litigation by investors on Wall Street, says Berry. The problem is solvable by erecting firewalls. But that won't necessarily stop speculation about "what it means" when the data safety and monitoring board (the formal term for DMC) wants to know more about a particular set of results or keep the study team from trying to "read" clues from the body language of the unblinded statistician.

Members of the DMC, as a rule, shouldn't have much interaction with the sponsoring company's senior executives, says Mundel. But there may be a clause in the DMC charter stating that any decision that would have major financial repercussions for the company, including stopping a study, would require talking to management first. "This clause may exist for Novartis," says Berry, "but it is not standard in the industry."

On confirmatory trials, the FDA may allow some senior managers of the sponsor company on the DMC—or none at all, says Michael Krams, assistant VP, adaptive trials, clinical development at Wyeth (See, "Biting the Adaptive Trials Bullet," *Bio•IT World*, May 2007). "There seem to be a lot of FDA 'positions' on that. My opinion is that sponsor involvement should not be totally excluded in meetings where the DMC reviews recommendations of the steering committee, because many of the decisions that have to be made are business decisions," with potentially huge financial implications.

DMCs overseeing ACTs may well need someone who "understands the [protocol] design and what the algorithms are supposed to be" for troubleshooting between meetings, says Berry. (Until now, that role has often been played by Berry's consulting firm.)

Shortage of Metrics

Based on the findings of an initial survey of 13 mid- and large-size pharmaceutical companies by the Pharmaceutical Research and Manufacturers of America, sponsor companies aren't overly chatty with the FDA about their phase II ACTs unless the information is expected to be used for a regulatory submission.

Of 37 identified ACTs, three were phase I, one combined phase I and II, 15 were phase II, two combined phase IIA and IIB, nine combined phase II and III, four were phase III, and three were phase IV, according to Judith Quinlan, co-chair of the group's case study work stream. "All but one focused adaption on dose." Only nine of the 37, including seven of the phase II trials, used the Bayesian statistical method that provides a transition from sequential to continuous monitoring of trial data and allows for various parameters to be changed. Adaptations can be made to number of patients needed, eligibility criteria, and how patients get randomized to different treatment arms as well as drug dose.

Late-phase confirmatory trials were underrepresented due to confidentiality issues, Quinlan adds, although smaller companies are now stepping forward to share their cutting-edge case studies via statistical clinical research organizations and consultancies.

The medical literature is virtually devoid of reports on large, pivotal pharmaceutical ACTs and will be for at least another two years, says Jay Herson, senior associate in biostatistics at Johns Hopkins University. The notable exception is Pfizer's oft-mentioned ASTIN (Acute Stroke Therapy by Inhibition of Neutrophils) study, published in *Stroke* in 2003, whose adaptive design was credited with killing the drug promptly and decisively. Only now are other companies beginning to approach the FDA with proposals for late-phase ACTs using novel methodologies.

Wyeth, a champion of the adaptive "Learn and Confirm" model of drug de-

velopment (See, "Ten Years After: Learn and Confirm," *Bio•IT World*, February 2007), started six adaptive dose-ranging studies involving "dynamic termination rules" last year, says Krams. Eight more will launch this year. Mundel reports that Novartis is operating more than a dozen ACTs across all clinical phases.

Most ACTs that have been done so far appear to involve group sequential design and sample size re-estimation, says Herson. While the number of ACTs involving seamlessly-combined phase IIB/III trials is growing, they're less understood than the older adaptive approaches and tend to stir controversy within the industry and, presumably, red flags within the FDA. "The big problem is that companies aren't getting the dose right even when they do many phase II trials in the traditional fashion. Now they want to learn a lot in one trial and there's a lot of room for error and a lot of room for the FDA to not approve a drug because [of recent product recalls and public safety concerns]," says Herson.

ACTs may be a convenient way for drug companies to size up questionable compounds. Berry points out that most ACTs his firm has done, including ASTIN, have been successful in that "they've killed off a drug very early. One possibility is that most drugs are duds. The other possibility, which worries me, is that companies use standard [trial] designs if they have a highly positive drug and do an [ACT] if they're not sure the drug is any good. Proving a drug doesn't work is a great service, but it's not making us famous."

Gains for Doctors and Patients

The major attraction of ACTs is the "higher information value for the research investment," says Krams. Sponsor companies aren't the only beneficiaries. "For investigators, [ACTs] are a more intelligent way to interpret the data. From the individual patient's perspective, there's a higher probability of getting a good treatment or not being allocated to a bad treatment."

This is especially meaningful when it comes to adaptive randomization in trials for life-threatening conditions, including most cancers, says Mundel. "If you can do this and you start to see a subgroup respond better to your drug, aren't you obliged to put more patients in that subgroup?"

Better treatment odds serve as compensation to investigators engaged in ACTs who face "an additional level of uncertainty" regarding study length and subject enrollment, as well as higher expectations in terms of timely data entry, says Krams. With adaptively designed studies, how long a study will run and how many patients will be involved "is not known at the beginning, but emerges as data accrues." Most investigators have never conducted an ACT and are understandably skeptical, "but once they've gone through the experience, they clearly want to do it again."

Study monitoring happens in an adaptive fashion, with site visits occurring "whenever there's data to look at," says Krams. Because data queries happen

Adaptive Players

Berry Consultants is one of the most experienced players in adaptive designs. This statistical consulting company has designed virtually every type of ACT, including adaptive sample size (stopping early or late for efficacy or futility), dose finding (and dropping), seamless phases (I/II and II/III), adaptive randomization (to better perform treatments), and identifying responding biomarker profile. Services include writing software, assessing a trial's operating characteristics, and modeling disease course over time for trials with long-term endpoints. Frequently involved in monitoring trials to ensure the design is working as prescribed, senior statistical scientist Donald Berry has helped design about 50 ACTs so far.

The leading technology provider for ACTs is **ClinPhone**, which has delivered applications for more than 85 protocols with design adaptations. Tailored, fully integrated combinations of solutions cover central randomization, trial supply management, EDC, and electronic patient reported outcomes. ClinPhone can also provide real-time integration with sophisticated statistical software. It has been involved in all types of ACTs, including those involving dropping/adding treatment arms, modifying the randomization ratio and/or sample size reviews in dose-finding studies, adaptive cohort designs, and seamless II/III designs.

For the past decade, **Tessella** has been providing simulation and analysis tools for ACTs as well as the know-how to build and run the requisite information technology. It has implemented statistical models for phase I trials, phase II dose-finding studies using Bayesian statistics, and phase II/III seamless designs. Six top international pharmaceutical companies have worked with Tessella on ACTs.

United BioSource Corporation (UBC) offers virtually everything sponsors need to do ACTs, including study design and protocol development, study simulation and adaptive statistical calculations, clinical technologies, logistics and supply management planning, creating interim DMC reports with trial data tables, and establishing and managing the study DMC. UBC has been involved with more than 100 ACTs, including both Bayesian and frequentist methodologies.

On a consultative basis, clinical trial design firm **Cytel** has been involved with more than 30 ACTs—presumably, some using its East system for design, simulation, and monitoring purposes. Experience in a wide variety of ACTs, including proof of concept, dose-finding using Bayesian methods, seamless phase II/III, and phase III adaptive variants such as population enrichment and re-estimate duration. Cytel offers a full line of services vis-à-vis DMCs and has custom software and computational tools for simulating adaptive designs (used by Merck, among others). It trained the FDA/CDER in adaptive design methodologies.

"without any delay," they double as an educational tool for ACT investigators.

There is a "clear need" for additional information sharing with institutional review boards and ethics committees regarding the intention of an ACT, says Krams. "Some ethics committees have asked if we could share interim results with them whilst the trial is still ongoing. We believe that the only body which should see the data from interim analyses is the independent [DMC]."

Running the Numbers

Statisticians hold a special position in this arena, as they're often the "gatekeepers of all that is quantifiable," says Mundel. Unfortunately, he says statistics are "a black box" to a many scientists who implement, run and manage ACTs. Much of the decision making rests in the hands of the number crunchers.

This is problematic only if in-house statisticians are rigid about "statistical purity" in all they do, says Mundel. "Some [statistical] techniques have been carefully worked on and the theories are well understood and usually lead to the right conclusion," he says, "but in the real world, there's no proof that they actually work." These include the routine practice of "analyzing data repeatedly over time when patients are dropping out of the study for various reasons."

ACTs are not inherently "good" or "bad" and thinking of them that way can lead to tunnel vision, says Mundel. Statisticians who are fervently pro-Bayesian and push for every study to be adaptive could lead companies to make impractical investments in data collection technologies. (Berry notes one case in which investors pressured a biotechnology company into using a Bayesian methodology against its better judgment.) "A lot of organizations are attracted to adaptive designs because they believe they will yield results faster. But it can take companies a long time to get these kinds of studies started. The notion that an [ACT] can get rid of the white space between study phases II and III is the worst reason to do them."

That's because the "white space" simply gets moved to the front end of a trial, says Mundel, working out the details of study design, achieving consensus with regulatory authorities, and getting the necessary information technology in place. "Time savings are fictional," he says. On the other hand, endless months of acrimonious debate about whether to utilize an adaptive design can also prove futile.

"From a design perspective, there's an extensive up front investment in thinking time and to construct documents, such as a simulation report summarizing operating characteristics," says Krams. "This is in addition to the protocol, interim and final statistical analysis plans, and DMC charter."

None of this means that the time savings associated with ACTs are fictitious, says Berry. "First, the 'white spaces' are not equal. Usually, more time is saved than is used in setting up the trial. More importantly, there is a set-up cost associated with ACTs. The first one takes the longest—for the obvious reason that the company has never designed one before. After experience with setting up five or ten trials, the white space at the design stage is tiny, perhaps no longer than the time it takes to design a typical trial now."

The expertise necessary to design and run ACTs is relatively scarce. Berry has helped design about 50 ACTs for two dozen pharma companies over the past couple of years. Quickly producing new randomization probabilities based on incoming data is a capability limited to a handful of companies, including Cytel, Tessella, and United Biosource Corporation. Among clinical research organizations (CROs), "maybe 5%" can handle ACTs. "They're learning by doing, and we are teaching them," says Berry. But someone at the CRO still has to "throw the switch" when, for example, patients begin to be randomized adaptively rather than equally across treatment arms.

The IT required for ACTs includes an interactive voice response system to accomplish adaptive randomization as well as electronic data capture to collect adaptive parameters in real time, says Mundel. The structure of the database also has to be finalized up front rather than mid-study.

Drug supply software is likewise a necessity, especially for adaptive dose-finding studies, to ensure there is sufficient quantities of the correct dose formulations at investigative sites, and "this has to be worked out well before the study starts," says Mundel. Current drug supply technology is far from ideal due to lack of uniformity. "I think it's the number one cause of delays across the board, not just for ACTs."

The "dream" at Wyeth is a UPS-like setup for real-time drug supply chain management that is part of a fully integrated system housing all trial-related clinical and financial data

Michael Krams, Wyeth

The "dream" at Wyeth is a UPS-like setup for real-time drug supply chain management that is part of a fully integrated system housing all trial-related clinical and financial data, says Krams. "We do a good job integrating all the different functions on individual trials, but we want to develop the IT infrastructure to do it in a way that's scalable."

Technology is not the only and clearly not the biggest impediment to the adaptive approach, now widely regarded as valuable to both sponsoring companies and human subjects. The evolution to this promising new era of clinical research appears inevitable. But the transition may be hindered due to the shortage of information and experience, as well as informed leadership at the FDA. •

Inside Intel's Interest in Sequencing

Intel strives to "standardize the base."

While Intel's digital health group is developing a new business for the company—creating products and services for more effective home-based care within the health care industry—other groups within the microchip titan are looking to apply Intel's general computing expertise to optimize performance in industries with growing high performance computing (HPC) needs.

Wilfred Pinfold is general manager of Intel's Integrated Analytic Solutions group. Originally from Liverpool, Pinfold trained in computational fluid dynamics, moving to United States in 1980 (and losing most of his scouse accent in the process.) Pinfold spoke at a BioTeam-organized pre-con workshop Bio-IT World Conference & Expo on Intel's interest in life sciences. Kevin Davies asked him to discuss Intel's growing interest in digital health, bioinformatics, and next-generation sequencing.

Bio•IT World: What is attracting Intel to the bioinformatics/life sciences fields?
Pinfold: There is a significant interest in accelerators and accelerated platform solutions. We've released a technology called QuickAssist, which allows you to plug accelerators into the platform directly, and we're looking at "many-core" architectures—highly accelerated platforms, we're already shipping quad cores, but we expect the core-count to continue to climb. These systems are extremely valuable for analytic workloads—things like bioinformatics, seismic work, engineering design work, workloads that have been considered HPC workloads...

What we find as we look into these analytic workloads is that the traditional ecosystems with independent software vendors (ISV) are difficult to form. If a user builds their own HPC system, these ISVs can not deliver an executable that will run consistently on every user's platform. To deal with this, customers exchange source code, compile it, and bring it up on their own system. To do this well requires a high level of expertise and a considerable amount of time.

Understanding that not everyone has the level of expertise or time available, we're doing the things that are necessary to make a turnkey accelerated platform available. To make this work, we then realized we needed to do something to help the ecosystem develop—for there to become a base of executable codes... We're trying to do what is necessary to get that ecosystem into place, such that if you want to buy a bioinformatics system, you can buy a highly accelerated platform that will plug into your sequencer and produce good sequence results in a reasonable time frame, without having to learn all about clusters and accelerators.

How did your interest in the next-generation sequencing arena begin?
Our interest in supporting accelerated workloads was high, and we realized, "Oh my god, this is a great place to be right now. This is crying out for a solution." Whereas the top institutes like Broad and Sanger can build their own solutions with large clusters, for the next tier of users, the people who will buy 1-2 systems to do serious biology, they don't want to have to buy a machine that's more costly than the sequencer itself and more complex to run. They want a solution.

So the bioinformatics space really stood out, particularly the task of dealing with sequence data off the high-throughput sequencers and how that was going to change the computational solution. And having the realization that it was becoming fragmented—people were looking at FPGA solutions, GPU solutions, a variety of solutions. If the market fragments in that way, it will make it impossible for software developers and ultimately stall the ability for high-throughput sequencers to be shipped in the quantities warranted.

Is this primarily a hardware or software initiative?
The solution has to combine hardware, software, and services. We want to work with existing providers in the ecosystem to deliver this solution. For example, BioTeam is an excellent bioinformatics services provider and we don't want to become the content experts in bioinformatics! There are plenty of people at Broad and Sanger who develop excellent alignment and assembly algorithms, and there are commercial entities providing other parts of the solution. We want to work with open-source providers, like Sanger, so whatever solution we put out there will be suitable for running things like MAC and VELVET. We also want to work with [companies like] ABI, Roche, Helicos, and Illumina to make sure their

codes like ELAND will run effectively on this solution. We want to provide a solution by working with and influencing, not fragmenting the market. We are talking with and working with many of these ecosystem providers to understand how best to do this. Our intent is to try to do what Intel has done so well in the PC field: to try to get people to standardize the base, to get to a point where the customer has the best of both worlds—they can get the stable platform they need, then on top of that, all the software and services will work. They don't have to worry about whether their HPC system will have 80 or 120-nodes in the cluster, Gigabit Ethernet or Infiniband, RedHat or Debian operating system, etc. We'll try and stabilize that.

Vendors ship sequencing instruments with huge clusters. Is this sustainable?

As sequencers become affordable for clinical applications, it will become increasingly important to offer a turnkey bioinformatics solution. It is this customer base we are targeting. As new sequencing technologies like those from Illumina and Helicos produce ever increasing amounts of raw data, there will be pressure to explore exotic computational solutions like FPGAs and GPUs. This will further fragment the market and disrupt the ecosystem. We believe an accelerated solution can help avoid this.

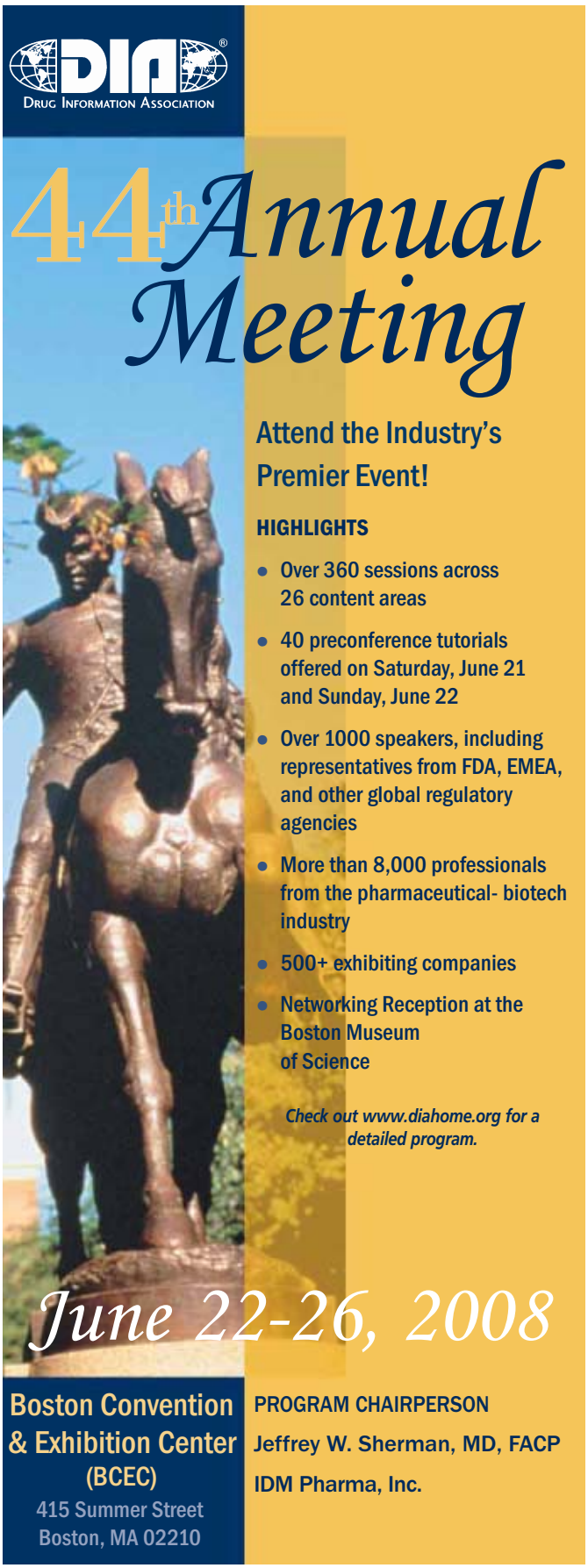
Would your device work with all the next-gen platforms?

We know that customers would like to use multiple sequencers to achieve their goal. For example, they might use 454 for the framework and fill in with short-read data. So the idea is this system could take data from multiple sources and integrate it effectively.

We're also interested in dealing with the image processing task. There are opportunities not yet taken to improve image quality in that cycle, because it's very hard. e.g. If you could do work to improve the resolution of the star-field image before you do base calling, then that's a very interesting workload—it benefits greatly from acceleration on special purpose silicon or an FPGA. So there are significant opportunities if we think about the workload throughout that transition. Clearly that requires working closely with all the instrument vendors and software providers. Our intent is not to bluster in and provide the solution, but to try to work with the community to make it attractive for all the players to come to a solution that then has some commonality, and allows an ISV community to develop services communities, then we get to stabilize the base and become a good provider to our customers.

What do you think about the pace of progress in this field?

The really exciting thing about this field is that it is moving so rapidly. If you can't get your machine out and generate revenue in the next 2-3 years, then you probably need to be working on your next generation machine! We at Intel are very familiar with rapid improvements—we've followed Moore's Law for many years. It's forced us to improve all our manufacturing and design techniques very rapidly. The majority of our products are replaced by new products every 12 months. •



Diversifying Research

ACORN offers equal opportunity research.

BY DEBORAH BORFITZ

Thanks to this deceptively simple strategy, one out of every five patients of Accelerated Community Oncology Research Network (ACORN) last year was African-American, according to CEO Steve Coplon. "We're bringing research to where patients are," he says. At individual clinics, the figure for African-American recruitment ranged from 3 percent (in a more rural setting) to 32 percent.

Minority accrual statistics were formally tracked for the first time last year, says Coplon, but have been improving over the past three years. The percentage of accruals for Asian-Americans and Latinos was less than 5 percent, which is believed to be roughly on par with the performance of the National Cancer Institute (NCI).

In terms of both education and outreach, ACORN—part contract research organization, part site management organization—has made no special effort to draw African-Americans into clinical trials, says Coplon. A small handful of the 150 clinical investigators in the network are black and practicing in predominantly black neighborhoods.

Community oncology clinics care for more than 84 percent of the nation's cancer patients, and they "cover the entire spectrum" in terms of race and nationality, says Coplon. The three dozen practices that compose ACORN also have a designated "physician champion" who is committed to clinical research as the means to wipe out cancer—and "not just for white males or women but for African-Americans and Latinos and Asians." The locations include urban centers such as Miami and Los Angeles and more rural ones, including Billings, MT.

ACORN's recruitment statistics more or less mirror local demographics, says Coplon. Conversely, participation in research housed in academia tends to reflect the populations that happen to live nearby or have the wherewithal to get to and navigate a university campus. That may contribute to the relatively poor minority inclusion statistics seen with studies placed at designated NCI centers. Recent NCI data show that African-Americans represent only 7.46 percent of all clinical trial participants, although the 2000 Census puts their representation in the overall U.S. population at 12.9 percent.

Nationally, overall accrual of adult oncology patients of all races into trials is only about 3 to 4 percent, says Coplon. Within the network, the figure is roughly 8 percent.

At any time, ACORN is actively involved in 125 to 150 trials, says Coplon. Last year, it also supported 40 to 50 trials initiated by network investigators.

"Sites generally don't have to pay us unless their performance falls below a certain objective and become a drain on the entire network," says Coplon. "Part of the plan this year is to remove a few sites that are under-performing." Given that more sites are simultaneously coming on board, ACORN will grow.

The network helps make participation in clinical trials palatable for time-pressed physicians, says Coplon. "No one gives more than 20 percent of their time to research, even our physician champions." •

Bio-Imaging Buys Phoenix

Bio-Imaging expects EDC synergies with PDS.

BY ANN NEUER

Bio-Imaging Technologies, a provider of medical image management for clinical trials, has acquired Phoenix Data Systems, a privately held electronic data capture (EDC) company. Phoenix is now a division of Bio-Imaging.

At first glance, this looks to be an unusual pairing as the two outfits occupy different niches in the clinical trials sector. But each company had been looking to move to thet next level within the industry by expanding their service offerings.

Mark Weinstein, president and CEO of Bio-Imaging, says that his company has had a tremendous interest in the EDC market, which it estimates as a $1 billion opportunity within five years. "We've been wanting to be a player in the EDC space, which we see as closer to the center of the clinical data universe," says Weinstein.

In Phoenix, Bio-Imaging found a rapidly growing company with a very hands-on management committed to top-notch customer service. "Phoenix has a good, solid EDC system that has been used in over 500 clinical trials... We realized we could leverage our core competencies to make more together than we could individually," Weinstein explained.

Bio-Imaging brings critical mass, financial stability, an international presence in the medical imaging market, and good business know-how to the table. Phoenix brings a strong client base of small to mid-size biopharmaceutical companies; nearly 200 new starts using the company's EDC solution, PDS Express, scheduled for 2008; and financial strength as the company has been built without taking in venture capital.

Both companies see clear opportunities for entry into each other's markets. At this time, sales forces will remain separate but will look for synergies. In the short term, data sets generated by Bio-Imaging and Phoenix Data Systems will not be integrated, although in the long term that may change. To get started, Bio-Imaging and Phoenix Data will continue to function separately although Bio-Imaging will be handling many back-office management functions. •

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Economic Development

Building Buzz in Singapore

The hub is selling location, talent, and the Biopolis of Asia.

BY ALLISON PROFFITT

SINGAPORE—In Singapore, the food is fantastic, the weather is warm, and the news is always good for scientific investment. At least that's the general impression. It can seem a little too good to be true, and you have to wonder about a massive public relations machine churning out glossy brochures and happy scientists in some back room.

But the country has built its buzz on a solid foundation. Like the three rules of real estate—location, location, location—Singapore sells its proximity to India, China, and the rest of Asia while boasting an English-speaking business environment and a very well-established infrastructure.

Then, of course, there's the issue of stem cells. While many Western countries are still embroiled in bioethical debates, Singapore supports and works to enable stem cell research. For many companies, that's the clincher. "We are focusing on oncology and diabetes drug discovery with cutting edge genomics technologies and stem cell research. Singapore has become the central location for these activities," says Yaron Turpaz at the Lilly Singapore Centre for Drug Discovery.

Biopolis is poised to serve as the heart of biotech in Asia.

Beyond this solid footing, the country has even more money and achievements to back up its claims.

The goal is nothing less than the "Biopolis of Asia," a hub in the heart of Southeast Asia for research, manufacturing, and all things science. Funded by the Ministry of Trade and Industry, the Biopolis R&D campus is the effort's nucleus and crowning achievement. The vision calls for "an international biomedical science cluster advancing human health through the pursuit of excellence in research & development, manufacturing, and health care delivery." It's a wide scope encompassing basic and clinical research, manufacturing, product and process development, and health care—a lot for an island nation comprising 704 square kilometers.

But the commitment seems strong. The effort boasts an international advisory board featuring scientists from the United States, United Kingdom, Sweden, Germany, Australia, Switzerland, and Canada. The public sector R&D budget nearly doubled from $6.9 billion (2001–2005) to $13.55 billion for 2006 to 2010.

Gained in Translation

The focus of all this funding is translational research. "As a logical extension of our work thus far," said Singaporean Minister for Health Boon Wan Khaw at the American Association of Cancer Research meeting last November, "we are moving into translational and clinical research [for cancer] with $1 billion of government funding committed."

Paul Herrling, head of corporate research, Novartis International, believes that Singapore is the place for bench-to-bedside research: "It's not the place you go to do very large phase 3 clinical studies. However, because it has a highly sophisticated hospital environment, and in addition, a very concentrated environment of basic biomedical sciences, drug discovery specialists, they are ideally suited to do scientific studies in patients, your proof of concept studies."

Paul Chapman, director of GlaxoSmithKline's Cognition and Neurodegeneration Centre agrees. "I think that Singapore has wisely chosen translational science as essentially a clinical niche for them," he said. "Because the patient populations are concentrated [and] because record keeping and sharing is very good, the opportunity to do that sort of early phase experimental translational medicine is a very obtainable goal."

In fact, phase two of the Biopolis project focuses heavily on translational research initiatives, including almost 400,000 square feet of new lab and office space and centers, investigator awards, and programs highlighting translational research. The forces behind the Biopolis movement include A*STAR, the Agency for Science, Technology and Research, Bio*One Capital, and Singapore's Economic Development Board (EDB), working with the public and private sectors.

A*STAR manages the R&D fund from

(CONTINUED ON PAGE 34)

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Eli Lilly and Company is a leading, innovation-driven pharmaceutical corporation with a firm commitment to help people live longer, healthier and more active lives by making breakthroughs in medicines and treatments.

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The Integrative Computational Sciences (ICS) group at Lilly Singapore Centre for Drug Discovery (LSCDD), provides state-of-the-art computational solutions to enable the global efforts of drug discovery, translational medicine and tailored therapeutics at the post genomic era.

The bioinformatics scientists and software engineers at the ICS team are leading the design, development, integration, deployment and support of drug discovery software tools and provide innovative algorithms and applications for integrated analysis of heterogeneous research and development datasets.

As an ICS team member, via the development of cutting-edge tools, you will have a global impact on the future of personalized medicine: 'The Right Drug, at The Right Dose for The Right Patient at The Right Time'!

Lilly Singapore is expanding and the ICS group is looking for candidates in the following positions:

- **Associate Director, Informatics**
- **Sr. Bioinformatics Scientist**
- **Sr. Software Engineer**

The successful candidates will work closely with their informatics and software engineering peers at ICS and will collaborate with the Discovery IT organization in Europe and the USA. These positions require the ability to communicate across domains with biologists and chemists in Lilly Drug Discovery Research teams at Singapore as well as with discovery and medical research scientists at Lilly headquarters in Indianapolis, Indiana, USA.

Minimum requirements:

- Ph.D. in Bioinformatics/Computational Biology/Biostatistics/ Biophysics/Computer Science/Engineering or a related discipline
- 3 years' post-graduation experience (or 7 years with MS)
- OS: Unix/Linux, Windows
- Programming: C++/C# .Net
- Databases: Oracle/SQL/mySQL
- Scripting: Perl, Shell

Preferred Experience:

- Industry experience in Biotech/Pharmaceutical/Drug Discovery
- Experience in developing software applications that are designed to handle large data sets such as microarrays, proteomics and imaging data
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Singapore

(CONTINUED FROM PAGE 32)

the Singaporean government. Within A*STAR, two research councils fund 14 established research institutes, including the Bioinformatics Institute, the Genome Institute of Singapore, the Centre for Molecular Medicine, and the Singapore Institute for Clinical Sciences along with additional research institutes located in an engineering cluster, chemicals cluster, information and communications cluster, and electronics cluster. If it's a growing area of science, A*STAR has a research institute for it.

The Biopolis effort has already established recruiting programs, developed an R&D infrastructure on campus, and built basic research capabilities. The Biopolis Science Park campus currently has nine tightly packed buildings housing the A*STAR research institutes and various corporate headquarters and offices. Named Nanos, Centros, Genome, Matrix, and the like, the steel and glass structures are nested together like an angular jigsaw puzzle. Three more buildings are planned for a total of 2.4 million square feet of office and laboratory space housing 2,000 scientists and 20 companies. The goal is to foster community and collaboration within the park. Common areas feature cafes and a dry cleaner; there's talk of a day care on site.

At the Genome Institute of Singapore, an A*STAR institute in the Genome building on the Biopolis campus, director Edison Liu believes that Singapore is "uniquely suited" to collaborative research, and the environment is only encouraged by the Biopolis footprint (See, "From Genomes to Systems," *Bio•IT World*, February 2008).

"There's an insularity that you sometimes get in organizations that are set out by themselves, apart from everybody else," agrees Chapman. "We don't have that here. Our scientists are talking to people from Novartis, and they're talking to people from the research institutes and there is a sense of a larger community."

"The fact that you physically bump into and interact [with other scientists]... there's more passing of ideas and interactions than you'd get with other facilities," adds Neil Miller, director of Medicinal Chemistry at GSK's Cognition and Neurodegeneration Centre.

"One of the critically important things for the long term is that collaborations don't just happen," says Chapman. "In fact the collaborations that tend not to work are the ones where the government puts out a grant proposal and says, 'You guys will get money if you bring in [specific partners].' And everybody looks for these partners that they can put down on paper together to do the research that they always wanted to do anyway. Where real genuine partnerships and collaborations come around is where people know each other and trust each other... When one day you say, 'We've really got this problem; I wonder how we can get around this?' to the guys you're used drinking coffee with."

Lilly

Lilly moved its newly-renamed Lilly Singapore Centre for Drug Discovery to Biopolis in March. The combined spaces in the Immunos and Neuros buildings include wet lab and informatics facilities in three functional units. The systems biology unit was established three years ago and focuses on biomarker discovery in oncology. The two new departments are Drug Discovery Research, which focuses on wet lab research in oncology and diabetes, and the Integrative Computational Sciences department, which focuses on the integration of heterogeneous datasets, algorithm development, statistical analysis, and integrated data analysis workflows, which eventually get wrapped up into state of the art software tools for global implementation and usage by scientists across all disease types at Lilly.

Singapore is now Lilly's research hub in Asia. "If you look at the seminars that are provided at Biopolis," says Turpaz, director of the center's Integrative Computational Sciences department, "then you will see that the audience is coming together from different companies and different government institutions to discuss how, through joint efforts, they can deliver the next generation of medicines and scientific discovery."

For Lilly, expanding in Singapore was a multi-faceted decision. "Strategically, it's about expanding into Asia, leveraging the talent found in Asia, [and] establishing a lot of collaboration with academia and industry in Singapore and the region," says Turpaz. For years, Lilly and other pharmaceutical companies were focused on a centralized model as a fully integrated pharmaceutical company (FIPCO). Turpaz says Lilly is now following a new model called FIPNET—fully integrated pharmaceutical network. "This is all about focusing on networking and outsourcing, as well as collaboration and risk sharing. And the key issue behind it, and the main difference between simple outsourcing, which has been done for years, is not to centralize everything in one location. Each of the hubs, such as Singapore, is generating a lot of collaboration and decision-making. And that's a change in mindset and strategy."

An hour-long cab drive across the island is Tuas, the manufacturing center, and there the same buzzwords are being thrown around. "There's a lot of interaction between the pharma companies," says Brian Hanifin, managing director and site head of Novartis Singapore Pharmaceutical Manufacturing. "We go to lunch together. We talk together. We meet with the EDB on a regular basis. We're not a number. It's exciting because there's so much going on and I can see 15 [other manufacturing] plants pretty much in my windows."

Built in 2004, Hanifin's twenty-acre facility is the first Novartis manufacturing plant in Singapore. The facility can handle six billion tablets for the U.S. and Japanese markets. It is part of a network of Novartis properties in Singapore including the Novartis Institute for Tropical Diseases (NITD), located in Biopolis, the Novartis eye care division, and regional sales and marketing offices. Novartis is currently constructing a $700 million cell culture production facility to support the Novartis pipeline of biologics, specifically monoclonal antibodies manufacturing products. Building should conclude in 2012.

"Scientists go where there is an environment," says Herrling. "Scientists don't work anymore like loners in their own basement without interacting. They are very much part of a culture, especially

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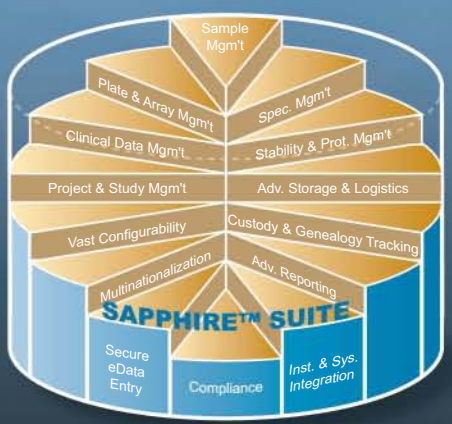

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Singapore

(CONTINUED FROM PAGE 34)

biomedical sciences... so you have to be in a place where all the kinds of sciences you need for biomedical [research]—and that's chemistry, physics, computing, genomics, robotics by now, electronics, all the way to biology, of course, and medicine—have to be there." The list should sound familiar; Herrling covers almost all of A*STAR's areas of focus.

The Neuros and Immunos buildings house Lilly's new Singapore Centre for Drug Discovery.

Pharma Presence

While the research institutes sound like a wish list of research areas, Singapore boasts an impressive list of pharma companies with either R&D or manufacturing facilities in Singapore. Add industry giants such as Genentech, Genzyme, Applied Biosystems, and Affymetrix, currently relocating most of its array manufacturing to Singapore, and you begin to wonder where they put the buildings.

In March, GlaxoSmithKline opened an $85 million R&D pilot plant in Singapore, to accommodate the final phase of drug development. PerkinElmer named Singapore its R&D hub as well, with a new facility in Singapore. In February, Pfizer opened a new clinical research unit on the island.

The EDB works to support local companies and recruit and aid companies seeking to set up shop in the tropics. "Singapore has made significant headway in terms of nurturing homegrown biotech companies such as MerLion Pharmaceuticals and S*Bio. Both companies have products undergoing clinical trials at present. S*Bio just received orphan drug approval from FDA to conduct clinical trials for a drug to cure myeloproliferative disorders (MPD), a disease which if untreated can lead to cardiovascular diseases and leukaemia," says Keat-Chuan Yeoh, executive director, biomedical sciences, EDB.

Their work with outside industry speaks for itself. Herrling says that EDB help was critical in helping Novartis set up NITD so quickly. Elsewhere, he says, "you have to run around to different ministries and get permission left and right and [the process] goes on forever. But the concept in Singapore was different because the EDB assigns a team of young people, mostly Ph.D.s that will be your liaison, so anything you need from the building to work permits, this team would put you together with the right people right away."

Hanifin agrees that political and social support is essential: "I would say location-wise and logistics, they have very sophisticated logistics operations that come from here, so all the importation and exportation is done very easily."

"We shouldn't underestimate the quality of the infrastructure here," says Miller. "We couldn't have established as quickly and to the same level of quality in the facility in any of the other countries in this region... It's well-supported. We can do science here."

Lilly has had a presence in Singapore for 20 years, with the establishment of a business office, followed by a clinical trial center, and recently with the addition of systems biology and new drug discovery center. "Our experience with the EDB has been absolutely great," says Turpaz. "The government and the EDB are supportive of research and generally of scientific activities in Singapore. The joint effort of Lilly and the EDB is well-established, and driven by innovation and scientific discovery."

Perfect People

The right location, the right companies, and the right infrastructure are all boons for Singapore. Yet executives continually mention the working climate and the people. In many ways, the allure is in the fresh field.

According to the government, Singapore's 2005 population topped 4.3 million and included almost 800,000 expatriates and migrant workers. Talent is essential to growing the type of biomedical research environment Singapore envisions, so phase one focused on attracting and developing human capital, or the "two-legged assets" as founding A*STAR chairman Philip Yeo calls them.

In recent years, Liu, Sir David Lane, Nobel laureate Sydney Brenner, Edward Holmes, and Judith Swain have all taken up directorships in Singapore, bringing a distinct element of star power to the venture. But the Biopolis team didn't stop at the "whales," as they call these researcher superstars—they went after "guppies" too. In order to develop talent in Singapore, the A*STAR Graduate Academy offers biomedical scholarships and fellowships to students to pursue undergraduate and graduate level education at local and overseas universities.

It's not just the public sector research that is finding the human capital eager to please, but industry is as well. Companies and organizations are finding a unique talent pool and culture in Singapore.

The most exciting attraction, says Chapman, is "the opportunity to have this fresh start to pull in a bunch of people

here who don't know how they were supposed to do things and didn't know they were not supposed to do things differently. We have a lot of open-minded people here who didn't say, 'biology is biology and chemistry is chemistry, and there's a wall between them.' "

"We've recruited fairly heavily at the bachelor level in terms of chemists," says Miller, "and I do think they're producing good quality scientists." Miller says the depth at the highest (Ph.D.) levels might be lacking right now, but with current investment, that will change in a few years.

"We've found the same with the biology grads that we've hired," agrees Chapman. "They're absolutely fantastic. They're very intelligent; they're well-trained; they're very hard working. They've got this real drive to broaden their skill base. That may just be a difference in attitude and approach. They're not here to say, 'Give me the job I'm going to have for the rest of my life.' They're here to say, 'Now how many different things can I learn to do? How much of this industry can I come to understand?' "

Miller agrees: "The view to life is very much, 'What can we do? We want to do it.' And that's refreshing. They're probably a little more receptive to change and doing things differently."

A*STAR is doing all it can to prepare Singaporean students and professionals to succeed in pharma. Together with the National University of Singapore (NUS), A*STAR and EDB have developed a host of focused education systems and attachment programs (similar to internships) to meet the needs of industry employers. In April, the National University of Singapore launched the Singapore Academy of GxP Excellence (SAGE)—a program designed to train high-quality workers for the pharma industry. Targeting pharma professionals, managers, executives, and technicians as well as those keen to move into the industry, SAGE offers continuing education for basic degree holders, diploma, and ITE qualifications. The Academy plans to train some 300 to 500 professionals annually.

"Part of [Lilly's] mission is giving back to the community by placing internally developed tools in the public domain and participating in the training of the next generation of scientists living in Singapore," says Turpaz. "In the coming years, we'll build a very experienced [work] force, and the people who come out of the industry in Singapore will be very valuable to the global scientific community." But while NUS and others are anxious to create curricula to equip Singaporean students to excel in the biopharma industry, that is a time consuming process.

The result is a very international community. At GIS, about 50% of the staff is from outside of Singapore, says Liu, and Herrling counts 22 countries represented among his NITD employees. Singapore has to entice not only the companies themselves, but the scientists too.

Not surprisingly, A*STAR has a plan for that as well. A*STAR Investigatorships offer outstanding young researchers positions at Biopolis research institutes for two to four years after their Ph.D. While postdocs are not particularly noteworthy, the $500,000 worth of funding for these positions per year for each lab is.

But aside from the salary, how does a country infamous for outlawing gum chewing present such a draw?

"Singapore is really a successful combination of the West and Asia" observed Turpaz. And within the diverse scientific constituencies in Singapore, there is a bond. "Within this community there's absolute social interaction... local and overseas," says Chapman of GSK parties. "Everybody has a great time together." The bond within the biomedical community is a key recruiting point. "It's been a real bonus for us... When people come out here and look around, they get hooked," Champan says.

Miller, formerly based in the United Kingdom, says, "It's a very easy place to live. It's functional. It's safe. It's warm. It's well-located for seeing the region."

While proximity can't be the only selling point, it's hard to overlook that you can be in Bali within two hours and Cambodia, Vietnam, or Australia for a weekend trip.

Miller also points out that some of Singapore's reputation for being "incredibly regulated" is undeserved. "When you get to a street corner and people are standing there waiting for the [walk signal] and there are no cars coming, they're tourists," he jokes.

Novartis' Hanifin moved his family from New York in August 2006. "It's a great place to be right now, because this area is really thriving and booming and there's just a lot of business going on here," he says. "[Personally] if schooling was all I was looking at, I would stay here until my kids went to college," he laughed. "And you have the cultural diversity piece. [My kids are] meeting people from all over the world. For them, I think it's exciting too."

> "In the coming years, we'll build a very experienced [work] force, and the people who come out of the industry in Singapore will be very valuable to the global scientific community."
>
> **Yaron Turpaz**, Lilly Singapore Centre for Drug Discovery

The Singapore buzz is building, and even for some of the seasoned transplants the bloom is not yet off the admittedly steamy rose. "[The heat] smacks you in the face even after three years," admits Chapman. But he is still happy to be a part of what's happening in Singapore. "Three years is certainly long enough for me to become disillusioned, and I'm not. I still have tremendous faith in the potential of Singapore biosciences and as much excitement about it as I had when I got here." •

Economic Development [GUEST COMMENTARY]

Scotland's Bonny Approach to Life Sciences

Collaboration is the life sciences strategy of the future.

The view south across the Edinburgh BioQuarter. In the foreground can be seen the medical school and Royal Infirmary. At the top of the picture, phase 1 development work reveals some of the first 10 development plots. Land has been also acquired beyond the tree boundary.

BY RHONA ALLISON

An international leader in life sciences, Scotland has a long, illustrious history of world renowned scientists and ground breaking innovations, from Sir Joseph Lister's pioneering antiseptic surgery to the cloning of Dolly the sheep by the Roslin Institute. Life sciences is undoubtedly one of Scotland's key strengths, with more medical research being conducted per capita in Scotland than anywhere else in the world.

Such history provides Scotland with a strong foundation and in the new economy—particularly in innovation-driven sectors such as the life sciences—countries must use such legacies to mobilize the entire community to catalyze and inspire future growth. Future success will come not from researchers or companies working in isolation, but from dynamic collaborations where all stakeholders are pulling their weight in the same direction.

Scotland is an environment where the next generation of life sciences innovation is flourishing. In addition to producing world renowned researchers, Scotland is also attracting some of the world's finest scientists, such as former Pfizer chemist Andrew Hopkins, the SULSA research professor of translational biology and chair of medicinal informatics at the University of Dundee, and Karen Vousden, director of the Beatson Institute for Cancer Research in Glasgow. By 2020, the country aims to create a globally focused, sustainable life sciences sector built on a national strategy that exploits strengths in scientific excellence, financial services, and innovative business models and that develops, retains, and builds upon Scotland's talents.

The Queen's Medical Research Institute at BioQuarter offers bright and spacious common areas to encourage interdisciplinary networking.

The vision is ambitious, but also achievable, as demonstrated by collaborative life sciences efforts already in place. From research centers to public-private partnerships, Scotland's life sciences community is distinguished by unique partnerships between industry, academia, and government that connect all parts of the life sciences community, enabling it to work efficiently and effectively.

Partners in Research

The new Edinburgh BioQuarter is one of the most significant life sciences developments in Europe. Combining the academic excellence of the University of Edinburgh, the clinical expertise of Edinburgh's Royal Infirmary and a government-supported research campus with 1.5 million square feet of accommodation, the BioQuarter typifies Scotland's collaborative approach.

Guided by a leading life sciences cluster developer, Alexandria Real Estate Equities, the BioQuarter will be a 100-acre site for biomedical research, co-located alongside the university medical school and the new Royal Infirmary at Little France. The development will create a unique environment to complement the significant advantages of co-locating so much expertise and technology in one place.

The BioQuarter will surely cement Scotland's reputation as one of the world's foremost life sciences hubs.

Public–Private Collaboration

An initiative aimed at developing a world-leading network of clinical and scientific excellence throughout Scotland, the Translational Medicine Research Collaboration (TMRC) combines four of Scotland's leading universities, Wyeth Pharmaceuticals, Scottish Enterprise, and four National Health Service Boards. The partnership is a world first in translational medicine, combining commercial, clinical, and academic expertise to better understand a wide range of diseases such as diabetes, mental health, women's bone disease, cancer, and stroke.

The TMRC released more than $30 million to support 39 new research projects spanning therapeutic areas including cardiovascular and metabolic disease, the central nervous system, women's health, inflammation, and oncology.

Strength in Numbers

The TMRC project typifies the strengths that Scotland has in terms of world-class scientific and academic clusters across its many centers of excellence.

As well as the Edinburgh BioQuarter, Scotland's capital is home to leading academic institutions such as the University of Edinburgh, Heriott Watt University, and the Roslin Institute. These research strengths are fueling growth within Edinburgh's life sciences companies, particularly in stem cells, medical devices, biomanufacturing, and drug discovery.

In Glasgow, the Beatson Institute and the Strathclyde Institute of Medical Devices are cementing the West of Scotland's reputation as a center of life science excellence with particular clinical expertise.

Dundee has emerged as a life sciences center in its own right, with world-class companies, universities, and research institutions within a 3-mile radius. Both of Dundee's universities undertake world-class research, with the University of Dundee globally recognized as a center of excellence for diabetes research.

With companies such as GlaxoSmithKline, Quintiles, Clintec, and Aptuit choosing Scotland as the place to invest and expand their operations, over 1,100 new jobs were created in Scotland's life sciences in 2007.

Scotland's life sciences environment is ripe for long-term success as a global center of excellence and a home for companies looking to access outstanding researchers, a skilled workforce, world-class facilities, and a supportive medical community. It is a model for collaboration that builds on Scotland's historic strengths, and designed for the future. •

Rhona Allison is director of life sciences at Scottish Enterprise. She can be reached at rhona.allison@scotent.co.uk.

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Economic Development [GUEST COMMENTARY]

Oxford Open for Business

England benefits from critical mass of clever individuals.

BY RENATE KRELLE

"It's fashionable to draw Silicon Valley over a map of England," says Tim Cook, visiting professor in science entrepreneurship at Oxford's Saïd Business School.

Cook, the former head of Oxford University's technology transfer company, Isis Innovation, has been part of a prospering of high-technology companies, particularly bio-focused companies, in the green valleys of England's south east—a region which includes the counties of Oxfordshire, Surrey, and Kent.

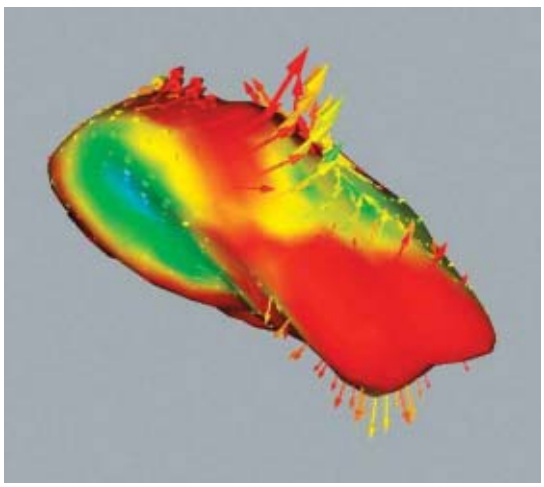
The area has an economic output on par with Austria and Norway, according to the South East England Development Agency. Together with London, it is very much the economic powerhouse of the U.K., and both established technology companies and start-ups are concentrated in the area.

Oxford, of course, is constantly vying for top billing in the U.K. academic charts with Cambridge University, two of the corners of what is often referred to as the "golden triangle" of academic institutions in the U.K.—the third geographic point representing the University of London and Imperial College, London. Together, these institutions receive a large slice of England's higher education research funding.

The concentration of health care and device companies in the region is impressive: some 900 companies, including nine of the world's ten leading pharmaceutical companies, according to SEHTA, the South East Health Technologies Alliance. But Cook downplays direct parallels with the technology hubs of San Francisco or Boston, although he agrees that the presence of a leading university such as Oxford creates a critical mass of clever individuals to seed innovation.

"The university has an impact in that it brings useful people into the area. It provides a forum or dating service in that useful people meet other useful people. And, in the case of students, it also expands the usefulness of those useful people," Cook says.

Cook believes that as well as entrepreneurs, other personalities are essential: "In nuclear reactors they have graphite blocks which slow down the neutrons until they're going slow enough to intact with the next piece of uranium. You need a certain amount of graphite people to facilitate the interactions between the dynamic ones. They might be landlords, lawyers, and the professional classes."



CENTRE FOR FUNCTIONAL MAGNETIC RESONANCE IMAGING OF THE BRAIN

Images from FMRIB help identify differences in brain structure caused by drugs or disease.

Cook has observed these reactions in progress many times as an entrepreneurial culture developed at Oxford. He built Isis from a tiny office back in 1997 to a 50-strong technology transfer group today, which spins out a new externally-funded company every couple of months.

Tom Hockaday, Isis' current managing director, says the company also has a strong "open innovation" model, through both its industry networks—including the Oxford Innovation Society—and a business division called Isis Enterprise. "For the last three years, Isis Enterprise has been working with public and private sector clients beyond Oxford, helping clients develop their own technology transfer processes using our experience, networks, and skills in evaluating new business options."

Cumulative Effect

Helen Lawton-Smith, of the Oxfordshire Economic Observatory, agrees that Oxford has been the beneficiary of a "cumulative effect" of serial entrepreneurs moving to their next ventures as early spin-outs such as Powderject and Oxford Magnet Technology have matured and been taken over by large companies. "The biotech sector is growing particularly well in this region," she says. "There is a growing specialization in biotechnology within the university."

Major government funding for U.K. biomedical research comes from the Medical Research Council (MRC). In 2006, Oxford was the largest recipient of both MRC funding and grants from the Wellcome Trust. Oxford's total external research income for the 2006–7 year exceeded $500 million, more than any other British university.

The leading universities such as Oxford, Cambridge, and London generate more spin-offs than other universities. The southeast attracts 60% of the total investment from members of the British Private Equity and Venture Capital Association—$12 million in 2006. "There is still a national problem of getting later-stage finance, but Oxfordshire can't solve that itself," says Lawton-Smith.

Spinning Value

In 2000, Oxford University struck a remarkable deal to build a new department of chemistry, the first such deal of its kind in the world. In return for a $40 million investment, a publicly-listed commercialization company, IP Group, acquired the rights to 50% of Oxford's equity in spin-out companies and technology licence revenues, based on intellectual property created in department, until 2015. The pace of chemistry spin-outs has accelerated, and Isis has helped launch 11 companies, four of which are now listed on London's AIM stock exchange.

Biotech Investments Across the Union

States make investments in the life sciences.

There are far more players than just San Francisco, San Diego, and Boston throwing their hats in the U.S. biotech ring these days. Dedicated efforts to sustainable biotech clusters and investments are popping up all over the country, with states and regions everywhere vying for big biotech business. Here's a recent sampling:

Washington State is focusing on biology, genomics, and genetics. The state's Life Sciences Discovery Fund issued $22 million in grants to five life sciences organizations. The health research initiatives focus on the areas of medical genetics, autoimmunity, cancer clinical trials, proteomics-based diagnostics and early learning and brain development and were given to researchers from the University of Washington; Benaroya Research Institute at Virginia Mason, Fred Hutchinson Cancer Research Center, and Pacific Northwest National Laboratory.

On the heels of **Ohio**'s second Governor's Cup win (an award recognizing the state with the most new or expanded capital projects in the previous year), the state has announced strong gains in the life sciences sector. Amylin Pharmaceuticals, based in West Chester, announced a $400 million expansion that is expected to create 500 new jobs.

The **Buffalo Niagara region** in upstate New York continues to win acclaim for the quality of life. But tucked away among the historic architecture and breezy commute is the Buffalo Niagara Medical Campus including the Roswell Park Cancer Institute, the Hauptman-Woodward Medical Research Institute, New York State Center of Excellence in Bioinformatics and Life Sciences, and the University at Buffalo. The region also boasts more than 130 life sciences companies. Recently, Buffalo-based Cleveland BioLabs won an $8.9 million federal contract in April to develop a drug to treat the effects of acute radiation syndrome, while Kinex Pharmaceuticals gained another $3 million of angel funding ($8 million total) in March for its anti-tumor drug candidate in Phase 1.

With pharma outsourcing to contract service providers (CSPs) increasing, **Indiana** has claimed a niche with more than 40 CSPs serving big pharma, biotechs, and international firms. In March, one of the largest CSPs, Cook Pharmica announced an $80 million expansion at their Bloomington location, and BioConvergence, another CSP, signed a 10-year agreement with Eli Lilly. Indiana also boasts one of the country's most successful regional health information networks.

Beyond Boston and Cambridge, **Massachusetts** is expanding its life science foothold thanks to Governor Deval Patrick's $1 billion Life Sciences Initiative proposed last year. Merck Serono and its U.S. affiliate EMD Serono—part of Germany's Merck KGaA—are expanding EMD Serono's U.S. foothold with a $50 million expansion at its research and manufacturing facility in Billerica, creating 100 new jobs in the process. •

News compiled by Allison Proffitt.

One of these companies, which recently raised $20 million from private investors, is Oxford NanoLabs, a 2005 chemistry spin-out based on the work of Hagan Baley, an expert in membrane protein engineering. The company, which is developing a next-generation sequencing platform, aims "to be to genomic medicine what broadband was to the internet," according to CEO Gordon Sanghera. "Our nanopore technology is much more elegant than existing technologies and avoids expensive and time-consuming labeling techniques."

Sanghera, an Oxford alumnus, began his commercial career at Medisense, a local blood glucose monitoring company acquired by Abbott Laboratories in 1996 for some $876 million. "Medisense created an exceptional talent pool that you can draw from," he says. "As a spin-out, you can also 'steal' some very good people coming straight out of Oxford. And we are also able to leverage places such as the Rutherford Appleton laboratories, which has a particle accelerator."

Although Oxford is ringed by science parks, Sanghera has found it difficult to the find the right "next level" of facility for the company—growing pains for the industry in the region. But at least "the proximity to London is important for access to the financial markets."

The Next Wave

Back in the labs, a new class of inventors are eyeing the world markets. Biochemist Andrew Pickford aims to leapfrog current protein analysis techniques by using an artificial intelligence technique known as "swarm intelligence" to analyze NMR data, speeding 3-D structure calculations from months to hours.

Software that provides a "color-blob" image of brain activity in real time produced by the Centre for functional Magnetic Resonance Imaging of the Brain (FMRIB), is helping assess how different brain structures are affected by drugs or disease, such as schizophrenia and Alzheimer's.

And former chair of chemistry Graham Richards, who has spun out several successful firms including Oxford Molecular in 1989, is working on an "ultrafast" molecular shape recognition software. It assists in screening potential drug candidates from huge libraries of molecules by measuring the positions of the atoms within a molecule, an approach that is orders of magnitude faster than current methods.

All of the technologies are patented and Isis Innovation welcomes interest from commercial partners.

Renate Krelle is business relationship manager at Isis Innovation. She can be reached at renate.krelle@isis.ox.ac.uk

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Trends in Economic Development

The 2006-07 Bio-Milestones Report from the Biotechnology Industry Organization (BIO) states that during that period the biotech industry attracted $45 billion in new investment, which is more than it generated during the entire 1990's.That signifies strong support of investor confidence in the biotech sector, and its long-term growth prospects.

Of interest is that BIO quantifies 89% of its members as being made up of R&D intensive companies and organizations generating less than $25 million in annual revenue. Additionally, 6% produce revenue between $25 million and $1 billion, while the remainder exceed $1 billion in annual revenue. This suggests that hundreds of companies can be viewed as smaller and developing, and offering high-potential for growth.

With company growth comes the critical hiring of new employees (as well as retention of existing personnel). Job creation is the cornerstone of economic development organizations. To attract growing and mature biopharma companies, local, regional, state, and national programs are actively in place to lure the biotech industry to set up operations in their locale.

So why biotech, and why now? One thing biotech offers differently than most other industries, by its nature, is the prospect for long-term stability. Drug development for even a single drug can span a decade or more. That type of potential staying power is something most economic development groups cannot ignore.

There are several key elements that might persuade a biopharma company to set up shop or expand its operations in a particular location. Those include proximity to present and future top-class scientists and researchers as a university setting can offer, location around government projects, ability to attract necessary grants and investment, and the availability of lucrative or creative incentives from economic development groups.

Trends in the area of incentives range from providing land, tax breaks, advanced and integrated technology infrastructures, and other resources such as bioclusters, where information can be shared and developed across similar and logically aligned interest groups within a given area.

If a geographic entity can offer the right mix of talent, technology, and incentives for a young biotech to become profitable, or an established pharma company to advance its initiatives, that entity will be well on its way to attracting new business, or reaching its goals. The ultimate payoff for the biotech organization and economic development group will be the creation of new jobs filled by qualified individuals promoting a value-chain benefitting all involved.

In the following pages, readers will find some of those attractive reasons to consider why location, or relocation, to a specific area makes good business sense for meeting their initiatives. We encourage you to read what these regions, states, and countries have to say about why you should consider their region as an ideal place to set up — or expand — your business. Please contact them for additional information concerning how they can assist your organization in meeting its bio business objectives. ■

06.08 THE STATE OF LOUISIANA:

THE PERFECT CULTURE FOR GROWING BIOTECH BUSINESSES.

▶▶ Pennington Biomedical Research Center, a world leader in nutrition and disease prevention research, is investigating genetic factors that may contribute to eating behaviors, body weight and binge eating ▶ NuPotential, located at the Louisiana Emerging Technology Center, has developed a revolutionary approach to reprogramming somatic cells into pluripotent stem cells ▶ Esperance Pharmaceuticals is developing a unique targeted anticancer drug that selectively kills cancer cells on contact ▶ Embera NeuroTherapeutics, based at InterTech Science Park, has developed patent-pending treatments for addiction and a wide array of neuropsychiatric disorders ▶ BioFluidica Microtechnologies is developing on-site DNA testing instruments for use in forensics, medical diagnostics and pathogen detection ▶ Louisiana's Angel Investor Tax Credit allows refundable Louisiana income or franchise tax credits of up to 50% of investments ▶ The Tulane Center for Gene Therapy is the first research facility in the nation dedicated solely to using a patient's own donated stem cells

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LOUISIANA ECONOMIC DEVELOPMENT

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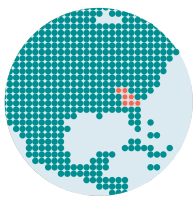
GEORGIA

Georgia: The Emerging Hotspot for Bioscience



The bioscience industry in Georgia is flourishing, thanks to a dynamic collaboration of the state's top corporate, academic and public resources who have joined together to accelerate the transformation of ideas into profitable businesses.

Innovation is the key to maintaining competitiveness, and thus the state of Georgia's Innovation and Technology Office (ITO) focuses on attracting innovative high-technology, bioscience companies and industries to Georgia and helping them thrive. The office is a vital part of the Georgia Department of Economic Development (GDEcD), the state's lead agency for promoting, marketing and supporting Georgia's economic growth.

Georgia's bioscience industry has more than doubled in the past decade and is now ranked seventh among the 50 U.S. states. The state is home to more than 270 bioscience companies, generating more than 15,283 private sector jobs and 6,500 public sector jobs annually.

Georgia boasts a diverse bioscience industry composed of new and existing companies in the fields of pharmaceuticals, medical instruments, agriculture and genetic engineering. The state's numerous universities have sprouted incubators and centers for innovation that are expanding rapidly and have pioneered significant advances in the bioscience field. Their activities span the gamut of research, technical development, manufacturing and sales.

The ITO team works with communities, companies and institutions all over the state to identify and cultivate the exceptional talent that keeps Georgia on the leading edge of research, product development and groundbreaking advances in science and technology. These unique partnerships efficiently mesh state, private industry and university resources for the benefit of innovative business. The office also vigorously recruits new companies and supports the growth of Georgia's existing industry.

Georgia's abundance of resources, cutting-edge research and access to global markets make it the "one-stop shop" for bioscience businesses. The fourth fastest-growing state in the U.S., Georgia attracts a young, educated population creating a strong, talented workforce. The state's colleges have attained global recognition for researching efforts.

Georgia has established strong research partnerships, among them:

- **The Advanced Technology Development Center (ATDC)**, a nationally recognized science and technology incubator that helps Georgia entrepreneurs launch and build successful companies. ATDC provides strategic business advice and connects its member companies to the people and resources they need to succeed. Headquartered at the Georgia Institute of Technology, ATDC has been recognized by Inc. Magazine as one of the nation's top non-profit incubators.
- **The Georgia Research Alliance (GRA)**, which brings together business, research universities and state government to build an innovative and technology-driven economy fueled by pioneering university research. The GRA attracts the world's pre-eminent scientists to Georgia's universities, which helps established companies grow and creates new high-wage jobs.
- **Georgia BIO**, representing the interests of companies, universities, research institutions, government groups and other industry associations involved in discovery and application of life sciences products and related services that improve the health and well-being of people throughout the world. The GBP is the state affiliate of the Washington, D.C.-based Bioscience Industry Organization (BIO). Atlanta will host the 2009 Annual BIO International Convention. ■

More than 250 bioscience companies have discovered Georgia offers more diversity than any other state in the Southeast, both inside the lab and out. There's so much growth here in exciting fields like advanced medical technologies, drug discovery, and biofuels that we were chosen to host the 2009 BIO International Convention. We offer a collaborative atmosphere with outstanding R&D support that includes business incubators, world-class research institutions, and partnerships like the Georgia Research Alliance.

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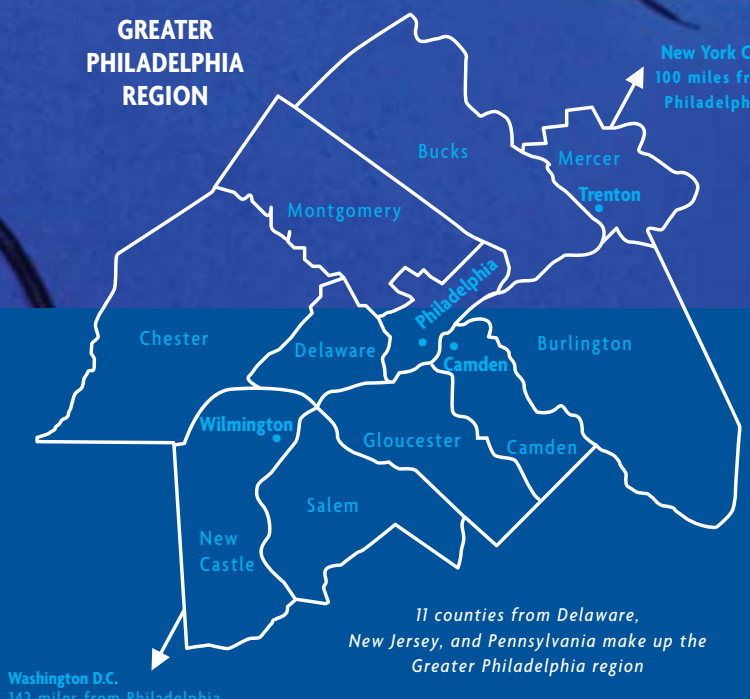

11 counties from Delaware, New Jersey, and Pennsylvania make up the Greater Philadelphia region

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*as of March 15, 2007. For a complete list, see our website.

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SPAIN

Spain's Emerging Biotech Revolution

Driven by a culture, government and private sector that are open-minded and optimistic, Spain-based companies are emerging as leaders in biotechnology.

There's no doubt Spain's strong scientific environment has provided a rich medium for its rapid growth. According to Spanish Genomic and Proteomic Research foundation, Genoma España, Spain's biotechnology sector is growing 10 percent faster than the biotechnology industry in the U.S.

From 2000 to 2006, the number of biotechnology companies in Spain has grown by 166 percent. There are solid foundations for future growth mainly through three critical assets: the endorsement of government and institutions, the excellence of Spanish scientists and a growing interest from investors.

PharmaMar uses marine-derived medicines to advance cancer treatments.

Government-Inspired

Historically, Spain has focused on producing quality scientific biotech research and papers. However, in recent years, there has been a more concentrated focus on technology transfer and spin-offs. At the same time, government support for biotechnology is stronger than ever at every level. R&D spending from 2000-2006 grew by an annual average rate of 34 percent. The country has also seen a 205 percent increase in acquisitions of scientific infrastructure, and a strong network of prestigious centers of excellence has surfaced.

Fueled by the Spanish government's aggressive policies and incentive programs, including the National Plan for Scientific Research and the Ingenio 2010 R&D initiative, Spain has become the fourth largest country in the EU-15 for scientific production in biotechnology and applied microbiology.

Rich Pipeline

A comprehensive portfolio pipeline of health care products developed and issued by The Spanish Association of Bioenterprises (ASEBIO) includes; 28 Spain-based biotechnology companies investing in 119 human drug projects; 26 new disease diagnosis and prognosis systems and; 12 animal health care products.

Current drugs in development are related to the treatment of cancers, infectious diseases, inflammations and nervous system illnesses. A recent report from ASEBIO features 40 developments in clinical phases and 50 projects in the preclinical phase.

A Standout in Biomedicine

Biomedicine is the biotech field in Spain that is the most developed and holds the most potential. Genoma España reports 35 percent of publicly funded research in Spain is conducted in biomedicine. Capitalizing on the country's strength, leading global pharmaceutical companies including, Pfizer, Merck, GlaxoSmithKline, Eli Lilly and Sanofi-Aventis, have opened research labs in Spain. From Spain's biotechnology leaders, small- and medium-sized spin-offs dedicated to research have emerged.

Spain's biotechnology sector is growing 10 percent faster than the biotechnology industry in the U.S.

Additionally, Bio-clusters in several regions of Spain have developed as a result of the collaboration of public administration, private firms and scientific parks. They offer a perfect setting for coordinating research and clinical investigations. They also allow for more efficient transfer of technology, therefore strengthening the introduction of new innovations globally.

Investing in a Partnership with Spain

Spain provides investors with impressive human resources, more than 9,000 biotechnology and biomedicine researchers, solid infrastructures for sector development and an extremely favorable regulatory system.

Levels of private investment have considerably increased; therefore suggesting a leap forward to even higher rates of growth for the biotechnology sector in Spain is imminent. The opportunities in biotechnology are ever-increasing. Spain-based enterprises are now bringing the spirit of collaboration to U.S. firms to help them capitalize on Spain's innovation and expertise to revolutionize their business. ■

The number of biotechnology **patents** awarded in Spain **increased by 30 percent** in 2007.

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SOFTWARE ENGINEER

The goal of this User Interface Design position is to improve the usability of existing and new tools developed by Discovery/Medical IT in order to enable Biomedical Scientists to materialize the benefits which the tools provide.

Qualified candidates must have a bachelor's or master's degree in computer science; experience in Human Factors and Ergonomics (HFE) principles and standards; and experience in designing, developing, conducting, and analyzing usability tests. Candidates must be legally authorized to be employed in the United States. Eli Lilly and Company does not anticipate providing sponsorship for employment visa status (e.g., H-1B or TN status) for this employment position.

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Lead and mentor a strong team for the Bioinformatics group at the Integrative Computational Sciences (ICS) department at LSCDD towards the development of novel algorithms, data analysis methods and software tools for drug discovery. Work closely with the Software Engineering group at ICS, and collaborate with the Discovery IT organization in Europe and USA. For additional information, or to apply visit: *www.lilly.com/careers*.

Lilly Singapore Center for Drug Discovery (LSCDD) — Senior Software Engineer

Join a strong team of software engineers in our Integrative Computational Sciences (ICS) at LSCDD. Collaborate with, and help develop integrated applications to process and visualize data from cutting-edge technologies used by scientists at Lilly Research Labs (LRL) and the Drug Discovery Research (DDR) teams. The Software Engineering team provides computational tools and tailored software solutions that enable the global effort of Tailored Therapeutics; 'The Right Drug, at The Right Dose for The Right Patient at The Right Time'. For additional information, or to apply visit: *www.lilly.com/careers*.

Lilly Singapore Center for Drug Discovery (LSCDD) — Senior Bioinformatics Scientist

Contribute to the development of novel algorithms, data analysis methods and software tools for drug discovery as part of the Integrative Computational Sciences (ICS) department at LSCDD. Work closely with informatics and software engineering peers at ICS, and collaborate with the Discovery IT organization in Europe and USA. The successful candidate will offer hands-on insight and expertise in tailored therapeutic

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Health Outcomes Informaticist

Eli Lilly and Company's Global Medical and Regulatory Information Technology division is currently seeking an Informatics Scientist to enable its health outcomes research and tailored therapeutic programs. Position will be based at the company's corporate headquarters in Indianapolis, IN. As a complement to traditional epidemiology, the advent of post-genomic technologies such as gene expression, genetic association studies etc. and their application towards the goal of personalized medicine (right drug for the right patient at the right dose) requires development of new informatics methods for integration and analysis of epidemiologic, clinical, and genomic data. The developed systems will be utilized by both Outcomes Research Scientists and Clinical Research Physicians. This position will directly support epidemiologic research performed by Epidemiology and Health Services Research, Global Product Safety, and Health Technology Assessment groups at Lilly.

Qualified candidates will have a M.S. in epidemiology/health services research/computer science or related fields; experience in applying various data management and analytic methods and techniques utilized for integrative analysis of epidemiological, administrative claims data, or other large population based data; expertise in heterogeneous data-mining/visualization methods and predictive modeling/simulation techniques relevant to development of tailored therapeutics; and proficiency in one or more mainstream programming languages (C, C++, C#/.NET, Java, Perl, etc.).

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Text Mining Informaticist

Eli Lilly and Company's Global Medical and Regulatory Information Technology division is currently seeking to fill multiple Biomedical Informatics Scientist positions globally to enable its translational research and tailored therapeutic programs. The advent of post-genomic technologies such as gene expression, proteomics, functional genomics, genetic association studies, etc. and their application towards the goal of personalized medicine (right drug for the right patient at the right dose) requires development of new informatics methods for integration and analysis of preclinical and clinical data. The applications developed by the candidate will provide decision enabling data and analyses in support of Lilly's pharmacogenomics and tailored therapeutics programs.

Qualified candidates will have a MS in Biomedical Informatics/Bioinformatics/Computer Science/Computational Biology or related fields; experience in text mining and NLP approaches and tools; previous experience of applying text mining technologies to biomedical or life sciences problems; knowledge of technical approaches such as POS tagging, named entity recognition, parse trees, indexing, inverted files, dictionaries, ontologies, machine learning, SVN etc; and proficiency in one or more mainstream programming languages (C, C++, C#/.NET, Java, Perl, etc.).

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Memorial Sloan-Kettering Cancer Center — Bioinformatics Engineer
MSKCC Bioinformatics Core in Manhattan seeks Bioinformatics Engineer. Design and develop bioinformatics processing and analysis pipelines for traditional and next-gen sequence data. Consult with, train, and analyze data for researchers. Master's degree and 5 years experience in Bioinformatics software development, sequence assembly, SQL, Perl, Python. Email *bicjobs@cbio.mskcc.org* or *www.mskcc.org #015415*. EOE/AA

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Featured Events

DIA 44th Annual Meeting — June 22-26, Boston, MA
The DIA 44th Annual Meeting will offer innovative ideas, provide answers to new questions, and help the pharmaceutical industry redefine the development, regulation, surveillance, and marketing of pharmaceuticals. Keynote addresses by Dennis A. Ausiello, MD, Jackson Professor of Clinical Medicine at Harvard Medical School and Chief of Medicine at MGH, and Kathy Giusti, Founder and CEO, Multiple Myeloma Research Foundation (MMRF) and Multiple Myeloma Research Consortium (MMRC).
www.diahome.org

BIO International Convention — June 17-20, San Diego, CA
Innovate. Heal, Fuel, Feed the World. Discover the latest in biotech innovations in San Diego. Join more than 20,000 industry professionals. Partner with pioneers in healthcare, agriculture, and the environment through the BIO Business Forum. Gain insights into trends with more than 175 sessions and keynotes.
www.bio2008.org/register

5th Annual Meeting on the NCIs Cancer Bioinformatics Grid—caBIG—Initiative — June 23-25, Washington, DC
Sponsored by NCI (free & open to the public). Omni Shoreham Hotel.
http://cabig.nci.nih.gov/2008annualmeeting/

2nd Label-Free Protein-Array-Latest Advances in Analysis of Macromolecular Interaction — July 3-4, Paris, France
The 2nd Label-Free Protein Array workshop offers a unique opportunity to learn about latest advances and emerging technologies in label-free detection. The workshop will gather world class speakers to review new enabling technologies, discuss major technological hurdles to understanding the potential of these new tools and examine current and future applications.
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Monitoring Clinical Drug Studies: Beginner — August 26-28, Chicago, IL
This is a basic "how-to" workshop with a strong grounding in current regulatory requirements designed for entry level monitors with less than one year of experience.
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Monitoring Clinical Drug Studies: Beginner — September 23-25, Boston, MA
This is a basic "how-to" workshop with a strong grounding in current regulatory requirements designed for entry level monitors with less than one year of experience.
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Auditing Techniques for Clinical Research Professionals — Sept 30-Oct 1, Philadelphia, PA
This workshop teaches practical, immediately usable techniques that top-notch Good Clinical Practice (GCP) auditors and FDA investigators employ. They include techniques that are useful when auditing clinical trials that employ Electronic Medical Records (EMR) and/or Electronic Data Capture (EDC). When monitors apply these techniques, they can better detect, correct and prevent clinical study performance deficiencies at clinical sites and within their organizations.
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Drug Development & FDA Regulations: A Regulatory Overview — October 23-24, San Diego, CA
This course provides a comprehensive overview of the drug development process, including GLP, GCP and GMP processes. Is it specially geared toward new industry professionals who need to develop an understanding of the drug development process.
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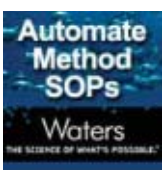

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Best Practices: Gloom and Doom Antidote

JOHN RUSSELL

After a two-year hiatus, *Bio•IT World* again conducted its Best Practices Awards program, culminating in a dinner and awards ceremony last month. The pause in the program was necessary while *Bio•IT World* was being integrated into its new parent organization, Cambridge Healthtech Institute (CHI).

For those of us involved, the Best Practices program is one of the most interesting and rewarding activities that *Bio•IT World* undertakes. It's a fascinating opportunity to identify and spotlight concrete projects that demonstrate how technology can improve drug development. No less important is the opportunity to foster the sharing of ideas within an industry known more secretiveness than forthrightness.

It was gratifying to discover the appetite for a Best Practices showcase is stronger than ever. This year, the program attracted a record 53 entries (thanks to all!), and our awards dinner—held this year in conjunction with Bio-IT World Conference and Expo in Boston—drew more than 200, also a record. I should note two sponsors Microsoft and Blue Arc were instrumental in helping reenergize the Best Practices program (thank you!).

Bio•IT World will publish a full account of the program and profile the 2008 winners in the July issue (See Box). There are lessons for all in the projects they undertook.

They say timing is everything, and at this year's Best Practices dinner, the three main speakers independently chose to talk about how "predictive" technologies are coming of age. In a real sense, this unplanned theme reflects important changes that have been occurring in biomedical research since last Best Practice awards dinner in 2005. The speaker trio included Phillips Khul, president of CHI; Colin Hill, founder and chairman of Gene Network Sciences; and Dietrich Stephan, co-founder and CSO, Navigenics, who incidentally won a Best Practice Award in 2005 for work done at TGEN.

In his opening comments, Khul suggested that the time was ripe for biopharma to wean itself from endless "trial and error and error" and increasingly emphasize what he called "predictiveness." Indeed, he believes *Bio•IT World*'s mission may be too narrowly focused. He argued that *Bio•IT World* magazine and its media portfolio (Cambridge Healthtech Media Group) should actively position itself as the champion of "predictiveness" and its various enabling technologies. He is the boss, so stay tuned.

Hill contended the industry was at the tipping point for achieving data-driven, computational discovery of key gene networks from SNP and clinical data. He cited recent work at Merck and back-to-back *Nature* papers describing efforts in which Rosetta (a Merck division) used computational techniques to reverse engineer critical gene networks involved in obesity and diabetes. He said 50 percent of Merck's pipeline in those areas stemmed from that work. (See p. 20).

Stephan was next up. His company is pioneering personal genomics (See, "Gore at Navigenics Launch," *Bio•IT World*, May 2008). Stephan argued the declining cost of DNA sequencing and advancing software will very soon make genotyping widely accessible. It will be possible to "push a button and get a rank-ordered list" of disease and health predispositions, he said. Prevention, based on understanding these predilections, will eventually transform health care.

This was all good stuff, though their thoughts on timing may be optimistic. Clearly something new is happening, or rather, the technologies that have been bubbling since the completion of the human genome project are now maturing.

What's your prediction? Write to me at john_russell@bio-itworld.com.

2008 *Bio•IT World* Best Practice Winners

- **Basic Research, R&D:** *Christian-Albrechts-University* and *Applied Biosystems*, for developing a pipeline to use for the identification of common susceptibility variants of functional significance for complex diseases, notably Crohn's disease.
- **Clinical Research:** *Eli Lilly & Company*, for managing and tracking metrics associated with implementing the SAS Drug Development solution and partnership.
- **Clinical Trials:** *GlaxoSmithKline*, for developing a novel industry capability which enables robust and efficient safety signal detection in clinical trials.
- **Drug Discovery & Development:** *Genstruct* and *Sirtris Pharmaceuticals*, for developing a Casual Network Modeling (CNM) system—a powerful approach to modeling complex biological systems to characterize the molecular MOA of a revolutionary set of bioactive, Sirt1—activating small molecules.
- **IT Informatics:** *AstraZeneca Pharmaceuticals*, for implementing the FDA's electronic submissions gateway with SAFE digital signatures.
- **Knowledge Management:** *AstraZeneca Discovery*, for standardizing screening data globally and making it available to all AstraZeneca sites.
- **Translational and Personalized Medicine:** *Merck & Company*, for breaking down clinical and research silos that allowed them to view the Biomarker Information Pipeline with the Moffitt Cancer Center.
- **Editor's Choice:** *National Cancer Institute* for caBIG—the Cancer Bioinformatics Grid—a tool that connects the cancer community through a shareable, interoperable infrastructure.

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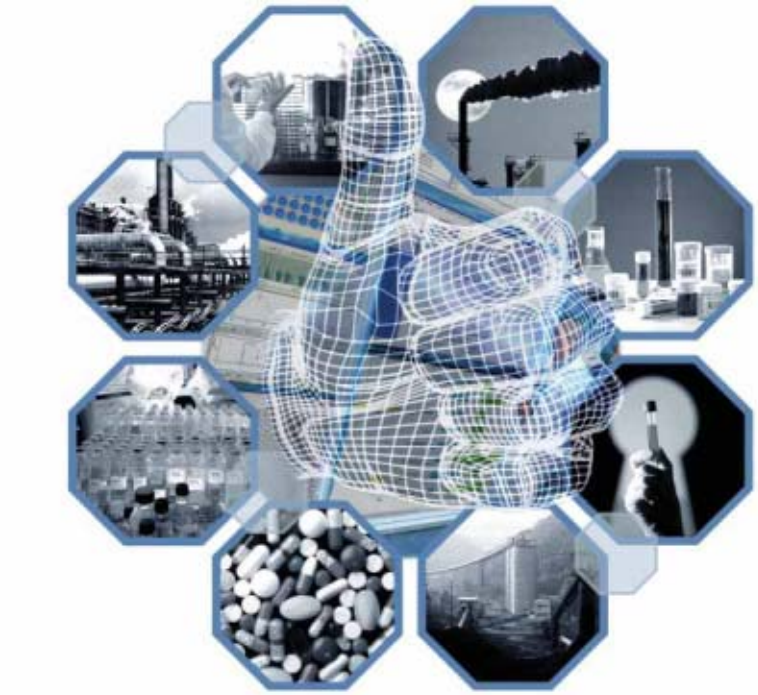

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