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Bio·IT World
Indispensable Technologies Driving Discovery, Development, and Clinical Trials

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We are genuinely excited about the prospects for this field—and the magazine—in the coming year. We've cemented our position as the flagship publication of Cambridge Healthtech Institute (CHI), and will continue to play a prominent role in hosting and reporting on the best CHI conference throughout the year.

We pride ourselves on publishing critical insights and analysis of innovations across the drug discovery pipeline — from molecular modeling of popular drug targets to biomarkers that discriminate cancer responders, and from data handling for next-generation sequencing to new strategies for increasing the speed and efficiency of clinical trials. We will work hard to surpass those stories in the coming year, continuing our pursuit of the most critical tools and strategies that epitomize the world of "predictive biology."

We hope to continue to engage you with our editorial content, and within our network, and as always, we welcome any and all comments or suggestions—editor@healthtech.com

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TEN BEST

Lisa La Luna, ePharmaSolutions, Jennifer Reichuber, Sudheer Swamy, Genentech

Meet the 2009 Best Practices Awards Winners

20–37

Exploring Next-Generation Sequencing

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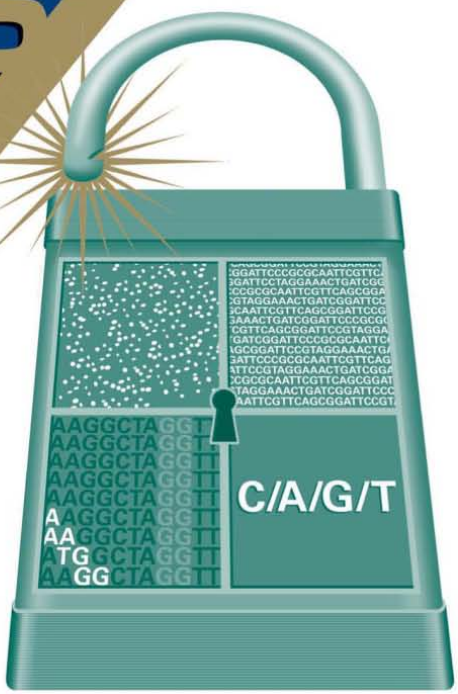
Second-generation applications to third-generation progress



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Cover photo by Mark Gabrenya

First Base

Bio•IT World's Oktoberfest

KEVIN DAVIES

Bio-IT World Expo debuted in Boston in 2002, and with one exception (San Diego later that same year) has made Beantown its home. But this October, we will be taking the show on the road… to Hannover, Germany, home of the BIOTECHNICA 2009 trade exhibition, with the exciting debut of Bio-IT World Expo Europe.

BIOTECHNICA is one of Europe's foremost biotech trade fairs, drawing thousands of attendees each year. This year, our parent company Cambridge Healthtech Institute (CHI) was invited to collocate one or more conferences at the show. The timing was perfect: we have been eager to take Bio-IT World to other locales for many years, and BIOTECHNICA provides the ideal platform. (CHI is also debuting PEGS Europe 2009.)

Elsewhere in this issue, you will find a full run down of the program (p. 38-39). The Bio-IT World conference will be divided into four tracks, each running about a day and a half. The conference contains plenty of heavy hitters from both sides of the pond. The Europeans are represented by the likes of Phil Butcher (Wellcome Trust Sanger Institute), Jan Korbel and Reinhard Schneider (EMBL), Corrado Priami (Microsoft Research/CoSBi), Hans Lehrach (Max Planck Institute), and John Overington (EMBL-EBI). Waving the flag for the U.S. are Matthew Trunnell (Broad Institute) and our 2009 Boston keynoter, Chris Dagdigian (BioTeam).

The conference also contains a wealth of big pharma representation, with talks on the agenda from companies such as AstraZeneca, Bayer Schering, Novartis, Merck Serono, and Pfizer.

You can find the full program at www.bio-itworldexpoeurope.com. We hope to see you in Deutschland!

Consumer Genetics Show and Tell

Illumina CEO Jay Flatley stole the Consumer Genetics Show by unveiling Illumina's new personal genome sequencing service priced at $48,000. He capped that by showing a picture of the first doctor's prescription for a whole genome sequence–his own. Flatley says he has wanted to embark on personal genomics for several years. "It started right when we bought Solexa," he told *Bio•IT World*. "It was just a matter of what was the right time in terms of the market and our technology."

Illumina's new sequencing service will be conducted in the firm's CLIA-certified laboratory, offering 30-fold sequence coverage assembled against the reference genome, plus information on single nucleotide polymorphisms, structural variations, insertions, and deletions. Illumina will not, however, be providing the detailed medical interpretation of the sequence, preferring to partner with 23andMe, deCODEme, Navigenics and Knome for consumers who want additional layers of analysis. "It's not Illumina's intent, nor is it our skill, to connect genetic information to medically relevant information, and that's a role we're going to ask other companies to help us play," Flatley said.

iPhone Personal Genomes App.

Flatley is the first of four volunteers for the new service, along with venture capitalist Hermann Hauser, Harvard professor Henry Louis "Skip" Gates, Jr., and his father Henry Louis Gates Sr. The pricing dramatically undercuts Knome's $99,000 personal sequencing service, although that includes very detailed counseling and interpretation and slick IT security. Flatley isn't expecting to be flooded with prescriptions, but believes that by providing the service now, "Illumina can help catalyze the development of the infrastructure and physician education that will be necessary as genomic information becomes medically more meaningful."

"Ultimately, we think the data needs to be mobile connected and wind up in the cloud," said Flatley. "You can't fit the entire genome onto an iPhone today, but once we've calculated the Vnome (variant genome), this becomes feasible." Flatley even showed a preliminary concept of the iPhone personal genomes app, produced by a developer in a mere ten days. Following fingerprint identification, the app would present data on many different diseases and traits. It could list by disease, drug response, or chromosome; search by genes; share facilities with friends and family; and so on. Finally, Flatley joked that if people spend too much time analyzing their genome on their iPhone and the boss walks in, "all they have to do is shake and they'll be right back to the spreadsheet analyzing their sales numbers."

The Consumer Genetics Show was the brainchild of John Boyce, former head of business development at Helicos. The event attracted hundreds of attendees with little advance marketing. Boyce is to be congratulated for pulling together this event, which promises to grow dramatically in the years to come.

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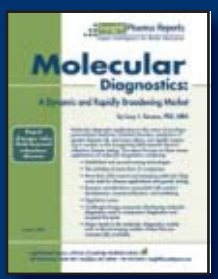

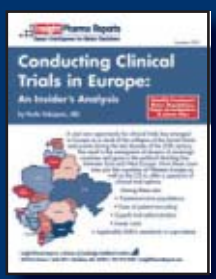

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Eric Schadt

MARK GABRENYA

PacBio Nets Eric Schadt as Chief Scientific Officer

Schadt still committed to Sage and Friend.

BY KEVIN DAVIES

Eric Schadt, the Merck biomathematician pioneering studies on disease pathways and genome data integration, has joined the next-generation sequencing company Pacific Biosciences as Chief Scientific Officer. Last February, Schadt joined then Merck vice president Stephen Friend at CHI's Molecular Medicine Tri-Conference to announce the creation of a new non-profit organization, Sage Bionetworks. Friend remains 100% committed to Sage and Schadt is helping to secure its launch.

Schadt, who said "things were brewing" when he delivered a keynote at Bio-IT World Expo in April, says: "Pacific Biosciences is at an amazing point, they've assembled an absolutely amazing team focused on this [next-generation sequencing] problem."

"Eric represents probably some of the most bleeding edge brilliant thinking on how biological problems are going to be unraveled," says PacBio CEO Hugh Martin.

"Sage is still screaming ahead," Schadt insists. Assets will have transitioned out of Merck by early July, and be based at the Fred Hutchinson Cancer Institute in Seattle. Schadt will devote some of his time to help Sage get launched. "It would have been a 'no go' for me if my making this move [to PacBio] wasn't seen as synergistic at this stage—I wouldn't have done it," said Schadt. "What Sage needs to make it are large-scale data; complex model-building expertise that can be represented on their platform; and then the platform piece. I decided that I will spend most of my time on the data generation and help enabling the model building."

Of most importance to Sage is producing "large-scale data that informs models in the best ways, and the model building." Schadt intends to dedicate more time to generating "the kinds of data that are going to take the model building to the next level. And the best avenue I saw to lead that kind of revolution was with Pacific Biosciences." Schadt says there is "a tremendous gap" between PacBio's

(CONTINUED ON PAGE 10)

Stephen Friend: On the Road from Merck to Sage

As Stephen Friend returns to Seattle to head up Sage, he spoke to *Bio•IT World* about the impact of Schadt's move and his thoughts on leaving Merck.

***Bio•IT World*: Stephen, how will Sage be impacted by Eric Schadt's move to PacBio?**

Friend: For the past year, I have known of Eric's interest in making sure that Sage was powered up properly, but also that his desire to be rich to the new technologies was going to be something that always had some possibility. In that context, what I'm pleased with is the commitment that he has to help drive the mission we're doing in Sage. I really feel that's important to him...

Where he feels a need to drive is both in building the models, which is always what he's enjoyed, but also [to] get involved in making the data, getting the data into the models. If you picture a Venn diagram, or two pieces, the primary Sage interest starts with the models and goes onto the platform on which you'd want to put those models... I actually think for a while, we thought, we can just do it all, the pieces will be on either side. I think we appreciated over the last couple of months that that was tricky to try and do it all.

Stephen Friend

You've checked all the boxes—medical research, a start-up, big pharma, now a non-profit...

I'm not trying to do a grand flush! The problem, which I

(CONTINUED ON PAGE 10)

Pubget Searches and Delivers Scientific Journal PDFs

The new tool offers full text versions to partner organizations.

BY KEVIN DAVIES

Pubget is a new search tool for the life sciences literature that pulls up full-text PDFs of any paper in a single click. Following a quiet launch last year, the Cambridge, Mass. startup just announced its first 50 partners, including Caltech, Dartmouth, Harvard, Massachusetts General Hospital, MIT, NIH, Princeton, University of California San Francisco, University of Michigan, and University of Virginia. A further 200 organizations are waiting to partner as well. Ryan Jones, Pubget president, says the firm has enrolled tens of thousands of users, and is doubling every month.

> Pubget knows exactly where on the web full-text PDFs live from 20,000 journal titles.

The original Pubget product was developed by Ramy Arnaout, a mathematician-turned-clinical pathologist at Beth Israel Hospital. He grew frustrated trying to get full-text PDF access to journal articles—even while working inside well-endowed institutions like Harvard and Oxford. Arnaout joined forces with Ian Connor, formerly with Lotus and IBM, and started building a new search tool.

"Pubget is a platform for life science research," says Jones, who explains that Pubget is built on three key components. "One is a search engine that has all the content that Medline or the NIH's PubMed has in it—20 million research documents." Pubget's open-source search engine uses a relevancy algorithm similar to PubMed, Jones explains, except a little fresher. "We took an initial data dump from PubMed, and now we've based direct connections to the publishers themselves."

Second, Pubget built a "pathing engine" that understands the location of the full-text PDFs across all 20,000 journal titles. "It knows exactly where on the web that full-text document lives," says Jones. "We have crawlers that go out and understand at *Nature* or *Cell* or *Science* where those full-text documents live. In very much the same way that Google finds HTML, we can find the PDF." The third component is what Jones calls a "credentials engine," which identifies the user's current subscription access. "It can go into a library's holdings page and interpolate what they have rights to."

Search results are delivered in the form of the full-text PDF, without having to navigate through abstracts or publisher's electronic portals. Users who are not associated with a larger institution can use the tool for free full-text document search via PubMed Central and other resources. Users affiliated with institutions use Pubget to take advantage of the host institution's subscriptions.

The first 50 partners are about two thirds academic institutions, as well as hospitals and some commercial organizations. Jones says Pubget already has users at all of the top 12 big pharmas, but no formal relationships as yet ("meaning we haven't turned them on yet").

Pubget will in time make money by offering premium services and aggregating analytics about current life science search topics. "We can help vendors like Agilent or Bio-Rad understand what the community is searching on," says Jones. "If you do a search on swine flu, and someone did a virus study and in the methods of that study cited a specific type of microscopy, we can present ads relevant to that." Pubget can be found at pubget.com •

INFORSENSE ACQUIRED

InforSense has been acquired by **ID Business Solutions** (IDBS), a private software company headquartered in the UK with offices worldwide. According to the InforSense announcement, IDBS will maintain the InforSense brand and continue to invest in the development and support of the established product lines both independently and jointly marketed. The announcement calls the two companies' products complementary and the acquisition reportedly makes IDBS the first organization in the R&D sector to provide the entire spectrum of products for data capture, storage, integration, retrieval, analysis, and visualization.

GENOMICS MACHINE

CLC bio has released their first turnkey solution for analyzing and visualizing Next Generation Sequencing data, called CLC Genomics Machine. The turnkey solution will consist of a hardware platform, pre-installed software including various accelerated algorithms for Next Generation Sequencing data analysis, and an enterprise level database—all ready to function straight out of the box.

SEARCH AND DISCOVER

The **European Molecular Biology Laboratory** has launched the Gene Expression Atlas and Reflect, an automated document annotation service. The Gene Expression Atlas allows scientists to search and compare gene expression data at unprecedented detail and scope. The Atlas collates data from over 1000 different studies, mostly microarrays. Reflect pinpoints all genes, proteins and small molecule names on any web page. With a single click, pop-up windows provide extra information on any molecule, such as domain structure, subcellular localization, 3D structure, and interaction partners in the case of proteins.

Friend

(CONTINUED FROM PAGE 8)

think is going to be the hardest one, the one I hope I can add the most to, is: How can multiple groups that until now have been siloed, be brought together in a way that they recognize that, by sharing that data, the models they build will get them each to their respective tasks. I saw the power of large groups working on things, but I also saw the limit to that large group... The complexity of biology is far greater than anyone is willing to admit. To actually be able to make sense of out of that will not be a solo group effort. It will not be a product. It will not be a company by itself, but instead, a community effort. That is really tough, but I think now is the time to work on it.

Do you see signs within pharma that pre-competitive sharing can gather momentum?

I think it is and it isn't... People are waking up: Oh my god, I don't know what to do with the data! Where they are not willing to be pre-competitive is when they start in with strategies. People have made a mistake in trying to get companies to cooperate when they absolutely need to have an advantage and to have something that's theirs. That split between what is and what's not pre-competitive has gotten garbled. Why won't pharma companies work together? That's the wrong argument.

What were your group's greatest achievements and frustrations at Merck?

On the frustration, I was naïve to the length of time required to move an idea through to a target, through to a compound, as all are. Anyone who has not been in pharma who says they know how long it takes—until you're there, you don't! It's not the company per se, but the process. We're frustrated that I can't move time.

The rest of it was actually a remarkable view into an efficient organism that outstrips so much that you can usually do if you have not had that coherence in a company. I was frustrated by some of the time elements, but I was impressed by the ability to execute on large projects.

Schadt

(CONTINUED FROM PAGE 8)

single-molecule sequencing technology "and the second-generation technologies like Illumina, which is going to be completely game changing."

Friend says Schadt's decision was not a shock. "For the past year, I have known of Eric's interest in making sure that Sage was powered up properly, but also that his desire to be rich to the new technologies was going to be something that always had some possibility," he tells *Bio•IT World* (see, "On the Road from Merck to Sage").

Martin's Man

PacBio CEO Hugh Martin says his company had always planned to hire a CSO when the time was right. He credited co-founder and chief technology officer Steve Turner for steering PacBio to the point that "we're actually in the middle of building the first commercial system. He's done a phenomenal job and will remain our CTO, focusing more on how we sequence and what other applications for this technology are there."

"The leverage Eric gets by being here on solving these problems is far greater than if he built a state-of-the-art sequencing center in Seattle," Martin continues. "Eric is going to be on the front lines for us, talking to all these [scientists] around the world, helping them think about what they can do with the sequencing capabilities third-generation represents and how to deal with all this data."

Schadt sees the speed and longer read lengths as major attributes of the PacBio platform.

He estimates that the PacBio technology is about 25,000 times faster than current methods. Moreover, "people are way under-appreciating" how important longer read lengths are going to be. •

[GUEST COMMENTARY]

Patent Rights and Civil Wrongs: The ACLU Lawsuit

BY ANDREW W. TORRANCE

The American Civil Liberties Union (ACLU) would seem an unlikely candidate to be interested in genetic tests for diagnostic mutations. From its origins in the struggle to prevent the United States from entering World War I, the ACLU has evolved into a self-proclaimed "guardian of liberty," traditionally focusing on provisions of the Constitution protecting freedom of speech, equal protection, and privacy.

However, last month (on May 12), on behalf of several medical associations, advocacy organizations, physicians, researchers, and individuals, the ACLU filed a lawsuit naming the United States Patent and Trademark Office (USPTO) and Myriad Genetics among the defendants in a potentially historic patent case.

The ACLU's lawsuit ostensibly focuses on the legitimacy of the infamous *BRCA1* and *BRCA2* breast cancer gene patents granted to Myriad Genetics, but it seeks nothing less than the elimination of human genes as patentable subject matter.

In the words of its complaint: "Every person's body contains human genes, passed down to each individual from his or her parents. These genes determine, in part, the structure and function of every human body. This case challenges the legality and constitutionality of granting patents over this most basic element of every person's individuality." The lawsuit calls out the dangers of more than just human gene patents. It also condemns the patentability of "the concept of looking at or comparing human genes, and correlations found in nature between certain genes and an increased risk of breast and/or ovarian cancer".

Roughly 13% of American women (1 in 8) will develop breast cancer at some point during their lives—almost 200,000 new cases and more than 40,000 deaths per year. Women who carry inherited mutations in their *BRCA1* or *BRCA2* genes face increased risk of 36-85%, as well as heightened risk of ovarian cancer (16-60%). The *BRCA1* gene was isolated and subsequently patented (along with *BRCA2*), and is now owned by Myriad, a Salt Lake City biotech company, which also maintains a patent monopoly on the diagnostic sequencing tests—tests that cost around $3000 and are out of reach to many lacking health care insurance.

Any Gene Under The Sun

But the ACLU patent case goes to the very heart of gene patents. Genes have long been patentable, and myriad genes (including Myriad's genes) are currently claimed in patents in the United States and elsewhere. Since 1975, the USPTO has issued more than 15,000 patents whose claims contain the word "gene."

> The ACLU lawsuit seeks nothing less than the elimination of human genes as patentable subject matter.

In 1972, Ananda Chakrabarty, a biologist at General Electric Company, filed a U.S. patent application for a genetically engineered strain of Pseudomonas bacteria. The U.S. Supreme Court, in a watershed 1980 decision (*Diamond v. Chakrabarty*), allowed the patent (4,259,444) to issue, and famously declared that "anything under the sun that is made by man" might qualify for patent protection. The USPTO waited until 1982 to issue its first patent claiming genes per se. The number of patents issued with claims mentioning "genes" or "DNA" peaked in 2001, declining since then.

Section 154 of The Patent Act confers on a patent owner "the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States." This right to exclude others is especially controversial in the realm of gene patents. Kyle Jensen and Fiona Murray estimated that, by 2005, almost 20% of human genes had been claimed in a U.S. patent "gold rush." Michael Heller and Rebecca Eisenberg worried that excess patenting of human genes could lead to a tragedy of the "anticommons" capable of chilling further genetic research. As the late Michael Crichton wrote in an outraged Op-Ed in the New York Times in 2007:

"YOU, or someone you love, may die because of a gene patent... Gene patents are now used to halt research, prevent medical testing and keep vital information from you and your doctor."

But the situation may not be as dire as opponents of gene patents suggest. In a study on litigations involving patents in his comprehensive database of human genes claimed in patents, Christopher Holman found that, "not one of the 4,270 patents in the dataset has ever been found to have been infringed or been the basis of a preliminary injunction."

The biotech industry argues, with some justification, that substantial investments in search of novel diagnostics and drugs would not be possible without patent protection for genes and their uses. As Sheila Jasanoff writes in her book, *Designs on Nature*, "extension of patents to the life sciences created new classes of property rights in things that were previously outside the realm of what could be owned, or even thought of as subject to ownership claims. As a result, these objects became commodities that could have value, be exchanged, circulate in markets, and foster productivity."

Nevertheless, in the absence of profitability for the biotech industry as a whole, it has been suggested that biotechnology has so far been more successful at producing patents than drugs. Availability

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Patent Rights

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of patent protection for genes has generally been assumed to spur the discovery and elucidation of more new genes, while simultaneously limiting others' access to those same new genes. In fact, Michael Meurer and James Besson, in their book *Patent Failure*, confirm the economic value of biopharmaceutical patents, even though they cast doubt on the value of patents in other industries.

One Appeal, Two Issues

In its lawsuit, the ACLU has decided to tackle two of the most controversial issues in patent law—human genes and diagnostic methods. It has gathered a group of extremely sympathetic plaintiffs, including patients seeking access to medical diagnosis of a devastating disease and medical professionals requesting the right to deliver such diagnosis without fear of infringing a corporation's patents. (One plaintiff was unable to get a second opinion on her breast cancer test; another could not get coverage of the test through Medicaid.) If successful, the ACLU could substantially redraw the patentability landscape that undergirds the biotech industry, and possibly alter the balance of incentives to promote new genetic discoveries and the development of new therapies and diagnostics.

Two hurdles stand in the way of the ACLU and its plaintiffs. First, genes have long been considered patentable subject matter. Despite arguments portraying genes as discoveries or the common patrimony of humanity, it is unlikely that any Federal court will overturn the 29 years of precedent beginning with *Diamond v. Chakrabarty*. To do so would invite vigorous opposition by the biotech industry and swift reversal by the Federal Circuit or the Supreme Court.

Second, none of the plaintiffs who sued Myriad have themselves been sued for infringing Myriad's patents. This could trigger a constitutional doctrine called "standing" that restricts who is allowed to bring a lawsuit. The USPTO is likely to be granted substantial deference in its interpretation of the Constitution, the Patent Act, and related judicial decisions; its interpretation that genes constitute patentable subject

Patently Controversial

Patent law has already responded to limit human gene patents. For example, in 2005, the Court of Appeals for the Federal Circuit decided a case called *In re Fisher* that involved claimed "expressed sequence tags" (ESTs)—gene fragments rather than whole genes. Monsanto cited the usefulness of ESTs in locating whole genes in the maize genome, but the Federal Circuit rejected the claim to ESTs on the grounds that it lacked enablement and utility.

While *In re Fisher* made it more difficult to patent gene-based inventions, the influential Supreme Court decision, *KSR International v. Teleflex*, by tightening the nonobviousness requirement, has made it more challenging to patent inventions in all areas of technology. Furthermore, a renewed judicial interest in patents that implicate human thought may signal difficulties for patents claiming gene diagnostic tests.

Congress has also noted the anxiety over gene patenting, even considering amendments to the Patent Act that would effectively ban gene patents. In 2007, Congressman Xavier Becerra (D-CA) proposed the "Genomic Research and Accessibility Act." This bill would have provided that "no patent may be obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies."

To date, genes remain patentable subject matter and gene patents remain potentially valid and enforceable. However, the future is now less certain in the face of increased judicial and Congressional scrutiny. In addition, empirical evidence suggests that issued gene patents are rarely asserted against others in litigation. The ACLU may have chosen a propitious moment to challenged Myriad's patents.

Thought Police

The ACLU's lawsuit against the USPTO and Myriad Genetics is something of a sequel. The organization previously filed an amicus brief in a high-profile Federal Circuit appeal called *In re Bilski*. This case considered an invention alleged to require a "mental step" capable of being carried out by a human mind. In the middle of the 20th Century, courts developed a judicial doctrine—"mental steps doctrine"—to limit patents whose claims implicated human thought. In 1951, the Court of Customs and Patent Appeals stated in its *In re Abrams* decision, "[i]t is self-evident that thought is not patentable."

In 2006, Supreme Court reversed its decision to decide an appeal on the patentability of method of medical diagnosis. The patent claim in *Laboratory Corp. v. Metabolite Laboratories*, was a method for detecting a deficiency of cobalamin or folate in warm-blooded animals based on "assaying a body fluid for an elevated level of total homocysteine; and correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate."

The litigants agreed that "assaying a body fluid" referred to any test that detects an elevated level of total homocysteine. Furthermore, the inventors testified that "correlating" simply referred to a doctor recognizing an elevated level of homocysteine, a result that "would occur automatically in the mind of any competent physician." After the Federal Circuit found that claim 13 was not invalid, and that Laboratory Corp. had infringed it, the Supreme Court granted Laboratory Corp.'s petition for certiorari. The court limited the appeal to a single question:

> Availability of patent protection for genes has generally been assumed to spur the discovery and elucidation of more new genes.

matter will be difficult to overturn unless Congress does, indeed, amend the Patent Act to ban gene patents.

On the issue of diagnostic patents, however, the ACLU may be on firmer ground. In light of recent decisions (see, "Patently Controversial"), methods of diagnosis that rely on correlation, or other relatively simple reasoning, appear vulnerable to challenges that they do not constitute patentable subject matter. A Supreme Court decision in *In re Bilski* could certainly be decisive, either for or against patentability of diagnostic methods. A year from now, the prospects for diagnostic methods such as Myriad's BRCA tests will likely be much clearer.

By forcing the issue into court, the ACLU has raised what were once esoteric issues of patentable subject matter to new heights of public awareness. Such prominence is unlikely to endear existing patent law doctrine to those who rely upon, pay for, and fear being excluded from medical care. Even if the ACLU fails in court, its gambit will likely harm the future prospects of human gene patents and diagnostic patents by emphasizing the image of patent monopolists who assert ownership over natural molecules and then restrict access to medical care.

Although the issues surrounding patentable subject matter in biotechnology are much more complex and important than this negative image conveys, the next time Congress rushes to limit such patents, it will likely find a much larger constituency supporting its efforts. •

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"[w]hether a method patent... directing a party simply to 'correlate' test results can validly claim a monopoly over a basic scientific relationship... such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result."

Despite widespread anticipation of a decision definitively affirming or restricting "human thought" patents, the court declined to decide the case on the grounds that the writ of certiorari had been improvidently granted. This left the decision of the Federal Circuit intact. Justice Breyer wrote a blistering dissent, in which he argued that claim 13, and claims like it, should be unpatentable.

In the wake of the Supreme Court's non-decision, the lower courts decided a flood of cases involving patent claims alleged to involve thinking steps. Among these were the *In re Comiskey* and *In re Bilski* cases, both recently decided by the Federal Circuit. The latter invention involved "a method practiced by a commodity provider for managing (i.e., hedging) the consumption risks associated with a commodity sold at a fixed price." The Federal Circuit stated the legal issue they would decide as follows:

Whether the claimed subject matter is not patent-eligible because it constitutes an abstract idea or mental process; when does a claim that contains both mental and physical steps create patent-eligible subject matter?

To decide the case, the court articulated a "machine-or-transformation" test, declaring that "[a] claimed process is surely patent-eligible... if (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." Neither applied in this case, and so the court held the claims to be unpatentable.

In re Bilski has important implications for medical diagnostic patents. Citing the *In re Bilski* decision in December 2008, the Federal Circuit, in *Classen v. Biogen*, affirmed a lower court's decision to invalidate patent claims on "evaluating and improving the safety of immunization schedules". The lower court found that "the correlation between vaccination schedules and the incidence of immune mediated disorders that Dr. Classen claims to have discovered is a natural phenomenon."

In another case decided last April, *Ariad Pharmaceuticals v. Eli Lilly*, the Federal Circuit found patent claims relating to modulating gene expression invalid for lack of adequate disclosure, and shed little light on patentable subject matter. Interestingly, Myriad Genetics considers the *Prometheus v. Mayo* appeal (which deals with patent claims covering methods of optimizing treatment of Crohn's disease) vital enough to its own interests that it has filed an *amicus curiae* brief urging the Federal Circuit to reverse the lower court's decision.

Allowing the patenting of "human thought" per se would clearly be problematic. As Dan Burk points out, "there would seem to be profound First Amendment implications to the concept of infringement by 'thinking patented thoughts'." The Supreme Court has just granted certiorari for *In re Bilski*, to clarify the patentability of inventions involving human thought, and to provide the sort of guidance it declined to provide in Laboratory Corp. Providing the Supreme Court actually renders a decision this time, the patentability landscape for biotechnological inventions may be altered significantly. **A.T.**

Only Moore's Law Can Save Big Pharma

BY BILL FREZZA

If ever there was an industry at risk of being sunk by not one but three hurricanes, it's the pharmaceutical industry. Whether it's on the political, economic, or scientific front, this major contributor to our nation's financial and physical well being is headed for wrenching transformations.

Politically, Big Pharma is at the mercy of all three branches of an increasing hostile government. The executive branch, through its regulatory agencies, has raised the cost of product development to astronomical heights. The judicial branch, through its class action machinery, has made the penalty for delivering anything short of zero-defects untenable. And the legislative branch, on its way to becoming the industry's monopsony purchasing agent, is hell bent to drive prices down to the marginal cost of production.

Economically, Big Pharma continues to deliver less and less for more and more. A new blockbuster cancer drug is almost never a cure. The "good" ones have no effect on most patients besides making their hair fall out while helping some "fortunate" subset die in 15 months instead of 12. For some advanced biologics, this pathetic result comes with a sticker price of $100,000. The only reason there are any customers at all for products this bad is that someone else is paying the bills.

Scientifically, the classic drug discovery paradigm has reached the end of its long road. Penicillin, stumbled on by accident, was a bona fide magic bullet. The industry has since been organized to conduct programs of discovery, not design. The most that can be said for modern pharmaceutical research, with its hundreds of thousands of candidate molecules being shoveled through high-throughput screening, is that it is an organized accident. This approach is perhaps best characterized by the Chief Scientific Officer of a prominent biotech company who recently said, "Drug discovery is all about passion and faith. It has nothing to do with analytics."

Does this sound like science to you?

The problem with faith-based drug discovery is that the low hanging fruit has already been plucked, driving would be discoverers further afield. Searching for the next miracle drug in some witch doctor's jungle brew is not science. It's desperation.

The only way to escape this downward spiral is new science. Fortunately, the fuzzy outlines of a revolution are just emerging. For lack of a better word, call it Digital Chemistry.

Drug companies of the future will be built around drug *design*, not discovery. Scientists cross trained in engineering will run product development teams with productivity levels comparable to other industries. Compare this to today's chemist, who can spend an entire career at a pharmaceutical company without ever working on a drug that gets to market. This is not just scientifically embarrassing, it's economically indefensible.

Tomorrow's drug companies will build rationally engineered multi-component molecular machines, not small molecule drugs isolated from tree bark or bread mold. These molecular machines will be assembled from discrete interchangeable modules designed using hierarchical simulation tools that resemble the tool chains used to build complex integrated circuits from simple nanoscale components. Guess-and-check wet chemistry can't scale. Hit or miss discovery lacks cross-product synergy. Digital Chemistry will change that.

But modeling protein-protein interaction is computationally intractable, you say? True. But the kinetic behavior of the component molecules that will one day constitute the expanding design library for Digital Chemistry will be synthetically constrained. This will allow engineers to deliver ever more complex functional behavior as the drugs and the tools used to design them co-evolve.

How will drugs of the future function? Intracellular microtherapeutic action will be triggered if and only if precisely targeted DNA or RNA pathologies are detected *within* individual sick cells. Normal cells will be unaffected. Corrective action shutting down only malfunctioning cells will have the potential of delivering 99% cure rates. Some therapies will be broad based and others will be personalized, programmed using DNA from the patient's own tumor that has been extracted, sequenced, and used to configure "target codes" that can be custom loaded into the detection module of these molecular machines.

When it arrives, the transition to Digital Chemistry will be similar to the revolution set in motion when engineers began using transistors as switches instead of amplifiers. Over the succeeding 40 years, the semiconductor industry used the simplest of components to design increasingly more sophisticated integrated circuits whose complexity now rivals that of many of the metabolic disease pathways we hope to control.

Only Moore's Law can save Big Pharma. We better hope it arrives soon.

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Analyzing the Next Generation of Sequence

In the upcoming report "Next-Generation Sequencing: Solving the Genome," Insight Pharma Reports spoke with Steven Salzberg, director, Center for Bioinformatics and Computational Biology, University of Maryland about managing and analyzing next-gen data and the software that's making it happen.

Insight Pharma Reports (IPR): Next-gen sequencers are churning out tons of data. How important and feasible is archiving all of that?
Steven Salzberg: It's important to keep the processed data, and it's important to distinguish the raw data from the sequencer's images. Files of imaging data from the sequencing plates, gels, or slides are gigantic. Image-processing software figures out the nucleotides from the images and generates files that are large, but not nearly as large as the images. So it's important to save all the sequence reads so you can recall them, but not the raw images. Those images, [can] generate on the order of a terabyte of data for one experiment. When you compress that terabyte of data down to DNA sequence, it's going to be tens of gigabases

IPR: You noted a year ago that data analysis software designed for Sanger sequencing, may not be adequate for short-read re-sequencing. Have instrument manufacturers been responsible for improvements in this area, or has it been largely academicians or third-party software companies?
Salzberg: Actually all three. I know the most about the ABI, Illumina, and Roche instruments. For the task of assembly, that is reconstructing a genome from the reads, there's an assembler the Roche people have developed called Newbler that's pretty good at assembling sequences of the type that their machine produces.

Recently, there have been several new assemblers released for use with very short reads. Three were published in the same issue of Genome Research. We tried them all. The one we like the most is called Velvet, and that's become pretty popular in the community. It was developed at the European Bioinformatics Institute in the UK, and it really works quite well for assembling very short reads. The only limitation, which is a major one, is that the new assemblers for very short reads don't yet seem able to handle something as large as a mammalian-sized genome.

The problem is there's so much data that if you're assembling a mammalian or animal genome from short reads, you have to be very careful in the way the algorithm works to manage the memory. It's not just CPU time, which is also an issue, rather it's memory issues. You have to read all this data in at some point, and if you don't have enough memory, the machine just can't handle it and the system will crash.

IPR: How much assembly is needed for resequencing?
Salzberg: For resequencing the first issue is mapping the reads onto the genome, it's not assembly. The mapping problem is different. You can use the software the vendors provide, but you can also use the open-source software which is being developed by a number of groups. We've developed a program called Bowtie which, without blowing my own horn, has quickly become one of the leading programs for mapping reads to a genome.

The Bowtie program adapted an algorithm and data structure that was previously developed in computer science, something called the Burrows-Wheeler transform, which was more or less unknown in bioinformatics. This adaptation produced a very efficient and very fast program for mapping reads to a genome. Bowtie can map reads to a human genome on a standard desktop PC at a rate of about 25 million reads per hour. To put that in perspective, a five-day run of an Illumina machine gives you 40 to 50 million reads. It will then take another two hours to do the mapping on a single desktop PC. Bowtie is multithreaded, so if you have a dual core machine, it will do it nearly twice as fast.

Recently there have been several new assemblers released for use with very short reads. The one we like the most is called Velvet.

IPR: Is there much use in sequencing centers for the kind of software that some people are putting out that kind of wraps up things in a big package with a neat user interface?
Salzberg: There's definitely use for that. There are companies that are producing such packages, and these are probably going to be quite valuable. I'm not an end-user, so I'm not an expert on that, but I know from a few collaborators that are looking at SNPs and they want an interface that lets them see the SNPs. They don't want to just do the mapping and get a gigantic text file as output. They want to be able to see some sort of graphical display, to see the SNPs with all the reads lined up on top of one another, to see what gene they're hitting, what region of the chromosome are they in, and what genes are nearby.

Further Reading: "Next-Generation Sequencing: Solving the Genome," June 2009. www.insightpharmareports.com

Computational Biology

Heir Jordan

Microsoft Names Les Jordan as BioIT Alliance Director

BY KEVIN DAVIES

Les Jordan, industry chief technology strategist for Microsoft's life sciences team, has been named the new director of the BioIT Alliance, succeeding Rudy Potenzone. Since joining Microsoft five years ago, Jordan has provided architectural and technical guidance to internal product teams, partners, and pharmaceutical companies, and was involved in the original concept and launch of the BioIT Alliance in 2006.

Jordan told *Bio•IT World* that there were going to be some changes, but pledged a renewed commitment to the industry consortium, which Microsoft launched in 2006.

Jordan serves as the chief architect of Microsoft's life sciences team, bridging the gap between customers and partners and the firm's internal product teams. Much of his recent effort has focused on Part 11 compliance. "We're also looking at how to use Geneva, our identity management application, in the cloud—how do we use that for things like clinical trial management or EDC?" he said.

Jordan says Microsoft is pleased with the adoption of the BioIT Alliance vision, evidenced by the dozens of companies that have joined. "We've been very pleased with the ad hoc collaborations between companies," he said. "We've seen a lot of things happen behind the scenes. But there's always room for growth. We'd like to see an even more rapid adoption of integration and interoperability methodology between the member companies of the BioIT Alliance."

Lack of Standards

"If you think about the early stages of discovery space in pharma and biotech and research, there's just a dearth of standards and interoperability. Clinical trials have CDISC; hospitals have HL7. There really isn't anything that bridges that space in the bio-IT early-stage discovery [space]. The original vision of the BioIT Alliance was to drive that, to enable that collaboration, to make our scientific life easier and to drive toward the vision of personalized medicine. The only way we're going to get there is with seamless integration of laboratory equipment, diagnostics, the hospitals, EMR. The only way we'll get there is if there's integration in this space."

Jordan's first order of business is to appoint a board of directors that will help guide and direct the Alliance. Two charter members are Becky Kush (president/CEO, CDISC) and Dave Champagne (Thermo Fisher). A call for nominations for two at-large directors will take place at a future meeting of the Alliance this fall. That should also be a chance for Alliance members to interact with the Amalga Life Sciences team.

Jordan says standards will be an early focus. "We want to reach out to the existing standards that are there and help them be implemented," he said, while looking at integration between LIMS and E-lab notebook vendors.

As he takes the reins, Jordan hopes that other companies will consider the possibilities for improving integration and interoperability as alliance members. He particularly wants to encourage participation from pharma and biotech companies. "We need to have their voice in this in order for it to be driven forward and legitimate." •

Microsoft BioIT Alliance Members

Aberdean
Accelerated Technology Laboratories
AccelrysActiveMotif
Agilent
AK Systems Inc
Axendia
Axiom Discovery
Biobase
BioDiscovery
Biomatters
Biotique Systems
Blue Reference
CambridgeSoft
Caresoft
CeuticalSoft
ChemAxon
ChemZoo/ChemSpider
Clarabridge
CLC bio
Core Informatics
CTIS
Digipede
Dotmatics
eXludus Technologies
FOCUS
Gencom
Gene-IT
Gentelligent
Geospiza
GGA Sofware Services
GrapeCity
GulfStream Bioinformatics
Hebrew University of Jerusalem
ILink Systems
IMC
Inforsense Limited
Infosys
Infusion
Integromics
InterKnowlogy
Invision
IO Informatics
IUPAC
Jubilant Biosys
KineMatik
LabKey Corporation
Linguamatics
m-Objects
Molegro ApS
NewtechGS
NextDocs
nFocus Technologies
Ocimum
Optra Systems
Paradigm Infotech
Persistent Systems
PointCross
POINTONE Systems
Premier Biosoft
Prodiance Corporation
Progeniq
ProSanos
QL2 Software
REvolution Computing
RND Group
SGI
SLIM Search
Strand Life Sciences
Sun Microsystems
Symyx Technologies
Syntel
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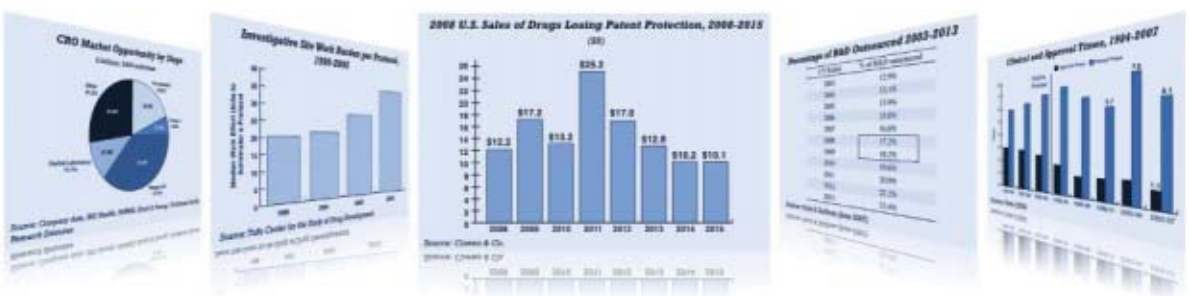

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Computational Development

Remodeling the FDA

Pharmacometrics gains ground in the FDA and drug approval.

BY JOHN RUSSELL

Very soon, FDA will restart its End of Phase 2A (EOP2A) meeting program during which sponsors and FDA collaborate, often using pharmacometrics (PM), to analyze current data, refine clinical trial design and to inform industry's critical go/no-go decisions on projects. The pilot EOP2A was halted in 2007, not so much to absorb its early lessons—though that was important—but because rising demand for PM reviewers on NDA (new drug application) approval decisions meant there simply weren't enough PM resources to go around.

In a bit more than a decade, pharmacometrics at FDA has grown from a small effort that was regarded with early skepticism and whose activities were mainly restricted to population PK questions into one of the agency's most promising priorities.

A small cadre of champions, some immediately recognizable (e.g. Lawrence Lesko, director, Office of Clinical Pharmacology) and others toiling quietly in the trenches, have worked steadily inside FDA to prove PM's value and to coax the agency to embrace it. The message that this PM stuff works and brings value is starting to sink in.

Drawing the Roadmap

Leading the charge at FDA is Joga Gobburu, a ten-year agency veteran, who heads the 17-person PM group embedded in CDER review divisions. Roughly a year ago, Gobburu presented Pharmacometrics 2020*, an ambitious manifesto in which he suggested PM will help industry and FDA reduce late phase attrition from 50% today to 15% by 2015 and to 10% by 2020. What's more, he says the practice of pharmacometrics and the restart of the EOP2A program will help transform FDA's working relationship with sponsors.

"The EOP2A meeting is not like [other regulatory FDA meetings.] The theme is to let us think through trial design together," he says. "What is the best trial design; can we think about alternative designs? The focus is more scientific and the meeting outcomes are not binding; so we want to take the binding thing off the table because we wanted the scientists to talk to each other."

In Gobburu's 2020 roadmap, he asks who will be PM's customers and what will its products be. "My personal opinion is the customers of this type of technology and science are going to change. Right now we are talking about drug developers, but the same information about exposure/response, dose selection, etc. could be useful to many others. The recipients of this technology won't just be FDA. It is possible we'll interact, for example, with CMS (Centers for Medicare and Medicare) or CMS forms its own PM group or the VA (Veterans Administration) forms one or Kaiser Permanente could form one."

It's good to have goals and the agency seems to agree. A planned move to elevate the PM group to division status within CDER is currently on hold while the Obama administration reviews all such proposed organizational changes, but most observers expect the change will go through.

This a far cry from PM's modest start at FDA in the mid 1990s. Then, the Office of Clinical Pharmacology (OCP) had three evaluation divisions aligned with various therapeutics areas. Each had one or two 'pharmacometricians.' By 2000, preliminary success and the desire to make PM practices more consistent prompted FDA to centralize PM into single group within OCP.

Gobburu divides PM's journey into three decade-long stretches. From 1990 to 2000, he says, PM growth was marked by technology development, early success, and the evolution of regulatory policy. 2000 to 2010, is being dominated by growing influence within and outside the agency and the development of more formal organizational structures. 2010 to 2020 will be about standardizing processes, increasing staff size, and expanding PM's scope.

Joga Gobburu

"Very early this field was an uncharted territory, nobody could even think of using modeling information to make a key agency decision," he says. The first population-PK guidance was issued in 1997 and it dominated thinking until about 2002 when the exposure/response guidance was issued. "With the exposure-response guidance our focus was more on new drug applications (NDAs) and that really started getting people's attention. We started to get into dose selection, trial design, and approval-related decisions."

Decades of Growth

Indeed, from 1995 to 2000, labeling and research were virtually the only work PM did. By 2005 the situation was quite different. The volume of labeling work had continued its impressive growth, but it now accounted for only 50 percent of the total workload as PM reviews also dealt with drug approval decisions and entered the trial design and approval

* American Conference on Pharmacometrics 2008

policy arena. By 2007, work on approvals reached parity with labeling at roughly 30 percent each, and the total volume of PM work was still growing. "We got into opportunities where modeling played the total role in making a decision of whether to approve the drug or not, substantially judging its effectiveness or not."

It should be noted that the 2005 International Conference on Harmonization issued guidance (E14 Variance) for evaluating the QT risk of new compounds. FDA responded by establishing a group inside CDER to review all QT-related submissions. That group is IRT (Interdisciplinary Review Team) for QT. Gobburu's PM group drew primary responsibility from the clinical pharmacology perspective to review the QT studies, causing a spike in PM's workload and adding to the scope of PM reviews.

The New Normal

"Once PM was established to constitute a big success by most people in the Office of Clinical Pharmacology, it branched out and that's when the centralized group was formed," says Gobburu. "We started having what are called scoping meetings. Every time there is a new NDA, we have an interdisciplinary scoping meeting where we go through the submission and come up with the key questions. If the key questions happen to be something that can be answered by a PM analysis, even if the sponsor has not performed such analysis, then we assign a PM reviewer to the submission."

Gobburu says the experience of participating on NDA reviews clearly identified poor dose selection and poor trial design as major problems. "These were two of the main determinants of the success of a particular clinical trial and there were several trials where a simple PM analysis could have identified a better way to design the study. So we introduced the concept of End of Phase 2A (EOP2A) meetings."

FDA rolled out the pilot program in 2004. There were about a dozen, he says, and the main focus was on dose selection and trial design for late phase trials. Prior knowledge and heavy use of modeling and simulation was employed to design future trials.

At least one EOP2A participant has had its drug approved. "There was an issue about the dose selection for a compound under development. The sponsor was heading in one direction about the dose selection. The studied doses failed to achieve the clinical significance. Then they came to the EOP2A meeting and we worked with them on the possibility of an alternative dosing which would enhance the success of the trial. The sponsor embraced that. They tested that dose in the next trial and bingo, it passed. And we approved it."

"The beauty is that since our reviewers are very familiar—through the EOP2A meeting—with the drug development program, it makes it much easier for us to review the NDA."

During the initial pilot, FDA often provided its own models, developed using historical FDA data, for sponsors to use. When program restarts, the intent is for sponsors to take more responsibility for model development. For FDA, the challenge is workload.

"EOP2A meetings have very tight deadlines. Our NDA timeline on average has 6 to 10 months; on EOP2A meetings we hardly have 3 to 4 weeks for the person who is doing the analysis. So it is very intense. We could not cope with the resources to manage both of them and could not sustain it any longer. We stopped accepting them until we got more resources."

Final EOP2A Guidance is still pending, but Gobburu says FDA will start accepting new requests soon.

Streamlining the Data

Gobburu says, "The key success basis for our group is not really the technology because the technology was taken care of before us. The academic institutions mostly and the commercial vendors made sure products were out there and were widely available to do most of our analysis. We continue to use those tools, but our focus was more on generating success stories and not so much about the technology. Our focus was more on how the concept of PM added value to decision-making for the whole enterprise," says Gobburu.

That said, there are technology issues now. "There is a burning need for us to streamline the way we manage our knowledge. That's something we are focusing a lot on here. For example, just imagine you have the next EOP2A meeting for an anti-diabetic compound, and yes we have a plethora of data here, but it is not easy to access that, and I don't think it is much different for the industry. We need smarter tools to bring previous data in your preferred format to you to make decisions in an efficient manner. Right now, the bottleneck is to get the data in the right format; so there is more think time."

The Right Tools

Both industry and FDA need to come up with better tools to manage knowledge, he says, and his group has two full time staff members devoted to technology evaluation and development. Armed with a bigger cluster, the PM group is also creating SQL databases of trials in those areas which "we think are of high priority to us. We cannot do it for every trial. Take, for example the QT workload. The immediate question [when work surged] was how can make the learnings from these 100s of QT reviews more efficient."

One staff member developed an automated tool that streamlined access to the input data, the modeling, the output data and the reports, "so by the click of a button" the analysis, standard graphs, standard tables and report are generated.

"We cut down a review which takes about 4-5 days to probably 15 minutes. By doing that, not only are we increasing the efficiency of the review but also we are streamlining the way we store the data. Now I can go back, or any reviewer can go back, and say hmm, what are the QT changes in the placebo arms for the last 50 trials and they can make a table or a chart at the click of a button," he says.

FDA has plans to create a scientific computational center and the PM group will no doubt plug into that effort and benefit from its efforts. Gobburu expects firmer budget and plans for that project to be announced soon.

Given the investment, early positive results, and growing demand from pharmacometrics, it seems clear that FDA has high expectations for modeling and simulation. So does Gobburu. •

Ten of the Best:

Bio•IT World's 2009 BEST PRACTICES AWARDS

MARK GABRENYA

A textbook example of adaptive clinical trial design... A soup-to-nuts next-generation sequence analysis pipeline... A biological registration repository developed collaboratively by two big pharmas... A computerized clinical alert system for physicians and patients... Sophisticated yet user-friendly imaging software for automated cell microscopy... Systems for monitoring and reporting adverse events... A one-stop portal for managing a major bitoech's clinical trials.

These were some of the undisputed highlights in our largest and most rewarding *Bio•IT World* Best Practices competition yet. This year's competition drew a record 72 entries—the most since we first held Best Practices in 2003—making the task of the judges harder than ever. Earlier this year, our judging panel spent two days in closed-door deliberations, debating and ranking every entry in eight categories. In addition to the winners in each category, we also awarded two special awards: the Judges' Prize and the Editor's Choice award.

While the winners in some categories were essentially unanimous selections, others provoked heavy debate. Despite the best efforts of our distinguished panel, selecting the most worthy "best practice" is often a complicated and subjective decision. Should we give credit to a big pharma with its vast resources or the innovation displayed by a small start-up? Is a convincing demonstration of ROI more important than potential of a newer unproven technology? Is a proprietary technology as worthy as a solution with potential to spread across the industry?

After all the deliberations, we firmly believe that the ten winners of this year's Best Practices Awards, profiled in the pages that follow, offer inspiring stories demonstrating the value of ingenuity, perseverance, and collaboration. As always, we hope that these articles—written by Deb Borfitz, Kevin Davies, Alissa Poh and Allison Proffitt—showcase the innovation coursing through our field, and capture technologies and strategies that will have an impact far beyond the groups and organizations recognized in this section.

We think it's also important to list and credit all 72 entries in this year's competition, including the entries that, based on their super scores, earned a well deserved Honorable Mention. It would not surprise at all if some of these 72 entries may yet have a bigger impact than our 2009 winners. Our judges are experts but hardly infallible. After all, each season on American Idol, one of the clear favorites is shockingly sent home early, only to upstage the eventual winner by bagging an Oscar or (this year's runner-up) posing for the cover of Rolling Stone. This may be of little comfort to those who entered and didn't win, but we hope to follow the progress of many more Best Practices entrants in the months ahead.

As always, we sincerely thank our judges for their time and insight, our CHI colleagues for putting on a memorable awards dinner, and everyone associated with the 72 entrants. We especially congratulate all the winners, their organizations, and nominating companies, and invite one and all to begin thinking about submissions for the 2010 competition. The entry process begins again this October. •

2009 Winners and Honorable Mentions

Basic Research: National Center for Genome Resources.
Nominated by SAS
"NCGR's Schizophrenia Genome Project"

Clinical Trials Management: Genentech
Nominated by ePharmaSolutions
"The Clinical Trial Portal"

Clinical Trials Design: Wyeth Research
Nominated by Tessella
"Design of adaptive clinical trials using Adaptive Design Explorer"

Drug Discovery & Development: Amgen
Nominated by Genedata
"Amgen Lead Discovery Informatics"

IT Informatics: The Broad Institute of MIT and Harvard
"CellProfiler"

Knowledge Management: Vanderbilt University
Nominated by ActiveHealth Management
"A computerized, clinically intelligent system to deliver clinical alerts to physicians and their patients improves care and lowers health care costs."

Knowledge Management, Pharma: Merck & Co. and Abbott Laboratories
Nominated by Accelrys
"Biological Knowledge Management: Registration, Association, and Sharing"

Translational and Personalized Medicine: GlaxoSmithKline
Nominated by ProSanos Corporation
"SÆftyWorks: Leveraging Observational data to explore the effects of medicines"

Editor's Choice Award: AstraZeneca
Nominated by BioWisdom
"Safety Intelligence Program"

Judges' Prize: The Children's Hospital of Philadelphia
"Pediatric Knowledgebase"

Honorable mention was given to the following entries:
- AstraZeneca *nominated by Medidata Solutions*
- Pathworks Diagnostics *nominated by Univa UD*
- Genentech *nominated by Dolcera*
- AstraZeneca *nominated by Thermo Fisher Scientific*
- CEA (Commissariat à l'Energie Atomique) *nominated by Bio-Modeling Systems*

One Laptop, One Hope

Michael Cariaso had been to Southeast Asia before, but when he saw an opportunity to take a leave of absence to volunteer with the One Laptop Per Child (OLPC) program, he knew he couldn't pass it up. In his guest speech at the Best Practices Awards dinner, Cariaso, a former consultant at BioTeam, gave attendees a photo tour of the OLPC program and several of the schools he worked with in Thailand and Cambodia. "I went to the original OLPC school," says Cariaso, but, "I'm not really affiliated; I'm an enthusiast."


MARK GABRENYA
Michael Cariaso and an OLPC.

OLPC is a nonprofit organization providing laptops to the world's poorest children. "The machine, in parts, costs $188," explains Cariaso, and comes with several ingenious hardware and software features specifically tailored to the users' needs. "The screen is unlike any screen, any laptop, any computer you've ever seen," Cariaso says. "You can take the brightness all the way down, and... you have a screen that's blocking out light and the sunlight itself provides the light." Using sunlight not only saves power for users who often have only sporadic energy available from a generator, but it allows them to work outside. The laptop also comes with "the same solid state storage that's getting raves as the next big thing... by not having a moving hard drive and no fan, you've reduced the possibility of wear and tear and made it much more rugged if it were dropped," Cariaso explains.

Even more impressive than the hardware, though, is the software designed to teach the children about programming and the internet and, as Cariaso points out, drastically broaden their later work opportunities.

The OLPCs come with Linux and "a lot of programs... with very friendly interfaces developed for someone that doesn't necessarily speak English at all and certainly not as a first language." The programs are designed as games to teach computer and internet skills. "While you think you're playing games, you're learning the basic concepts of things like programming!"

"Here's a way for some six year old kid to click on an icon, see the little Python [programming language] interpreter, play with a couple of programs," says Cariaso. "[It's] sitting there meant to do hands on examples. The whole thing is just mind-blowing." •

2009 Best Practices Judges

Stephen Fogelson, *Devolotron*
Stan Kachnowski, *Health Information and Technology Lab*
Jerry Schindler, *Merck*
Sandy Aronson, *Harvard Medical School*
Ernie Bush, *Cambridge Healthtech Associates*
Joseph Cerro, *Consultant*
Al Doig, *CHI Insight Pharma Reports*
Bill Van Etten, *BioTeam*
Noemi Greyzdorf, *IDC*
Jim Kremidas, *Quintiles*
Alan Louie, *Health Industry Insights/IDC*
Eric Neumann, *Clinical Semantics Group*
Deepak Thakkar, *SGI*
Phillips Kuhl, *Cambridge Healthtech Institute*

Bio·IT World Best Practices 2009

Carpenter Builds Open Source Imaging Software

BY KEVIN DAVIES

Anne Carpenter trained as a traditional cell biologist specializing in microscopy with no intention of writing image analysis software. "It wasn't until I needed software to do something that existing commercial software couldn't do that I became interested in writing software myself," says Carpenter. The genesis of CellProfiler was "completely out of necessity."

Best Practices Winner: The Broad Institute of MIT and Harvard
Project: CELLPROFILER
Category: IT & Informatics

Carpenter found that the commercial software bundled with automated microscopes was good at measuring certain cell types, but little help measuring the size of *Drosophila* cells during her postdoc with David Sabatini at the Whitehead Institute. She came across some promising algorithms doing a literature search, but didn't have any way of implementing them. "So I sent an email to the MIT computer science department asking if anyone could help out for a couple of hours a week." A student named Thouis Jones agreed to help, and soon made it the subject of his Ph.D.

The satisfaction of developing useful software for the cell biology community persuaded Carpenter to abandon her postdoc project and focus on CellProfiler software development, training and implementation. "It became much more compelling to help dozens of other people working on image analysis for their projects versus doing my own," she says.

One of those grateful beta testers was Scott Floyd, a cell biologist and physician at Beth Israel Deaconess Hospital. Floyd was screening for genes involved in cellular response to DNA damage in the search for drugs that could protect cancer patients against the side effects of radiation. He could recognize telltale increases in the speckled appearance of cell nuclei by eye, but struck out using commercial software.

The software Carpenter built—CellProfiler—made its free open source debut in December 2005, and was detailed in *Genome Biology* in 2006. In January 2007, Jones and Carpenter established the Imaging Platform group at the Broad Institute, focusing on new algorithms and data analysis methods. From here, Carpenter can help dozens of researchers working on clinically relevant projects. "Everything we develop becomes open source, and the easiest way to get that out to the public is to put it into the CellProfiler interface."

Profiler Packages

In contrast to the tedious and error-prone manual inspection of identifying specific cell shapes or morphology, CellProfiler's easy point-and-click interface and modular structure allows operators to customize the workflow to a particular experiment—even computational novices. Researchers can build a "pipeline" of modules, each performing a set function on the images. This might be followed by measurements for each cell or for an entire image, such as size, location, and shape or the intensity and texture of the staining pattern within cells.

Carpenter's team of computer scientists and biologists helps Broad colleagues test hundreds of thousands of samples to understand gene function and identify drug candidates. Her group operates "like a faculty research lab at any academic institution, but we are unique in having a very strong technology focus, and secondly, in being extraordinarily more collaborative than a typical faculty lab."

Anne Carpenter, The Broad Institute of MIT and Harvard

CellProfiler comes into its own in the high-throughput analysis of images from robotic fluorescent light microscopes, such as those offered by companies like Cellomics, GE Healthcare, and PerkinElmer, essentially turning images into numbers. The software's strength lies in its flexibility and sophistication, which allow "accurate and rich measurements coming out of the cells." But Carpenter says the commercial packages still excel in their prepackaged convenience, and her team will recommend using commercial software when collaborators are screening a simple phenotype. "We only get involved when people are stumped on their project."

Maturity Level

Although CellProfiler has been gaining admirers for a few years, Carpenter only submitted for *Bio•IT World*'s Best Practices competition once she was satisfied that the program had reached a certain level of maturity and popularity. Signs of maturity include the fact that the software was downloaded 300 times per month in 2008 and in total some 9000 times since its introduction, and has amassed more than 100 citations.

Perhaps most important was "the killer application"—CellProfiler Analyst—which was submitted for publication in late 2008 and published in *Proceedings of the National Academy of Sciences* in early 2009. This tool looks at those measurements and performs machine-learning cell sorting. Says Carpenter: "You don't need to know anything about machine learning to use the software.

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Jumping on Next-Gen Sequence Data Analysis

BY KEVIN DAVIES

In 2007, the National Center for Genome Resources (NCGR) in Santa Fe, New Mexico, best known for the development of bioinformatics tools, established the Schizophrenia Genome Project. Taking Illumina GA sequence data, NCGR scientists used a combination of homegrown Alpheus software and JMP Genomics (from SAS) to develop a streamlined workflow for the acquisition, analysis, and management of huge amounts of next-generation sequencing data—in this case, mRNA.

"This was the first time that these technologies had been integrated for a case-control study," says Faye Schilkey, associate director of NCGR's sequencing center. The project offers important insights into a devastating disease and the development of a sophisticated and accessible data analysis pipeline for translational next-gen sequencing projects for groups who might not have the resources of the major genome centers.

Because of the notoriously complicated genetics of schizophrenia, NCGR scientists under director Stephen Kingsmore examined variations in gene expression between cases and controls. The first phase of the project was published last November in *PLoS ONE*.

"We used mRNA sequencing, which typically hadn't been done before," says Schilkey. Using Illumina GA sequencers, the NCGR team generated 16.7 billion bases (473 million reads) of shotgun DNA sequences of cDNA from post-mortem cerebellar cortex of 14 patients and six controls. Those reads were analyzed using Alpheus, which NCGR calls a "web-based cyberinfrastructure platform for pipelining, visualization, and analysis of gigabase-scale medical resequencing studies."

The sequence reads were aligned to some 33,000 transcripts in each sample, which in turn were used to generate digital gene expression values. Using Alpheus, NCGR identified gene expression differences, splice site differences, and sequence variants (single nucleotide polymorphisms) of more than 33,000 transcripts, while minimizing false positives. (The web portal enables investigators worldwide to explore the results in a highly flexible manner, without the need for a massive local computational infrastructure or advanced bioinformatics expertise.)

Next, NCGR staff adapted Alpheus to export the variant or digital expression data to JMP Genomics statistical software from SAS for visualization and statistical analysis. JMP Genomics is better known for microarray analysis—it produces interactive graphical representations of large volumes of exported data, and is particularly useful for identifying outlier samples, and it worked right out of the box for the analysis of next-gen sequence expression data based on read counts. A bonus was that JMP Genomics could detect and visualize the sensitivity of the Illumina GA. "The dynamic range is much greater than that of arrays. Illumina reads mass units of cDNA and a zero is a true zero compared to arrays where approximately 30% are absent calls due to array hybridization noise," says Schilkey.

NCGR analysts used principal components analysis and hierarchical clustering to assess the data. The variance attributable to disease status was higher for the Illumina digital expression data than from conventional array analysis. "Visualization tools, such as Principal Component Analysis, readily separated the cases and controls, we spotted differences right away," says Schilkey. Given more than 11,500 schizophrenia candidate genes in the literature, the Illumina/Alpheus/JMP Genomics pipeline revealed "23 genes with altered expression and involvement in presynaptic vesicular transport, Golgi function, and GABAer-

(CONTINUED ON PAGE 37)

Best Practices Winner: National Center for Genome Research
Project: NCGR Schizophrenia Genome Project
Category: Basic Research
Nominated By: SAS Institute

Shannon Conners, SAS; John Crow, NCGR; John Leary, SAS

Trial Portal Tightens Bond with Investigative Sites

BY DEB BORFITZ

When it comes to streamlining and systematizing the clinical research process, it's unlikely that any company is doing more than biotechnology founder Genentech. Its relationship with investigative sites is being wholly managed through a single-sign-on Clinical Trial Portal (CTP). Pilot- and production-level rollout is resulting in quicker study start-ups, improved enrollment rates, and significant cost savings (around $10,000 per site).

Best Practices Winner: Genentech
Project: Clinical Trial Portal
Category: Clinical Trial Management
Nominated by: ePharmaSolutions

Commenting on the CTP, a Genentech executive who was not directly involved in the project said, "Alyssa [Ventura, head of clinical information systems management at Genentech]... and her small team jumped through untold fires to make it happen. It is a well deserved victory."

CTP is "a portal facilitating drug development and research—automating all the regulatory documentation, drug safety reporting, adverse event reporting for clinical trials," explained Jennifer Reichuber, senior manager, Clinical Information Systems Management, Genentech, when accepting the award.

The features of CTP cover the full gamut of activities in which clinical trial stakeholders are collaboratively engaged. From the perspective of sites, the enchanting feature of the CTP is that it provides a single point of interaction with Genentech for all studies conducted on the sponsor's behalf, says Lisa La Luna, senior VP corporate development and implementation for nominating organization ePharmaSolutions, which eight years ago developed the portal for clinical trials. The fact that sites can always log on to Genentech trial management technologies with the same user name and password significantly reduces the "burden" on study sites.

Market research conducted by ePharmaSolutions in 2008 found that sites were struggling to recall an average of seven to ten—and sometimes as many as 15—user names and passwords associated with technologies required by multiple sponsors, says La Luna.

For project managers at Genentech, CTP makes it easier to improve site selection and activation through a proprietary application that ranks sites according to their ability to succeed in each study; completes the regulatory document and contracting process with digital signatures; and delivers and tracks safety letters (SUSARS), study training, and online investigators' meetings, says La Luna. It also shields studies from informational black holes created by a departing study coordinator or a change in clinical research organization (CRO).

CTP is being integrated with Genentech's interactive voice response, electronic data capture, and clinical trial management system. All user activity is time stamped and tracked for regulatory purposes. Conducting site feasibility, study documents, and study training through a Corporate Portal in a "parallel process" generally expedites study start-up by up to 30-40%, says La Luna. As a standard service, the Corporate Portal helps "enforce" timelines by sending sites electronic and telephonic reminders to submit/edit study documents, read SUSARs, and complete training.

A patient recruitment hub gives sites access to institutional review board-approved recruitment material and a recruitment referral tracking system detailing the referral source, cost per referred patient, and whether or not the patient was ultimately enrolled into the study.

Lisa La Luna, ePharmaSolutions, Jennifer Reichuber, Sudheer Swamy, Genentech

Full Embrace

La Luna points out that ePharmaSolution has built and hosted a Corporate Portal for a dozen study sponsors, but Genentech is the only firm to embrace the entire suite of available features and integrate the solution with its existing trial management technologies.

"We really appreciate all the work EPS has put into the project for us," said Reichuber. "[This has been an] excellent collaboration with EPS."

ePharmaSolu-

(CONTINUED ON PAGE 36)

Boosting Adaptive Clinical Trials

BY DEB BORFITZ

Wyeth Research and partners are developing trial simulation software to streamline the process of designing and running adaptive clinical trials (ACTs).

The Adaptive Design Explorer (ADE) is essentially an "educational platform" allowing biostatisticians to quickly and easily identify potential design options and compare their performance, says Michael Krams, VP of adaptive clinical trials and applied program strategies. "The beauty of [ADE] is that it enables simulation-guided clinical trial design, assessing our ability to accurately estimate the dose response and determine the target dose in an efficient manner," says Krams.

ACTs are inherently complex in that they use accumulating data to decide in a predefined manner how to modify key aspects of a study, including sample size and allocation of patients to different doses, says Vladimir Dragalin, Wyeth's assistant VP of statistical research and applications in the division of global biostatistics and programming. "Simulating clinical trials allows us to formally compare and contrast the operating characteristics of the different design options."

One of a Kind

The ADE, now in its third major release, serves as a catalogue of adaptive and non-adaptive designs against which simulations can be run and candidate designs can be assessed on a common platform with a friendly graphical user interface, explains Dragalin. "There's nothing on the market like it."

Making comparisons across a "level playing field" helps identify when an adaptive design approach is justifiable and which design is the most appropriate for a particular trial, says Dragalin. Adaptive design programs were heretofore created one at a time to answer a particular research question. The ADE "enables planning and implementing adaptive designs in a much more resource-efficient manner, allowing scalability."

According to Krams, "response adaptive dose-finding designs" are now routinely considered across all therapeutic areas at Wyeth. The aim is to strike a balance between needed dose response information and increased costs.

Design options within the ADE are based on different what-if scenarios and can be "fine tuned" to reflect user-specified trial characteristics, says Dragalin. Users also have the option of developing an entirely new adaptive design by choosing from a la carte menu items. These include trial stopping rules (for efficacy, harm, or futility), allocation rules (assignment of subjects to available treatment arms), and sampling rules (number of subjects involved in the next stage). "Different designs have one such rule or several."

Importantly, ADE's graphical user interface is largely standardized across designs with a common workflow: specifying the nature and target(s) of the trial, the trial execution model and scenarios for simulations; selecting designs and specifying their parameters; running simulations; and evaluating and comparing the designs' performance over the scenarios.

Development of the "design engine" began in the fall of 2006 as a team effort involving Wyeth's in-house researchers and ACT specialists at Berry Consultants. The British consultancy Tessella was tasked with the development of the software-user interface. ADE underwent pilot testing about a year later. The ADE includes a database that holds all executed simulations, created designs, and the corresponding results. The database is connected to a grid of computers that perform the simulations.

Best Practices Winner: Wyeth
Project: Adaptive Design Explorer
Category: Clinical Trial Design
Nominated by: Tessella

Ultimately, through an "adaptive execution environment," the ADE will be communicating with every other information system at Wyeth, says Dan Burns, program manager of applied program

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Tom Parke, Tessella; Krishna Padmanabhan and Michael Krams, Wyeth

Integrating Lead Discovery

BY ALISSA POH

Like most other industries, pharma has its trends and recurring themes. Of late, a good many companies have been partnering with vendors to customize software for data consolidation. One such partnership, between Amgen and in-silico solutions specialist Genedata, yielded Amgen Lead Discovery Informatics (ALDI).

Best Practices Winner: Amgen
Project: Amgen Lead Discovery Informatics
Category: Drug Discovery and Development
Nominated by: Genedata

There's always need for a more consistent view of research data—small wonder, given that many companies are really patchwork quilts of M&As. "Scientists tend to store their data in ways they like and can easily manipulate and view," says Randal Chen, Amgen's director of information systems. These seemingly small nuances in storage formats, he adds, actually add up to a large difference.

The Tripos-Wyeth-Accenture initiative—Next-Gen Discovery IT (see "Triple Play," *Bio•IT World*, Nov 2008)—is another example, albeit a more generic solution tying together Wyeth's disparately-located databases. On the other hand, Chen notes that ALDI focuses on managing voluminous information from Amgen's high-throughput screens.

"We'd acquired several other bio/pharma companies over the years, which gave us complementary core capabilities for finding new lead compounds," says Bill Goode, a senior systems analyst within Amgen's research informatics department, and project manager for ALDI. "But we also had to deal with the drawback of numerous legacy tools, different practices and workflows." As such, Amgen's research and information systems groups spearheaded ALDI as an effort to select a commercially available platform that would align the company's multiple research sites, as well as support standardized methods for data analysis and progressing compounds.

Amgen and Genedata collaborated on the ALDI project, with the goal of developing a product capable of not only handling large volumes of information but also integrating with other Amgen systems. The choice of Genedata's Screener came after extensive review of products on the market, as well as a joint Amgen-Genedata workshop to establish a framework for additional customization. "We had to see how Amgen's requirements and our existing [Screener] product would fit together," says Stephan Heyse, head of lead discovery informatics at Genedata.

Bill Goode, Amgen Inc.; Kurt Zingler, Genedata (USA)

Agile Development

The collaborators agreed to use an agile approach that broke development into "sprints." Two-thirds of each three-week cycle were spent writing new software on Genedata's part, followed by a week of testing by Amgen's end users. Goode says this allowed for quick feedback and course correction as bugs and feature gaps were found. Heyse adds that it "took a lot of risk out of the whole project, as there was always control from both sides as to where this was heading."

Heyse was enormously impressed that, right from the start, Amgen had "done all the work in aligning the overall project goals. They had a clear vision and a practical way of approaching it. We saw even then how much Screener could deliver and what was missing."

Goode agrees that defining ALDI's goals from the outset was vital in ensuring its successful implementation. The team sought an overall performance increase; better quality control in distinguishing compounds of interest from artifacts; a shorter period of data analysis for new assays without needing to increase support staff; and improved consolidation of workflows.

"The results were fairly impressive," he says. "Our productivity increased by 50 percent on average—sometimes as high as 80 percent. Screener offered a bunch of intrinsic tools that allowed us to... rescue compounds we hadn't previously identified as true actives. We removed the support staff bottleneck—it takes one week at most now to analyze new assay data. We also worked with our lead discovery scientists to define best practices, and [integrated these with Genedata's] modules for curve-fitting, kinetics analysis, and hit selection that have had enormous impact on the quality of our data."

Given these results, end user accolades, and the fact that ALDI was implemented in under a year, the collaborators felt that their system was ready to withstand scrutiny as a Best Practices entry—and they weren't disappointed. "[The award] establishes that this type of software development, in this space, is valuable, and that the overall strategy we laid out for handling scientific data also worked," says

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Ensuring Excellence with a Trusted Intermediary

BY ALLISON PROFFITT

The success of Vanderbilt University's disease management program is not just due to the technology provided by ActiveHealth Management, the company responsible for alerting Vanderbilt physicians to potential discrepancies in a patient's care, but to Vanderbilt's Internal Medicine team that vets the alerts before passing them on to other physicians.

In 2007, Vanderbilt implemented ActiveHealth's CareEngine System, a clinical decision support technology, with the goals of improving the quality of care through fewer adverse events, such as heart attacks, strokes, or exacerbations of certain chronic conditions, and as a result, decreasing the cost of care.

Typically, a clinical alerting system, "sends information to a physician and patient at the same time that says, 'We have found something... going on with this patient', maybe a patient is taking medications from two different doctors that shouldn't be taken together. Sometimes there's a valid reason, but sometimes it's a mistake and one or the other doctor will fix it," explains Ginny McLean, marketing coordinator and benefits communicator for Vanderbilt.

ActiveHealth's CareEngine System runs "a set of about 1000 highly-specific clinical rules against an integrated and constantly-refreshed set of eligibility, demographic, claims (medical and pharmacy), lab results, and physician- and patient-reported data." Any red flags are sent as "Care Considerations" to the doctors. "Some doctors will get the information from a disease management company and just toss it, or say I don't need to be verified by a disease management company," says McLean.

Vanderbilt solved the problem by pairing ActiveHealth's existing CareEngine System with "triage" by Vanderbilt's Health Promotion Disease Management Center. Vanderbilt established a "trusted clinical intermediary," a team of clinical nurse specialists who first review the alerts to ensure they are accurate at the time of receipt, and consider any additional patient data not available to the CareEngine.

"The process we developed with ActiveHealth has helped us measurably improve the quality and safety of the care we provide," says Jim Jirjis, medical director, Vanderbilt Primary Care group. "Having our nurses review the Care Considerations before sending them on to the physicians personalizes health management for the patient."

Best Practices Winner: Vanderbilt University
Project: A Computerized, Clinically-Intelligent System to Deliver Clinical Alerts to Physicians and Their Patients. Improves Care and Lowers Health Care Costs
Category: Knowledge Management
Nominated by: ActiveHealth Management

Workflow Integration

"Care Considerations are uniquely valuable to Vanderbilt because it's information they wouldn't otherwise have," says Henry Wei, medical director, ActiveHealth Management. "And you have the combination of that factor with another that you don't often have in that these alerts are integrated into their daily work flow through a trusted intermediary... We at ActiveHealth view this as a best practice."

The goal of the effort was to increase the likelihood that Care Considerations would be viewed as current and appropriate by physicians, and ActiveHealth measured a 5% increase in physician compliance by the doctors supported by the Health Promotion Disease Management Center's efforts. The financial ROI was just as encouraging. Vanderbilt Health Plan compared the cost savings between the population that see Vanderbilt doctors and benefit from the alert triage and the population that see non-Vanderbilt doctors that do not have access to the alert triage. The group without triage saw a savings $45.06 per insured patient thanks to ActiveHealth's product. The

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Ryan Jacobs, ActiveHealth Management; Luke Beauchamp, Vanderbilt University; Henry Wei, ActiveHealth Management

Bio·IT World Best Practices 2009

Two Pharmas Are Better than One

BY KEVIN DAVIES

Following the acquisition of biotechs such as GlycoFi and SiRNA in 2006, Merck management faced a critical challenge to register its biologics—to provide a corporate identifier and tracking attributes. Lori Harmon, manager of information services, says Merck soon ruled out internal inventory applications but couldn't find a commercial option either. "We could have had a vendor do a custom solution, but that was costly."

Best Practices Winners: Merck & Co.; Abbott Laboratories
Project: Biological Knowledge Management: Registration, Association, & Sharing
Category: Knowledge Management, Pharma
Nominated by: Accelrys

A discussion with Accelrys revealed that the San Diego informatics company had received a similar approach from Abbott Labs. "Chemistry is a field that's very well developed, with very specific rules, chemical names, and so on," says Accelrys VP Marketing, Jonathan Usuka. "Biology has nothing similar. We saw a real problem with these global organizations... Biologists hadn't met each other and yet needed to share information. The nomenclature is not standardized—what do you search on? And the work was so specialized, they couldn't convey what they need to see to an IT professional to make a database."

And so two years ago, the parties agreed to explore a consortium approach to building the robust IT infrastructure for registering biological materials. Biological materials require a sophisticated understanding to define them uniquely. Realizing economies of scale and utilizing an extensible SOA architecture and knowledge model, the system developed in conjunction with Accelrys solves a host of challenges related to IP protection and knowledge sharing.

Setting Standards

Much of the intellectual property of pharma companies is locked up in their use of biological materials, but ensuring researchers understand specifics about materials used in complex, reproducible workflows is a major headache. Enterprise-wide standards must be adopted for a company's crucial biological inventory to be transformed from a confused grab bag into an organized treasure trove.

For more than 18 months, Merck, Abbott, and Accelrys hammered out biological definitions that could become industry standards. The two pharmas defined the respective challenges using biological entities in their own workflows, while CSO Frank Brown and colleagues at Accelrys developed capabilities for defining, storing, searching, and retrieving the information. The project was divided into phases, with multiple meetings to nail down priorities and understanding which challenges are tractable.

The biological registration system sits on top of Accelrys' popular workflow platform, which was initially developed for the chemistry world. "The bioregistration solution is not a collection of components and it's not standalone software either. It's completely integrated into Pipeline Pilot," says Usuka. "[Now] as a drug discovery informatics platform, it's starting to find areas to impact biological discovery as well as intellectual property protection."

A key lesson, the parties agree, was the use of business rules. By enabling both partners to customize the application, the consortium realized an economy of scale without sacrificing the unique nature of their internal processes.

Another priority was to encourage collaboration across global sites, allowing Merck and Abbott scientists to locate proprietary plasmids, or RNA vectors distributed across the organization. Moreover, patent applications are no longer jeopardized by duplicate registrations or by misreferencing the same material.

The first phase focused on basic biologic resources—cell lines, plasmids, proteins, and antibodies—but

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Jonathan Usuka, Accelrys; Martin Leach, Merck & Co.; Derek Debe, Abbott Laboratories; Frank Brown, Accelrys

Safety Works at GlaxoSmithKline

BY ALISSA POH

Several years ago, recognizing the need for more efficient access to new sources of safety information, GlaxoSmithKline (GSK) joined forces with ProSanos Corporation in developing SÆfetyWorks, a web-based software system for drug surveillance that leverages observational databases, namely health care insurance claims and electronic health records, as rich sources of safety information. It simultaneously interrogates multiple databases, allowing pharmacovigilance professionals to more accurately compare the information therein with data from traditional sources like adverse event reports or epidemiological studies.

"These databases have three things in common: patients, prescriptions [representing drug exposures], and diagnoses [representing conditions]," says Stephanie Reisinger, senior VP for product development at ProSanos. "So the big-picture idea here is organizing data related to these three factors, and looking for a relationship between when a patient takes a drug and a condition that occurs afterwards, temporally to that prescription."

It's a timely development, since interest in utilizing observational data is growing within the drug safety community. But systematic approaches toward accomplishing this goal have, to date, been few and far between. Prior to SÆfetyWorks, GSK scientists wishing to analyze observational databases "did it kind of piecemeal," says Gregory Powell, manager of global clinical safety and pharmacovigilance at GSK and team leader for this project, noting it was "very expensive and time-consuming, it could take six to 12 months. Now we can combine as many analyses as we want, so the incremental cost is minimal, which wasn't the case before."

Multi-Question Approach

"Not only were previous analyses costly, people would just ask one question per database," says Edward Pattishall, GSK's VP for clinical safety. "SÆfetyWorks normalizes data from multiple sources such that you can ask the same safety question of different databases in real time. If you get the same answer with multiple databases, you have more confidence that there's an issue."

GSK scientists first contemplated technologies for manipulating observational data back in 2005. Two years later, the company engaged ProSanos to collaboratively formulate their plan into software. As Reisinger puts it: "GSK developed a proof-of-concept for their idea. We took that and turned it into something their safety scientists could touch, sign on to, and make work."

The project team faced two key hurdles early on: drug and condition vocabularies had to be normalized, and inconsistent data storage formats standardized to enable systematic identification of potential drug safety issues.

Best Practices Winner: GlaxoSmithKline
Project: SÆfetyWorks
Category: Translational and Personalized Medicine
Nominated by: ProSanos Corp.

For the first, the group selected two reference ontologies—MedDRA for describing conditions and SNOMED CT for describing drugs—to which all observational databases with their disparate vocabularies and coding schemes were converted. They also developed a "person-time analysis data model"—built on standard concepts found within all observational databases—for the purpose of addressing the second challenge.

Advances in technological know-how, not to mention increased storage capabilities at lower cost, made SÆfetyWorks feasible where, even a few years earlier, it wouldn't have been cost effective. "You could say the stars aligned in our favor, given that we're now able to manipulate terabytes of data," Powell says.

SÆfetyWorks users have three tools for rapidly analyzing observational data. They can use the Natural History module to better understand drugs and diseases by exploring—across multiple databases—gender breakdown, age range, and average length of drug exposure, among other statistics. The Screening module is essentially data mining; a broad-reaching look at all

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Stephanie Reisinger, ProSanos Corp.; Ed Pattishall and Gregory Powell, GlaxoSmithKline

A Medical Decision Support System That Learns

BY ALLISON PROFFITT

"Wouldn't it be great if we could [build a system] that 'learned' every time a patient walked in the door?" asks Jeff Barrett, director, Pediatric Pharmacology Research Unit, at the Children's Hospital of Philadelphia, or CHOP. He's envisioning a solution that's part electronic medical record, part drug encyclopedia, and part patient chart. The result was the Pediatric Knowledgebase (PKB).

Best Practices Winner: Children's Hospital of Philadelphia
Project: Pediatric Knowledgebase
Category: Judges' Prize

PKB was designed to meet many of the challenges of pediatric pharmacotherapy including, 1) provide dosing guidance consistent with formulary standard of care, 2) examine patient pharmacotherapeutic indices with respect to agent performance relative to controls derived from the hospital data warehouse, 3) explore treatment-diagnoses-drug correlation in conjunction with use and 4) educate physicians on clinical pharmacologic principles specific to population and drug combinations of interest."

The PKB integrates the hospital's medical records with drug-specific decision support generated by clinical pharmacology experts and clinical caregivers and predictive models generated by CHOP's pharmacometric and informatics team. Forecasting tools evaluate dosing scenarios to be explored via a user friendly interface that front-ends a pediatric population-based PK/PD model. The result is therapeutic drug monitoring for children that uses patient data to help predict outcomes and inform clinical decisions in individual patients.

"Drug monitoring with a decision support system is sort of novel," says Barrett. "There are services for [drug monitoring], but it's disconnected from the patient's history." The PKB solution, however, is closely tied to personal data. The interface currently has drug dashboard prototypes for methotrexate (chemotherapeutic agent), tacrolimus (used to prevent organ rejection) and vancomycin (antibiotic) that are being evaluated clinically. "The dashboards are based on one drug, but they're designed to go across drugs as well and monitor drug interactions," explains Barrett.

Building the system was a multidisciplinary project, Barrett says. "We have an extremely varied group of individuals [involved in the project], and it's the primary reason we've been able to get this far: pharmacometrics, clinical pharmacology, clinical/medical roles, programming/information technology, bioinformatics, data management and data integration."

The project demanded that both the IT and the clinical communities be able to "look behind the curtain," says Barrett. "We are integrated with the hospital's information management system, [and]... we've got investment from the care givers. We knew that unless they were part of the process and actually designed what these systems looked like, [it wouldn't work]."

In order for PKB to grow, partnerships have to expand outside of CHOP. The drug dashboards will eventually be populated with data through external collaborations. CHOP is part of the Pediatric Pharmacology Research Unit Network of children's hospitals, Barrett says, and the PKB will receive data from several member hospitals. "This environment accumulates clinical outcomes including adverse events in a HIPAA-compliant informatics system," the entry states.

Full Production

At CHOP, the production version of the PKB is waiting for the hospital's new EMR system to be fully rolled out. It is planned for piloting at Cincinnati Children's Hospital and LeBonheur Children's Medical Center in Memphis. The results have been good with "emphasis on clinical outcomes including reduced medication errors and length of hospital stay have been used to demonstrate the ROI for individual dashboards."

The PKB was designed to work with various EMR systems, though customization will be required for each implementation. "It's web based, and we want to see it go globally... first within the U.S., but there is some very strong expertise particularly in Europe and in the Netherlands

(CONTINUED ON PAGE 35)

Sundararajan Vijayakumar, Intek Partners; Jeffrey S. Barrett and Mahesh Narayan, The Children's Hospital of Philadelphia

Intelligent Drug Surveillance

BY ALISSA POH

Good collaborations in drug discovery are often "happy coincidences," says David Cook, AstraZeneca's associate director for global safety assessment, when describing the company's partnership with BioWisdom in developing the Safety Intelligence Program (SIP).

"Back in 2007, AstraZeneca was focusing on how best to affect early decisions in drug discovery; how we could influence the daily decisions our project chemists and pharmacologists were making, and get them thinking about safety assessment. Julie [Barnes] rang me up around then and said BioWisdom was thinking of formulating a general problem-solving approach to toxicology issues in drug discovery. She asked if we'd like to come on board."

The result was SIP, described as the "largest forever-expanding collection of known chemical effects occurring in different tissues, drug effects on clinical biomarkers of tissue injury, and drug molecular mechanisms." Currently, SIP contains almost 100,000 individual facts, or "assertions," related to the liver's response to more than 5,500 different compounds in over 20 species.

The collaborators began with the liver, as acute hepatic injury is among the most common forms of preclinical and clinical toxicities seen with drugs, responsible for more than 30 percent of all drug withdrawals.

"The word 'idiosyncratic' is key in liver injury," says Julie Barnes, BioWisdom's chief scientific officer. "Those unexpected, adverse reactions in humans that we just can't predict, because we don't know enough of a given compound's biology, in the context of individual patients."

"Our project teams always want to do the best job possible, but the mechanisms of retrieving and analyzing information they need are often tedious," Cook says. "I was thus very intrigued by the application of text logic and mining to the problem of retrieving data of interest from the pile."

Meanwhile, BioWisdom had begun dealing with the problem of language inconsistencies in medical literature and regulatory documents by building Sofia, an ontology-based platform capable of liberating intelligence from multiple source formats. The coalescence between both companies, then, was perfectly natural, with the idea of exploiting this platform as a foundation for SIP. Sofia was used to generate liver-related "assertional metadata," which comprises thousands of highly accurate and comprehensive key observations distilled from over 19 million documents and database records.

A key feature of SIP is that these assertions are all rendered in a semantically consistent format, with an accuracy level of 97 percent. "There're so many ways someone will describe a disease, protein or drug—for example, problems associated with bile excretion can be called biliary stasis, cholestasia, or cholestatic injury," says Jane Reed, a principle consultant in BioWisdom's health care sector and team leader for this particular project. "So if you're trying to work out a particular compound's side effects, you need to know the different descriptions, which our vocabularies cover. Users can also clearly visualize such diverse information, as our technology pulls it all together."

Best Practices Winner: AstraZeneca
Project: The Safety Intelligence Program
Category: Editor's Choice
Nominated by: BioWisdom

Verb Relationships

In other words, SIP very much highlights the science of ontology. "We use the language of verb forms and their relationship with nouns to sort out what things really are," Barnes explains, "so in defining an obscure statement like 'AZ binds BCEP,' the verb 'binds' immediately implicates AZ as the chemical Aztreonam and not AstraZeneca, because companies don't bind proteins!"

SIP's nascent form was delivered in January 2008. Its potential was evident even then, Reed says, but it wasn't applied to AstraZeneca's business issues until version 2.0—complete with in-depth liver data—was released in September. The program's improved user functionality helped drive the collaborators'

(CONTINUED ON PAGE 37)

Kerstin Wilke, BioWisdom; David Cook, AstraZeneca; Chris Hodkinson, BioWisdom

2009 Best Practices Entries

IT & Informatics

Company Name	Key Tech Partner	The Project
Biomatters		Supercomputing on Your Desktop – Geneious Grid Enablement
Bristol-Myers Squibb		Grid Solutions for High Performance Computing in Computer Assisted Drug Design
★ Pathwork Diagnostics	Univa UD	Cloud Implementation for Molecular Diagnostics Data Processing Aids in Cancer Diagnosis
Ruppin Center, Bio-technology Dept. AND Applied Immune Technology	SparkLix Bio-computing	360° Bio-computing on-demand
Telemedicine and Advanced Technology Research Center; U.S. Army Medical Research and Materiel Command	Interactive Supercomputing	Comparing the Capabilities of Individualized Models of Cognitive Performance Impairmen
✹ The Broad Institute of MIT and Harvard		CellProfiler
The Center of Inherited Disease Research (CIDR) at Johns Hopkins University	Caringo	Johns Hopkins selects Caringo CAS software for data archiving
UCB S.A. (Belgium)		NONMEM cluster and add-ons
HCL Technologies		
Wyeth Pharmaceuticals	Metastorm	C-TRAX

Translational & Personalized Medicine

Company Name	Key Tech Partner	The Project
Biodesix		Implementation of a MALDI-TOF mass spectrometry-based platform in clinical diagnostics
Center for Prostate Disease Research (CPDR)		Integrated data platform to streamline and optimize complex translational research management
Crown Biosciences		HuPrime – Predictive Platforms for Pre-clinical Studies
Cyberpulse	Rulester	CQUIZ – Cardiac Quality Improvement System
Fujirebio Diagnostics		HE4 EIA as an aid in monitoring epithelial ovarian cancer
✹ GlaxoSmithKline	ProSanos Corporation	SÆfetyWorks: Leveraging Observational Data to Explore the Effects of Medicines
In Silico Biosciences		Reducing attrition in Schizophrenia Drug R&D by mathematical disease modeling
Monash Antibody Technologies Facility		Ultra high throughput monoclonal antibody production
National Institute on Drug Abuse, Division of Pharmacotherapies and Medical Consequences of Drug Abuse	Information Management Consultants	PKMS
Optimata		Clinically Validated Medical Software Device for Predicting Drug Safety in Oncology Patients, Based on a Mathematical Model Integrating Physiology and Pharmacology Knowledge

✹ Winner
★ Honorable Mention
✚ Editor's Choice Award
✔ Judges' Prize

Basic Research

Company Name	Key Tech Partner	The Project
Applied Biosystems AND Centers for Disease Control and Prevention (CDC)		Development of New Diagnostic System for Influenza
Applied Biosystems AND the Institute of Molecular Bioscience at the University of Queensland		Stem Cell Transcriptome Profiling Via Massive-scale mRNA Sequencing
★ CEA (Commissariat à l'Energie Atomique)	Bio-Modeling Systems	The pathophysiological mechanisms of neurodegenerative diseases
Lawrence Berkeley National Laboratory		Berkeley Lab PhyloChip
✹ National Center for Genome Resources	SAS Institute	NCGR Schizophrenia Genome Project
Sigma-Aldrich & Sangamo Biosciences		Targeted gene knockout in mammalian cells using engineered zinc-finger nucleases

Knowledge Management, Pharma

Company Name	Key Tech Partner	The Project
★ AstraZeneca	Thermo Fisher Scientific	Accelerated decision-making in early drug discovery
Bristol-Myers Squibb	Visual i|o	Project Portfolio Data Visualization
Conformia		Product/Process Lifecycle Management for Large Pharmaceuticals
Envision Pharma		Datavision
✹ Merck & Co. & Abbott Laboratories	Accelrys	Biological Knowledge Management: Registration, Association, & Sharing
Collaborative Drug Discovery		ChemSpider
Wyeth Pharmaceuticals (With Tripos & Accenture)		NextGen

Clinical Trials Management

Company Name	Key Tech Partner	The Project
★ AstraZeneca	Medidata Solutions	AstraZeneca Revolutionizes Investigator Site Payments with Clinical Financial Services and Medidata Rave EDC/CDM
Clinical Trials & Surveys Corp. (C-TASC)		Site Visit QA System (SVS)
Coalition of Cancer Cooperative Groups		TrialCheck Increasing Cancer Clinical Trial Participation through Technology
✹ Genentech	ePharmaSolutions	Clinical Trial Portal (CTP)
GWU Biostatistics Center		IRB submission tracking
Investigator Relationship Management Solutions	ePharmaSolutions	ClinicalCollaborator
MDS Pharma Services	Exco InTouch	Patient Communication via SMS
Omnicare Clinical Research		Subject Confidentiality Training via eLearning - Are 3D Graphics just for Games?
Target Health		The Paperless Clinical Trial Master File
Al Azher University		Ureterorectostomy as a continent urinary diversion

Drug Discovery & Development

Company Name	Key Tech Partner	The Project
Amgen Inc. & Genedata		Amgen Lead Discovery Informatics
AstraZeneca	BioWisdom	Safety Intelligence Program
Cellumen		Failing Early — *In Vitro* Assays to Predict *In Vivo* Toxicity
Cognigen Corporation		A Wiki-Based Collaboration Tool to Support Model-Based Drug Development
Gemin X Pharmaceuticals	Metabolon	Gemin X Pharmaceuticals: Finding a Drug's Mechanism of Action
Genstruct and GlaxoSmithKline		Identification of Mechanisms for Sensitivity to GSK1059615 via Causal Network Modeling: A Rapid Innovative Approach for Elucidating Complex Biological Networks
Infinity Pharmaceuticals		Hsp90 inhibition
Pfizer PGRD UK		New concepts for work organisation and optimisation in drug discovery laboratories

Clinical Trials Design

Company Name	Key Tech Partner	The Project
Abbott Laboratories	Tessella	M06-876 Adaptive Study Design
Perceptive Informatics		Unifying paper and electronic data capture in clinical trials: First true thin-client hybrid EDC/CDMS from Perceptive Informatics
Clinical Ink		EDC 2.0: Extending Electronic Data Capture to Source
Duke Clinical Research Institute (DCRI)	Phase Forward	Advanced Data Reporting at the Patient Level
Eli Lilly & Co	Tessella	GBCF Adaptive Clinical Trial Design
ERT		EXPERT DEVELOPMENT
Health Decisions		Smart Monitor
IXICO		Tools for streamlined collection of clinical data
SGS Life Science Services	Phase Forward	Central Designer adoption
Wyeth Research	Tessella	Design of Adaptive Clinical Trial with Adaptive Design Explorer
Wyeth Research	Tessella	Design of Adaptive Clinical Trial with efficacy and tolerability endpoints

Drug Discovery

(CONTINUED FROM PAGE 26)

Goode. "It's a great validation by our industry peers."

Amgen is looking to reap ALDI's benefits beyond lead discovery into therapeutics and eventually large-molecule studies. One unexpected benefit from this collaboration, says Goode, is that "our system's foundation won't need retooling or major redesign; we can build on other areas without rewriting the software from the ground up."

Amgen viewed the ALDI project as a partnership. "Genedata brought their best expertise out from the very beginning," says Goode. "It was much more a technical and scientific collaboration as opposed to them trying to sell us a piece of software."

On Genedata's part, Heyse was impressed by Amgen's general lack of micromanagement. "They didn't feel a need to specify every single detail in advance—we were simply told to go ahead and do our work, which was great," he says. "You could say we 'sprinted' at this together." •

Winner
★ Honorable Mention
✚ Editor's Choice Award
✔ Judges' Prize

Knowledge Management

Company Name	Key Tech Partner	The Project
Abbott Laboratories	Synaptic Science	Seurat: Integrating Assay Data Retrieval and Analysis in One Easy Application
★ Genentech	Dolcera	Innovation Dashboard
Geospiza		GeneSifter: Next Generation Knowledge Management for Next Generation Sequencing
LabRoots		labroots.com
Scoren International		Paradigm shift in data mining process, industry experience (IT, biopharma etc)
Sigma-Aldrich	Ingenuity Systems	Your Favorite Gene powered by Ingenuity
SRA International		SPS Orion Global Collaboration Implementation
✔ The Children's Hospital of Philadelphia, Division of Clinical Pharmacology & Therapeutics		Pediatric Knowledgebase
Vanderbilt University	ActiveHealth Management	A Computerized, Clinically-Intelligent System to Deliver Clinical Alerts to Physicians and Their Patients Improves Care and Lowers Health Care Costs
Vivus	JaPa Incorporated	Executive Trial Report

Judges' Prize

(CONTINUED FROM PAGE 30)

especially. They've been doing [therapeutic drug monitoring] a lot longer."

In the meantime, the team is "trying to create a consortium around this so that we have other folks participate in the development of this system. Cincinnati Children's has already committed to going down this path with us," Barrett says.

"We have an external advisory board that helps us plan for the IT challenges across the globe." Specifically, the PKB plans to make use of technology solutions that have broad appeal, "in particular SAS and the JMP product." Also in the works: "We're planning for a PKB-Lite version that allows people to upload data into a larger system, meant to accommodate a smaller outpatient setting."

"This has been such a blessing for us," says Barrett of winning the Best Practices award. "As we're putting together the documentation for the consortium and identifying what the PKB is and seeks to do, we [now] have some external validation that this is a project that's been well thought out and has the right sorts of teams interested. It will improve the visibility of our efforts and we're looking at this to kind of kick this over the top.

Translational Medicine

(CONTINUED FROM PAGE 29)

conditions occurring in a patient, without focusing on any particulars. Both modules produce information in under an hour for small cohorts (thousands of patients), and less than a day for large cohorts (millions of patients). On the other hand, the Risk Estimation module zooms in on suspicious indications, letting users explore these and estimate the potential risk.

"We've done a lot of validation work, looking at examples of past safety issues in published literature and verifying that our results were similar to these studies," Powell says. For example, the group used SÆfetyWorks to retrospectively evaluate pergolide (Permax), FDA-approved for Parkinson's disease in 1988, but withdrawn nine years later over concerns about leaky cardiac valves. In a case study conducted in less than two days, they found that a safety signal for pergolide first surfaced in 2001, and further evidence connecting the drug with valve disease appeared by 2002. They've also explored fracture risk in patients taking antidepressants (as a drug class). "We found a small but probably real risk, and we'll need to alert [antidepressant] prescribers and put it on the labels," Pattishall says.

It took about a year for SÆfetyWorks to be fleshed out. Soon after its implementation at GSK in 2008, the collaborators decided that their new system was ready to be spotlighted in this year's Best Practices. ProSanos also acquired marketing rights to the software, and several regulatory agencies have since expressed interest in possibly making use of SÆfetyWorks, among them the FDA.

The SÆfetyWorks team is hardly resting on its laurels. Besides insurance claims and health records, they're in the process of incorporating laboratory data for patients, and information on procedures performed, into the system. Pattishall says this will allow a better definition of both patient populations and disease outcomes that occur during medications. They're also considering a European database, to more accurately reflect medical practices in other regions.

"We put a significant amount of hard work into developing SÆfetyWorks, so it's gratifying that *Bio•IT World* recognized this," Powell says. And beyond such validation, SÆfetyWorks' profile should gain in visibility. "Hopefully there'll be more users," Pattishall adds, "as this will more rapidly improve drug safety in patients, which is our main interest."

IT & Informatics

(CONTINUED FROM PAGE 22)

It really just looks like a video game."

"We knew that would be a slam dunk popular tool for using CellProfiler data," she says. "Previously, if a biologist had a tough phenotype, they'd need six months writing a new algorithm. Here, provided we can find the cells in the image, we can use this machine learning. It typically takes a biologist anywhere from 1 hour to 1 day of scoring cells by eye, and the computer has learned what they're looking for. So pretty much any phenotype we come across, we can score in a day."

CellProfiler has won many dedicated fans over the past few years. Michael Yaffe (Floyd's boss) calls CellProfiler "an indispensable component of a large-scale high-throughput screen" that "adds an entirely new dimension to analysis, leading to generation of a robust and novel dataset that will be extraordinarily useful for years to come."

Another satisfied user is John McLaughlin, who runs a screening facility at Rigel Pharmaceuticals producing thousands of images weekly, and hasn't looked back since trying CellProfiler two years ago. "It had everything I needed," he says. McLaughlin likes the underlying Matlab platform, and its compatibility with a compute cluster, which is not found with all commercial packages. "My goal is to find drugs to cure disease, not learn (yet another) computer language," says McLaughlin.

Carpenter's team is currently involved in numerous wide-ranging collaborations, from studying the genetic underpinnings of breast cancer with Eric Lander's group to improving the analysis of neuronal cell types, which she calls "challenging for the best algorithms." Other projects involve screening potential drugs for infectious diseases including tuberculosis in human cells, and whole-organism analysis of the nematode worm to develop novel antibiotics. On the technology side, her team is working to enable CellProfiler to do movie analysis and 3-D image analysis. "Right now, it's fairly impractical to collect large sets of 3-D images, but as that becomes more practical, we'll work on algorithms to study those images." •

Clinical Trial Design

(CONTINUED FROM PAGE 25)

strategies at Wyeth. "We are [currently] integrating the IT systems relevant in the conduct of ACTs." Up to now, ACTs have been run without the benefit of this integrated system, "but we want to enable scalable implementation of adaptive dose-finding studies, running up to 30 ACTs simultaneously."

Linking drug supply software with the ADE will bring real-time supply chain management capabilities to the implementation of ACTs, "ensuring the right drug and doses arrive at clinical trial sites at the right time," says Krams. ACTs routinely require many more treatment arms than traditional trials and can thus become the more costly alternative unless the drug supply problem is addressed.

Adaptive designs address the pressing need, referred to in the FDA's 2006 *Critical Path Opportunities Report*, to more efficiently develop drugs and learn about dose response, says Dragalin. For Wyeth, ADE is a Critical Path Opportunities enabler. ADE has proven essential to elevating adaptive designs from a being a "small specialist niche" to a technology that can be deployed across a significant proportion of the company's trials.

Krams says the ROI is potentially huge. "Each design proposal we bring forward is accompanied by a formal business case analysis. Millions of dollars can be saved by stopping trials early and tens of millions of dollars can be banked by avoiding having to do rework. Our ability to accurately determine the correct dose to take forward into confirmatory phase III trials has improved considerably."

"The results Wyeth achieved in transforming clinical processes is a great case study of what can be accomplished by a focused, dedicated and determined team; and ought to be a wake-up call to the rest of the industry," said Grant Stephen, CEO Tessella. "It is satisfying to see that their success has been recognized by the BIO-IT judging panel and Tessella is proud to have been part of the program team. If you are serious about improving how clinical trials are done, Wyeth's comprehensive approach to adaptive trials demands careful study." •

KM

(CONTINUED FROM PAGE 27)

group benefiting from CareEngine and Vanderbilt's nurse review saw savings of $83.73 per patient.

"This approach to disease management has resulted in a significant increase in compliance and adherence through this joint effort between Vanderbilt University and ActiveHealth," says Luke Beauchamp, benefits administrator for the Vanderbilt Health Plan.

The relationship between ActiveHealth and Vanderbilt was a strong one. "From the beginning we wanted [ActiveHealth] to be involved," says McLean. "We were on conference calls together; we were setting up the system to do this."

Wei agrees. "The work with Vanderbilt is a great example and we believe we can continue to build upon that innovation... We continue to work with financial data to make sure this is a sustainable initiative. It's not just IT for IT's sake. It's truly sustainable and leading to improved outcomes [for patients]." •

CT Management

(CONTINUED FROM PAGE 24)

tions credits the Corporate Portal with an estimated 25% improvement in study launch times, a 15% reduction in tasks associated with overall trial management times, a 50% reduction in travel requirements for investigator meetings, and an 80% reduction in paper documentation. Cost savings estimates were calculated at $50 million when compared to traditional CRO rates annualized across 75 studies utilizing 75 sites each. La Luna says feedback about CTP has been collected from more than 2000 sites over the past two years. The study portal process received a 94% approval rating among sites participating in the 2008 survey.

It appears that Genentech has met all of its primary objectives for the project as described by Ventura: To "introduce a means for adding speed and efficiencies to our clinical trial execution process, in an eco-friendly environment, and enhance the clinical trial sites experience in working with Genentech." •

Editor's Choice

(CONTINUED FROM PAGE 31)

decision to submit SIP for this year's Best Practices competition in the Drug Discovery and Development category.

"Really, it just felt like the right time," Reed says. "But at the awards ceremony, when they announced the winners [Amgen and Genedata] in our category, everyone in our group was disappointed. Then they announced the Editor's Choice award at the end—we were taken by surprise and thrilled."

The collaborators have extended SIP's focus to the cardiac system. Next, they'll hone in on kidney issues. Besides such detailed tissue-specific mining as goes into the development of SIP data, Cook says, the program also provides a sweeping glance at all other toxicities within its vocabulary.

"We're looking to use similar approaches to leverage our internal knowledge," he adds. "There's a huge amount of information within AstraZeneca on compounds that went through rigorous testing but never got out into the clinic—we'd apply the same exercise here, pulling out relationships and generating assertions, to learn from our home history."

Moreover, says Barnes, "we've been discussing drug signatures and how to develop patterns from our data that take us all the way into later phases of the clinical pharmacovigilance space." The opposite end, in effect, of AstraZeneca's business needs in early risk detection, and an expansion of the safety arena.

"It's about breaking down the clinical barrier both ways," Cook says. "How do we translate both forward to clinical situations, then take what we learn and recycle it to the earlier stages of drug discovery, to make sure we're really using that information to influence the next generation of drug development?"

Ultimately, it's about generating new knowledge from old, using SIP analyses to form new hypotheses that can then be explored with actual experimentation. "That, I think, is really exciting stuff, because toxicology is such a broad area to work in," Cook says. "To focus on a few key areas at a time minimizes our chances of charging up blind alleys." •

Basic Research

(CONTINUED FROM PAGE 23)

gic neurotransmission define a unifying molecular hypothesis for dysfunction" in schizophrenia.

The project represents the first large-scale case-control study to utilize mRNA sequencing, yielding novel insights into the molecular mechanisms underpinning this disease. NCGR believes the Alpheus/JMP Genomics pipeline offers a turn-key approach for visualization, results identification, and statistical analysis of next-gen sequencing data. While next-gen sequencing technologies have democratized genome sequencing, Kingsmore points out that "visualization, analysis, and discovery in massive sequence sets remains limited to a few centers nationwide. Alpheus with JMP Genomics has been designed to provide end-to-end democratization of genome, methylome, and transcriptome analysis."

The Best Practices award will help garner attention from scientists who may not enjoy the same access to resources as a major genome center. The Alpheus/JMP Genomics combination provides a data management, visualization, analysis, and statistical framework for the application of next-generation sequencing data to hypothesis-based, investigator-initiated experiments. Alpheus, which is available as a service, applies vast computational resources with intuitive web-based visualization and query to help relieve the analysis bottleneck, while JMP Genomics delivers robust statistical results. The pairing provides an excellent tool for individual researchers who perhaps lack the extensive bioinformatics expertise required to analyze large-scale sequencing projects.

Schilkey and Kingsmore are delighted to have demonstrated that the workflow works. "More people will catch on, I expect, once they get the volumes of data. We're a little ahead of the curve," says Schilkey. "This is a soup-to-nuts solution for next-generation sequence analysis." Near term additions to the project will be to incorporate Ingenuity's Pathways Analysis tools and to add functionality to identify splice isoform differences between cases and controls. •

KM, Pharma

(CONTINUED FROM PAGE 28)

will expand to vaccines and small interfering RNA (siRNA). The latter is especially important for Merck in light of its push into RNA interference screening. Usuka says this will be "one of the major areas we want to nail in phase III," while the partners retain some flexibility. "If a company wants to define special features of viruses or vaccines or RNAi, they can build those themselves."

Merck found that joining forces in the consortium lowered development costs considerably, to an estimated 25% of the putative cost had they gone it alone.

"It's been very successful," says Harmon. "It's really enabled a sharing, a best practices between companies. Each company has been able to bring requirements from individual scientists." Harmon says there has been fruitful give and take from both companies. For example, Merck embraced Abbott's use of the term "moniker" for the sample names.

Harmon adds that, "External collaborations are a key strategy for Merck, and by doing this we feel we share both the risk and the rewards of the collaboration." Merck is exploring additional precompetitive alliances with other pharma companies, seeking new ways to share data with external collaborators.

For its part, Abbott said the joint approach "afforded significant savings over the likely cost of developing such a system internally." Abbott also praised the agile approach to software development that enabled iterative refinements to the requirements following review of prototype systems. Merck and Abbott received 100 perpetual seats, and Lilly recently became the third member of the consortium, which has one year left to run.

Accelrys' Usuka can't resist pointing out that the underlying LMQS (List Management and Query Services) registration system was itself an award winner at CHI's 2009 Molecular Medicine Tri-Conference Best of Show awards. Usuka thinks the Bio-IT World Best Practices Award helped attract Lilly, and has seen a resulting surge of interest since the presentation. As Usuka says, "It's a great way to start a conversation!" •

DISTINGUISHED FACULTY

- *Dr. Mario Albrecht, Group Leader, Molecular Networks in Medical Bioinformatics, Max Planck Institute for Informatics*
- *Chris Asakiewicz, Ph.D., Affiliate Professor of Information Management, Wesley J. Howe School of Technology Management, Stevens Institute of Technology*
- *Andrew Berridge, Bsc, Delivery Advisor, Informatics, Pfizer*
- *Richard Bickerton, Medicinal Informatics, Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee*
- *Bernd Bischl, Fakultät Statistik, Technische Universität Dortmund*
- *Phil Butcher, Head of Systems, Sanger Centre*
- *Lars Carlsson, Ph.D., Global Safety Assessment, AstraZeneca R&D, Mölndal, Sweden*
- *Dr. Andrew Chadwick, Principal Consultant (Life Sciences and Healthcare), Tessella*
- *Karim Chine, Software Architect and Coordinator, Biocep*
- *Guy Coates, Ph.D., Group Leader, Informatics System Group, The Wellcome Trust Sanger Institute*
- *Chris Dagdigian, Founding Partner and Director of Technology, BioTeam, Inc.*
- *Panos Deloukas, Ph.D., Senior Investigator, Human & Medical Genetics, The Wellcome Trust Sanger Institute*
- *Jacob DeVlieg, Ph.D., Global Head, Molecular Design & Informatics, Schering Plough*
- *Christian Herhaus, Ph.D., NCE Technologies, Merck KGaA*
- *Professor Andrew L. Hopkins, D.Phil., FRSC, SULSA Research Professor, Translational Biology & Chair, Medicinal Informatics Division, University of Dundee*
- *Oliver Karch, Ph.D., Bio- and Chemoinformatics, Merck Serono*
- *Camille Laibe, Software Developer (Computational Neurobiology), European Bioinformatics Institute*
- *Jerry Lanfear, Ph.D., Head, Data Support and Management, Research CoEs, Pfizer*
- *Hans Lehrach, Ph.D., Founder, Alacris Pharmaceuticals; Director, Molecular Genetics, Max Planck Institute; Professor in Biochemistry, Free University of Berlin*
- *Nick Lynch, Ph.D., Chemistry Domain Expert, AstraZeneca*
- *M. Scott Marshall, Ph.D., W3C HCLS IG co-chair, Informatics Institute, University of Amsterdam*
- *Carsten Möller, Ph.D., Lab Head, Therapeutic Research Group, Women's Healthcare, Bayer Schering Pharma AG*
- *Ian Mulvany, Product Development Manager, Nature Publishing Group; Project Manager, Nature Network and Connotea*
- *Ingela Nyström, Ph.D., Director of UPPMAX, Centre for Image Analysis, Uppsala University*
- *John Overington, Ph.D., Team Leader, EMBL-EBI*
- *Julen Oyarzabal, Ph.D., Head, Drug Discovery Informatics Section, Spanish National Cancer Research Centre (CNIO)*
- *Tommaso Piazza, Eng.D., Chief Information Officer, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT)*
- *Corrado Priami, Professor of Computer Science, University of Trento; President and CEO, The Microsoft Research - University of Trento Centre for Computational and Systems Biology (CoSBi)*
- *Sándor Szalma, Ph.D., Senior Research Fellow, R&D Informatics, Centocor R&D, Inc.*
- *Josef Scheiber, Ph.D., Research Investigator/Knowledge Engineering Consultant, NITAS/TMS, Novartis Pharma AG*
- *Reinhard Schneider, Ph.D., Team Leader, Structural and Computational Biology Unit, European Molecular Biology Laboratory (EMBL)*
- *Raza Shaikh, Associate Director of Informatics, Chemical Biology Platform, The Broad Institute*
- *Ola Spjuth, M.Sc., Bioclipse Coordinator, Uppsala University*
- *Eike Staub, Ph.D., Research Scientist, Bio- & Chemoinformatics DA, Merck-Serono R&D, Merck KGaA*
- *Mats Sundgren, Ph.D., Principal Scientist, Global Clinical Development, AstraZeneca R&D*
- *Fabio Triolo, D.d.R., M.Phil., Ph.D., Technical Director, Regenerative Medicine and Cell Therapy Unit, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT)*
- *Matthew Trunnell, Manager, Research Computing, Broad Institute*
- *Tibor Van Rooij, Bsc, Bioinformatics Director, Génome Québec & Montreal Heart Institute Pharmacogenomics Centre*
- *Jörg Kurt Wegner, Ph.D., Scientist, Integrative Chem-/Bio-Informatics, Tibotec (J&J, Belgium); Blogger, Mining Drug Space; Project Administrator, Open Source Development*
- *Edgar Wingender, Ph.D., President & CSO, BIOBASE; Professor and Director Dept. Bioinformatics, UMG, Univ. of Goettingen*
- *Hans Winkler, Ph.D., Senior Director, Global Head, Oncology Biomarkers, Ortho-Biotech Oncology R&D*

Pre-Conference Workshop

Co-organized by CHI and BioTeam

Monday, 5 October * 14:00-17:30

BIOTEAM
Enabling Science

Sequencing Data Storage

Matthew Trunnell, Manager, Research Computing, Broad Institute
Chris Dagdigian, Founding Partner and Director of Technology, BioTeam, Inc.
Guy Coates, Ph.D., Group Leader, Informatics System Group, The Wellcome Trust Sanger Institute
Additional Speakers to be Announced

BioTeam has been on the frontlines of next-generation sequencing integration, having helped several organizations with the unique next-gen IT, storage, and data management challenges.
This workshop will present real-world customer experiences straight from the trenches. You'll get practical information about the storage support needed by research organizations in the next-gen world.

For more speaker additions,
please visit Bio-ITWorldExpoEurope.com

Please mention keycode U02 when registering!
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IT/Workflow

Infinity's Informatics Solutions

Notwithstanding a sudden setback over its lead cancer drug, Infinity Pharmaceuticals has the tools and imagination to become a success.

BY KEVIN DAVIES

The creation of Infinity Pharmaceuticals in 2001 had all the right ingredients: Distinguished scientific founders, including Harvard chemist Stuart Schreiber and Broad Institute director Eric Lander; an experienced management team including ex-Millennium Pharmaceuticals veterans; and a cutting-edge approach to chemical synthesis and drug discovery (see, "Conquering Infinity with Chemical Genetics," *Bio•IT World*, Feb 2003). When the company recruited Julian Adams, chief developer of Millennium's cancer drug Velcade, it seemed like the icing on the cake.

Last April, however, Infinity hit a major bump in the road when a review of the first few dozen patients in its Phase III trial for its lead compound, IPI-504, seemingly on course for approval around 2011, prompted the company to instantly halt the trial.

Just hours earlier, I was listening to Adams and John Keilty, Infinity's VP IT and Informatics, discuss Infinity's evolution from a discovery to a clinical company. Both men were relaxed and upbeat. Since Adams' arrival five years ago, Keilty says Infinity has found its direction. "Everything's been focused on one purpose: What is the best way to get drugs to patients?" That mission has been accompanied by a wholesale operational rethink, led by informatics/IT, to leverage what was learned in the past.

Discovery Channel

"Drug discovery doesn't happen overnight," says Adams. "It *can* happen overnight, but it's the drug development that takes five years." Infinity continues to have high hopes for IPI-504, which was in an international Phase III trial for GIST (gastrointestinal stromal tumor). The drug targets the chaperone Hsp90, a key molecule in regulating protein folding. Inhibiting the chaperone drives unfolded proteins in the cancer cell to the proteasomes for degradation. At ASCO in June, Infinity released more promising data on IPI-504 for non-small-cell lung cancer and other indications.

The discovery team (some 60 scientists) examines cutting-edge mechanisms for novel cancer targets, looking for genes and pathways that are differentially expressed in cancer cells and druggable. "We take a lot of inspiration from the original concepts from Schreiber," says Adams, but adds it is absurd trying to build and screen huge chemical libraries.

"I don't care if you have 5 million compounds, I'm unimpressed!" says Adams. "We have abandoned the synthesis part of it—we just go directly to nature, and have found a number of natural products that represent the starting point for our discovery programs. [When] Nature makes a molecule, we say, 'God did a nice job—we can do better,' without any hubris! God didn't plan for good PK, the FDA, and all that. So we have to add some bells and whistles."

In Keilty's view, there are "no tricks" to expediting drug development. "I say this as the IT guy—I think technology gets you [only] so far. What we've really focused on is, how can we put tools in the hands of folks to empower them? Technology, in and of itself, doesn't do it for us."

Nevertheless, Keilty points to important capabilities in molecular modeling, using third party tools such as MOE and Schrodinger for ligand-receptor docking. His colleague Tom Tibbitts works with discovery and clinical teams, looking at modifications to improve drug-target binding. A lingering issue is the ability to dock small molecules into a protein's active site, or what Adams calls "the solvation/desolvation problem—and no one has solved that." It's not just a matter of high-performance computing but the development of the proper algorithms.

Julian Adams

EDC Evolution

Over the past few years, Keilty's Informatics team (see, "Informatics Infrastructure") has grown from supporting a pure discovery platform—collecting terabytes of data from registering and tracking compounds—to building a relational database for clinical data.

Five years ago, before implementing electronic data capture, or EDC, Infinity began filing everything electronically to the FDA—before it was the law—beginning with the IND for IPI-504. "We were the first fully electronic regulatory submission to the oncology division of the FDA," says Keilty proudly. "It was an unbelievable company-wide effort. Some folks didn't sleep for a month as we ensured every PDF was perfect. We actually downloaded the software from the FDA..." His voice trails off for effect. After evaluating a lot of alternative platforms, he settled on ISI [Image Solutions]. "Over time, we've built other tools to complement their system."

Infinity is at 150 submissions and counting. Worldwide regulatory filing IT is handled by a younger Infinity employee. "[Our Hsp90 program is] unpartnered,"

says Keilty. "We use CROs, particularly for Europe, and for external regulatory submissions. Basically, we pack our own parachute. We do everything from discovery phase to regulatory filings and the intended launch—upon approval."

Infinity's first trial was performed on paper. "Mercifully only 18 patients," recalls Adams, but he quickly figured they needed EDC, which would let them interface with the web-based data collection systems at the clinical sites. "EDC is much simpler than so many of the tools used in discovery," says Keilty. Medidata edged out offerings from Phase Forward, DataTrack, and others, and Keilty was able to get EDC up and running at the Dana-Farber Cancer Institute a month after signing the contract.

One reason for choosing Medidata was that Keilty had moved from a Java-centric shop to a mostly .NET shop. "We were able to take their system and expand on it," says Keilty. "Regardless if it comes off the shelf or not, there are a lot of steps to make sure it works exactly as it was set up to do." Keilty's team has become adept at knowing what to look for.

Adams and Keilty soon realized that some of their discovery tools, like Spotfire, could be applied to looking at clinical data as well. Each night, the EDC system exports SAS datasets over secure FTP to Infinity. "This is such a rich data source, both for prospective and retrospective analyses... [If] I see an abnormal lab value, it's nice to look across studies to see if we've seen that lab value before."

Today, Infinity collects hundreds of fields of data, from age and body weight to lab chemistries and imaging results, in a clinical data warehouse designed by Keilty's Informatics team—the Clinical Data Integration Platform (CDIP). Scientists can query the data in any number of ways, looking for gender differences, lab values, CT scans, tumor shrinkage, EKG monitoring, and so on.

This could expand to genomic differences too. "We haven't ruled that out," says Adams. At ASCO, Infinity reported better Phase II results for IPI-504 in patients with non-small cell lung cancer with the wild-type epidermal growth factor receptor than mutated forms. Eventually, Adams anticipates sequencing patients' entire genomes before validating a multiplexed set of say 5-50 genes that defines a more homogenous sub-population. "If you could correlate that with better responses, we would absolutely go in that direction," says Adams.

But Keilty cautions that next-gen sequencing is just a commodity. "We really want to be biomarker agnostic. We need something that's really usable in the clinic." It may be genome sequencing, it may be circulating tumor cells, or something else. "All we care is that this is a way to separate the patient populations into those that will respond, and those that don't."

Due Process

Another homegrown application—a transactional database called iTRAC—tracks all the processes around a clinical trial. Keilty calls it a "clinical trial management system on steroids." A big component of the IPI-504 Phase III trial was imaging. Although challenging, all the imaging is analyzed centrally as the data arrive at Perceptive Informatics in Waltham, Mass. Perceptive turned around the results within five days after review by independent radiologists, which became the primary blinded input. Trial managers logged into iTRAC to see if an imaging read was missing and ensure the information was on schedule. Electronic queries were generated automatically, saving Infinity staff auditing hassles. Adams received an email every morning providing a snapshot of the number of patients in the study, the proportion in screening, randomization, and so on.

"The same person doing regulatory submissions is also using iTRAC," says Keilty. He can call up the CRO and find a missing read if necessary. "We can control the study without really being the one doing a lot of the work." But normalizing those eclectic sets of data across studies and sites poses a challenge. If certain lab values look strange, the team needs to be able to retrieve similar incidences and "pull those data together instantly. We've done a good job of that." Over time, Keilty says iTRAC will become an important data source. If Infinity wants to expand into a new disease area, then it can be used to formulate a feasibility survey to identify the right people to run the trial.

For all Infinity's intellectual and informatics capabilities, Adams admits that not all hypotheses bear out. His prelimi-

(CONTINUED ON PAGE 42)

Informatics Infrastructure

John Keilty

John Keilty, Infinity's "IT guy," leads an informatics staff of a dozen spanning everything from software engineering, discovery and development to clinical and business. Flexibility has been vital in assembling the team's infrastructure, applying staff to different areas. "Do we have a Linux cluster? Do we have modeling software? Are we able to do virtual screening? We have all those capabilities, and if the need arises, we'll make it happen. But this is a lean and mean operation, and we just try to be very careful where we apply the most expensive resource of all, which is the human resource."

There are three full-time IT staff handling the network architecture and building expansion. The informatics team is tightly integrated, with core areas including clinical informatics (data management, regulatory submissions); discovery informatics (molecular modeling); cheminformatics; and bioinformatics. There's also business informatics, currently focused on supporting the finance team but likely to change as the commercial group expands. "We're Sarbanes Oxley compliant too. It's a pretty eclectic mix."

The IT group also handles EDC user management. Says Keilty: "We've leveraged a core software engineering team, 1 full-time database, 1 part time, and three engineers. These teams can leverage other core competencies within the team. So far it's worked pretty well." K.D.

Infinity

(CONTINUED FROM PAGE 41)

nary conclusion from the IPI-504 setback is that patients were receiving too high a dose of the drug. Until then, Infinity was planning to expand headcount this year by one third to more than 200 staff. "We want to be very pragmatic about this," says Keilty. "We're not Novartis. How can you do the most with the people you have?"

Keilty says the company's three lead programs all stemmed from intellectual insights. Adams, he says, pragmatically applies his deep understanding of biology and chemistry. "He can look at something and say, 'If we threw this functional group on here and tweaked this a little bit, I bet that works.' It's kind of annoying—but mostly he's right!" Adams admits he doesn't mind occasionally breaking a Lipinski Rule or two. But he's not infallible, and there have been times when the pharmaceutical group has "totally made a fool out of me."

Infinity has "every intention to stay in oncology," says Adams. The key, he says, lies in the ability to serially sample tumors, which is "the single biggest impediment to understanding how one's drug is impacting the tumor. The future's going to be in circulating tumor cells," says Adams. "I want to have one of those [Mass General CTC Chip] machines in here—I'll even be a beta tester! Serially sampling the tumor—I want to collect those cells, grow them up, see what genes are being displayed, [learn] what's the impact of drugs on an ongoing basis. And I want to know when to switch drugs because [the patient has] just developed resistance."

Infinity has some promising cancer programs entering the clinic, including the Hedgehog pathway inhibitor, IPI-926, in Phase I, which targets an embryonic growth pathway that has been hijacked in adult cancers and could explain why some cancer cells metastasize.

Despite the industry's travails, Adams sees a silver lining. "It's raining talent with the consolidation in the industry. There are divestitures of pipelines from failing companies who basically can't afford to stay alive," or are simply looking to trim their portfolios. "If we license it, we have to love it as if we discovered it." •

IBM Touts Clinical Cloud

Clinical technologies benefit from cloud computing.

BY DEB BORFITZ

An increasing number of the top life science companies are considering a switch to "clinical clouds" for their e-clinical technologies. Indeed, it may be the only sensible way to access needed software and information as they engage in more collaborations, alliances, and partnerships to weather the "perfect storm of unprecedented challenges" bearing down on their collective bottom line, says Paul Papas, the Americas life sciences leader for IBM Global Business Services.

Historically, most large pharma firms have chosen to only "selectively outsource where appropriate," says Stuart Henderson, IBM's Americas life sciences research and development leader. But many are moving to a network business model where they share resources with a portfolio of partners to develop and commercialize drugs. As companies do less internally and seek to reduce the time and cost of clinical development, the demand for hosted, fully integrated, end-to-end clinical solutions will rise.

Cloud computing is an Internet-based model wherein a broad range of applications can be tapped from just about anywhere. Users pay cloud computing service providers like IBM and Amazon only for the resources they need and use.

"Building a smarter clinical cloud will enable collaboration, transparency, and access to real-time information wherever it is created," says Papas. According to IBM, a "smarter" clinical cloud consists of ten core capabilities: multi-tenant security, file sharing, data sharing, help and support, collaboration, analytics, compliance, clinical application suite, process integration and orchestration, and infrastructure.

Clinical cloud computing is certainly more economical for companies than buying licenses for separate electronic data capture (EDC), clinical trial management (CTM), and information management systems, integrating them internally, and then redundantly paying for the same services whenever they use a clinical research organization, says Henderson.

The FDA already trusts external servers when clinical trial data is sent by email from labs to investigators and from investigators to sponsors, says FDA spokesperson Crystal Rice. But if the data is archived using cloud computing, sponsors will have to convince the agency that there are adequate "write protection" safeguards to prevent tampering. The FDA would be particularly interested in data security measures if the cloud computing service provider has other "sensitive users" such as insurance companies and banks. "The agency might [also want to] check for assurance that investigator records correspond with the data in the cloud repository."

IBM predicts that life science companies will "flip" to buying technology in a cloud-provisioned way within no more than three to five years. "The majority of talented clinical IT resources now focused on operational efforts will instead be focused on the science of analytics," says Papas. "IBM's approach is to enable a phasing to cloud computing where a client uses a combination of their in-house applications and the applications available as part of the cloud solution."

The move to cloud computing will essentially force companies to agree not just on how they will collect and exchange clinical data, but also how they will manage and warehouse it, says Henderson. "What companies increasingly agree on is that the differentiation they bring is in the study design, the assets being progressed through the pipeline, and their relationships with clinical investigators."

When done right, Papas says, a clinical cloud will facilitate company-specific variations via configuration rather than customization. "Companies will have to realize and accept that most customizations are costly and do not provide differentiation." •

Clinical Research

Archimedes Turns Clinical Trial Models into Reality

The modeling project creates virtual trial populations with which to run studies.

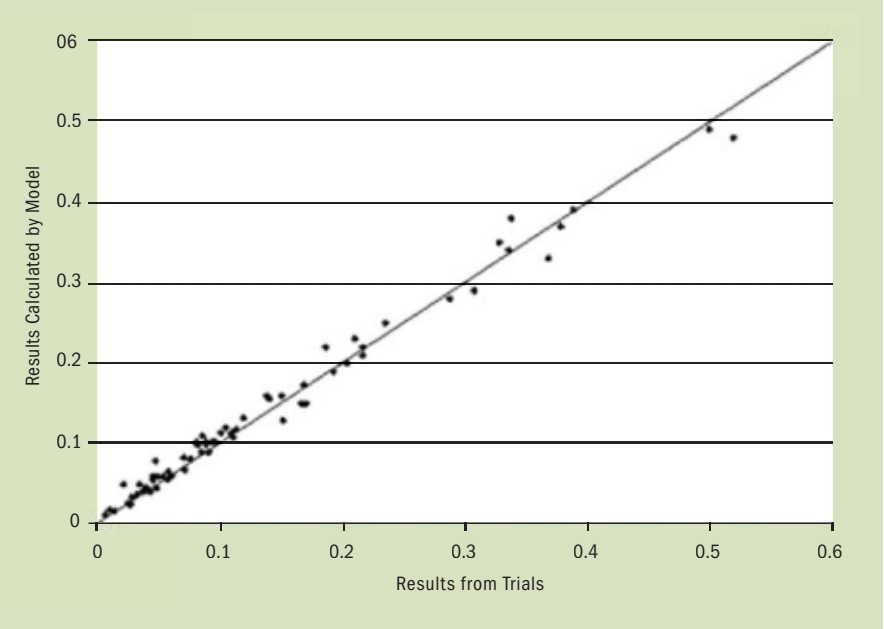
BY VICKI GLASER

In the early 1990's the co-founders of Archimedes, physician-mathematician David Eddy and physicist Len Schlessinger, began building the Archimedes Model (AM) as a consulting project for Kaiser Permanente (KP). The AM is a mathematical model that simulates human physiology (and the surrounding health care system) by creating virtual trial populations. Each individual does not represent a real person; rather the virtual people, in aggregate, represent a target population. Drawing on public data, the model can accurately simulate and predict the outcomes of trials.

"What sets Archimedes apart from other modeling companies is that not only does the Archimedes Model capture and integrate actual physiology into a single model, it also incorporates the interaction of individuals with the greater health care system. This allows Archimedes' clients to understand the direct effects of interventions on actual health outcomes, such as in clinical trials, and the impact of these interventions in real world settings," says Peter Alperin, medical director at Archimedes.

The AM evolved over a decade under the KP umbrella. In 2003, a seminal paper in *Diabetes Care* (Eddy, D. *et al.* 26:3093; 2003) validated the model by modeling 18 published trials selected by the American Diabetes Association (ADA), demonstrating its ability to predict the trial outcomes retrospectively.

Soon afterward, the Collaborative Atorvastatin Diabetes Study (CARDS), sponsored by Pfizer and reported in 2004, evaluated the effects of atorvastatin in type 2 diabetes patients, focusing on CV outcomes. Before the trial ended, the investigators invited Archimedes to model the trial prospectively. Archimedes created a virtual population reflecting the characteristics of the trial population, modeled the effects of atorvastatin, and ran the model for five "virtual" years. The results, revealed shortly before presentation of the actual trial data, closely matched the trial results. Recognizing the model's commercial potential, KP spun out Archimedes as an independent, for-profit entity in January 2006.



Comparison of AM results with actual diabetes trial results (74 validations). These included 18 distinct trials, 10 of which were not used to build the AM, providing independent validation of its accuracy.

Virtual People

The AM relies on publicly available datasets and clinical trial data that form the basis for the relational differential equations. Archimedes uses new trial results to challenge the model and determine if the existing equations adequately represent these new data. In this way, the model evolves to incorporate new knowledge about disease pathways, interventions, and outcomes.

"When we recruit virtual patients for our trials, they are individual virtual people that we build by pulling them out of a publicly available dataset," explains Alperin. He says it's easier to teach mathematically oriented modelers that create the algorithms a little medicine than teaching medics heavy math.

The equations are solved simultaneously using a technique called event queuing. This asks, "What is the next thing that will happen?" Alperin explains. "Each time there's an event, the output of the model is the health outcome that took place. Events... can be as massive as an MI (myocardial infarction) or as simple as going to see the doctor. After every event, all the equations are recalculated," resulting in a reordering of the predictions of future events.

With a grant from the American

(CONTINUED ON PAGE 46)

Longevity and Agility

Health Decisions celebrates 20 years of adaptive clinical research.

Michael Rosenberg

BY KEVIN DAVIES

In building a company of 150 employees over the past two decades, Health Decisions founder and CEO Michael Rosenberg has presumably done something right. But he maintains the industry is still doing a lot wrong. "The drug industry's remarkable success has made it reluctant to change, but some changes are long overdue," says Rosenberg .

The Durham, N.C.-based CRO espouses the concept of "agile clinical research," an adaptive system that allows mid-trial improvements to both operations and design that can help sponsors get drugs and diagnostics to market faster and cheaper. Rosenberg's success is predicated on technology as a platform. "Clinical research has not taken advantage of technologies that other industries have been using for years. When you look at the economic difficulties the industry is having, I think that technology as an enabler is way, way overdue," says Rosenberg. "Efficiency is going to determine who leads the industry into the next era, not megamergers and off shoring."

Rosenberg continues: "Outsourcing early drug development doesn't reduce risks—it delays risks and raises the stakes. It makes more sense to develop your own drugs, but learn how to do it more efficiently. It's pretty sad when a major company thinks it's incapable of becoming efficient."

Rosenberg maintains that web-based EDC is not up to the task. Health Decisions placed its first remote EDC system more than 15 years ago, but "somebody's [still] got to sit down at a keyboard and enter data. Until they have the time and inclination to do that tiresome chore, data sits around in batches. That delays finding out about problems. Meanwhile, the same problems recur again and again."

For example, the industry recruits about 85% of studies late. Web-based EDC "doesn't tell you which recruitment strategy is working and which isn't, or what's responsible for screen failures, or how different inclusion/exclusion criteria are affecting recruitment. There's no quick way to find out if I'm spending money well on recruitment strategies. Our system tracks information that lets you manage recruitment efficiently."

According to Rosenberg, "about 1/3 study budgets are spent redoing stuff that wasn't done right the first time." Take the query rate. Automated queries are necessary to ensure accuracy, but that does not mean study managers should be complacent. The query ratio for web EDC systems is usually 5-7 queries per 100 fields. Health Decisions seeks to help sites avoid making "the same inadvertent or dumb mistakes while waiting for queries to come back. You don't want to find out six months later that ambiguous instructions for the CRF were causing the errors."

"The institutionalized query system with all its delays is like the rework area in an obsolete car factory. You expect queries, and clinical studies focus on processing queries, but there's not much urgency about it. Queries often get resolved when regularly scheduled site visits roll around, not immediately. Meanwhile, errors and queries proliferate."

Digital Penmanship

Rosenberg says the most important metric is, what's the interval between when a data point is generated and when the CRO gains access to it in house? "In typical studies, there's a very long feedback loop... If you want people to decrease their frequency of errors, you have to provide quick feedback." This is where machine-read entry and the digital pen (a Health Decisions hallmark) come in handy.

There are usually 1-2 digital pens per site. The digital pen writes on special paper with a fine grid pattern, which orients the pen on the form. Once the pen is docked, the data are transmitted to Health Decisions, much like a PDF, read into the system and validated. "If I'm collecting data in Croatia, and its 4 p.m. there and somebody's interviewing a patient, I can have this information on your desktop in digested form before the patient walks out the door," says Rosenberg.

The system delivers improved query rates of about 1 per 100 fields, even lower in bigger studies. Each query costs about $350. "Take that $350 and multiply by 10,000 queries over the life of a study... You're wasting a couple of million dollars." A new release of Health Decisions includes Web 2.0 capabilities to enhance collaboration between sites.

David and Goliath

Health Decisions recently finished a sizable study of 4,000 patients for a start-up company that was battling a big pharma. "This was a David v. Goliath story," says Rosenberg. The CEO of his client said: "You did for $7 million what Roche failed to do for $20 million." "We catapulted them ahead of Roche," says Rosenberg. "This [diagnostic] product was just approved by the FDA."

Health Decisions was able to do everything quickly: recruitment, data entry, and study turnaround. "The FDA audited this study, and normally they'd come out to the CRO. They were comfortable enough with the pen that we could provide everything online. I believe this sets a new benchmark."

[GUEST COMMENTARY]

Trial Planning: Drug Development's Unsung Hero

Proper trial planning can save time and money.

BY ED SEGUINE

Generally speaking, the pharmaceutical industry has lagged far behind other sectors in leveraging technology to streamline core processes. While the industry is in the midst of a stampede toward enterprise adoption of electronic data capture (EDC) technology as a way to achieve process efficiencies, EDC is just one piece of the puzzle. The only way to achieve lasting productivity gains is to apply lessons learned from other process-intensive industries—notably manufacturing, construction, and retail.

Each of these industries identified their business processes as a system of interdependent, often time-delayed events with various feedback loops, and deployed technology to optimize performance across the enterprise rather than simply improving discrete activities. For example, look at Dell's integrated approach to manufacturing user-configured computers. Or, a major Las Vegas hotel construction project with computerized blueprints that provide detailed resource and timeline forecasts. Or, Wal-Mart's retail empire managing inventories that rely on past data and current sales performance.

These industries have achieved astonishing transformations by applying two key principles: 1) Implement technology at the early planning stages of core business processes and 2) Architect a data feedback cycle to supply those planning tools with meaningful information—preferably real-time. The same principles should be applied to help pharmaceutical companies improve clinical trial planning and development.

Clinical Development Today

Within the pharmaceutical industry, trial planning—and specifically protocol design—has traditionally been viewed as an art rather than a discipline. Generally speaking, study designer or protocol authors painstakingly focus on the scientific details of each individual trial with very little understanding of the operational impact of their decisions. Typically, at this point in the process, the only technologies being applied are Microsoft Word to access approved templates, a regulatory repository such as Documentum to store documents, and email to solicit comments from colleagues and potential investigators.

Only later in the clinical trial process does technology really come into play; in some cases, more than 100 separate systems are involved in the executing, analyzing, and submitting of clinical trial data. Unfortunately, most of these systems have their own data structures and few can work together, or even work at all, without substantial manual intervention. Almost all represent solutions to very specific problems—site selection, investigator contracting, lab management, statistical analysis, etc.—but generally contribute little to optimize the overall process.

Benefits of Early Planning

Electronic protocol solutions offer the greatest potential for comprehensively addressing the complexities and dependencies of the entire clinical development process. The ideal e-protocol solution simultaneously captures critical study design information both as a document and as data.

Consequently, the business processes that are dependent on that data (which were previously "locked" within the document and had to be manually input in multiple single-purpose systems) can now leverage technology as part of a unified system to do things that have never previously been possible. Multiple benefits accrue from this early planning:

- EDC database setup and CRF development times are reduced;
- Data collection variables can be analyzed in conjunction with the statistical plan to identify missing and unnecessary variables before the study begins;
- Rationale and relevancy of data variables can be propagated to downstream systems—e.g. the EDC system recognizes which data queries relate to variables associated with the primary objective and require greater validation through edit checks or query resolution;
- Study designs can be critiqued by applying rules to the data specification to identify inconsistencies or extraneous details that could lead to amendments.
- Protocol feasibility can be performed by comparing defined inclusion/exclusion criteria to existing databases to determine the availability of patients meeting the criteria;
- Budgeting and resource estimations can be made based on key trial parameters and previous cost/performance metrics; and
- Clinical supplies can be forecast based on the study requirements and expected recruitment projections.

Heroic Efforts Ahead

With the relatively recent availability of eProtocol tools (within the last 24 months), a number of major pharmas have experimented with various in-house applications and the few commercially available tools.

The feedback to date has been "mixed" as early adopters struggle to quantify the immediate benefits of an integrated planning/execution systems view of clinical development when most of the related systems don't work together either. That's not surprising at the early stages of technology adoption and the most recent experiences have shown great potential to reduce CRF build times by up to 40 percent.

Clinical research is a heroic endeavor—but it will take a different brand of hero to champion the adoption of a more disciplined and systematic approach to clinical development—starting with study design—to achieve the transformation the industry claims to be seeking. •

Ed Seguine is the former general manager of Trial Planning Solutions, Medidata Solutions. Email your comments to Glen de Vries, president, Medidata Solutions, at GdeVries@mdsol.com.

Archimedes

(CONTINUED FROM PAGE 43)

Cancer Society (ACS), Archimedes built cancer into the AM with the goal of developing a simple, prioritized standard for a preventive encounter that pinpoints lifestyle factors and specifies tests for physiologic parameters. (Kahn, R. *Circulation* 118:576-585; 2008).

Robert Smith, ACS' director of cancer screening, says that the trials could not be done—they would be too enormous, too expensive, and too lengthy. The ACS plans to use the AM to predict the outcomes of different cancer screening interventions, such as relative costs and benefits of increasing adherence with regular testing vs. improvements in quality, and the combined effects of each. "You can simulate unique populations or organizations and say, 'There is an opportunity to deliver preventive health and here is what the impact would be on your employees and your bottom line.'"

GE Healthcare hoped to focus on heart disease and explore the cost effectiveness of screening for MI risk among millions of asymptomatic people. The AM enables testing of the effects of a newly discovered biomarker, for example, without having to rebuild the model to accommodate a new component. GE and Archimedes ran a simulated clinical trial in a virtual population over 30 "years" to predict outcomes for various screening and preventive strategies. Results showed that unconditional treatment with statins would be the most cost effective approach, but if imaging of obstructed coronary arteries could boost compliance rates, then imaging would be the most cost effective screening tool.

Back to the Future

Archimedes has also developed models of kidney function, metabolic syndrome, and obesity. The obesity model can be applied to study the effects of various weight reduction methods and how those affect biomarkers and use of health care resources. "We have a laundry list of what we would like to do next," says Newton, including mental health (schizophrenia and bipolar disorder), inflammation, Parkinson's, and multiple sclerosis.

The AM runs on a dedicated grid environment, performed as fee-for-service consulting. "The output of the model is very complex and it takes our scientists and medical team to interpret it appropriately," says Newton. But that business model is changing following a $15.6-million grant from the Robert Wood Johnson Foundation to build the Archimedes Healthcare Simulator (ARCHeS) web-based interfaces. That work would provide access to federal, state, and local governments, for example, to predict future needs. Archimedes would provide the model at cost to subscribing organizations. Newton anticipates the first software releases in about two years. •

New Products

High Sensitivity

Shimadzu's AXIMA *Resonance* MALDI QIT TOF mass spectrometer provides the structural characterization and sequencing of biomolecules. The combination of quadrupole ion trap (QIT) and high-performance reflectron time-of-flight (TOF) analyzer provides the highest sensitivity and mass accuracy in Shimadzu's line of AXIMA MALDI systems. The AXIMA *Resonance* provides MS/MS and MSn spectra for a wide range of analytes, including pharmaceutical compounds, peptides, glycans, lipids and polymers. A variety of software tools comes standard with the AXIMA Resonance, facilitating manual or fully automated operation and seamless analysis.

Product: AXIMA *Resonance*
Company: Shimadzu
Available: Now
For more information: www.ssi.shimadzu.com

ADME Analysis

BioTrove has launched a new platform for drug discovery researchers' screening and analysis of *in vitro* ADME data. The RapidFire 300 provides scientists a label-free, high throughput, mass spectrometry-based instrument for several in vitro ADME applications, including pre-validated CYP Inhibition and Metabolic Stability analytical methods. Previously limited by time and labor intensive screening platforms, BioTrove has met researcher demands for high quality *in vitro* ADME data with a short turnaround time.

Product: RapidFire 300
Company: BioTrove
Available: Now
For more information: www.biotrove.com

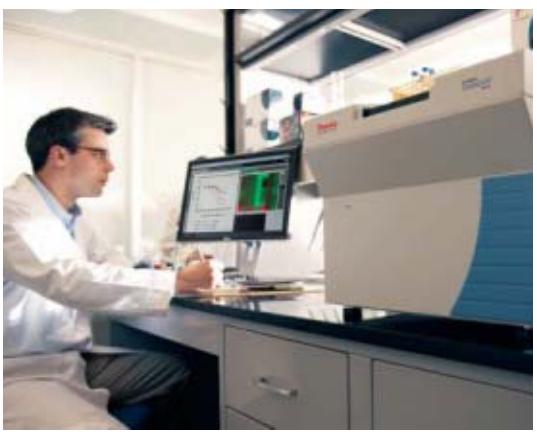
Global Clinical Trial Management

Phase Forward's InForm Global Trial Management (GTM) eClinical solution provides a single environment that enables study sponsors to streamline the management of clinical trial data from design through submission, all within a single environment for use in regional or global trials. The ability to efficiently code multi-trial adverse event terms, written in a variety of languages and syllabaries, to common industry-standard terms within one central environment helps maximize operational efficiencies.

Product: InForm Global Trial Management (GTM)
Company: Phase Forward
Available: Now
For more information: www.phaseforward.com

Imaging and Analysis

The Thermo Scientific Cellomics ToxInsight Solution offers a unique combination of imaging hardware and analysis software, and couples pre-validated panels of toxicity assessment targets, to provide a robust risk assessment tool for *in vitro* toxicity testing. Harnessing the power of cell imaging to make multiple toxicity assessments on a cell by cell basis, the ToxInsight IVT Platform, for the first time, unites automated instrumentation, software, and reagent 'cartridges' within a simple, intuitive workflow, offering improved sensitivity and specificity compared to traditional methods.



Product: Cellomics ToxInsight Solution
Company: Thermo Fisher Scientific
Available: Now
For more information: www.thermo.com/toxinsight

Educational Opportunities

This section provides a variety of educational events in the life sciences industry that will help you with your business and professional needs. To list an educational event (print & online), contact **Sales_chmg@chimediagroup.com**. To preview a more in-depth listing of educational offerings, please visit **www.bio-itworld.com**

Featured Events

CHI Events

For more information on these conferences and other CHI events planned, please visit **www.healthtech.com**

Clinical Adoption of Next Generation Diagnostics
August 11–12, 2009 • Washington, DC

Molecular Diagnostics for Infectious Disease
August 11–12, 2009 • Washington, DC

Production & Manufacturing of Vaccines
August 17–18, 2009 • Providence, RI

Novel Vaccines: Adjuvants & Delivery Systems
August 18–19, 2009 • Providence, RI

The Bioprocessing Summit
August 24–27, 2009 • Cambridge, MA

Optimizing Cell Culture Technology
August 24–25, 2009 • Cambridge, MA

Exploring Next Generation Sequencing
September 21–23, 2009 • Providence, RI

Next Generation Sequencing Data Analysis
September 21–23, 2009 • Providence, RI

High Content Data Analysis
September 21–23, 2009 • Boston, MA

ADAPT 2009
Accelerating Development & Advancing Personalized Therapy

ADAPT 2009: Accelerating Development and Advancing Personalized Therapy
September 22–25, 2009 • Washington, DC

Personalized Medicine
September 22–24, 2009 • Washington, DC

Translational Cancer Medicine
September 22–24, 2009 • Washington, DC

EUROPE
Bio·IT World
CONFERENCE & EXPO '09
6–8 October 2009 • Exhibition Grounds • Hannover, Germany

Bio-IT World Conf & Expo Europe
October 6–8, 2009 • Hannover, Germany

PEGS Europe
October 6–8, 2009 • Hannover, Germany

Pipeline Success Summit
October 13–16, 2009 • Boston, MA

Accelerating Proof of Concept
October 13–14, 2009 • Boston, MA

Immunogenicity Summit
October 26–29, 2009 • Philadelphia, PA

Clinical Training Forum
October 26–27, 2009 • Boston, MA

GPCR-Based Drug Discovery
November 2–3, 2009 • Boston, MA

Barnett Educational Services

Visit **www.barnettinternational.com** for detailed information on Barnett live seminars, interactive web seminars, on-site training programs, customized eLearning development services, and publications.

Live Barnett Seminars

Working with CROs
August 11–12, 2009 • Philadelphia, PA

IRBs: The Changing Landscape and the Effect on Conduct of Clinical Research
August 11–12, 2009 • Philadelphia, PA

Writing for Clinical Research
August 25–26, 2009 • Chicago, IL

Managing and Conducting Global Clinical Trials
August 27–28, 2009 • Chicago, IL

Mastering Cost Management for Global Clinical Trials
September 22–23, 2009 • Boston, MA

GMP for Pharmaceuticals
September 24–25, 2009 • San Diego, CA

Drug Safety and Pharmacovigiliance
September 29–30, 2009 • Philadelphia, PA

Drug Development and FDA Regulations
October 20–21, 2009 • San Diego, CA

Fraud in Clinical Research
October 20–21, 2009 • San Diego, CA

Patient Registry Programs
October 21–22, 2009 • San Francisco, CA

Interactive Web Seminars

The Performance Improvement Monitoring Model
August 5, 2009

Quality Improvement Strategies at Clinical Research Sites
August 21, 2009

Fraud in Clinical Research: An Overview
August 25, 2009

Clinical Investigator Site Inspections
August 27, 2009

New Developments in FDA's Human Subject Protection/Bioresearch Monitoring Initiative
August 28, 2009

Introduction to Signal Detection and Data Mining
September 1, 2009

Examine Approaches for Investigator Initiated Trials
September 9, 2009

Critical Decision Points in Design and Conduct of Patient Registries
September 17, 2009

Approaches to Address Challenges in Vendor Management
September 25, 2009

White Papers, Webcasts, and Podcasts

Keep abreast of current industry trends and developments. Browse our extensive list of free Life Science white papers, webcasts, and podcasts on **www.bio-itworld.com**. Interested in learning about developing a multi-media solution to generate leads? Please email **Sales_chmg@chimediagroup.com**

White Papers

Biomarkers: An Indispensible Addition to the Drug Development Toolkit Examining the Potential of Biomarkers

Sponsored by Thomson Reuters

Biomarkers are becoming an essential part of clinical development. In this white paper, Thomson Reuters provides insight from experts in industry and academia, and explores the role of biomarkers as evaluative tools in improving clinical research and the challenges this presents. Discover the potential of biomarkers to:

- Improve decision making
- Accelerate drug development
- Reduce development costs

Scientific Data Lifecycle Management: Preparing for Storage in an Uncertain Future

Sponsored by BlueArc

Managing vast and overwhelming streams of gene sequencing data today requires ultra-high performance systems and processes. With continued rapid advancement and improvements in gene sequencing, expect tomorrow's instruments to output quantities of genomic information that will dwarf current levels. Help your organization maintain data control and prepare for the future of sequencing through this informative paper that discusses:

- The information technology challenges of gene sequencing
- "Intelligent" methods for data management and customization
- System survival tips...Deciding what data to keep or delete
- New tools to keep scientists ahead of impending data torrents

Managed Innovation, Assured Compliance Developing, Executing and Managing the Transformation, Analysis and Submission of Clinical Research Data with SAS® Drug Development

Sponsored by SAS

Get better products to market faster. Discover the top ten challenges facing life science executives and how to overcome them in this white paper. Read how SAS Drug Development transforms clinical data into true innovation.

What's Wrong with Biomarkers?

Sponsored by Definiens

The hype around biomarkers has reached such a fever pitch that it risks provoking a backlash among needed constituencies such as payers, physicians, and patients. No one doubts biomarkers' long-term value, but many obstacles remain, and that time still seems distant. Read this in-depth analysis in which distinguished experts examine biomarker challenges and follow along as they:

- Identify the need for change in research and clinical trial strategies
- Concede biology is more complicated than first expected
- Explore barriers to physician adoption of biomarkers
- Review assay technology and sample access limitations
- Examine nascent efforts to develop needed standards
- Discuss some notable biomarker failures and their lingering impact
- Tackle thorny commercialization issue holding back biomarkers

Protecting Intellectual Property

Sponsored by IDBS

Intellectual property (IP) remains one of the most important assets of any commercial entity. Historically, paper has been used to establish, maintain and defend IP, but as industry becomes increasingly digital, new tools must be used to ensure IP protection. This white paper explores the issues facing patent creation and defense in the electronic age and discusses the tools and functionality required to protect innovation.

Webcasts

Secure Web Conferencing for Healthcare & Life Sciences

Sponsored by Adobe

Web conferencing is now established as one of the most essential tools for business communications. From collaboration around new drug development and clinical trials to marketing new healthcare products and research, Web conferencing can save time and money while increasing productivity. The webcast provides a comprehensive overview of the features and benefits of Adobe Acrobat Connect Pro for secure web conferencing in the healthcare and life sciences industry.

Electronic Submissions Adobe's Prescription for Insuring Success

Sponsored by Adobe

In the time-consuming and costly battle to gain market share, faster time to market equals a competitive advantage for life sciences companies. Efficiencies in the product development cycle impact the bottom line. To succeed, companies must streamline the collaborative processes of creating, assembling, and delivering accurate, approvable electronic submissions. Adobe LiveCycle ES (Enterprise Suite) solutions help simplify the submission process, enabling life sciences companies to achieve earlier filing dates, greater accuracy and quality of data, and ultimately faster time to market. The webcast covers how to:

- Gain a competitive advantage with faster time to market
- Realize immediate ROI
- Improve document collaboration across your organization

Podcasts

Spain Biotech: An Engine for Economic Change

Sponsored by Trade Commission of Spain

Discover how Spain is focusing on biotechnology to be an engine for economic change through gradual internationalization, development and technology transfer. Regional governments are actively investing in public and private biology research and promoting the creation of knowledge-based companies. Spain's human capital combined with aggressive investment in biotech research and infrastructure has led to the creation of bio-clusters.

What Will Drive Tomorrow's Health Business Innovation: Technology, Standards, or New Business Models?

Sponsored by Medidata

Executives from Medidata and SAS discuss the current state of health business innovation, particularly around providing solutions for clinical trials and drug development and address the following questions:

- Does the health industry need more technology to drive business innovation?
- How does the current state of industry standards impact the ability of technology to drive business innovation?
- Is the lack of integration, inability to enter clean data or data privacy issues posing barriers to fully exploiting today's technology?
- Are standards and technology adoption hindered by misaligned business models?

The Russell Transcript

Two Sides of Network Biology 2.0

JOHN RUSSELL

The roster of speakers at the Network Biology 2.0 symposium*, sponsored by Gene Network Sciences (GNS) and the Broad Institute, featured some of the most influential people in systems biology and personalized medicine: Jim Collins, George Church, Mark Boguski, and Peter Sorger to name a few. Eric Schadt was a no show, but with his dramatic move to Pacific Biosciences (see p. 8), he probably had an excuse.

Chaired by GNS co-founder and executive VP Iya Khalil, the symposium speakers discussed various approaches for taking diverse data, transforming that into models, validating those models, and using the model to infer new insight. Here are a few of the highlights:

• Examining extrinsic ligand-induced death pathways, Sorger used modeling at different levels—quantitative and Boolean—to study why some cells dies rapidly and other slowly. The modeling ruled out genetics and epigenetics and stochastic biochemical reaction rates. Sorger suggested a third hypothesis: unequal concentrations of the reactants in different cells are the drivers of variability.

• Dana Pe'er (Columbia University) discussed changes in gene regulatory networks that drive phenotype. In one case, she applied Conexic, a Bayesian algorithm, to a melanoma dataset comprising 62 tumor samples and correctly identified most known 'driver' events, while also connecting these to their known targets. The analysis also suggested a number of novel drivers, including genes involved in regulation of protein trafficking and endosome biology.

• The GNS platform REFS (reverse engineering/forward simulation) can take large data sets and, without prior knowledge, use computational techniques to find novel associations. Paul McDonagh (GNS) has used REFS to analyze liver gene expression, serum lipid profiles and body weight in 120 male mice from a mouse intercross. An ensemble of 1024 networks accurately predicted animals that were not part of the training data and explained almost twice the variance compared to quantitative trait loci alone. Further *in silico* experiments identified dozens of additional transcripts predicted to play a significant role in controlling HDL and triglyceride levels.

• In a talk on "Customized Care 2020," Mark Boguski (Harvard Medical School) argued precision diagnostics will be a disruptive innovation in medicine by 2020, and that clinical pathology will play a central role in personalized medicine. "Pathology is moving beyond diagnostics and classification of disease to providing customization information and therapeutic recommendations," he said, adding that data-driven reverse engineering of disease processes will identify the relevant molecular pathways in individual patients. These pathways will then be forward-simulated in the presence of virtual drug combinations to predict individualized therapies.

• George Church (Harvard Medical School) argued that "we stand on the cusp of a remarkable opportunity for connecting data for personalized medicine via web 2.0 volunteerism, personally controlled health records, and inexpensive personal genomes." Next-generation genome sequencing advances would be accompanied by understanding of regulatory variants (via allele-specific RNA quantitation) and environmental components (via pharmaceutical, microbiome and immune system datasets).

Pin Drop

One of the most interesting moments of the day occurred at the symposium's concluding panel: "The Future of Integrative Genomics and Network Biology." After a day packed with science and optimism, Gurinder "Mickey" Atwal (Institute for Advanced Study, Princeton, New Jersey) expressed resolute skepticism that systems biology could ever fulfill its promise of predictiveness.

You could have heard a pin drop as the audience's buoyant spirits were suddenly sobered by this challenging view. A physicist by training, Atwal argued that the search for biology's first principles around which to organize data and create truly predictive models was probably fundamentally flawed. He cited several long-term research projects that have made, essentially, no progress. Atwal hoped he was wrong, but fundamentally doubted the field would fulfill its expectations.

McDonagh took on the role of defender, and Boguski, whose 2020 talk brimmed with rosy forecasts for medicine, treaded carefully in rallying a counter argument. Stolovitzky offered that progress would be measured as the iterative process of experiment, model, and simulate gradually moved our understanding closer to comprehensive principles.

Usefully, the full assembly seemed to recognize the road to comprehensively predictive models for biology is unlikely to be short, even against the backdrop of solid science presented optimistically throughout the day and aiming for that very goal. But if Atwal saw the predictive biology glass forever half-empty, most saw it half-full and rising, though with varying ideas of how full it could get and when.

*Network Biology 2.0. The Broad Institute, Cambridge MA. May 20, 2009

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