TECHNOLOGY MONITOR

New technologies show promise for antifungal treatments, faster cloud computing and more efficient biofuels production

The WARF Accelerator Program speeds the development of technologies with exceptional potential for commercial success. With targeted funding and expert advice from seasoned business mentors known as Catalysts, the Accelerator Program helps inventions clear technical hurdles and advance to the marketplace. Following are the latest developments.

BIOPHARMACEUTICALS
• Antifungal drug discovery: The National Institutes of Health has initiated work on a collaborative, fast-track research project with an Accelerator Program team led by Dr. Bruce Klein, a UW–Madison School of Medicine and Public Health professor specializing in infectious disease. NIH lab collaborators are conducting a high throughput screen of their 500,000 compound library of small molecules for candidate compounds that target the Drk1 signaling pathway. Following two rounds of screening at NIH, Klein will conduct a third round of screening in his campus laboratory.

The project centers on the discovery and characterization of histidine kinase inhibitors for treating fungal infections. The sought-after compounds are expected to offer therapeutic benefits without the toxicity associated with conventional treatments.

The screening work is expected to be completed over the course of two months. Klein noted that an especially appealing element of the collaboration centers on the availability of medicinal chemistry for compound structural analysis and modification through chemistry experts at NIH. In addition, the collaboration has helped a graduate student working on the project in Klein’s lab secure a predoctoral fellowship from the American Heart Association.

Based on suggestions from the WARF Catalyst group, Klein’s team has been involved in implementing analysis of antifungal compounds and natural products using a Candida albicans haplotype insufficiency test. The assay is designed to identify the mode of drug action of promising natural products with antifungal activity. The work is part of a campus-wide, interdisciplinary program on antimicrobial drug discovery and Klein noted that funds from the Accelerator Program have allowed his group to generate important early results related to antifungal drug discovery.

COMPUTER AND INFORMATION TECHNOLOGY
• Virtual network services in the cloud: Srinivasa “Aditya” Akella, a UW–Madison associate professor of computer sciences, is developing a framework called Stratos to speed the work of computer “middleboxes” such as firewalls and wide area network optimizers that transform, filter, route and secure data. The Stratos framework features algorithms that help keep data flowing smoothly to enable applications for cloud computing, rather than use of local servers.

In recent months, Akella’s team has enhanced the Stratos prototype with an improved algorithm used to detect bottlenecks. The improvements address transient bottlenecks first and also work to alleviate more persistent computational and network bottlenecks.

In addition, the team has developed a new scheme to steer traffic with Stratos that permits more variety in the way traffic can be forwarded. The current approach supports a much larger variety of organized uses.

From a commercialization standpoint, Akella reported that many companies continue to struggle on a more basic level

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In a story of scientific discovery filled with as many twists and turns as a Northwoods trail, a rare insight from a massive public database and charitable support from an off-road motorcycle group have paved the way for work that may help some 20 percent of breast cancer patients with hard-to-treat tumors.

Now, funding from WARF’s Accelerator Program is helping transform the discovery by Avtar Roopra, a University of Wisconsin–Madison associate professor of neuroscience, into a predictive test and treatment kit that may serve as a model for other diseases.

“The project really encompasses the idea that we should be able to predict how a patient is going to do as soon as that person walks into the doctor’s office,” says Roopra. “From the patient’s standpoint, the benefit of the predictive assay is that it would be coupled to a second, ultimate part of the project — the development of a personalized medicine tool kit.

Roopra’s project builds on his previous research related to epilepsy and the workings of a long, powerful gene known as REST that regulates nearly 2,000 other human genes. In 2002, Roopra began exploring connections between excess REST and epileptic seizures — research that led to the development of a drug now in clinical trials to block action of the gene.

After his sister, Gurcharan Roopra-Ryatt, succumbed to an aggressive form of breast cancer, Roopra decided to turn his knowledge of gene interactions as well as his skill in computation and bioinformatics into a search for the genetic underpinnings of hard-to-treat tumors.

“I felt I should dedicate some of my effort to breast cancer research,” Roopra says. “We had no funding so we started out kind of small and we began with databases that already existed. There are literally tens of thousands of gene sets that have been archived at the National Center for Biotechnology Information (NCBI) including breast cancer and prostate tumors, all waiting to be analyzed. That’s how we discovered — utterly to our surprise — that there was a role for REST, a factor that I’d been studying for decades, in breast cancer. It had never been noticed before. It was incredibly compelling.”

In another series of unlikely coincidences, Roopra’s work caught the attention of cross-campus colleague John Newton, an HVAC specialist with the UW Biotron and an avid cross-country motorcyclist. Newton’s cycle group, the Wisconsin Dual Sport Riders, organizes two charity rides through the Northwoods each year and after learning of the work by Roopra’s team, the group selected the lab as one of its beneficiaries for the past five years.

“The effort to understand the role of REST in breast cancer has really been done on a shoestring budget and almost the entire work has been funded by this bunch of bikers raising money in northern Wisconsin,” Roopra says. “We’ve been extremely fortunate not only for the money, but because for the past three years, we’ve succeeded in getting papers published in peer-reviewed academic journals starting with PLOS Genetics. And of course in all of these publications we credit the work as being funded by the Wisconsin Dual Sport Riders.”

Now, however, the research has progressed to the point where additional money is needed to validate the reliability of the predictive tests in mouse models of cancer and begin identifying the best treatment tools to include. WARF’s Accelerator Program is providing the funding for this next step in the commercialization process.

The project revolves around identification of antibodies that detect when the REST gene is missing from breast tumors. In these tumors, exons needed to form a normal REST gene get spliced and reconnected in alternative ways, generating a truncated protein.

“We know how REST is lost, in at least some of the cases,” Roopra said. “And when REST is lost, a number of signaling pathways get elevated. There are existing, continued on page 4 >
Some industry estimates now peg the cost of developing a new pharmaceutical — including human clinical trials — at $1 billion or more.

Marty Rosenberg, chief scientific officer of Promega Corp. and a Catalyst for the Wisconsin Alumni Research Foundation’s Accelerator Program, says this costly reality factors into the advice given to campus inventors hoping to see their research evolve into new medicines. Rosenberg says he and other Catalysts encourage campus researchers to consider the perspectives of regulatory agencies and industry as they pursue their research with translational medicine potential.

Q: In working with a variety of projects arising from campus labs, what are some of the biggest challenges you see?

A: Every invention has its own particular issues in terms of how best to commercialize it. There’s no set formula that works for everything. We start by exploring how far along in the validation process the invention is to determine whether it would actually be of interest to the pharma industry. For example, is it still mainly early conception with high expectations or is there sufficient data in cell and animal models that provides strong validation for the work?

Another issue is the scope of the project. Will it be of direct interest to a pharmaceutical company or does it require further support as an independent activity or as a spin-out into a startup company in order to add sufficient value to attract a pharmaceutical partner?

What I like about the Accelerator Program is that it looks at each project independently. Often, the investigator comes in with one idea in mind as to how to develop their effort and the discussion at the Accelerator level may open up alternative pathways. This may give the investigator the opportunity to rethink how they wish to proceed and what is most critical for developing the approach as a therapy.

For example, we’ve seen cases where the pharmacology looks interesting on a molecular level but the candidate drug substance has problems. We’ve looked at peptides with important potential benefits for different diseases. The proposed mechanisms appear novel and exciting, but the problem is whether a clinical effect could be achieved by delivering the peptide into the bloodstream. So they appear to have an interesting target but not necessarily the right material to convert it into a real drug.

Q: What are some of the biggest challenges you see with the current FDA approval process?

A: The pharma industry now projects an average cost of up to $1 billion to do everything needed for regulatory approval of a new therapeutic. However, there are drugs that can advance pretty far in development without requiring a $1 billion price tag. In order to take a new drug from its inception to see whether it actually works in humans, you have to be willing to spend at least hundreds of millions. And there’s no guarantee of success. Drug discovery and development remains a very high-risk business.

Some of the Alzheimer’s drugs under development have gone through multiple phase three testing where they’ve gotten hung up for various reasons. In the case of drugs such as anti-infectives, the animal models are more predictive and clinical testing in a single indication can be more cost effective.

One of the reasons for the spiraling costs is the expense of clinical testing combined with the number of indications that have to be studied in human subpopulations. As we have learned more about the complexity of diseases, testing must be done in each subcategory in order to demonstrate benefit in that particular patient population. The number of disease indications and patient subcategories has expanded significantly over the past few decades. To achieve the broadest and most commercially valuable approvals, the drug has to be shown to work and be safe in each indication and in each subpopulation, thereby requiring more extensive clinical investigation.

Q: Given the high costs to move projects down the road to commercialization, where do the best opportunities lie for academic researchers?

A: The pharma industry has clearly struggled in recent years in developing novel therapies despite the explosion in human genome information. We may claim to know all the genes, but in terms of how they biologically function, how they interact and what goes wrong in the subtleties of their expression to cause different diseases, well, we are still missing a lot of the fundamental biological understanding. We require far better validation of complex disease etiology.

The best place for getting this kind of basic work done is in the academic setting. Once it is recognized that some fundamental aspect of biology is likely to lead to or modify the progression of a disease, this basic information becomes the engine you need to run a drug discovery program. With today’s economic pressures on big pharma, they are doing less and less basic research and turning to the best academic centers for access to this kind of information.

The problem for academics is how best to organize themselves in order to attract interest and resources from industry. They need to ask themselves how far their work has to progress in order to achieve sufficient validation and what the best mechanism is to translate those efforts into a commercial setting.
with methods to link middleboxes together. As a result, Stratos remains ahead of the curve with respect to licensing interest. A video highlighting the technology can be found at http://warfaccelerator.org.

CLEAN TECHNOLOGY

• Production of high-concentration sugars directly from lignocellulose: The project involves development and demonstration of an innovative chemical process for producing high-concentration sugars from lignocellulosic biomass such as corn stover, switchgrass, hardwood and softwood in a short time and under mild conditions. Sugars obtained through the process would serve as a valuable feedstock for production of clean fuels and chemicals.

So, Roopra’s team is now making a major push to complete development of the antibodies that will detect the loss of REST and serve as the diagnostic portion of the tool kit. Work is underway in mouse models with completion expected in 2014.

Thanks to the long-term research on the unique genetic signature of REST and an understanding of the mechanism behind it, Roopra has identified several potential therapies likely to benefit patients who have lost REST in their tumors.

“‘We have a good handle on why loss of REST drives tumor progression and we’ve found points to interfere in the progression of the disease and stall tumor growth and that’s what we’re looking at right now,’” Roopra says. “‘We know what those elevated signaling pathways are and there are already drugs that exist that inhibit those pathways. So, it’s very exciting.’”

Beyond his team’s eagerness to demonstrate in more detail the initial findings of the work, Roopra also understands that subsequent phases of the project will entail greater costs to establish clinical safety and efficacy of the suite of targeted drugs. However, potential commercial partners stand to benefit not just from the immediate boost of a powerful new tool against breast cancer, but from the broader implications of Roopra’s antibody-based assay.