

Association of University Technology Managers®

The Better World Report

The Positive Impact of
Academic Innovations
on Quality of Life



2010 Edition
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Special Edition
30th Anniversary of Bayh-Dole

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The Better World Project

The Association of University Technology Managers launched the Better World Project in 2005 to promote public understanding of how academic research and technology transfer have changed people's way of life and made the world a better place. The project draws from more than a decade's worth of case studies and news from AUTM members — the professionals who make academic technology transfer happen.

This 2010 edition of the project focuses on innovations that positively impact the quality of life of people around the world.

Materials and Support

The Better World Project materials are available in print and electronic formats.

Visit the Better World Project Web site or contact AUTM headquarters for details.

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The Association of University Technology Managers

AUTM is a nonprofit professional association with a mission to advance the field of technology transfer and enhance the ability to bring academic and nonprofit research to people around the world. AUTM's 3,000 members represent intellectual property managers from more than 350 universities, research institutions, teaching hospitals and government agencies as well as hundreds of companies involved with managing and licensing innovations derived from academic and nonprofit research.

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The *Better World Report* is a testament to the efforts of institutions' technology transfer offices, their directors and staffs, who gathered and submitted these stories and more. These contributions tell the story of how institutions are doing their part to improve the world we live in not only through education but through innovation. It is the return on investment that AUTM brings to light in this report.

Editors and Staff

The stories in the *2010 Better World Report* were researched and written by Pam Baker, Ellen Blum Barish, Jock Elliott, Ralph N. Fuller, Mary Roberts Henderson and Dave Perilstein. (For more information on the writers, see the Writer Biographies section.) Lisa Richter served as managing editor.

The vignettes were researched and written by *Better World Report* Committee members Nikki Borman, co-editor; Kevin Fiala; and Laura Savatski. (For a full list of the committee, see the 2010 *Better World Report* Committee section.)

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Preface



AUTM is pleased to present the 5th edition of the *Better World Report*, its annual compilation of some of the human stories behind successful transfers of academic technologies to the marketplace. With the stories contained in this report, AUTM will have presented hundreds of success stories.

This year marks the 30th anniversary of the Bayh-Dole Act, the landmark legislation that allowed universities to obtain patents on inventions that had been federally funded. As Sen. Birch Bayh tells in the foreword of this report, one of the things that kept him and Sen. Bob Dole driving forward in their battle to pass the legislation was a desire to see the practical applications of the results of federally funded research become reality and make a difference in peoples' lives rather than languishing unused in scientists' laboratories or bureaucrats' offices. This seemed to them such an unconscionable waste.

The theme of this year's report therefore is "The Positive Impact of Academic Innovations on Quality of Life." It presents 30 technology development success stories of ideas that have successfully navigated their way from a scientist's dream to practical reality to make a real difference in peoples' lives. The stories come from institutions across the United States — and the rest of the world — from federal laboratories, from universities both public and private, from teaching hospitals and from independent research institutes. Some of the stories are from overseas, because the success of the Bayh-Dole model has not been lost on global competitors, and dynamic technology transfer professions are rapidly developing round the globe.

What is staggering is the sheer diversity of ideas and needs that these successful transfers address. Much of the research carried out at universities relates to health care, so it should not be surprising that many of the inventions the report describes improve health care, ranging from early diagnostics for retinopathy to vaccines to prevent cervical cancer in women and shingles in the elderly to a device to let the wheelchair bound move over any type of rough surface. Agriculture is not forgotten, with tools for improved plant breeding and an antifreeze for plants. There is a better road surface, a better noise filter, a better battery, a better water purifier, better fabric with the potential to protect our armed forces and police.

Truly there is no end to the imagination of scientists and the ideas they will come up with, as long as they continue to receive the funding for basic scientific research, the fuel that drives the entire process. This richness and diversity is what makes the profession of technology transfer such a labor of love for those of us who are privileged to practice it every day. Academic inventions are not born fully formed and market ready. It takes vision (and a lot of faith) to see what they can become, and there are few moments more satisfying for a technology transfer professional than when a company shares his or her vision and agrees to devote the substantial resources needed to take one of his or her embryonic ideas and make it a reality.

So it is my pleasure to invite you to read these stories, to wonder, to marvel and to applaud them. And to ask you to keep supporting the federal funding agencies, the scientists they fund and, not least, the technology transfer professionals who start these inventions on the long road from lab to market.

Ashley J. Stevens, D. Phil. (Oxon), CLP
AUTM 2010 President

Foreword



After 30 Years of Bayh-Dole, It's a Better World Indeed!

By Sen. Birch Bayh

Has it really been 30 years since we enacted the Bayh-Dole Act? Many don't remember the time when university inventions were unlikely to benefit the American taxpayer. But I do.

The Bayh-Dole Act arose as the United States faced a steady rain of discouraging economic news. One thing was evident: America could not invest billions of hard-earned dollars in a public research system that did not maximize its economic impact.

Sen. Bob Dole and I looked into why so few federally funded inventions ever reached the market. There was not a lack of innovation — government bureaucracy was strangling entrepreneurs under reams of red tape. We found 28,000 government-funded inventions gathering dust on agency shelves with *not a single drug commercialized when the government owned the patent*.

We believed that if universities and small companies were allowed to own and license their inventions free from Washington micromanagement that we could right the ship. We worked closely with the founders of AUTM in crafting our bill. Because of their support we overcame incredible odds, and Bayh-Dole was approved at the last possible moment.

The rest, as they say, is history.

Our goals were really two-fold. One was to strengthen the economy. Impressive evidence shows that the law more than met this test:

- More than 6,000 new U.S. companies were formed from university inventions.
- 4,350 new university licensed products are in the market.
- 5,000 active university-industry licenses are in effect, mostly with small companies.
- More than *153 new drugs, vaccines or in vitro devices have been commercialized from federally funded research since enactment of Bayh-Dole*.
- Between 1996 and 2007 university patent licensing made:
 - a \$187 billion impact on the U.S. gross domestic product,
 - a \$457 billion impact on U.S. gross industrial output; and
 - 279,000 new jobs in the United States.

However, the second goal captured my heart. *We wanted to improve the quality of life worldwide by transforming federally funded discoveries from ideas into products.*

In reviewing this *Better World Report*, I think back to a press conference Bob Dole and I held in 1978. The National Institutes of Health had reversed its administrative policy granting universities patent rights, forcing them to endure lengthy case-by-case reviews. Several scientists whose inventions were caught in this bureaucratic tangle spoke.

An inventor of an ointment for burn victims described the incredible pain his patients endured. He asked: "Who's benefitting while my discovery is delayed from alleviating their suffering?"

His question haunted me. I was determined to pass our bill.

Bob and I wrote numerous bills — and passed a good share into law. However, few became so personal as we learned of many potentially important discoveries senselessly bottled up in Washington.

Foreword

Abraham Lincoln said that the patent system was intended to add the fuel of interest to the fires of genius. Yet, policies claiming to protect the public by mandating that federally funded inventions be made freely available to all had extinguished the fires of interest and, thus, innovation. Bayh-Dole relit the flame.

Thirty years later AUTM members have made our dream a reality. Just look at some examples from the new report:

- Indiana University (dear to my heart) creates a retinal imaging technology that could make health care more affordable while protecting diabetes patients at risk of losing their eyesight.
- The University of Delaware's water treatment filter that has the potential to provide safe drinking water to reduce 3.4 million deaths worldwide.
- MIT's robotic elbow brace allows stroke victims to recover the use of their arms.

We found 28,000 government-funded inventions gathering dust on agency shelves with *not a single drug commercialized when the government owned the patent.*

- The University of Colorado's new vaccine relieves the intensely painful disease of shingles.
- The Lawrence Berkeley National Laboratory's new lithium-ion battery makes batteries more energy efficient and more affordable.

It is fitting to say a word about the unsung heroes of Bayh-Dole. They are the companies that devote the considerable development dollars and hard work necessary to turn early-stage university inventions into products. No one guarantees their success after taking these risks. Linking the entrepreneurial spirit in our public and private sectors benefits us all.

Finally, the members of AUTM who devote their lives to fulfilling our dream deserve the thanks of the millions of people worldwide whose lives are better as a result. You've created a better world indeed!

For more information on the Bayh-Dole Act see page 9.

Birch Bayh was a member of the U.S. Senate from 1962 – 1980. During his Senate career, he authored two amendments to the Constitution — the 25th Amendment on presidential and vice presidential succession and the 26th Amendment lowering the voting age to 18 years of age. He is the author of *Title IX to the Higher Education Act*, which mandates equal opportunities for women students and faculty; co-author of the Bayh-Dole Act, which revitalized the nation's patent system; and chief architect of the Juvenile Justice Act. Currently, Bayh is a partner in the Legislative and Regulatory Group of Venable Inc.'s Government Division in Washington, DC.

Argonne National Laboratory

Rapid, Cost-Effective Diagnostic System Based on Innovative Nano Biosensors Helps Identify and Slow Spread of Major Diseases

Throughout history, human migration has contributed greatly to the spread of infectious diseases. Trade caravans, religious pilgrimages and military maneuvers spread many diseases such as influenza, plague and smallpox.

Today, epidemics continue at an accelerated rate thanks to an internationally mobile population with unprecedented access to quick, global travel. This increased international mobility has created the potential for a serious and costly health crisis, prompting world health authorities to seek rapid, high-throughput disease surveillance and reporting programs as a first line of defense. A solution needs to identify, manage and contain

highly communicable infectious diseases such as tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis, influenza and severe acute respiratory syndrome (SARS).

Infectious diseases can be separately diagnosed with existing highly effective gold-standard diagnostic tests such as culture and/or polymerase chain reaction (PCR). But, the most sensitive and accurate tests conducted in clinical labs usually take days to provide an answer, while the very rapid tests that require only a few minutes are usually less sensitive and inaccurate.

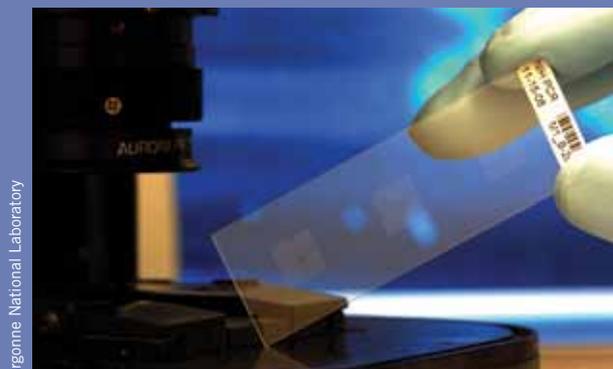
Performing individual tests for each of

these diseases at a reasonable cost, though, creates formidable logistical and financial challenges. A more innovative solution that cuts down the number of tests is needed.

Next Generation Disease Screening

One possible solution that shows great promise is a high-throughput diagnostic system, which is commercially available from Akonni Biosystems, a private molecular diagnostic company based in Frederick, Md. Called TruSentry, the system can extract DNA and/or RNA directly from either a tiny spot of dried blood or whole blood and then subject the single sample to testing for 10 to 20 of the most prevalent diseases at the same time. Results are available in less than five hours — fast enough to allow the analysis of thousands of samples per day.

The TruSentry diagnostic system can also be deployed in a single national reference lab, processing millions of samples per year or as part of a larger network of separate satellite facilities that are at, or closer to, the point where samples are collected. Other configurations can be deployed remotely in the field, for example, at the point of an infectious disease outbreak.



The Argonne-Engelhardt biochip resembles a traditional glass microscope slide that contains grids of small wells or “dots.”

At the heart of the TruSentry system is nanoscale biosensor technology on three-dimensional gel-drops licensed from Argonne National Laboratory in Illinois. Known as a biochip, this high-throughput form resembles a 96-well microtiter plate but in a 1 centimeter by 1 centimeter area that contains several dozen to several hundred “dots” or small drops. These biochips also are available in a microscope slide-size format for use in point-of-care settings. Each serves as a miniature laboratory with a unique protein, antibody or nucleic acid that will attach to a particular DNA sequence or antigen to identify infectious diseases such as TB, multidrug-resistant TB, HIV, viral hepatitis B, hepatitis C, syphilis and influenza.

“What Akonni has been able to do with the innovations licensed from Argonne is a very fascinating success story,” says Yash Vaishnav, Ph.D., M.B.A, senior manager, intellectual property development and commercialization, Division of Technology Development and Commercialization (TDC), at Argonne National Laboratory. “It illustrates what can happen when innovative technologies, developed by two international research facilities, with cultural and geopolitical differences, fit well together, and a technology transfer office and licensee work together to overcome challenges.”

International Collaboration Leads to Biochip

The special nanoscale biosensor technology is the result of an international research collaboration originally started in 1988 by the late Professor Andrei Mirzabekov,

Ph.D., and his team at the Engelhardt Institute of Molecular Biology in Moscow and subsequently advanced via a joint research agreement in 1995 with Argonne National Laboratory. Argonne is one of the U.S. Department of Energy’s (DOE) oldest and largest national laboratories for science and engineering research.

Each serves as a miniature laboratory with a unique protein, antibody or nucleic acid that will attach to a particular DNA sequence or antigen to identify infectious diseases such as TB, multidrug-resistant TB, HIV, viral hepatitis B, hepatitis C, syphilis and influenza.

One of the many inventors who worked on developing this innovative technology is Daniel Schabacker, Ph.D., team leader, Bio-Detection Technologies at Argonne, where he is the lead scientist for the development of the biochip portfolio. Schabacker helped develop the technology for manufacturing the biochips in a commercial setting.

“When I joined the Argonne team, many aspects of manufacturing and scalability

of biochips had not been worked out,” Schabacker says. “It was interesting, with a lot of capabilities, but there was no manufacturing mindset — the manufacturing process needed to be scalable to be commercially viable.

“We really developed a package of standard operating procedures and a cost analysis that showed how our biochips could be marketable and manufactured in a commercial environment. We also transitioned from the original gel-pad concept to gel drops, which increased efficiency and produced a robust product.”

Since this international group of researchers started collaborating in 1993, development of the biochip has been supported with \$22 million in funding from government and private sponsors — U.S. National Institutes of Health, DOE, U.S. Department of Defense, U.S. National Institute of Allergy and Infectious Disease, Centers for Disease Control, Motorola Inc., and Packard Instrument Co.

The Argonne National Laboratory biochip point-of-care diagnostic portfolio contains 29 issued U.S. patents with six pending applications, and the Argonne TDC has granted three exclusive licenses with defined fields of use to:

- Safeguard Biosystems — focusing on veterinary diagnostics
- Aurora Photonics — developing biochip imager for research and diagnostics
- Akonni Biosystems — developing human diagnostics

Innovations Licensed to Startup

Akonni first approached the Argonne TDC in 2003 after hearing Mirzabekov talk about detecting TB in human samples. As a startup biotech company, Akonni wanted to license the strong portfolio of intellectual property relating to this innovative microarray technology to raise funds.

After submitting a business plan and completing a licensing questionnaire, Argonne worked with Akonni to identify key patents and exercise an option agreement to negotiate a license prior to the request for seed funding. After the funding was obtained, they entered into license negotiations.

Argonne's Vaishnav says the first exclusive license included biochips for TB and a few other infectious diseases, a reasonable upfront fee and royalty rates, and due diligences based on sales and commercialization activity. As the relationship matured, it became clear to both that they needed a more dynamic agreement beyond standard licensing. The result was a collaborative research approach with the guidelines that allowed for advancing the technology and developing prototype applications of the biochip.

Over the years, many of them filled with time-consuming processes and difficult challenges, Vaishnav says both parties took a flexible approach that resulted in the agreements to evolve so they could overcome risks, attract more investors and collaborators, and take advantage of growth opportunities.

Today, the relationship is guided by a fine-tuned license that includes an equity stake for Argonne in Akonni and a cooperative research and development agreement. The result is a successful relationship: So successful, in fact, that former Argonne staff, including a key biochip researcher, have joined Akonni, and both entities are working constructively

Over the years, many of them filled with time-consuming processes and difficult challenges, Vaishnav says both parties took a flexible approach that resulted in the agreements to evolve so they could overcome risks, attract more investors and collaborators, and take advantage of growth opportunities.

with others to bring the technology to the marketplace.

"This technology adds a molecular diagnostic solution where the current technology, while good, simply can't perform," says Kevin Banks, vice president of sales and marketing at Akonni Biosystems.

Unlike today's real-time PCR-based platforms, the Akonni TruSentry system, Banks says, can rapidly screen a sample for hundreds of disease markers at one time by using hundreds of molecular biosensors in a microarray the size of a fingernail thanks to all the work, not only at Argonne and Akonni, but the original research started by Mirzabekov and his team.

Akonni, which is deploying the technology in both point-of-care and high-throughput screening settings, is in the process of attaining U.S. Food and Drug Administration approval for its diagnostic tests. Banks says this is a major milestone on the road to clinical trials and eventual clearance to market it as a commercially available diagnostic system.

"At the end of the day, what we have developed together is a third-generation molecular diagnostic solution that can provide truly accurate and trusted results, combined with alert detection and reporting on the world's most prevalent and dangerous infectious diseases," Banks says. "It represents the future of molecular diagnostics — a rapid, cost-effective diagnostic system can greatly help immigration and health care officials identify and slow the spread of potentially dangerous diseases and would benefit all people."

— David Perilstein

For another approach to molecular diagnostics, read about the Naval Research Laboratory's technology in "Genetic Testing Takes Guesswork out of Diagnosis," on page 27.

Beth Israel Deaconess Medical Center

New Diagnostic Test Warns Mothers Before Preeclampsia Strikes

Preeclampsia is a potentially dangerous complication of pregnancy that can strike women as early as the 20th week of gestation with little notice. It is characterized by a sudden spike in maternal blood pressure, edema and protein in the urine. In severe cases, preeclampsia escalates to eclampsia, which can cause the mother to suffer potentially fatal complications and lead to forced premature delivery of the infant.

Preeclampsia adds significantly to infant mortality rates in all countries and regions, but most especially so in areas where there are insufficient resources to save and treat premature infants. According to the Preeclampsia Foundation, this disease strikes 5 to 8 percent of all pregnant women in any given population, some 200,000 annually in the U.S. alone.

The foundation also estimates that preeclampsia is responsible for more than 70,000 maternal and 500,000 infant deaths globally per year. The only cure for preeclampsia is forced labor or cesarean section to deliver the infant prematurely.

Despite the severity and high prevalence of preeclampsia, an ancient affliction, very little is known about mechanisms behind development of preeclampsia and less yet about early diagnosis and potential therapies.

“In an average OB-GYN practice in the United States, the doctor will see 25 to 50 women with preeclampsia every year,” says Ananth Karumanchi, M.D., a Howard Hughes Medical Institute investigator and associate professor of the Division of Nephrology and the Division of Vascular Biology at Beth Israel Deaconess Medical Center (BIDMC), a teaching hospital of Harvard Medical School located in Boston. “Even though doctors know they will see many women with the disease, there has not previously been a way to tell which of them has preeclampsia until the onset of signs and symptoms,” says Karumanchi.

Finding the Warning Markers

That is, until now. Karumanchi and his team of researchers are developing the

first diagnostics test for preeclampsia. It is work born from years of careful research.

Starting with the knowledge that after the placenta is delivered, the disease gets better, Karumanchi became intrigued with the role of the placenta in preeclampsia. A kidney specialist by training, he hypothesized that the placenta must be secreting toxic substances into the mother’s blood, either subsequent to the disease process or as the cause of the disease.

“We took a molecular approach to studying this hypothesis. We took an approach that was not possible in the past because the technology did not yet exist,” explains Karumanchi, who began this research in 2001.



Shutterstock

Preeclampsia strikes 5 to 8 percent of all pregnant women.

The BIDMC research team studied placentas to find the molecules that might cause high blood pressure, kidney protein spillage, vascular impact and/or seizures in a pregnant woman — all symptoms of preeclampsia. “We found a number of molecules, but one in particular proved very important,” explains Karumanchi.

That molecule is a protein called sFlt-1 — an antagonist of circulating vascular endothelial growth factor and placental growth factor (PlGF). sFlt-1 was later confirmed to be present in large quantities in the bloodstream of patients with preeclampsia.

“We found that the sFlt-1 protein levels increased several weeks ahead of signs and symptoms. By finding that early warning marker, we now have a way to predict which women will suffer from the disease, and we can prepare early to address the problem,” says Karumanchi.

Co-investigator Vikas P. Sukhatme, M.D., Ph.D, Victor J. Aresty professor of medicine at Harvard Medical School and chief academic officer and Harvard faculty dean for academic programs at BIDMC, adds. “Down the road, the contemplated treatment would be through administration of drug therapies that neutralize the effects of sFlt1,” he says.

Identified but not Arrested

However, the discovery of the sFlt-1 protein did not arrive in a lightning strike. It was a painstaking process. “There was no Eureka! moment,” reports Karumanchi. “It took time for us to appreciate the

discovery, and it took time for a number of colleagues across the field to confirm the findings.”

By testing the sFlt-1 protein in pregnant rats, Karumanchi discovered that sFlt-1 reproduces the characteristics of preeclampsia: high blood pressure, protein in urine and glomerular endotheliosis — a classic lesion found in preeclampsia cases. This established a relationship

Over time, the discovery may be offered as a point-of-care test in a doctor's office. A pregnant woman and her doctor would know her preeclampsia risk in a matter of minutes, rather than in several days, when a result comes back from a lab.

between excess sFlt-1 in the bloodstream and the presence of the disease. Working with scientists at the National Institutes of Health, Karumanchi and his team were able to demonstrate that circulating sFlt-1 and PlGF levels can be used for the clinical diagnosis and prediction of preeclampsia.

The team is currently studying the role of

certain placental cells in the regulation of sFlt-1 production. They are concurrently characterizing other elevated gene products that may also play a role in preeclampsia and may serve as biomarkers for early disease detection.

Moving this knowledge into clinical trials, and then commercial use, whereby it can potentially save thousands of women and infants, however, requires more than the efforts of the scientists in the lab.

Finding a Champion

“The technology piqued a lot of interest, but we had difficulty licensing it,” explains Mark Chalek, director of Technology Ventures Office (TVO) at BIDMC. “We spent the better part of one year trying to find a big pharmaceutical company to license the technology. Most large pharmaceutical companies were concerned that the clinical trials would be too risky and that the preeclampsia market would be too small to justify an investment.”

But the support for the diagnostic could not be denied.

“It was vital to bring this technology to the bedside, which is consistent with BIDMC's mission and its unique strength in translational medicine,” says Karumanchi. “We are fortunate to have highly competent staff in TVO, capable in acting as catalysts to accelerate the project.”

Part of that acceleration was making the decision in 2005 to license the technology to Nephromics, a Massachusetts-based startup company.

Spearheading the negotiations was TVO's Christine Jost, who serves as associate director. She explains that Nephromics is a private startup company based on intellectual property (IP) arising from both BIDMC and Massachusetts General Hospital. While this maneuver established a focused champion, it also posed both funding and management difficulties.

The initial laboratory research that led to this discovery was funded by the National Institutes of Health. However, Nephromics was precluded from sponsoring Karumanchi's research in compliance with Harvard's and BIDMC's rules.

Yet Nephromics needed capital to market the IP to companies that would actually develop a commercial test kit and handle the clinical trials, testing, manufacturing, marketing and distribution. The company also required managers to complement the scientific expertise of Karumanchi and others.

"We are not venture capitalists in the traditional sense of managing a fund," explains Patrick Jeffries, president of Nephromics. "We are good at the business side; and the scientists, such as Karumanchi, are good at the science side. We complement each other.

"In essence, our team believed in the science, trusted the scientists and figured out how to work well together to attract larger companies as sublicensees to get this product out," Jeffries says.

This approach — to offer nonexclusive

sublicenses to several manufacturers — would allow the test to get to patients faster by creating a competition between the companies.

"For example, when we began to negotiate with Abbott, Roche pushed back hard, claiming there must be only one manufacturer for the purpose of competitive exclusivity," Jeffries says. "We explained that the big companies such as Roche, Abbott and others compete in laboratory testing equipment, but not in individual tests, so no exclusive license was warranted. We won that argument."

Nephromics has now successfully sublicensed the preeclampsia diagnostic to several leading diagnostic companies such as Beckman Coulter, Roche Diagnostics, Johnson & Johnson and Abbott Pharmaceuticals.

"Our objectives are to get the diagnostic kit standardized across the sublicensees, get it to market and get doctors ready to use the kit to save lives," says Jeffries.

Over time, the discovery may be offered as a point-of-care test in a doctor's office. A pregnant woman and her doctor would know her preeclampsia risk in a matter of minutes, rather than in several days, when a result comes back from a lab.

The interest in this discovery is, for now, focused mainly on diagnostics rather than therapeutics. "That begs the question, of course, as to why we should use the test if there is no specific treatment. Babies will still need to be delivered ear-

ly," says Karumanchi. "By eliminating the guesswork in diagnosis, we may prevent unnecessary premature deliveries."

Despite the current absence of a cure, a future treatment may indeed eventually result from the research under way today. "We are hopeful that the markers will prove useful in developing new therapies and may lead us to a cure one day," Karumanchi says.

"Thus far," Jeffries says, "we have awakened the scientific community to the importance of markers we can now utilize to find a cure. We are a long way off, but we are definitely on that path." At some point, the test may enjoy a groundswell of public support.

"This story is a tremendous example of the marriage of great science, effective technology transfer and commercialization, leading to the development of a preeclampsia diagnostic," says Chalek. "And if we are lucky — it will be accomplished in less than a decade."

Even luckier still are the mothers and their children who might be spared unnecessary risks. As Jeffries says, "Nearly everyone would want to prevent the risks of complications stemming from premature delivery."

— Pam Baker

Dartmouth College

Protecting Hearing: Spinout Advances Innovative Noise-Filtering Device

Members of a flight crew work in a dangerous job environment — it's chaotic and deafening.

Loud jet engines generate noise levels that can exceed an excruciating 130 decibels (dB), a measurement of the loudness or strength of sound vibration. This is well above the 90 dB that may cause vibration intense enough to damage the inner ear and, according to the National Institute for Occupational Safety and Health, the threshold of 100 dB for more than 15 minutes where hearing loss is likely. The U.S. Department of Veterans Affairs (VA) spends more than \$1 billion per year for hearing-loss cases.

To survive this job environment, flight crews must keep a constant vigil, wear protective ear plugs or earmuffs, and

primarily communicate via hand signals. But what if there was a headset that enabled communication while shielding flight crews from ear-damaging noise?

That's the challenge from the VA and branches of the military, one willingly picked up by Sound Innovations Inc., a privately held corporation in White River Junction, Vt. Launched in 2004, the spinout from Dartmouth College started with:

- The desire to develop a noise-filtering device
- A small team of engineering and business graduates and researchers from the private college in Hanover, N.H., whose expertise complemented one another
- \$300,000 in early funding from industry and government, including the U.S. Army and the U.S. National Science

Foundation, to advance the academic research, which had been supported by earlier rounds of research funding to Dartmouth from the U.S. Air Force, the VA and the Lemelson Foundation of Portland, Ore.

- A letter of intent from a flexible Dartmouth Technology Transfer Office for an exclusive license with delayed royalties for the faculty-developed innovative digital-signal processing control algorithms

Dartmouth Spinout Delivers First Product

Today, thanks to more than \$4 million in development contracts from the U.S. Army and the U.S. Air Force, Sound Innovations has its first product, the ACE — an earplug for aircrew that incorporates an active noise reduction module that protects hearing and improves communication in high-noise environments. Based on mathematics that successfully conjoin noise-control algorithms, this highly stable, hybrid system is undergoing qualification testing by the U.S. Air Force with expected market entry in 2010.

“Looking back over the last several years, this has been one of the most exciting things I’ve ever done,” says Dartmouth’s Laura Ray, Ph.D., who worked out the groundbreaking mathematics behind the proprietary algorithms. “I wear many hats

Dartmouth’s noise-filtering technology helps industrial workers — and others who work in noisy environments — protect their hearing



Shutterstock

now, so it's very different than my life as a professor, where I do research, publish and find funding."

The professor in the Thayer School of Engineering at Dartmouth co-founded Sound Innovations with fellow Professor Robert Collier, Ph.D., who died in 2009 shortly after the earplugs were flight tested at more than a half-dozen air force bases. Together, they were assisted on the project by two former Dartmouth students, David A. Cartes, Ph.D., and Alexander Streeter. Today, Cartes is an assistant professor of mechanical engineering, Department of Mechanical Engineering, at the Florida Agricultural and Mechanical University—Florida State University's College of Engineering in Tallahassee, Fla. Streeter is an engineer at DEKA Research and Development Corp. in Manchester, N.H.

Ray recalls how serendipity played a big role in early successful formation of the startup. She and Collier, a retiree who specialized in acoustics, hearing protection and environmental noise control, ran into each other at Thayer where they combined their interests in signal processing and developed their innovative technology. Their efforts to commercialize their discovery really took off when they started working with the Technology Transfer Office staff, which helped them develop a technology disclosure, secure U.S. patent protection and locate funding for their new venture.

"We marketed this technology in the usual way but had little success in attracting

interest," says Glennis Gold, assistant director, Dartmouth Technology Transfer Office. "Then we started recognizing the inventors were enthusiastic about the possibility of starting a company."

Next, they met someone who helped them solidify their thoughts about founding a company. At the time of the encounter, Chris Pearson, a graduate of the Tuck

To survive this job environment, flight crews must keep a constant vigil, wear protective ear plugs or earmuffs, and primarily communicate via hand signals. But what if there was a headset that enabled communication while shielding flight crews from ear-damaging noise?

School of Business at Dartmouth with a master's in business administration, was focused on finding a startup opportunity through the Dartmouth Entrepreneurial Network (DEN). According to Ray, Sound Innovations might never have taken off without Pearson because he brought a business sensibility that complemented the two professors' academic focus, and

this critical contribution has helped the new company avoid a lot of the problems that cause startups to stumble.

"I knew I wanted to start a business so I was working with several teams at DEN," says Pearson, who is now the chief executive officer at Sound Innovations. "Since I was focused on finding a startup company through DEN, I was introduced to Dr. Ray. We started to work together, built a small team and matured an early-stage technology into a product and other technologies."

Elements of Success

Both Ray and Pearson credit the successes to date to some key elements:

- A common willingness to take risks
- The ability to make the right contacts and attract students/employees at the right time
- An early link they established between the business and scientific side of their endeavor

"Dr. Ray isn't caught up with control, and I'm willing to spend time on developing a company," says Pearson. "These key ingredients don't always come together in an academic spinout company.

"It's important to remember that commercialization and research are two different worlds. Unless you've been involved on the business side of taking a product to market, it can be a difficult process for academic professors to understand."

But learning about the commercialization process is exactly what Ray finds so inter-

Bayh-Dole Act

Enacted on Dec. 12, 1980, the Bayh-Dole Act created a uniform patent policy among the many federal agencies that fund research, enabling small businesses and nonprofit organizations, including universities, to retain title to inventions made under federally funded research programs. This legislation was co-sponsored by Sens. Birch Bayh of Indiana and Robert Dole of Kansas. The Bayh-Dole Act was especially instrumental in encouraging universities to participate in technology transfer activities.

The act is “perhaps the most inspired piece of legislation to be enacted in America over the past half-century,” according to *The Economist*. “Innovation’s Golden Goose,” an opinion piece published in the Dec. 12, 2002, edition, the respected publication, states: “Together with amendments in 1984 and augmentation in 1986, this unlocked all the inventions and discoveries that had been made in laboratories throughout the United States with the help of taxpayers’ money. More than anything, this single policy measure helped to reverse America’s precipitous slide into industrial irrelevance.”

Major provisions of the act include:

- Nonprofits, including universities, and small businesses may elect to retain title to innovations developed under federally funded research programs.
- Universities are encouraged to collaborate with commercial concerns to promote the utilization of inventions arising from federal funding.
- Universities are expected to file patents on inventions they elect to own.
- Universities are expected to give licensing preference to small businesses.
- The government retains a nonexclusive license to practice the patent throughout the world.
- The government retains march-in rights.



esting — it’s a new level of knowledge that she feels will help make her a more valuable resource to her students at Dartmouth.

“I feel like the many hats that I wear at Sound Innovations keep me connected to the real world,” she says. “For example, it’s been a true learning experience to understand our customers — 17- and 18-year-old soldiers aren’t interested in their hearing when they need to focus on survival. Our challenge has been to find a way to enable them to focus and protect their hearing, all at the same time.”

The Sound Innovations team is well on its way to developing the next generation of aviation communications headsets that rely on their patented digital-signal processing methods for active noise reduction that cancel noise by producing diametrically opposed sounds. They’re also developing proprietary chip and electronic designs and innovative mechanical designs for advanced noise reduction and communication products. These products are expected to improve the work environment of active-duty soldiers and industrial workers by protecting and enhancing their hearing, allowing clear, two-way communication in noisy environments and enabling them to effectively listen to sounds from a distance.

“In the case of Sound Innovations, we were right to support this spinout that needed latitude to build a business and it’s worked out so beautifully,” Gold says. “The inventor was able to pair herself with the right manager and team to help commercialize this licensed Dartmouth technology that shows great promise of benefiting the public, exactly the kind of realization envisioned in the Bayh-Dole Act.”

— Dave Perilstein

Deutsches Krebsforschungszentrum (German Cancer Research Center, DKFZ)
Georgetown University
National Institutes of Health
University of Queensland, Australia
University of Rochester Medical Center

HPV Vaccine: Global Effort Defeats Cancer-Causing Virus

The world's first vaccine against human papilloma viruses (HPV) is also the world's first vaccine developed to specifically combat cancer. Distributed under the brand names Gardasil and Cervarix, by Merck & Co. and GlaxoSmithKline, respectively, the vaccine is widely known for its effectiveness against precursors of cervical cancer in women. The breakthrough medical advancement, recently approved for use in males, stands to benefit men too.

According to the World Health Organization (WHO), some 500,000 women a year worldwide develop cervical cancer, and 274,000 die from the disease. Cervical cancer is caused by HPV and is the most common cancer affecting women in developing countries. The virus, however, does not restrain its attack to women or even to the female reproductive tract; there are more than 100 known types of HPV, and at least 13 are cancer-causing. WHO estimates it also causes 90 percent of anal cancers, 40 percent of cancers of the external genitalia, at least 12 percent of oropharyngeal (throat) cancer cases and at least 3 percent of oral cancer cases. In the United States, HPV is the most common sexually transmitted disease,

according to the Centers for Disease Control and Prevention, and will infect at least 50 percent of sexually active people at some point in their lives.

In other words, HPV strikes more humans than it spares and it continues to spread.

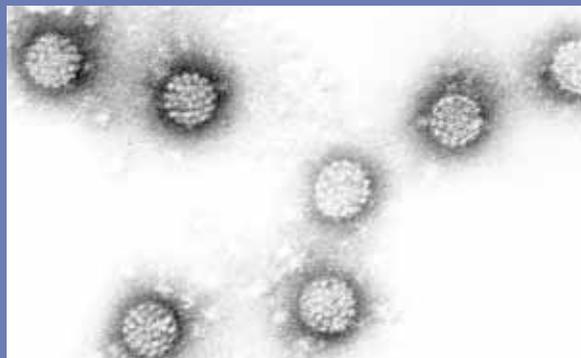
The need to confront and prevent this threat is universally recognized. As such, it came as no surprise that scientists, working separately and under different flags, would toil to the same end: Find a way to stop HPV.

Miraculously, an HPV vaccine was created. Science did prevail. But the pro-

phylactic protection followed a long and complicated path of conflict, collaboration and cooperation on its way to your doctor's office.

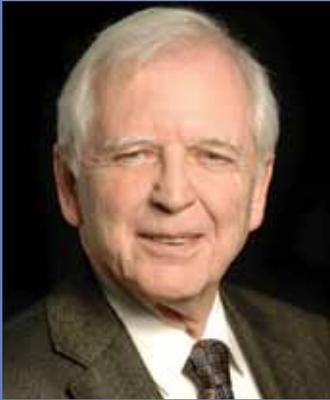
The Race for Answers

Research groups around the world — funded by government institutions in Germany, Australia and the National Institutes of Health in the United States — worked furiously on solving the puzzle of how HPV infects the human body. There were promising signs in several laboratories in the early 1990s. Leading the pack toward a breakthrough were the German Cancer Research Center (DKFZ); University of Queensland, Australia; and, in the



Hanswalter Zentgraf

HPV causes cervical cancer, the most common cancer affecting women in developing countries.



Nobel Laureate Harald zur Hausen

United States, the National Institutes of Health (NIH), the University of Rochester Medical Center and Georgetown University. The knowledge gained by each was leading to a single conclusive answer.

While their research paths took different routes, the starting point for all of the scientists was the same — the findings of Harald zur Hausen, M.D., D.Sc. (Hon), M.D.s (Hon), professor emeritus. A virologist and former chair and scientific director of the DKFZ, zur Hausen is credited for discovering that HPV causes cervical cancer, in particular HPV 16 and 18. The Nobel Committee awarded zur Hausen the 2008 Nobel Prize in Medicine for discovering the mechanism of HPV-induced carcinogenesis that made vaccine development possible.

“The global public health burden attributable to human papilloma viruses is considerable. More than 5 percent of all cancers are caused by persistent infec-

tion with this virus,” the Nobel Committee said in its statement explaining its decision for the award.

The combined achievements of the contributors proved extraordinarily successful. The HPV vaccine was nearly 100 percent effective — a rare result in clinical trials — in preventing precancerous lesions in young women. Gardasil also proved to be 90 percent effective in preventing anogenital warts. In both cases, the extremely high success rates were in women 16 to 18 years old with no previous HPV infections. This rare success rate eventually helped fuel collaboration as competitors readily acknowledged the vaccine’s worth to humankind.

The Many Paths to Collaboration

Zur Hausen’s co-worker, Lutz Gissmann, Ph.D., a professor and head of the Division of Genome Modifications and Carcinogenesis at DKFZ, contributed significant findings crucial to vaccine development: Chief among them were virus-like particles (VLP) discoveries.

Several researchers concluded that the use of virus-like particles (VLPs) were the most likely answer to the HPV problem. VLPs prevent infection by papillomaviruses by inducing an immune system response, also known as neutralizing antibodies. Early on, Gissmann and team noted that the HPV 16 isolate had to be taken from samples with active virus production in order to generate VLPs.

Further research showed that VLPs consist of only one protein (L1). Gissmann



Lutz Gissmann

suggested that the L1 gene worked in VLP generation only if active virus production was present. The L1 protein has the ability to spontaneously assemble into VLPs, hence they can easily be manufactured by standard molecular biology technology.

Scientists at other institutions, including the team led by Ian Frazer, M.D., of the University of Queensland, Australia, and another organized by Gissmann while at Chicago’s Loyola University, were rapidly gaining ground on the same or similar solutions to the universal HPV problem. The University of Queensland scientists had narrowed down the virus to L1 and L2 proteins, but had yet to narrow it further to just L1. They were, however, on a significant path and closing in on the solution that others would arrive at as well.

Meanwhile in the United States, principal scientists at NIH, Douglas Lowy, M.D., and John Schiller, Ph.D., were also working on HPV vaccine development. This

team examined biochemical and genetic aspects of the papillomavirus oncogenes and their protein products. Once VLPs were discovered to be an effective immunization agent, the NIH team developed techniques for large-scale production. The NIH team also found that little cross-immunity exists between different HPV types. This information is important to developing a polyvalent vaccine, which is a vaccine that can simultaneously protect against several HPV types.

Over at the University of Rochester, virologists Richard Reichman, M.D., William Bonnez, M.D., and Robert Rose, Ph.D., had set out 20 years before to discover how the immune system fights HPV infection. They too created VLPs by putting an HPV gene into insect cells using a virus, which then produced particles that mimicked the shape of real HPV particles and incited the immune response.

Still more scientists at Georgetown University, a team led by Richard Schlegel, M.D., Ph.D., chair and professor of pathology, looked at how the mechanism of papillomavirus-mediated cell transformation can eventually lead to the design of viral-specific therapeutics. Following the development of the first-generation HPV vaccine, his work led to second- and third-generation vaccines that enable rapid purification of the vaccine and stabilization of its protein conformation.

The events of discovery were thus sufficiently entangled as to cause confusion over who should own any resulting patents.

Commercial Interest Sputters

Despite overwhelmingly similar findings in many of the world's leading research institutions, commercial interest in the imminent vaccine was mixed.

“DKFZ had a long cooperation on HPV with the former ‘Behringwerke,’ a vaccine company in Marburg, Germany,” explains Ruth Herzog, Ph.D., head of the Office of Technology Transfer at DKFZ. “So they were aware of HPV, but the company

The need to confront and prevent this threat is universally recognized. As such, it came as no surprise that scientists, working separately and under different flags, would toil to the same end: Find a way to stop HPV.

completely underestimated the market potential of a HPV-vaccine, as did others.”

In the United States, reception was not so chilly but still a long way from the fanfare many thought the accomplishment deserved.

“NIH did receive interest early on from vaccine companies, but there was initially

some doubt as to how effective the approach would be using virus-like particles and the challenging fact that such a vaccine would be used as a preventative against cancer, rather than simply against an infectious agent,” explains Steven Ferguson, CLP, deputy director, licensing and entrepreneurship, Office of Technology Transfer at the NIH.

“There was significant risk and questions in the early days, which provided a small company at the time, Medimmune, to become a significant player in the field in the early 1990s,” he adds. “Medimmune was able to leverage their prior research experience with VLP vaccines — in this case, parvovirus, also licensed from NIH — to form an early belief that the VLP approach could also be commercially developed into a product for HPV.”

Had it not been for U.S.-based Medimmune, the outcome for this breakthrough may have been much bleaker.

“Medimmune did what a biotech should do and did at the time very well: Take on early innovative projects, develop them and sell them to big pharma,” says Herzog. “Medimmune gambled that the HPV vaccine would be a big winner and made strategic investments into the technology. In addition, Medimmune assembled intellectual property from different sources, including the NIH, and moved the project to the clinic. Eventually they were able to interest a partner in the project, SmithKline, which later on became GlaxoSmithKline.”

In a parallel effort, U.S. pharmaceutical giant Merck & Co. acquired some licensing rights from NIH and the University of Queensland, Australia.

Patent Claims and Clashes

The question of who owned the patent on the technology remained.

The U.S. Patent Office (USPTO) was left to sort which of the many scientific teams was the first to make the pivotal invention.

In the end, the players themselves resolved the problem. In early 2005, Merck & Co. and GlaxoSmithKline entered into a crosslicense agreement. To facilitate the settlement of the patent cases, the U.S. licensors renegotiated their shares of vaccine sales revenues with licensees. This paved the way for millions of women to benefit from the vaccine's life-saving benefits.

"That there were so many institutions involved both on the research and com-

mercial development sides represents both the size of the market need for this product as well as the unproven initial difficulty and complexity of the underlying science," explains Ferguson.

Although the dispute at the USPTO was hard-fought, the resolution itself proved peaceful.

"In the end, an increasing awareness by all parties that the underlying science for the vaccine was in fact sound and that a solution to this very difficult public health problem was actually close at hand, provided a means for an agreement that recognized the contribution of all the parties," says Ferguson.

While the path to the vaccine was challenging, competitive and even combative, the successes were counted on many fronts.

"The development of the HPV vaccine was a complicated story with many play-

ers, but it is a great testimony to the success of academic and federal tech transfer," says Marjorie Hunter, J.D., associate vice president, Office of Technology Transfer of the University of Rochester Medical Center.

Even so, the best barometer of success is measured in human lives saved. The inventors and investors have not lost sight of that fact.

"I consider myself extremely lucky," says Gissmann. "It does not happen often that a researcher — within his own lifetime — participates in the process of discovery of the link between an infection and a disease, is part of the development of a vaccine against it and then lives to see it being successfully used."

The sentiment is echoed by all who contributed.

— Pam Baker

Indiana University

Camera Takes Aim, Shoots at Diabetic Eye Disease

Of the myriad complications wrought by diabetes, few are as stealthy as diabetic retinopathy, a deterioration of the retina that affects nearly 80 percent of those who live with the disease for more than 10 years.

While slowly wreaking havoc on the retina — the light sensitive membrane that receives and transmits visual images to the brain — early-stage retinopathy often produces no noticeable changes in vision. Yet left untreated, it can lead to blindness.

“Symptoms may appear only when the condition is in an advanced stage,” explains Ann E. Elsner, M.A., Ph.D., professor and director of the Borish Center for Ophthalmic Research at Indiana University in Bloomington, Ind.

As a result, diabetic retinopathy robs as many as 24,000 diabetics of their vision each year and is the leading cause of blindness among adults between the age of 20 and 74.

Elsner hopes a new invention, a patented laser scanning digital camera, will broaden the opportunities for diabetics and others to be screened for retinopathy — and stave off the effects of the devastating disease.

Early Detection: The Key to Maintaining Sight

The National Institutes of Health estimates that more than 23 million people in

the United States — or 7.8 percent of the population — have diabetes, a chronic, lifelong disease marked by high levels of sugar in the blood. To avoid the serious complications of the disease, such as kidney damage, heart disease and the loss of vision, patients must control their blood glucose and blood pressure — and receive regular eye exams.

But due to a lack of time or resources, many diabetics — as well as approximately 6 million Americans who are unaware they have the disease — do not receive appropriate eye care.

“Some people with diabetes are busy working two jobs, some don’t have transportation and still others see many different doctors and there are only so many appointments they can get to,” says Elsner.

The lack of availability of eye specialists in all parts of the country is also an issue.

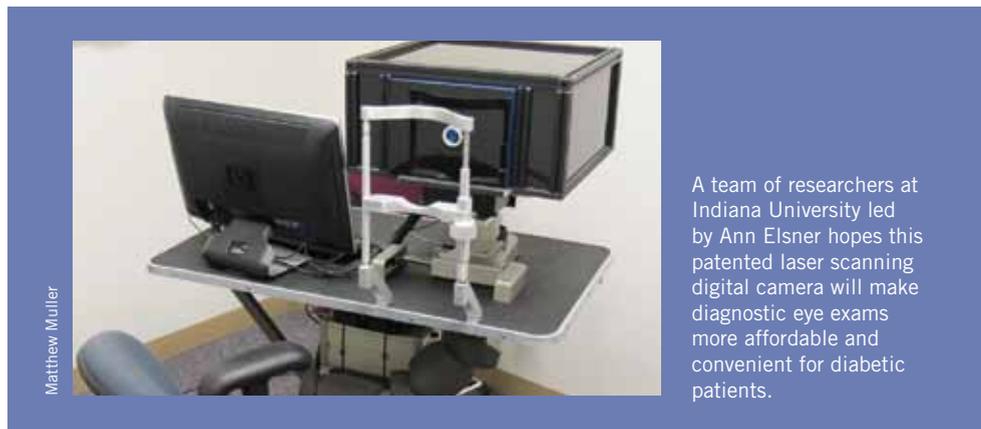
“We simply do not have the capacity to provide everyone with annual eye exams,” she says.

What is more, a typical eye exam involves dilating the pupils, which aside from being uncomfortable, lasts for several hours and can render the patient unable to drive.

Elsner’s invention, which she says is more like a digital camera than a high-end imaging device, was designed to overcome each of these obstacles.

How the Camera Works

With a singular focus — to image the retina — the new device is essentially a stripped-down version of the multifeature cameras used in an eye doctor’s office.



Matthew Muller

A team of researchers at Indiana University led by Ann Elsner hopes this patented laser scanning digital camera will make diagnostic eye exams more affordable and convenient for diabetic patients.

By simplifying subsystems and using modestly priced components that need only minor assembly, the cost of the camera will be significantly below that of current models on the market.

“There are devices out there that provide really high-quality pictures,” says Elsner team member Matthew S. Muller, M.B.A. “But for screening purposes, all we need is good enough pictures to know whether or not an individual needs a more thorough examination. Cameras with expensive technology are overkill for mass screening.”

By using infrared light, the novel camera not only quickly images the retina without dilating the pupils, it provides sharp, high-contrast pictures of any eye — young, old, blue, green or brown.

“No matter how high the resolution, you can miss the pathology for diabetic retinopathy if the contrast isn’t there,” says Elsner.

Finally, because the camera is compact and easy-to-use, it can be operated by specially trained personnel in remote locations, as opposed to only in a doctor’s office by an ophthalmologist or optometrist. Images recorded by the camera are then transmitted via computer to physicians or specially trained graders, who share results with patients.

Bringing Diagnostic Screening to the People

The combination of features makes the new imaging device perfect for screen-

ing both diabetics and those without the disease to detect the early signs of retinal damage. By widely deploying the camera in locations such as community and senior centers, government offices or even in a mobile van — Elsner hopes to make diagnostic eye exams more affordable and convenient, especially to underserved populations.

But Elsner and her team are anxious to begin sales of their camera for another reason: They know that the early detection of diabetic retinopathy has the potential to save a diabetic’s life.

“Our goal is to decrease health care costs and increase availability by putting the camera in places that can’t afford expensive machines,” she says.

An Invention Decades in the Making

Like many new inventions, Elsner’s camera concept incubated for several years before coming to fruition.

As a postdoctoral fellow working at the University of Chicago and researcher at the University of Pittsburgh, Elsner spent decades immersed in diabetes research

and clinical care. But it was while studying another eye disease called age-related macular degeneration at the Schepens Eye Research Institute in Boston that she discovered — quite by accident — a new application for imaging the innermost layer of the eye.

“We found that infrared imaging worked better at imaging the retina than anyone could have imagined,” says Elsner. “Using infrared imaging, our camera provides sharp, clear-cut pictures, which is really helpful when imaging older eyes.”

Elsner began working in earnest on the various technologies behind her new imaging device in 1999. By the time she joined Indiana University (IU) in 2004, she had several patent applications to bring with her. With the help of the IU Research and Technology Corporation (IURTC), Elsner established a startup company, Aeon Imaging L.L.C., to begin the commercialization process.

The Licensing Deal

“Given that she was early in the process of commercializing her technology, we granted a research field-of-use license with an option to convert to a commercial license,” says Bill Brizzard, director of technology transfer at the IURTC. “This gives Dr. Elsner full rights but is initially less burdensome cost-wise.”

In addition to managing the prosecution of her patent applications, the IURTC has assisted Aeon Imaging by putting Elsner in contact with consultants and research collaborators at Purdue University in La-

fayette, Ind., as well as providing input on business plans and grant applications.

The camera project has attracted significant funding from multiple sources, including more than \$1.5 million from the National Institutes of Health and \$200,000 from the Indiana Economic Development Corp. The Small Business Innovation Research Program and Indiana Clinical and Translational Sciences Initiative are also backing the Aeon invention.

“The amount of funding the camera has attracted is impressive,” says Brizzard. “I think it’s attributable to a combination of Dr. Elsner’s credentials, the merit of the project and the technical expertise of the team she has assembled.”

That team includes Benno L. Petrig, Ph.D., an electrical engineer from Switzerland with significant experience developing medical applications for the eye; Dean A. Van Nasdale, O.D.; and software expert Bryan P. Haggerty.

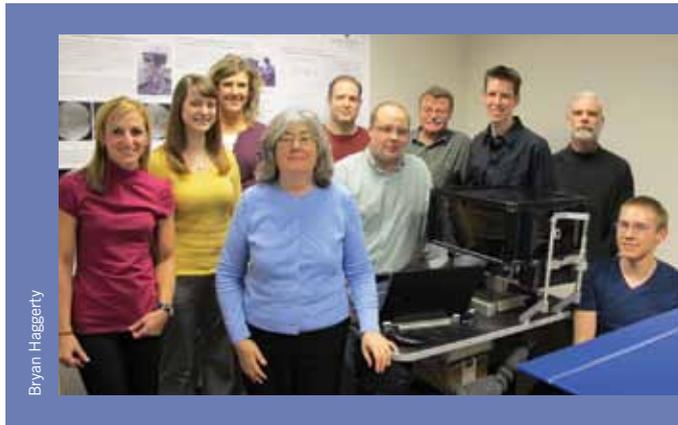
Muller, an optical engineer and M.B.A. graduate from IU’s top-ranked Kelley School of Business, is not only serving as principal investigator on the project’s most recent grant, he is also orchestrating Aeon’s marketing efforts.

“There are a lot of individuals who have either technical or business skills, but not many with both,” says Brizzard. “Matt is a sharp guy and a real find.”

The Final Phase: Testing

Elsner and her collaborators are currently

www.betterworldproject.net



Pictured here with the laser scanning digital camera they hope will identify early eye disease in diabetics are Indiana University staff members (from left to right) Victoria Rosati, Kate Montealegre, Ann Elsner, Dean VanNasdale, Chris Clark, Benno Petrig, Matt Muller, Bryan Haggerty and Joel Papay.

testing the diagnostic camera in multiple locations to ensure the device is optimized and meet requirements for U.S. Food and Drug Administration approval. In addition to testing in Bloomington, Muller’s new grant supports the testing of thousands of volunteer patients in Oakland, Calif., through a collaboration with the University of California, Berkeley.

“There are other screening technologies out there that have gotten bad reviews,” says Elsner. “We need to know that our camera will work for all patients.”

Seeing her camera become operational will be the culmination of decades of research on the eye — a body of work that has given Elsner a keen appreciation for eyesight.

“This has been a longtime dream of mine,” she says. “Diabetic retinopathy is the No. 1 cause of vision loss in working adults in the country. It’s an extremely important problem that involves loss of income and other social costs.”

But Elsner and her team are anxious to begin sales of their camera for another reason: They know that the early detection of diabetic retinopathy has the potential to save a diabetic’s life.

“When diabetics have eye problems it often means their disease is out of control,” says Elsner. “It’s a warning sign that they need to pay more attention to their health.”

Elsner hopes widespread retinal image screening will lead not only to a better quality of life for diabetics — but also to fewer lives lost to the disease.

— Mary Henderson

Lawrence Berkeley National Laboratory

Academic Research Leads to Solid Electrolyte Lithium-Ion Batteries Without Achilles' Heel

Most of the major automotive companies are developing them. Demand for their crucial ingredient is poised to take off. And the mainstream public is enamored with the products they power.

The focus of all this attention is a battery with core material — lithium, a soft, light-weight silver-white metal. Lithium-ion (Li) batteries, which have ushered in a new age of portable electronics, hold out a promise of mass-market electric vehicles, EVs for short. They are poised to overtake the nickel-metal hydride (NiMH) batteries used in the famous electric-gasoline hybrid Toyota Prius that's come to stand for green motoring in the consumer's eye.

Advocates claim new advances in technology have enabled the lithium-ion battery to leap frog the lead-acid or NiMH

versions because it carries more energy with less weight than other materials. But before EVs can ever surpass gasoline-powered vehicles, researchers need to address weight, as well as a propensity to catch fire and explode — the long-term Achilles' heel in battery technology.

One approach to reduce the weight of the battery is to replace the graphite electrode in current lithium-ion batteries with a lithium metal electrode. The problem with this battery is the growth of minute metallic lithium spikes, called dendrites, that grow on the lithium metal electrodes with repeated charge and discharge cycles, especially if the battery is charged quickly. The dendrites reduce battery life and can cause electrical short circuits that make the battery overheat and catch fire. This is a major problem that must

be solved before the next generation of lithium batteries can safely be used in a wide range of applications.

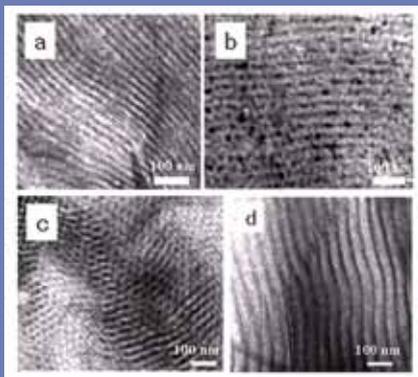
A Lightweight Polymer-Based Solution

For years, researchers have explored ways to improve the reliability and safety of lithium batteries. They've tried to replace the volatile liquid electrolytes in use today with a stiff polymer electrolyte to prevent the dendrites from forming. Unfortunately, stiff polymer electrolytes have never provided the high conductivity needed to justify the development of this type of battery — until now.

Seo Inc., a Berkeley, Calif.-based battery startup company founded in 2007, believes it has found the perfect lithium chemistry to make batteries that can hold lots of energy, are cheap to make and safer to use than current lithium-ion batteries on the market. A team of scientists at Seo has developed a nanostructured solid-state battery with no flammable or volatile components, which makes it ideal for use in:

- Batteries for electrically-powered vehicles
- Electrical-grid load-leveling devices
- Medical and other specialty devices

Seo claims its battery can deliver an energy density beyond 250 watt hours per



In Figures 1a and 1d, lamellar structures — lengthwise channels along which ions can travel — are visible. Figures 1b and 1c display the block copolymer with hexagonally lamellar structures.

kilogram (Wh/kg) today with a research and development (R&D) path toward 400 Wh/kg vs. today's lithium-ion batteries that normally deliver less than 200 Wh/kg. Seo also says its battery can operate at higher temperature than standard lithium-ion batteries, making it a good choice for more rugged, outdoor applications attached to a solar energy system.

At the core of this battery technology is a novel solid polymer electrolyte material that can transport lithium ions while providing inherently safe and stable support for very high-energy electrode chemistries. Seo has an exclusive license to this advanced technology from Lawrence Berkeley National Laboratory (Berkeley Lab), a U.S. Department of Energy (DOE)-funded national laboratory managed by the University of California.

“The novelty of the technology is in the perfect marriage of materials engineering, polymer science and electrochemistry. World-renowned experts from these disciplines were able to share their ideas and collaborate under the prestigious Batteries for Advanced Transport Technologies (BATT) Program at Berkeley Lab to come up with a new platform for Li batteries,” says Mohit Singh, who led the academic research project as a postdoctoral student at the University of California, Berkeley (UC Berkeley) under the guidance of Nitash Balsara, Ph.D., a scientist in Berkeley Lab's Materials Sciences Division and a researcher with the Lab's Environmental Energy Technologies Division. “We had the opportunity to

collaborate with some of the top battery scientists in the world and ensure that the research never lost practical relevance.”

Singh, who received a doctorate degree in chemical and biomechanical engineering with a focus on the self-assembly of soft materials such as biosurfactants and polymers, went on to co-found Seo in 2007 with Balsara and fellow doctoral student Hany Eitouni, who received a doctorate degree in chemical engineering with a focus on polymer materials and specialized expertise in ionic transport through polymers. Today, Singh and Eitouni are vice president of R&D and engineering and director of materials development, respectively.

Academic Research at the Core

Balsara and his research team of talented students refined techniques and developed an unusually hard ion conductor — 50-nanometer channels composed of a softer polymer laced with lithium salts encased in a hard polymer matrix. Since a lithium dendrite is 20 times as large as the soft polymer channels, it is too large to force its way into the material. Their technology offers:

- High thermal stability
- Low rate of self-discharge
- Safe, stable operation in a wide range of environmental conditions
- Flexibility to novel forms and packaging
- Manufacturing capabilities with conventional polymer processing methods

“I came to Berkeley and challenged my students: What can we do with polymers that we don't do today? We decided to

look at how ions flow through polymers,” says Balsara, who also is a professor in the Department of Chemical Engineering at UC Berkeley. “The relevancy of our research on batteries didn't hit until after we started.”

The team found out the idea of mixing polymers with ions wasn't new. Researchers in the 1990s tried to make ions conduct, but soon abandoned their research because the:

- Solids they were experimenting with wouldn't conduct and
- Plasticizers and/or solvents added to the host polymer matrix to achieve high conductivities deteriorated the mechanical properties needed to ensure the electrolyte could be manufactured, stored and used.

They also uncovered research articles with “fuzzy” conclusions that the non-conductive part of a battery needed to be soft to assist conduction of the ions in the conducting part. This later research helped the team decide to construct a nanostructure ion electrolyte using ordinary polymers. Their Berkeley Lab-funded research allowed them to completely decouple the electrical and mechanical properties of the polymer electrolyte materials, which allowed them to optimize both these properties at the same time.

“We revisited one of the longest-standing challenges in Li-batteries: stabilizing the Li-electrolyte interface and making the switch to a higher energy density system safer,” Singh says. “We started with research conducted by a UC Berkeley

chemical engineering group, led by Professor John Newman, that essentially explained why polymers that conduct ions can't stabilize the Li-electrolyte interface. The conclusion of the research was that ion-conducting polymers don't have sufficient mechanical strength to stabilize Li-electrolyte interface, as there is an inverse relationship between mechanical properties and ionic conductivity.

"So, we approached the issue from a different angle: We asked how we can make a very mechanically stable polymer conduct ions? We came up with what I think is an elegant approach of using a nanostructured polymer electrolyte to decouple mechanical properties from ion conduction."

'Something Weird' Led to Technology Transfer

"As we were writing the paper about our discovery, something really weird happened," Balsara explains. "We said wait a minute, we may be on to something that has implications beyond an academic paper."

At this point, Balsara and his team found out about Berkeley Lab's Technology Transfer and Intellectual Property Management Department.

"Initially, I thought we were going to find out about a mountain of stuff that we weren't interested in doing," Balsara says. "The reality is they were very helpful in taking the paper we were writing and molding it into what we needed to file for a patent."

Berkeley Lab marketed the technology to a number of companies working in the lithium-ion battery arena. This nanostructured polymer electrolyte technology was competitive because it won one of *R&D Magazine's* prestigious R&D 100 Awards

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In addition, predictions based on recent tests indicate that Seo batteries will

achieve the United States Advanced Battery Consortium goal of 5,000 cycles.

"We knew this technology had potential," says Berkeley Lab's Virginia de la Puente, a senior licensing associate in Technology Transfer and Intellectual Property Management. "We had about 15 prospects but no one was willing to take a risk on an academic-based technology except one venture capital firm focused on early-stage companies."

Academic Adds Entrepreneur to Resume

Balsara hooked up with Khosla Ventures (KV), which was established by Silicon Valley's influential Vinod Khosla. Taking a sabbatical, Balsara convinced his former students, Singh and Eitouni, to join him and co-found Seo with about \$2 million in funding from KV. Seo also raised an additional \$3 million in 2008 from KV and \$8.6 million in 2009 from a group of investors including GSR ventures and Google.

"If it weren't for Professor Balsara getting the early-stage government funding for his battery research and a gestation period over a couple years with interesting results, this team might not have come up with something no one has seen before," says Atiq Raza, a serial entrepreneur who served as the chief operating officer and the president of AMD and now is the chair of the board at Seo.

"But Seo is not just a story about funding. We're also the product of timing and the ability to make things happen — the

opportunity to introduce an innovation in energy that promises to solve a problem with one of the strongest material development groups and scientists in the country that have made leaps and bounds in taking a concept and building batteries, which, we hope, will go into the next generation of cars and grid backup solutions.”

One new area where the team at Seeo is looking to make things happen involves a DOE Smart Grid Demonstration Project for which the company has received \$6 million to develop and deploy a 25 kilowatt-hour (kWh) prototype battery system based on its proprietary nanostructured polymer electrolytes. The award is designed to demonstrate the substantial

improvements offered by solid-state lithium-ion technologies, which would be targeted for utility-scale operations, particularly Community Energy Storage projects.

“Sometimes you can have a really promising technology, but the only party that’s willing to take a risk is a startup company,” says Berkeley Lab’s de la Puente. “For this technology, the best placement

was a small company. Established companies sometimes don’t have the level of intensity required to develop and commercialize an innovation like this.”

Today, Balsara is back on campus. Singh says he is still involved, offering “optimism and support through his insights and contacts” that help to lead the charge in a lot of directions the Seeo group is going. But the fundamental goal for the scientists and engineers is to improve the reliability and safety of lithium-ion batteries, which both business and society appear ready to embrace as the next crucial source of mobile energy.

— David Perilstein

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Massachusetts Institute of Technology

Armed With Robo Rehab, Stroke Patients Gain Mobility and Hope

Some robotic devices are designed to give people superhuman powers. Others are made to unleash the power of human potential.

Such is the case with the Myomo e100 NeuroRobotic System, a wearable robotic brace that helps stroke patients recover the use of their arms. While the 1 lb., 11 oz. Myomo system is decidedly more compact — and less complicated — than futuristic exoskeletons that offer super strength and extra protection, this “smart” elbow brace has the potential to help millions of stroke survivors perform the tasks of daily living and reduce one of the nation’s major causes of disability.

The Stroke Effect

According to the American Heart Association, every year in the United States nearly 800,000 people suffer a stroke, a potentially life-threatening event in which the blood supply to the brain is temporarily disrupted. Of those who survive, as many as half experience partial paralysis in one arm — and only one in five regain full use of the limb.

Because brain cells and neurological pathways are damaged by stroke, patients cannot effectively control their weak muscles, resulting in partial paralysis. But new studies reveal that the brain is capable of re-wiring — making

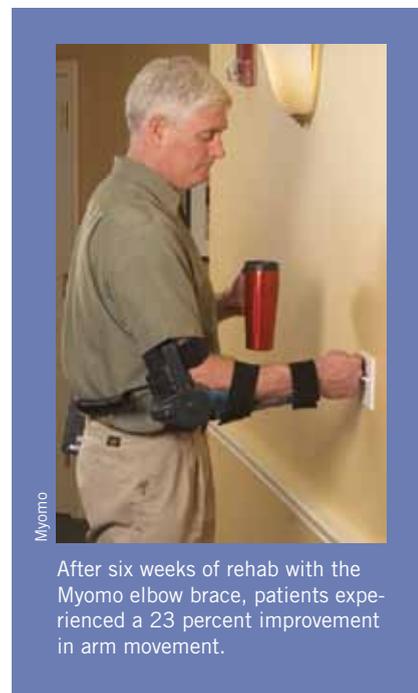
new connections in order to complete a desired movement. For new connections to form, brain cells must begin communicating — which is where the Myomo system comes in.

How the Myomo System Works

When patients attempt to move their arms, electrical muscle activity signals are sent from the brain to the arm muscles along the skin’s surface. The Myomo system detects and processes these signals with software and forwards the data to a robotic device that provides just enough assistance to help patients complete the intended movement.

With repeated use over a period of weeks or months, the patient performs simple tasks they would do at home — such as opening a jar, turning on a light switch or carrying a laundry basket — all while wearing the elbow brace. The experience of attempting and then completing the movement — a process completed with the help of a “power assist” from the Myomo device — appears to be the impetus for the brain’s relearning process.

The theory, according to leading stroke rehabilitation expert Joel Stein, M.D., is that, by facilitating patients’ ability to practice tasks repeatedly, new connections are formed in the brain and existing connections are reinforced, resulting in



After six weeks of rehab with the Myomo elbow brace, patients experienced a 23 percent improvement in arm movement.

improved ability to move the arm. Results of a pilot study showed that, after six weeks of rehabilitation with the Myomo elbow brace, patients experienced a 23 percent improvement in arm movement.

Myomo's Inventors

The Myomo NeuroRobotic System was developed by John McBean and Kaila Narendran as part of their graduate studies at Massachusetts Institute of Technology (MIT) in Cambridge, Mass.

As kids, both McBean and Narendran suffered fractures that required rehabilitation to reawaken atrophied muscles. Using those experiences as a jumping-off point, the two friends applied their knowledge of robotics and a cursory understanding of neurology to create a prototype of the Myomo device.

Early feedback from Stein, professor and chair at the Department of Rehabilitation Medicine at New York's Columbia University College of Physicians and Surgeons, empowered the inventors to push forward with their idea.

"Dr. Stein was convinced that stroke survivors could benefit from the device," McBean says.

MIT's Entrepreneurial Ecosystem

Receiving a grant from MIT's Deshpande Center for Technology Innovation in 2001 put the Myomo invention on the fast track. In addition to providing the inventors with critical funding, the center also supplied valuable support services including a volunteer mentor named Steve Kelly, an entrepreneur with three successful technology startups under his belt.

With guidance from the Deshpande Center, Kelly and other mentors, the inventors scored the top prize at the 2004 MIT \$50K Entrepreneurship Competition.

"MIT sets a model for commercialization of late-stage research projects and tech transfer," says Kelly, who eventually became president and CEO of the Boston-based Myomo Inc.

www.betterworldproject.net

The Myomo inventors continued to tap into what Narendran calls MIT's "entrepreneurial ecosystem," an array of support services that includes the Venture Mentoring Service and Technology Licensing Office (TLO).

"MIT's licensing office is viewed as among the best by entrepreneurs because they are straightforward and consistent to ne-

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gotiate with; you know what the rules of the game will be and they don't change. They also have a lot of support infrastructure," says Kelly.

Working with MIT's TLO, Myomo completed a license agreement in 2006, and,

in 2007, the company received approval from the U.S. Food and Drug Administration for its robotic elbow brace.

The experience was validating for McBean and Narendran, who, despite their initiative and drive, were surprised by the product's success.

"As graduate students, we didn't know a lot about business, but we had this idea and it seemed to us it should work," says McBean. "We couldn't believe it when it actually did and no one had done it."

Myomo Market Potential

Kelly says the market potential for the Myomo NeuroRobotic System is vast.

"Our potential is embarrassingly large," he says. "There are more than 5 million stroke survivors in the country, and about 3 million of them have some level of arm disability. Personal robotics, like PCs, have portability and multiple uses. We can take the Myomo and drive it across the care continuum from rehab hospitals to home health agencies."

What's more, recent studies — as well as clinical experience with the Myomo device — show that patients can improve up to 20 years following a stroke, not just within a six-month window as originally thought.

There are also rehabilitative needs for other joint braces as well as different patient groups, such as those with spinal cord injuries and degenerative diseases, who could benefit from wearable robotic devices.



Steve Kelly

But Kelly says the company will expand slowly and deliberately to a national footprint.

“We’re eager to get this out to people who need it, but we are conservative about making sure everyone has a positive first experience,” he says.

According to MIT’s James R. Freedman, technology licensing officer, the company’s strategy is a good one.

“Myomo has done a good job of staying focused and on track,” Freedman says. “For startup companies, it can be hard

to take a manageable bite and digest it. Myomo has stayed focused on how to bring value back to their investors and what they need to do to create commercial value in the face of market realities.”

Putting Myomo to Work

For now, under Kelly’s leadership, Myomo has established some half-dozen clinical partnerships. Now deployed throughout myriad hospitals, long-term care facilities and home health agencies, the robotic elbow brace is receiving positive reviews.

“Rehabilitation specialists, including both occupational and physical therapists, are all finding the product very useful,” Kelly says. Some therapists have dubbed Myomo therapy “robo rehab,” while others say

that seeing hope return to patients’ faces after using the device validates their choice to work in rehabilitation.

“Seeing the reaction on someone’s face when they move their arm for the first time, it’s powerful,” says Kelly. “For people who had a stroke yesterday, they put the brace on and realize all is not lost. For stroke patients who lost use of an arm years ago, it’s powerful to see that limb move again.”

Patient reaction to the Myomo device even inspired the company’s name, according to Narendran. A stroke survivor, surprised by her newfound ability to move her arm after using the device, exclaimed, “It’s my own motion!”

The success has had an equally big impact on its inventors.

“It’s every engineer’s dream to make something that goes on to affect a lot of people in a positive way,” says Narendran. McBean couldn’t agree more. “It’s not hard to drag yourself to work when you know you’re restoring quality of life for people who had otherwise given up hope.”

— Mary Henderson

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Michigan Technological University

SafeLane Surface Overlay Improves Winter Road Safety

When an experimental strip of SafeLane surface overlay was laid down on the icing-prone Wolf River Bridge at Crandon in northeastern Wisconsin in 2003, officials hoped to cut down on the four to five weather-related motor vehicle accidents the structure saw each winter.

It reduced them by cutting them to zero for all of the next five years.

A SafeLane system installed in 2005 on a problematic ramp for the Blatnik Bridge at Superior, Wis., yielded the same, zero-accident results. An analysis of other test sites in several states during the 2005-2006 winter season — all normally hazardous — reinforced those results: no ice-and-snow-related accidents.

At the same time, similar untreated stretches of roads and bridges near each were a mess.

“Rather than putting down chemicals to melt snow and ice once they’ve accumulated, SafeLane embeds anti-icing chemicals in the roadway ahead of time,” says Russ Alger, the technology’s inventor and director of the Institute of Snow Research at Michigan Technological University in Houghton, Mich.

“Melting agents are stored for release when they’re needed — when a storm comes. They help prevent ice from forming from the time the storm begins. This

improves safety tremendously.

“Beyond this,” Alger notes, “the epoxy overlay ‘armors’ the roadway and extends its useful life. And, the system reduces the amount of chemicals needed to keep it ice-free, so it’s a big advance environmentally.”

However, SafeLane overlay is more expensive than regular paving, so it is used mostly to target specific trouble spots like bridges, access ramps and intersections rather than to cover full-length roadways.

Patented by Michigan Tech in 2001 and licensed to the Deicing Technology Division of Cargill Inc. in 2004, the SafeLane product has now been installed at more than 85 highway and 15 sidewalk and airport sites in states from Maine to Texas to California.

To De-ice or to Anti-ice?

Creation of the SafeLane surface overlay represented a combination of several technologies. One is the epoxy coating on the surface of the roadway, most commonly a two-part glue designed to expand and contract like the underlying roadway itself.

The epoxy hardens the surface, but, more importantly, it provides the base for an overlay of small, aggregated quarter-inch pebbles — somewhat like the texture of rough sandpaper — that can soak up and hold anti-icing agents like a hard sponge. Applied ahead of time, these chemicals remain dormant until the moisture of snow or sleet releases them and their anti-icing action.

“There are a couple of different ways to maintain a highway in winter,” Alger says.



“One is the traditional de-icing approach — plowing the roadway and applying chemicals to melt the ice that has been formed. The other is anti-icing — using chemicals to keep snow and ice from accumulating at all.”

Alger continues, “There are different ways of anti-icing. You can focus on the pavement or on the chemicals. Or, you can do what the SafeLane system does and combine the two — creating a pavement that releases the salt brines that prevent ice from forming in the first place.”

When researchers began looking at anti-icing in the mid-1990s, it was a new idea. Working with liquid sodium chloride on different pavements, Alger realized the samples were behaving differently.

“I found the difference was in the pavements themselves,” he says. “At the same time, in a separate project I was looking at epoxy overlays to armor pavement. The two of them crashed together, and I saw some possibilities.”

To test his ideas, Alger explored a broad range of pavement materials, aggregates and chemicals in his 10'x15' cold lab, subjecting six-inch- and eight-inch-square blocks to temperatures as low as -400 F. Between tests, they would be washed and subjected to cold temperatures multiple times to assess the chemical's lifespan.

While several types of chemicals are utilized as melting agents, the most common is sodium chloride — the equivalent of table salt. Solid salt granules work best

for de-icing, but Alger found that sodium chloride in a liquid brine is more effective for SafeLane application.

“The aggregate has to hold onto the anti-icer and release it in reaction to moisture,” Alger notes. “It has to be durable and able to hold the chemical well. Those two characteristics don't necessarily go hand in

“I met some folks from Cargill at an AUTM conference. They responded quickly. We now have a series of patents that the university owns and have exclusively licensed to Cargill. The initial research was supported by university discretionary funds, with Cargill supporting some of the later work.”

hand. Very porous isn't really good for an aggregate material — the anti-icer stays in the pores. We want it to stay at the surface, where the ice forms.”

Limestones and dolomites proved to be excellent for this. Not so porous, they keep the anti-icer at the surface — it dries out and crystallizes in tiny surface pores. Also, Alger believes that a chemical reaction

bonds them to the stone.

Field Testing and Licensing

By the time Alger contacted Michigan Tech's Technology and Economic Development office, he had taken his findings beyond the simple idea stage.

“Russ worked on it in earnest before he disclosed it to us in 2001,” notes Technology Director Jim Baker. “We filed for a patent that year and began a search for a corporate partner. We undertook tests with the Wisconsin Department of Transportation.

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A study of 26 sites during the 2006-2007 winter repeated earlier observations of excellent results — but added a caveat: At a few test sites it appeared that wet, heavy snowfall diluted the chemicals to the point that the test segments performed no better than control stretches.

Overall, the analysis revealed, SafeLane surface overlay worked well: It kept treated segments free of ice and snow and it dramatically improved safety. It cited one interchange in Superior, Wis., that had seen 87 accidents before installation and just one afterward.

The 2006-2007 study's finding that dilu-

tion over time can diminish effectiveness wasn't a surprise.

"Chemical duration is a function of the frequency and vehemence of a site's weather," Baker notes. "Areas with heavy precipitation likely need more frequent application. Even so, SafeLane overlay sites tend to need less treatment than other roads. A bridge that used to get anti-icer two times a week may now need it only once a month."

Corporate Licensing

Since those 26 sites of 2006-2007, the number of SafeLane surface overlay installations has increased exponentially, says Sean Riley, marketing manager for Cargill's Deicing Technology Division. Today, he notes, there are SafeLane product sites in more U.S. states than not, and installations have begun in Canada.

"From our point of view it has several benefits," Riley says. "Most importantly for our mission, it's a great anti-icing product. But it also helps preserve the pavement. And, since customers can use less chemical, it's more environmentally sound."

Michigan Technological University



The SafeLane product has now been installed at more than 85 highway and 15 sidewalk and airport sites in states from Maine to Texas to California.

Cargill focuses on selling the two-part system — epoxy and aggregate — but installation, although specialized, relies on subcontractors (Alger, for one, has founded a company that does this). Cargill sells the chemicals as well, but not as part of the SafeLane system. It's up to the customers to buy and apply it.

Alger and Cargill have developed a second version of the SafeLane technology — a product that uses eighth-inch stones in a single layer, versus the highway's double layer of quarter-inch stones, for use on sidewalks, bike paths and airport taxiways and service roads.

"The fact that it's a single layer lowers the cost substantially," Alger notes. "And the smaller aggregate means it's a little easier for somebody with a snow shovel to clean up.

"Most importantly," he adds "the evidence is clear is that SafeLane technology improves highway safety significantly for drivers forced to deal with winter-time ice and snow. And it does it in a way that's better for the environment."

— Ralph N. Fuller

Naval Research Laboratory

Genetic Testing Takes Guesswork out of Diagnosis

Interpreting a patient's symptoms, then working backward to determine the cause could be made obsolete by a digital and genetic tool that is mistake-proof, faster and rapidly improving. TessArae LLC is accelerating the process of diagnosing infectious diseases using resequencing pathogen microarray (RPM) testing. The process uses tiny computer chips that take details from culture swabs to identify bacteria and virus samples using a portion of genetic code then matches it against a database of known diseases. Even better, after thousands of RPM tests, there have been no false positive results.

The venture merges information technology, medicine and microbiology. RPM begins by removing everything from the sample organism except nucleic acids, permitting genetic codes to be read. What begins as a patient's throat swab contents ends up as a series of pathogen genetic code. When compared against databases of known codes, test results are returned with pinpoint accuracy.

Those details can be critical when doctors need to identify a particular flu, disease variant or even a co-infection — such as during the 2009 flu outbreak. RPM technology quickly detected an H1N1 virus sample even before the organism's genetic sequence was known. When those results did not fit any known flu strain, it pointed to a new influenza. A week later, when the sequence became

available, the RPM test sample was a perfect match. More remarkably, the test — developed in 2006 — identified the H1N1 strain several years later. No other test today can do that without specifically being designed against the target organism it seeks to identify.

“The beauty of it is the computer does all the work in converting the sequence into A, C, G, T,” says TessArae Chief Executive Officer Klaus Schafer, M.D. “Even if doctors think they know what they're looking for, they are often wrong or find out too late. This test is especially useful when vague symptoms such as cough or fever are all that is known. I'm a physician by training,



Resequencing pathogen microarray testing has the potential to remake the delivery of health care.

Today's process is always to start with a hypothesis and ask, What should I test for? But one only gets results of what one is testing for — so these tests could change our understanding of epidemiology.”

Although there are no reliable measures of missed diagnoses, adverse treatment reactions or those made too late to identify and cure patients, RPM's creators say it can remake the delivery of health care. It can reduce errors and improve targeted treatment to provide cost savings, better results, more quickly than current practices.

From the Air Base to the Lab

With a story as complex as a prime-time medical drama, RPM technology began as an experiment to spot infectious diseases at U.S. Air Force bases. The path began with concerns over biological weapons in 2001 — when deliveries of anthrax via mail made headlines, prompting research on computer-assisted diagnostics to protect against biological attack.

At the same time, Affymetrix Corp. was pioneering the lab on a chip — computer-assisted diagnostics using genetic codes of virus and bacteria samples. Schafer calls RPM microarrays “the software to Affymetrix hardware.” By the mid 2000s, genetic medicine was getting recognition for treatments, but diagnostics was still emerging.

Virologist Clark Tibbetts, Ph.D., teamed

with RPM co-inventor David Stenger, Ph.D., of the Naval Research Laboratory in Washington, D.C. While serving as a civilian Air Force official, Tibbetts had proposed using RPM predecessor tools to monitor virus and flu outbreaks at Lackland Air Force Base in Texas. Medical teams knew that military installations — especially during initial basic training — were prone to infectious virus outbreaks when recruits came together from all over the world. After Air Force tests, a later proof-of-concept test of RPM was used to safeguard Washington, D.C., during the 2004 presidential inauguration.

Several scientific breakthroughs were combined by the RPM team to increase its capabilities, gradually expanding the number of samples on each array microchip. Up to 70 nucleotides can be scanned simultaneously and quickly compared to genome databases. According to its patent, issued in July 2009, more than a dozen contributors shared credit with the Naval Research Laboratory (NRL).

Building ongoing research relationships and multidisciplinary talents were crucial to commercialization. Joel Schnur, Ph.D., directed NRL's Center for Bio/Molecular Science and Engineering, contributing his experience in transferring nonmedical military technology to the marketplace.

The route from government lab to business plan can be challenging, because of federal regulations on publishing details of intellectual property in full view of companies that might be pursuing similar advances in private, Tibbetts notes, "The

key thing is that all parties have an interest in moving things forward. And by starting in and moving outward, TessArae really mastered this genetic testing for inherited diseases, as well as infectious diseases, where there are chances to leverage the technology and grow more rapidly."

From Military to Marketplace

Tibbetts and Schafer left the government to start the company and signed a cooperative research and development agreement with the NRL, giving TessArae time to continue while seeking investors and customers. "Part of the challenge in developing new technology in Washington, D.C., is that it can be a conservative place," Stenger adds. "And what we were trying to do was rather ambitious. I wrote most of the patent applications in 2004. Just before people thought we would fail, they began to see potential to be a real gold standard in medicine."

Those prospects took shape when TessArae opened in Potomac Falls, Va., in 2007. Regulatory approvals from the U.S. Food and Drug Administration and other agencies are still based on polymerase chain reaction (PCR) testing developed in the 1980s. So the company is helping federal officials develop new frameworks for evaluating digital alternatives and modernizing aspects of genetic diagnostics.

Other opportunities for RPM are opening up in unexpected fields, and Stenger notes the database of known genetic codes is growing logarithmically every year, which will advance applications. Beyond current testing for avian influenza,

Ebola virus and other human diseases, TessArae received a U.S. Department of Agriculture innovation award for food safety, applying RPM tests to finding obscure, rare diseases in food stock. Single-use tests wouldn't be cost-effective, Stenger says, but can be profitable when multiple tests deliver more results. Additional applications have emerged in tracking genetic, inherited diseases. Also, because the same condition may affect two people in different ways, having proof — instead of waiting for symptoms or reactions — means patients get treated sooner.

In 2009, TessArae and Affymetrix collaborated to identify H1N1 flu strains within hours — while the National Institutes of Health used older, slower methods. Outside the medical office, RPM test results will allow doctors to more accurately report a specific strain of influenza and geographically map the spread and speed of outbreaks.

Yet RPM applications intended for soldiers have not been implemented. Commercial prospects and other forces have shifted attention — another unexpected, but not unusual, result in the path of a trailblazing technology, Schnur says.

— David Wallace

For another approach to molecular diagnostics, read about the Argonne National Laboratory's technology in "Rapid, Cost-Effective Diagnostic System Based on Innovative Nano Biosensors Helps Identify and Slow Spread of Major Diseases," on page 1.

Oregon Health & Science University

Jolene Delivers a Message Kids Can Hear

She may appear an unlikely superhero — dressed in thrift shop fashions and outlandish hairstyles — but Jolene is coming to the rescue of schoolchildren around the world, teaching them about the danger of hearing loss caused by loud music played through headphones.

Developed from the research and innovative outreach by the Oregon Health & Science University (OHSU) in Portland, Jolene is changing behaviors at a critical time. More of a what than a who, Jolene is a mannequin equipped with off-the-shelf electronics that measure sound level in decibels and a sidekick who simply and clearly explains the effect loud noise has on the human body. Wherever she visits, people use a music player to identify the volume they normally listen to, and then the earpieces are shared with Jolene.

In her ears, however, she records the sound volume in decibels, and then her creator, Genevieve “Genna” Martin, hands over a piece of paper saying how long it is safe to listen.

“I wanted to make a cooler version that appealed to young people — not just measuring the output of an iPod but something that people want to interact with at a health fair or event,” she says. “The average concert is 120 decibels, and it only takes 10 seconds before your ears may begin to get damaged. So we ask, would you buy a ticket for a concert

if you had to leave after 10 seconds? That gets people thinking about using earplugs or other protection.”

Jolene is part of a broader education program, called Dangerous Decibels, that began in the Portland area in 2000. Genna Martin’s innovation — much like the iPod itself — was not in being first with new technology. Instead, it was about democratizing and spreading the popularity



Jolene is part of a broader education program, called Dangerous Decibels, that began in the Portland area in 2000.

using a new and popular platform. Just as the iPod supports the iTunes music store, Jolene provides a friendly introduction to Dangerous Decibels.

In many ways, hearing and public health are both a professional and personal concern for William Martin, Ph.D., creator of Dangerous Decibels and an OHSU professor who does research on noise-induced hearing loss (NIHL) prevention. He holds a joint appointment in otolaryngology/head-neck surgery and public health preventive medicine. He launched Dangerous Decibels to educate kids about NIHL — a condition he experiences firsthand. Over the last decade, the program has worked with other groups in the region and nationwide including a walk-through giant ear exhibit at the Oregon Museum of Science and Industry.

“There are consequences as you get older, and kids, by the time they’re 30, could have the hearing of a 60-year-old because of overexposure,” says William Martin.

A Growing Problem, Often Overlooked

The Dangerous Decibels group started with a National Institutes of Health grant to educate children about hearing health. According to the National Institute on Deafness and Other Communication Disorders, approximately 30 million Americans are affected by hearing loss. And as many as 25 million have experienced

tinnitus, the ringing that indicates ear damage most commonly caused by loud sound exposure. Without much education into what sound levels are normal or safe, people can be at risk for NIHL — both from one-time extreme exposure or ongoing loud sound. For example, usual conversation is approximately 60 decibels, and city traffic noise can reach 85 decibels. Hazardous noise starts above 85 decibels for a period of eight hours during one day.

An explosion or gunshot can reach 140 decibels. Riding a motorcycle — even with a helmet — can average 100 decibels. Persistent loud sound in enclosed space such as subways or sports arenas can also accelerate hearing loss when exposure causes damage to the sensitive hair cells of the inner ear and related nerve endings.

The Pacific Northwest has a cluster of organizations devoted to the science and public health aspects of hearing issues. The American Tinnitus Association is based in Portland. Among military personnel, tinnitus is the most common service-related disability and NIHL ranks second. The U.S. Department of Veterans Affairs has its national research center in Portland devoted to preserving hearing for affected soldiers.

During her high school years, Genna Martin volunteered with Dangerous Decibels, educating fourth graders on hearing safety. In 2005, she took a summer internship at OHSU's Center for Research in Occupational and Environmental

Toxicology to pursue a project that could spread the message about hearing safety and portable music.

She modified a second-hand mannequin using some power tools and a silicone ear used to demonstrate hearing aids. After

“The average concert is 120 decibels, and it only takes 10 seconds before your ears may begin to get damaged. So we ask, would you buy a ticket for a concert if you had to leave after 10 seconds? That gets people thinking about using earplugs or other protection.”

mounting and wiring a microphone and sound-level meter, Jolene was created — named for a minor TV series character and dressed in a leather jacket and blue-dyed hair.

From there, the duo traveled to conferences and events where people asked for their own model. That led to the Jolene Cookbook, an online guide with photos that OHSU makes available as a simple, royalty-free download agreement through

its technology portal. Organizations in 44 states and 21 countries have downloaded the instructions.

Operating more like an open-source development project, where each user can customize a Jolene with a unique look, clothing or style, the venture is managed by the Martins and the university's technology transfer office, which chose to freely share the plans to encourage broader use. No wonder Jolene has siblings Günter, Shoque, Flame and Deci-Bell as far away as Australia, Canada and on military bases in Europe. They appear on a family album Web site hosted by Dangerous Decibels (www.dangerousdecibels.org).

“It really has its own momentum, and getting it out to groups worldwide has been great,” says Michele Gunness, OHSU senior technology development manager. “And when it's built by young people, they're more likely to pay attention to the message.”

The construction isn't that technically difficult, adds Genna Martin, but it's not always easy finding torso-and-head mannequins. So she often scours eBay for auction items. What makes Jolene unique is her approachability. People often come and ask about it in public, and that curiosity makes them receptive to the advice of reducing volume, limiting the duration of loud noise and wearing protective gear.

Jolene Makes New Friends

One hallmark of Jolene's success is the students willing to counsel younger kids

about the dangers of extreme noise. Martin's advice is spreading to new audiences thanks to the reach of the Web and social media such as Facebook — where Jolene Ohsu has more than 100 friends, and explains "I'm pretty quiet but I love music and meeting new people!"

"In our study, we saw that 16 percent of 16-18 year olds were listening consistently at levels above safe limits every day of the week — it was like working in a factory or at a logging site listening to a chainsaw for eight or nine hours a day," William Martin adds. "We gave people the measurements showing how long they could listen safely, and 44 percent of

people who were at dangerous levels said they would change the behavior. That's a remarkable feat with a really simple and fun innovation."

Research shows that in a 24-hour-period, every additional 3 decibels above 85 increases and accelerates hearing damage, according to Genna Martin, who

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graduated from Boston University in 2009 and now works as a researcher in OHSU's department of otolaryngology. So a 91-decibel sound starts to cause harm in half the time of an 88-decibel level. That bit of science is easier to accept from a neutral third-party like Jolene.

"It's gone far beyond anything we imagined, especially the requests to translate into Chinese, Spanish, Portuguese and other languages," William Martin says. "It's changing young lives. This is probably the single thing in my career that will have the greatest impact."

— David Wallace

Pacific Northwest National Laboratory

Power Puck Replaces Batteries With Energy From Air

The quest for renewable energy is not entirely fueled by recent political winds or green movements. Much of the momentum comes from earlier efforts to overcome the one obstacle that prevents nearly every technological achievement from reaching its zenith: cheap and continuous energy.

The Perpetua Power Puck, a source of energy for remote wireless sensors and radio frequency transmitters that lasts for decades, thus sprang from a recurring need for new energy sources but debuted in a most timely fashion. The device completely eradicates the need for batteries or an electrical supply by using ambient temperature differences. Although in development for years, the technology appeared to burst onto the commercial scene, but not without its trials and not without the intricate work of several partners.

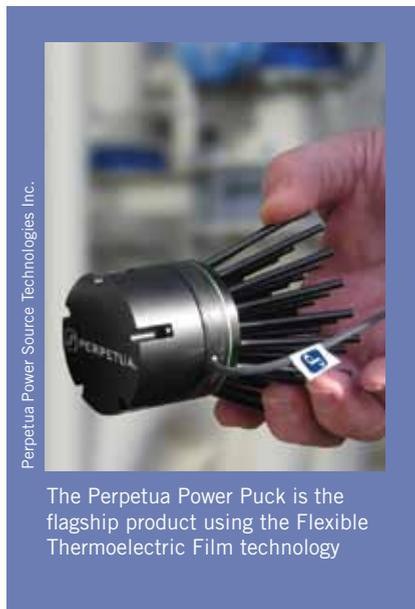
“Research and development work on this technology began over a decade ago,” explains Cheryl Cejka, technology commercialization director at Pacific Northwest National Laboratory (PNNL). The timing of its completion as a marketable technology, however, could not have been more perfect. “We were fortunate to have someone interested in the very early stages of our marketing efforts,” says Cejka.

“One of the founders of Perpetua Power Source Technologies Inc., Jon Hofmeis-

ter, did market research and came back and said he wanted to license it,” she explains.

Thus the technology known as Thermoelectric Ambient Harvester (TEAH) became a near-overnight success and the basis for the product called Perpetua Power Puck.

“The deal still took about a year to put together,” says Cejka. “Considering that over the course of the process, a company had to be established, investors had to be engaged and the terms of the license concluded, this deal went relatively quickly.”



Perpetua Power Source Technologies Inc.

The Perpetua Power Puck is the flagship product using the Flexible Thermoelectric Film technology

The discovery, however, always precedes the deal and is rarely achieved in a hurry.

The Path to Power

Back in the 1990s, John DeSteeze, an engineer at PNNL in the Energy Technology Development Group, proposed and conducted a funded project to explore a large variety of energy conversion technologies that can produce electric power from all forms of environmental energy. Wind and solar power are common examples that are now in commercial use.

“My emphasis was on devices that operate indefinitely in remote areas without human attention,” he says. “I recognized little work had been done to exploit the natural thermal energy in the environment, particularly in devices that produce less than a watt of electricity.”

He continues, “I invented the conceptual energy-harvesting basis of the Power Puck when I discovered the limitations of the prior design of this kind of device.”

TEAH, the technology in the Perpetua Power Puck, directly converts heat into electricity using the thermoelectric effect. In other words, it produces electrical power from the heat that is available in its surroundings.

“It’s the way some digital thermometers work,” explains DeSteeze. “If I make two junctions of dissimilar metals, holding one

junction at, say, the freezing point of water (32 F) and the other junction in air, the circuit of just these elements will produce a voltage proportional to the difference in temperature of the two junctions.”

Using just the right combination of materials maximizes the effect, he says. “Optimizing the material properties enables the effect to significantly increase performance,” he adds. “Now, multiply the number of junctions by a factor of thousands using semiconducting manufacturing processes, and we have a device like the Power Puck that produces renewable energy to run sensors and data communication equipment.”

Cejka says the PNNL team and Perpetua have created “a remarkable amount of new materials and embodiment technology that culminates in Perpetua’s current product.”

Because it has no moving parts, the Power Puck is ideal for harsh climates and remote industrial, military, environmental and agricultural applications. The company recently won government contracts to develop wearable energy harvesters that convert body heat into energy for powering wireless sensors. Market applications include powering ultra-long-life location devices for military personnel and first responders. It is also ideal for some medical applications, such as those that help patients with diabetes, heart disease and sleep disorders.

The Power Puck can power virtually any wireless sensor, regardless of the sensor’s

purpose. Among the applications identified so far are sensors for law enforcement, border security, hospitals, automotive, consumer electronics and tracking devices for outdoor sportsmen, athletes or pets.

Market applications include powering ultra-long-life location devices for military personnel and first responders. It is also ideal for some medical applications, such as those that help patients with diabetes, heart disease and sleep disorders.

Green Aspect Adds Commercial Appeal

The green aspect of the Power Puck added additional commercial appeal as countries around the world seek new sources of renewable or alternative energies and a means to reduce landfill poisons.

“Energy harvesting can make a direct environmental impact by reducing the number of batteries disposed of in landfills every year, save businesses significant money by eliminating costly battery replacements and enabling valuable elec-

tronics to be deployed in areas otherwise not practical,” explains Hofmeister, who serves as Perpetua’s president.

Perpetua negotiated an exclusive license from Battelle, the entity that has operated PNNL for the U.S. Department of Energy since 1965, to develop and commercialize the technology in 2007. Perpetua then worked on ways to improve volume manufacturing of the thermoelectric material, which it branded Flexible Thermoelectric Film. The film is incorporated into marketable products and solutions such as the plug-and-play Perpetua Power Puck.

“We first heard about Pacific Northwest National Laboratory’s work with flexible thin-film thermoelectrics through relationships with the University of Oregon,” says Hofmeister. “The southern Willamette Valley area here in Oregon, including the University of Oregon, Oregon State University, and Oregon Nanoscience and Microtechnologies Institute, is one of the top thermoelectric research areas in the world.”

Perpetua began selling products in early 2009, and the Perpetua Power Puck is the flagship product using the Flexible Thermoelectric Film technology.

“They are designed to harvest waste heat from almost any warm surface for powering wireless sensors used in industrial applications such as condition-based monitoring of critical equipment,” he says.

“We’re teaming with wireless radio providers, energy storage companies, industrial equipment manufacturers and

facility owners bringing our industrial solutions to market.”

The Power of Partnerships

Hofmeister credits the PNNL team for being “extremely helpful in making sure that Perpetua succeeds in bringing thermoelectric energy harvesting to market.”

Indeed, it takes a team effort to bring any new idea to market, but it isn’t a true partnership unless the effort benefits all.

“Collaborating with commercial partners on efforts like this reduces research and development costs for companies and allows the development of new products,” says Cejka. “And, each successful effort recognizes the work of our talented R&D teams and further fuels the desire to commercialize their innovations.”

PNNL also has a rewards and recognition program that has recognized the team’s efforts which DeSteele applauds.

“I can only speak for myself,” says the primary inventor, DeSteele, “but being recognized as an inventive individual by peers and the scientific community is my biggest motivation.”

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Everyone involved likes to see the research out on the market helping people in all walks of life and in real scenarios.

“Because so many ideas, and even those that get as far as being reduced to practice in the laboratory, still fail to find commercial application, the special joy that comes from this invention and its subsequent development is knowing that it will actually enter the marketplace as a useful and hopefully socially beneficial product rather than remaining a soon-forgotten laboratory curiosity,” says DeSteele.

The Power Puck may power sensors for decades, but its success also helps power the next batch of discoveries at PNNL.

— Pam Baker

Portland State University

Malaria: A New Approach Takes on an Old Disease

As a professor of chemistry specializing in nuclear magnetic resonance spectroscopy at Portland State University in the 1990s, David Peyton, Ph.D., was studying the structures of molecules when a colleague asked him for assistance with spectroscopic analysis of a new class of drugs.

That collaboration two decades ago was Peyton's introduction to malaria, a scourge that annually infects more than 300 million people and causes 1 million deaths worldwide, according to the National Institutes of Health. From that early collaboration, he developed a deep concern about the disease.

"First and foremost," Peyton says, "malaria is a human problem. More than 40 percent of the Earth's population lives in areas where it is a health risk — primarily in Africa and Asia. It's estimated that a

child dies from malaria somewhere in the world every 40 seconds."

Children and pregnant women are especially at risk. If young children survive their first malaria infection, their risk of death from subsequent bouts is diminished, since their immune systems will have adapted somewhat. But their vulnerability during the first infections is very high. Pregnant women are vulnerable because their immune systems are lowered by their condition. Unborn children are also greatly at risk.

"Frustratingly," Peyton says, "there are drugs for malaria that have been effective in the past — particularly chloroquine — but that have lost their potency as the malaria parasite evolved an ability to resist them."

Today, Peyton is still a professor of chemistry at Portland State University (PSU) and still immersed in nuclear magnetic resonance spectroscopy, but now he is the inventor of a potentially significant breakthrough in the treatment of malaria. By chemically bonding chloroquine with drugs called resistance reversal agents, he's created a new, hybrid agent more effective than either one alone. He calls it reversed chloroquine.

Malaria in Brief

Malaria is caused by tiny, single-celled parasites of the genus *Plasmodium*. There are more than 100 species, and different species of malaria are found in many kinds of birds and animals. Humans are vulnerable to just four species. One, *P. falciparum*, is responsible for the great majority of the most serious human infections and for most deaths, especially in Africa.

Key to human *Plasmodium* infection is the *Anopheles* mosquito. Infected *Anopheles* inject the parasite into humans as they feed on their blood. The parasites then begin a cycle of invading their human hosts' liver cells and releasing merozoites that invade the red blood cells. Some of these transform into sexual forms that, ingested by mosquitoes as they prey on humans, repeat the cycle.

Chloroquine was developed in 1934, but ignored until after World War II, when



Chemistry Professor David Peyton developed a hybrid drug to treat malaria.

Kelly James

it became widely used to treat — and prevent — malaria. Optimally, it works by establishing itself in a *Plasmodium*'s digestive vacuole, binding with heme, a component of hemoglobin released by its digestion. This binding prevents the parasite from sequestering the toxic heme and leads to the death of the parasite. But over time, *P. falciparum* evolved an ability to eject the chloroquine from its vacuole, rendering the drug ineffective.

Resistance Reversal Agents

Peyton settled on the concept of combining resistance reversal agents with chloroquine because he believed that restoring the effectiveness of a standout medication like chloroquine was more promising than trying to develop a new malaria drug from scratch.

“Resistance reversal agents are drugs that have little or no anti-malarial properties of their own,” he says. “In fact, they include things like antidepressants and blood pressure medications. But administered in combination with chloroquine, they help it overcome the parasite’s resistance. The catch is, as separate medications in the combination, they have to be used in very large doses. I wondered what would happen if they could be chemically bonded to chloroquine.” He and his graduate student, Steven Burgess, decided to find out.

What happened in laboratory tests was that a hybrid version of chloroquine and resistance reversal agent proved remarkably effective in remarkably lower doses — much lower than either when used alone.

The specific mechanisms are unclear, but Peyton suspects that when a reversal agent is administered with chloroquine as two separate parts of a simple cocktail, the reversal agent has trouble getting into the *Plasmodium*'s digestive vacuole where it is needed to keep chloroquine from being ejected. Thus, large doses are required. In a chemically bonded hybrid, he suggests,

Today, Peyton is still a professor of chemistry at Portland State University (PSU) and still immersed in nuclear magnetic resonance spectroscopy, but now he is the inventor of a potentially significant breakthrough in the treatment of malaria.

the chloroquine pulls the reversal agent along with it all the way into the digestive vacuole where it does its work.

An important aspect of the approach, Peyton notes, is that as the parasite evolves to resist the new drug, the hybrid can be reengineered with new resistance reversal agents.

In 2005, Peyton informed PSU’s technol-

ogy transfer office that he might be onto something. PSU submitted its first patent application for the work that year. Thus far, outside funding included National Institutes of Health grants. The next step was to find funding to move the research and development forward.

“David was so concerned with advancing the research that he became involved in the search for a company,” notes Dana Bostrom, the university’s director of innovation and industry alliances. “We sent him to a weeklong ‘boot camp for scientists’ at the university called Lab2Market. It focuses on technology transfer and commercialization. One part is a mentorship program, matching them with experienced entrepreneurs. Through it, he met Lynn Stevenson and Sandra Shotwell.”

Designing DesignMedix

Stevenson and Shotwell had both been technology office directors at separate universities before they joined together to form a consulting firm, Alta Biomedical Group, based in Portland, Ore. Since each had had experience with malaria drugs in the past, they were intrigued by Peyton’s work.

“As a team,” Shotwell says, “we decided the next step in moving the technology forward was getting funding for focused drug development.” They felt that by forming a company, they could pursue federal small business grants. DesignMedix was established in 2006. Stevenson serves as the chief executive officer, Shotwell as the chief operations officer and Peyton — still full time at

PSU — as chief scientific officer.

“We were lucky enough to get a Phase I small-business grant on the first try,” Shotwell notes, “and the results of that work were exciting.” This helped DesignMedix get a larger Phase II grant, as well as private equity funding from investors, including the Oregon Angel Fund.

In 2009, DesignMedix won the top prize in the Angel Oregon competition, sponsored by the Oregon Entrepreneurs Network. By 2010, they had six employees, including Burgess (by now a doctorate), an active laboratory and were moving into formal preclinical studies. Support from the university was essential to their progress.

“Portland State is committed to fostering entrepreneurship,” says PSU’s Bostrom. “We operate a 40,000-square-foot Business Accelerator to support startups. It houses 20 companies and will soon add more than 2,000 square feet of wet-lab space, including a new laboratory for DesignMedix.”

DesignMedix/PSU ties are financial as well as logistical — in 2008, the university negotiated a license with DesignMedix. One provision dictates that in any com-

mercialization of the technology, the university won’t receive royalties from sales in specified developing nations — reflecting a concern that, often, the people most in need of such medicines are the ones who can least afford them.

An important aspect of the approach, Peyton notes, is that as the parasite evolves to resist the new drug, the hybrid can be reengineered with new resistance reversal agents.

Preclinical Studies and a Pipeline

As 2010 began, reversed chloroquine was in preclinical studies. The product has been through laboratory and animal tests, with highly encouraging results. DesignMedix hopes to go to the U.S. Food and Drug Administration to seek approval for clinical trials within two years.

In the meantime, the company has licensed additional technology from the Portland VA Medical Center and the Oregon Health & Science University for a different class of antimalaria molecules and has begun research on applying Peyton’s hybrid techniques to overcoming resistance in bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), an increasingly common, infection-causing bacterium that has been highly resistant to treatment.

How does David Peyton the chemistry professor react to the prospect of being David Peyton the entrepreneur — and creator of a significant drug?

“This is the first time I’ve even been involved in commercialization,” he says. “I do spectroscopy. I study molecules. We’re all involved in academia because we enjoy learning. This isn’t academic, but, boy, has there been a learning curve!”

He adds: “The process is arduous, but the end result may be a solution to a terrible disease that affects millions of people. It’s worth it.”

— *Ralph N. Fuller*

Roswell Park Cancer Institute

Photodynamic Therapy: A Light at the End of the Tunnel for Cancer Patients

Almost a decade ago, a woman in her 60s was in extreme pain from a tongue tumor that was spreading along the floor of her mouth. The cancer surgeon whom she consulted removed the lining of her mouth with a laser incision and cut out the tumor. Two months later, the woman's pain level was the same as before surgery and the tumor returned. The surgeon repeated the procedure, yet three months later there was no progress.

"This was a case of the cure being worse than the disease," says Nestor R. Rigual, M.D., a head and neck surgeon at Roswell Park Cancer Institute in Buffalo, N.Y., who struggled with this woman's case.

Recognizing that what he was doing wasn't working, Rigual consulted Thomas J. Dougherty, Ph.D., at Roswell Park who had invented a light-targeted cancer therapy called photodynamic therapy or PDT. Dougherty was then head of the PDT Center. Rigual's patient was a good candidate because her lesion was accessible. With the woman's approval, Rigual treated her with PDT.

"The initial result was quite dramatic," Rigual says. "The disease went away for more than a year."

Shining a Light on the Matter

"PDT is an entirely unique concept in

cancer treatment," says Richard R. Matner, Ph.D., director of technology transfer and commercial development at Roswell Park Cancer Institute. "It's possible that one application may be able to control a cancer, but multiple applications are possible since the treatment is nontoxic."

Where the light strikes the tumor cell, Matner explains, it releases oxygen and, simply put, "It's killed." Matner experienced the treatment himself when a basal cell carcinoma on his shoulder "disappeared" with a single treatment of PDT.

As an alternative cancer therapy, PDT dramatically reduces many of the side effects of standard treatments that include surgery, radiation and chemo or hormone therapies. Unlike radiation or surgery,

there are no permanent or deleterious effects like scarring with PDT.

If PDT doesn't work, says Rigual, "you haven't burned any bridges" to try other treatments, which is an important concept in medicine.

Rather than using toxic radiation to kill cells, a surgeon shines a light at the tumor. This powerful beam of light, directed by a tiny diode laser or endoscope via a particular wavelength that fits in a briefcase-size pack, creates energy that destroys vessels by stopping blood supply. The tumors then starve to death.

"PDT's impact is akin to a combination of chemotherapy and radiation," says Matner. "It takes the best of each and



Photodynamic therapy reduces many side effects of standard cancer treatments.



Chemist Ravindra Pandey's work reduced patient recovery time significantly.

eliminates the worst of each.”

Bringing PDT Into the Light

The first indication that light could damage living organisms was discovered by a German scientist in 1900. He found that a single-cell paramecium was killed when a fluorescein-type dye was added and then exposed to light. Years later, others recognized the role that the oxygen played — and this ultimately became known as the photodynamic effect.

“My first exposure to this phenomenon was accidental,” says Dougherty. “I was testing a potential radiation sensitizer that I had made for its cellular toxicity using a fluorescein derivative that produces fluorescence to remain in live cells but not in dead ones. I was told to do this testing in subdued light since light would kill all the cells in the presence of this stain.”

Like a curious scientist, Dougherty found this intriguing, and so he tried it. “Sure enough,” he says, “all of the cells died.”

And an area of cancer research was born.

His first experiments using fluorescein as the PDT photosensitizer on mice “sort of” worked, says Dougherty. “It slowed the growth but didn’t kill the tumor.

“I soon realized two problems with using fluorescein,” he continues. “First, it produces very little singlet oxygen when activated by light, and, second, the light needed to activate it does not penetrate very far into the tissue. I needed a drug — a photosensitizer — that could be activated by red light (which penetrated tissue the deepest) and produced a large amount of the oxygen needed to kill the cells. I chose a class of compounds called porphyrins since they possess both of these properties. When porphyrins were used, the tumors on the mice completely disappeared.”

The results stunned the researcher. “I couldn’t believe it,” says Dougherty, “I repeated the experiment at least a dozen times!”

Many more experiments took place on numerous mice. Then, with permission

from the U.S. Food and Drug Administration (FDA) to start clinical trials on a few brave people with advanced cancers (some who suffered a great deal of pain from overtreatment until the researchers got the dosages right), Dougherty, with the help of many others including various pharmaceutical companies, achieved the one-chance-in-a-thousand odds for FDA approval in 1995.

Not everyone saw the light of PDT at first. Some of the researchers from Roswell, including Dougherty, created a company to commercialize the original compound that Dougherty had identified and patented, called Photofrin. Funding was first provided by the National Cancer Institute in 1974 as a grant and renewed many times over the course of their research. Financial support also came from The Oncologic Foundation of Buffalo. These funders, along with money from Johnson & Johnson for the Photofrin rights, officially launched and carried the program.

When the Photofrin was licensed to the company, it, in conjunction with Lederle Laboratories, obtained approvals for obstructive esophageal cancer in 1995 and for lung cancer in 1998. When Axcan Pharma of Quebec obtained the license from the company, the group earned approval for high-grade dysplasia in Barrett’s esophagus in 2003.

At that time, Barbara Henderson, Ph.D., and current head of the PDT Center at Roswell Park, discovered that destruction of the tumor blood vessels, in addition to the tumor cells, was key to the complete

destruction of the tumor. Henderson helped change medical minds with this finding. “She translated the PDT technology into patients,” says Matner.

But there was still a concern with one of the side effects of the drug, says Dougherty. “There was skin phototoxicity, which meant that patients had to stay out of the sun for six to eight weeks after the procedure.”

Ultimately this problem was solved by Ravindra Pandey, Ph.D., a chemist at Roswell. He worked on a series of compounds that would be as effective as Photofrin, but without the skin toxicity. The breakthrough came when Pandey synthesized compounds that reduced skin phototoxicity from several weeks to three or four days. This dramatically impacted quality of life for patients following the PDT cancer treatment.

How Brightly the Light Can Shine

PDT has been used for essentially every conceivable cancer as well as many noncancer indications. Some of the most promising are cancers of the head, neck and bile duct. The only approved noncancer uses are for vision loss and skin lesions. It is approved in the United States, Canada, Europe and Japan for palliative use and cure for certain cancers of the

As an alternative cancer therapy, PDT dramatically reduces many of the side effects of standard treatments that include surgery, radiation and chemo or hormone therapies. Unlike radiation or surgery, there are no permanent or deleterious effects like scarring with PDT.

esophagus, lung, skin, cervix and bladder (bladder cancer is not yet approved in the United States).

Pandey's new photosensitizer has been licensed in China and in India where it will be used for treatment of head and neck cancers that are prevalent in these countries. This will greatly expand the number of patients who can benefit from PDT.

As for the woman whose tongue cancer was treated with PDT by Rigual over a decade ago — she is in her 70s now and cancer free. At the rate it is being studied and applied, PDT is not only likely to extend the lives of many more people with cancer, but will allow clinicians to make earlier and more precise diagnoses that will prevent the growth of more life-threatening cancers.

— Ellen Blum Barish

The University of Alabama

FreezePruf Offers Protection for Crops Threatened by Falling Temperatures

When freezing temperatures hit Florida with unexpected strength in early 2010, they wiped out 30 percent of some growers' citrus crops, killed 70 percent of tomatoes in southwest Florida and wreaked havoc on crops ranging from sweet corn to green beans. Losses were estimated in hundreds of millions of dollars, according to the *Wall Street Journal*.

The impact was felt well beyond the growers themselves. One northeastern supermarket group reported a 40 percent increase in wholesale prices for tomatoes, lettuce and other produce.

If the risk of a killing freeze is growers' collective nightmare, biologist David Francko, Ph.D., has a solution — an antifreeze for plants that can keep oranges, tomatoes

and other vulnerable crops growing past killing frosts and well into the fall.

“FreezePruf helps plants survive a freeze,” says Francko, a professor of biological sciences at The University of Alabama (UA). “Applied at least 12 hours ahead of a projected freeze, FreezePruf can help crops avoid the blossom loss and fruit rot normally associated with freezing temperatures.”

So far, the FreezePruf spray appears to be effective on nearly every kind of plant, from fruit trees to vegetable plants to ornamental flowers and shrubs. Francko and his team are working to extend the list.

“With almost 300,000 species of plants in the world,” he says, “there’s bound to be

at least one it won’t work on. But I haven’t found it yet.” In fact, the list of applicable plants is growing not just from his research but also from customer input.

“A real surprise was a call I got from the owner of a small vineyard in Virginia,” Francko says. “We hadn’t worked on grapes, so they weren’t on our list of applicable plants, but the client said he used it on his Chardonnay grapes before an unexpected frost and they came through just fine.”

As Francko sees it, FreezePruf is valuable for both commercial growers and home gardeners. With it, flowering and setting of fruit can be extended by as much as three weeks on either end of the season. Cold tolerance of foliage can be increased by as much as 9 degrees Fahrenheit, depending on the type of plant. He compares it to moving a growing zone 200 miles south.

He is quick to point out, however, that the product does not make plants invincible. “Expectations have to be reasonable. FreezePruf can protect tomato plants at 31 to 32 degrees, but it won’t protect them for extended periods at 25 degrees,” emphasizes Francko. “It likely won’t save 100 percent of an orange grower’s crop during a truly deep freeze, but it may save 50 percent of the crop

Laura Shill,
University Relations, The University of Alabama



FreezePruf, developed by Professor David Francko (right), will help gardeners and commercial growers alike to survive frosts and extend their seasons. GroTech President Mark Russell (left) is working with Francko to take the product to market.

rather than the 5 percent that might survive untreated.”

Transition Zones

Francko began working on cold-hardiness issues while on the faculty at Miami University in Ohio in the late 1990s. He continued the research at UA, where he relocated in 2006. He also serves as dean of the UA Graduate School and associate provost for the university.

“Southern Ohio is something of a transitional growing zone, and we were wondering whether some southern ornamental plants could succeed there,” Francko says. His team at Miami included geneticists Kenneth Wilson, Ph.D., Quinn Li, Ph.D., and postdoctoral associate and co-inventor Maria Alejandra Equiza. Focusing on plants like palms and crape myrtles, Wilson and Li found that they relied on the same genes and pathway systems as cold-hardy varieties.

“That suggested that we might be able to genetically engineer plants,” Francko says, “but I also wondered if there was something we could do with existing plants. I started looking for a mechanical approach.”

At Miami, the work was supported by university funds and a grant from the Ohio Plant Biotechnology Consortium. A significant part of the work was done at Miami, and he couldn’t have developed the technology without its support, Francko notes.

“Dave wanted to bring the project with

him to Alabama so we worked out a compensation arrangement with Miami,” notes Richard Swatloski, Ph.D., a licensing associate in UA’s Office for Technology Transfer. “His UA work has been supported with university funds — and without any corporate support. Dave was

“If things like ‘polyethylene glycol’ and ‘surfactants’ sound unappealingly chemical,” notes Swatloski, “they’re all currently present in many consumer products and incorporated in many edible products. All of FreezePruf’s components are agents already widely used in foods and to grow fruits. It’s absolutely green — safe to eat and biodegradable.”

concerned that the technology not be tied to a large manufacturer, where it might end up a minor side-product.”

Simulating Drought Stress

At Miami, Francko’s search for a “mechanical approach” led him to think about “drought stress,” the phenomenon plants rely on to avoid damage from low moisture levels and that can also make

plants more cold hardy. A big issue in simulating drought stress was making sure that, as cells shrink in reaction to water stress, they do so uniformly, retaining their integrity and their ability to function.

It took him six months to find the right combination of agents. The key was polyethylene glycol (PEG), a common polyether compound that has applications ranging from lubricants in eye drops to pollutant removal in power plants. Its ability to prevent warping or shrinking in wooden objects by replacing the water in the wood has been utilized to preserve sunken wooden ships when they are raised.

“PEG drives the whole process, but FreezePruf is a combination of agents that work together, each with a specific role,” Francko says. One, a surfactant, helps the agents quickly pass through the surfaces of leaves, flowers and fruit. Another, an antidesiccant, reduces water loss from plant structures once the surface is dry.

Two cryoprotectants insulate against freezing temperatures. High-molecular-weight PEG stays largely outside the cells, pulling water from within them to lower the freezing points in both cell interiors and extracellular spaces. A second, low-molecular-weight compound partitions between the interior and exterior cell spaces, contributing to lower freezing points.

The high-weight PEG also interacts with cell membranes and walls to increase their resistance to ice crystal damage,

increasing plants' cold hardiness. And a silicate compound binds to cell walls to strengthen against ice crystal damage.

Going to Market

"If things like 'polyethylene glycol' and 'surfactants' sound unappealingly chemical," notes Swatloski, "they're all currently present in many consumer products and incorporated in many edible products. All of FreezePruf's components are agents already widely used in foods and to grow fruits. It's absolutely green — safe to eat and biodegradable."

Using existing ingredients also meant the product could bypass federal approval, although it still faced challenges.

"With its makeup of existing, approved ingredients, FreezePruf didn't require federal review," says Swatloski. "On the other hand, that meant we've had to get state-by-state approvals for it. We've worked our way through most of them."

"We applied for a patent on FreezePruf in 2007 and licensed the technology to a small company called GroTech-SM in 2008."

In fact, Oregon-based GroTech-SM has exactly one employee and one product — FreezePruf. Founder and President Mark Russell has worked for more than a decade as an independent consultant

focused on commercial agriculture, dealing with issues ranging from crop development to product promotion to market expansion. He founded GroTech-SM — SM stands for sales and marketing — as a potential venue for his work in 2007.

He saw a UA news release about FreezePruf and called Francko to pursue the possibility of representing it in the Northwest. When he was told that the university was first looking for a company to help with commercialization, he explained instead that he thought he could take the new product to market.

"We thought we could make FreezePruf available at the retail level fairly quickly," Russell says. "We contracted with Liquid Fence to manufacture and distribute it, and it began appearing on shelves in the late summer of 2009."

Based in Brodheadsville, Penn., the Liquid Fence Co. specializes in gardening and farm materials such as deer and rabbit repellants, insect repellants for animals, and gardening accessories. It sells its products through retail distribution and by mail order, bottling FreezePruf in quart and gallon to multigallon quantities. At present, the majority of FreezePruf sales are at the retail level through independent garden centers, Russell says.

"Our agreement gives Liquid Fence the

rights to package and sell at the retail level nationally," Russell notes, "but we hold the trademark and the rights to produce for the commercial market separately. I'm currently negotiating with several companies for commercial-level production and distribution."

It is, he notes, a relatively easy product to produce but an expensive one to ship. He expects to have several regional manufacturers producing FreezePruf PRO for the 2011 season.

A Ripe Future

"FreezePruf can be a valuable tool for commercial growers, whether for fruit trees, vines or vegetable crops," Russell says. "The challenge for the commercial market is that growers will test a product for two or three years before committing to it on a large scale. But I'm confident that will happen."

"This technology has the potential to help home gardeners get more from their plants, both vegetables and ornamentals. But in my mind it holds tremendous economic benefits for commercial growers in avoiding crop damage and financial losses due to freezes. And that will help all of us in terms of the prices we pay at the supermarket."

— *Ralph N. Fuller*

The University of Tennessee

Advanced Plasma Technology Zaps Deadly Microbes

Though we rarely admit it, human beings live in a kind of organic stew, surrounded virtually everywhere by bacteria, viruses, fungi, endospores and volatile organic compounds (VOCs). Most of the time, the presence of our tiny companions is of no particular concern, but there are certain settings — such as in hospitals, hotel rooms and locker rooms — in which a quick and effective means of air purification is not only highly desired but a potential life-saver. Now, thanks to technology that sprang from curiosity about ball lightning at The University of Tennessee (UT), people are able to enjoy healthier, safer, more sanitary environments.

The Genesis of the Idea

In the early 1990s, John Reece Roth and his colleagues Peter Tsai, Chaoya Liu, Mounir Laroussi, Paul Spence and Larry Wadsworth at UT became interested in a natural phenomenon: ball lightning. They wondered: Would it be possible to recreate it in a laboratory?

Ball lightning is atmospheric plasma. Plasma is an energized gas, the fourth state of matter (the first three are solid, liquid and gas) and the most abundant form of matter in the universe. For years researchers had experimented with plasmas in the laboratory, but most of these experiments required the use of vacuum chambers and exotic gases. At the time the UT researchers turned their eyes toward ball lightning, very little was under-

stood about atmospheric plasmas. From their subsequent studies, a whole new field of scientific endeavor would emerge.

During their investigations, they found that atmospheric plasmas — plasmas that occur in ordinary air at standard pressure and ambient temperatures — could indeed be created in the laboratory. After considerable research, they developed a One Atmosphere Uniform Glow Discharge Plasma (OAUGDP) technology that generates atmospheric plasmas comprised of highly reactive chemical species. Funding from several government agencies, including the Department of Defense and NASA, was obtained to demonstrate the technology for several practical applications.

Yes, but What Is it Good For?

In 1996, Kim Wintenberg, Ph.D., a microbiologist and now director of new busi-

ness development for Advanced Plasma Products, was asked to join the UT team to study the ability of the OAUGDP to kill microorganisms. As far back as the 1930s, researchers had killed microorganisms with plasma, but all of these techniques involved extreme heat, vacuums or specialty gases. Wintenberg and the team found that the highly oxidative gases in OAUGDP are extremely effective at killing microbes and oxidizing VOCs.

Further, the team discovered that OAUGDP had two key characteristics that might lend themselves to using this technology against microorganisms that are commonly found on surfaces. First the glow discharge is relatively uniform, unlike some other plasma technologies. Second, sensitive materials, such as textiles, can be immersed in the plasma field without pitting or burning. This bodes



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The ability to purify air by killing harmful microorganisms can save lives.

well for a system that could be used to destroy microbes.

Licensing the Technology

The long road to licensing began in 1993, when the OAUGDP team disclosed several inventions to The University of Tennessee Research Foundation (UTRF). UTRF spent some years looking for potential licensees. In time, Atmospheric Glow Technology licensed the technology but eventually Atmospheric Glow Technology went bankrupt, and the technology reverted to UTRF.

At that time, four entities were interested in the assets of Atmospheric Glow Technology, and one of them was Ken Wood and his business partners. They had joined Applied Science Products, a publicly traded parent company, and saw the opportunity to create a new company. In 2008, he formed Advanced Plasma Products, based in Knoxville, Tenn., bought the physical assets of Atmospheric Glow Technology, brought on some of the key personnel, licensed the technology and began working on a focused commercialization effort.

“They have a robust diligence plan for commercializing product,” says John Hopkins, vice president for UTRF. “The Advanced Plasma Products team is building good future value for the company, and they have done it in poor economic circumstances and in a short time.”

One reason for the team’s success is simple experience. “I approached the licensing process with some measure of

familiarity,” says Wood, now president and chief executive officer of Advanced Plasma Products, “and I was comfortable with assessing the technology and understanding the scope of the underlying intellectual property.

“As a land grant university, we have a responsibility to ordinary people to impact their lives in a positive way,” he says. “We want to do that by getting beneficial technologies into society, by providing job opportunities for our students, by supporting the tax base of the state and by the direct return of license revenues to the university.”

“After that, it was a matter of stepping through the various processes,” Wood says. “The UTRF people are pros, so we were able to work through the steps relatively quickly and efficiently. If both sides know what they are doing, it’s a bit like getting a mortgage for a house. The UTRF people facilitated the process.”

The First OAUGDP Product

Using and building upon the technol-

ogy developed at UT, Advanced Plasma Products has already brought to market its first offering, the TriClean Pro. The TriClean Pro is a standalone air purification system with capabilities of exchanging and sanitizing the air at least 3.4 times per hour in a 4,000 cubic foot room.

The TriClean Pro operates in two phases. During the capture phase, ambient air that contains microorganisms and VOCs is drawn into the unit. Large particulates are removed by a prefilter, while smaller particles and microbes are removed by a very efficient particulate filter with a low-pressure drop. VOCs are trapped by a carbon filter. During the destruction phase, the fan operates at lower speed and the plasma grid is energized. The reactive gases produced by the plasma oxidize VOCs and kill trapped microorganisms. Air is passed over a catalyst to neutralize reactive gases and returns to the air free from odors and harmful contaminants. The TriClean Pro, which requires about 65 watts of power to operate, has met all necessary UL safety tests for ionizing air purifiers, including the tests for ozone.

Applications for the TriClean Pro include health care settings, such as surgical suites, intensive care units where immunocompromised patients are more susceptible to infection, medical waiting rooms, general patient rooms, nursing homes and offsite surgical centers. Additional applications outside of health care include veterinary offices, athletic locker rooms and training facilities, and the hospitality industry, where guests’ expectations of clean facilities during their

stay are important.

Advanced Plasma Products has invested heavily in developing the technology it licensed from the UT. One of the key developments has been to engineer systems in which the plasma is generated at one site and then the reactive species are delivered to a remote site. Without this capability, plasma systems are limited to treating materials that can fit between the two plasma-generating electrodes,

which are typically millimeters apart. By contrast, the new Advanced Plasma Products system can deliver the reactive species onto a wrapped object like a surgical instrument, and those species survive long enough to sterilize it.

In the end, Hopkins has high aspirations for technology transfer through UTRF. “We’d like to grow advanced technology companies in our region that contribute to economic prosperity, hire our graduates

and foster entrepreneurialism in the area.

“As a land grant university, we have a responsibility to ordinary people to impact their lives in a positive way,” he says. “We want to do that by getting beneficial technologies into society, by providing job opportunities for our students, by supporting the tax base of the state and by the direct return of license revenues to the university.”

— *Jock Elliott*

Tufts Medical Center

Promising Proteases Have Potential to Reverse Incurable Kidney Disease

As diseases go, IgA nephropathy (IgAN) has a low profile among Americans. A disorder that can lead to total kidney failure, it is present in the United States, but it is much more prevalent in Asia. Often, it is not recognized until it is far along.

“Several factors make this illness fly under the radar in the Western world,” says Andrew G. Plaut, M.D., a professor of medicine at Tufts University School of Medicine in Boston. “It’s not common in the West, it has a very slow progression and it requires a kidney biopsy for diagnosis — a procedure many clinicians are reluctant to order because effective treatment is not available.

“The illness is common in Japan, which screens children for IgAN rigorously. It’s

estimated that more than 1 percent of the population in China is afflicted with it. Singapore and South Korea have similar numbers, and it’s probably abundant in India. It’s a serious problem but there really are no effective treatments and no cures.”

That, hopefully, will change as a result of work done by Plaut and Jiazhou Qiu, M.D., at Tufts Medical Center, where they’ve pioneered techniques of using proteases — enzymes whose many functions include roles in immunity — to eliminate IgA1 protein from kidneys and clear the disease. Patented by Tufts Medical Center in 2003, development of the technology is in the preclinical stage by IGAN Biosciences Inc., a Boston-based company founded by Plaut and Qiu, and by BioMarin Pharmaceutical Inc. in Novato, Calif.

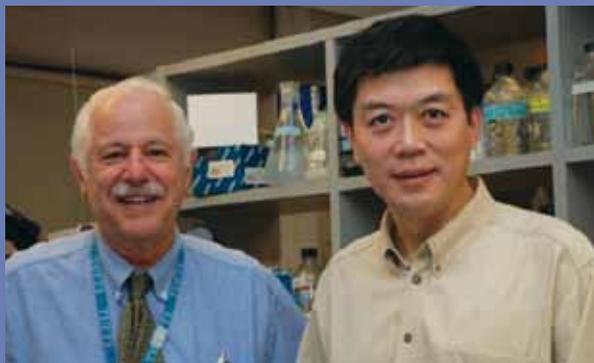
IgA Nephropathy

IgAN develops when immunoglobulin A (IgA1) proteins in the blood accumulate in an affected kidney’s million glomeruli — the tiny capillaries that filter wastes from the bloodstream. As these deposits build up over time, the glomeruli become inflamed and damaged, slowly losing function and eventually closing down altogether. Treatment has generally been focused on drugs that limit inflammation, but, at best, they only slow the loss of kidney function.

IgA is one of five major types of antibodies — gamma globulin proteins found in bodily fluids — that play important roles in fighting off pathogens. IgA1, present in the blood of all healthy persons, is the version of IgA that causes IgAN.

“In patients with IgAN, the protein is already a bit larger than normal as it circulates in the plasma,” Plaut notes. “It also has a tendency to aggregate into small clumps. And it looks like an abnormal protein to the immune system, which binds antibodies to it — making it even bigger. As it passes through the glomeruli, it settles, building up and degrading the kidney’s ability to function.”

Numbers of patients with IgAN are hard to pin down, since the only definite numbers apply to the 40 percent of IgAN



Andrew G. Plaut (left) and Jiazhou Qiu have developed techniques to use IgA protease to clear IgA1 protein from kidneys.

Tufts Medical Center

sufferers who have progressed to end-stage renal failure. An IgAN Biosciences analysis suggests as many as 125,000 cases of IgAN in the United States and, because of large Asian populations, as many as 2 million worldwide. Regardless, IgAN is considered to be the most common cause of glomerulonephritis worldwide, and one of the leading causes of kidney failure.

It's not even clear what causes the disease. There appears to be a genetic factor that groups it in families, and perhaps among populations, but it isn't understood. The incidence of IgAN is low among Africans and high among members of the Zuni Indian tribe in the American Southwest. Asian countries like Japan and China may report higher levels because they are more likely to screen for it.

"It's most likely underdiagnosed," Plaut says, "because biopsying someone's kidney to prove a diagnosis is pretty invasive — it requires a long needle, some pain and potential risk. And since there aren't any cures, diagnosing it may be a Pyrrhic victory."

The Protease Approach

Working with bacteria in the 1970s, Plaut realized that an IgA protease produced by a bacterium called *Haemophilus influenzae* — already known to help bacteria avoid immune attack by IgA antibodies — could be used to clear IgA1 proteins. Proteases are proteolytic enzymes found in living organisms — they have the ability to cut proteins. Hundreds of types are known, ranging from papain, the agent

in meat tenderizer, to the virus protease targeted in HIV therapy.

"We studied the unique IgA proteases for a long time," Plaut notes. "In the 1980s we began to gain insight as to how these enzymes could be used to cut the human IgA1 molecule. It's effective for bacteria

An IgAN Biosciences analysis suggests as many as 125,000 cases of IgAN in the United States and, because of large Asian populations, as many as 2 million worldwide. Regardless, IgAN is considered to be the most common cause of glomerulonephritis worldwide, and one of the leading causes of kidney failure.

because it cuts IgA antibody in half, making it useless. And the only thing that it cuts is IgA1. This makes it very useful for our treatment plan."

Understanding the concept of cutting a protein is different from having a protease that can clear it from a kidney. One question was whether IgA1 in the kidney is permanently attached to the glomeruli.

The answer turned out to be no. While recurrences develop in IgAN patients who receive transplants of non-IgAN kidneys, in cases where non-IgAN patients (mistakenly) receive IgAN kidneys, the IgA proteins disappear from the kidneys within weeks.

The next question was how much enzyme was needed. The answer was a lot. Qiu, who began working with Plaut as a member of the scientific staff in 1987, first focused on growing the bacteria and identifying interactions between the enzyme and human IgA1.

"During the 1990s," he notes, "I worked on purifying the enzyme. It was difficult to get the high levels needed for animal studies."

Working with a Case Western Reserve University team headed by Michael E. Lamm, M.D., and Steven Emancipator, M.D., Plaut and Qiu conducted animal tests in 2004. They demonstrated that the protease efficiently removed some 85 percent of human IgA1 they had deposited into the kidneys of mice. The group published the results in the *American Journal of Pathology* in January 2008.

Seeking a Partner

While Plaut's and Qiu's initial research was supported by National Institutes of Health grants, it became clear early on that developing the protease concept further would require additional, outside funding.

"Andrew and Jiazhou disclosed their invention to us in 2003," notes Nina Green, director of the Office for Technology

Licensing and Industry Collaboration at Tufts Medical Center. “We filed a patent and immediately began seeking a corporate partner to work with us.

“Andrew felt very passionate about this work. Progress was slow. Some companies said it was too early in the development process, and Andrew and Jiazhou decided to start their own company.” They secured private funding from a senior portfolio manager at Boston-based Ironwood Investment Management.

IGAN Biosciences was founded in 2005, with Plaut serving as chief medical officer and Qiu as chief scientific officer. Tufts executed an exclusive license with the company in 2007. That same year,

IGAN began collaboration with BioMarin in California.

“Preclinical work is something BioMarin is good at,” Qiu says. “They’re doing the animal testing, developing techniques for producing the protease in large amounts, everything needed to take the product to the Food and Drug Administration to apply for clinical trials.” It’s a three-party agreement between Tufts Medical Center, IGAN and BioMarin.

While BioMarin is working with the original protease version, Plaut and Qiu have moved on to a second generation, filing a patent in 2009 to modify the protein to make it smaller.

“Todd Holyoak, Ph.D., a colleague at the University of Kansas, worked with us to develop an image — a crystal structure — of the protein so that we can understand how it’s shaped,” Plaut notes. “If we want to make changes, knowing the structure can tell us where the changes would be tolerated. I’m prepared to see obstacles rise up, but everything we’ve seen in the animal studies is favorable.

“As many as 40 percent of IgAN patients go on to experience complete kidney failure and the need for renal dialysis or a kidney transplant. This is a disease that severely impacts people’s lives. It can kill them. We have a chance to eliminate it.”

— *Ralph N. Fuller*

University of California, Los Angeles

Detachable Coils Defeat Brain Aneurysms With Skill and Ingenuity

Brain aneurysms are usually symptom-free while they are developing but are devastating when they finally make their presence known. Most of these bulges in the arteries of the brain remain undetected until they've swollen to the point of bursting and begin smothering brain cells with free-flowing blood.

Only a small percentage of people with brain aneurysms experience ruptures, but as many as 50 percent of those whose aneurysms do burst die before reaching the hospital, according to figures compiled by the nonprofit Brain Aneurysm Foundation. Half of those who get to the hospital go on to die within 30 days, while survivors often suffer from brain damage and lingering disability, the foundation notes.

Conversely, some patients receive prompt care with minimally invasive detachable platinum coils. While surgery is sometimes appropriate, coils avoid the need for physically opening patients' skulls to access aneurysm sites. Threaded with extreme care through the arteries by highly trained and skilled interventional neuroradiologists, the soft, flexible coils are packed inside the aneurysm pockets to close them off, ending the danger of continued bleeding.

The best possibility is for the procedures to be performed preventively, before the

aneurysms actually rupture. Usually, however, the aneurysms' presence is discovered only by accident, during tests for other problems.

Shape-Shifting Flexibility

Somewhat resembling tiny slinky toys, detachable coils are comprised of spiraling wires thinner than strands of hair. Platinum is used because it is visible to a fluoroscope, is flexible and can assume the shape of the aneurysm it fills. Delivered through catheters inserted into the arterial systems, the coils are detached by low-voltage electrical currents that dissolve the connection between them and their delivery wires.

"Before coiling was approved in 1995, the best tools we had for treating aneu-

rysms were either surgery that involved removing a section of skull or the use of balloons we could inflate within the aneurysm to try to fill it," says Fernando Vinuela, M.D., director of interventional neuroradiology at the University of California Los Angeles' (UCLA) Ronald Reagan Medical Center. He was a member of the team that invented the Guglielmi detachable coil (GDC), named for Guido Guglielmi, M.D., the Italian physician who led the project.

"Balloons weren't a satisfactory solution because they didn't adjust to the shape of the sac. The Guglielmi detachable coil proved to be a superb technology — soft and flexible, forgiving, with a low complication rate. The Matrix detachable coil, approved a few years ago, accelerates



Neuroradiologists Fernando Vinuela (left) and Yuichi Murayama refined the Guglielmi detachable coil to give doctors another option for treating aneurysms.

the clotting process with a biopolymer coating.”

Since the GDC’s approval for commercial sale by the U.S. Food and Drug Administration (FDA) in 1995, coils have been used on more than 500,000 patients worldwide, Vinuela notes.

A Silent Stalker

One in every 15 people develop brain aneurysms during their lifetime, according to the American Society of Interventional and Therapeutic Neuroradiology (ASITN). Aneurysm bulges grow at weak spots in arterial walls, believed to be promoted by risk factors as diverse as smoking, hypertension, infection and traumatic injury. A tendency for the development of brain aneurysms can be inherited, so family history is also a risk factor.

As many as 3 percent of those aneurysms rupture, resulting in a total of more than 30,000 people who are affected in the United States each year, the ASITN organization says.

The most common type of brain aneurysm is a sac attached to the artery by a neck, or stem. Often, this develops within a “vee” where one artery branches off from a larger one. The danger is that a burst aneurysm lets blood flow into the subarachnoid space surrounding the brain — a subarachnoid hemorrhage that damages brain cells and, if severe enough, leads to death.

“Sometimes, bleeding from a rupture stops fairly quickly — a warning leak

— giving us a window of opportunity for treatment,” Vinuela notes. “A burst site needs to be treated as quickly as possible to prevent additional rupturing. When additional rupture occurs, the mortality rate is about 75 percent.

“It’s even more desirable to treat aneurysms before they burst, if possible,” he adds. “Most unruptured aneurysms are found in the course of brain MRI or CT scans for other concerns. The complication rate for closing them off is very low, and treatment is well-justified in many patients.”

Guido Guglielmi’s Mission

The development of the detachable coil began with Guglielmi’s arrival in 1989. His father had died of a brain aneurysm and he wanted to find a way to deal with the disorder. Lacking the resources in Italy, he came to UCLA. His original idea was to use a powder to seal aneurysms off by causing the blood inside them to coagulate.

“I formed a research team involving Guido, Ivan Sepetka and myself in order to develop the first prototypes to be used in ruptured aneurysms,” Vinuela notes. Sepetka was an engineer with Target Therapeutics, a medical device company.

Guglielmi ultimately dropped the idea of developing a powder, and, at Sepetka’s suggestion, the group began working with the soft, platinum helical coils. Following animal tests, their first human case was a patient in 1990 with an aneurysm involving the cavernous sinus — nothing in

contact with the brain.

“We were elated with the results,” Vinuela says. “We presented our work to the American Society of Neuroradiology that year.”

Licensing, Variations, Limitations

Approved for use by the FDA in 1995, the Guglielmi detachable coil was licensed to Target Therapeutics (which was acquired by Boston Scientific Corp. in 1997), notes Emily Loughran, director of licensing at UCLA. Guglielmi and Sepetka were determined to be the inventors and were named on the patent.

“Since then,” Loughran says, “numerous companies have developed coils — today, there are more than 140 versions in varying sizes and characteristics. But the GDC has been the gold standard.”

Published in 2002, the International Subarachnoid Aneurysm Trial, a large-scale study of ruptured aneurysms in patients equally suited for coiling or surgery, found a 22.6 percent lower relative risk of death or significant disability after one year for patients treated by coiling. A follow-up study published in 2005 found that the benefit continues for at least seven years after the procedure. It also found that, while the risk of repeated bleeding is low with both techniques, it is slightly higher with coiling.

In fact, recanalization, or reopening of the aneurysm, was identified as a problem early on. “By the end of the ‘90s,” Vinuela says, “we recognized that 18 to 21 percent of aneurysms were recanalizing

— that is, their stems were reopening — particularly large ones with wide necks.”

Illustrations of coils in aneurysms usually depict them as completely filling the sacs, but actually they generally occupy no more than 30 percent of the aneurysms’ volume. The rest is filled with clotted blood. When an artery’s blood flow is strong, the pressure can push a coil from the neck into the body of the aneurysm, allowing blood to flow back into the sac and presenting the risk of re-rupture.

Solutions

Faced with these issues, the UCLA team went back to the lab and changed the size and radial force of the coil.

“Beyond this,” Vinuela notes, “we started looking at more sophisticated changes we could make to the GDC.” By the mid-1990s, Guglielmi had retired and returned to Italy, but Vinuela worked with fellow UCLA neuroradiologist Yuichi Murayama, M.D., to refine the GDC.

“Drs. Vinuela and Murayama coated the GDC with a biopolymer material,” Loughran says, “a polylactic acid that accelerates inflammation within the aneurysm. It speeds up clotting, eventually degrades and is absorbed by the body. By 1998 they had perfected a new, coated version called the Matrix detachable coil.”

While development of the Guglielmi coil was supported by Target Therapeutics, the Matrix coil was developed with National Institutes of Health funding. With Vinuela and Murayama designated as the

co-inventors and named on the patent, the Matrix device was licensed to Boston Scientific in 2000.

“With these changes in size, strength and materials,” Vinuela says, “the recanalization rate is down to 9 percent. At the present time, endovascular technology has dealt very well with small aneurysms.”

**“Most importantly,”
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a good feeling.”**

Surgery is still necessary for many brain aneurysm cases, but at medical centers like UCLA, the majority are treated by coiling — in Europe, coiling accounts for more than 90 percent of treatments, according to Vinuela. In large part the choice of the approach depends on the type and location of the aneurysm, the patient’s general health and the patient’s preference.

New techniques are being explored for large aneurysms. One innovation uses balloons to divert blood flow from the aneurysm while coils are placed within it. Another technique utilizes combinations of stents and coils. However, the newest idea is to use stents by themselves as flow diverters for very large aneurysms so as to stimulate clotting without the use of a coil at all.

“Coils are very successful,” Loughran notes. “Studies of unruptured patients have indicated that coiled patients require much shorter hospital stays, experience dramatically shorter recovery periods and report far fewer new symptoms afterwards than surgical patients.

“These factors are good for both patients and our society. A study in California found both adverse outcomes and hospital costs to be considerably lower with coiling than with surgery.”

Vinuela adds: “We started working on these devices 30 years ago and I don’t remember stopping for a minute. It’s been an extraordinary, unique experience.

“Most importantly,” he says, “we can look back and see that these devices have helped half a million people, all over the world, cope with problems that otherwise would have been fatal or disabling to many of them. That’s a good feeling.”

— *Ralph N. Fuller*

Industry and Academic Research in Regenerative Medicine Leads to Biological Treatment for Damaged Joints

Professional athletes are well-aware of the damage their sport may wreak on their bodies. So too are many of the millions of weekend warriors, overweight and others whose age, activities and medical conditions may one day lead to pain brought on by degradation of the cartilage in the linings of their joints.

Many with the onset of degenerative joint disease and osteoarthritis will find respite in a range of symptom-relieving products, from physical therapy and orthotics to anti-inflammatory and analgesic over-the-counter medications. Seniors, who are in a more advanced stage of this condition, may require surgery to replace the damaged or diseased joint with a prosthesis.

Then there are the individuals with big cartilage lesions who no longer find pain relief from traditional treatments but are too young for total joint replacement. For this group of patients who are in the prime of their life, there are few available options today.

It is in this space, between symptom-relieving products and surgical treatment, where industry and academia are conducting regenerative medicine research to develop a biological solution that might stem the projected six-fold increase for total knee replacements by 2030 cited in *Health, United States, 2009*, by the Centers for Disease Control and Prevention.

One possible biological solution is Chondromimetic, a collagen scaffold developed by the British medical technology company Orthomimetics. As a porous, bioresorbable tissue regeneration scaffold, it stimulates bone and cartilage growth when implanted into the knees and other joints, which could offer a more effective, economical, easier and less painful means of treatment than current methods. A research group is conducting clinical trials in Europe to gather data on its ability to help regenerate articular cartilage and provide durable solutions for degenerative joint disease and osteoarthritis.

Groundbreaking Transatlantic Collaboration

Orthomimetics, part of the Belgian biotech company TiGenix since December 2009, is a relatively young academic spinout with a list of accomplishments:

- Chondromimetic received CE Mark approval ahead of schedule, which allows the company to market its line of bioresorbable implants for bone or soft tissue repair in the European Union.
- Orthomimetics was featured in the “Killer 50” list of the most “disruptive technology” businesses in Eastern England for 2009. Unveiled by



Chondromimetic stimulates bone and cartilage growth when transplanted into knees and other joints.

Business Weekly in association with Mathys & Squire Intellectual Property, the Killer 50 companies are chosen on raw technology that has either achieved commercial success or promises to do so.

- Andrew K. Lynn, Ph.D., Orthomimetics' founder and chief executive officer, who successfully made the transition from academic to entrepreneur, received the top European Award for University Entrepreneurs in Chemistry and Materials in the inaugural Academic Enterprise Awards 2008.

Orthomimetics' products are based on a proprietary technology platform, with patent-protected technology that was developed during a groundbreaking collaboration between the University of Cambridge in Cambridge, United Kingdom, and the Massachusetts Institute of Technology (MIT), in Cambridge, Mass., under the Cambridge-MIT Institute (CMI) alliance. CMI was an experimental transatlantic collaborative program between two of the world's leading research universities. It was launched in 2000, funded by the British government, in recognition of MIT's commitment to share its successful approach to connecting public research with innovation and economic growth.

"Orthomimetics brings a new dimension to the treatment of joints thanks to its heritage in this trans-Atlantic collaboration between our two world-leading academic institutions and its researchers who have contributed more than 30 years of experience to the repair of bone and soft tissues, respectively," says Margaret

Wilkinson, technology manager at Cambridge Enterprise Ltd, the commercialization arm of the University of Cambridge that helped Lynn spin out the company, and, on behalf of CMI, negotiated the license.

As the first product to come out of this collagen biomaterials platform, Chondromimetic is designed to stimulate regenerative repair in millions of young and aging patients who suffer from damaged joint surfaces and bony defects caused by degenerative diseases such as osteoarthritis, trauma or surgery.

A Marriage of Two Technologies

While working on the CMI project as a doctoral student at University of Cambridge, and collaborating with a team at MIT, Lynn played a leading role in developing the technology platform on which Orthomimetics' products are based.

He co-founded Orthomimetics with a core group of CMI-funded researchers who are pioneers in the fields of artificial bone and artificial skin:

- Artificial-bone pioneer William Bonfield, Ph.D., professor of medical materials in the Department of Materials Science and Metallurgy, University of Cambridge
- Lorna Gibson, Ph.D., Matoula S. Salapatas professor of materials science and engineering, MIT
- Ioannis Yannas, Ph.D., professor of mechanical engineering, biological engineering, and health sciences and technology, MIT, who developed a scaffold for the regeneration of skin that is now in clinical use
- Brendan Harley, Sc.D., a graduate of MIT and now an assistant professor in the Department of Chemical and Biomolecular Engineering at the University of Illinois at Urbana-Champaign

"This really ended up as a marriage of two technologies: at MIT we had an expertise in the fields of tissue engineering and artificial skin, while Professor Bonfield at Cambridge and his team of international researchers had an expertise in bone replacement and biomaterial innovation," says Gibson, who knew of Bonfield and his work and had firsthand knowledge of the University of Cambridge system as she did her doctoral degree there.

The CMI-enabled collaboration began when the team of academic researchers and students decided to build a biological scaffold based on an existing method to produce a skin scaffold that could provide support for tissue regeneration in the areas of orthopedics and regenerative medicine. The result was a technique to mineralize the collagen scaffold by add-

Estimates for Osteoarthritis*

- Global data estimates the prevalence rate of 10.1 percent for osteoarthritis and about 76 million patients worldwide (mainly in the United States, Europe and Japan).
- In the United States, 35 million persons suffer from osteoarthritis resulting in 11 million annual visits to doctors for consultations.
- About 40 million Europeans suffer from osteoarthritis.
- The annual cost of joint replacements, hospitalizations, disability and joint devices to society is estimated at \$30 billion.
- The average annual cost of an osteoarthritis patient is \$5,700, including \$2,600 in direct costs.
- About 1 in 5 of world's population lives with chronic pain.

* *U.S. Department of Health and Human Services, Agency for Health care Research and Quality*

Joint Replacement Costs*

- In the United States, about 400,000 patients have one or more joints replaced each year.
- Cost of a new hip or knee joint is \$30,000 to \$40,000.
- Out-of-pocket patient contribution is \$3,000 to \$4,000.
- Total cost of hip replacement is \$19 billion.
- Total cost of knee replacement is \$26 billion.
- 27 percent of hip replacements and 69 percent of knee replacements are due to obesity.

* *National Institute of Arthritis and Musculoskeletal and Skin Diseases*

ing calcium and phosphate to mimic the structure of bone, which then led to the development of a two-layer scaffold to regenerate both bone and cartilage.

Orthomimetics' products are based on this leading collagen biomaterials platform they developed for the production of scaffolds for cartilage, meniscus, ligament and tendon repair. Orthomimetics' technological advantage lies in the patent-protected ability to combine three natural biomaterials — collagen, glycosaminoglycans and calcium phosphate — into bioresorbable tissue regeneration scaffolds.

As the first product to come out of this collagen biomaterials platform, Chondromimetic is designed to stimulate regenerative repair in millions of young and aging patients who suffer from damaged joint surfaces and bony defects caused by degenerative diseases such as osteoarthritis, trauma or surgery. It was shown in a head-to-head preclinical trial to outperform leading synthetic products, and a simple and accurate delivery system has been designed and tested by surgeons. TiGenix expects Chondromimetic to join a growing number of market-ready products in the field of regenerative medicine, which the U.S. Department of Health and Human Services in 2006 cited as a technology that is "desperately needed to combat rising health care costs."

The Art of Reaching Consensus

As the first spinout from CMI, Orthomimetics licensed the exclusive rights to four patents covering the revolutionary

technology that had resulted from the team's research and was funded by the University of Cambridge and MIT.

The negotiation on the licensing agreement with CMI was a delicate process, due to opinions about the terms for an exclusive license, especially on future revenue streams. Traditionally, Cambridge had taken equity stakes in its startups, while MIT had rights not only to equity but also to milestone fees, royalties and license fees. Lynn and his co-founders wanted to make sure the right balance was struck between early milestone payments and equity or other compensation linked to progress when the company was more mature.

Eventually, the parties succeeded in finding licensing terms that worked for everyone. And, despite the delicate process of the license negotiations, all involved credit CMI and the collaboration it fostered as the reason they "gathered in the same room, put all the technologies together" and launched a spinout company.

"I think our success is due in large part to CMI, which enabled an international team of academics with a prior track record of producing commercially successful innovations to come together and develop our new technology platform," says Lynn.

Technology Transfer Offices Give an Assist

Lynn gives Cambridge Enterprise and the Technology Licensing Office at MIT a lot of credit for helping the startup gain a

solid financial footing.

"They did a good job of pointing us in the right direction," Lynn says. "Our story was good, and we had a great business case. But first and foremost, we had to learn how to talk to investors, which the technology transfer offices facilitated."

Building on this support, they established links with venture capitalists, business angels and potential company directors in both Cambridge communities, suc-

Lynn gives Cambridge Enterprise and the Technology Licensing Office at MIT a lot of credit for helping the startup gain a solid financial footing.

cessfully raising an initial funding round of \$8.5 million (£5.65 million) in 2007 from the United Kingdom equity firms Schroders Investment Management Ltd, Oxford Capital Partners Sloane Robinson Private Equity and a group of private investors of Eden Financial. In 2008, the company received funding from United Kingdom funding bodies; \$1.5 million (£747,000) from the Technology Strategy Board for the commercial development of the company's second commercial product, LigaMimetic; and a \$953,440

(£600,000) Technology Strategy Board grant to support a research and development project for improving joint tissue regeneration.

Today, the onetime CMI spinout is part of TiGenix. The Belgian developer of regenerative medical products that treat damaged and diseased joints now has two complementary products to market in the European Union — its own Chondrocelect, a cell-based product that helps to regrow cartilage in the knee, and Orthomimetics' Chondromimetic, a scaffold for the repair of damaged joint surfaces and underlying bone defects.

"This is a really sensible and exciting way forward," says Lynn, who is now the chief business officer at TiGenix. "I'm delighted with this development because it is the culmination of the Orthomimetics story."

Orthomimetics is a successful technology transfer story that is taking the next step in delivering innovative commercial products in the field of regenerative medicine.

— *Dave Perilstein*

National Center for Research Resources

Clinical and Translational Science Awards: Accelerating Bench-to-Bedside Research to Improve Health

“You need to take your kid to a pediatric neurologist.” Few words are more terrifying to a parent, yet thousands must face, every day, diagnoses ranging from life-threatening brain tumors to the life-altering Tourette syndrome (TS).

Changing heart-stopping terror to heart-lifting hope for people of all ages facing health issues lies at the core of the Clinical and Translational Science Award (CTSA) program. Administered by the National Center for Research Resources (NCRR), part of the National Institutes of Health (NIH), the CTSA program is designed to transform how biomedical research is conducted and currently supports a national consortium of 55 medical research institutions.

“Our aim is to transform laboratory discov-

eries into better preventions, treatments and cures as quickly as possible,” says Barbara Alving, M.D., NCRR director.

CTSAs Support Leading-Edge Research and Collaborations

For families coping with TS — a chronic neurological disorder characterized by motor and vocal tics — there is now new hope thanks to the work of CTSA-funded researchers at the Yale Schools of Nursing and Medicine. In a study also funded in part by the NIH’s National Institute of Mental Health, researchers have developed a behavioral intervention approach to reduce chronic tics in children and adolescents with TS.

The study results, published in the May 19 issue of the *Journal of the American Medical Association*, found that 52.5

percent of the children receiving a behavioral intervention developed at Yale showed improvement. Further, the degree of improvement with the behavior intervention — which taught the kids how to recognize emotional triggers — was similar to that found in recent anti-tic medication studies.

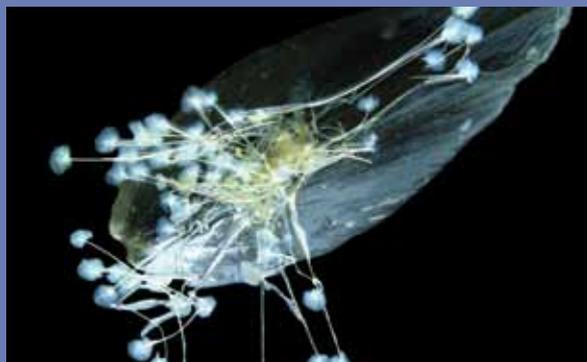
Until now, the only treatment available for TS, which is found in six children per 1,000 according to the Yale researchers, is antipsychotic medications, which often have side effects that limit usefulness in children.

Just as important, the study investigators said, is that this treatment expands the range of clinicians who can treat TS because medication is no longer the only option.

“Our study is just one example of how the CTSAs are helping to advance research in many disease areas and conditions,” says Larry Scahill, Ph.D., CTSA principal investigator. “By encouraging collaboration across disciplines, CTSAs help spark innovative approaches to tackle research challenges.”

CTSAs Enhance Infrastructure and Science Advances

At the Northwestern University in Chicago, a 2008 CTSA recipient, faculty



The foot of the common mussel (*Mytilus edulis*) produces sticky proteins that allow the organism to glue itself onto rocks, keeping it from being tossed around by waves. Researchers at Northwestern University in Chicago are developing synthetic materials with properties similar to these mussel proteins for a variety of medical applications.

and staff are using the CTSA support to improve collaboration in a variety of ways. One of the most successful programs, says Phillip Greenland, Ph.D., director of the Northwestern University Clinical and Translational Sciences Institute (NU-CATS), is the university's recent investment in biomedical informatics. As part of this infrastructure, an Enterprise Data Warehouse (EDW) enables researchers to mine all the data that is available about patient outcomes from Northwestern Memorial Hospital and other affiliated networks.

"Since we received the CTSA in 2008, we've invested a fair amount in biomedical informatics," Greenland says. "We recognize that the future of clinical research is very heavily dependent on the availability of electronic data and storage and the ability to share that information across the research community in a safe and highly secure environment."

Giving scientists access to patient information opens up whole new worlds of possibilities as researchers can use real-world data for outcome and comparative effectiveness research.

Greenland cites as an example a Northwestern neurologist who used the EDW to question the protocol of prescribing anti-seizure medication to stroke survivors to prevent seizures. He discovered, based on the real-world data, that patients on the medications did not have better outcomes, and in fact, they did worse.

NUCATS also provided pilot funding for

www.betterworldproject.net

Phillip Messersmith and his colleagues to develop synthetic materials that mimic proteins produced by sea mussels and can stick to different surfaces even in wet environments. Messersmith has been testing these mussel-based "glues" to seal tears in amniotic sacs, a complication of some pregnancies.

CTSAs Foster Public-Private Partnerships to Accelerate New Health Options

The theme of collaboration is also strong at the University of Pennsylvania (Penn), which received a CTSA in 2006. There, the Office of Corporate Alliances (OCA) — the first of its kind for a medical school — is forging industry partnerships as part of its objective to help move medical advances more quickly to the marketplace.

According to Terry Fadem, OCA managing director, having the relationships in place *before* an innovation needs support, financial or otherwise, means it can move much more quickly through the pipeline process. He cites Penn's School of Medicine's long-standing relationship with Pfizer Inc., one of the world's largest research-based pharmaceutical companies, as an example of how public-private partnerships can be a win-win.

Since 1985, Pfizer has sponsored more than 130 clinical studies at Penn across 10 therapeutic areas, including oncology, psychiatry and infectious diseases. In addition to the financial support, the relationship with Pfizer gives Penn researchers something even more valuable: time, or rather, a decreased amount of it.

"Established industry-public alliances reduce the time it takes to move an idea forward," Fadem says.

"Because Penn physicians are already familiar with Pfizer scientists, we talk to each other, making it easy to quickly evaluate a proposal," he continues. "That means we can remove some time delays from the process. For example, about a year ago, we evaluated a proposal about a cancer drug and from there, we were able to initiate trials in 21 different sites within months. It was launched in January and fully enrolled in May."

Based on the success of initiatives such as the public-private partnerships, Fadem says, "The CTSA program has been immensely positive."

Another example of a successful partnership is The Scripps Translational Science Institute, a CTSA consortium member near San Diego, which partnered with wireless telecommunications company Qualcomm to launch the world's first physician-scholar training program on wireless and mobile health care research in 2009.

"Within the CTSA consortium, Scripps is positioned to become an invaluable resource for this emerging, high-impact field of research," Alving says.

CTSAs Engage Communities in Clinical Research

Meanwhile, the University of Pittsburgh (Pitt) is leveraging its CTSA, also received in 2006, in a variety of collaborative ways as well. Margaret C. McDonald, Ph.D.,

About the Clinical and Translational Science Awards

Led by the National Institutes of Health's National Center for Research Resources, the Clinical and Translational Science Awards (CTSA) program was launched in 2006 to accelerate research from laboratory discoveries to improved patient care. For more information, visit www.ncrr.nih.gov/ctsa.

assistant professor of epidemiology and associate vice chancellor for academic affairs, health sciences, Pitt, reports that its Clinical and Translational Science Institute (CTSI) has supported 1,500 investigators from more than 75 disciplines in 12 different schools.

"We've tracked that work and so far we've seen more than 46,000 citations in peer-

reviewed journals from 2007 through April 2010," McDonald says. "That's a significant contribution to the knowledge base."

Other ways that Pitt's CTSI is collaborating and making a difference is through its community outreach efforts. Whether it is using a mobile lab to reach more than 5,000 middle and high school students or renting a booth at a local Race for the Cure event, McDonald says the CTSA has supported the CTSI's efforts to reach the community on a grass-roots level. The results are paying off there too.

"Our community outreach efforts have produced more than 130 programs about health-related issues that were attended by 285,000 people," she continues. "We want to engage the communities as real partners and work with them in their own neighborhoods."

Yet another way the CTSI is reaching out to the community is by starting a research registry — which has acquired 14,000 members since its inception in 2008 — that matches volunteers with researchers and educates the public about the importance of participating in studies.

CTSAs Help Train a New Generation of Clinical and Translational Researchers

As mandated for all CTSA institutions, the Pitt CTSI also fostered the growth of a new "academic home" in clinical and translational science for the university, facilitating cross-pollination between different areas of study.

"Pitt's secondary appointment program has been approved for 162 faculty members from 46 disciplines in 10 different schools," McDonald explains. "We've always been a pretty interdisciplinary institution, but the CTSA funding has enabled us to bring in even more investigators."

Pitt, like many of the others in the CTSA consortium, also has established a doctoral program in clinical and translational science, for which it encourages health care research diversity aimed at building the cadre of underrepresented populations in that field.

In all, the aim is to accelerate bench-to-bedside research across many disease areas and conditions, in unprecedented ways, to improve health.

— Lisa Richter



In 2009, the University of Pittsburgh's Clinical and Translational Science Institute unveiled a new mobile science lab that includes 26 workstations and sits inside a 70-foot tractor-trailer. The result of collaboration between two NCRR-funded programs — a Clinical and Translational Science Award and a Science Education Partnership Award — the new lab will provide precollege students in western Pennsylvania with hands-on opportunities to learn about the latest science research while using state-of-the-art lab technology.

University of Chicago

Minichromosomes Carry the Key to Improved Crops, Better Yields

The projections are dire. “World Population in 2300,” a report released by the United Nations’ Expert Meeting on World Population in 2004, predicted that the planet’s population will grow nearly 50 percent — to more than 9 billion people — by the year 2075.

“Reaping the Benefits,” a study released by the United Kingdom’s Royal Society in 2009, concluded that current food production systems will be unsustainable for future needs, with few opportunities for increasing crop-producing lands without inflicting environmental damage.

“In the future, the ability to grow more — and better — crops on existing farmland will be essential to meet expanded population demands,” says Daphne Preuss, Ph.D., chief executive officer (CEO) of Chicago-based Chromatin Inc. By altering plants’ genomes, today’s researchers can improve production on limited acreage with crops that can be planted closer together and are more resistant to pests and diseases.

“But these plants have been developed by adding genes incrementally — a very slow process,” she says. “The technology we have developed — minichromosomes — lets us add a larger number of genes simultaneously and breed varieties containing those changes much more quickly.”

Laboratory Research

Minichromosome (or gene-stacking) technology grew from a discovery by Preuss while working with a small mustard plant called *Arabidopsis thaliana* in her laboratory at the University of Chicago, where she served as a professor of molecular genetics and cell biology.

“Daphne found a mutation with characteristics that let us develop a genetic mapping technique for plants,” notes Gregory Copenhaver, Ph.D., who began working on the project with Preuss as a postdoctoral student in 1996. “We devised a technique for identifying the centromere, the spot on chromosomes that a cell grabs onto when it needs to move them during division. We were able to figure out how to catch hold of the cen-

tomere ourselves and use it to work with other plants.”

Building Chromatin Inc.

The question was what to do with those discoveries. During the course of the 1990s, the University of Chicago secured the rights to them with a series of patents. “To take it beyond that,” notes Heather Walsh, Ph.D., project manager in the university’s Office of Technology and Intellectual Property, “Daphne and Greg believed they needed to commercialize it. But they felt that if gene-stacking was simply licensed to a single big organization, their work would be relegated to a limited set of plant products. They thought a smaller operation would be able to make the technology more broadly available for use with a multitude of crops.”



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By altering plant’s genomes, researchers can improve production on limited acreage with crops.

Preuss and Copenhaver founded Chromatin Inc. in 2001, with the university licensing the technology to the new company. The name draws on the DNA and protein material that make up a cell's chromosomes.

Copenhaver put his pursuit of an academic career temporarily on hold to serve as president, eventually going back to academia as an associate professor with joint appointments in the Department of Biology and the Carolina Center for Genome Sciences at the University of North Carolina. He continues to serve Chromatin as a consultant, working through teleconferencing and monthly trips to Chicago.

Preuss, who has now left the University of Chicago, has been leading Chromatin for the past three years, serving as president and CEO of a company that has grown to more than 30 employees and facilities at several sites. In its primary DNA workshop in Chicago, the company builds and analyzes chromosomes. At labs in Urbana, Ill., researchers focus on plant growth and manipulating plant tissues and DNA.

Additionally, Chromatin operates field stations in other locations where higher-yielding crops are bred. Among a series of additional patents secured by the company is one in 2007 granting it exclusive minichromosome rights in all plants.

Autonomous Chromosomes

"People have been able to alter plants by putting genes in chromosomes for several decades," Copenhaver says, "but that's essentially a random approach. When you

place a new gene within a cell's nucleus you can't be sure where it's going to land. First, the gene must insert itself into an existing chromosome. The position it lands in may affect its functioning. Or, it might disrupt other genes during insertion."

Preuss, who has now left the University of Chicago, has been leading Chromatin for the past three years, serving as president and CEO of a company that has grown to more than 30 employees and facilities at several sites. In its primary DNA workshop in Chicago, the company builds and analyzes chromosomes.

As a consequence, researchers often have to work with thousands of plants in order to find a few that achieve the sought-after alteration. And since the point is that new traits have to be successfully passed on to succeeding generations, it's a long, labor-intensive — and expensive — process.

Preuss and Copenhaver thought a better approach would be to create their own chromosome, stack it with the genes they

wanted and insert it into the cell.

"We were able to identify the centromere region in corn and work from there," Copenhaver says. "We tested a lot, using marker genes that fluoresce under ultraviolet light. We could see if the genes were being expressed and make sure they were autonomous — that they didn't insert themselves into existing chromosomes."

"Being autonomous solves a lot of problems," Preuss adds. "It makes it easier to pass on traits. It makes breeding new plants faster, better, cheaper and more predictable."

It's still an empirical process. As the Chromatin researchers build up a catalog of minichromosomes, they can compare traits and make better predictions as to what a combination of genes is going to do. Testing is still necessary but the ability to predict results shortens the process.

They reported their results in corn in the journal *PLoS Genetics* in the fall of 2007; the company has also had ongoing programs in a number of other crops, including soybean.

Corporate Licensing

Initial research was supported by funding from the university; private foundations; the National Science Foundation; and the Consortium for Plant Technology Research, a Department of Energy/industry-funding collaboration. As a company, Chromatin was launched with venture capital and federal Small Business In-

novation Research (SBIR) financing. It subsequently has gone through additional rounds of venture capital and SBIR funding. And, it receives revenues from its licensing contracts with agricultural companies.

These include a 2007 collaborative agreement with agricultural giant Monsanto Co. allowing that organization to adapt Chromatin technology for its research crops. Also in 2007, Chromatin granted Syngenta Biology Inc. a nonexclusive license to use the technology for corn and soybeans.

Other agreements have followed — with Dow AgroSciences for research on combining Chromatin minichromosomes with Dow technology and with Bayer Crop-Science for its use in cotton plants. An exclusive agreement with Syngenta lets that company pursue minichromosome technology in sugarcane.

“Our first mission has been developing crops that leading agricultural companies are pursuing today — crops like soybeans that farmers can plant more closely together to increase yields, allow more efficient use of pesticides or are resistant to drought,” Preuss says.

Preuss, who has now left the University of Chicago, has been leading Chromatin for the past three years, serving as president and CEO of a company that has grown to more than 30 employees and facilities at several sites.

“In the future, minichromosomes can bring about improved types of crops — foods high in Omega 3 oils, cottons with different types of fibers, new medicines and biofuels,” Preuss continues. “Manufacturers have been seeking to derive insulin from safflower plants and antibodies from aquatic plants. Crops like sugarcane and sawgrass offer the prospect of becoming very productive, efficient biofuel sources.”

That’s why the importance of minichromosomes’ capacity for stacking unlimited numbers of genes can’t be understated, Copenhaver says.

“Science’s ability to discover new genes and be sure what they’re doing has outstripped our ability to use them,” he says. “Most companies have a lot more genes than they’ve been able to implement. This opens new doors for making important advances available to people.”

— *Ralph N. Fuller*

Shingles Vaccine Outwits the Suffering of a Painful Disease

Nobody who has shingles forgets the experience — an outbreak of often-painful blisters in a belt-like band on the torso or face. Worse, while the shingles itself may clear up in a matter of weeks, for 1 in 10 victims, the pain can linger for many weeks, even months, the consequence of inflamed nerves.

For some people, the effect can be incapacitating, making actions as simple as walking utterly painful and dictating lengthy confinement in bed. Some victims find their bodies so sensitive to pain that they can't stand to be touched or even to wear clothes.

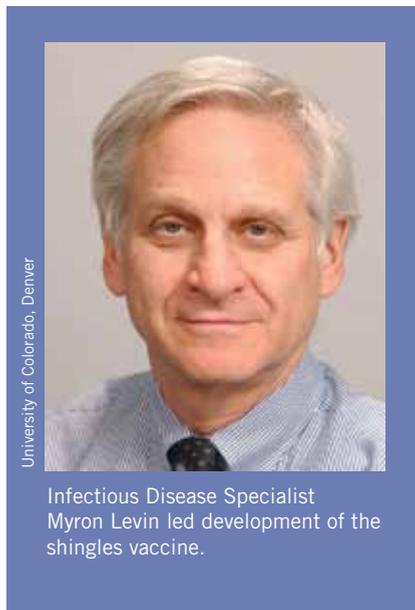
The irony is that shingles is directly linked to a childhood disease most people remember as having coasted through — chicken pox. In childhood, an attack of the varicella-zoster virus usually meant a couple of weeks with spots all over the body, itching and perhaps a period of “feeling poorly.” And, probably, ice cream.

But even though the chicken pox clears up, the varicella-zoster virus doesn't go away. It migrates from the skin up the nerves to nestle in nerve roots, hiding in the body for decades before coming back with a vengeance.

“Even for people who breezed through chicken pox as children, shingles surfaces in as many as 1 in 3 adults who've

had chicken pox — most of them over 60,” says infectious disease specialist Myron Levin, M.D., a professor of pediatrics and medicine at the University of Colorado Anschutz Medical Campus and the Children's Hospital in Denver who led development of a vaccine for shingles. That vaccine, Zostavax, was licensed for sales by the U.S. Food and Drug Administration in 2006.

“Most people who've had chicken pox won't get shingles, but those who do amount to about 1 million sufferers each year,” Levin says. “And for many of them, the misery far exceeds the suffering associated with ‘breezing through’ chicken pox.”



A Migrating Virus

Once the embedded varicella-zoster virus becomes active and moves back along the nerves to the skin to cause blisters, the issue is not so much itching as it is pain, burning, numbness or tingling caused by inflamed nerves.

“More importantly,” notes John Grabenstein, Ph.D., senior medical director of adult vaccines at Merck & Co. Inc., “while a shingles attack — the rash and its accompanying pain — typically lasts three to five weeks, about 10 percent of patients experience postherpetic neuralgia, the intense, chronic pain that can continue long after the blisters have disappeared.” The definition of postherpetic neuralgia is pain of significant intensity that continues at least 90 days after the rash began.

“The pain is the worst part,” Levin adds. “It's the main reason you want to get the shingles vaccine. The vaccine reduces the prospect of intense pain tremendously.”

There are other potential consequences. Unlike chicken pox, in which the rash is scattered all over the victim's body, the shingles rash is limited to the area of skin that one nerve is responsible for, usually in a belt-like band on one side of the face or torso (the term *shingles* comes from the Latin word for *belt*).

Shingles anywhere presents a danger of

bacterial skin infection and a risk of permanent nerve damage that can make the pain resistant to treatment. But shingles on the face compounds this with risks of infections that can cause blindness, hearing and balance problems, and facial paralysis.

Like Disease, Like Vaccine

Just as shingles the disease grows out of chicken pox, the Zostavax vaccine is a legacy of the chicken pox vaccine — the Varivax vaccine — developed by a Japanese physician in the 1970s. Levin was involved in work at Colorado to test the earlier vaccine for its safety before it was approved for use in the United States in 1995.

“He was familiar with the varicella-zoster virus,” notes Rick Silva, Ph.D., director of the Technology Transfer Office at the University of Colorado. “He reasoned that a version of the childhood vaccine could be used in older people to prevent shingles.”

While there are antiviral treatments for shingles, these are imperfect and it’s far preferable to prevent the disease with Zostavax. The duration of a bout of shingles can sometimes be shortened with early antiviral therapy, but such therapy is often delayed, and shingles is difficult to treat once it is established. Painkillers like oxycodone may become necessary.

“For a long time,” Levin says, “it wasn’t clear why the virus resurfaces after so much time, and so often in people over age 60. But we pretty much know that as we age, our cellular immunity to the

varicella-zoster virus — as to many other infections — wanes. The likelihood is that the virus is kept quiet by the body’s immune system, and, once the immune protection drops to a certain level, the virus is able to break out as shingles. And, the older you are when you develop shingles, the greater your chance of getting postherpetic neuralgia.”

But even though the chicken pox clears up, the varicella-zoster virus doesn’t go away. It migrates from the skin up the nerves to nestle in nerve roots, hiding in the body for decades before coming back with a vengeance.

Similarly, shingles can be a problem for younger patients whose immune systems are compromised by other diseases or treatments.

Same Vaccine, Higher Dosage

The concept for developing the new vaccine was that the chicken pox vaccine could prevent shingles in adults — but that much larger dosages would be necessary.

“The virus in the shingles vaccine is

exactly the same as in the vaccine for chicken pox but it’s more potent,” Levin notes. “Our initial study involved 240 adults, focusing, in large part, on testing different amounts of virus in the vaccine.

“This wasn’t easy on the volunteers in the study,” he adds, “since the vaccine we had at the time required as many as four shots at once to give the largest dose tested.” In the end, the dosage for successful shingles vaccine was set at 14 times that of the chicken pox vaccine — in one small shot.

To that point, Levin’s research was supported by National Institutes of Health funding, but he then approached Merck, the only company licensed to produce the chicken pox vaccine for use in the United States.

The next step was a large-scale trial, and Levin proposed partnering with the Veterans Administration’s Cooperative Studies Program in a study that would involve some 38,000 men and women aged 60 or older. The Shingles Prevention Study was also supported by the National Institute of Allergy and Infectious Diseases, and by Merck, which provided the vaccine. The tests began in 1999, but the results weren’t clear until 2005.

“The bottom-line answer was that the vaccine would prevent shingles in about 50 percent of the people who received it,” Levin says. “More importantly, it would prevent or reduce chronic pain by some 67 percent among people who did get shingles.

“That’s a very significant reason to get the shot.”

Larger Benefits

Once approved, the new vaccine was licensed exclusively to Merck. The patent is held jointly by Merck and the university.

“On the individual level, this is an important vaccine,” says the University of Colorado’s Silva. “In broader terms, it holds the potential of reducing shingles-related doctor visits in the United States each year by perhaps 300,000 and hospitalizations by 10,000. That would be a savings of as much as \$100 million spent on shingles-related care in the United States annually.”

Because it’s estimated that there are some 50 million people over 60 in the United States, and Merck has shipped more than 6.5 million doses, there’s still a long way to go in protecting the population.

Because it’s estimated that there are some 50 million people over 60 in the United States, and Merck has shipped more than 6.5 million doses, there’s still a long way to go in protecting the population.

“It’s a general phenomenon,” Grabenstein says, “that other than flu shots, adults don’t give the attention to vaccines for themselves that they do for their kids or grandkids. They should. Shingles is a miserable illness that can be minimized, possibly prevented.

“People who’ve had chicken pox are vulnerable to shingles and should get the Zostavax vaccine when they reach the appropriate age of 60 years. It can make life better for a lot of them.”

— *Ralph N. Fuller*

Shear Thickening Fluid Fabric Technology Promises to Save Lives, Protect Bodies and Much More

The improvised knife was a blur in the convict's hand. It struck the prison guard squarely in the back, but the blade never penetrated, thanks to the light, flexible vest the guard wore.

The 76-year-old woman slipped on the ice and slammed to the sidewalk, but no bones were broken. A special garment helped absorb the energy of the fall and protect her fragile hip.

A football quarterback cuts through the line and avoids tacklers with astounding dexterity. His new lighter, closer-fitting helmet provides better protection than the old one but saves precious weight for greater agility on the field.

What do all these incidents have in common? All three show the potential of shear thickening fluid (STF) fabric technology, which was developed at the Center for Composite Materials at the University of Delaware (UD) and is now moving into commercial application for ballistic, impact and puncture protection.

The Origin of STF Technology

"Shear thickening fluids have a peculiar property," says Norman J. Wagner, Ph.D., and chair of the Chemical Engineering Department at UD. "They act like a liquid at rest but thicken quickly or behave like a solid when subjected to mechanical

stress. So in some ways, a shear thickening fluid behaves a bit like the clutch on your automobile seat belt. If you pull the belt slowly, you can slide it out to the length you need. But if you yank the belt quickly, it locks in place and won't move.

"These liquids have been around forever," he adds. "The best-known example is corn starch. Drop some in warm water, stir it and — bingo! — it thickens."

While Wagner and his students didn't invent shear thickening fluids, since the early 1990s they have been doing basic research into them. Funded by the National Science Foundation, they have been investigating colloidal suspensions — fluids with particles in them — trying to understand their basic physics and chemistry.

"Our group was one of the first to discover the science behind how and why shear thickening happens and then to be able to use that knowledge for engineering," Wagner says. "We've looked at the problem from both sides. Sometimes — like when you're pumping a fluid that is loaded with particles — you don't want shear thickening to happen, and you look for ways to prevent it. Other times, you want shear thickening, and you want to tailor the way in which it happens."

Body armor, for example, is an application in which shear thickening would be an advantage. The problem with conventional body armor is that, to provide protection against higher energy bullets, additional layers of ballistic fabric must be used. As the energy of the bullets



University of Delaware researchers discovered a shear thickening fluid that can be applied to ballistic fabric allowing it to withstand bullets, knives and other weapons.

rises, so does the number of layers of ballistic fabric needed to provide protection. Eventually, the ballistic vest becomes extremely thick, stiff and bulky, and people stop wearing them because they are so uncomfortable. Further, the body armor that can stop a bullet from a handgun won't necessarily be able to stop a penetrating object like an ice pick that can work its way between the threads of the ballistic fabric.

The Invention of STF Fabric

What Wagner and his team discovered was that you could take extremely finely divided silica (submicron-sized particles, with a surface area of hundreds of square meters per gram), suspend it in water or polyethylene glycol and apply it to ballistic fabric made from Kevlar or other high-performance fibers, and now you have an STF fabric that instantly stiffens, by locking the fiber network, on impact. When you apply the STF treatment to the ballistic fabric, it becomes more effective. That means you can reduce the number of layers needed to provide a particular level of protection, which reduces the weight, increases the flexibility and makes the body armor more wearable.

Further, the shear force causes the suspension to lock the threads in place, so that a penetrating object, like an ice pick, can no longer get through.

Licensing the Technology

"The key UD STF-related technology that we have already licensed is an STF treatment that can be applied to many fabrics — Kevlar, nylon, polyester — to

improve their performance," says Bruce Morrissey, director of technical development in the Intellectual Property Center at UD's Office of Economic Innovation and Partnerships (OEIP).

Because STF fabric technology offers so many potential uses, identifying the full scope of potential products is challeng-

It's Butler's view that the marketplace is barely at the tip of the iceberg in terms of potential applications for STF fabric technology. Beyond protection for police, soldiers, prison guards and the like, there are applications in heavy industry, sporting goods, energy absorbing pads and even blast containment.

ing. "One of the most prominent features of this technology is that it can be tailored for various applications," says Brad Yops, assistant director of UD's Intellectual Property Center. "So we've taken a team approach to characterize the various business opportunities where Kevlar or ballistic-type fabrics, as well as traditional woven fabrics such as nylon and polyes-

ter, are used in the real world."

Ultimately, licensing will benefit not just end users, but the university and its researchers as well. "We have several motives behind our desire to license," Morrissey says. "First, the university and researchers like Norm Wagner really want to get their technology, their ideas, into the public arena for public benefit. The second is to generate a revenue stream. One-third goes to the inventors, a third to the College of Engineering and Center for Composite Materials, and a third to UD's tech transfer office to fund proof-of-concept work for other licensable technology.

"In due course," Morrissey says, "we settled on a preferred supplier — Barrday Inc. — a textile supplier based in Cambridge, Ontario, Canada, that invested in basic research related to this technology and that could supply STF-treated fabrics to just about any company that wants to produce a product based on STF technology."

Responsibility for the economic development of the STF technologies lies with the university's OEIP. "The office functions as a communication gateway that provides the outside world with access to the university's knowledge-based assets, and UD personnel and students with a window to opportunities outside the university," says OEIP Director David S. Weir.

Moving the Technology Forward

"Originally, we were partnered with the university and a third party that had licensed STF technology for ballistic defense," says Keith Butler, vice president

of sales and marketing for Barrday Inc. “But when the ballistic license ended, we had already invested heavily in moving this technology from the beaker to the production line, so we decided to pursue a more broad license directly from UD.”

Barrday faced and overcame significant challenges. “Three years ago, we could only make a 10-inch by 10-inch square of STF-treated material. We had to figure out how to produce it in a continuous process,” he adds. “Now we can deliver the industrial quantities needed to manu-

facture, for example, thousands of ballistic vests. Our business model is to be partnered with the university to supply treated rolled goods to companies that want to make innovative products that incorporate STF fabric.”

It’s Butler’s view that the marketplace is barely at the tip of the iceberg in terms of potential applications for STF fabric technology. Beyond protection for police, soldiers, prison guards and the like, there are applications in heavy industry, sporting goods, energy absorbing pads and

even blast containment.

“Fortunately, we’re in a position to tailor materials for specific applications and to provide advice on how to use them,” Butler says. “It will be very interesting to see what the impact of STF technology will be in the next few years, whether it is protecting people and equipment or making sports safer and more pleasurable.”

— *Jock Elliott*

University of Florida

Alcohol Sniffer Gives Hospitals a Hand Tackling Super Bug Infections

According to the Centers for Disease Control and Prevention (CDC), health care-associated infections (HAIs) are the fourth leading cause of death in the United States. This despite the fact that something as simple as hand washing could drastically reduce the death rate.

HAIs can be fatal and are often highly resistant to antibiotics. Prevention, primarily through stringent hygiene practices to avoid transferring infections between patients, is the only known means of curbing these deadly unintended effects of health care.

HyGreen Sniffs out Poor Hand Hygiene

Now, thanks to researchers at the University of Florida hospitals and other

health care settings have a new tool to help enforce hand-washing adherence. They recognized that their work on a project to detect alcohol and other volatile compounds could easily be adapted to aid hand-hygiene practices in health care environments. Since proper hand-hygiene practices are the first line of defense in the prevention of HAIs, it made sense to develop a system that ensures this simple hygiene protocol is always followed.

Enter HyGreen — a transparent system that ensures health care workers wash their hands before delivering care and, thus, prevents the spread of infection from one patient to another. The system consists of a badge, an alcohol sniffer, a bedside monitor and a wireless reporting system.

“Virtually all hand-hygiene products — both soap and waterless — contain an alcohol,” explains Richard Melker, Ph.D., M.D., the primary inventor and professor at University of Florida’s College of Medicine, Anesthesiology. “A hand-wash station is positioned wherever these products are dispensed and detects the presence of the alcohol on the health care workers’ hands immediately after they practice hand hygiene. The health care worker wears a badge that broadcasts a unique identifier so the database knows who washed their hands and where they were washed.”

This is just the first step of the system’s process. The following step is designed to protect the next patient the health care provider approaches.

“The invention provides a safety net around the patient, so that a health care worker can only enter a safe area around the patient if his or her hands are clean,” says Melker. “If not, the “unclean” badge status is communicated to a bed monitor, which, in turn, activates the badge to provide a series of vibrations reminding the health care worker to wash before entering the safe area around the patient,” he continues.

The system also wirelessly records all interactions in a central database so that the hospital, clinic or health care facility



Richard Melker (left) and Donn Dennis were part of the team that developed HyGreen.

Elena Casson

is notified in real-time which health care workers are complying with hand-hygiene recommendations and which are not. This allows the health care institution to intervene quickly if necessary and keep accurate incident records. It also provides a means to report to entities such as the CDC for accurate national incident trend tracking.

Change Saves Lives and Money

While saving lives has always been of high importance to health care workers and institutions, recent developments have heightened concerns over HAI rates.

“The change in reimbursements by Medicaid and Medicare really was a significant influence on the market acceptance of this invention,” explains Bruce Clary, assistant director of the Office of Technology Licensing at the University of Florida.

As part of the Deficit Reduction Act of 2005, Congress required the Secretary of Health and Human Services (HHS) to identify a number of circumstances that are preventable, avoidable or containable and that adversely affect health care delivery or outcomes — so-called never events, since they should not occur and are not the reason the patient was admitted to the hospital. HAIs are counted among those circumstances.

Thus Medicare and Medicaid will not pay hospitals for treating infections the patient did not arrive with (nor allow them to charge the patient directly). In other words, health care institutions are required to provide care for HAIs but will

not be paid for delivering treatment for these infections.

This is a significant change in insurer reimbursements, but it’s a move that is likely to be popular with health care consumers concerned with the consequences of HAIs.

“Health care-associated infections account for over 250 deaths every day in the United States,” exclaims Melker. “Imagine what the public outcry would be if a commercial jetliner crashed every day in the U.S.!”

HHS considers the change in Medicare and Medicaid reimbursements as an important part of its mission to make American health care safer and more affordable. It is largely accepted that private insurers will soon follow suit and refuse payment for the treatment of HAIs. This is no surprise considering the impact of these unintended diseases on both the health care system and health care consumers.

“Health care-associated infections are the fourth leading cause of death in the United States and cost the U.S. health care system between \$30 and \$40 billion per year,” says Clary.

A Chance Remark Leads to a Handy Discovery

Despite the obvious need for better hand-hygiene systems, however, the inventors of HyGreen, who, in addition to Melker, included Nikolaus Gravenstein, M.D., Christopher Batich, Ph.D., and Donn



Eliana Casson

Health care workers wear badges that allow HyGreen to document who washed their hands and when.

Dennis, M.D., did not start out to tackle the problem of HAIs. They heard the cry for a solution while they were working on another project.

“A colleague commented that hand hygiene was a problem in hospitals and was a major cause of health care-associated infections and asked if we might come up with a solution,” explains Melker. “There was an immediate Eureka! moment, since we were already working on the detection of ‘taggants’ and ethanol for other products.

“Our experience with sensors for ethanol and other compounds made it very easy for us to develop a prototype/proof-of-concept system,” he adds.

Good Chemistry Facilitates Clean Deal-Making Process

Also relatively easy, says Melker, was get-

ting the product to market. “It took a very short time to prepare a patent disclosure to the University of Florida and to begin development of the technology at Xhale Inc.,” says Melker. “In this instance, the university licensed the technology to a company in which the inventors were actively involved, so commercial interest dramatically helped in the very rapid development of the technology.”

Indeed, two of the inventors — Melker who serves as Xhale’s chief technology officer, and Dennis, who is Xhale’s chief science officer — were co-founders of the company, which is also located in Gainesville. “We had licensed other technology from these inventors two years earlier, while we were creating the company,” says Richard Allen, chief executive officer of Xhale.

“We had started the company to work on the other suite of patents, so we were already working with this group of inventors when they conceived of HyGreen,” explains Allen. “In this case the first idea came from a team of University of Florida researchers who were already tied into Xhale, and, therefore, the licensing effort and ‘commercial finish’ were a bit easier than normal,” he concludes.

Xhale invested \$5 million to speed HyGreen’s development.

“The process was very serendipitous right from the start,” agrees Clary. “The chemistry between the primary inventor, Richard J. Melker, M.D., and Xhale’s CEO Mr. Richard Allen was terrific. So our role

“Health care-associated infections account for over 250 deaths every day in the United States,” exclaims Melker. “Imagine what the public outcry would be if a commercial jetliner crashed every day in the U.S.!”

as the Office of Technology Licensing was very easy, simply protect the intellectual property, quickly get a license agreement in place and allow the Xhale team to run with it.”

Clary says the most important thing in this story was the close and collaborative working relationship the University of Florida had with the licensee, Xhale. “We tried to place as few hurdles in front of them as possible and to be a positive influence,” he says. “They responded by really creating value and moving through the product development cycle amazingly fast.”

Allen says HyGreen has enjoyed a huge amount of market interest since the change in hospital reimbursement by Medicaid and Medicare. “So no, the economy hasn’t dampened interest at all in HyGreen. It seems to be the right time for this,” says Allen.

He expects interest to climb with the passing of the health care reform bill. “When the government is striving to save money and lives in health care, this is a good fit,” he says.

The highest cost tied to HAIs, however, is calculated in terms of human lives.

“It feels good to save lives, to prevent disease and to make a difference,” says Melker.

— Pam Baker

MuniRem Makes Contaminated Land and Water Safe for Use

Long after they have served their explosive purpose, the munitions of war continue to damage lives and the environment. Their detonating capacities may be expended in battle or training, but the substances that made them volatile persist, contaminating the soil and ground water with carcinogens and other highly toxic substances.

It is a more complex problem than simple pollution. Many of these materials may also cause hard-to-extinguish fires or leach dangerous chemicals into lakes, streams and aquifers where they are subsequently incorporated into the food chain. Discarded and corroded munitions are found when foundations for new buildings are laid in certain areas. Moreover, munitions dumped at sea are now washing up on the shores of the Great Lakes and the Eastern Seaboard.

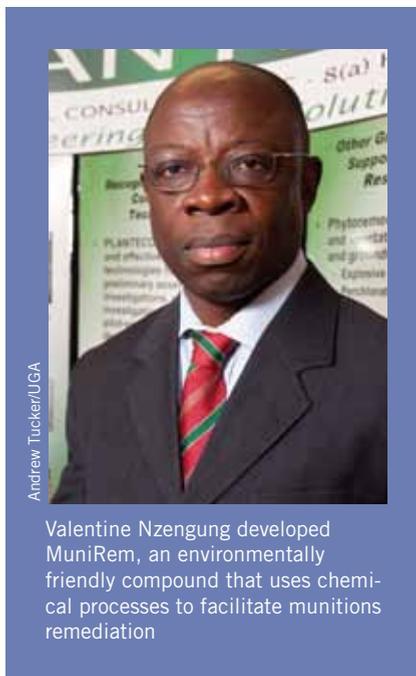
“When we hear ‘bombs and ammunition,’ we think of their destructive power in combat,” notes Valentine Nzengung, Ph.D., professor of geology at the University of Georgia (UGA) and president of Planteco Environmental Consultants LLC, based in Athens, Ga.

“Their explosive effect is gone quickly,” he says, “but their residues of nitrates, ammonia, perchlorates, mercury, chromium and other substances linger indefinitely. Munitions residues make soil sterile and unable to support vegetation,

water unsafe to drink and streams unable to support healthy aquatic life. They place people at risk for ills like convulsions, central nervous problems, leukemias and other cancers.”

Typically, these problems have been dealt with by hauling away the contaminated soil and treating it as hazardous waste, or, sometimes, by incinerating the soil.

However, Nzengung has developed a different approach involving the use of MuniRem, an environmentally friendly compound that uses chemical processes



to facilitate munitions remediation. This compound converts explosives contaminants into “nature-usable” components that are safe when humans are exposed to them. MuniRem is applied much like new seed is sown on cropland — it is broadcast, tilled in and watered.

“Once the chemical action starts,” Nzengung says, “nitrates are degraded and heavy metals are converted into nontoxic metal-sulfides, reducing soil contamination by more than 98 percent within 24 hours. These byproducts are easily metabolized by plants and bacteria and other organisms in the soil. Once treated, land has been planted with grasses and trees for several years, it’s safe for habitation.”

Remediation Missions

With a doctorate in environmental geochemistry, Nzengung has long had a strong focus on contaminant remediation. Nzengung founded Planteco in 2000 and now, with a dozen employees, the company has developed remediation approaches ranging from bacterial treatments that deal with oil sludge to bacterial mats and manmade wetlands that treat contaminated surface water.

Nzengung was studying perchlorate — a compound used in explosives and solid rocket propellants — with funding from the U.S. Air Force when the Department of Defense established the Military Mu-

nitions Response Program in the early 2000s to clean up former military sites with contamination problems. Contamination was a long-standing issue for military bases, but once the armed services began closing bases — often for conversion to civilian use — the need to deal with this contamination became more urgent.

Nzengung expanded his focus to general munitions. After initial work with soil samples in his UGA laboratory, he obtained funding from the Georgia Research Alliance through the Georgia BioBusiness Center (the university's incubator) and, subsequently, the U.S. Army, to further develop and test the technology.

“Valentine holds a number of patents on environmental remediation techniques,” says Gennaro Gama, senior technology manager at the University of Georgia Research Foundation Inc. “He began working on munitions remediation — the technology that became MuniRem — with the belief that contaminated soils could be reclaimed rather than just hauled away.

“For one thing, it's much less expensive. It opens the door to similar treatment of exhausted farmland — the remediation of nitrates in soil that has been overfertilized. And, most importantly, it makes our world safer for people to live in. It will address environmental contamination caused by wars past, present and future.”

Nzengung worked on the project for several years before bringing a completed prototype to the UGA Research

Foundation in early 2007, Gama notes. The group filed the first of two patents in May 2007, licensing the technology exclusively to Planteco.

Confronting Contamination

Residue contamination occurs at every developmental stage and site of a bomb or artillery round's existence including the land surrounding munitions manufacturing plants, artillery firing ranges and

Other metals normally found as environmental contaminants in military areas include mercury, cadmium, arsenic and depleted uranium, all of which can be passivated by MuniRem and, if needed, extracted from the soil in subsequent processing steps.

aerial-bombing practice ranges. Although some contamination occurs in actual war zones, the residue levels are most concentrated at plants and practice ranges where the materials are used continuously.

The three main forms of munitions are unexploded ordnance; discarded military munitions; and munitions constituents from stockpiled munitions, former military facilities and manufacturing installa-

tions. Some of these are present in land that is now privately owned, while some is public land used for recreation or other purposes.

At rifle ranges, the primary issue is lead contamination from bullets. But at artillery ranges the powder charge bags used in cannons to propel rounds exude mixed residues along the firing lines, and the target areas become residue-contaminated where the rounds detonate during impact. Many sites involve contaminated bodies of water — like artillery ranges on the Chesapeake Bay and Great Lakes, for example — complicating cleanup.

“Beyond the inevitable contamination associated with training,” notes Catherine Knudsen, Planteco's vice president of federal programs, “the military commonly dealt with excess munitions for years by burying them in the ground or disposing of them in the sea. As these materials corrode, leakage from the stocks into groundwater is a major problem. And once they are there, these pollutants stay in the environment.”

The most common types of highly explosive materials are the familiar TNT (trinitrotoluene), the more recent RDX (royal demolition explosive) and variations like HMX (high melting explosive). RDX is among the most frequently used type of ordnance today, but any munition is likely to consist of a formula combining different substances for desired characteristics. Their manufacture is a complex process of combining, altering, refining and synthesizing a myriad of often-vola-

tile chemicals for desired characteristics — perchlorates, sulfuric and nitric acids, many variations of nitramine compounds, and toluene (the second T in TNT).

“MuniRem utilizes a sulfur-based compound to address explosives and metals,” Nzungu says. “By attacking the nitro groups, our formula reduces them to nitrogen gas or to a low-oxidation state — nitrogen oxide. And it causes sulfide from the reaction of MuniRem to bond to heavy metals that may be present, like chromium and lead, to form a nonsoluble metal sulfide — the way iron sulfide can be turned into pyrite, or fool’s gold.”

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On the Ground

Before any treatment is undertaken, the Planteco team takes soil samples for analysis to determine the types and concentrations of contaminations and soil characteristics such as the pH value — necessary information for creating the right mixture of MuniRem chemicals.

For soil remediation, MuniRem is usually applied in granular form, broadcast on the soil and tilled in. If the soil column is deep, an auger with a large-diameter tip may be used to embed it. Then the area is saturated with water to activate the compound.

“You can see the reaction,” Knudsen says. “If you have a high concentration, you can see the soil change color, becoming a dark brown. It becomes warm. If it reacts to certain explosives, it may turn pink.”

The U.S. Army Corps of Engineers has awarded Planteco multiple contracts for demonstrating the MuniRem technology, and the company is poised to receive a series of remediation contracts from the Department of Defense and military munitions manufacturers.

“We return a day later and take more samples. Our experience is that almost all the chemical action is complete within 24 hours. But we take more samples two weeks later to confirm permanency.”

MuniRem, Knudsen notes, may also be sprayed in liquid form to treat the walls of a contaminated building or injected down a borehole to reach a contaminated groundwater aquifer.

Pilot tests at munitions plant sites in Ohio

and Wisconsin — the Department of Defense prefers that specific sites not be identified — demonstrated MuniRem’s effectiveness. At a former plant in Ohio, just under an acre of contaminated land was treated successfully — basically overnight. In Wisconsin, the Planteco team quickly neutralized the explosive material from 10 artillery rounds, demonstrating the procedure for dealing with live munitions recovered intact, whether from in-ground burial or from underwater disposal. The recovered munition is split open with a water jet cutter (no sparks) by explosive ordnance specialists and the volatile materials inside placed in a chemical reactor to neutralize them.

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“It’s very difficult to get a new product like this adopted by large, established contractors,” notes UGA’s Gama. “Progress is being made in demonstrating its capabilities and fostering its implementation.”

“As it should be. MuniRem can play a great role in resolving threats to our environment and our health. It’s not just that it makes land safe for habitation by local residents. It’s a key for making groundwater aquifers safe for populations as a whole and for reclaiming the ecosystem.”

— Ralph N. Fuller

University of Maryland

Plastics Manufacturing Process Reduces Need for Crude Oil, Conserves Resources

When Professor Lawrence Sita, Ph.D., joined the chemistry and biochemistry department at the University of Maryland in 1999, he was determined to figure out the most effective way to make the kinds of plastics used in shopping bags and automobile dashboards, known as polyolefin plastics.

Then he took a “world-view-changing trip” to India in 2004, where he saw discarded plastic everywhere across the countryside. Trees were laden with plastic bags — so much so that they looked like they were growing plastic.

“What I saw just staggered me,” Sita says. He realized that wanting his contribution to science to be a way to simply make more of the same type of plastic “was a

very naïve and pretty ignorant viewpoint.”

But by that point, in 2004, Sita had already made important discoveries in plastics manufacturing. He was working on a new, more efficient way to make polyolefin plastic out of the simple raw materials obtained from natural gas as opposed to crude oil, which is used in the manufacture of many plastics. So he switched his focus from making plastics to making pure, synthetic oils and waxes through the same process.

In 2008 he finalized his invention and founded a company, Precision Polyolefins, which he hopes will soon start selling his products. His technology is a more environmental solution than current manufacturing processes because similar

products made from crude oil require so much more refining and shipping — not to mention the geopolitical issues involved — than more readily available natural gas.

Creating a Catalyst

Sita’s research has focused on the agent, called a catalyst, that causes the long molecular chains of plastics to form out of the raw materials. In much the same way that enzymes in our body create new materials by controlling chemical reactions between molecules, an artificial catalyst in plastics manufacturing controls how the molecules join up in a specific way to form long chains from which the plastics are derived.

Plastics manufacturers have used various catalysts made from different metals to achieve this goal. But each catalyst can only make one type of plastic, meaning that if companies want plastics of different strengths they have to stop the manufacturing process and substitute in a new catalyst they designed to specifically produce a different type of plastic. Polyolefin synthetic oils and waxes are made using the same process, but by creating shorter chains of molecules than plastics require. (A polyolefin is a chain of repeating hydrocarbon molecules, petroleum being a mixture of different hydrocarbons.)

Sita discovered a sort of universal catalyst



Lawrence Sita has created a system that takes natural gas and turns it into pure synthetic oil that can be used as lubricants or hydraulic fluid. It is more environmentally friendly than refining crude oil.

that can take the raw materials obtained from natural gas and turn it into any desired type of polyolefin plastic, oil or wax. The final product depends on the amount of time the catalyst and building blocks spend in the reactor creating shorter or longer chains. Additionally, the process uses special chemical additives that instantaneously reprogram the exact way in which the catalyst stitches the molecular building blocks together to form the molecular chains.

Sita and his graduate student coworkers achieved this by spending 10 years in his lab, picking apart the mechanisms that make catalysts function. They studied them until he could reassemble a new, more versatile catalyst, as opposed to the traditional industry approach of simply screening thousands of different catalysts by trial and error until a new product is “discovered.”

“Through generous support by the National Science Foundation over the past 10 years, I had the luxury of saying, ‘How do these catalysts work?’ instead of needing to make something commercially successful,” he says. “The traditional approach is much more empirically driven. We want to have absolute knowledge and control over the structure of both the catalyst and the material.”

By 2008 he had developed his universal catalyst and the manufacturing technology that utilizes the new catalyst. The catalyst is made with a tiny amount of an expensive metal called hafnium and a much larger amount of inexpensive aluminum.

The university had been obtaining patents for his work along the way and was eager to recoup on its investment. With the help of the school’s Office of Technology Commercialization (OTC), he started looking for companies interested in licensing the technology.

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“My preference would have been for some company to come in and license everything,” he says. “That would have left me peacefully doing my lab work.”

It didn’t work out that way.

From Competition to Company

After striking out with existing companies, the OTC invited Sita in 2007 to participate in an annual competition it holds for faculty members to present their business ideas to local entrepreneurs and venture capital investors. Sita won the “Best Inventor Pitch.”

“He stood out right away,” says Gayatri Varma, OTC’s executive director. The key was that Sita stuck to explaining his business plan and didn’t veer into the heavy science, as researchers are prone to do.

“I got my plaque and good feedback,” Sita says of the competition. He also realized that he needed to do the heavy lifting to bring his catalyst to market. “If something was going to happen, I should take a leading role in trying to get it out the door.”

In 2008 he founded Precision Polyolefins, and the university licensed the catalyst technology to him. Sita is about to move the operation into incubator space on campus.

The company is currently a one-man show, but hopefully not for much longer.

In addition to feeling better about his contribution to the environment, Sita realized that it would be much harder to enter the plastics market against giants like The Dow Chemical Co. than it would be to introduce new synthetic oils and waxes.

“The plastics market is very competitive,” says Varma, who applauds Sita’s business



Professor Lawrence Sita thought his career would focus on creating better ways to make more and more plastic. Instead, he now uses his knowledge to figure out ways to make plastics, oils and waxes in more environmentally friendly ways than current manufacturing methods allow.

decision. “The price point is very low.”

Sita is working hard to find the right investors in this sour economic climate. Varma has helped negotiate a loan from the university to keep the company moving forward.

“We’re trying to be a little creative because we want to see this company be successful,” she says.

Producing Oils and Waxes

Sita’s plan is to focus on synthetic oils at first, and he hopes to have a product out by next spring. These oils could be used as lubricants in places where clean oil is required, such as food processing or medical equipment, or as hydraulic fluid.

The advantage to his universal catalyst in producing synthetic oils is that he can change the desired viscosity of the oil without having to change the catalyst. So he could easily switch between oils and lubricants needed for cars in the Arctic to your run-of-the-mill city car needs.

Eventually he hopes to add waxes to the mix, focusing on high-tech products such as those used in thermostats that have to

melt at a specific temperature. The United States currently imports a billion pounds of wax per year — and this will soon increase to 2 billion pounds, he says.

In addition to easing the manufacturing process, Sita says his catalyst is better for the earth. As crude oil becomes scarcer, companies are looking to import cruder and cruder sources that require more and more refining, which is an energy-intensive process.

“In the U.S. we have an abundance of natural gas, so it’s a highly desirable starting material for petrochemicals,” Sita says. “The energy required for manufacture is a fraction of what is currently required by crude oil refining. And it would limit the amount of energy that goes into transportation of crude oil, which is not insignificant when you have tankers chugging around the world.”

And, as the country continues to recuperate from the Gulf of Mexico oil spill, people are eager to find ways to reduce the need to find more and more sources of oil.

— *Emily Stone*

University of Nevada, Reno

New Protein Therapy Shows Promise for Treating Muscular Dystrophy

Prothelia Inc. may be a new company, but the research and relationships supporting it have been decades in the making. Devoted to researching new treatments for muscular diseases, the people at Prothelia are motivated not only by scientific inquiry and business opportunity, but also have motivations that are heartfelt and deeply personal. A laboratory's "What if?" experiment years ago has grown into a new company that is working to validate and market new therapies for muscular dystrophies.

Prothelia has licensed rights to a protein known as Laminin-111 from the University of Nevada, Reno, (UNR), along with several other potential promising treatments. Laminin-111, which is naturally produced by the body, assembles into a matrix around muscle cells and helps promote muscle-cell health and survival.

Prothelia's technology originated from Dean Burkin, Ph.D.,'s exploration into whether Laminin-111 could restore muscle function after the onset of a disease. Burkin is an associate professor at the university's School of Medicine. He directs a biomedical research program focused on studying the molecular basis of muscular dystrophies to develop potential treatments.

"In Duchenne and other forms of muscular dystrophy, we've been able to show

that alpha7beta1 integrin, a laminin receptor in muscle, prevents muscle disease," explains Burkin. Using this knowledge, Burkin established a drug discovery program, developed a novel muscle-cell-based test and identified several molecules that increase alpha7beta1 integrin in muscle. Burkin discovered that these compounds can help repair and prevent muscle damage.

"It was really surprising to us that such a large protein could be delivered to muscle

and protect the muscle from damage," Burkin says, describing mouse-model experiments that began in 2007 at the university.

Muscular dystrophy patients experience tears in muscles, usually starting in childhood, that weaken the muscles and limit their use. As the disease progresses, the heart, diaphragm and other organs can atrophy. More than 40 genetic diseases are categorized as muscular dystrophy — some marked by an absence of critical muscle proteins, causing progressive muscle weakening and degeneration.

According to the National Institutes of Health (NIH), the most common variants — Duchenne and Becker muscular dystrophy — affect approximately 1 in every 3,500 to 5,000 boys, or as many as 600 boys born every year in the United States. Most cases are a result of new mutations or a family history of the disease.

Reconnecting at the Right Time

A biochemist and pharmacologist originally from New Zealand, Burkin was pursuing a postdoctoral fellowship at the University of Illinois in the mid-1990s and collaborated with Bradley Hodges, Ph.D., then a doctoral student in neuromuscular biology. Both scientists worked on the alpha7beta1 integrin, a molecule located on the surface of muscle tissue that



Dean Burkin directs a biomedical research program focused on studying the molecular basis of muscular dystrophies to develop potential treatments.

holds the tissue together. Over the next decade, Burkin continued his research at the UNR Center for Biomedical Research Excellence.

Hodges worked for seven years in the laboratories of Genzyme Corp., a Cambridge, Mass., biotechnology company. In 2007, he was ready for a new challenge and contacted several university technology transfer offices to ask about research on treating muscular dystrophy. Then he reconnected with Burkin to ask about his research, and both men started down the path to collaboration. Burkin needed a corporate partner to continue development of laminin compounds and had filed a patent.

Longstanding relationships appear to be a major strength for Prothelia. As a graduate student, Jachinta Rooney did the original laminin-111 experiments in Burkin's lab. She is now continuing the work as a postdoctorate researcher studying the effects of protein therapy in mouse models.

"Muscular dystrophy is one of the most common 'rare' diseases, so there is a good market opportunity for a drug that can help some of the 20,000 patients out there," Hodges says. "When I decided to start a company I knew it would address muscular dystrophy because I knew the issues." Hodges also knew that large companies are hesitant about emerging treatments, so he incorporated Prothelia and made his case to UNR officials. Hodges approached the university at the right time.

"In academia, you can only get research so far before you have to get industry to come in," explains Burkin. "Brad's background, interest and enthusiasm were key to the development of this discovery. The Technology Transfer Office here at the university eased the process toward development by licensing the intellectual property."

Bjur and current Technology Transfer Office Director Ryan Heck say the choice of a licensing deal with a startup instead of a much larger company made sense because of the early stage of laminin research.

As it turns out, the technology office also saw a unique opportunity.

"Protein therapeutics was the area Brad wanted to pursue and I was convinced very quickly that there was a good relationship here," says Richard Bjur, former director of the UNR Technology Transfer Office. "There was a lot of serendipity here since Brad and Dean know each other." Bjur and current Technology Transfer Office Director Ryan Heck say the choice of a licensing deal with a startup instead

of a much larger company made sense because of the early stage of laminin research.

"One barrier we see to commercializing our faculty's research is that it can be difficult to find someone who grasps the science well enough to understand and overcome the challenges posed by an early-stage technology," adds Heck, who has a doctorate in chemistry and, as an outside attorney for the university, wrote the initial patent applications. "Brad comes from a scientific background and understands what he's getting into."

Devoting a Company to Muscle Disease Treatment

Armed with the license agreement, Hodges began writing grant applications to the NIH and the Small Business Innovation Research program and was awarded on the third try. He also recruited Richard Cloud to serve as the company's chief executive. They met at a conference Cloud helped organize in Atlanta for parents seeking a cure for congenital muscular dystrophy. Cloud's oldest daughter has MDC1A — one of the variants of muscular dystrophy Prothelia expects to address.

"The research community for muscular diseases including ALS (Lou Gehrig's disease) and muscular dystrophy is a tight-knit group," Hodges notes, "with a lot of cooperation between the NIH and the many patient advocacy groups devoted to muscular dystrophy." The diseases have been recognized since the mid-1800s yet have eluded treatment despite a relatively high public profile. The genetic mutation

causing Duchenne muscular dystrophy was identified in 1986.

The Challenges and Possibilities of a Young Technology Transfer Office

The state of Nevada's only public medical school is fairly new, founded in 1969, and officials there recognize the need for impact that will draw corporate partners. The laminin technology has great potential, and its partners share a passion needed to reach that potential. The university's Center for Economic Development estimated that \$74 million in research expenditures in 2009 meant a regional impact of nearly \$300 million for Nevada. The university has more than 30 active business and industry

partnerships, and the university technology transfer program is pursuing goals of expanding that local impact, Heck says.

"Our office started small, with just me, and expanded back in 2003 and grew into a full-time office," Bjur adds. "We're trying to bridge the gap between the uni-

The university's Center for Economic Development estimated that \$74 million in research expenditures in 2009 meant a regional impact of nearly \$300 million for Nevada. The university has more than 30 active business and industry partnerships, and the university technology transfer program is pursuing goals of expanding that local impact, Heck says.

versity and community, and one way is to create economic opportunities." He cautions that in technology transfer, "What you don't want is a situation where there are unrealistic expectations."

Thus far, the UNR Technology Transfer Office has been able to capitalize on such opportunities. As one example, Prothelia, which appears to be well-positioned for success, is pursuing both venture capital funding and strategic relationships.

But for the people who suffer with muscular dystrophy, these opportunities provide something even more valuable: hope.

— David Wallace

University of Pittsburgh

Artificial Lung Helps Patients Breathe Easier

A 76-year-old woman with chronic emphysema was admitted to a hospital in India earlier this year. She was complaining of shortness of breath and was diagnosed as being in respiratory failure, meaning she had a buildup of carbon dioxide in her lungs and couldn't take deep enough breaths to push it out and suck in oxygen instead.

Normally doctors would put such a patient on a mechanical ventilator, which would mean sedating her so they could insert a breathing tube down her throat. Instead, her doctors decided she was the ideal person to be enrolled as the first patient in a study of a new artificial lung initially developed by researchers at the University of Pittsburgh, called the Hemolung.

The device is connected to a patient by

a catheter. It pumps blood out of the patient, runs it across a bundle of fibers that pull out carbon dioxide and infuse oxygen, then sends the blood back into the patient, thus doing about 50 percent of the work of the person's failing lungs.

The woman was hooked up to the Hemolung and quickly began breathing more easily. By the time it was removed three days later, her carbon dioxide levels were down, and she could breathe on her own. Equally importantly, she had avoided needing to be put on a mechanical ventilator and, therefore, spent her time in the hospital alert and able to eat and talk with her family.

"It was very rewarding to see that happen," says Nick Kuhn, chief operating officer (COO) of ALung Technologies, the Pittsburgh company developing the He-

molung. ALung is hoping to finish its first clinical trial on patients in Europe and India early next year and then apply for approval in the United States. The goal is to be able to help the 450,000 people in this country and millions more worldwide avoid temporary hookup to a ventilator, thus granting them a shorter and more comfortable stay in the hospital.

Carbon Dioxide out and Oxygen in

The innovation grew out of work in the Medical Devices Laboratory at the University of Pittsburgh. The external device now known as the Hemolung has changed shape considerably, having started as an internal device. Professors Brack Hattler, M.D., Ph.D., and William Federspiel, Ph.D., designed what they called the Hattler catheter in the mid-1990s. The catheter held a series of tiny hollow fiber tubes that were bundled together and was inserted into a patient's large vein during respiratory failure. The tubes had oxygen running through them, so when the patient's blood ran across them, it picked up oxygen and left behind carbon dioxide.

ALung is focusing on two types of potential patients, those with chronic obstructive pulmonary disease (COPD) and those with acute respiratory distress syndrome (ARDS). COPD patients, who often have emphysema, have trouble breathing deeply because the airways in their lungs are restricted, having grown stiff or swol-



ALung is focusing initially on patients with chronic obstructive pulmonary disease, who often have emphysema. When these patients come to the hospital because they're having difficulty breathing due to a respiratory illness, they would be put on a Hemolung to pull out excess carbon dioxide in their blood and send in oxygen.

len over the years. ARDS patients' lungs have been damaged as a result of another disease or accident, and they tend to develop ARDS while in the hospital.

In its first trial, ALung is looking at the Hemolung's effect on people with COPD who have a sudden drop in respiratory function.

"They could get a cold or a flu or anything that puts these patients over the edge," Federspiel explains. "If you or I get a bad cold in the winter, we don't have to go to the intensive care unit because we breathe fine. If they get a bad cold, they can't breath."

The artificial lung is a temporary device needed to get them through that period of acute need, usually three to four days. "Eventually the cold or flu resolves itself and they get better," he says.

Starting a Company

Hattler, who died in 2008, and Federspiel patented the catheter-based artificial lung with the help of the University of Pittsburgh's Office of Technology Management (OTM) and founded ALung in 1997. They didn't have any plans to commercialize the device at the time, but needed to work with a company to apply for grants. The research has been funded by the National Institutes of Health, the U.S. Department of Defense and the U.S. Army.

By 2001, they were presenting their idea at scientific conferences and had started generating enthusiasm for an actual catheter-based device, Federspiel says.

They couldn't find an established company interested in licensing the technology, so they decided to set out on their own.

But first they needed to negotiate a one-year licensing option with the university, explains Maria Vanegas, OTM technology licensing associate. The office generally

For patients like the woman in India, the device's long evolution was definitely worth it, both for the medical care it provides and the ability to avoid being hooked to a ventilator.

grants options to startups because this strategy is a simpler and less expensive way to investigate whether there really is a market for the product. Startups can use that year to perform due diligence on the technology and to start fundraising, she says.

They also brought in an outside chief executive officer for the first time, choosing Kuhn (who switched to COO in 2009), a veteran of other medical device companies. Kuhn worked at raising money, while Hattler and Federspiel toiled in the lab to make the catheter as small as possible. After the one-year option was up, the com-

pany fully licensed the technology.

In 2005, they found that the miniaturization of the catheter device topped out at about 1 centimeter in diameter. While it worked well in animal studies, the scientific advisory board assembled by Kuhn opined that such a large a catheter would be unappealing to many medical professionals.

"It became obvious that we needed to make a change," Kuhn says.

After much deliberation, they decided to scrap the Hattler catheter and turned to a related innovation — the one that eventually became the Hemolung.

Breathing New Life Into the Project

Federspiel had been working on another iteration of the technology that used the same fiber bundle but positioned it outside the body. Because the bundle didn't have to get inside the person's vein, the catheter size dropped to 5 millimeters in diameter, the same size used in kidney dialysis.

There was a precedent for an external artificial lung. A technology called extracorporeal membrane oxygenation (ECMO) is used at a small number of hospitals in the country. It removes a patient's blood, adjusts the gas levels and then pumps it back into the body. But, because it removes two to three liters of blood a minute, the patient has to be very carefully monitored.

"If there's a complication in the line, they could bleed out," Federspiel says. "The



ALung's Hemolung device runs a patient's blood along hollow fibers filled with oxygen to pull carbon dioxide out of their blood and infuse it with oxygen. It could replace mechanical ventilators for many patients, reducing the length of their hospital stay and improving their comfort while there.

technology is considered very invasive and complex.”

Federspiel figured that if he could come up with a way to remove sufficient carbon dioxide using a much smaller amount of blood per minute, the technology would be a far more attractive. But removing less blood meant that the artificial lung had to be more efficient in restoring the correct carbon dioxide and oxygen levels to have the same desired effect.

That's when he had the idea of rotating the fibers. Spinning the fibers allows them to come into contact with more blood as it's pumped out and so it works more efficiently, Federspiel explains. The Hemolung removes about 400 milliliters of blood a minute, or between a 5th and a 10th as much as the ECMO machine. ALung changed the design while retaining the concept so that the blood now rotates around stationary fibers rather than the opposite.

ALung is now focusing exclusively on the Hemolung. While this switch has slowed down the company's plans for generating a product, everyone agrees that it has made the device much more marketable. Vanegas applauds Hattler and Federspiel's determination to see the project succeed, despite the initial setback.

“It's unique when you find dedicated inventors who don't get frustrated with the process, especially when they had one device and then had to switch,” she says.

For patients like the woman in India, the device's long evolution was definitely worth it, both for the medical care it provides and the ability to avoid being hooked to a ventilator.

“They're able to move around, get out of bed,” Federspiel says. “They have the ability to eat normally, talk normally and express how they're feeling. It's a significant quality-of-life improvement.”

— Emily Stone

MobiliT Rover Converts Wheelchairs to All-Terrain Vehicles

Sometimes the best inventions are inspired by the closest pain. In a senior projects class at the University of South Florida (USF) in 2005, Travis Watkins listened to his professor suggest potential devices for individuals struggling with disabilities. Watkins was one of many mechanical engineering students required to design a device that showcased their education. The professor's menu of projects was intended to guide them to build devices with direct and immediate real-life applications.

"I had someone else in mind," says Watkins. "If I was going to build something for a disabled person, it wasn't going to be for some stranger. It was going to be for my father."

Inventing for the Individual

Watkins' father had once been very physically active. He enjoyed tennis, boating, rock climbing, skiing and exploring among other highly physical activities. "He wasn't one to sit around and go down the common path or follow the person in front of him," says Watkins. "He was a trailblazer and flaunted his freedom and independence in the face of those who forgot that anything is possible."

That came to an end when Lou Gehrig's disease (amyotrophic lateral sclerosis) weakened and then destroyed the motor neurons that operated his father's muscles.

"I thought about how now he couldn't go anywhere that wasn't paved and smooth due to the poor capabilities of his top-of-the-line wheelchair," explains Watkins. "I thought how difficult this must be for him, to be confined to a road that someone else paved going somewhere where nothing exciting or really interesting is likely to take place."

Watkins says images of machines, power transmission methods, capabilities and limitations started flashing through his head. "I instantly analyzed and either accepted or rejected each idea," he says. "I thought of hundreds of different ways of giving my father his freedom back but only one that could feasibly work."

Designing a Destination Vehicle

With that one idea in his head, Watkins joined fellow students Robert Burn and

John Hopkins to form a research team. Burn and Hopkins left Watkins to design his dream machine while they worked on the research documentation and verifications. Soon, they had a working prototype.

The resulting rover device is an attachment for an electric wheelchair. A disabled person simply drives his or her electric wheelchair on top of the rover via an integrated ramp. Once positioned on top of the rover, the electric wheelchair automatically and securely locks into place.

Once secured, each of the wheelchair's drive wheels is positioned on top of and in between two rollers. When the electric wheelchair's wheel rotates, it turns the rollers. These rollers turn a shaft with a sprocket attached at the end. In addition, the rover has huge extreme off-road capable wheels on axles with sprockets.



The MobiliT Rover turns electronic wheelchairs into all-terrain transportation.

A chain links the roller sprocket to the wheel sprocket so that when the wheelchair operator activates the wheelchair, the wheelchair wheels turn the rollers. Those turn the sprocket, which rotates the chain, which turns the extreme off-road wheels.

“Basically, when the wheelchair is locked in place on the rover, the wheelchair’s controls now control the entire rover,” explains Watkins. “One of my main requirements was to use the wheelchair controls to control everything. The rover is so easy to use. Just drive your wheelchair up on it, it automatically locks into place, and you drive the rover away ready to take on any obstacle in your way and go wherever you please, even places you can’t get by foot!”

He called it the ATEWA — All Terrain Electric Wheelchair Attachment. It was later nicknamed the “Tank” for its ability to overcome numerous terrain obstacles. It is now known as the MobiliT Rover.

Carrying the Idea to Market

By any name, the device thrilled disabled users but fell short in attracting commercial interest.

“We require our students to focus their senior design projects on solving real-

world problems,” says Stephen Sundarrao, associate director of USF’s Center for Rehab Engineering and an instructor in its Department of Mechanical Engineering. “We thought this particular project would appeal to commercial companies, but they were oddly noncommittal.”

“I had someone else in mind,” says Watkins. “If I was going to build something for a disabled person, it wasn’t going to be for some stranger. It was going to be for my father.”

Determined to see this invention get to the people who needed it, Valerie McDevitt, assistant vice president of patents and licensing at USF, urged faculty to create a company to commercialize the product.

“It took a fair bit of instigating on our part,” says McDevitt. “But this was one instance where we saw a real benefit to starting a spin-up company, not only be-

cause of the rover design, but because there was a considerable pipeline of good ideas coming from this group.”

Using cash provided by angel investors, the faculty started Rehab Ideas in late 2007. “We selected five of the senior projects initially, and one of them was the rover,” explains Sundarrao.

By 2008, Rehab Ideas was selling products. “We worked with Dixie Chopper in Indiana on distribution and manufacturing,” says Sundarrao. “And we have the backing of GE Capital to finance floor plans with dealers.”

Watkins’ father was the first to own a MobiliT Rover, but he isn’t the first to feel the freedom it brings.

“It was the most amazing thing to witness the first person who bought it,” beams McDevitt. “It was a young person who promptly drove all over the lawn laughing. His caregiver and best friend even jumped up and rode on the back.

“It was a touching and exhilarating moment to witness, and it brought home why these projects matter.”

— Pam Baker

Researchers Realize a Vision to Help the Blind

Sometimes the path technology takes to the marketplace is dotted with people who raise a quizzical eyebrow and say, You want to do what? In the case of the Brainport vision device, some of the first people to do so were two of the co-inventors.

The innovation started with Paul Bach-y-Rita, M.D., who was an early pioneer in the field of neuroplasticity — the idea that the brain can be trained to process information in a new way. In the 1960s, he became interested in using that concept to design a device that would transfer the sense of sight into touch, a process known as sensory substitution. He did this by creating a machine out of an old dentist chair with a camera attached. Four hundred little rods popped in and out against a person's back mimicking the patterns of the objects the camera was seeing.

Though Bach-y-Rita proved that the system worked, not much happened with that invention. When he came to the University of Wisconsin in the 1980s he picked up the idea of sensory substitution again. He was particularly interested in using electrical pulses instead of manual stimulation to represent shapes.

Bach-y-Rita, along with Kurt Kaczmarek, Ph.D., then a staff scientist at the university, designed a system that translated black-and-white images into electrical pulses against a blind person's fingertip. The strength of the pulse depended

on how black, white or gray an object appeared on a computer screen. The device worked well, but it was bulky and cumbersome. Still, it gave people with no sight a way to visually perceive objects for the first time.

"These are truly visual tasks and they did them without their eyes," says Kaczmarek, now a senior scientist in the university's Tactile Communication and Neurorehabilitation Lab.

That rudimentary device eventually turned into the Brainport vision device, which gives blind people a way to "see" their surroundings through electrical pulses. But first the device had to get much smaller, which led to a switch away from fingertip stimulators and the first round of skepticism.

Transferring to Tongues

Bach-y-Rita started talking to Kaczmarek and another research colleague, Mitchell Tyler, about using people's tongues instead of fingertips. His reasoning was that the tongue is super sensitive, a large part of the brain is devoted to processing information from the tongue, and except for when we're eating and talking, the tongue doesn't do a whole lot.

"We looked at him kind of funny," Kaczmarek says. "Mitch and I thought he was being a little crazy."

Bach-y-Rita, it turned out, was onto something. He spent a couple years mulling over ways to use the tongue for sensory substitution. Kaczmarek and Tyler finally acquiesced and agreed to give it a try. They took the fingertip device, and stuck it on their tongues. The pulses it



Blind adventurer Erik Weihenmayer demonstrates how he can rock climb while wearing the Brainport.

delivered were comfortable and effective. People have described it as feeling like champagne bubbles are painting a picture in their mouth. The researchers did some preliminary studies and proved that people could recognize basic geometric shapes while wearing it, and it performed as well as the fingertip version.

One of the key “aha moments” Kaczmarek recalls was realizing that the tongue required much less circuitry than fingertip devices. The surface of our skin changes depending on whether we’re hot, cold or sweating. Tongues stay uniformly wet and warm. So the electrical circuitry needed to generate and control the pulses is much simpler, meaning the device can be much smaller. Kaczmarek, who designed the first tactile tongue display, got the hardware down to the size of a shoebox. It would eventually become the size of a cell phone.

Road to Commercialization

The group published its results in 1998 and approached the school’s private, non-profit technology transfer organization, the Wisconsin Alumni Research Foundation (WARF), about patenting the invention. WARF eagerly proceeded. Then it started looking for companies interested in licensing the technology. It found none.

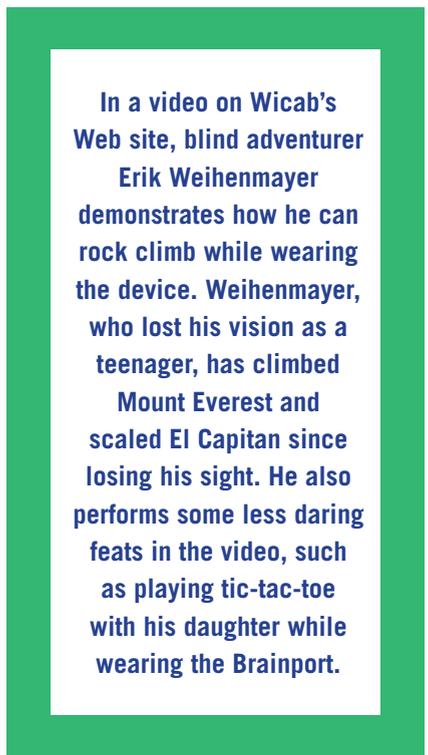
“It was a little off the wall — thinking about seeing with your tongue,” says Jeanine Burmania, a licensing manager with WARF. She says the market didn’t fully appreciate the device’s potential at the time.

Or, as Kaczmarek says: “We were viewed

as those crazy people in Madison who were doing things with the tongue.”

So Bach-y-Rita, who passed away in 2006, decided to found a company called Wicab, after his wife’s maiden name.

“It’s a good example of the passion of an inventor who wanted to see his technology commercialized,” Burmania says.



WARF exclusively licensed the technology to Wicab in 1999. WARF received equity from Wicab in lieu of an upfront licensing fee, an arrangement WARF frequently makes with startups, Burmania says.

“Sometimes, technologies developed at universities need further development prior to attracting interest from existing companies,” she continues. “This development is often outside the scope of traditional university funding mechanisms and no longer feasible within the university setting. The Brainport technology is an example of a device that could have languished in the lab from lack of exposure, but was able to make it out of the university because of Wicab.”

For the first several years, Wicab operated mostly as a research and development company, and the personnel overlapped entirely with the university staff.

A couple years into their work with Wicab, the team discovered a new way to use the tactile tongue display. Tyler had a bad inner-ear infection, which caused him to have balance problems. The group decided to try putting a sensor on a helmet that monitored tilt and then translated that information to people’s tongue via electrical pulses that let them know if they were off balance. After seeing that it worked, they started developing a balance device in addition to the vision device.

In 2005, Robert Beckman took over as chief executive officer of Wicab. A veteran of other medical device companies, Bach-y-Rita invited him to helm the still fledgling company. Beckman realized that the commercial viability of the Brainport balance device was much higher than the vision device because there are many more people with balance problems than those who are totally blind. So

they pushed ahead aggressively with the balance device, using much of the \$10 million he raised from angel investors during his first year on the job. The vision device was still being developed, mostly with the help of funding from the National Institutes of Health, the National Eye Institute, the Defense Advanced Research Projects Agency and the State of Pennsylvania.

Then Wicab got some bad news. The company had received approval in Europe and Canada to sell the device, but that process is based only on proving the safety of the device not its efficacy. During U. S. Food and Drug Administration (FDA) trials earlier this year, the company discovered that its balance device, while effective 60 percent of the time, was not more effective than the “sham device” that half of the people in the study used. Beckman believes the benefit came from the training and exercises that both groups of users went through in conjunction with their participation in the clinical study. Kaczmarek isn't convinced that it was the training and exercises alone that helped 60 percent of the people in the study and is trying to puzzle this out in his lab.

Either way, Beckman says of the results: “It's good for science. It's bad for commercialization.”

Independence Through Improved Sight

Wicab's full attention has now turned to the vision device, which could get FDA approval as early as the end of the year, Beckman says. They have proved that the device works by testing it on more

than 100 people who have had great success with it.

While there are 300,000 people with no sight in the United States, the company is focusing only on the 100,000 who are not elderly and, therefore, probably more receptive to new technology. He's also interested in the potential market in China and India.

The device has shrunk considerably since its days in the University of Wisconsin lab. Users now wear a pair of sunglasses with a camera mounted on the nose bridge. A lollipop-sized square, which has 400 electrodes in it, sits on their tongue. The stimulation pattern of those electrodes mimic whatever the camera is picking up, essentially acting as the camera's pixels. So if the camera is seeing white, the user gets a stronger pulse, gray gets a medium pulse and black gets no pulse. A cell phone-sized control box is attached by a wire to the camera and allows the user to zoom in and out on specific objects. Beckman says the next step is to make the device wireless.

Users get trained for 10 hours on the device, and almost all are very comfortable with it at the end and eager to take it outside or use it at home, says Aimee Arnoldussen, Ph.D., a neuroscientist with Wicab. They've listed the many tasks and activities they would love to use the device for, from simply reaching directly for a cup of coffee on the table instead of having to feel around for it to being able to run a marathon by following a guide instead of having to be tethered to him.

“They talk about the independence that the devices can give them,” Arnoldussen says. Unlike many devices for the blind that read aloud the information people can't see, the Brainport allows people to dictate what they want to pay attention to.

“The user gets to control this technology and what information they'd like to understand,” she says. “They get to decide where their attention is drawn.”

In a video on Wicab's Web site, blind adventurer Erik Weihenmayer demonstrates how he can rock climb while wearing the device. Weihenmayer, who lost his vision as a teenager, has climbed Mount Everest and scaled El Capitan since losing his sight. He also performs some less daring feats in the video, such as playing tic-tac-toe with his daughter while wearing the Brainport.

Some of the most emotional users, Arnoldussen says, are military personnel who lost their sight in explosions in Iraq and Afghanistan. “In many ways they've given up having visual perception, and we can provide that for them,” she says.

The Rotary Foundation has bought early versions of the vision device to help blind children in Central and South America. “Can you imagine the experience of a child who hasn't had sight before being able to comprehend objects around them?” Arnoldussen says.

Who would raise a quizzical eyebrow to that?

— *Emily Stone*

Turning the Page on Middle and High School Illiteracy

At age 12, Julio Ruiz of Midland, Texas, avoided participating in class. When he was pushed to contribute, or was not able to answer a question, he would misbehave.

“When [my teachers] called on me,” Ruiz says about his sixth-grade experience, “I would get in trouble so I could go to the office.”

Now at 14, and in the eighth grade, Ruiz has made a remarkable transformation. He is eager to join in class discussions, no longer gets scared or nervous in class and, most importantly, his schoolwork has shown improvement.

What happened?

He learned how to read.

Ruiz was one of the thousands of middle and high school students in the United States who slide by year after year with reading skills that are far below their grade level.

Most children learn to read by the time they have reached third or fourth grade unless they have the added challenge of learning a second language, have a learning disability or a difficult home life.

But what happens when a child has moved through middle school and into high school and still cannot read?

According to the National Center for Education Statistics, more than 7,000 high school students drop out every day. That is equivalent to one-third of the entire U.S. high school population. Two-thirds of students in eighth grade read below grade level.

Without the ability to read, students’ grades can go down, they may withdraw, act out or lose confidence or interest in what is going on around them.

Ruiz is a good example. While he could actually read words, Ruiz did not comprehend what he was reading. He was not understanding and putting things together.

Until his teacher started him on Read 180.

Interactive Reading Intervention

Back in the early 1980s, before “reading intervention” and “no child left behind” became programs, Ted Hasselbring, Ph.D., a research professor of special education at Vanderbilt University’s Peabody College, bridged the gap between computer technology and teaching children to read.

Hasselbring first applied his new technology for use in diagnosing spelling errors for special education and special needs children. From there, he and his graduate student team took this interactive program, which utilized video, audio and digitized speech, and applied it to adult learners.

But it was a Department of Education call for grants — and computers donated by Apple — that set Hasselbring’s reading intervention tool on the path to help middle and high school age students. His team applied for, and twice received, grant money to further develop the pro-



As a student moves through the Read 180 program, his or her reading level is assessed and the material is customized.

gram. By 1992, the Learning Technology Center had a prototype program that was making a difference with students in the Nashville area.

Word traveled quickly in educational circles and led Hasselbring's team to a five-year literacy project in Orange County, Fla.

"For every year of intervention, we were seeing two to three years of growth," says Hasselbring.

A Program — and a Partnership — Is Born

News of the Florida program's success made it to Boston, where Hasselbring met Margery Mayer, president of Scholastic. They were attending a meeting at the Center for Special Technology and were introduced by a colleague. Mayer saw the potential right away and scheduled a site visit to Vanderbilt.

Hasselbring subsequently visited Scholastic headquarters in New York. In less than two years, with the help of Janis Elsner, associate director at the Office of Technology Transfer and Enterprise Development at Vanderbilt, Scholastic licensed the intellectual property rights in Read 180 from Vanderbilt.

"Ted is the connective tissue between Vanderbilt and Scholastic," says Mayer. "The roots of this program fit perfectly with Scholastic's credo that all children can learn, deserve to learn and can succeed at high levels. It's even woven in our office carpeting."

What made the program so powerful is that children were working at their own speed, selecting their own subject matter and receiving immediate feedback, says Elsner.

Hasselbring says he has received letters from students saying that before they were exposed to the Read 180 program, they either never read a book or they wanted to quit school. But after experiencing the program, these behaviors and feelings disappeared. "When I'm having a bad day," Hasselbring says, "I can pick up those letters and remember why I do what I do."

"There really wasn't that much out there at the time for middle to high school age students struggling with reading," says Elsner. "Ted had the data, Scholastic was a great partner — they really know publishing and distributing educational technology." Scholastic took the basic program, added components, and turned

it into a comprehensive reading project available for adoption by schools.

"This program enables students to turn their lives around; they take a 180-degree turn," Elsner says.

Which is how the program got its name.

Breaking it Down Into Parts

Once a teacher chooses Read 180 for the classroom, rescheduling and classroom rearrangement is strongly encouraged for best results. Desks are set up in a conversation layout, not in rows. Beanbag chairs and comfortable couches are often used for the independent reading rotation. In addition, the teachers — and students — need to commit to 90 minutes every day.

Students begin by listening to an introduction session given by the teacher. The students then rotate through small group instruction with the teacher, individual computer tutorial and independent reading sessions. As a student moves through the program, his or her reading level is assessed and the material is customized. Many of the topics are taken from headline news (an incident where whales were trapped in Alaskan ice), from real-life situations (how to get your first job) or from history (such as the story of Hiroshima). After students rotate through the sessions, they meet in a large group to conclude the class.

Technology Meets the Page

Read 180 is not only turning literacy around for students who are two or more years below their reading proficiency, the

program also created a successful new business arena for Scholastic.

Read 180 makes up the majority of Scholastic's educational technology sales, which reached more than \$200 million in the first three quarters of 2010.

And there is still plenty of room to grow. According to Scholastic, there are 100,000 middle and high schools in the United States. About 18,000 classrooms incorporate the reading program into the curriculum; some schools have more than one classroom using it.

But it is not just the financial benefits that Hasselbring and others find rewarding. It's making a difference in children's lives.

Hasselbring says he has received letters from students saying that before they were exposed to the Read 180 program, they either never read a book or they wanted to quit school. But after experi-

encing the program, these behaviors and feelings disappeared. "When I'm having a bad day," Hasselbring says, "I can pick up those letters and remember why I do what I do."

There is a good bit of teacher enthusiasm too, Hasselbring says. "I also hear from teachers saying that they were ready to retire but once this program was put in their classroom, their job satisfaction went up."

Readers Are Leaders

Vanderbilt and Scholastic may have co-created a highly effective new reading intervention program, but the real stars are the students. Every year since 2005, Scholastic honors 12 students who stand out from among the many who turn their reading around with Read 180. Ruiz was one such student, however, there are many others.

"These students are an inspiration to all

of us," says Mayer. "Through hard work and the help of their amazing teachers, these All-Stars have proven that there is no goal that they cannot reach."

Some of the past few years' recipients of the All-Star Award have reported that they are getting As and Bs rather than Ds and Fs. They are reading at home after school, running for student council and writing skits for classmates to perform. They have overcome shyness and are letting go of self-destructive behavior issues. Most importantly, they are graduating from high school and are college-bound.

"If you can't read, school is not a great place. No wonder kids drop out of school," says Mayer. "We'd like to see Read 180 in every single school."

It is very possible that every school would like to see that, too.

— *Ellen Blum Barish*

Woods Hole Oceanographic Institution

Tiny Sentinels Could Keep World Water Supplies Safe

Just as coal miners once carried canaries to alert them to toxic gases, Woods Hole Oceanographic Institution biologist Scott Gallagher, Ph.D., envisions living sentinels watching over the world's water supplies.

But rather than the warbling of canaries, Gallagher and colleagues at Petrel Biosensors Inc., based near the Woods Hole institution on Massachusetts' Cape Cod, are targeting the swimming talents of protozoa in the genus *Tetrahymena*, each organism smaller than the width of a human hair.

Petrel's prototype monitoring system, the Swimming Behavior Spectrometer (SBS), is designed to provide virtually instant warning for a broad range of toxins that might be introduced to water supplies as diverse as municipal reservoirs, industrial water caches and military water sources in the field.

"Current testing techniques are somewhat cumbersome," says Bob Curtis, Pharm.D., Petrel's interim chief executive officer (CEO). "Generally, they require manual sampling, laboratory analysis, testing for specific agents and waits as long as 72 hours for results.

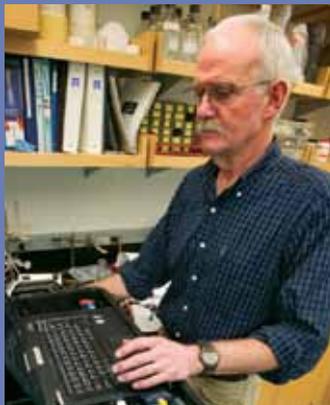
"By introducing protozoa into water samples in small test chambers, and comparing them to control samples, SBS continuously monitors for toxic agents or contaminants," he says. "It's sensitive to a full spectrum of chemical and biological contaminants — pesticides, industrial chemicals and biological warfare agents."

The Beginning: Ocean Research

Gallagher, an associate scientist at Woods Hole Oceanographic Institution (WHOI), was concerned with understanding how global climate change might affect microscopic plankton in the ocean when he began to look for ways to characterize their behaviors.

Specifically, amidst the plankton's soup of bacteria, larvae and other microscopic organisms, he was focused on protozoa, a myriad of one-celled creatures that swim using tail-like flagella or short, hair-like cilia. There are tens of thousands of protozoa species, typically ranging in size from 20 to 60 microns. Collecting water samples,

Tom Kleindinst, Woods Hole Oceanographic Institution



Biologist Scott Gallagher demonstrates the prototype monitoring system that uses tiny organisms to detect changes in water quality.

Gallagher developed a technique for visualizing their swimming patterns with a digital camera and created a system for defining their swimming behaviors under differing conditions — temperatures, nutrients in the water, pH levels and other factors.

"Sometime after the 9/11 attacks," he notes, "a friend told me the Defense Department was looking for ways to monitor water supplies. We submitted a proposal in 2002 — and never heard back. I literally forgot about it."

But he did hear the next year. With a Defense Department grant, Gallagher developed a model for predicting how different protozoa react to varying water conditions. After narrowing it down to 15 species of protozoa that worked well, he selected a handful of species that were ideal for specific uses — two or three for fresh water, a few for brackish water.

Swimming Behaviors Key

It's protozoa's cilia that make Gallagher's system of assessing water quality possible. An individual protozoan can have hundreds of thousands of cilia covering its body.

"Protozoas achieve propulsion by beating their cilia like paddles in water," he says. "The shorter the cilia, the faster they can beat. Some normally swim with a rotational torque — sort of a corkscrew motion. Except that when water conditions change, behavior changes.

“The key is calcium. It’s always present in an ionized form, and its presence fundamentally controls how the cilia work. Toxins like heavy metals inhibit calcium transport and affect cilia motion. Sometimes the cells just stop, sometimes they begin spinning around.

“It depends on whatever is inhibiting the cell, whether it’s changing uniformly or just in a part,” Gallagher explains. “If the front cilia move into a toxin and slow down while the back cilia don’t, the cell is likely to start tumbling.”

Biological products like anthrax produce toxins that don’t affect the cilia but do inhibit the protozoa’s metabolism at the cellular level. Because so many variables are possible, it’s important that any monitoring system also be able to assess control samples — water with known characteristics — for comparison.

Enter Petrel Biosensors

Gallagher and a team of engineers constructed the first sampling prototype on a workbench in his laboratory — a device measuring 2 feet by 3 feet. A nonprofit virtual incubator affiliated with WHOI, the Regional Technology Development Corp. (RTDC) stepped in to assist Gallagher and his team in forming a new company to commercialize their invention.

With that assistance, Petrel Biosensors — named for a sea bird that flies in circles as a sentinel to an approaching storm — was incorporated in 2009 as RTDC’s first endeavor. Under the arrangement, Petrel was granted an option for an exclusive worldwide license for the intellectual property

surrounding SBS technology.

Curtis, the development group’s CEO, also presently functions as Petrel’s interim CEO. The company started in 2010 with two employees — Chief Technical Officer Kevin McManus and Vice President of Engineering Lamar Bullock, Ph.D. Gallagher, who remains a full-time member of the WHOI staff, serves as chief scientific officer.

A Strong Outlook

Curtis notes that the company is in discussions with several large corporations about partnership arrangements and that it hopes to achieve significant funding by the end of 2010.

As chief technical officer, McManus says his role “is to take this very elegant technology, make it into a commercial product that can be put in the back of a pickup truck and taken to a water supply, where it can provide continuous sampling and transmit the results to those in charge.

At present, an emphasis is on updating the software, optics and other aspects of the technology first developed in 2004-2005. Future efforts will focus on miniaturization, with the goal of developing units that can be hand-carried — perhaps the size of a laptop computer.

“Municipal water supplies aren’t generally space-limited,” McManus notes, “but it probably won’t be sufficient to just place one at a reservoir and ignore the upstream source waters and downstream flow channels. This is where smaller units will be

valuable. And portability will be important for industrial operations and military units in the field.

“Ideally, a water system would have a distributed network of these sensor systems to provide ongoing real-time local, regional and, ultimately, global assessments of water supply quality.”

SBS’s current prototype, Version 1.4, is designed to provide continuous monitoring, simultaneously filling its dual test-sample and control-sample flow chambers at regular intervals, introducing the testing protozoa from a culture, assessing them, emptying the chambers and preparing them for the next sample. Each sample involves about a milliliter (or one-fifth of a teaspoon) of water containing several hundred protozoa. It can be programmed to test as often as the user wants, from every 10 seconds to once a day, or any time period in between.

“The longer the sampling time, the more sensitive the results,” Curtis notes. “It seems to work well with 30 seconds. That means a user can be alerted almost instantly if a problem exists. You may not know what the exact toxin is, but you’ll know you’ve got a problem and be able to take action.”

He adds: “This system has gone through extensive validation trials by outside testers, with very strong results. It offers real-time, broad-spectrum capabilities not available in the market now. I envision commercial opportunities domestically and internationally — the quality of water is a worldwide issue.”

— Ralph N. Fuller

Other Promising Technologies

Promising Mayo Clinic Technology Joins the Fight Against Breast Cancer

Most of us know someone who has been affected by breast cancer.

In fact, the American Cancer Society estimates that roughly 1 in 8 women will have invasive breast cancer at some point in her life, and that approximately 1 in 35 women will die from breast cancer. However, the number of deaths resulting from breast cancer is on the decline, and many people believe this decline is due to earlier detection and better treatment.

A team of researchers at the Mayo Clinic, including Deborah Rhodes, M.D., Michael O'Connor, Ph.D., and Carrie Hruska, Ph.D., has spent the last seven years developing and evaluating ways to improve the detection and monitoring of breast cancer. This research, supported by Mayo Clinic, Gamma Medica Ideas Inc. and the National Institutes of Health, has resulted in technologies exclusively licensed to Gamma Medica Ideas for use in their molecular imaging systems. This set of intricate algorithms and hardware embedded into the imaging device allows for efficient detection of breast cancer and a drastic reduction in the radiation dosage administered to women during screening procedures.

At times, current mammography technology is unable to detect breast cancer, especially in women with dense breast tissue. The molecular breast imaging algorithms and device hardware technol-

ogy from Mayo Clinic, coupled with the detector technology at Gamma Medica Ideas, creates a method of diagnosis and monitoring that can overcome the detection problem involved with dense breast tissue. Molecular breast imaging is also less expensive than alternative techniques like contrast enhanced breast MR.

This technology has the potential to improve the quality of life of large numbers of women, provides a less expensive alternative method for detecting breast cancer and offers a more robust detection system. Most importantly, earlier detection and lower doses of radiation make it very appealing to patients and practitioners.

National University of Singapore and Others Develop 3D Bone Implants to Improve Skull Repair

"Brain injury occurs more frequently than breast cancer, AIDS, multiple sclerosis and spinal cord injury," remarks Allan I. Bergman, president and chief executive officer of the Brain Injury Association in a recent article (<http://www.medscape.com/viewarticle/412192>).

Standard treatment to prevent brain injury caused by pressure on the brain following stroke or trauma involves drilling burr holes into the skull to relieve pressure. Typically the holes are closed with a titanium plate or bone grafts. These approaches each have drawbacks. The use of a titanium in either mesh or plate form can be expensive, and bone grafts are difficult to perform, painful and prone to

infection. Each of these techniques can lead to deformity of the skull curvature.

A team of doctors and engineers from the National University of Singapore (NUS) and the National University Hospital, collaborating with Temasek Polytechnic, saw the need for something better. Inventors Swee Hin Teoh, Dietmar Hutmacher, Kim Cheng Tan, Kock Fye Tam and Iwan Ziein developed a biocompatible polycaprolactone polymer-based implant for the burr holes that provides a base for the bone of the skull to regenerate after repair at half the cost of a titanium mesh or plate. The invention is currently licensed to Osteopore International Pte Ltd., a NUS spinoff.

The technology works by rapid prototyping and design of a 3D patient-specific burr plug. It uses fused deposition modeling and enables the fabrication of the exact shape needed for the patient without a mold. This approach is not only economical but minimizes infection. This invention has received support from various organizations, including the Ministry of Education, the National Medical Research Council and the Tote Board.

One of the first patients treated was a 23-year-old man who suffered an injury on the job. The engineering team fashioned a precise scaffold infusing some of his living bone cells into the scaffold to "seed" the growth process. The bone plug has achieved wonderful results, and two years later the scaffold has fused with the surrounding tissue, with no trace of the

original hole. His hair has even grown back.

Toeh indicated in the *Far Eastern Economic Review* (Oct. 21, 2004) that this new technology might be used in developing countries, where medical imaging equipment is scarce, causing doctors to drill multiple holes in a patient's skull before they may find the correct entry point. Other anticipated applications for this technology include treatment of patients with facial injuries and uses in cardiovascular, orthopedic and dental treatment.

University of Buffalo Pill Crusher Makes Medicine Easier to Swallow

Have you ever had to manually crush a pill for a child, an elderly person or one of the millions of Americans with documented swallowing difficulties (dysphagia)? Perhaps you have had to crush medication for yourself because the large pill size would lead to discomfort during swallowing. Now, imagine having to perform this tedious task several times a day while suffering from arthritis, multiple sclerosis, cerebral palsy, carpal tunnel syndrome or poststroke difficulties that severely limit your ability to crush the medication. Sounds incredibly challenging, doesn't it?

To address this challenge, James Peron, James Leahy, Jonathan Leahy and Robyn Washousky of the University of Buffalo have created First Crush, a battery-operated and easy-to-use machine that quietly and automatically crushes pills. First Wave Products Group has commercialized the technology whose initial development was funded by the National Institute on Disability and Rehabilitation Research of the

U.S. Department of Education and supported by the Rehabilitation Engineering Research Center of Technology Transfer and the University at Buffalo. The result is a machine that generates medication in the form of a powder that can be mixed with food or liquid for easy ingestion.

The primary beneficiaries of this technology are the elderly and people with disabilities. Interestingly, statistics from the U.S. Census Bureau indicate that adults age 65 or older consume more than 30 percent of all prescription medication and purchase more than 40 percent of all nonprescription medication. This elderly population continues to grow due to improvements in health care and the aging of the baby boomer generation, with the number of elderly expected to increase from 39.4 million in 2010 to 53.2 million in 2020. In addition, as the elderly population increases there is an inherent increase in the number of people who develop various disabilities, who could benefit from assistive-technology devices such as First Crush.

But the elderly and those with disabilities are not the only ones to significantly benefit from this new technology. A survey of 540 nurses indicated that more than 80 percent of nursing homes either crush pills or open medication at least once a week. The same survey indicated that 58 percent of these nurses reported receiving instructions from the prescriber to crush or open the medication. Notably, some health care professionals in nursing homes and hospitals, for example, are known to crush hundreds of pills a day and would thus

greatly benefit by using First Crush.

So whether it is people with disabilities who rely on assistive-technology devices, health care providers who crush thousands of pills in a year or patients of any age who have difficulty swallowing their medication, there is a significant segment of the population that would benefit from a reliable and durable device such as First Crush.

University of Colorado Software Makes Kids Game for Learning

If you are a parent who is always telling your children to stop playing video games, wait until you hear this.

My Virtual Tutor is an interactive video game available for the handheld Nintendo DS system that makes the process of learning to read fun, affordable and portable. The Foundations to Literacy project, nationally recognized for its innovative and engaging educational approaches, started at the University of Colorado at Boulder after receiving a five-year National Science Foundation grant in 2000 and additional funding from the National Institutes of Health, the Coleman Institute for Cognitive Disabilities and the University of Colorado Technology Transfer Office.

According to the National Institute for Literacy (NIL), the period in a child's life between birth and age 5 is crucial for the development of literacy skills that will influence how the child will perform academically. Young children can be taught to read long before they start kindergarten. The NIL suggests that children

be exposed to environments that support literacy skills in a manner that engages them, like songs, games, activities and puzzles.

The foundation of the proprietary software for My Virtual Tutor was developed by a team of 18 researchers at UCB's Center for Computational Language and Education Research before being licensed to Mentor InterActive Inc. in 2006. Mentor InterActive Inc. added features to the child-friendly product capable of improving the reading comprehension and language skills of young children making it available on the extremely popular Nintendo DS platform.

So before you tell your children to put down the video games and pick up a book, make sure they are not already enriching their academic future by playing My Virtual Tutor on their Nintendo DS.

University of Delaware Technology Provides Safer Drinking Water

Worldwide, about 1.2 billion people lack access to safe drinking water, and twice that many lack adequate sanitation. As

a result, the World Health Organization estimates that 3.4 million people, mostly children, die every year from water-related diseases.

In a paradigm shift researchers Pei Chiu and Yan Jin of the University of Delaware have developed a new nonchlorine-based technology (funded by a National Science Foundation Small Business Innovation Research grant and a University of Delaware subaward, Corporate Environmental Solutions) that is able to purify water to remove 99.999 percent of bacteria and viruses. Viruses have been extremely difficult to eliminate in drinking water since they are smaller than bacteria, highly mobile and resistant to chlorination and filtration. Chiu and Jin discovered that by using elemental iron in the filtration process, they could effectively remove viral agents from source water. The process causes the viruses to be chemically inactivated or irreversibly adsorbed to the iron.

The use of elemental or "zero-valent" iron in this technology is also much cheaper than current techniques because this material is a normal byproduct of iron and

steel production, an important consideration in both the developed and developing world. The zero-valent technology has been licensed to the Center for Affordable Water and Sanitation Technology (<http://www.cawst.org/>), a nongovernment organization, licensed for humanitarian purposes to provide pure water to impoverished areas of the world. The center is investigating its use in a portable water treatment unit.

The research team envisions use of this technology to safeguard the water supply in other applications such as agriculture where, for example, it could be integrated into the wash system of a produce production facility. In such a setting it could make an important contribution to safeguarding fresh vegetable production. In addition it could help avoid water- and food-borne illness outbreaks such as that experienced in the United States in September of 2006. That outbreak, according to the Centers for Disease Control, was responsible for sickening 276 people and killing three.

Production Notes

The paper used for the *Better World Report* contains a minimum of 10% postconsumer waste and carries the FSC environmental certification.

The 2010 *Better World Report*, published by the Association of University Technology Managers, celebrates real-world examples of technologies that directly impact the health, well-being and overall quality of life of people around the world.

Here are a few examples of the innovations showcased in this book:

- A mechanical engineering student designs a device that transforms electronic wheelchairs into all-terrain vehicles giving disabled people — including his father — the freedom to roam a whole new world
- An international team of scientists, organizations and laboratories collaborate to produce the world's first vaccine developed to prevent cancer
- An interactive software program allows children to work at their own speed, select their own subject matter and receive immediate feedback giving thousands of students a precious gift: the ability to read
- Chromosome research leads to specialized gene-stacking technology for crop research that may one day allow farmers to increase yields, grow more nutritious plants and help meet the demands of an exponentially increasing worldwide population
- A biologist envisions tiny living sentinels watching over the world's water supplies with a system that monitors the swimming habits of protozoa that can provide an instant warning for a broad range of toxins

Read more about the diversity of academic innovation and the world of technology transfer at www.betterworldproject.net.



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