Wisconsin's Biotechnology Frontier

Current Trends and Future Challenges
in Research-Driven Economic Development

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Introduction: A Window of Opportunity for Wisconsin

"In just a few years, we have gone from studying one or two genes to analyzing tens of thousands of genes in one afternoon. With the imminent completion of the human and plant genomes, we are revealing the structure of 100,000 mammalian genes and 25,000 plant genes that comprise the book of instructions for life. In my opinion, we are ushering in a new age of understanding of how life works, something that happens perhaps once every millennium."

—Michael R. Sussman, Director, UW-Madison Biotechnology Center

In the realm of biotechnology and genetics research, the complete sequencing of the human genome accomplished this summer by a massive team of public and private researchers will be viewed as one of those rare and monumental milestones in science. But the importance of that feat is not as an end, but a beginning. The real work of putting genetic data into useful contexts, and finding new pathways to cure disease and promote better health, will be coming in the years and decades ahead. The Human Genome Project is a good barometer of the vast potential of biotechnology: Society is only beginning to scratch the surface.

Wisconsin, more than any other Midwestern state, is in a unique position to take advantage of the emerging biotechnology economy, primarily because the raw materials of this new economy are not minerals or forests or dairy cattle, but intellectual property. It will be driven by fundamental new discoveries in biosciences laboratories that further reveal the machinery of living things. Biological research is an abundant raw material at the University of Wisconsin-Madison. This is one of the few campuses in the nation that has all five biology-related schools or colleges: medicine, pharmacy, veterinary medicine, agriculture, and letters and sciences. UW-Madison has nearly 800 biosciences faculty across these units. And UW-Madison ranks in the top three of public universities in total research expenditures, which last year approached $500 million. Approximately half of that support is fueling biosciences research.

Another strength of UW-Madison is in engineering and the foundational areas of the physical, computational and information sciences. Medical physics, parallel computing, biomedical engineering and math and science education are a few examples of UW-Madison's national leadership. It is rare for universities to have the combined breadth of talent in both the physical and the biological sciences. The new interdisciplinary linkages that are forming in these fields will make UW-Madison a bigger player in biotechnology, since the most exciting advances are happening at the boundaries of traditional fields. In recent years, UW-Madison has led the nation in the total number of conferred doctorates in science and engineering.

Across the higher education system in Wisconsin, one can find innovative examples of biotechnology research, outreach and training. Medical College of Wisconsin, for example, is a growing power in basic biomedical research with more than $72.5 million in extramural funding, and Marquette University has an influential research program in

biomedical engineering. UW-Platteville and UW-River Falls have a strong legacy of agricultural teaching, research and outreach programs that have made Wisconsin farms more productive and environmentally sound. UW-Eau Claire has a strong program in basic biology education and molecular biology training that prepares students for biotechnology careers. UW-Stevens Point has the leading natural resources program in the nation, with an integrated curriculum that covers land, water and species management issues. And Madison Area Technical College has one of the most established two-year training programs in the nation for biotechnology lab technicians.

Wisconsin has a century-old tradition of supporting agricultural and biological research, which helped make the state a national leader in the dairy industry. State strengths in traditional agriculture research such as selective breeding (sometimes called "slow biotechnology") have led to improvements in crops such as soybeans, cranberries, carrots and potatoes. In fact, Wisconsin is No. 1 in cranberry and alfalfa production. But if one thinks more broadly about the industries that made Wisconsin famous – paper-making, dairying, agriculture and brewing – all of them rely in some essential way on biological processes. And all will be affected by advances in biotechnology research.

Bioscience research pays enormous social dividends. According to a 1997 study by the Wisconsin Association for Biomedical Research and Education (WABRE), Wisconsin citizens save an estimated $1.7 billion annually in health care costs thanks to the public investment in biomedical research and development. Wisconsin ranks third among all states in total federal expenditures for bioscience research. The same report showed that 160 bioscience industries in Wisconsin employed nearly 16,000 people and contributed $6.6 billion to the state economy. Those numbers almost certainly would be more impressive today given the consistent biotechnology business growth.

Wisconsin's legacy as a life sciences pioneer is precisely why the state stands to benefit in the highly competitive biotechnology industry. Beyond the science that fuels the field, other basic ingredients of the industry are beginning to form. There is a growing cultural change within the UW System that encourages researchers to recognize and pursue the applications of their scientific work. The change has led to a remarkable rise in research-based spinoff companies in the past decade. Wisconsin is beginning to see the development of an entrepreneurial culture that is producing the talent to lead these companies. There is an emerging base of venture investment capital, still small by Silicon Valley standards but growing at a rapid rate. And biotechnology has become a priority for Gov. Tommy Thompson, the state Legislature and the UW System, which together are crafting an agenda for economic growth.

These issues will be discussed in greater detail in this report, which will attempt to take stock of Wisconsin's current status in biotechnology and identify key issues to promote continued progress. The report also explores the serious ethical challenges posed by biotechnology research, and the need for greater research and public discussion.

Defining biotechnology and Wisconsin's academic strengths

Bioethics Professor Robert Streiffer provides the following definition of the field: "Biotechnology consists of a set of tools which allow for the use and modification of the genetic capabilities of organisms, including micro-organisms, plants, animals and humans." While that definition covers the genetics research landscape, the entire range of medical technology development should also be included in this discussion. Biotechnology often relies on a collaboration between biology, computer science, engineering, and physical sciences. Applications can range from the development of new drugs that counter disease at the molecular level, to new computer technology that speeds up genetic sequencing, to medical instrumentation that diagnoses or treats disease, to genes introduced into food crops that can promote insect resistance.

Biotechnology is not "new" in the purest sense, since biology-based tools can include everything from fermentation in beer-making to selective breeding of crops. But there are clear lines of distinction between classical and modern biotechnology, the most important of which is the speed of change. Modern biotechnology tools have given scientists increased accuracy and precision, the ability to analyze genes *en masse* rather than a few at a time, the ability to work across species boundaries and accelerate a genetic process that once took generations with traditional breeding. Three basic categories — medical, agricultural and environmental biotechnology — provide convenient groupings for a discussion of the state's research landscape.

Medical biotechnology
Currently, many hundreds of known diseases are caused specifically by a genetic malfunction, and many can have devastating effects on a person's health and quality of life. It is expected that the number of identified disease-causing genes will increase into several thousand before the end of this decade. At present, many of these diseases have no fundamental cure. The Human Genome Project, which ultimately hopes to identify the specific functions of all genes, will allow scientists to study the genes that are implicated in specific diseases in much greater detail. It may be the first step toward drug treatments and genetic therapies that may ameliorate some of society's most serious illnesses, including Alzheimer's disease, diabetes, birth defects and schizophrenia. Another research area with tremendous medical implications is in the isolating and culturing of human embryonic stem cells, an area in which UW-Madison is a world leader through the work of James Thomson's research team. Stem cells have the capability to develop into virtually any cell made by the human body, including bone marrow, neural tissue or muscle cells. This work opens the door to treating a wide range of cell-based diseases, such as Parkinson's disease and multiple sclerosis. Wisconsin projects include:

• Insights into the genetic basis of aging. In studies with mice at UW-Madison, researchers have identified a small group of genes — less than 2 percent of all genes — that change dramatically in response to aging, and govern key tasks such as stress response, protein repair and energy production. The scientists also found that reducing caloric intake can slow that process.

• Discovering the genetic origins of a number of serious illnesses. At Medical College of Wisconsin (MCW), scientists are working to identify the genes that cause juvenile diabetes and hypertension. Researchers already have isolated the genes responsible for a severe form of arthritis, and developed an accurate and fast genetic test to diagnose color blindness.

• Advances in cancer research. At UW-Madison's McArdle Laboratory, one project is looking into the molecular genetics of Epstein-Barr virus, which is causally associated with several human cancers including lymphomas and carcinomas. Another project is helping identify mutant enzymes that may protect healthy cells from the toxic effects of cancer chemotherapy. Another group is studying natural tumor suppressors that may help control or stop cancer growth.

• Genetic studies of bacteria that cause human illness. A research team in UW-Madison's Genome Center of Wisconsin is honing in on "the pathogenic genome," a grouping of genes that appear to be the illness-causing factors in some of our most dangerous food-borne illnesses, including *E. coli* and *Salmonella*. It is the first step toward therapies that could disable the illness-causing machinery of these common bacteria.

Agricultural biotechnology

On a parallel pace with the human genome sequencing project is an effort devoted to the model plant genome, a small mustard plant called Arabidopsis. The sequencing for this important genome has been completed and is slated for publication in December. UW-Madison is the international center for the creation of a complete library of 30,000 "knockout genes" for Arabidopsis, which will reveal the function of genes by eliminating them one at a time. The rice genome is nearing completion and will be a major achievement because of its importance as a worldwide food crop. The applications envisioned in plant and animal biotechnology include finding natural resistance to pests and disease that can reduce reliance on chemicals; improved growing characteristics that will improve yields and maximize the use of available farmland; and the development of value-added products such as "nutraceuticals" that will express healthful compounds in common food products, such as fruits or milk. Wisconsin examples include:

• Developing a strain of alfalfa that can serve as a "factory" for an enzyme called phytase, a compound that could reduce one of Wisconsin's biggest pollution threats. When fed to farm animals, this phytase-rich diet would help animals absorb phosphorus and reduce phosphorus in manure by up to 50 percent. This UW Biotechnology Center project could dramatically reduce phosphorus loading in soils, a major polluter of Wisconsin lakes and rivers.

• Tracking down the genes responsible for twinning, or the production of two calves at once. The UW-Madison research is advantageous to the farmer in helping control the birth rate for beef cattle, dairy cattle and other livestock. While increasing twins would have obvious benefits for meat livestock, dairy farmers have a need to reduce twinning because of the health risk posed to pregnant cows.

• The development of food crops that may help extend the growing season in Wisconsin by two to three weeks by controlling plant senescence. The gene can disconnect the aging process that causes plants to drop their leaves and transfer their energy to seeds. The UW-Madison technology could increase yields of food and forage crops by reducing spoilage and helping farmers make better use of available land. This same technology could also help the floral industry extend the freshness life of cut flowers.

• A UW-Madison corn research project that is looking at chromatin genes, which control the packaging of DNA within plant cells. Understanding how chromatin controls which genes are "on" and which genes are silenced can have implications for developing more efficient methods of genetically modifying agricultural crops.

Environmental biotechnology

A growing number of microorganisms are being discovered that have the ability to clean up toxins in the environment or reduce industrial reliance on pollution-causing techniques. Some of the most efficient strains of bacteria that help decompose garbage are being bioengineered and used in landfills. Other microbes have been cultured for their ability to clean shorelines marred by oil spills, or for gobbling PCBs and other chemicals from contaminated soils. A few examples from Wisconsin research:

• The Biopulping project. Scientists at the UW Biotechnology Center and the Forest Products Laboratory have developed a fungal treatment for wood chips that reduces the need for environmentally harmful chemicals in the paper industry's pulp production process. Not only does biopulping reduce chemicals, it increases the speed of pulping, produces a net energy savings of 30 percent and leads to increased paper strength.

• The creation of a “systems research farm” at UW-Platteville that will serve as a test bed for the latest research on environmentally sensitive farming. The experimental farm will model different agricultural practices and carefully monitor the resulting environmental impacts. The goal will be to model experimental farming techniques that are both profitable and reduce surface and ground water pollution.

• UW-Madison researchers discovered a bacterium in the Badger Army Ammunition Plant near Baraboo that degrades dynamite. The scientists identified the genetic factors that enable the bacteria to degrade TNT, and eventually hope to engineer strains that can help clean up contaminated sites. There are an estimated 10,000 U.S. sites contaminated with explosives and related compounds.

• A faculty team at UW-Oshkosh is directing research on biofiltration, which is the use of biologically based systems to clean contaminated air. The team has pilot-scale demonstrations in the Fox Valley region that are capable of removing air toxins and odors from industrial settings. They are also investigating a larger-scale reactor system that could be used for greenhouse gas reduction from point sources. The technologies are a practical and cost-effective solution to clean-air problems for industry.

Innovative training and education in biotechnology

As many as one-third of all registered biotechnology companies in the United States employ fewer than 50 people. That poses a significant training challenge to the industry, since firms will need well-rounded technicians with the ability take on both scientific and business tasks. Wisconsin has a remarkable range of academic programs, from two-year certificates to postdoctorate training, that produce a ready talent supply for the industry, and raise society's understanding of the biosciences.

Examples include a biotechnology major at UW-River Falls, which draws on the expertise of faculty in biology, chemistry, animal and food science, and plant and earth science. Madison Area Technical College has an associate degree in biotechnology that has enrolled 40 to 70 students per year since 1987, and has a high job placement rate with state companies. The program has articulation agreements with UW-Whitewater, UW-River Falls, UW-Platteville, Upper Iowa University and Edgewood College. UW-Oshkosh is in the process of building a centralized DNA sequencing facility that will address a wide range of research topics as well as hands-on student training and public outreach. UW-Whitewater has a unique degree program in marine and freshwater biology, providing a core curriculum of chemistry and biology and a final year of instruction at Deakin University in Australia. Whitewater also unveiled this year a new Integrated Science-Business Major, the first undergraduate program of its kind in the nation.

Another national first is the graduate program in Healthcare Technologies Management run by Medical College of Wisconsin and Marquette University. The program combines background in business and biomedical engineering to train professionals in the design, development and commercialization of medical technology. Applications include devices for anesthesia, medical imaging, patient monitoring and therapeutic interventions. Medical technology is a growing industry in southeast Wisconsin and Madison.

Many campuses are extending programs to the community. UW-Parkside's department of biological sciences has a continuing education program in biotechnology serving employees of Abbott Laboratories, and is expanding the program locally to Great Lakes Biosystems and Trans Chemco. UW-Madison's Biotechnology Center houses a statewide educational outreach program that trains hundreds of K-12 school teachers and thousands of children each year in biotechnology principles. At UW-Green Bay, the faculty-inspired Northeast Wisconsin Science Forum has been helping teachers from about 40 area middle and high schools stay current on a variety of science and technology topics. UW-Madison's Biotechnology Training Program, sponsored by the National Institutes of Health (NIH), offers pre-doctoral training to 33 students and has a year-long internship requirement that has placed students in dozens of state companies. And UW-Extension's Small Business Development Center launched a business planning course this summer for people trying to start technology-based companies.

Directing greater energy toward technology transfer

"If you look at what happened after World War II, the great advances and the great economic boom in the United States was really based on a lot of people going to college, getting educated, and coming up with new ideas and new research. I'm a firm believer that research is the economic engine that drives the nation. Now, more people are realizing that economic development should be a natural part of what a university does. We recognize that a part of our social responsibility is to make that happen."
—Virginia Hinshaw, dean of UW-Madison Graduate School and senior research officer

UW-Madison has long had world-class assets in basic research and a record of putting that research to work to solve medical and social problems. For example, biochemist Harry Steenbock's 1920s discovery that vitamin D can be produced in foods with ultraviolet irradiation led to profound applications for human health. In the 1930s, UW-Madison scientists solved the riddle of iodine deficiency that led to the formulation of iodized salt; another team found that niacin supplements prevent pellagra, a disease that once killed 5,000 people annually. Scientists here have developed scores of cancer-fighting advances, including improvements on imaging technologies such as MRI to help identify and fight tumors. UW-Madison has been a campus of scientific firsts: first genetics department in the United States (1918); first university to create its own independent agency for steering intellectual property, the Wisconsin Alumni Research Foundation (WARF) (1925); the first introduced strain of hybrid corn in Wisconsin (1932); and the first bone marrow transplant in the United States (1968).

But what is genuinely new at UW-Madison is a coordinated strategy for helping the university translate its basic research discoveries into useful applications and new companies that benefit the Wisconsin economy. In recent years, a cultural shift has occurred on campus, where technology transfer is being recognized not just as a happy accident of research, but a direct responsibility. The culture change is embodied in Chancellor David Ward's creation in 1997 of the Technology Transfer Council, which brings "a more deliberative style" to applying the great discoveries on this campus. The council pulls together the major players in technology transfer, including WARF, University-Industry Relations and the University Research Park. The following is a closer look at recent developments in UW-Madison's technology transfer engines:

The Wisconsin Alumni Research Foundation. The importance of this organization to UW-Madison research — and to the Wisconsin economy — cannot be overestimated. Through its 75-year history, WARF has granted more than $580 million in royalties back to UW-Madison, including this year’s $80 million commitment to the BioStar building campaign. WARF has licensed more than 3,000 technologies from campus discoveries and ranks in the top six nationally in total royalty payments and licensing fees received. The famous quote by Thomas Edison — "The value of an idea lies in the using of it" — serves as the foundation's operating principle.

WARF is averaging about 275 invention disclosures a year from UW-Madison, and just began a program called WiSys for managing disclosures from researchers throughout the UW System. The program has led to seven disclosures to date, and more are expected as the program is promoted statewide. Recently, WARF has been taking an equity interest, in lieu of its normal licensing fees, in some of the companies developed from UW-Madison research to help those companies conserve capital. WARF currently has equity interest in 18 companies, and all but one are in Wisconsin.

Carl Gulbrandsen, managing director of WARF, said the intellectual property pipeline for biotechnology applications is extremely strong, accounting for about one-third of all disclosures. Especially important is the emergence of "platform technologies," which can cover a wide array of applications, including diagnostics, research or direct therapies. One of the most important and medically valuable platform technologies in UW-Madison history is biochemist Hector DeLuca's vitamin D discoveries, which have been used to treat osteoporosis, cancer and other diseases. New platforms on the horizon include embryonic stem cell technology and "optical mapping," a method of analyzing whole genomes that has become the gold standard of the sequencing field. A third platform technology is the creation of synthetic viruses, which open the door to developing more efficient vaccines and safer gene therapies.

The University Research Park. Created in 1984, the park on Madison's west side has experienced an unprecedented growth spurt during the past five years, primarily by cultivating its mission as a home for technology-based spin-off and startup companies. The park currently has 88 business tenants with more than 2,500 employees, and approximately two-thirds of those companies are high-tech or biotech in nature. One of the park's most important developments has been the MGE Innovation Center, a truly novel incubator for the very types of companies that evolve from scientific research. The center housed 10 tenants a decade ago, but increased demand led to a new building in 1999 that doubled available space. By 2001 the center will have doubled again, with space for up to 40 companies. This center provides shared services, a blend of office and laboratory space, and a collaborative environment that helps companies learn from each other, all of which helps meet the unique needs of biotechnology startup companies.

University-Industry Relations (UIR): This campus-wide program serves as the primary liaison between university expertise and private sector interest, and plays a role in helping UW-Madison spin-off companies get started. One important example of its work is in helping Wisconsin entrepreneurs apply for and receive federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants. These have become critical sources of seed capital for small technology-based ventures. More than 100 Wisconsin companies have received these federal grants since 1983, and they have been an early ingredient in the success of companies like Third Wave Technologies, Quantum Devices and PanVera Corp. UIR is in the process of hiring additional staff to assist in new spin-off venture creation.

The Wisconsin Distinguished Graduate Fellowship Program. Created by the UW-Madison Graduate School, the UW Foundation and WARF in 1997, this program has an

unprecedented goal of creating a $200 million endowment to support the recruitment of as many as 400 graduate students at a time. This program will enable UW-Madison to attract the best and brightest graduate students in the nation, people who represent the next generation of knowledge creation for the university and the state. While not directly a tech-transfer program, it underscores a key point about technology transfer: The greatest transfer that occurs from a research university is that of highly trained people, many of whom forge their careers in Wisconsin.

Biotechnology Companies: An Emerging Force in Wisconsin

"In the 1980s, nearly all of my graduate students were leaving after graduation to get jobs on the coasts. There were few companies in Dane County interested in hiring Ph.D. scientists. Now there are many jobs available and the promise of more as these companies grow. We are retaining more value in the state of Wisconsin. We are stopping the drain of highly trained people that the state has experienced."

—Richard Burgess, oncology professor and founding director, Biotechnology Center

The rapid rise in new spin-off companies in Wisconsin is perhaps the clearest sign that progress is being made in capturing the economic benefits of research. The most comprehensive analysis of this trend comes from the 1999 book "Creating High-Tech Business Growth in Wisconsin," written by UIR Associate Director Philip Sobocinski. His study identified 178 technology-based companies in Wisconsin whose origins are tied closely to UW-Madison people or intellectual property. These firms employ more than 6,700 people, and they had aggregate gross revenues in 1999 of $1.01 billion. More than half of these companies are affiliated with a biological sciences product or service, and 68 percent of all UW-Madison spin-offs in the last decade could be defined as biotechnology-based. Perhaps the most significant trend is the accelerated rate of company formation in the past ten years: 107 new companies formed from 1989-1998. UW-Madison is now averaging about 14 new spin-off companies each year.

One strong economic niche for Wisconsin is in life science tools, the "picks and shovels" for genetics-based research and medicine. **Promega Corp**., formed in 1978, is one of Wisconsin's early biotechnology pioneers, specializing in products like biological reagents that are basic ingredients in biological research. It now has 700 employees, 1,200 products and annual sales exceeding $100 million. It is one of only two companies providing DNA test products to criminal justice systems around the globe. Promega has taken a visible leadership role in promoting state biotechnology. It founded the BioPharmaceutical Technology Center Institute, a not-for-profit organization that offers programs on biotechnology for K-12 students, teachers and the general public.

The latest major player in medical diagnostics is **Third Wave Technologies**, which employs approximately 250 people and is poised for major growth. Third Wave develops tests that work like credit-card readers in verifying the presence of specific DNA sequences responsible for disease. It is rapidly becoming a high-profile Wisconsin success story: Earlier this summer, Third Wave filed with the U.S. Securities Exchange Commission for an initial public offering of $100 million in common stock, and recently

received a $48 million infusion of venture capital. The company has a number of active partnerships with UW-Madison researchers.

A growing number of biotechnology-related companies are forming in Milwaukee and southeastern Wisconsin, a trend fostered by research from Milwaukee-area universities. One of the greatest strengths of that region is in medical technology, and is home to the world leader in that industry, **GE Medical Systems**. Founded nearly a century ago, GE Medical Systems has 5,000 employees in Wisconsin and more than 25,000 employees worldwide. It is a leading manufacturer of a variety of medical technology, including computer tomography (CT), magnetic resonance imaging (MRI), positron emission technology (PET), x-ray and ultrasound technology, and medical information systems. It has developed a very close relationship over the years with Wisconsin research universities. Thanks in part to an array of new technologies and recent acquisitions, the company's total sales to health care institutions around the globe has doubled since 1996 and totals $7.4 billion this year.

While difficult to predict where the next Promega, GE Medical Systems or Third Wave might be incubating in Wisconsin, the following are some promising companies that have strong potential to create new jobs. The majority of these companies have received federal SBIR or STTR grants.

• **Nimblegen**: This Research Park company is commercializing a new approach to "DNA chips" pioneered at UW-Madison by the interdisciplinary team of Fred Blattner, Franco Cerrina and Mike Sussman -- professors of genetics, electrical engineering and horticulture, respectively. DNA chips allow scientists to analyze thousands of genes at one time, and the current technology is extremely expensive. Nimblegen promises to make gene chips accessible to most scientists at a fraction of the current cost. Current surveys estimate the DNA chip market may reach $40 billion in the next decade.

• **Medical Advances Inc.**: This Milwaukee company was formed in 1985 to commercialize innovations in magnetic resonance imaging (MRI) technology from the Biophysics Research Institute at Medical College of Wisconsin. The company maintains an active research and development partnership with MCW, and has a product list of more than 150 items that enhance the value of MRI as a clinical diagnostic tool. The company employs more than 70 people.

• **SLIL Biomedical Corp**.: Based on the research of pharmacy professors Donald Witiak and Benjamin Frydman and pathology professor Laurence Marton, the company has developed a pipeline of 16 different compounds targeted against cancer and other human health diseases. SLIL is also developing a potential breakthrough technology called sequential pathogenesis, which is a new model of disease that could lead to entirely new cancer therapies. The company has 15 employees and $7 million in current funding.

• **Tomotherapy Inc**.: This company is based on the work of UW-Madison medical physics professor Thomas Rock Mackie, who has developed a new paradigm for radiation-based cancer treatment. The tomotherapy approach may allow doctors to

deliver hundreds of precisely tailored beams of radiation in exactly the dosage needed to kill cancer with virtually no residual damage to healthy tissue. The approach could work on currently untreatable diseases such as pancreatic cancer. Clinical trials are planned for the alpha device, built at the Physical Sciences Lab in Stoughton and installed at UW Hospital.

• **Stratatech LLC**.: Formed in March 2000 at the MGE Innovation Center, Stratatech is based on a unique human skin cell line discovered and patented by UW-Madison Medical School Professor Lynn Allen-Hoffmann. This immortal cell line perfectly mimics the behavior of human skin layers, giving it many potential uses in the marketplace. For example, the technology offers an alternative to using animals in product testing. Current clients include a global cosmetics company and an international consumer and household products company.

• **Merge Technologies Inc.**: Based in Milwaukee, this company develops integration technologies for radiology departments of more than 350 hospitals and clinics around the world. The technology helps pull together a normally disconnected flow of clinical records and medical images into a system that improves patient care. The 13-year-old company has more than 100 employees, including 70 in Wisconsin, and collaborates with Medical College of Wisconsin on professional training programs.

• **Gala Design LLC**: This Sauk City-based company has a uniquely Wisconsin spin on the development of new drugs. The company uses dairy livestock as a means of producing a large supply of genetically engineered protein drugs, or "biopharmaceuticals." New genes are introduced into the animals that allow them to produce medically beneficial proteins in their milk. Those are then extracted and used as basic ingredients in protein-based drugs, a huge class of drugs that include insulin and growth hormone. Cows are ideal for the production of beneficial proteins because of milk's high protein content.

• **3-D Molecular Designs**. This Milwaukee startup company combines expertise in materials research and science education into a new genetics curriculum tool. The company was formed by Michael Patrick of UW-Madison and Tim Herman of the Milwaukee School of Engineering. Using a rapid prototyping technology pioneered at MSOE, the company is producing accurate physical models of proteins, DNA and other biomolecules for use as visual learning tools. The models help make the molecular world visual and real in both education and research settings. The company received an SBIR grant this spring and is pursuing partnerships with textbook companies.

• **Forgene Inc**.: This Rhinelander company is built around a number of successful technologies for genetically improving trees for forestry, landscape, Christmas trees and other applications. Founded in 1985 by Neil Nelson and Julie Berndt Nelson, Forgene produces a fast-growing hybrid poplar species that is used by the pulp and paper industry and the energy industry. It also produces a spruce tree that has enhanced resistance to late spring frost. Forgene was the first company in the nation to receive a patent for a genetically enhanced tree.

• **Wisconsin Whey International**: In the Green County town of Juda, entrepreneurs Bill Buchholz and Linda Smith lead this company devoted to customized, value-added products from whey, normally a byproduct of cheesemaking. The company, like many other state cheese industry firms, are reaping benefits from the product-enhancement innovations at the Wisconsin Center for Dairy Research.

Beyond helping diversify Wisconsin's economy and expand the tax base, these emerging companies offer highly skilled, well-paying jobs that represent Wisconsin's best chance at stemming the "brain drain" of college-trained talent to more established biotechnology hubs like San Francisco and Boston. Burgess, reflecting on when the Biotechnology Center began 17 years ago, said the big change today is the ability to capture research benefits locally. "Now instead of just enhancing the economic strength of the coasts, we will do it here," he said. “This allows for a larger return on the Wisconsin taxpayer’s investment in the UW System.”

The ethical issues: Potential dangers and a path to solutions

"If the Wisconsin debate plays out in the same way as the national and international debates, then unbridled optimism about biotechnology is not going to be all that helpful. People are suspicious. They want an honest discussion of risk and they want issues that are not normally considered scientifically valid to be on the table. People are looking for less assurances and more information."

—Robert Streiffer, UW-Madison professor of biotechnology ethics

As biotechnology applications increase, people are beginning to recognize that the scientific, social, ethical and moral issues of this field cannot be separated. The guiding public question regarding our new biological frontier is not "can we?" but "should we?" The answer may be much clearer in some cases than in others. For example, the recent development of "golden rice," a form of genetically altered rice that has enhanced vitamin A and beta carotene content, may help solve a nutritional deficiency that causes blindness and other health problems in many undeveloped nations. That is likely to garner more public support than biologically enhanced products that do not have the same social benefits. There is a range of responses to biotechnology, from enthusiasm to suspicion to fear, that need to be accommodated in policies. There are generally three categories of ethical cautions: One is a generalized moral objection to the practice of manipulating life; the second is the issue of "unknown risks" posed by the speed of new applications; and the third covers questions of who benefits from – and who controls – biotechnology.

Regarding moral issues, we currently have a debate in Wisconsin and the nation over the appropriateness of using stem cells derived from embryos for medical research. Streiffer notes another strong line of opposition to the notion of crossing species boundaries in genetic engineering and violating species integrity. Other biotech opponents such as Jeremy Rifkin argue that biotechnology is a reductionist line of thinking that reduces

organisms, including people, to a collection of genetic material that can be manipulated at will.

The issue of unknown risk is playing itself out most prominently in the area of genetically modified foods. There is an element of irreversibility that raises the stakes of altering genes in agriculture. Some people contend that the speed of biotechnology makes it impossible to know for sure whether unintended negative consequences have been eliminated from genetically modified crops. That issue is being hotly debated with genetically modified Bt corn. New strains of corn that have the *Bacillus thuringiensis* (Bt) gene spliced into the plant gene can produce a protein that naturally kills insect predators. An initial study from Cornell University found that pollen from the modified corn could pose a threat to Monarch butterfly caterpillars. This fall, however, a new report by the Environmental Protection Agency found no “unreasonable adverse effects” with the technology. Scientists also worry that adding Bt genes to plants will promote resistance and erode the power of this natural insecticide.

The question of who ultimately benefits from biotechnology incorporates a range of fairness and equity issues. For Wisconsin, one question is whether agricultural biotechnology creates greater advantages for large multinational companies and places small farmers at an even greater competitive disadvantage. Other cautions have been raised about "bio-piracy," where companies can exploit indigenous peoples' knowledge of native medicinal plants, isolate and patent the beneficial chemicals, but confer no benefits to the people or country of origin. Regarding who controls genetic information, there are current debates over whether it is appropriate or ethical for genes to be patented. Another major concern is over privacy of personal genetic information, and whether people could face discrimination from insurance companies or employers based on their genetic profiles.

Some of the societal response to biotechnology likely stems from the fact that major biomedical advances typically receive a cool reception, until their value is demonstrated and a comfort level is achieved. Streiffer noted that organ transplant technology, the use of pig valves in heart repair surgery, and the use of anesthesia during childbirth all received an initial negative reaction from a public that worried such advances were unnatural. Hinshaw noted another example: When Edward Jenner first developed smallpox vaccines from cow viruses, the disease was still a major killer. But there was initial public controversy. One editorial cartoon showed people first getting the vaccines, then growing horns and tails.

The purpose of raising these issues is not to answer them here, but to demonstrate the responsibility society faces in sorting through ethical dilemmas, attempting an objective assessment of risk and working to reach a viable consensus. Governmental responses so far have been varied around the world. In Europe and other influential nations, including Japan and Australia, governments have placed trade and consumer barriers on genetically modified foods. In the United States, the Food and Drug Administration recently strengthened its pre-market regulation of bioengineered foods, requiring all companies to notify the FDA of a new genetically modified product at least 120 days in advance.

Government responses are being driven by public input and the need to promote consumer confidence. Given the uncertainty, this is an area in which universities should play a leadership role as an objective source of new research and public information.

UW-Madison may have one of the largest and most respected teams of medical and biological ethicists of any university in the country. Robin Alta Charo, professor of law and history of medicine, brings a unique interdisciplinary background to controversial topics such as cloning, reproductive technologies, human subjects research and embryo research. She serves on the President's National Bioethics Advisory Commission. Pediatric Professor Norm Fost is also a national leader in the field of medical ethics. He directs the UW Hospital and Clinics ethics and human subjects committees and his views are sought nationally on issues such as health care access, genetic testing and patient's rights. Daniel Wikler, professor of philosophy and medical ethics, has expertise on health care resources and access, and law Professor Alan Weisbard teaches biotechnology law.

Streiffer will teach new courses on biotechnology ethics, including an upper-level seminar and a cross-listed undergraduate course designed for hundreds of students. He is one of two new faculty who are part of the strategic hiring initiative in bioethics. The other is Pilar Ossorio, who studies legal and ethical issues in genetics and race and ethnicity issues in health care. The hires are meant to provide a strong ethical grounding for the biosciences across campus. The goal of the strategic hiring group is to integrate ethical decision-making campuswide, rather than creating a separate enclave.

Next steps: Recommendations for continued growth

"Unlocking the mysteries to this small strand of DNA is just one way we will ignite a New Industrial Revolution through the unlimited potential of the bioscience and high-technology industries. New discoveries in science and technology will create high-skill, high-paying jobs in Wisconsin. These jobs will provide a higher quality of life for our families and a brain gain for our state."

—Gov. Tommy Thompson, January 2000 State of the State Address

Despite the promising current status of research and commercial development, the biotechnology industry is still in its infancy worldwide. It will require the diligent attention of state leaders in order to continue to thrive. Gov. Thompson's State of the State address, which used biotechnology as a centerpiece of the new economy, brought a galvanizing focus on the opportunities ahead. But the momentum could just as easily slip away in the extremely competitive environment among states to become "the next Silicon Valley." The following are suggested priorities in the years ahead for the governor and the state Legislature, business and economic development agencies, and the UW System.

• **Continued support for the BioStar Initiative**. This $317 million initiative entails a public-private partnership to help build four new bioscience facilities at UW-Madison and complete a modernization of science facilities that began more than a decade ago. Why are facilities improvements so important to biotechnology? Simple: The competitive battle between the states for biotechnology research leadership will be won or lost based

on who can provide the best research environment. No fewer than 13 universities have major biosciences initiatives in the works. The University of Michigan embarked on a $250 million effort, Yale University intends to spend $500 million on facilities upgrades, UC-Berkeley also will spend $500 million to restructure its biology program, and the University of Minnesota plans to spend $123 million. Across the nation, universities and state governments have recognized that this new science demands new kinds of facilities and those who do not modernize will be unable to compete. The BioStar investment is proposed on the heels of Gov. Thompson's previous support through the 1990s of the WisStar and the HealthStar initiatives. These represent a combined public-private investment in science facilities of roughly $900 million.

"BioStar is needed to attract the talent for the university's future," said Elton Aberle, dean of the College of Agricultural and Life Sciences. "It allows you to compete nationally not only for the people, but for federal funding — and that's where the real impact comes. The state investment can be leveraged four or five to one with federal funding." BioStar would fund four new buildings over the next decade: A biotechnology center addition; a new microbial sciences building; a biochemistry building addition; and an interdisciplinary biology building. In addition to research, BioStar will help accommodate the phenomenal surge of student interest in the biosciences.

• **Completing Phase II of the Madison Initiative**. The first phase of the Madison Initiative enabled the university to take a revolutionary new approach to hiring faculty in interdisciplinary teams rather than along traditional department lines. This had a direct bearing on biosciences research, since many emerging fields are outgrowing the confines of the traditional departments. With the first phase, the university was able to attract world-class faculty through our genomics cluster hire group, and also build formidable new faculty teams around the fields of bioethics, biomedical engineering and nanoscale medical technology. The second phase of the Madison Initiative will allow UW-Madison to continue this influential approach to hiring. It will also place special emphasis on economic development by spurring more technology transfer and creating capstone degree programs in disciplines with high economic growth.

• **Approving a System-wide Master's program in biotechnology**. The $4 million proposal would enroll about 60 students per year from campuses across the UW System, and be tailored to respond to the needs of the Wisconsin biotechnology workplace. One key feature of the program is that state biotech firms would be involved in the hands-on practical training aspects of the curriculum, which would require a close partnership between faculty and private sector leaders. The program would be essential for training future leaders in both the science and the business aspects.

• **Promoting greater technology transfer statewide**. Wisconsin has an illustrious track record of putting its knowledge to work for the greater public good, a goal embodied by the century-old Wisconsin Idea. A major part of that principle today means ensuring research discoveries are being made available to society. Two upstart programs in Wisconsin are working toward this goal and deserve greater recognition and support. The first is WiSys, a program started this year by the Wisconsin Alumni Research Foundation

that offers patenting and licensing services to all UW System campuses. The second is TechStar, a technology transfer alliance unveiled this fall between Marquette, UW-Milwaukee, the Milwaukee School of Engineering and Medical College of Wisconsin. The institutions plan to join forces to promote commercial opportunities and technology businesses based on the Milwaukee area's collective research strengths. This could be a step toward promoting an "economic corridor" that builds on the strengths of Madison and Milwaukee.

• **Continuing to expand the availability of venture capital**. The venture investment landscape is improving quickly in Wisconsin, especially in the past year, but still has not reached its potential. Venture Investors of Wisconsin is an established investment fund that continues to grow, and was a important leader in the early growth of Madison's biotechnology industry. Some new developments are especially promising. Mason Wells, a spin-off of M&I Bank, is hoping to raise $75 million in technology-based venture investments and has already closed on a $30 million fund. A new investment network called Wisconsin Investment Partners has brought together a group of 18 investors who are interested in pooling resources to fund biotechnology startups in increments of $200,000 or more. Two other similar venture capital networks have formed in the past six months, Early Stage Research and Venture Investors Management. The Wisconsin Venture Fair is a successful matchmaking service between out-of-state investors and Wisconsin startups.

The state Department of Commerce's certified capital company, just started this year, consists of a $50 million pool for investment in high-growth ventures. The firms managing this fund have received more than 125 business plans to date. It is also important to note that nearly every company cited in this paper has received early stage funding from DOC. The department estimates more than $150 million in venture capital has been raised this year alone in Wisconsin. Given the level of innovation coming from Wisconsin research, the potential is for multiples of that amount.

• **Providing more incentives for attracting and retaining industry**. In addition to supporting basic research and teaching in biotechnology, Wisconsin state government could join others in considering incentives that will benefit existing companies and possibly attract new ones from outside Wisconsin. Many states are pursuing strategies, such as tax credits for corporate research and development, employee training, or for companies that invest in university-based research. Another possibility includes aggressive incubator programs that can help build a "critical mass" of companies more quickly. Companies looking to relocate will view intellectual resources and business climate as equally important factors.

• **Furthering smart growth of University Research Park – and beyond**. The fact that the MGE Innovation Center will quadruple in size over the course of four years — and probably still fall short of meeting demand — is evidence enough that a facilities shortage looms for laboratory-based companies in the region. Research Park Director Mark Bugher notes that the current location is quickly reaching its maximum of development and will soon need to expand into other university-owned property to

continue to meet its charge of serving campus-based commercial innovations. But the responsibility to meet demand goes beyond the park. "As the Wisconsin story continues to be told, the level of interest from venture capitalists and other biotechnology firms will substantially increase," Bugher said. "Other developers in the state will need to become sensitive to the unique needs of biotechnology companies and be prepared to respond."

• **Improving public education and involvement in biotechnology**. This science cannot thrive without public support, and scientists and business leaders need to do a better job of translating their work to the general public and explaining its benefits. Innovative web-based publications like UW-Madison's Why Files, which investigates the science behind everyday news, can go a long way toward increasing science literacy during this period of massive change. Other educational programs run by the Biotechnology Center have thousands of Wisconsin school children and their teachers learning how to extract and clone DNA, helping demystify the field for the next generation. Beyond public education, there needs to be some formal means for the public to have a greater say in the direction of biotechnology. Between the positive focus of the biotech industry and the criticism of industry opponents, there must be a trusted objective party that is replacing rhetoric with sound science. Universities and government agencies need to shoulder their share of responsibility for that outcome.

• **Getting the attention of the rest of the world**. Wisconsin has a proud national identity as a dairy industry leader, but it needs to do more to tell its story as a major emerging force in biotechnology. The successful models are out there. For example, Third Wave Technologies and Promega Corp. are visible successes that help translate Wisconsin's biotechnology potential to the nation. And beyond singular stories, Wisconsin needs a more concerted marketing strategy that promotes its identity as a biotechnology leader. A promising example of this just occurred this summer, when Secretary of Commerce Brenda Blanchard led a venture capital mission to California with representatives of Tomotherapy, SLIL, Stratatech and Gala Design. Wisconsin is currently ranked 10th in the nation in total biotechnology employees and companies, but the pace of growth suggests it will continue to climb. Greater interaction with national and global biotechnology interests will be essential. Leaders must continue to demonstrate to the world that biotechnology is a natural fit for Wisconsin, given its pioneering life sciences legacy.

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Since May 1994, John Wiley has served as the University of Wisconsin-Madison's Provost and Vice Chancellor for Academic Affairs, which carries the responsibility of chief operating officer and deputy chancellor for the university. From 1989 to 1994, Wiley served as Dean of the UW-Madison Graduate School, a position which combines the responsibilities of Dean of Graduate Studies and Vice Chancellor for Research.

In both campus-level positions, Dr. Wiley has served as an institutional representative for a variety of external constituencies, including alumni groups, the boards of trustees of university-affiliated foundations and other organizations, domestic and international inter-university cooperatives, chambers of commerce and service clubs, the state legislature and governmental bodies, the UW System Administration, and the UW System Board of Regents. In addition, he has been deeply involved in fundraising from individual and corporate donors as well as from charitable foundations.

Wiley received his bachelor's degree in physics from Indiana University in 1964. From there, he immediately attended graduate school at the UW-Madison as an NSF Fellow. He received a master's degree in physics in 1965 and a Ph.D. in physics in 1968. After graduating, he joined the technical staff of Bell Telephone Laboratories at Murray Hill, N.J.

Dr. Wiley was appointed a faculty member in the Department of Electrical and Computer Engineering at UW-Madison in August 1975. His research and teaching focused on a variety of advances related to semiconductors and other materials and processes important to the electronics field. He is a co-founder of several highly successful research centers at UW-Madison, including the Center for X-Ray Lithography and the Engineering Research Center for Plasma-Aided Manufacturing.

From 1982 to 1986, he chaired the Materials Science Program, a graduate-level, interdepartmental-committee program for master's and doctoral degrees that is associated with an instrumentation center that serves as a shared resource for research and teaching in materials science. In 1986, Wiley was named Associate Dean for Research in the College of Engineering. In this capacity, he had oversight responsibility (at the college level) for all aspects of grant submission, agency liaison, research infrastructure, engineering research centers, and technology transfer.

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Brian Mattmiller joined the UW-Madison Office of University Communications in 1994 as a university relations specialist and science and general assignment writer. A significant portion of his job is devoted to promoting UW-Madison's research enterprise through internal publications and media relations at the local, state and national level.

Responsibilities also include editorial contributions to annual reports for the Chancellors Office; speech writing; developing Internet-based news packages on special topics; and presentations related to university priorities. Special projects include serving on the On The Road Committee, which organizes service projects across the state; and serving on the internal committee that steers the strategic direction of university advertising.

Previous professional background includes nine years of work as a reporter for daily newspapers, including *The Southern Illinoisan* in Carbondale, Ill and the *Wisconsin State Journal* in Madison. Mattmiller received his bachelor's degree in journalism from UW-Madison in 1986.

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