Where are the Cures?

BY SALLY POBOJEWSKI

THE COST OF GETTING NEW DRUGS TO MARKET IS FAST BECOMING PROHIBITIVE, BUT REGULATIONS AND SIGNIFICANT RISKS AFFECT THE PROCESS AS WELL.

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$1 Billion

We live in a golden age of biomedical research where scientists seem on the brink of unlocking the basic secrets of life itself. Today, it's possible to sequence your entire genome — the genetic code that influences your medical destiny. Researchers have identified thousands of genes that, when defective, either cause or increase your risk of getting a disease.

Billions of taxpayer dollars are used to fund biomedical research at universities and non-profit research institutions. Results are reported in glowing terms every day on the Internet, in newspapers and on television, making it seem as though new treatments for every disease that afflicts humankind must be just around the corner.

But in spite of all the money and all the knowledge, only 21 new drugs, therapies or vaccines came on the market in 2010 — according to the annual report on the use of medicines in the U.S. prepared by the IMS Institute for Healthcare Informatics. And just 10 of these were what the Food and Drug Administration calls a new molecular entity — an innovative approach to treating a specific disease.

So it's reasonable for patients and taxpayers to ask: Where are the cures? What happened to all those promising new treatments for diabetes, heart disease and cancer we've heard so much about? Why does it take so long to get these discoveries out of the laboratory and into medicine that can help me today?

One big reason is what researchers call the "valley of death." It's the stage of drug development that's required to transform a discovery that works in research animals into a new drug that works in people. The valley of death is where all those experimental therapies that showed such promise in laboratory mice go to die.

The cold, hard reality of biomedical research is that ideas are cheap and plentiful, while the process required to transfer those ideas to the clinic is long, risky and extremely expensive.

To turn a research discovery into medicine, university scientists have two options. They can license the discovery

James Baker

ERIC BRONSON, U-M PHOTO SERVICES

to a pharmaceutical or biotechnology company and hope it gets on the market eventually. Or they can start their own company and have more control over what happens to their discovery. Either way, success depends on having a corporate partner willing and able to raise the money and take the risk of shepherding a discovery through the lengthy and complicated new drug approval process required by the FDA.

James Baker Jr., M.D., the Ruth Dow Doan Professor of Biologic Nanotechnology, is one of a handful of U-M researchers who know what it takes to get a new drug on the market. He has a lot more gray hair now than he did in 2000 when he started his Ann Arbor spin-off company, NanoBio Corporation, and began turning a laboratory discovery into a treatment for cold sores.

"Starting a company and doing a clinical trial are the most difficult things I've ever attempted in my life," Baker says. "You are really putting yourself on the line, because you are much more likely to have failure than success. It's a road most academics don't want to take, because it can put your career at risk."

About 136 million Americans have *Herpes labialis* — recurrent cold sores caused by a virus called HSV-1 or herpes simplex virus, type 1. The sores aren't life-threatening, but they are painful, disfiguring and can last for days. The pharmaceutical firm GlaxoSmithKline (GSK) makes an over-the-counter product called Abreva, which is the only FDA-approved topical treatment currently available for cold sores.

Jim Baker believes he has a better idea. He calls it a "salad dressing that kills herpes," but to the FDA, it's NB-001. It's a proprietary nanoemulsion — made of soybean oil, water, surfactant and other ingredients — that penetrates the skin and kills the virus. It also inactivates many other infectious agents, according to NanoBio officials, and has the potential to treat more diseases.

It took 10 years and $5 million to complete the initial phases of human clinical trials for NB-001, according to Baker. Now, NanoBio has begun enrolling patients in two large multicenter phase 3 trials — the final stage of tests required before the FDA will approve a new therapy for use in people. GSK is financing the phase 3 trials, which Baker estimates will cost more than $14 million, and the company has an agreement with NanoBio to market the new drug in North America. If all goes well, Baker hopes to have NB-001 on the market by 2013 as an over-the-counter treatment for cold sores.

What does it take to get experimental drugs like NB-001 on the market? "It's 99 percent determination," Baker says. "It's making that last flight to the coast to talk to the last venture capitalist who finally comes across with the money. It's also a lot of luck. You can have the best idea in the world but, if one thing goes wrong, the product is dead."

TOP 10 REASONS NEW DRUGS DON'T MAKE IT TO MARKET

1) Lack of financial support
2) Works great in mice, but not in people
3) Can't recruit enough patients for clinical trials
4) Company sponsoring drug trial goes out of business
5) Competitor comes out with a better drug
6) FDA terminates trial — says risks exceed benefits
7) FDA approves, but company delays market launch
8) FDA wants more specifics on how it works
9) Lack of patent protection
10) Virus contaminates drug manufacturing plant

Crossing the Line

Biomedical research in the United States has been divided for decades into two halves with a bright shining line down the middle. University researchers stayed on the "basic science" side of the line. In the process of probing

the mysteries of biochemistry, genetics or molecular and cell biology, they sometimes identified possible new drug compounds or drug targets, but that was not the goal. Their goals were to advance knowledge in the field, teach students and publish their research findings in a prestigious scientific journal.

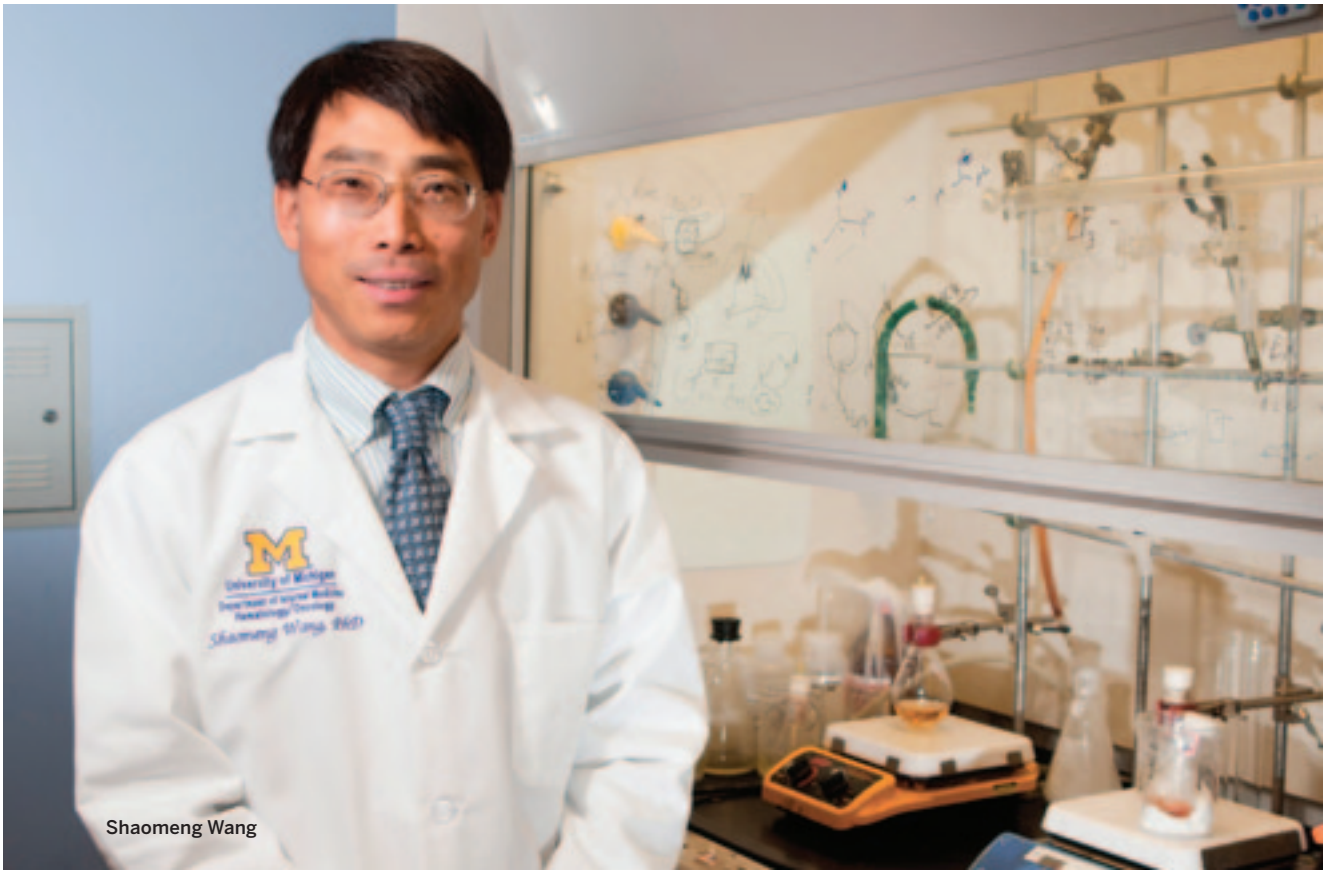
It was left up to scientists in corporate pharmaceutical labs to handle all the so-called "applied science" involved in turning potential drug compounds into human medicine. It takes years of pre-clinical laboratory and animal studies, all conducted under the watchful eye of Food and Drug Administration officials, to determine the pharmacokinetics, efficacy and toxicology of an experimental drug compound — how it works, how it is metabolized and whether any toxic side effects are acceptable. Then, the company must demonstrate that the experimental drug can be manufactured in large quantities under strict quality control standards.

Only after all this work is completed and approved by the FDA can the company apply for permission to begin a series of clinical trials to test the experimental drug in human volunteers and patients with a specific disease or medical disorder. Under the best of circumstances, the entire process takes at least 10 to 15 years and can cost as much as $1 billion.

The division of labor between university and corporate scientists worked well for years, but recently major changes have swept through the pharmaceutical industry. A depressed economy, reduced sales and widespread availability of cheaper generic drugs have slashed profit margins, leading to major cutbacks in R&D and a wave of corporate takeovers and serial acquisitions.

Today's investors want quick returns and are unwilling to assume the risks or take the time required for early-stage drug development. So instead of paying for a large research facility staffed with expensive scientists and state-of-the-art equipment, pharmaceutical companies find it more profitable to purchase promising new drugs by buying up the smaller companies that develop them.

The changing business climate also has increased corporate interest in drug compounds discovered at universities, says



Shaomeng Wang

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Shaomeng Wang, Ph.D., the Warner Lambert/Parke-Davis Professor of Medicine. Wang directs the Cancer Center's Cancer Drug Discovery Program and is a co-founder of a U-M spin-off company called Ascenta Therapeutics.

Wang uses computer-assisted design technology to create drug compounds customized to bind to the three-dimensional structure of a specific molecule in a way that blocks that molecule's pathological activity. Organic chemists synthesize the most promising compounds, which are tested for their effectiveness at killing tumor cells — first in a test tube and then in animal models of human cancer.

A more traditional academic scientist might simply publish the results of the work at this point and move on to the next drug compound, but Wang says that's not enough. "I want to move our compounds quickly into clinical development to help patients and ultimately become marketed medicines," he says. "We started the company to help us achieve these goals."

Two of Wang's compounds, AT-101 and AT-406, were designed to trigger tumor cells to undergo programmed cell death, or apoptosis. Wang's laboratory research showed that both compounds were effective at killing cultured cancer cells and reducing the size of tumors in research mice. Ascenta Therapeutics licensed the development rights to AT-101 and AT-406 and is currently sponsoring several phase 1 and phase 2 clinical trials in patients with different types of cancer.

"The company supports our research and has an option to license our technology," says Wang. "It's a win-win for the university and the company, because if you don't get new technology on the market, nobody will benefit from it — not the university, not the inventors and, more importantly, not the patient."

Wang says his interest in drug discovery was encouraged from the moment he joined the U-M faculty in 2001. He credits leaders in the Cancer Center, Department of Internal Medicine and the Medical School for providing administrative and financial support and an infrastructure that facilitates drug discovery research in an academic environment. Wang adds that the U-M Office of Technology Transfer protects faculty research discoveries aggressively and is very helpful to researchers who want to create start-up companies.

Cancer Center Takes the Lead

ONLY 21 NEW DRUGS, THERAPIES OR VACCINES CAME ON THE MARKET IN 2010, AND JUST 10 OF THESE WERE WHAT THE FOOD AND DRUG ADMINISTRATION CALLS A NEW MOLECULAR ENTITY — AN INNOVATIVE APPROACH TO TREATING A SPECIFIC DISEASE.

"We believe strongly that what we do in our basic science research only has value to our patients and to society if it's translated into actual drugs that can benefit patients," says Max Wicha, M.D., Distinguished Professor of Oncology and director of the U-M Comprehensive Cancer Center.

Nine U-M spin-off companies have been created by researchers affiliated with the Cancer Center, including a California-based company called OncoMed, which was founded by Wicha and other U-M researchers in 2004, and currently has several experimental therapies in phase 1 clinical trials.

Recent advances in cancer research have accelerated the push toward new drugs targeted at specific genetic mutations and signaling defects that trigger the development of malignant tumors.

"We're learning that cancer, even the same type of cancer — like breast, colon or prostate — is really many different diseases," says Wicha. "Our scientists are developing technology that will make it possible to perform a complete molecular analysis of each patient's tumor. Then we can select

Max Wicha

the best therapeutic agents to match that patient's molecular profile. So instead of treating all lung cancer patients with one drug, just 5 percent of lung cancer patients might get that drug, but 5 percent of ovarian cancer patients with the same mutation would get it, too."

Cancer Center administrators have created a central Clinical Trials Office with staff trained to manage the financial and regulatory issues involved in a human clinical trial and to provide administrative support to research investigators.

In 2008, the Cancer Center established its own phase 1 clinical trials program. A private gift from the Ravitz Foundation made it possible for the Cancer Center to create a dedicated unit called the Ravitz Center for patients enrolled in these trials. During 2010, the center conducted 13 phase 1 studies with 102 patients. The center is available for phase 1 trials of experimental cancer therapies developed at the U-M and by companies outside the university. Plans are under way to increase staffing and conduct more phase 1 studies in the future.

Research entrepreneurs like Baker, Wang and Wicha believe that closer collaboration between universities and private industry is vital to the success of university drug discovery research. They say universities can do their part by encouraging more innovative public-private research partnerships and providing more incentives for clinical scientists to pursue drug discovery research.

The gulf between academic and corporate culture is deep and wide and major changes will be required on both sides in order for collaboration to work. The journey is risky and success is not guaranteed. But if universities and corporations can work together to bring the products of biomedical research to patients, the payoff will be worth it. [M]

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WHATEVER HAPPENED TO BEXXAR?

It seemed like a miracle. Patients in clinical trials who were dying from non-Hodgkin's lymphoma went into remission and survived for years after just two injections of an experimental cancer treatment using antibodies to deliver radioactive isotopes to malignant cells.

It was called radioimmunotherapy and it was a revolutionary approach to treating cancer developed in the 1990s by Mark Kaminski, M.D., a U-M professor of internal medicine, and Richard Wahl, M.D., a former U-M professor now at Johns Hopkins University. Licensed to the pharmaceutical firm GlaxoSmithKline (GSK), the treatment was named Bexxar. It was approved by the FDA in 2003 for use in patients with relapsed or refractory non-Hodgkin's lymphoma.

There is no question that Bexxar is an effective therapy, especially for a major subset of an incurable form of non-Hodgkin's lymphoma called follicular B-cell lymphoma. Clinical trials in patients with follicular lymphoma who had already undergone multiple chemotherapy treatments showed that one treatment with Bexxar induced progression-free survival for up to 10 years in 20 percent to 30 percent of patients. In another study conducted at the U-M, 40 percent of patients who received Bexxar as their first and only treatment remained disease-free for 10 years.

Unfortunately, sometimes just being effective isn't enough.

Bexxar had one big problem. Oncologists and hematologists who treated patients with non-Hodgkin's lymphoma didn't understand it and weren't interested in using it. They preferred traditional chemotherapy that can be given in a doctor's office. As a result, Kaminski estimates that fewer than 10 percent of patients who are candidates for Bexxar have received it.

"Many lymphoma patients who come to U-M for a second opinion have never heard of radioimmunotherapy," says Kaminski.

Because Bexxar includes a radioactive isotope, iodine-131, it must be dosed and administered by a physician who is licensed in nuclear medicine or radiation oncology. Under a fee-for-service payment system, the doctor who gives the treatment gets the fee. So Kaminski says oncologists have a financial incentive to treat lymphoma patients with repeated infusions of drugs they can administer themselves, instead of referring them to another specialist.

Mark Kaminski

"There are many treatments available for lymphoma, and doctors tend to do what they know how to do best," says Kaminski. "But look at it from the patient's perspective. We're talking one week of treatment compared to months of repeated infusions with chemotherapy drugs that have toxic side effects."

Kaminski doesn't know what the future holds for Bexxar. In November 2010, GSK announced it was cutting back on production due to infrequent demand.

"These circumstances send a chilling message not only to people with lymphoma, but to people in research," says Kaminski. "There's no incentive to develop new radioimmunotherapies for other kinds of cancer. If you can't make Bexxar work, what's the hope of developing new drugs along the same line?" —SP