HELP THIS MAN CURE ALZHEIMER'S

NEW DRUGS FOR MANY DISEASES LIE LANGUISHING AS SCIENTISTS ARE FORCED TO SCROUNGE FOR THE CASH TO CONDUCT CLINICAL TRIALS
SCIENCE

Researchers can no longer be content with discovering the next miracle drug. They have to find the millions it takes to get it out of the lab and into your medicine cabinet.

For Sale

At Northwestern University’s Falk Center for Molecular Therapeutics in downtown Evanston, a family of potential miracle drugs lies idle. Called glyxsins, these compounds offer a treatment for stroke and many other neurological ills. But for now, they are stored within three 7-foot stainless steel freezers kept at a constant -112 F.

Five feet away stand two tanks, one orange, one blue. Frigid vapor rises from the nitrous oxide that maintains them at a hard-to-imagine -256 F. Deep within the tanks are vials filled with copies of a gene that might hold a cure for malignant brain tumors. But the genes, too, lie fallow.

These dormant drugs are the brainchildren of Dr. Joseph Moskal, biochemist, molecular biologist and neuroscientist. They represent the 20 years of basic research he conducted before becoming director of the Falk Center. which was established last April.

Although hundreds of millions of people who suffer from Alzheimer’s disease, learning disabilities, neuropathic pain and stroke ultimately might benefit from glyxsins, the afflicted may never get a chance to use them.

And though there are between 10,000 and 30,000 new cases of brain cancer in the U.S. annually, these patients may never have a chance to be treated with the gene Moskal has identified, which is formally known as the alpha 2,6 sialyltransferase gene.

Moskal’s discoveries, like those of hundreds of other researchers around the country, remain mothballed because of the difficulty in getting funding to move them through human clinical trials and into the marketplace.

The spiraling cost of popular new drugs has received the lion’s share of the media’s attention recently, with the pharmaceutical industry arguing that such costs are necessary to reimburse it for the huge investment it has to make in initial research and in drugs that fail to achieve their promise. But what might be the bigger story is that the drug industry has, with little fanfare, largely stepped out of the business of conducting early-stage human trials and has ceded this costly task to venture capitalists willing to take on big risk. But the availability of venture capital is subject to wide fluctuations. The result: A pharmpaeoica of promising new drugs that could alleviate untold human misery is gathering dust in the nation’s research laboratories.

“Great drugs can go unfunded because the venture markets are inherently less efficient than other markets,” says George Arida, an associate partner at Venture Investors, a

By Lee Scheier  Illustration by David Plunkert
biotech venture capital firm in Madison, Wis. "People assume that the invisible hand of economics that moves to make markets efficient will ensure that money will flow to good ideas. This may be true in the stock market and debt markets, but not the venture market."

Dr. Frank Scherer, an economist who specializes in the pharmaceutical industry and is emeritus professor of public policy at Harvard University, says the venture capital market is down "80 to 90 percent" since its peak of three years ago. "It has been devastating," he says. "There are thousands of drugs sitting on shelves. In 1988, people would have pushed to Moskal's doorstep."

The reality is that the modern scientific community has become a cutthroat arena, where brilliant researchers are forced to become crass entrepreneurs, and the benefits of new discoveries may not be as important as the workings of a mercurial marketplace. And while some may view this convergence of business and science as a positive development, believing that it enhances the scientific enterprise, others see it as an unholy alliance that has damaged the image and effectiveness of the profession with conflicts of interest, a suffocating secrecy and a vulnerability to bias.

The situation, which finds scientists racing to patent their discoveries and going hat in hand to glynixin, which are compounds that modulate the brain's glutamate receptors, have produced astounding results. The glutamate receptor, whose technical name is the N-methyl-D-aspartate, or NMDA receptor, allows brain cells to process the crucial neurotransmitter glutamate, and this pathway is one of the most fertile areas of neurological research. When administered to gerbils in high concentrations, a glynixin called NT-13 completely protected their brains from any damage caused by induced strokes. Meanwhile, in rat experiments, NT-13 relieved neuropathic pain at levels superior to any drugs now on the market without their toxic side effects. Neuropathic pain plagues millions of people who suffer from back conditions, diabetes, cancer, neuralgia and HIV.

On the other hand, in low concentrations, the glynixin enhanced cognitive function in certain species. Rabbits and mice given NT-13 mastered mazes and other tasks twice as fast as animals that didn't receive them.

Glynixins, which work in the brain's hippocampus, were the first drugs to flow from Moskal's chief drug-development program, which goes by the acronym MADCP, for monoclonal antibody-derived custom peptides.

"Glynixins sound extraordinarily promising and should be funded," says Dr. Marshal Nirenberg, chief of the Molecular Biology Section of the National Institutes of Health (NIH) in Bethesda, Md. Nirenberg is an iconic figure who won the 1968 Nobel Prize for deciphering the genetic code, the chemical instructions our bodies' cells use to synthesize the proteins we need to grow and survive. Moskal worked with Nirenberg at NIH from 1979-81 and regards him as his mentor.

Moskal's other work has also excited colleagues. In studying tumor cells, he found that a particular gene, the alpha 2,6 sialyltransferase gene, is overexpressed in those cells—that is, it creates an excessive amount of the substance it is designed to produce. In later experiments, he found that he could manipulate the gene to reduce that excess, and that this, in turn, disabled a molecule in the brain that seems to contribute to the growth and spread of brain tumors. When Moskal tested the gene by putting it into the brains of mice, it suppressed tumor growth without side effects.

As the drugs began coming together a decade ago, Moskal, acknowledging the new convergence of science and business, teamed up with a fellow scientist, Dr. Jan Leestma, to found a biotech company. The firm, which they called Nyxis Neurotherapeutics, hired Dr. Christopher Price to help raise the millions of dollars they were going to need to get the drugs into human clinical trials.

The first thing the company did was to pursue patents on its drugs. Glynixins were awarded a patent in 2000, and two years later the U.S. Food and Drug Administration approved human trials for NT-13. The alpha 2,6 gene and Moskal's MADCP concept have patents pending, even as alpha 2,6 awaits FDA approval for human trial.

The patent was a milestone in Moskal's journey from basic to applied researcher, a journey that...
has bridged two eras of science. "There was an idealism about the pursuit of knowledge when I entered the world of science," he says. "Business was not a viable model. There was no biotech. Scientists were in it for tenure, recognition and the pursuit of their ideas. Basic research scientists back then would even boast that their work had no practical relevance."

Nurnberg says Salk embodied an era of science that no longer exists, "I've never considered patenting anything," he says. "You want to make the information freely available to other scientists so they can use it."

Leestma, a former professor of neuropathology at Northwestern and the University of Chicago, says that researchers trained in the old school can get lost in the changing world of science.

"Scientists in this new business environment can be a bit naive, like Adam and Eve in the Garden of Eden," says Leestma, who went back to get a master's degree in management from the Kellogg School of Business at Northwestern. "The rules of the commercial world are so different. It used to be just publish. Now it's patent first, then publish."

"If you publish first you give up your rights," adds Moskal. "You have to protect your technology."

Three years ago, patent portfolio in hand, Nyxis began making presentations to big pharmaceutical companies such as Merck, Novartis, and Johnson & Johnson, to get them to finance the human trials. But the firms—part of the hugely worldwide drug establishment that criticizes Big Pharma—had already tried drugs similar to glyxins and had lost enthusiasm.

"Big Pharma is typically not interested in early-stage drugs," says Moskal, "and they already had too many failures with NMDA receptor drugs and had soured on them."

So in 2001, Nyxis turned its attention to courting venture capital firms. Moskal says Nyxis needed $1.5 million to $2 million to get the ball rolling.

He estimates that nearly 50 venture firms showed initial interest in Nyxis. Over the next months, Moskal says, he was constantly on the go, attired in sharp business suits and burning up cell-phone time. "I was always on the 30th floor of some swank office building looking out over the park of some city giving PowerPoint presentations," he says.

Eventually, Venture Investors of Madison, which specializes in early-stage biotech companies, expressed a serious interest in Moskal's creations. "We saw the glyxins as the first drugs of many that would come from Moskal's MADCAP platform technology," says Arida, the partner at Venture Investors who handled the deal. "Once we got that going, then the alpha 2.6 gene would be produced further down the line."

Venture Investors studied the glyxins from every angle for more than a year and a half. "We scrutinized the science, the market, the financial costs, legal aspects, intellectual property and we were getting more and more excited," Arida says. "By the summer of 2002 we felt everything looked really good and we wanted to put a deal together."

But the timing couldn't have been worse. The venture-capital markets, which had peaked in 1999, had basically collapsed. With money so tight, Venture Investors told Moskal and his colleagues...
that it would do the deal only if other investors were willing to partner with them.

Providentially, they did find two other investors willing to pick up a third of the cost. The deal seemed to move forward.

“We had closing documents drafted and it looked like we’d close the deal around Christmas,” says Moskal. “Then a pharmaceutical industry consultant for one of the investors said that the animal data wasn’t strong enough. He wanted different types of animals, a higher number of them and tests run in different ways. I felt that since the FDA had studied the tests and approved the drug for the clinical trials the tests were probably sound.”

Moskal flew to Ann Arbor to make his case. “I felt I easily countered every criticism raised by the consultants,” says Moskal. “To me they were trivial.”

Nevertheless, last January, the investors dropped out and the deal was off. “I was devastated,” says Moskal.

Nyxis’ cash reserves went to nothing overnight. Convinced it was a deal, the firm had engaged attorneys at considerable cost. It now owes them $100,000. And the glibmans languish in cryogenic purgatory at the Falk Center.

“In the end the investors were too easily spooked because they saw us as too avant-garde,” says Moskal.

Investors want innovation but they don’t want too much risk,” agrees Arida. “In Moskal’s case, most of the scientists felt his work was incredible, but one scientist felt it was too innovative. And if it’s too innovative, it can be seen as too risky. This is a dilemma we face in this business.”

Managing risk is an important business strategy and science, for better or worse, has become big business. Industry now funds 62 percent of all biomedical research, compared with 32 percent in 1980, according to NIH. This includes about 7 percent of all university research.

David Blumenthal, professor of health care policy at Harvard University, has been one of the most prolific researchers on industry-university relationships over the last 20 years. His study published in the New England Journal of Medicine in 1996 showed that more than 90 percent of U.S. biotech firms have some relationship with universities. Eighty-eight percent use faculty members as consultants, with 67 percent of faculty holding equity in the companies. Fifty-nine percent of the companies supported university research.

The most recent survey by the Association of University Technology Managers shows that the 168 U.S. and Canadian universities participating in the survey received an adjusted gross income of $1.071 billion from 22,837 licenses and options on their patents.

Dr. Mildred Cho, co-director of Stanford University’s Center for Biomedical Ethics, says that patents and licenses create a windfall for some universities, but overall there is a very low success rate with patented products. “It is mainly a fantasy that scientists will get rich,” she says. “And the pursuit of patents removes many scientists from doing long-term basic research and their business entanglements force them to focus on short-term applications.”

However, Patricia Harsh, director of the Association of University Technology Managers, says there is no evidence that basic research has been diminished by the commercialization of science. “In the last five years, NIH has doubled its funding away data that undermine their claims.”

“There are large amounts of discretion and judgment involved,” says Cho. “The data, whether you use this population or another, and the way you interpret the probability, can affect the statistical significance, particularly in clinical research.”

Dr. Marcia Angell, former editor of the New England Journal of Medicine, says, “I would see studies that were funded by drug companies that were designed to look good. It is becoming standard.” Angell says that the drug companies know that their new drug will look better if they compare it with a placebo instead of going head to head with the best drug already in use.

“I believe the FDA should not approve drugs based on this kind of research,” she says.

A study in the New England Journal in 1998 found that 86 percent of researchers whose results supported a certain drug had financial relationships with the drug’s manufacturers, compared with 8 percent of neutral authors and 37 percent of critical authors.

The universities that used to be the watchdogs are now involved with the companies they used to watch,” says Angell. “Nobody is watching anymore. Can you believe the research?”

Drug companies are led by marketers, argues Dr. Drummond Rennie, deputy editor of the Journal of the American Medical Association (JAMA). “They don’t have the same ethics as scientists and that’s a major problem. Money always has strings attached for clinical as well as basic research.”

The strings that money brings are control over data, secrecy and failure to share information.

Openness and sharing are vital to scientific progress, as is independence, says Dr. Sheldon Krimsky, a professor of Urban and Environmental Policy and Planning at Tufts University whose research has focused on the linkages between science, technology, ethics, values and public policy.

He cites the legendary sociologist Robert K. Merton, of the University of Chicago, who more than 50 years ago wrote that the open and free exchange of knowledge, as well as “disinterestedness” should be the watchwords of research.

“A central part of the scientific enterprise is organized skepticism and criticism, which has no part in the business enterprise, which is based on benefits, costs, promotion and marketing,” says Krimsky. “I think the potential to compromise the integrity of science and its objectivity is real and that there is data to support it.”

A article recently published in JAMA analyzed 37 studies conducted between 1986 and 2002 on the effect of conflicts of interest on the outcome of research. The review found that industry-sponsored studies were significantly more likely to reach conclusions that were favorable to the sponsor than were non-industry studies.

“When you pull all the evidence together,” says Krimsky, “you see that scientific researchers who have received industry funding have internalized the values and interests of the funders as a statistical event. There is a weighting towards the interest of the private funders called the funding effect.”

A study by Cho and Lisa Berlo, published in the
Annals of Internal Medicine in 1996, showed that 98 percent of the clinical research funded by industry yielded favorable results as compared with 79 percent favorable when their was no drug industry support.

"Outstanding studies designed to show the added effect of industry influence," says Cho. "Our conclusion was that the drug companies withheld negative results, put a positive spin on negative or ambiguous results or selectively studied drugs where there was already an indication that they would work.

"Whatever the reason, my biggest concern is that bias causes the overall literature to be skewed and scientists then have to build on an incomplete and inaccurate body of knowledge. By not publishing research on the adverse effects of drugs you can do harm."

BUSINESS ENTANGLEMENTS were unavoidable by the time it became necessary for Moskal to raise money for Nyxas. But while there was big money to be made from molecules and genes, becoming wealthy was something that Moskal says he had never sought.

"The excitement of discovery is more addicting than getting $50 million," he says. "My Dad always told me: 'Have rich friends. Let them buy the boat.'"

He had to patent his inventions, he says, in order to get the necessary funding and still maintain control of the process of bringing them through the FDA trials and to the marketplace. It was a means to an end, and he had to play by the new rules.

"Nobody is interested in a compound that isn't patented," says Arida. "No company wants a compound that doesn't offer exclusivity."

Moskal's values were formed while growing up in Saginaw, Mich. As a high school senior, he did a science project with a local neurosurgeon on brain tumors because he hoped to cure them one day.

After completing his thesis in neurochemistry on how brain cells link up with each other, Moskal received his doctorate in chemistry from the University of Notre Dame in 1977 and went on to do cancer research at Michigan State University.

Moskal had followed Nirenberg's work at NIH through journals and was fascinated by the work the older man was doing with neurons and the connections they make, called synapses. One day he met Nirenberg at a symposium and they wound up having lunch. "I remember he had deep-fried clam strips," says Moskal. "We talked about our work. I asked if I could work with him. It was my dream to work on mechanisms of synapses and learning. He said yes.

"It was incredibly exciting to work with the man who had deciphered the genetic code," recalls Moskal. "He pushed us to ask significant questions, to do significant research and to be careful and thoughtful about the experiments we did and their interpretation."

It was during the formative years of Moskal's career that three events occurred that would irrevocably alter the landscape of science.

The first was the discovery in 1973 of recombinant DNA by Stanley Cohen of Stanford University and Herbert Boyer of the University of California at San Francisco. In 1976, Boyer would become a cofounder of Genentech, the first biotechnology company formed to apply genetic engineering long done that. In academia, individuals are encouraged to get papers published and make a name for themselves, but it was the synthesis of components from several different disciplines that led to this discovery."

This synthesis began at Abbott Laboratories in North Chicago, where Kraft studied the way enzymes in the body slice proteins into shorter chains. This process gives HIV its extraordinary power to destroy the immune system, and his findings helped Abbott develop drugs against AIDS.

By 1989, Kraft thought that Alzheimer's disease might be triggered by the way enzymes split proteins in the brain, so he launched a drug-discovery project to investigate that possibility. He recruited Klein, a professor of neurobiology at Northwestern with a deep understanding of how brain cells work, to be on his scientific advisory board. He also asked Finch, an expert on human longevity, to contribute.

Even though drug companies were pouring millions into the development of drugs to prevent or dissolve plaques in the brain, Kraft believed something else must trigger the cognitive collapse that characterizes Alzheimer's disease. In 1994, Finch tried to prevent the protein from forming fibrils—the precursor to the dreaded brain plaques—by adding a compound called APO-J, also known as clusertin. Although clusertin did indeed prevent A-beta 1-42 from forming fibrils, it made the resulting solution highly toxic to neurons. Kraft suspected that something in the solution was the real cause of Alzheimer's disease.

Kraft was not satisfied with the reigning explanation of Alzheimer's disease—that starry clumps of protein known as amyloid plaques, first identified by Dr. Alois Alzheimer in 1907, somehow damage neurons. For one thing, virtually everyone over the age of 70 or so has brain plaques, but only a small percentage of the elderly develop Alzheimer's. Moreover, some people with a lot of plaques never get Alzheimer's, while others with just a few are ravaged by the disease. The other hallmark of the disease—strands of tau protein—seemed to be tombstones marking the death of neurons, not the cause of their death.

While at Abbott, Kraft learned how to synthesize a brain protein called A-beta 1-42, which was suspected of contributing to Alzheimer's disease. In 1994, Finch tried to prevent the protein from forming fibrils—the precursor to the dreaded brain plaques—by adding a compound called APO-J, also known as clusertin. Although clusertin did indeed prevent A-beta 1-42 from forming fibrils, it made the resulting solution highly toxic to neurons. Kraft suspected that something in the solution was the real cause of Alzheimer's disease.

He left Abbott the following year and joined the faculty at Northwestern where, with the help of Klein and Finch, he tried to figure out what it might be.

To get a better picture of what they were looking at, Kraft recruited a colleague to produce images with an atomic force microscope, which runs a super-fine needle back and forth over the surface of a specimen and produces a topographic "map" showing the shape and location of everything it touches.

What Kraft and Klein found was a form of the A-beta 1-42 protein that had not been previously recognized—tiny globules that resembled soccer balls. They then discovered that these
globsules floated freely in the brain and attached themselves specifically to the neurons affected by Alzheimer’s disease. Rats injected with the proteins developed severe memory loss.

The discovery pointed to possible new treatments for Alzheimer’s, including a vaccine or an antibody to counter the globsules' effects, and drugs to prevent them from forming in the first place. At first Kraft considered forming a not-for-profit institute to do the necessary research, but realized he could not raise enough money. He decided instead to create a company and then form a partnership with a large pharmaceutical company that had the resources to develop the drugs he envisioned.

He called Seth Harrison, a venture capitalist who had made several presentations at Abbott, and explained how Finch’s findings might lead to a treatment for Alzheimer’s. Harrison, who studied to be a doctor before obtaining his MBA, was impressed by the theory. “Grant always struck me as a visionary,” Harrison says. “It was the earliest-stage thing I had ever thought about backing.”

Harrison agreed to help Kraft create Acmuen, and suggested they come up with a catchy name for the new protein molecule they had discovered. While sitting with the three scientists around Finch’s dinner table in Altadena, Calif., Harrison suggested the acronym ADDL, as in “adder,” which is what Alzheimer’s does to people. The scientists then provided the words to match the letters: “amyloid-derived,” because the molecules came from the amyloid proteins abundant in the brain; “diffusible,” because the molecules are soluble and can move around in the brain; and “ligand,” because these amyloid-derived diffusible proteins bind to nerve-cell receptors.

At Abbott, Kraft had learned that drug companies wouldn’t be interested in developing an Alzheimer’s treatment without strong patents to protect their discoveries, so he persuaded Northwestern and USC, where Finch had done his early work on ADDLs, to obtain a joint patent and license the intellectual property to Acmuen.

Harrison felt there was no hope of attracting venture capital for Acmuen, especially since the ADDL theory was so contrary to the prevailing explanation of the disease. But it turned out that even the big drug companies, under pressure to boost profits, were reluctant to back such a novel approach to Alzheimer’s when so many others had failed. “The reaction was a big yawn,” Harrison says.

Kraft left Northwestern, giving up his salary, to devote himself full time to promoting Acmuen. He and his wife agreed to live on her salary. “Getting Acmuen off the ground took longer than either of us expected, and there were times when my resolve faltered,” says Kraft’s wife, Patty Cain, an attorney with the Chicago firm Neal, Gerber and Eisenberg. “What got us through was Grant’s unfailing belief that Acmuen’s approach would lead to effective drugs.”

Over the past year, the tide has turned in the company’s favor. In August, the Proceedings of the National Academy of Sciences published a paper by Kraft, Klein, Finch and others demonstrating that high levels of ADDLs exist in the brains of Alzheimer’s patients, and the scientific community has begun to embrace the idea that ADDLs are implicated in the disease process. David Tiplow, a veteran researcher at Harvard, recently tried to organize a debate on ADDLs, but says he couldn’t find any scientists willing to defend the old notion that clumps of protein fibrils—plaques—cause Alzheimer’s. “There’s a critical point at which people’s opinions change, and the new idea becomes dogma. That’s where we are now.”

Even Harvard’s Dennis Selko, who did groundbreaking research based on the theory that plaques cause Alzheimer’s disease, now supports the ADDL theory. He says the recent paper by Kraft, Klein and Finch is “very exciting,” and takes “good steps in the right direction.”

Kraft’s ultimate vision is to develop a vaccine that can be administered to everyone past the age of 50 or so. The vaccine would stimulate the immune system to attack ADDLs and prevent them from binding to the neurons responsible for memory formation. Mouse studies support the notion that removing ADDLs from the brain restores the neurons to health, often within 24 hours.

But an Alzheimer’s vaccine makes drug companies nervous. In one case, Elan Pharmaceuticals of Ireland developed a vaccine that attacked the plaques assumed to be the cause of Alzheimer’s disease. The vaccine did indeed stimulate patients’ immune systems to create antibodies against plaques during clinical trials, but the plaques, which are as insoluble as tar, resisted destruction. The futile prolonged attacks by antibodies against the sticky clumps of protein triggered severe brain inflammation in some subjects that Eln halted the trials.

That experience is why Kraft plans to develop an antibody against ADDLs before he develops a vaccine. People developing memory problems could receive monthly injections of the antibody, which would attack and destroy the ADDLs. “We’re focusing on an antibody techniques to drug development. Five years later, it was reported that his stock had appreciated to $40 million. “The lure of rapid financial success ran through the field of biology like an infectious virus,” recalls Krimsky.

The second event came in June 1986, when the U.S. Supreme Court ruled 5-4 that a human-modified microorganism can be classified as a product of manufacture and thus falls under patent protection. Products of nature, such as genes and proteins, cannot be patented, but as Krimsky notes, if a gene is modified, it is considered to be man-made and patentable under section 101 of the U.S. Patent Act that states that the subject matter must be novel, useful and non-obvious.

The third event also occurred in 1986, when Congress passed the Bayh-Dole Act to help the United States compete technologically with the rest of the world. The act directed universities to patent the results of federally funded research and work with “commercial concerns” to “promote the utilization of inventions” based on that government-financed research.

“The Bayh-Dole Act was the event that changed the face of science,” says Rennie. “Before Bayh-Dole, regulations made it virtually impossible for scientists or the universities they worked at to make money off their inventions. Bayh-Dole essentially took nonprofit institutions and given them the mandate of a for-profit institution, which contradicts their original mission statement.”

With Bayh-Dole came the emergence of technology transfer offices on every campus whose function is to license their scientists’ inventions to whatever company they feel is best able to commercialize the product. “These offices are the locus of conflict of interest,” says Cho.

Defending Bayh-Dole, Rennie says that if inventions don’t get to consumers, they are not contributing to the public good. She notes that a Government Accounting Office study estimated that 40,000 inventions were sitting on shelves unable to make it into the marketplace before Bayh-Dole. The reason: Scientists had no incentive to commercialize their inventions.

“Tech transfer offices look at the marketplace and license discoveries to the most appropriate biotech or pharmaceutical company or even start a new biotech company,” says Harris. “In return, the university and the scientist get royalties and/or equity in the company and support to further the research.”

Tech transfer offices like those at Stanford and UCSF started the biotech industry and made universities and scientists partners in the new companies. Protecting proprietary interests with patents became crucial to the profit potential of every newly discovered molecule or device.

Patents, however, were far from Moskal’s thoughts in 1988 when he began studying the neu
ological potential of monoclonal antibodies, custom-made biological homing devices first created in the laboratory in the 1970s. "Traditional thinking was that an antibody was a gigantic molecule and when it bound to a receptor it would either do nothing or turn the receptor off," says Moskal. "I thought they could work as modulators, inhibitors and activators."

In the spring of 1984 Moskal found antibodies that selectively recognized the receptors on the surface of hippocampal neurons. Soon, he was able to show that some of the antibodies could enhance the synaptic transmission between neurons that is associated with learning and memory. The research was published in the Proceedings of the National Academy of Science.

While heading the research laboratories at Albert Einstein Medical Center in New York City, Moskal pursued his work, finding a specific antibody that affected the NMDA receptor. Then in 1990-91, he collaborated with Dr. John Disterhoff of Northwestern to show that this antibody enhanced learning and memory in animals.

Moskal came out of the insular world of the lab when he was hired by Leetsma in 1990 to build and administer a center for clinical brain research at Columbus Hospital in Chicago. "I learned how to put on a tux and put on an event," says Moskal. "I learned how to host golf tournaments and raffles and raise money."

But Moskal the impresario did not inhibit Moskal the researcher. In 1997, he took another major step when he transformed the glycine antibody, which was too large to cross the blood-brain barrier, into small synthetic peptides that mimic the antibody but can cross the blood-brain barrier. That turned glycine into a drug candidate.

"Once we converted the molecules from antibodies to peptides," says Moskal, "we stopped publishing so we could apply for our patent."

Glyxens and the alpha 2,6 gene both have had dazzling results in animal studies. But the sheer heap of science is piled high with positive animal results that could not be repeated in humans.

The facts are mind-numbing. According to Arida, for every 1,000 drugs that begin with animal studies, only 10% will make it into human clinical trials. Of that 10%, about 20 will make it through phase one human trials, which test for safety and toxicology and cost, on average, from $3 million to $10 million. Of that 20, only about six will make it through phase two, which tests how well drugs work within a safe dosage range. Phase two trials generally cost up to $15 million.

Of the six drugs left, only four will make it through phase three, which consists of very large studies that test dose regimen and response. These studies, which are a drug's final hurdle, are the most expensive, costing in the $10 million to $80 million range. Thus, of the original 1,000 drugs, just three or four will likely get to market.

The pharmaceutical industry puts the cost of developing a drug at $867 million. But that includes the cost of the drugs that have failed, experts say. Public Citizen, a watchdog group, puts the actual figure at $110 million—still a very large number.

Whatever the costs, the big drug houses seem to be evading enough of them that, according to data published in Fortune Magazine last year, the annual profit of Fortune 500 drug companies are hovering around 18 percent while those of all Fortune 500 companies are below 4 percent.

Venture capital companies are willing to accept the early funding risks that the pharmaceutical companies shy away from, says Arida. "We invest in intellectual property, which is the main asset." But it has to be patented—"not vulnerable to competitive action."

Krimsky points out that in some areas of research that require the use of patented technologies or patented genetic markers, scientists must now pay licensing fees to share the data. "Since universities are now into the commercialization of science, they are withdrawing the traditional use of the research exemption" that allowed other scientists free access to research findings.

A recent study by Cho showed the chilling effect of patents and licenses on genetic testing and research: 25 percent of all respondents had stopped performing a clinical test because they had been contacted by a patent holder saying that they might be infringing on a patent. More than 50 percent of lab directors decided not to develop a new clinical genetic test and had halted research for fear of being sued for patent infringement.

Although it is generally accepted that without patents there would be no drug industry, Angell feels that because of patents there are fewer and
of my life," says 46-year-old Barbara Stoffel, a banking executive in McHenry, Ill., who is part of the reunited group. "I've had broken and jammed fingers, sore neck and shoulder. Was it worth it? Absolutely!"

Eventually, Lurye's ambition for the Royal Airs outstripped his ability to generate funding for their tours. He sold all his parking lots to pay for the team buses, occasional charter airplanes and many other expenses the kids and their parents couldn't afford. The group gave its last performance in 1968, and Lurye retired to Phoenix two years later, nearly penniless and somewhat heartbroken. He died in 1987 at 72.

Last year he was chosen to be inducted posthumously into the Drum Corps International Hall of Fame. Several of the old Royal Airs approached his daughter, Jackie Lurye Borrelli, to suggest an alumni council be organized to play at the ceremony. She remembers laughing. "What do you think you'll be able to do?" she asked. A group got together, rehearsed for a day, then played for Borrelli. She couldn't believe how good they sounded. "All I could do was cry," she says.

Since their first reunion two summers ago, these boys and girls—all now in their 50s and 60s and spread out over 12 states and Canada—have been touring the country together as they did during the 1960s. They pay their own way to places like Seranton, Pa., and Milwaukee and practice an average of four days a week during the season. They wear exact reproductions of the white and blue uniforms they wore all those decades ago, and they perform their precision routines for roaring crowds of nostalgic baby boomers.

At the end of a recent long day of practice and performance the 150-old-timers were crowded into a nearby pub, leaving regular customers gaping at the strange middle-aged love fest. "We're big huggers," says Carm LoGalbo, an original Royal Air and now vice president of marketing for the 2003 group. "We're big kissers too!"

The Royal Airs are not in great shape physically, even considering that their average age is around 55. Mercy Ann Hueseth, the baby of the group, "corps nurse," says 45 of the current Royal Airs have diabetes, several have cardiac stents and one has an artificial leg. Once, when the corps marched off the field during a rehearsal, one baton-bugle player was left behind—passed out on his back in the grass. He was quickly revived and performed that evening.

But many of the members relate the reunion experience with miraculous drops in blood pressure, increases in vitality and wholesale changes in personality. Robert Reeyes, a 48-year-old electrical foreman for the City of Chicago, was embarrassed when he showed up at the reunion weighing 487 lbs. He wanted desperately to play his horn, but couldn't fit into a uniform. So he underwent bypass surgery and he's now down to 235 pounds and ready to play next year.

If there is a next year. As in 1968, willing marchers aren't enough to keep a corps together. Leadership and money are two other necessary ingredients.

All the travel has taken a financial toll on many of the members; some have maxed out their credit cards and dipped into their families' savings. Marketing chief LoGalbo is trying to find a corporate sponsor, but the prospects are not bright. Moreover, musical director John Zimmy hints he may not be back next year if corps leaders don't make a commitment to improve musically. It's not that they're still competing; they typically march as an exhibition at the end of modern competitions. And they perform at a remarkably high level considering their age and rehearsal time. But, like Truman Crawford before him, Zimmy wants to do what the Royal Airs have always done: strive for perfection.

If they manage to stay together, the group hopes to perform at a prominent venue in Chicago next year, setting their sights on playing at halftime at a Bears game in Soldier Field, as they did 40 years ago at Wrigley Field. Meanwhile, LoGalbo is lobbying the city's Cultural Affairs Department for financial support and other venue possibilities.

Beyond that, the reunited members would like to find a way to use the Royal Airs to help give today's kids the sense of discipline, teamwork and drive that Sie Lurye gave hundreds of kids in Humboldt Park.

If all that sounds too ambitious for a group of middle-aged Chicagoans, it's because you don't know who the corps director is. Jackie Lurye Borrelli now runs the Royal Airs with a rough approximation of her father's musky heart and iron will.

"We dislike the word, 'No,'" she says with a wink. □

David Murray last wrote for the Magazine about the road-weary life of a stand-up comedian.

Science for sale
(Continued from page 21)

fewer innovative drugs produced each year.

"Changes in case law weakened the language of patent law so that now new drugs don't have to be "useful, novel and not obvious," she says. "Seventy-five percent of research now goes to the development of copycat drugs that are essentially identical to existing drugs. Instead of putting R&D money into truly innovative drugs, the pharmaceutical companies play patent games to extend exclusivity on already proven blockbuster drugs."

For example, the heartburn remedy Prilosec was the No. 1 selling drug in the world with sales of $6 billion until its patent expired in 2001. To regain its monopoly, the maker, AstraZeneca, patented a copycat form of the drug just as the patent ran out and named it Nexium. Similarly, Schering-Plough created Clarinex, a copycat of its $2.7 billion-selling Claritin last year, just as Claritin lost its exclusivity.

Moskali says he has no problem with patents and entrepreneurialism driving science. Although he believes that money is a corrupting force he also believes, like his mentor Nirenberg, that most scientists are still highly principled and dedicated to the search for truth. "It is an extraordinary privilege to do research. To have that privilege is something you don't want to abuse," Moskali says.

Although the disappointment of not getting funding has temporarily taken the wind out of his sails, Moskali remains undaunted. He is excited by the basic research on affective disorders that he is doing at the Falk Center, collaborating with scientists like Roger Kros and Jack Pansepe to identify genes that cause depression, while continuing his tumor research.

"The march goes on," says Moskali. "I'm most enthusiastic. In a blink of an eye you can get more money and resources to get the work done. My foray into the business world has been good because it has been so practical. You learn about defending yourself. I guess I didn't realize how many hoops I was going to have to jump through."

And the winds of science may be shifting in Moskali's direction. A recent article in Science, titled "Excited about Glutamate," talked about newfound interest in the kind of NMDA receptor brain research that Moskali has done.

A new drug on the market to alleviate neuropathic pain, Memantine, is an NMDA receptor drug similar to glixyn, and Airda thinks that glixyns are superior to it. "I think when the venture markets come back, Moskali has a very good chance of realizing his dream," he says.

Until then, his discoveries wait in the deep freeze. And hundreds of millions who might be helped by them also wait. □

Alzheimer's
(Continued from page 20)

because drug companies like it," Krafts says. "It's safe, and they like safe—everybody likes safe. Four or five human antibodies have been FDA-approved, and the framework of human antibodies is the same for all these products, so the safety profile is very good."

After bringing an effective antibody to market, Krafts hopes to begin testing a vaccine that will provide permanent protection against ADDIs. He also has started work on three drugs that would prevent ADDIs from forming at all.

Besides therapies, Krafts wants to develop a test for ADDIs, preferably a simple one that could be done with a blood sample, like a cholesterol test.

"ADDIs are able to cross the blood-brain barrier and we can measure them in [blood]," Krafts says. "We have the ability, we think, to detect at a very early stage who has ADDIs in their bloodstream. If they went in for extensive memory tests, I'd be willing to bet some of my investors that those people who show levels of ADDIs in the bloodstream will show some short-term memory impairment."

David Summa, the man Kraft enlisted to serve as CEO for Acumen, believes the therapies and diagnostic methods Kraft envisions have an excellent chance of getting to market before any other treatment for Alzheimer's. "We have a horse race going on when it comes to finding a cure for Alzheimer's disease," he says, "but we have more entries in the race than anyone else. And in this race there can be more than one winner."

Tom Vabile is an Arlington Heights writer and author of a newspaper column on geriatric health.