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Desperately Seeking Cures

How the road from promising scientific breakthrough to real-world remedy has become all but a dead end.

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From 1996 to 1999, the U.S. food and Drug Administration approved 157 new drugs. In the comparable period a decade later—that is, from 2006 to 2009—the agency approved 74. Not among them were any cures, or even meaningfully effective treatments, for Alzheimer's disease, lung or pancreatic cancer, Parkinson's disease, Huntington's disease, or a host of other afflictions that destroy lives.

Also not among the new drugs approved was A5G27, or whatever more mellifluous name a drug company might give it. In 2004 Hynda Kleinman and her colleagues at the National Institutes of Health discovered that this molecule, called a peptide, blocks the metastasis of melanoma to the lungs and other organs, at least in lab animals. The peptide also blocks angiogenesis, the creation of blood vessels that sustain metastatic tumors, they reported six years ago in the journal *Cancer Research*. Unfortunately, A5G27 has not been developed beyond that discovery. Kleinman was working at NIH's dental-research institute, and, she says, "there was not a lot of support for work in cancer there at the time. They weren't interested." She did not have the expertise to develop the peptide herself. "I continued doing cancer research on it, but I couldn't take it to the next level because I'm not a cancer specialist," she says. "I was trained as a chemist."

No one is saying A5G27 would have cured metastatic cancers, which account for some 90 percent of all cancer deaths; the chance of FDA approval for a newly discovered molecule, targeting a newly discovered disease mechanism, is a dismal 0.6 percent. Diseases are complicated, and nature fights every human attempt to mess with what she has wrought. But frustration is growing with how few seemingly promising discoveries in basic biomedical science lead to something that helps patients, especially in what is supposed to be a golden age of genetics, neuroscience, and biomedical research in general.

From 1998 to 2003, the budget of the NIH—which supports such research at universities and medical centers as well as within its own labs in Bethesda, Md.—doubled, to $27 billion, and is now $31 billion. There is very little downside, for a president or Congress, in appeasing patient-advocacy groups as well as voters by supporting biomedical research. But judging by the only criterion that matters to patients and taxpayers—not how many interesting discoveries about cells or genes or synapses have been made, but how many treatments for diseases the money has bought—the return on investment to the American taxpayer has been approximately as satisfying as the AIG bailout. "Basic research is healthy in America," says John Adler, a Stanford University professor who invented the CyberKnife, a robotic device that treats cancer with precise, high doses of radiation. "But patients aren't benefiting. Our understanding of diseases is greater than ever. But academics think, 'We had three papers in *Science* or *Nature*, so that must have been [NIH] money well spent.'?"

More and more policymakers and patients are therefore asking, where are the cures? The answer is that potential cures, or at least treatments, are stuck in the chasm between a scientific discovery and the doctor's office: what's been called the valley of death.

The barriers to exploiting fundamental discoveries begin with science labs themselves. In academia and the NIH, the system of honors, grants, and tenure rewards basic discoveries (a gene for Parkinson's! a molecule that halts metastasis!), not the grunt work that turns such breakthroughs into drugs. "Colleagues tell me they're very successful getting NIH grants because their experiments are elegant and likely to yield fundamental discoveries, even if they have no prospect of producing something that helps human diseases," says cancer biologist Raymond Hohl of the University of Iowa. In 2000, for instance, scientists at four separate labs discovered a gene called ABCC6, which, when mutated, causes PXE (pseudoxanthoma elasticum), a rare genetic disease in which the skin, eyes, heart, and other soft tissue become calcified—rock hard. By 2005, scientists had genetically engineered lab mice to develop the disease. The next step would be what's called screening, in which scientists would laboriously test one molecule after another to see which had any effect on ABCC6. But "academic scientists aren't capable of creating assays [test systems] to do that," says Sharon Terry, CEO of the Genetic Alliance, which supports research on rare genetic diseases (her children have PXE). "It's time-consuming drudgery and takes an expertise that hasn't trickled down to the typical academic scientist." Ten years later, there is still no cure for PXE.

Should a lab be so fortunate as to discover a molecule that cures a disease in a lab rat, the next step is to test its toxicity and efficacy in more lab animals. Without that, no company—for companies, not academic scientists, actually develop drugs—will consider buying the rights to it. "A company wants to know, how specific and toxic is the molecule?" says Kenneth Chahine, an expert in patent law at the University of Utah. "It might work great in a mouse, but will it make a rat keel over? Doing this less fun research is not something an academic lab is interested in. The incentive driving academic labs is grants for creative, innovative research, and you're not going to get one to learn how much of a compound kills a rat."

How this culture works against finding treatments can be seen in Huntington's disease, a single-gene, fatal

illness. "We have something like 300 targets [genes, pathways, and other mechanisms thought to cause the disease] and almost as many theories," says an official at a disease foundation, who asked not to be identified so as not to anger scientists he has to work with. "The way science careers are structured, big labs get established based on a theory or a target or a mechanism, and the last thing they want to do is disprove it and give up what they're working on. That's why we have so many targets. We'd like people to work on moving them from a 'maybe' to a 'no,' but it's bad for careers to rule things out: that kind of study tends not to get published, so doing that doesn't advance people's careers."

For scientists who are willing to push past these obstacles, the next one is the patent system. When Robert Sackstein was a bone-marrow-transplant surgeon in the 1980s, he noticed that fewer than 5 percent of the transplanted blood stem cells reached their target in a patient's marrow. He therefore decided to study how cells navigate, what beacons they follow. A decade-long search led to the discovery of a molecule on the surface of blood stem cells that turns out to be the master molecule used by those cells to home in on any site in the body.

Sackstein named the molecule HCELL. If stem cells were tagged with HCELL, he thought, they would make a beeline for the correct tissue—say, to regenerate bones in patients with osteoporosis. In 2008 he and colleagues announced in a paper in *Nature Medicine* that they had managed to do just that: when he injected human bone-forming stem cells tagged with HCELL into mice, the cells headed for the mice's bones and began forming human bone there. HCELL-tagged stem cells, in other words, could be the long-sought cure for osteoporosis, as well as other diseases that might be treatable with stem cells.

But because Sackstein had described HCELL in a scientific paper, the U.S. patent office told him it was rejecting his application. Ten years of appeals have cost hundreds of thousands of dollars in attorney fees. Sackstein fervently believes his discovery deserves a patent, and it was granted one in Europe and Japan. "You have to persevere," he says. "I can't let it go, because I think the impact on patients could be so great. We've cured osteoporosis in mice." But without patent protection, no company will develop HCELL for people, even in Europe or Japan. For a multinational drug company to go forward, it needs patent protection in the U.S. as well.

If a discovery is patented, the next step is for the university or NIH technology licensing office to find a commercial partner to develop its professors' discoveries. (The institution where a scientist works, not the scientist herself, owns the intellectual-property rights to discoveries, and thus the exclusive right to license it.) Licensing typically involves upfront fees, plus a promised share of royalties should the molecule become a commercial drug. One biotech startup in the Midwest has been trying for three years to license a discovery made when some of its founders worked at the NIH. Vascular surgeon Jeffrey Isenberg, now at the University of Pittsburgh Medical Center, and colleagues were studying how the gas nitric oxide promotes blood flow. They discovered a pathway that inhibits nitric oxide and thus impedes blood flow. By blocking the blocker—to football fans, adding an extra guard to your offensive line—the scientists got nitric oxide to open blood vessels again and increase blood flow, at least in lab animals. The molecule that works

this magic is a protein called thrombospondin-1, or TSP1, suggesting that this particular offensive guard might be a potent drug for saving heart-attack victims; restoring blood flow in patients with severe diabetes, in which impaired blood flow leads to gangrene; and treating hypertension.

Unfortunately, attempts to negotiate the rights to develop this discovery were Kafkaesque. NIH's licensing office demanded payments that the startup—which, unlike the Pfizers of the world, has zero revenue—couldn't make. "NIH has no skin in the game, so they have no inducement to work with a company" to get a discovery from the lab to patients, says Eric Gulve, president of BioGenerator, a nonprofit in St. Louis that advises and provides seed money for biotech startups. "There isn't a sense of urgency." A top lab chief at the NIH laments that when scientists like himself push the licensing office to move a discovery toward commercialization, "it's just another piece of paper to them." Without the license, the startup struggles to stay alive. In its defense, Mark Rohrbaugh, the director of NIH's technology-transfer office, notes that it licensed 215 discoveries last year (though that is down from the 2004–2008 average of 273 a year, with a high of 313 in 2005). "I think we do incredibly well accommodating the needs of a company," says Rohrbaugh. "We have even linked milestone payments [made when a company achieves a goal such as starting a clinical trial] to a company raising money. The last thing we want to do is slow down the science."

If a discovery is licensed, the licensee then has to raise enough money to test the compound's toxicity (does it kill the lab rats? give them seizures?), to figure out how to make it in quantity and with uniform quality, to test the drug in larger lab animals such as dogs, and then to test it in people. Because large drug companies have been merging and retrenching (the industry laid off 90,000 people last year) and have become more interested in buying early-stage research than in doing it themselves, this role has been falling to biotech firms, which are smaller and poorer. It is at this step—turning a discovery into something that can be manufactured and that is safe and effective—that the valley of death has gotten dramatically more fatal over the last few years. "NIH grants don't support the kind of research needed to turn a discovery into a drug," says Gulve, so the money has to come from elsewhere. Traditionally, that has been venture capital. But "over the last four or five years VC funding for early-stage drug discovery has decreased dramatically," says Utah's Chahine. "You used to be able to go public, raising millions of dollars, based on a couple of genes in a rat. Now you can't even get a venture capitalist's business card for that."

Instead, VCs—essentially the only source of money to move preliminary discoveries forward—are demanding that startups prove themselves far more than in the past. Francis "Duke" Creighton had a eureka moment a few years ago: use magnets to amplify the effects of drugs that dissolve stroke-causing clots. He founded Pulse Therapeutics to develop the discovery, in which tiny magnetic particles would be mixed with a clot-busting drug, and a magnet would be used to get more of the drug to its target. He had enough money to do experiments for six months in vitro, "then we ran out," says Creighton. "Venture-capital firms said, 'Show me animal data and we'll talk,' but running animal experiments would cost $300,000 at the least." No money, no animal studies; no animal studies, no money. BioGenerator helped Creighton raise $100,000, but he's still short of what he needs.

Human testing is even more expensive—tens of millions of dollars—so commercial calculations stalk the decision like Banquo's ghost. Research funded by the Multiple Myeloma Re--search Foundation at a small biotech led to a promising new drug for multiple myeloma, a cancer of plasma cells in bones. But the firm was bought by a large drug company that decided against testing the drug in that cancer, calculating that the payoff would be greater if it could be shown to work against the big four (breast, lung, prostate, colon) or leukemias. "It's our feeling that if it had been tested in myeloma only, it would have moved faster," says Louise Perkins, chief scientific officer of the foundation.

If we are serious about rescuing potential new drugs from the valley of death, then academia, the NIH, and disease foundations will have to change how they operate. That is happening, albeit slowly. Private foundations such as the MMRF, the Michael J. Fox Foundation for Parkinson's Research, and the Myelin Repair Foundation (for multiple sclerosis) have veered away from the NIH model of "here's some money; go discover something." Instead, they are managing and directing scientists more closely, requiring them to share data before it is published, cooperate, and do the nonsexy development work required after a discovery is made.

For instance, the Chordoma Foundation, which supports research into that rare cancer, found that there was only one decent chordoma cell line in the whole world—in a freezer in Germany—and it hadn't been used for new research since 2001. The foundation obtained the legal rights to it and distributed it to some two dozen researchers, jump-starting studies that otherwise would never have been done. The cell line is being used to, among other things, screen existing drugs to see if they might work against chordoma.

Forcing that kind of cooperation among turf-jealous academics could break a lot of logjams. "There are thousands of researchers working on exactly the same thing," says Bruce Bloom, whose Partnership for Cures foundation supports research on new uses for existing drugs. "Under the current system they cannot and will not collaborate for fear that it will jeopardize funding, patent protection, and publication. Look at the progress open-source software has made in IT. Imagine the progress open-source research could make in biomedicine."

Perhaps the greatest sea change is that "more academics are starting to ask, 'How can I get funding to turn this discovery into something?' so universities are encouraging the creation of drug-development groups," says Jeff Ives, president of Satori Pharmaceuticals, a biotech in Cambridge, Mass., that is searching for Alzheimer's drugs. "The ivory-tower separation from the real world isn't acceptable anymore."

Stanford Medical School realized that. Although the NIH has increased support for research intended to help patients, points out Daria Mochly-Rosen of Stanford, there is still very little funding for steps such as testing a compound's toxicity in several species of lab animals, synthesizing the molecule, and scaling up that synthesis. "What we lack in academia is an understanding that these steps can be intellectually interesting, too," says Mochly-Rosen. To foster that, she founded Spark four years ago. It scrutinizes discoveries from Stanford scientists that have not been licensed to a company and, with industry input,

identifies 20 per year that have promise. The inventor is taught the basics of drug development and gets funding support to carry out the "drudgery."

In perhaps the clearest sign that patience among even the staunchest supporters of biomedical research is running thin, the health-care-reform bill that became law in March includes a Cures Ac-celeration Network that Sen. Arlen Specter, a longtime supporter of biomedical research, sponsored. Located at the NIH, the network would give grants ($500 million is authorized this year) to biotech companies, academic researchers, and advocacy groups to help promising discoveries cross the valley of death. It may or may not make a difference. But something had better, and soon.

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