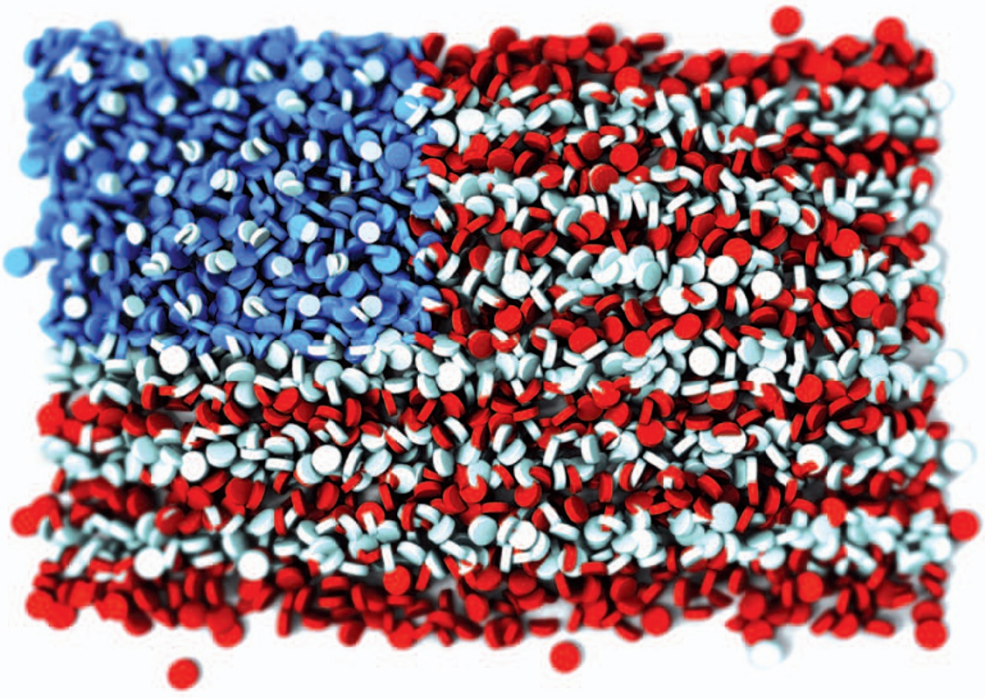

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TRANSLATIONAL RESEARCH

The American way

The United States publishes more biomedical research papers than ever before, yet drug development is stagnating. Several new initiatives aim to turn this knowledge into new remedies.

BY AMY MAXMEN

On being asked to grade the United States on its performance in biomedical research, Bill Chin, executive dean for research at Harvard Medical School in Boston, Massachusetts, responded: "If the measure describes how much we understand about disease, I think we're on a good road. If it's how often we turn basic science ideas into potential medicines, we aren't doing that well." For Chin and other scientists, discoveries don't matter tremendously if their potential goes unrealized. Although research papers by US scientists document great strides in understanding human physiology, genetics and disease, a failure to efficiently translate those findings into diagnostic tests and medicines foments frustration among researchers and the public alike.

Advances in basic science abound. Of the 196 Nobel laureates in physiology or medicine since 1901, 46% have been US researchers. According to the National Institutes of Health (NIH) in Bethesda, Maryland, sequencing the first human genome took five years of work and US$450 million. Today it can be done in 90 days and for US$9,500. By the end of 2011, it is estimated that North American scientists will have sequenced 9,000 genomes — an indispensable resource in genome-wide association studies that attempt to link genetic variants to common maladies. Although knowledge of these variants has yet to make a substantial impact on patient care, the trickle into the clinic has begun. For example, hepatitis C patients can now be tested for a variant of the *IL28B* gene, discovered by researchers at Duke University in Durham, North Carolina, to determine whether they will respond favourably to the gruelling treatment.

"Anyone who says there hasn't been progress hasn't been paying attention," says Mary Woolley, president of Research!America, an advocacy group based in Alexandria, Virginia, committed to making biomedical research a higher national priority. "We've made progress in women's health, including getting women into clinical trials," she says. "We've made progress in medicine," Woolley adds, citing cancer and heart disease in particular. Between 2001 and 2007, the annual mortality rate from cancer dropped by 9.1% and by 23.5% for cardiovascular disease (see 'Getting on top of cancer'). However, these positive trends are failing to convince the public. "Our polls show that two people to every one believe we aren't making enough progress in biomedical research, and that's kind of disturbing," says Woolley.

This lack of belief might reflect frustration at the poor rate of return. According to Research!America, US national expenditure on health reached US$2.6 trillion in 2010, representing 17.8% of gross domestic product (GDP) — a higher proportion than any other country. Yet the United States ranks middle-to-poor in measures of health outcomes, including longevity and infant mortality (see 'Life expectancy' and 'Infant mortality' graphs). And although several thousand reports claim particular genes or proteins have disease-fighting potential, the US Food and Drug Administration (FDA) has approved just 111 novel drugs in the past five years, slightly fewer than the five years before that (see 'Drug approvals stagnating'). Likewise, the pace and price of drug development haven't improved despite technological advances. Crucial molecules discovered in disease pathways have a 2% chance of being translated into a therapy. Any drug that makes it through the pipeline typically takes13 years and more than US$1 billion, including the cost of the failures. This is an inefficient process, to say the least, says Francis Collins, director of the NIH, who also addressed the 2011 Lindau meeting. "An engineer looking at this would go, 'What? You're going to base the future of human health on a pipeline that works like that?'"

Despite advances in understanding the pathogenesis of disease, Collins says the translation of these findings into clinical applications remains a slow, expensive and failure-prone endeavour. The blockages in the biomedical pipeline need to be identified and dissolved. And, given that the economy is weak, the US federal budget is in distress, and 10 blockbuster drugs are about to come off-patent to the tune of more than US$50 billion in lost sales, drug developers face an especially challenging time. "The science has never been more exciting with the potential to revolutionize human health," says Collins. "But support for this science has never been as threatened as it is right now." Consequently, biomedical leaders in the United States recently launched a bevy of new programmes to accelerate drug discovery and attempt to reverse the decline in the pharmaceutical industry.

At about US$45.9 billion per year, the federal government supports one-third of US biomedical research. Most of these funds are channelled into the NIH. Pharmaceutical and biotech companies fund most of the rest, spending about US$76.5 billion in 2010. Universities,

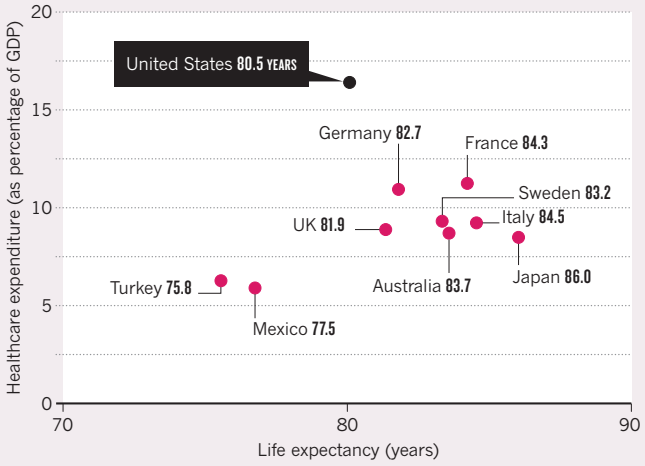
LINDAU 2011

Each year the Lindau Meeting of Nobel Laureates in Germany has an international sponsor and a scientific focus related to a Nobel Prize. The United States and physiology or medicine took centre stage in 2011. *Nature Outlook* explores the intersection of these areas in a special report.

OECD

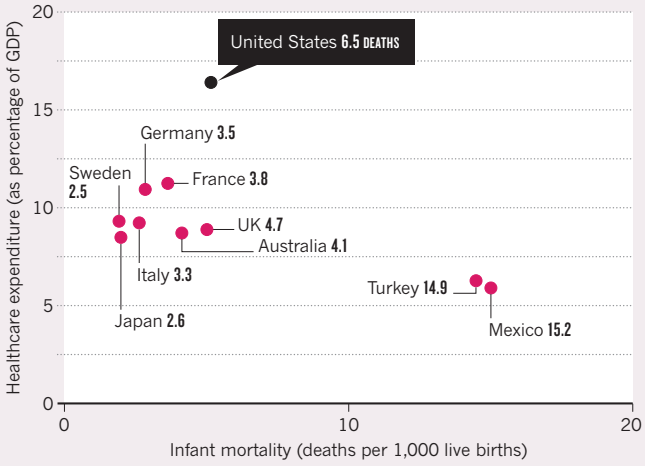
LIFE EXPECTANCY

As a percentage of GDP, the United States spends considerably more than any other country on healthcare, yet this does not result in the highest life expectancy.



INFANT MORTALITY

Many countries with lower healthcare spending have a lower rate of infant mortality than the United States.



Data from 2008

philanthropic foundations and other sources also sponsor some research and development (R&D). Altogether, R&D accounts for less than 5.5% of the nation's health expenditure; hospital care and clinical services account for a much bigger slice of the pie.

To sustain their R&D expenditure, pharmaceutical firms need new drugs to sell. "We really are not the bottomless pit of money we were when I entered this business 25 years ago," says Charles Lunn of Merck Research Laboratories in Kenilworth, New Jersey. "If a programme is unsuccessful, we lose a lot of money. So when we go out looking for new opportunities to collaborate with the academic community, we are very careful."

RISKY BUSINESS

Kyle Palmer, director of research at Redpoint Bio, a small biotech company in Philadelphia, Pennsylvania, experienced this risk adversity firsthand as his company nearly folded. In the late 1990s, neuroscientist Robert Margolskee founded the company, hoping to bring taste-modulating compounds to market. A few years later, researchers discovered that some of the compounds modulated insulin, and therefore held potential as new therapies for type 2 diabetes. Redpoint Bio was awarded a patent that granted exclusive rights over several compounds involved in taste- and insulin-modulating pathways, and began testing the compounds in mice. Then everything changed. "Just as I thought we were poised to make all kinds of discoveries, with several big drug companies interested, the economy crumbled and the rug was pulled out from under our feet," says Palmer. With no promise of investment, Redpoint Bio shelved its compounds. "It seems like pharma are dropping out of basic research," says Palmer. "They're farming out some preclinical research to biotech and academic operations, so biotech has responded by changing model from early phase drug discovery to providing services to pharma like *in-vivo* testing, and that's exactly what we've done. We've auctioned off our drug discovery arm."

Lunn explains that pharma now need a mountain of evidence before investing in turning a discovery into a therapy. This is partly because biology has turned out to be more complicated than previously thought. "You can make up a good story about how any number of targets might have a useful benefit, but human biology is so complex that proving their validity requires a lot more information than is asked for by premier journals," he says.

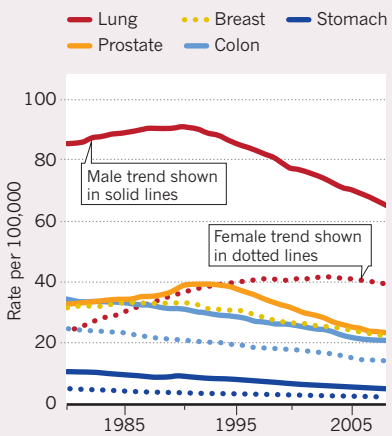
The barren stretch between the abundant fields of molecular discovery and the sparse world of late-stage clinical trials has been dubbed the 'valley of death'. Traversing it means that academic researchers and industrial drug developers must move their domains closer together. This will require changes in incentives. For instance, academic researchers are rewarded for reporting novel discoveries rather than for replicating experiments in different animal models to support their initial findings. Eric Perakslis, at Johnson & Johnson Pharmaceutical Research & Development in Raritan, New Jersey, says that current practice leaves too much risk for pharma. Hundreds of posters at conferences claim that a gene or protein represents an effective antitumour target, he complains, without adequately showing what type of tumour it's most active in. Thus, he says, "you're talking about a few people in pharma making a billion dollar decision based on low correlation data".

On the other side of the valley, pharma impede translation when they file early for intellectual property (IP) that grants them exclusive rights to work on a compound before they have proof that it works in clinical trials, says Chas Bountra, a translational medicine scientist at the University of Oxford in the United Kingdom. If a company with IP puts a project on hold (as Redpoint Bio has), its compounds become inaccessible. "We're taking a process that is already incredibly difficult," says Boutra, "and making it more difficult and more expensive ."

Rules and regulations provide another point of contention. Bill Crowley, professor of medicine at Harvard Medical School, says the conflict-of-interest policies at many research institutions give off a message of industry-distrust to young investigators and thereby inhibit collaboration. Crowley explains that investigators with potential conflicts of interest are often lumped together even when their conflicts vary dramatically: a researcher who once shared data with a company must complete the same lengthy paperwork as an investigator who is paid for ongoing, long-term

GETTING ON TOP OF CANCER

Over the past 30 years, the rate of cancer mortality in the United States has almost universally fallen.



CANCER FACTS AND FIGURES, ACS 2011

consultation. Furthermore, "how much institutions 'lump' varies widely and in a most confusing way that makes life more complex for clinical investigators," he adds.

Crowley also takes issue with tighter federal regulations on human studies, which he says have bogged down drug development without making studies much safer. "In the 1980s, consent forms for patients entering clinical trials were about a page long and almost invariably engaged a detailed discussion between the patient and me," he says. "We now have a standard 19-page consent form written by lawyers, for lawyers. Most patients don't bother to read it, and if they do, they don't understand it."

TIPPING POINT

There have been many attempts to close the gaps in translational research over the years, with little success. "People are so frustrated on both sides of the divide that they are coming together and learning about each other's incentives and disincentives," says Johnson & Johnson's Perakslis. "If my academic colleagues can't get their grants renewed, that's not good for me because if they can't survive, they can't be my partners."

A number of partnerships between the public and private sectors have recently cropped up in various disciplines to free the flow through the biomedical pipeline. For example, the Foundation for the NIH, a nonprofit organization in Bethesda, Maryland that aims to accelerate NIH research, established the Biomarker Consortium in 2006. With participants from the NIH, FDA, industry and universities, and about US$35 million in funding from nonprofit groups and pharmaceutical companies, the consortium has launched 12 projects to help take biomarkers through the large-scale clinical trials required to gain FDA approval. Combining their results allows all the partners to access cumulative data on thousands of patients.

Another such movement, the Structural Genomics Consortium led in part by Bountra, involves sharing information on molecular structures. Drug developers can increase the likelihood of finding an effective drug when they know the 3-dimensional structure of the human protein it's intended to inhibit. Teams from academic centres and industry share data on a large number of drug targets, as well as reagents and assays. If no IP is filed until compounds complete early stage clinical trials, participating companies gain knowledge without hefty initial investments. "The beauty of these public–private partnerships, is that we're saying let's pool our resources and not worry about IP, and not worry about the slim chance this idea will generate money because frankly, most of the time it won't," says Bountra. He bets that prepublication sharing shouldn't hurt academics either. Bountra has already posted on his website the structural details of a high-impact human membrane protein recently revealed by his team, and a paper is in preparation. He's confident that *Nature* or *Science* will not reject the paper on account of his openness. Indeed, both journals state that they allow pre-submission publication of information on nonprofit preprint servers, provided no conclusions are drawn. "I'm taking this risk because I'm less concerned about publications than I am about generating new drugs," adds Bountra.

Scientists lacking Bountra's optimism might take comfort in hearing that leaders at some top institutions including Harvard Medical School, Princeton University in New Jersey, and University of California, San Francisco, now look beyond the number of manuscripts an investigator has published to other factors, like contribution to collaborative research. And to ease fears about perceived conflicts of interest, Harvard Medical School revised its conflict-of-interest policies to more clearly delineate acceptable and prohibited activities. The revised guidelines encourage collaboration, explains Chin, by explicitly outlining allowable activities. "Faculty may continue to: conduct research sponsored and supported by industry; collaborate with industry on research and serve as co-authors in these efforts; consult for industry; start biotechnology companies; serve on scientific advisory boards; and hold equity in most companies," he states.

Repairing the pipeline is important to Collins; for the first time in the NIH's history he has proposed closing one of its centres and reshuffling others to make space for the National Center for Advancing Translational Sciences (NCATS). NIH Investigators and scientists supported by NCATS grants will concentrate on the early stage drug development research that is often ignored by industry, including the development of methods and technologies to hasten target validation. Although these studies might not result in top-tier publications, they're needed to bridge gaps in drug discovery. As for persuading scientists to focus on optimizing methods rather than discovering new targets, Collins believes being part of a large-scale effort is encouragement enough. When Collins led the Human Genome Project, he says peer-pressure proved a driving force. "You didn't want to be the part of the team that missed the deadline. Everybody else was depending on your success for their success." This feeling spread beyond the individual scientists. "There was a gradual recognition in academic centres that an investigator's involvement with a successful scientific project was as important as how many papers that person had published," he adds.

Over the next decade, success in closing this translational gap will largely be measured in tool development. Lee Nadler, dean for clinical and translational research at Harvard Medical School, says that helping clinicians prognosticate disease or adverse outcomes to medicine will be crucial. "If biomarkers told us who to treat, who not to treat, and who will react poorly to a drug," says Nadler, "that would revolutionize drug development."

Better medicines will bring society closer to the ultimate goal of alleviating disease. However, they aren't enough alone. Disease prevention is another factor; for this, federal support is essential. "If you're a pharmaceutical company and your goal is to sell therapeutics, prevention is not your best idea of a business plan," explains Collins. "But the NIH — with its mission to both understand the basics of how life works and apply that to the betterment of human health — has to have prevention front and centre."

The public's confidence in biomedical research is influenced by the health of the nation. Thus beyond lab work, the public health sector needs to work with health insurers, drug companies and the FDA to reduce the high cost of medicines and healthcare in the United States, says Harvard's Crowley. Until all parties involved in health unite towards a common goal, no one scores an 'A' on the biomedical report card. Crowley says gravely, "The whole therapeutic programme in the US will go under if the jump from bench to bedside doesn't go smoothly." ■

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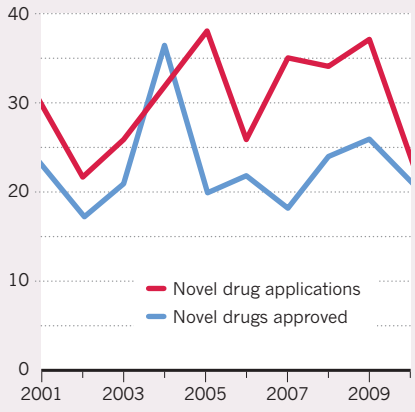
DRUG APPROVALS STAGNATING

Despite years of attention and investment, neither the rate of FDA approvals nor new drug applications have improved.



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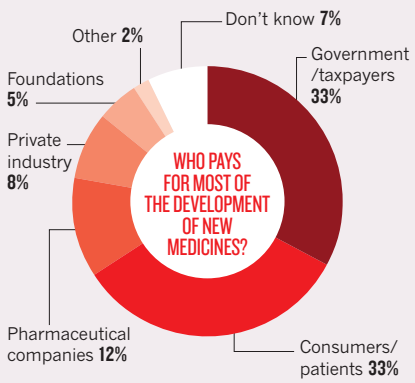
PUBLIC MISPERCEPTIONS

Most people in the United States do not know that pharmaceutical companies fund the majority of new drug research.



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