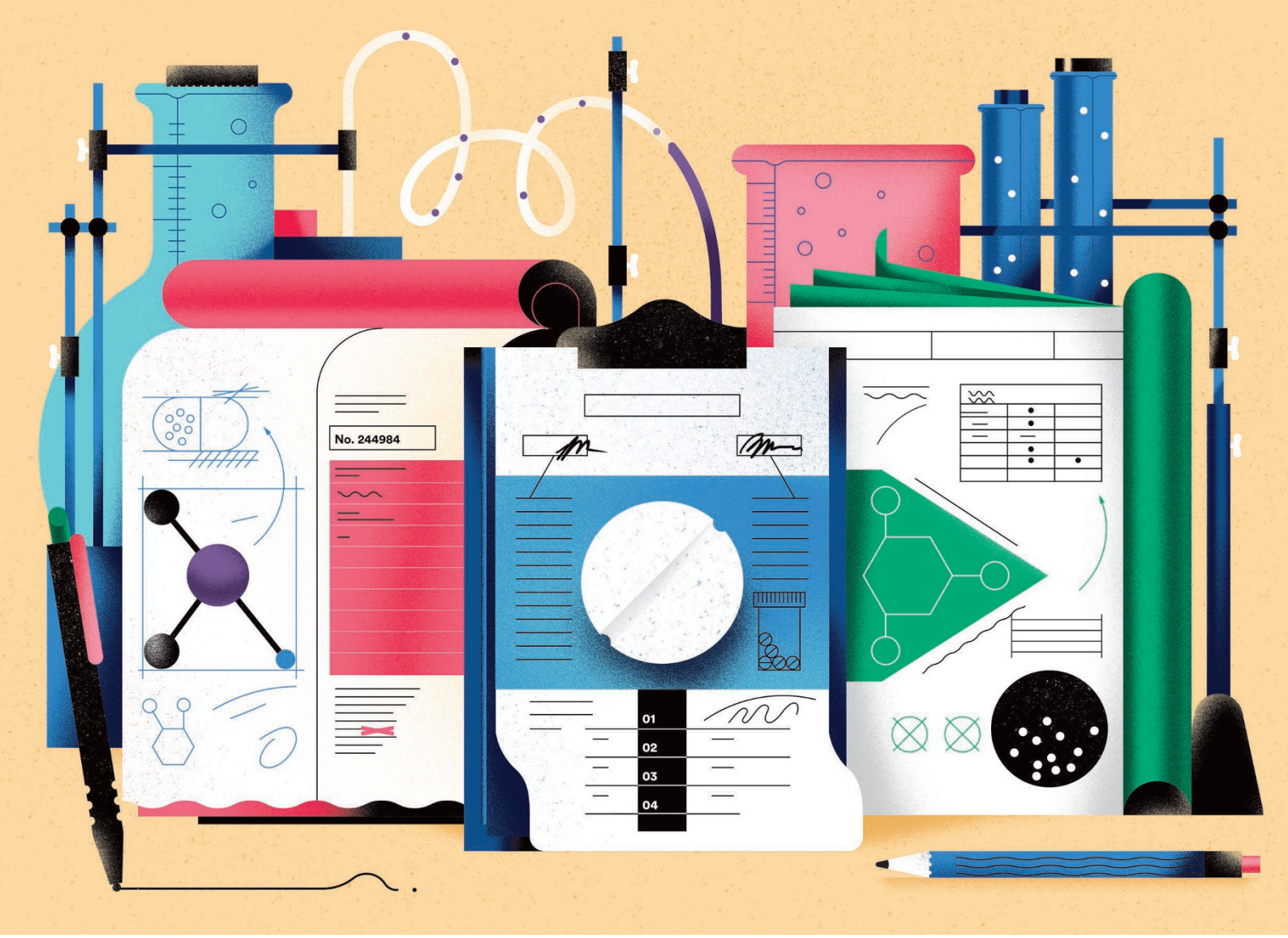


BRATISLAV MILENKOVIC

COMPETITION

Unlikely partnerships

Drug discovery is time-consuming and full of blind alleys. Pharmaceutical rivals are cooperating in the early stages to accelerate and improve the efficiency of the process.

BY NEIL SAVAGE

The protein ubiquitin, as its name suggests, is found in almost all living tissue. It plays an important part in the death of old or damaged cells, by attaching to other proteins and labelling them for destruction. Failure to mark proteins in this way can lead to inflammation, cancer or neurological disorders such as Alzheimer's disease. If scientists can unravel the mysteries of this pervasive molecule, they may find new targets for drugs to treat these diseases.

Pharmaceutical companies are already selling three drugs that target processes involving ubiquitin as a way to treat the bone-marrow cancer multiple myeloma: bortezomib, approved by US regulators in 2003; carfilzomib, approved in 2012; and ixazomib, which got the nod last November. But because the system for attaching and detaching the protein has so many moving parts, including 2 activating enzymes, about 40 conjugating enzymes and some 600 ligases, there may be many more therapeutic targets still to be found. With so much to study, researchers at the University of Dundee, UK, and six pharmaceutical companies are collaborating to share their resources and findings, in the hope of gaining insights that will lead to new drugs. "I think this is going to become pretty big," says Philip Cohen, a biochemist at Dundee and one of the leaders of the collaboration, called the Division of Signal Transduction Therapy (DSTT). "The things we discover here will be helpful to alleviate disease and also to generate a lot of money, not only for the companies, but for our own research."

The DSTT is a pre-competitive partnership — a type of collaboration in which pharmaceutical companies join together with one another, and often with academic researchers and the support of government funders, to tackle questions that they hope will lead to therapies. The idea is to share the cost of making early-stage discoveries, such as identifying biomarkers or disease pathways, that lay the groundwork for drug development. Armed with such basic knowledge, the companies can then identify specific molecules that might make drugs and study them in-house, developing proprietary therapies.

FRIDA YGGESETH

Protein structures solved by the Structural Genomics Consortium are made publicly available.

Beyond sharing costs, partnerships can also help with the sheer volume of biological information now collected. This will only continue to grow as DNA sequencing of individuals becomes more widely available. "The work is very large, and no single company or academic group can do it alone," says Sylvain Cottens, who heads the Center for Proteomic Chemistry at the Novartis Institutes for Biomedical Research in Basel, Switzerland. If academic and industry researchers can pool their resources and share skills, they may be able to improve efficiency and speed up the creation of therapies for a wide variety of diseases.

THE COST OF FAILURE

Most drug candidates go nowhere. In 2004, the US Food and Drug Administration (FDA) estimated that only 8% of the compounds that enter phase I trials — many of which have been in development for more than a decade — actually make it to market. In 2015, the industry group Pharmaceutical Research and Manufacturers of America put that figure at less than 12%. The average cost of developing a drug in the first decade of the twenty-first century was US$2.6 billion — up from an average of $1 billion in the 1990s (see 'Under pressure').

Pre-competitive partnerships could be a way to dramatically improve the efficiency of drug development. For starters, they could reduce the large amount of duplication. Companies conduct their research in secret and tend not to publish the results of failed studies, meaning that other groups are likely to follow the same fruitless lines of inquiry. "If ten companies are working on Alzheimer's disease on exactly the same target and it's failed, that's ten times the investment that is down the tubes," says molecular biologist Pierre Meulien, who heads the Innovative Medicines Initiative (IMI) in Brussels, a partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. Because of the secrecy, it's difficult to come up with specific figures for duplication. But in 2009, it was estimated that 85% of research is wasted (amounting to $170 billion worldwide each year), at least some of which is because of failed or redundant studies (P. Glasziou & I. Chalmers *Lancet* **374,** 86–89; 2009).

"The patent system has not been designed with open collaboration in mind."

Greater openness could reduce redundancy and save money, as well as spare patients from enrolling in trials that are doomed to fail. But as Cohen sees it, the real promise of pre-competitive partnerships is improving our understanding of the biological mechanisms that underlie a particular process. The DSTT's focus on deubiquitinating enzymes, which modify the effect of ubiquitin, is already helping to speed up the discovery of candidate drugs. One company, Dundee-based Ubiquigent, has already been formed to provide drug-development companies with assays and reagents developed by researchers at the University of Dundee. Cohen hopes that deubiquitinating enzymes will follow the path of kinase inhibitors, which the DSTT also studies. Once the first kinase inhibitor, imatinib, was approved by the FDA in 2001 to treat chronic myeloid leukaemia, researchers began devoting more resources to them. Since then, more than 25 drugs that target kinases (which help to control the function of certain proteins) have been approved.

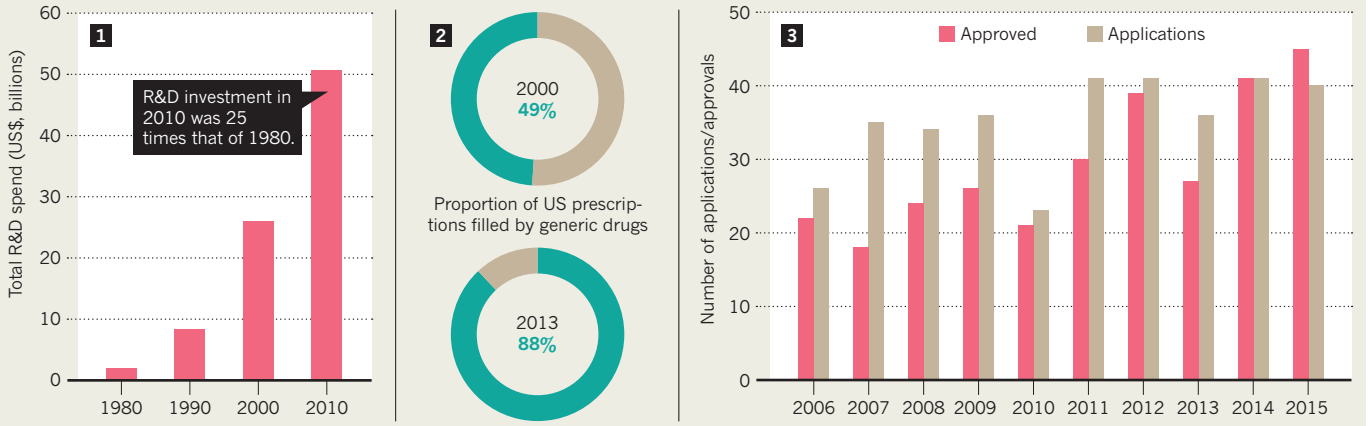
The DSTT, which was formed in 1998, is made up of AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen Pharmaceutica, Merck KGaA, Pfizer and 20 academic research teams, and according to Cohen is probably the longest running collaboration of its kind. Under the terms of the agreement, all unpublished results are shared between the collaborators, along with reagents, technology and technical know-how. Faculty and students must sign confidentiality agreements regarding the companies' intellectual property, although they can still publish papers based on the collaboration's research. The first drafts of articles are shared on a private website. Any member that wants a head start on development and patenting before the information reaches the public has 45 days to request a 9-month publication delay. Cohen says that the number of papers delayed is low — perhaps around 10 out of the past 400 — and that in practice, the delay is not as long as it seems because researchers tend to share drafts at earlier stages than they would submit them to journals. "We actually think that the threat of this delay has caused us to publish more effectively and efficiently," he says.

By contrast, the public–private partnership the Structural Genomics Consortium (SGC) has no members-only viewing period. Its policy is to release data to its members and the rest of the world simultaneously, with no restrictions on use. The SGC also promises never to patent anything. "That openness does lead to faster science," says Aled Edwards, a protein biochemist at the University of Toronto, Canada, and founder of the SGC. The SGC determines a protein's structure and publishes the information in the international repository the Protein Data Bank. Under the policies of many scientific journals, anyone who describes a protein structure must deposit their data in the bank to make it available to all researchers. In the past 12 years, the SGC has deposited more than 1,500 descriptions of protein structures, from both humans and parasites, into the data bank. It also develops antibodies and chemical probes — small molecules that test how a potential drug interacts with biological targets (see page S60).

SGC members all have different strengths. Academic researchers, Edwards says, are good at making basic discoveries, but have no incentive to take them beyond published papers. Participating pharmaceutical companies, however, are much more focused on creating marketable therapies. They are very good at high-throughput screening of drug candidates, but don't spend much time on the most basic science. "We do get knowledge from the academic groups, but we also provide knowledge about how to develop assays," says Cottens — Novartis is an SGC partner.

UNDER PRESSURE

The pharmaceutical industry estimates that it is now more expensive to bring a drug to market than ever. Research and development (R&D) investment by members of the trade group the Pharmaceutical Research and Manufacturers of America was more than US$50 billion in 2010 **1**. Pressure from generics (identical or equivalent versions of drugs for which patent protection has expired) that are typically substantially cheaper than branded options is also increasing **2**. But the number of drugs coming to market each year is rising — 2014 and 2015 saw the highest number of US Food and Drug Administration approvals in the past ten years **3**.



SOURCE: LEFT AND MIDDLE, PHRMA; RIGHT, FDA

Unlike the DSTT and the SGC, the IMI has no general rules about intellectual property. Instead, Meulien says, details of what can be shared and what stays proprietary are agreed in advance between collaborators on a given project. "We have a whole spectrum of types of arrangements."

Between 2014 and 2024, the IMI will receive €1.6 billion ($1.82 billion) from the European Commission and €1.4 billion from European pharmaceutical companies. This will fund projects that focus on neurological conditions, diabetes, cancer, tuberculosis, obesity, vaccine safety, the use of stem cells in drug discovery and antimicrobial resistance, among others. One IMI effort, the European Lead Factory, provides small- and medium-sized companies, as well as academics, with free access to half a million chemical compounds, which they can use to screen potential drug targets.

NOT HITTING THE PRICE POINT

Although a promising approach to point the way to therapies, partnerships that focus on fundamental science may have little impact on the overall cost of research. This is because it is during clinical trials, rather than early research, that most drug candidates fail. The SGC, for instance, is "at a fairly inexpensive part of the pharmaceutical discovery process," Edwards says.

So, in 2011, he and SGC chief scientist Chas Bountra, a translational medicine specialist at the University of Oxford, UK, joined with Sage Bionetworks, a nonprofit biomedical research organization in Seattle, Washington, to form a partnership they called Archipelago to Proof of Clinical Mechanism (Arch2POCM). The idea was to extend pre-competitive cooperation on a few drug targets into phase II clinical trials, after which the risk of failure drops substantially.

But the vision proved too ambitious, says chemist Thea Norman, Sage's director of strategic development. She says that the pharmaceutical companies worried that it might prove too difficult to base intellectual property on compounds and information that would be in the public domain. "The idea was a new one and one that maybe at first glance for a pharmaceutical company takes a little explaining," she says. "We had at least two pharmaceutical companies that were ready to sign up, but we felt we needed a little more critical mass than that." To get enough funding for what they had in mind, she says, they needed three to five companies on board.

> ***"We hope to really transform the ecosystem for how these things are done in Europe."***

When the first approach turned out to be more than the industry was willing to sign up to, Arch2POCM's founders launched a smaller-scale project, but one that still went beyond previous collaborations. The group began a 3-year UK effort in late 2013 with the Institute of Cancer Research and Newcastle University, with funding from Cancer Research UK and the Avon Foundation for Women, but with no pharmaceutical companies involved. The scaled-back programme aims to find a candidate compound that works on the enzyme KDM4B, which is implicated in people with breast cancer, but won't take the compound all the way through phase II trials. Norman says that the hope is that, whatever the scientific outcome, the project will demonstrate that cooperation can benefit drug development beyond the earliest stages of discovery.

Another way to maintain the openness between pharmaceutical companies further into the drug-development process may be to change financial incentives. Liza Vertinsky, who focuses on intellectual property at Emory University in Atlanta, Georgia, says that current patent law encourages companies to jealously guard their intellectual property, because if they lose patent protection they could lose out on the profits that come with a successful drug. "The patent system has not been designed with open collaboration in mind, so the mechanism of how you would share intellectual property is not built into the system," she says. An alternative would be for lawmakers and courts to develop a concept of fair use, analogous to laws that allow people to quote a passage from a novel or sample a snippet of a song while not violating copyright, for example. That way, she argues, companies could share some portion of their research findings without giving up all claims to their intellectual property. Vertinsky intends to look more closely at pre-competitive partnerships in the coming year to better understand how changes in the law might affect the way they work.

Even if the cooperation between pharmaceutical companies cannot be expanded further, pre-competitive partnerships are still having a positive effect on drug discovery, participants say. Although Cottens won't go into specifics about propriety work, he says that the collaboration "has clearly accelerated" the projects that Novartis is working on. Meulien says that these efforts are already helping to translate academic knowledge into practical applications. "We hope to really transform the ecosystem for how these things are done in Europe," he says. "We do things that no one company or university could do alone." ■

Neil Savage *is a freelance writer based in Lowell, Massachusetts.*