



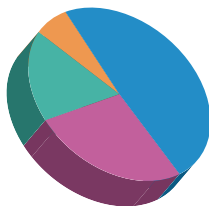
Antisense progress p401



NIH drug database launched p403



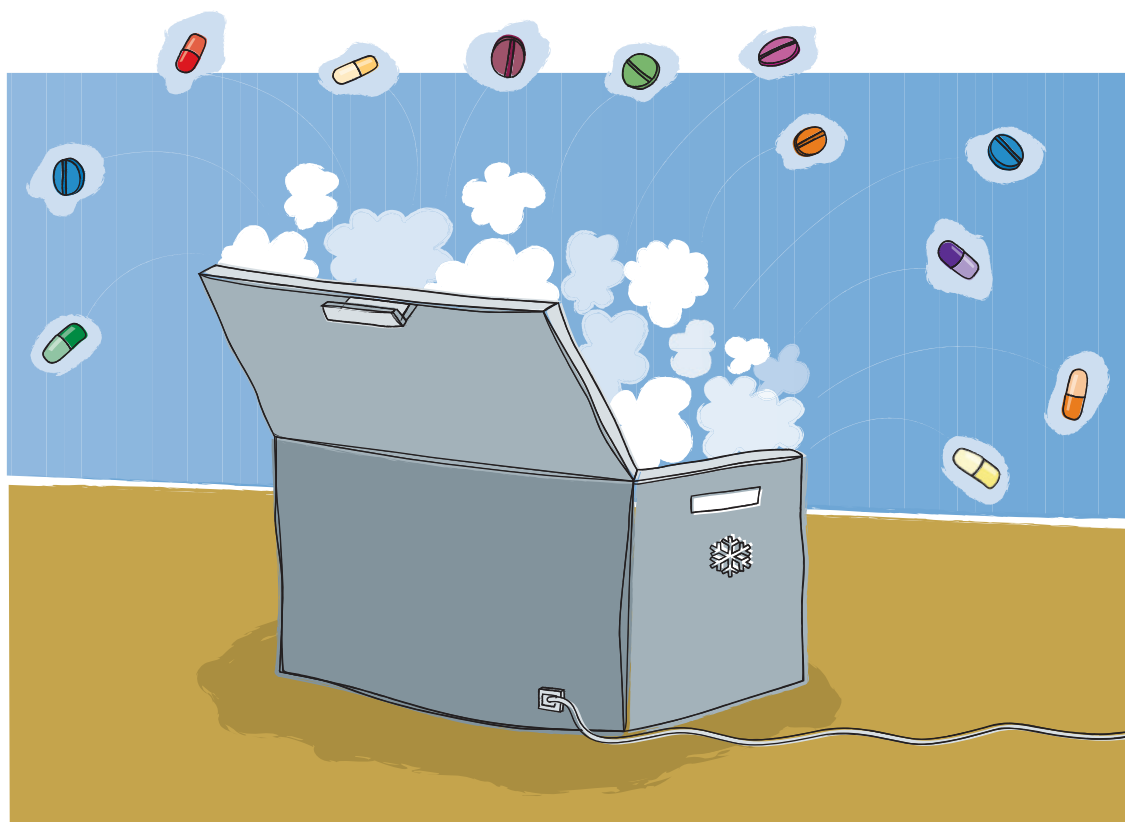
EFPIA Director General discusses his agenda p408



Academic drug discovery trends p409



Antibody approved for melanoma p411



Could pharma open its drug freezers?

The NIH wants industry to contribute old, new and experimental drugs to a systematic, collaborative approach to drug rescue and repurposing.

Asher Mullard

Around 80 representatives from the pharmaceutical industry, government and academic institutions met for 2 days in April 2011 to discuss repurposing and rescue efforts for old and new drugs. Although drug repositioning is not a new concept, US National Institutes of Health (NIH) officials asserted that the different sectors could better capitalize on advancing science and accumulating clinical data by working together on a systematic approach for screening clinical-stage, abandoned and approved compounds for new uses.

Already, plans are underway to embed such a strategy into the new National Center for Advancing Translational Sciences (NCATS). “So

far as repurposing gives us a running start on development activities, it will be an important activity of the NCATS,” says Amy Patterson, Associate Director for Science Policy at the NIH. (See also accompanying Comment on page 397 and news in brief on page 403.)

Repositioning has already yielded several successes — including the rescue of thalidomide through the discovery of its efficacy in both leprosy and multiple myeloma. It is also already broadly pursued as a route to cost-effective drug development for compounds with known safety profiles: Pfizer’s Indication Discovery Unit (IDU) is dedicated to repositioning, biotechnology companies have built business models around the strategy,

and academic groups have applied this approach to neglected diseases. “Repositioning is very fertile ground,” says Garret FitzGerald of the Institute for Translational Medicine and Therapeutics.

But whereas current attempts are limited by the scope of an organization’s chemical library and assay know-how, the NIH hopes that a collaborative approach encompassing a broader science base would be more fruitful. “By pulling resources together and working in a synergetic fashion, we can distribute the risk and hopefully come up with something that’s a win-win for everyone,” says Patterson.

If all goes to plan, drug firms will open their freezers to the NIH, sharing compounds and the

associated data. Old and new drugs could then be screened for activity in unexpected indications, and abandoned candidates with efficacy or safety problems could perhaps find new life in different patient populations.

Varied strategies

As yet, the details and structure of broad-scale collaboration between industry and academic institutions remain hazy. In part, this stems from the range of compounds that the NIH has asked for access to, including off-patent generics, branded blockbusters, experimental candidates and abandoned products.

A first question that attendees at the round-table meeting grappled with is how products and associated data could be made accessible to the NIH and its academic partners. On one end of the spectrum, the NIH hopes that companies

Pharma was concerned that systematic screening might open up a can of worms.

might voluntarily pool some compounds — perhaps off-patent products — into a shared resource. Alternatively, the NIH could solicit industry to donate compounds with specific mechanisms of action. Or the US Food and Drug Administration (FDA), which holds proprietary information on experimental drugs, could ask drug makers whether they have abandoned their stalled products and are willing to donate these to the pool.

With compounds and associated data in hand, how would they be used? Under one proposal laid out by the NIH, investigators would screen the library of drugs with known safety profiles in *in vitro*, cellular and phenotypic assays. When investigators get promising hits from patented products, they could then share data or negotiate co-development rights with the relevant industry partner. For off-patent or fully abandoned products, they could head straight into clinical trials in search of proof-of-concept (POC) data that would attract private sector investment.

Other approaches that were discussed included repurposing efforts from not-for-profit organizations on neglected diseases and a Pfizer–Washington University collaboration. Under the terms of the latter partnership, which involves Pfizer's IDU, all Washington University faculty members have access to proprietary data from over 100 Pfizer products, and can submit proposals

to the company to initiate small-scale, hypothesis-testing, preclinical and clinical studies. This deal has already opened some unexpected doors, including a clinical trial testing a non-antibiotic for activity against a hospital-acquired infection.

For now, it remains unclear whether such case studies are useful models for expansion at the NIH level. The Pfizer–Washington University deal — which harnesses the in-depth knowledge base of academics rather than the brute-force power of broad-scale screening — may, for instance, be difficult to scale up. Nevertheless, it and other examples show the value of intellectual property (IP) free spaces in which investigators on both sides of the industry–academia divide can experiment and collaborate. “There are varied strategies that are not necessarily mutually exclusive,” says Patterson.

Overcoming obstacles

Obstacles abound, but the chief stumbling block against collaboration is probably IP. For patented and experimental drugs, companies are unlikely to enthusiastically sacrifice IP that is crucial to their value. In the case of the abandoned and off-patent products — for which lack of patent protection can make commercialization of an eventual product difficult — the NIH faces the inverse problem of attracting private partners who will run with POC data to the finish line.

Presenting at the meeting, Bryan Roth of the University of North Carolina at Chapel Hill, USA, argued that the patent landscape is already fit for purpose in some instances. He pointed to a recent lawsuit over Bristol-Myers Squibb's blockbuster antipsychotic aripiprazole, in which the judge ruled that a genus patent — which can claim trillions of compounds for a broad set of indications — did not invalidate a newer, more focused patent. “If an old patent encompasses trillions of compounds and every disease known to man, this should not stop you from gaining IP for a closely related compound, metabolite or the compound itself for new indications,” says Roth.

Several other potential work-arounds were also proposed. For patented and experimental products, the NIH and industry could draw up royalty- and revenue-sharing agreements. Early collaborations could also perhaps focus on developing therapies for rare and neglected diseases, where legislative provisions such as the US Orphan Drug Act provide marketing exclusivity for drugs that lack patent protection.

Another point of discussion was how this repurposing approach would cut into industry's bottom line. Companies were

worried that they would have to dedicate resources into making products and data available for compounds that may have been discontinued years or decades ago. Potentially more problematically, they raised fears that collaborations could uncover unexpected off-target activities that would cast dark clouds over the marketability of approved or experimental products. “Pharma was concerned that systematic screening might open up a can of worms,” says Roth.

For FitzGerald, who also presented at the meeting, such concerns have already stymied research plans. When COX2 inhibitors were in clinical trials, he wanted to test their cognitive effects because their target is expressed widely in the brain. But upon approaching companies with a research proposal, he was told: “No, you can't do that and you can't have our drug if you're going to do that.” “For them, it was only an opportunity to get bad news,” he explains.

The flip side of this problem is that if there is bad news, it will probably emerge at a later date anyway. “I believe that there is a real role for the regulatory body to try and rearrange incentives so that it is in a company's interests to explore the full potential spectrum of its drugs' effects as soon as possible,” adds FitzGerald.

Despite the hurdles, Roth at least emerged optimistic about the future prospects for collaboration. “Drug companies all agreed that it is a great idea to do broad-scale phenotypic and molecular target-based screening — if a drug is already generic,” said Roth. “I was hopeful, coming out of the meeting, that some framework for agreement on the sticky points for other drugs could be worked out too.”

Pfizer, AstraZeneca and Novartis — who all had representatives at the meeting — were unavailable for comment. But Steven Paul, a former head of research and development at Eli Lilly who is now at Weill Cornell Medical College, New York, USA, and did not attend the round-table talks, says that industry players are increasingly keen to test out new models. “I view repurposing as one initiative among several that could be helpful to re-energize drug discovery.”

The NIH is now working to resolve some of the issues. It is setting up another meeting with stakeholders, and may create some working groups to iron out key concerns. It is also aiming to finalize an umbrella framework for collaborations within the next 6–8 months and is assembling a team that will be responsible for repurposing and rescue work within the NCATS. “These may sound like baby steps, but I think they're the beginnings of something more substantial,” says FitzGerald.