Playing dirty

Forget drugs carefully designed to hit one particular molecule — a better way of treating complex diseases such as cancer may be to aim for several targets at once, says Simon Frantz.

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It's not often that a science lecture can turn a person on to the idea of promiscuity. But when Michael Heinrich heard a talk about a promising new cancer drug, it triggered a transformation of his ideas about how to target disease. It sounds heretical, but Heinrich and others are now saying that 'magic bullet' drugs designed to hit single biological targets might not be the answer to treating complex illnesses such as cancer and cardiovascular disease. The future, they say, could be in drugs that are less picky about their molecular partners.

Heinrich's turning point was a seminar given in early 1998 at the Oregon Health and Science University Cancer Institute in Portland, where he worked. Brian Druker, a molecular biologist in the medical department at the same university, was talking about the revolutionary leukaemia treatment Gleevec (imatinib mesylate). Made by Swiss drug company Novartis, Gleevec was designed to zero in on a single protein in cancerous cells, specifically killing them while leaving healthy cells unharmed. It proved to be spectacularly effective and non-toxic. Compared with the relatively indiscriminate action and distressing side effects of conventional cancer treatments, Gleevec seemed to vindicate the single-target approach to drug discovery.

But it soon became clear that Gleevec was not as specific as its creators had thought. The drug works by attaching to a key part of an overactive protein that causes chronic myeloid leukaemia. In his lecture, Druker revealed that the drug also inhibits a second protein, known as the PDGF receptor. Sitting in the audience, Heinrich had a brainwave. At the time, he was working on a protein similar to PDGF called KIT. "We became interested in the idea that Gleevec could probably inhibit KIT as well," he says. Working with a team led by George Demetri and Jonathan Fletcher at the Dana-Farber Cancer Institute in Boston, Massachusetts, Heinrich found that Gleevec was also remarkably effective against a rare cancer called gastrointestinal stromal tumour, known to be linked to faulty KIT activity[1].

What Heinrich and his colleagues had stumbled on went the opposite way from the direction that drug companies have been heading in since the beginning of the 1980s. In a bid to take much of the guesswork out of drug discovery, companies tried to avoid treatments that non-selectively bound to several targets — what they term 'dirty' or 'promiscuous' drugs — and focused on creating selective magic bullets such as Gleevec. But researchers are now realizing that too much specificity can also be problematic.

> "The idea of magic bullets is great, but in practice it's probably not going to be the right approach for complex diseases." — Bryan Roth

Take aim

Before the 1980s, drug discovery began by using animal models to test compounds created by medicinal chemists. Drugs were deemed successful by virtue of their effects rather than the number of molecular targets to which they bound. For every safe and effective promiscuous drug such as aspirin, there were good treatments that caused major side effects, and plenty of other drugs that were just plain unsafe. Trying to predict side effects and understand them was almost impossible as in most cases no one knew exactly how the drugs worked.

The selective approach to drug discovery was made possible once biochemical and genetic studies began to reveal the molecular mechanisms that underlie common illnesses such as cancer and cardiovascular disease. Companies were able to pick a protein that they thought would make a good target, design compounds that interact with this protein, and test these compounds to find potential drugs.

But 20 years down the line, it turns out that this target-based approach doesn't always guarantee success. Some of these selective drugs work in only a select population of patients. AstraZeneca's Iressa (gefitinib), for example, is designed to treat lung cancer by targeting a protein called EGFR. The drug does give an incredibly potent response, but only in about one-tenth of the patients who receive it[2]. And, as Gleevec fortuitously showed, treatments that block more than one target can be tolerated better than previously thought.

The idea that promiscuous drugs might be more effective than targeted ones has also been emerging from efforts to understand how antipsychotic drugs work. The schizophrenia drug Clozaril (clozapine), for example, works because it targets a large number of proteins, says Bryan Roth, a biochemist at Case Western Reserve University in Cleveland in Ohio. Variations designed to bind to fewer targets and reduce Clozaril's unpleasant side effects don't work as well and still have similar side effects[3].

In the 1990s, Roth and his team investigated which nerve-cell receptors were being targeted by a range of antipsychotic drugs. They found that the drugs that bound to the most receptors were the most successful in the clinic. "What became clear to us when we examined antipsychotic drugs was that the more targets they hit the better," says Roth.

Multiple choice

The reason for this is that common disorders such as cancer, cardiovascular disease and depression tend to result from multiple molecular abnormalities, not from a single defect. What's more, pinpointing a single target is unlikely to help in many cases because cells can often find ways to compensate for a protein whose activity is affected by a drug, a phenomenon known as redundancy.

Using what Roth calls 'magic shotguns' to target multiple points in these complex systems, could reap bigger therapeutic rewards than fully blocking one target. "The idea of the magic bullet continues to be a great idea, but in practice it's probably not going to be the right approach for complex diseases," says Roth.

Findings such as those of Heinrich, Roth and their colleagues have triggered a recent shift in efforts to create drugs that hit more than one target simultaneously. A number of companies and research groups are now screening compounds that stick to several targets, or are even trying to engineer promiscuous drugs. Arguably, the biggest area for promiscuous drugs at the moment is cancer[4].

A key set of targets includes enzymes called kinases. Many of these, such as EGFR, influence how cells divide and are often abnormally active in cancers. A slew of treatments (see '"Dirty" drugs under development', right) that block several kinases together are now in clinical trials. The hope is that these will work better than highly selective treatments, and that hitting more than one kinase at once will reduce the chance of tumours becoming resistant to the drugs. In August, Pfizer submitted a cancer drug called Sutent (sunitinib malate), acquired when it bought the biotech company SUGEN, for approval to the US Food and Drug Administration. The drug blocks not only the proteins targeted by Gleevec, but also two other similar molecules[5].

Hitting the spot: Gleevec was seen as proof that the 'magic bullet' approach to drugs was a success.

Nevertheless, researchers in the field are frustrated that large drug companies seem to be ignoring the advantages of promiscuity, or polypharmacology as it is sometimes known. "There is still a perception in the field that multi-kinase inhibitors are going to be inherently toxic and non-selective and it's absolutely untrue," says Julie Cherrington, executive vice-president for research and development at Phenomix in San Diego, California, who helped develop Sutent when she was at SUGEN. "I can remember having conversations about this when we started to develop Sutent, and I'm still having these conversations now."

Big pharmaceutical companies are largely still wedded to the 'one-target one-disease' model, and it's not easy to change this culture, says Simon Mencher, principal at Natrogen Therapeutics in Milwaukee, Wisconsin. "The first person I ever talked to in a large company about promiscuous drugs said: 'I agree with you but I can't convince the management to change the way they work,'" he says. "Too much funding has been sunk into targeting single agents."

'Dirty' drugs under development

Sutent
Pfizer has submitted Sutent to the US Food and Drug Administration (FDA) for approval as a therapy for kidney and gastrointestinal cancer.

Sorafenib
Created by Bayer and Onyx Pharmaceuticals, this treatment for kidney cancer is currently being considered by the FDA for approval.

Zactima
Made by AstraZeneca, Zactima is undergoing final (phase III) clinical trials in lung cancer.

AG-013736
Designed by Pfizer, this drug is undergoing efficacy (phase II) clinical trials for kidney and thyroid cancer.

Culture shock

Andrew Hopkins, head of knowledge discovery at Pfizer in Sandwich, UK, agrees that the single-target approach remains the main strategy in big companies. But this is now being challenged by fresh information on some compounds, as well as by models mimicking the effect of compounds on cells. In addition, large-scale genetic projects have confirmed the extent of redundancy by showing that altering the activity of many genes one at a time may have limited clinical effect[6]. "Polypharmacology isn't new, what is new is the realization of its importance in efficacy," says Hopkins.

But screening for compounds that hit multiple targets is a difficult task. Unlike the single-target strategy, in which the compound selected is generally the one that sticks best to the target, the most likely candidate for a multi-target drug will be one that moderately influences several targets positively and negatively at the appropriate concentrations.

Overcoming this problem requires a deeper understanding of the cellular mechanisms at which the drug is aimed. To tackle this, researchers have turned to the emerging field of network biology, which can model the complex interactions between all the molecular constituents of a cell[7]. By building these networks, researchers can identify molecules and processes that are altered in diseases. They can also predict whether it is better to design drugs that hit multiple points in one process or that dampen parallel processes, and whether redundancy will be a factor.

If multiple-kinase inhibitors prove successful in the clinic, they could drive more efforts towards promiscuous drugs. Already the Gleevec story is having an impact in industry, says Roth. He has noticed a subtle change in the drugs that large companies are licensing from smaller companies. "Both Pfizer and Merck have licensed relatively non-selective antipsychotic compounds," says Roth. "The fact that they are doing this shows that they're getting the message." ■

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