University of Strathclyde Glasgow

It's a Question of Balance

Broadening Concepts of Drug Discovery

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How we get new drugs, or used to...

Since the 1960s it's been accepted that the way to discover new drugs is to take a well-characterised disease with a good understanding of the biological cause of the disease. This would require the identification of a functional biological unit such as a protein that was critical to the process underlying the disease. The candidate drug was then designed and tested to engage with this single functional biological unit, essentially switching it off or on as required thereby treating the disease. We usually refer to the functional biological unit as the drug target. The single target, single drug, single effect paradigm has been remarkably successful and with refinement and elaboration became the conventional approach to small molecule drug discovery in the pharmaceutical industry. For example, penicillins and cephalosporins are effective antibacterial drugs because they block the assembly of bacterial cell wall without which the bacteria cannot survive. Statins reduce cholesterol levels because they prevent the biosynthesis of cholesterol by blocking its biosynthesis at a specific step. There are dozens of other examples. It's a logical, linear sequence but it promotes a rigid sequential process for drug discovery.

When in the 1990s it began to emerge that most of the easy single targets for new drugs had been hit a great deal of effort went into the discovery of new, more arcane targets, often with the assistance of sophisticated genetic approaches. Many reports were highlighted in the popular media when a scientific team discovered that a particular gene was connected in one way or another with a disease. This would lead to a cure in 10 years (or so) the popular science piece would run. It hasn't happened. One reason is that complex diseases in which the balanced function of the body is disturbed cannot be associated with linear processes. This is particularly the case with

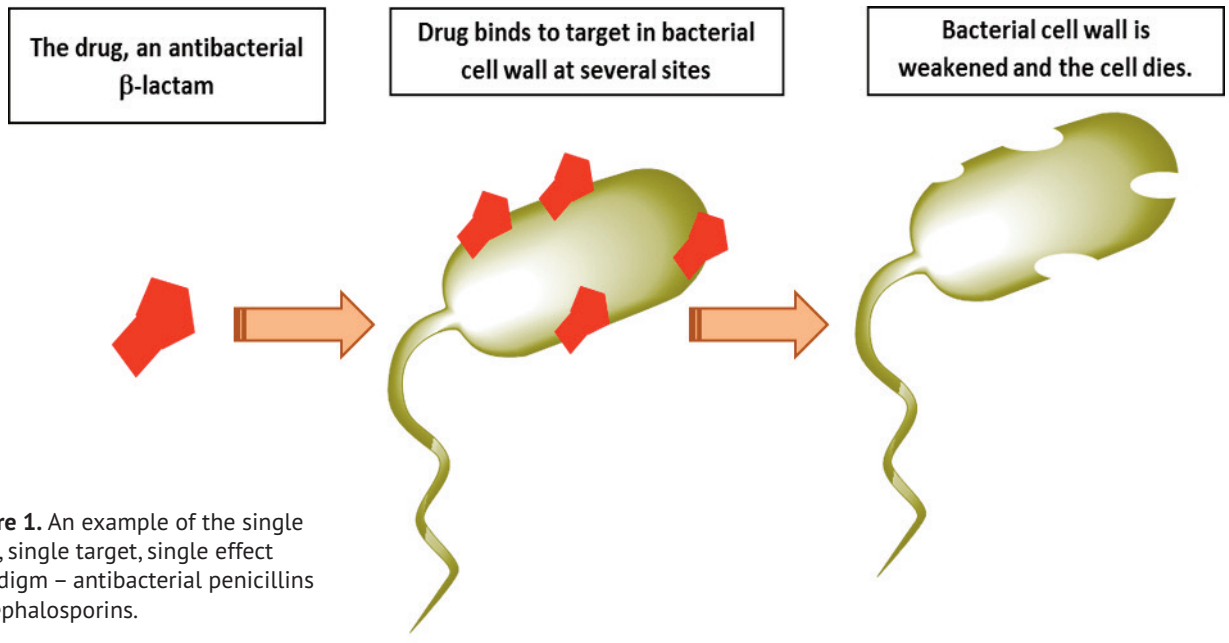

Figure 1. An example of the single drug, single target, single effect paradigm – antibacterial penicillins or cephalosporins.

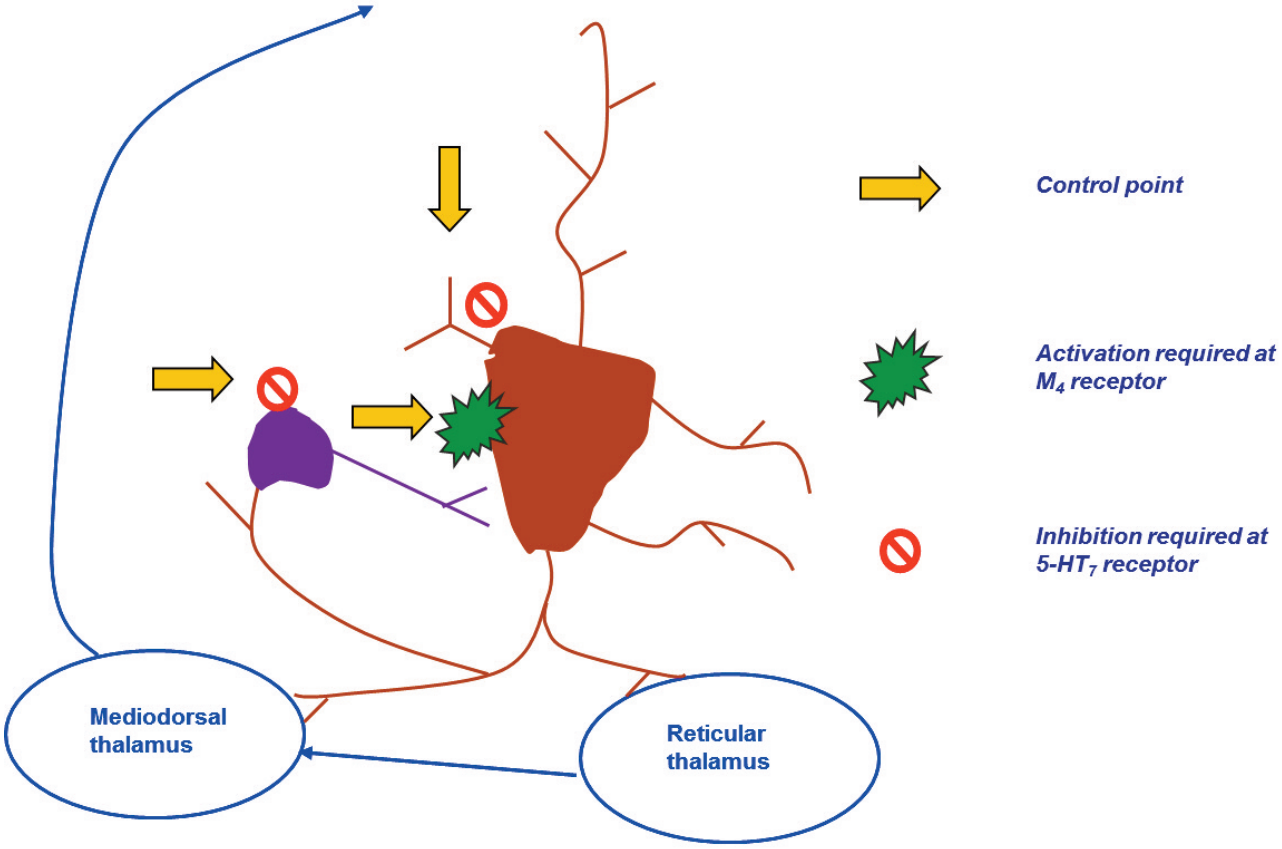

Figure 2. Basis for the action of seromincs. 5-HT_7 antagonist activity, M_4 agonist activity, and low affinity for the D_2 receptor to minimise side effects. The thalamus is the region of the brain of importance. The brown and purple shapes represent brain cells that are connected by the 'fingers' of the same colour to make up a neural circuit, the balance of which is to be restored by the seromínic drug.

diseases of the central nervous system and the immune system in which interacting networks of biological systems play key roles, now reasonably well but still imperfectly understood. Let me illustrate this with two projects to which I've contributed some chemistry and in doing so note some points of relevance to drug discovery today that these studies raise in my mind.

Can we really treat schizophrenia?

Some years ago I took part in a project aimed at the discovery of new treatments for schizophrenia, a disorder that affects about 1% of the population worldwide and that has no satisfactory treatment. Current drugs fail to treat some symptoms, such as include loss of emotional responsiveness, lack of motivation and social withdrawal, and also in the remediation of cognitive defects in working memory, attention and executive function; there is also a problem with weight gain. Our project was very unusual in that it was an early stage industry-academic collaboration involving Japanese companies, firstly Yoshitomi and subsequently Mitsubishi Pharma. It was also collaborative between Universities (Strathclyde and Glasgow) and scientific disciplines (neuroscience, pharmacology, and chemistry). My role was initially as an academic manager but gradually transformed into leading the medicinal chemistry as the project developed. It's perhaps easiest to understand the 'Question of Balance' in a disease such as schizophrenia for which people with the condition might be described in common speech as 'unbalanced'. Scientifically, however, we can try to be more precise and to discern what the imbalance is and then try to put it right. This is exactly what my neuroscience colleagues did addressing the challenge of finding new drugs.

There was an experimental model (the PCP model) of schizophrenia available in rats. By comparing the brains *post mortem* of rats that had been introduced into the experimental model with those of rats that had received no treatment, it was possible to

Figure 3. Berberis, the plant that was the source of compounds that fed into the serominics design concept.

Figure 4. The serominic team. The First Minister of Scotland, Donald Dewar, is standing at lower right hand corner of the Scottish lion rampant flag with myself on his right and Professor Judy Pratt on my right.

identify certain circuits within the brain that were malfunctioning. These circuits were characterised by the action of two of the internal communicating molecules of the brain (neurotransmitters) namely muscarine and 5-hydroxytrypamine. From their data the team's lead biologists, Judy Pratt and Brian Morris suggested that what was required to restore the brain's balance in schizophrenia was a compound that acted in the same way as muscarine and also blocked the effect of 5-hydroxytryptamine. The technical shorthand for this was that we required M_4 agonist and 5-HT_7 antagonist in the same compound (Figure 2). We called such compounds 'serominics'.

You'll have realised that we're not dealing with a linear sequence of biological events, a simple cause and direct effect, but a network of interacting neurological pathways. Also you'll have noticed that our proposal was to create compounds that have not one but two designed activities, contrary to the single target single drug paradigm. One justification for attempting such a feat in a university-based team is that its probability of success might appear too slim to an industrial team with the opportunity to select from many projects; an academic project can afford to be more speculative and, in my opinion, should take on challenges that industry would avoid. We had a go at meeting this challenge. Our starting points were largely compounds from plants, the so-called alkaloids, a class of compounds known for their central nervous system activity; LSD and morphine are well-known examples.

There wouldn't be a story if this approach had not worked. We designed and synthesised some new compounds with M_4 agonist and 5-HT_7 antagonist activity and took them forward for evaluation in the PCP mouse model of schizophrenia. It was very gratifying to find that indeed the symptoms of schizophrenia were mitigated using our serominic compound, thus establishing proof-of-concept for a new class of anti-schizophrenic drug. The project had a notable political profile and was presented to the first ever Scottish First Minister, Donald Dewar at a reception in Osaka (Figure 4).

At the proof-of-concept stage, academic research largely ends. Although we did carry out some further chemical and biological studies, the opportunity was then handed over to our Japanese industrial partners to evaluate and develop. Although this series of compounds did not proceed to preclinical development perhaps the Japanese stayed with this project as long as they did because they had been closely involved in deciding the biological strategy. Maybe as a drug discovery community we could do better if academic insight and industrial systems could find ways of working together better.

The Worms Project

Where we've really run into problems with the linear conventional drug discovery paradigm is in taking forward some remarkable immunomodulatory compounds that we have discovered. Like the central nervous system, the immune system is composed of many interacting networks of cells that communicate with each other by releasing signalling compounds known as cytokines and chemokines. Again it's a question of balance. A healthy person has a balanced immune system, coping with opportunistic infection and attack, but not causing internal damage. In many diseases, however, the immune system is out of balance. If it is too feeble, a fatal condition may result. If it is too active, diseases such as asthma, rheumatoid arthritis, or lupus, for example, may occur. It's as good as intuitively obvious that in such a situation a single drug single target approach is unlikely to succeed. How, then, to proceed?

In the Worms project, a parasite suggested to us how to create compounds that modulate the immune system in other words, correcting its balance. A husband and wife team of professors from the University of Strathclyde and the University of Glasgow, respectively Billy and Maggie Harnett, have made their careers from the study of a protein known as ES-62, which is secreted by a worm *Acanthocheilonema viteae* (Figure 5) that is a parasite of gerbils. Billy and Maggie isolated and purified ES-62 and showed that it lowered the activity of the immune system so that the parasite was not attacked by its host but not so much that the host was killed by bacterial or viral infections. Obviously the parasite needs its host to reproduce and survive so the immunomodulation by ES-62 was very important. Billy and Maggie were convinced that there could be a useful drug somewhere related to this biology. However the protein itself was not suitable: it was too big a molecule to be formulated easily as a medicine. Moreover, because it is not a human protein, the human immune system would most probably be stimulated and ES-62 destroyed. What was needed was a small, drug-like molecule that could reproduce the potentially

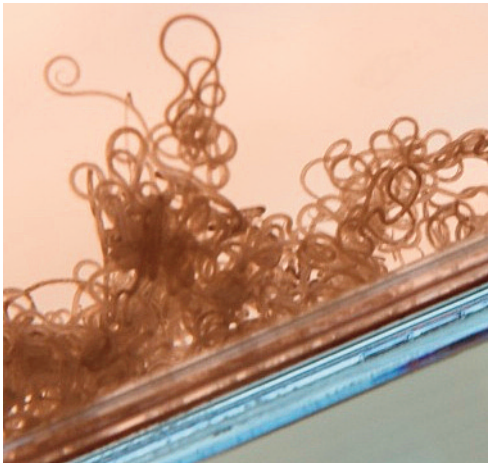

Figure 5. The parasite Acanthocheilonema viteae that secretes ES-62 to maintain its balance with its gerbil host. Image courtesy Prof W Harnett.

beneficial immunomodulatory properties of ES-62. An interesting ethnological and philosophical aspect of this opportunity is that it considers the immunological balance in a person to be important for their health and the success of their treatment. It thus connects with eastern medicinal traditions, including the Ayurvedic medicine of India.

Transforming biology into manageable chemistry

In the schizophrenia project we had somewhere obvious to start designing compounds, namely the structures of the naturally occurring alkaloids. Here, however, there were no such templates. Moreover in a further contrast, we had no idea what the molecular target or targets for ES-62 are. To put it another way, we did not know the chemistry by which ES-62 worked. And to make it even more challenging, there was no crystal structure of ES-62 available; there still isn't. So none of the usual starting points for a medicinal chemistry project was present. Fortunately one small aspect of the structure of ES-62 that was important to its function had been identified by the biologists. Attached to the surface of ES-62 were many small molecules known as phosphoryl choline (PC) and through a number of experiments it had been shown that these PC components were important in the biological activity of ES-62. That gives a starting point, but PC is so common in biology

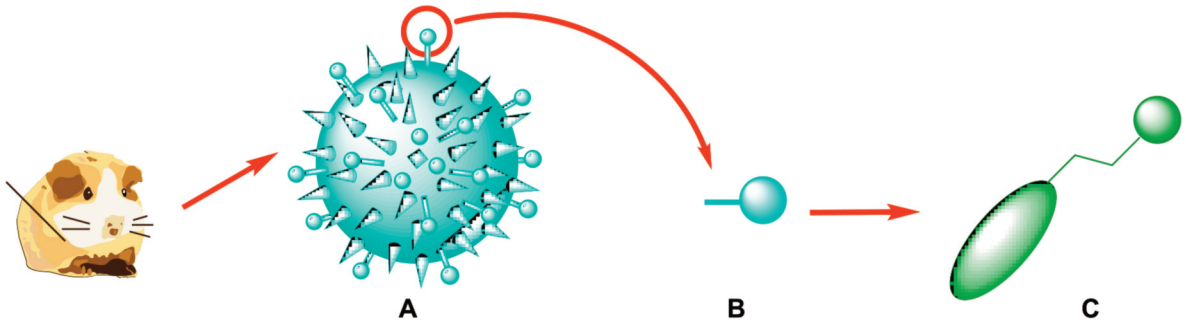

Figure 6. A cartoon representation of the design of the small molecule analogues (SMAs) of ES-62. **A.** A representation of the ES-62 protein secreted by the parasitic worm in the gerbil with many surface groups. **B.** The phosphorylcholine (PC) component to be mimicked. **C.** The SMA in which there is a carrier part of the molecule (oval) linked by a flexible chain to the PC-like head group.

that simple analogues of it as potential drugs would be unlikely to be selective enough to be developed as medicines. However with one or two other clues from PC-containing molecules that the Harnetts had studied, it was possible to design some compounds that would be worth testing. Figure 6 illustrates how this was done.

If you look at a chemical structure with the eyes of a chemist, you can identify those parts of the molecule most likely to be important in determining the chemical and biological properties of the compound represented. In the case of the PC component of ES-62, the most important feature was electrostatic charge, both positive and negative. To create a small molecule analogue (SMA) of ES-62 we needed to include positive and negative charge in the right relative positions to each other and with the right shape. In this way we should obtain a compound that will interact with the biological systems that lead to immunomodulation in a manner similar to that of ES-62. We can also build into the design features of chemical stability and variability so that an optimised drug can be obtained in due course from the same molecular template.

Having solved the conceptual chemistry design problem we had to test the compounds that we made to see if they could replicate the functions of ES-62. This relied upon the skill of the biologists, Billy and Maggie Harnett, and their teams to devise assays that would lead us in the right direction. By carrying out a wide range of assays using cultured human cells important in the immune system, the Harnetts identified compounds that stimulated or depressed the immune response or did nothing at all. From the very first set of compounds that we tested, two were found that had strong and similar effects to those of ES-62. That success was just lucky, but still more surprising was that when these compounds were tested in animal models for the treatment of inflammatory diseases including asthma, rheumatoid arthritis, and lupus they were found to be safe (non-toxic) and effective both curatively and prophylactically.

Where does this leave drug discovery?

So we now have compounds with the potential to be beneficial in a wide range of diseases in which the balance of the immune system is important. The task now is to fund an optimisation and development programme. This is proving difficult because despite the demonstrated efficacy of the SMAs, industry is reluctant to form a partnership with us because the biological mechanism of action of the SMAs has not been established. We understand as academics the wish of industry to minimise risks but wonder whether it is appropriate to expect the academic world both to discover new drugs and opportunities and to undertake their initial development. The pharmaceutical industry is no charity nor does it sometimes appear to be philanthropic but is the

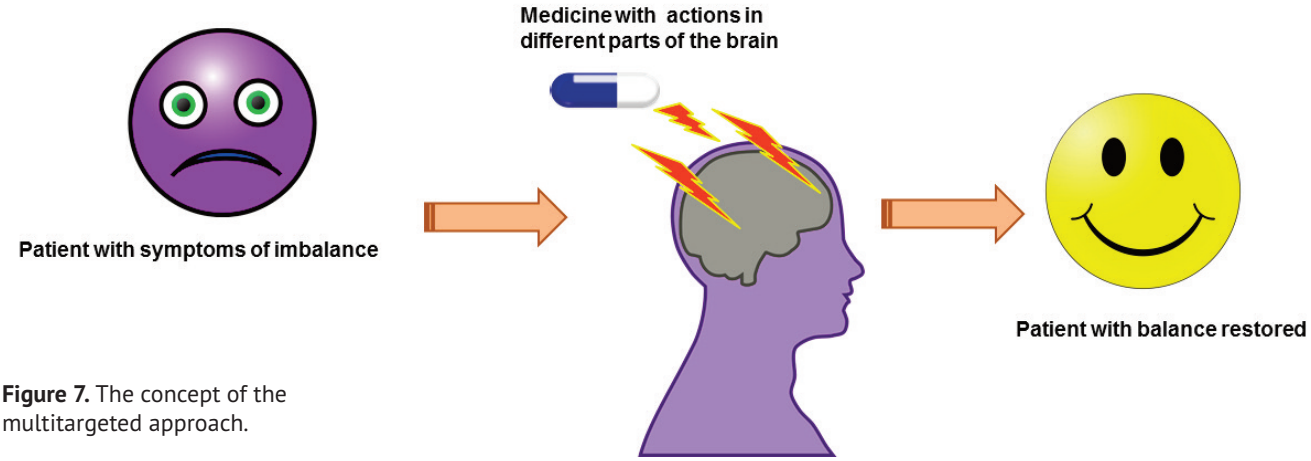

Figure 7. The concept of the multitargeted approach.

balance right? I'm not referring to the rigours of development here that are necessary to satisfy the regulators who work on behalf of the public. However a drug is discovered, those rigours must be faced and surmounted. My point concerns a more open-minded approach to discovery. But happily, we now have two industrial partnerships evaluating our compounds, one with AZ and another with Jubilant. Moreover there is information emerging about the mechanism of action through a study in collaboration with the US Army.

My comments notwithstanding, there are some examples of drugs in the clinic that do not match the single target – single effect paradigm. Pirfenidone, is a drug that can be used to treat idiopathic pulmonary fibrosis, a rare disease for which other treatment options scarcely exist.
www.nice.org.uk/guidance/ta282/chapter/1-guidance?unlid=101941910320162260141 2

It is a small molecule drug that contains a single heterocyclic ring and no obvious structural features that suggest what its biological target might be. Apart from positive clinical results from the relevant trials, the information brought forward for regulatory approval indicated that pirfenidone suppresses the immune system and reduces inflammation thereby inhibiting fibrosis. Evidence was produced to show that it reduces the production of inflammatory mediators in relevant cell types, studies with some similarities to the experiments that we have carried out in our own 'Worms Project'. So perhaps our contra-paradigm approach will come together with the industry and regulatory standard of development after all.

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