Commentary: Nick Ray

The lasting value of small molecule drugs

Over the past two decades we have witnessed a dramatic shift in the type of molecules that have produced the most sales for the pharmaceutical industry. In the year 2000, all of the top 10 selling drugs were small molecules. By 2010 the proportion of small molecules on the best-seller list had dropped to five. Last year the number was just four.

These four small molecule drugs generated $47.9 billion in revenue in 2021. By comparison, six biologic drugs produced sales of $110.7 billion – a figure that was heavily influenced by sales of $54.5 billion from the two mRNA vaccines against Covid-19, Comirnaty and Spikevax. But does this mean the era of the small molecule drug is drawing to a close?

I would argue not. In fact, evidence is pointing in the opposite direction. A key event over the past 20 years has been the rise of the biologic, a category of drug that includes monoclonal antibodies, interleukins and vaccines. The rise of biologics has been driven by their ability to address targets considered 'undruggable' by small molecules, such as protein-protein interactions. But biologics also have their limitations.

Monoclonal antibodies, an important new drug class, are large proteins which are produced by way of a complex manufacturing process involving living cells and requiring an extensive QC process. They tend to have a long half-life in humans, leading to a significantly longer dosing interval than that for small molecules. This can be beneficial for patient compliance, but it presents a safety issue when adverse effects are triggered and drug concentrations cannot be lowered quickly. Immunogenicity is also an issue. Monoclonal antibodies, and biologics in general, can be recognised as 'foreign' by the body's immune system, leading to the development of an anti-drug antibody which can counteract the therapeutic effect and in rare cases, cause adverse reactions.

However the most significant limitation for biologics is their molecular size which makes it difficult for them to cross membranes. As a result, targets tend to be extracellular and peripherally located, and the therapy needs to be delivered parenterally. By comparison, small molecules can be designed to have appropriate properties for varied routes of administration; the targets can be intracellular or extracellular; they can be CNS-penetrant or peripherally restricted; and they can be systemic or targeted to specific organs. These physico-chemical properties are significantly easier to optimise alongside, but independent of, potency in the small molecule space.

Given these favourable features, how then can small molecule drugs be designed to reach targets previously considered undruggable? Small molecules have traditionally been directed against multiple target classes, for example, G-protein-coupled receptors (GPCRs), ion channels, enzymes and nuclear hormone receptors. All of these targets have well-defined binding sites that can be occupied by a small molecule of approximately 0.5kDa molecular weight with enough potency to be formulated into a pill or capsule.

There are at least three reasons why a resurgence of small molecule modalities are likely to make the undruggable target druggable.

The first is a better understanding of target structure. Protein, and protein-ligand crystal X-ray structures have long been available for certain target classes, such as soluble enzymes. But other targets such as GPCRs have been much harder to crystallise - a problem solved in the last decade. Additionally, cryo-electron microscopy can now provide structures of 'hard-to-crystallise' proteins with sufficient atomic resolution to be useful for molecular design. Both techniques provide a snapshot of the small molecule bound to the target. Drug discovery scientists now understand that the protein structure is dynamic, not static. Some proteins, in the absence of a suitable ligand, may appear to have no suitable binding site. But the presence of a suitable ligand can either induce pocket formation or trap out a transiently formed pocket.

Another class of proteins known as intrinsically disordered proteins do not settle into a single 3D structure but instead fluctuate between an ensemble of short-lived conformations. Up to 30% of the proteome may fall into this class. Drug discovery scientists are now developing both biophysical and computational methods to better understand how these transient protein pockets and conformations can be targeted by small molecules.

Second, new small molecule modalities have come to the fore within the last decade. For example, rather than blocking the activity of a target, these new modalities actually cause that protein target to be degraded by the ubiquitin-proteasome system which is the cell's own waste disposal system for proteins.

Third, we are now better able to measure the shapes of ligands in solution. This permits the design of potent ligands against targets, even when the 3D structure of the target is not known. There is also a growing body of knowledge on how molecular shape can influence the properties of a molecule - one shape may bind effectively to the target, but another shape of the same molecule may be better at passing through membranes. Understanding and specifically designing in these features has the promise of generating 'larger' small molecules that still share the optimal properties of solubility and permeability that are required for an oral drug.

Targets previously considered 'undruggable' have now seen small molecules directed against them enter the clinic. Examples are KRAS, STAT3, IL-17 and TNFa. The new small molecule modalities and targets, together with the technology to make this feasible, means it's a great time to be involved in small molecule drug discovery.

This commentary was written by Nick Ray, PhD, Senior VP Drug Discovery at C4X Discovery Ltd in the UK.