Drugging the undruggable: how emerging modalities can offer new promise to patients

For generations, the pharmaceutical industry has relied on small molecules as the basis for treatments of most illnesses and conditions. But with new technologies emerging and our knowledge about human biology growing, researchers are beginning to scratch the surface of alternative disease treatments, with many more interventions waiting to be discovered. Now, therapeutic modalities such as PROTACs, nucleotide medicines, and cell and gene therapies are within our reach and show great promise in treating what were previously considered undruggable targets.

Steve Rees, Vice President of Discovery Biology, Discovery Sciences, AstraZeneca, believes these new modalities hold the key to developing treatments that not only alleviate symptoms but potentially cure the target disease. In this blog, Steve talks to us about the importance of new drug modalities, recent progress in their development, and how these modalities will impact healthcare over the coming decades.

Join researchers across academia and industry to learn about emerging therapeutic modalities: register for the New Modalities in Pharmacology and Drug Discovery event from 4-5th July 2022 at The Crick, London.

New beginnings

Small molecule drugs are still the backbone of the pharmaceutical industry, representing over half of the top 200 brand name drugs sold in 2021. They offer many benefits as treatments, including the possibility of oral delivery and the ability to pass through cell membranes to reach intracellular targets. And with companies having decades of experience and knowledge in their back pocket, it's no surprise that small molecules are still a major focus of drug discovery programs.

Yet, small molecule medicines have challenges. Traditionally, these treatments work by inhibiting or activating a protein of interest, which is a generally effective approach. However, it is thought that no more than 30% of the genome is tractable to small molecule drug discovery, limiting the application of small molecules as potential treatments. In addition, small molecules generally need to be administered stoichiometrically. This means higher doses are required, increasing the risk of

unfavourable interactions in the body. Therefore, researchers are focusing on new and more effective ways to treat disease.

Over the last decade, new understanding of disease pathways and new modes of activation has accelerated research into alternative drug modalities. Novel technologies have now begun to emerge, offering excellent promise for addressing drug targets previously thought to be untraceable. These new therapeutic modalities work via different pathways to traditional small molecules, offering new ways to treat disease.

"There are many patients today that have no available treatment options. With new modalities, we hope to be able to deliver medicines to patients that work against drug targets that we've failed to progress in the past. There's a huge opportunity to deliver truly transformative life-changing medicines to broad patient populations with these new approaches," explains Steve.

The first approved modality

Although many modalities are still in their infancy, in December 2020 one new therapeutic approach took the world by storm: messenger RNA (mRNA) medicine. The Pfizer/BioNTech and Moderna COVID-19 vaccines, developed in response to the pandemic, became the first mRNA medicines to be approved by the FDA. Unlike traditional vaccines that build immunity through injecting a dead or weakened form of a pathogen, the mRNA vaccine contains genetic instructions for the person's own cells to produce antigens and generate an immune response. Thousands of lives have been saved by this technology, with almost 27 million people in the UK having received at least one dose of these vaccines.

"Our understanding of how we can approach vaccinations has been transformed. I expect over the next few years we'll see floods of new mRNA vaccines for a wide range of different diseases," says Steve.

The COVID-19 mRNA vaccine appears to have been quickly developed and approved from the ground up, but it was in fact built on decades of research and studies of companies who were aspiring to make cancer vaccines for individualised medicines. Originally, researchers aimed to understand cancer-causing mutations and the antigens that cancer cells express. A vaccine could then be developed by cloning the antigen to generate an immune response and kill that tumour in a patient. "Researchers are still struggling to make these challenging cancer vaccines a reality. It did mean, however, that the technology was readily available to be adapted for COVID-19 vaccines," states Steve.

Further research and increased understanding — through collaboration and knowledge-sharing events such as New Modalities in Pharmacology and Drug Discovery — is imperative to expand the technology for other chronic diseases and realize these treatments. "The disease and the modality need to come together to find a sweet spot. This happened with COVID-19, and I believe the same will be true for many diseases and modalities," comments Steve.

An armoury of opportunities: Promising modalities

Many other modalities are already in the pipeline as promising treatments and are waiting for their chance to shine, including proteolysis targeting chimeras (PROTACs) and antisense oligonucleotides (ASOs).

PROTACs

PROTACs are bivalent small molecules, one part of the molecule selectively binds to a target protein, the other binds to a E3 ubiquitin ligase. The PROTAC brings together the target protein and the E3 ligase to mediate ubiquitination of the target protein, marking it for degradation and utilising the cell's own waste disposal system to eliminate the protein.

PROTACs are highly specific molecules that can bind anywhere on a target protein, rather than just an active site, and work by *degrading* proteins. This means that PROTACs can offer long-lasting biological effects to the patient compared to traditional small molecule inhibitors (SMIs), which inhibit proteins through active site binding.

We're now starting to see the power of these PROTACs as potential treatments.

Antisense Oligonucleotides (ASOs)

And what if the detrimental protein product was never created in the first place? That's exactly how ASOs intervene in disease pathways. ASOs are chemically modified chains of oligonucleotides that can target any gene product of interest. These ASOs work by interfering with transcription translation, which prevents mRNA being translated into harmful disease proteins.

ASOs are already showing their prospects as a new modality, with the FDA approving Amondys 45 for treatment of Duchenne muscular dystrophy (DMD) last year. "ASOs are incredible, as you can design an oligonucleotide to any gene. If you know the sequence of the gene, you can design an ASO. This is really exciting for treating diseases that aren't amenable to traditional small molecule treatments," comments Steve.

Fostering collaboration through networking

Steve will give the plenary session at the New Modalities in Pharmacology and Drug Discovery event. In his talk, Steve will provide an overview of these modalities, as well as others, and their

potential transformative effects. “We can look forward to a time in the near future when many of the new medicines developed are curative, rather than simply treating the symptoms of the disease,” he explains.

Through the event, Steve hopes that broader discussion of the science around new modalities will be enabled. The event, a joint meeting from the British Pharmacological Society (BPS) and ELRIG, provides a unique opportunity to bring together different expertise. Steve says: “To date, most new modalities are still in pre-clinical research. This meeting will synergise the clinical and research experience from two important communities. Only by sharing our knowledge and working together can we translate these innovations into new and effect medicines that will benefit patients.”

The New Modalities in Pharmacology and Drug Discovery will be held from **4-5th July 2022** at The Francis Crick Institute, London. The **free in-person event** brings together researchers from academia and industry to foster cross-collaboration and stimulate discussion on how emerging therapeutic modalities can transform drug discovery. Register here: https://meetings.bps.ac.uk/bpsevents/system/proweb/start.csp?pageID=54219&eventID=90