Into the Future with Next-generation Small Molecules

Heightened interest in small molecules is likely to continue in 2023 and beyond as several biotech companies look beyond biologics to bring medicines to patients in need.

Advances in the field of biotechnology have tended to excite interest in their potential as targeted therapies. Vaccines, monoclonal antibodies, cell and gene therapy and other biotechnology innovations have been researched and developed to offer patients targeted treatments.

Despite the high-profile of these therapies, small molecules continue to be the mainstay in disease treatment and increasingly are gaining the attention of traditional biotech and specialty companies looking to build their therapeutic portfolio and provide a wide range of treatment options for patients in need.

In fact, the majority of US Food and Drug Administration (FDA) approvals of new molecular entities (NMEs) continue to be small molecules. In 2022, 22 out of 37 novel drugs approved by the FDA were small molecules.

What is particularly notable is a trend amongst traditional biotech companies to expand their research and development portfolio into the area of small molecules. These innovative products are more complex than traditional small molecules but with fewer of the regulatory and manufacturing challenges faced by more innovative biologic products, such as cell and gene therapies.

Biotech Expands its Portfolio

Among the companies turning their attention to small molecules are Amgen and Biogen. In January 2022, Amgen announced a collaboration with Arrakis Therapeutics focused on research into RNA degrader therapeutics against a range of difficult-to-drug targets in multiple therapeutic areas. This is a new class of RNA degraders consisting of small molecule drugs, which "selectively destroy RNAs encoding disease-causing proteins by inducing their proximity to nucleases."[1]

The company has been exploring a range of small molecule products across its oncology platform. For example, its product Lumakras® (sotorasib) is a small molecule indicated to treat adults with $KRAS^{G12C}$-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC).

At Biogen, small molecules are part of the research arsenal aimed at treating neurological diseases. The company has several small molecules in phase 3 studies, including for depression and stroke, as well as research in phase 2 for multiple sclerosis and various other neurological conditions. In relapsing MS, the company is studying orelabrutinib, a small molecule Bruton's tyrosine kinase inhibitor (BTKi) which researchers believe will help to reduce damage caused by BTK cells.[2]

It's not only the biotech heavyweights that have been getting into small molecules. Mirati, a small biotech company from California, in December 2022 received breakthrough therapy designation from the FDA for its small molecule product Adagrasib (MRTX849) in combination with cetuximab for patients with KRASG12C-mutated advanced colorectal cancer.[3] In November 2022, bio-pharmaceutical innovator Agios Pharma was granted marketing authorisation for its small molecule product Pyrukynd to treat PK deficiency in adults suffering from chronic anemia.

Small Molecules of the Future

The next generation of small molecules are structurally diverse and complex, which is paving the way for these NMEs to be targeted at underserved therapeutic areas, such as in cancer and neurological conditions such as Alzheimer's disease, MS and Parkinson's disease.

There has been promising research into targeting RNA structures with small molecules to alter the way RNA functions. Several small molecules that bind RNA structures have been shown to modulate a range of biological processes.

The FDA has already approved risdiplam, the first small molecule splicing modifier drug, for the treatment of spinal muscular atrophy. Marketed by Roche as Evrysdi®, the product, which was approved for adults and children 2 months of age and older, was shown to improve motor function in people living with SMA over a broad spectrum of ages and levels of disease severity.[4]

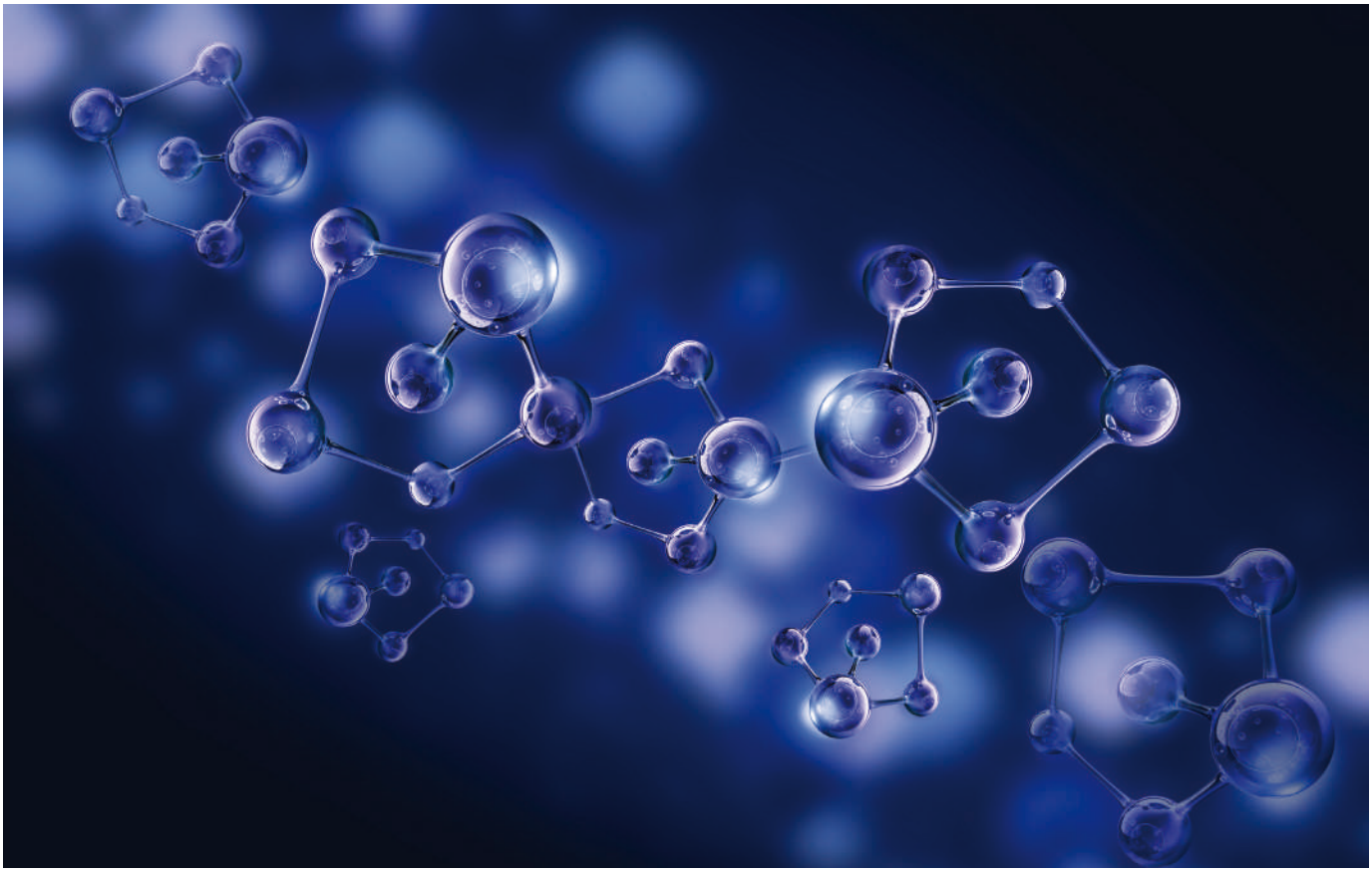
Another large pharma company carrying out research in this area is Bayer, which is drawing on its library of more than 4 million compounds and next-generation cell biology technologies to create a platform targeting RNA to develop innovative small molecules to treat diseases with high unmet need.[5]

Many other smaller companies are also pursuing research into RNA-targeted small molecules, including Accent Therapeutics, which is developing small molecule therapies in the field of epitranscriptomics – a collection of RNA-modifying proteins (RMPs) that control many aspects of RNA biology – to develop cancer medicines.[6] Drug discovery and development company Epics Therapeutics is focused on small molecule drugs targeting RNA epigenetic mechanisms involved in cancer development.[7]

Another small biopharma company developing small molecules to correct RNA expression is Skyhawk Therapeutics. The company has several programs underway targeting autoimmune disease, cancer, neurodegenerative conditions as well as neuromuscular disorders.[8] There are many other small companies pursuing RNA targets through small molecules, paving the way for many more breakthroughs and advances in the near future.

These treatments tackle inflammatory conditions in a different way to established treatments, offering hope of both symptom relief and slowing the progression of disease.

Small molecule Janus kinase (JAK) inhibitors are also emerging as innovative new treatment options. JAK inhibitors to treat several chronic inflammatory disorders such as rheumatoid arthritis, ulcerative colitis and atopic dermatitis have recently been approved. These include Pfizer's tofacitinib (Xeljanz®) for the treatment of arthritis and ulcerative colitis and Eli Lily's baricitinib



(Olumiant®), which the European Medicines Agency approved in 2017 for rheumatoid arthritis, with the FDA approving a lower dose of the drug a year later.

There are several companies focused on next-generation JAK inhibitors with the goal of lessening adverse side effects.

Navigating Health Crises with Small Molecules

With pressing healthcare issues, such as antimicrobial resistance, there is a specific need for new antibiotic and antibacterial agents. Since small molecules act at the cell level they are potentially more efficacious for targeting these types of pathogens. The World Health Organization (WHO) and global governments have highlighted the need for investment in treatments for fungal or bacterial diseases and several studies indicate the potential of small molecules to tackle these challenges.[10]

With many countries facing aging populations, treatment for diseases such as Alzheimer's is a priority and there is some promise with small molecule innovation in this field. In animal studies, KARI 201, a dual-action small molecule, was found to improve neuropathological features of Alzheimer's disease in mice, suggesting its potential as a multifaceted drug to treat Alzheimer's.[11]

Other areas where small molecules will play an important role in managing health challenges include autoimmune disorders such as Type 1 diabetes. With studies showing an increase in autoimmune disorders over the past 25 years,[12] there is an urgent need for innovation to address these diseases and small molecules potentially hold the key.

REFERENCES

1. Amgen and Arrakis Therapeutics announce multi-target collaboration to identify novel RNA degrader small molecule therapeutics, Amgen, Jan 2022. https://www.amgen.com/newsroom/press-releases
2. https://www.biogen.com/science-and-innovation/pipeline.html
3. Mirati announces Adagrasib (KRAZATI™) Receives Breakthrough Therapy Designation from FDA for Patients with Advanced, KRAS-Mutated Colorectal Cancer, Dec 2022, Mirati. https://ir.mirati.com/press-releases
4. FDA approves Roche's Evrysdi (risdiplam) for treatment of spinal muscular atrophy (SMA) in adults and children 2 months and older, Aug 2020. https://www.roche.com/investors/updates/inv-update-2020-08-10b
5. RNA-Targeting Small Molecules, Bayer. https://www.bayer.com/en/pharma/rna-targeting-small-molecules
6. https://www.accenttx.com/our-scientific-focus/
7. https://www.epicstherapeutics.com/
8. https://skyhawktx.com/pipeline/
9. Antibacterial Activity of Small Molecules Which Eradicate Methicillin-Resistant Staphylococcus aureus Persisters, Feb 2022. https://www.frontiersin.org/articles/10.3389/fmicb.2022.823394/full
10. A small molecule that mitigates bacterial infection disrupts Gram-negative cell membranes and is inhibited by cholesterol and neutral lipids, Dec 2020. https://pubmed.ncbi.nlm.nih.gov/33290418/
11. Discovery of a dual-action small molecule that improves neuropathological features of Alzheimer's disease mice, Proc Natl Acad Sci USA, Jan 2022. https://pubmed.ncbi.nlm.nih.gov/35027452/
12. Research round-up: autoimmune disease, Nature, July 2021. https://www.nature.com/articles/d41586-021-01834-x

Dr. Patrick Larcier

Dr. Patrick Larcier, Senior Director at PharmaLex, has worked in drug development and regulatory affairs for 30 years, at biotech companies, at CROs and in consulting. Until April 2022, he led drug development and pharmacovigilance activities for PharmaLex France and Benelux; he now provides support for PharmaLex's growing EU and US activities in these areas.