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Pharma Ignite

Shaping The Future Of Novel Therapy Development

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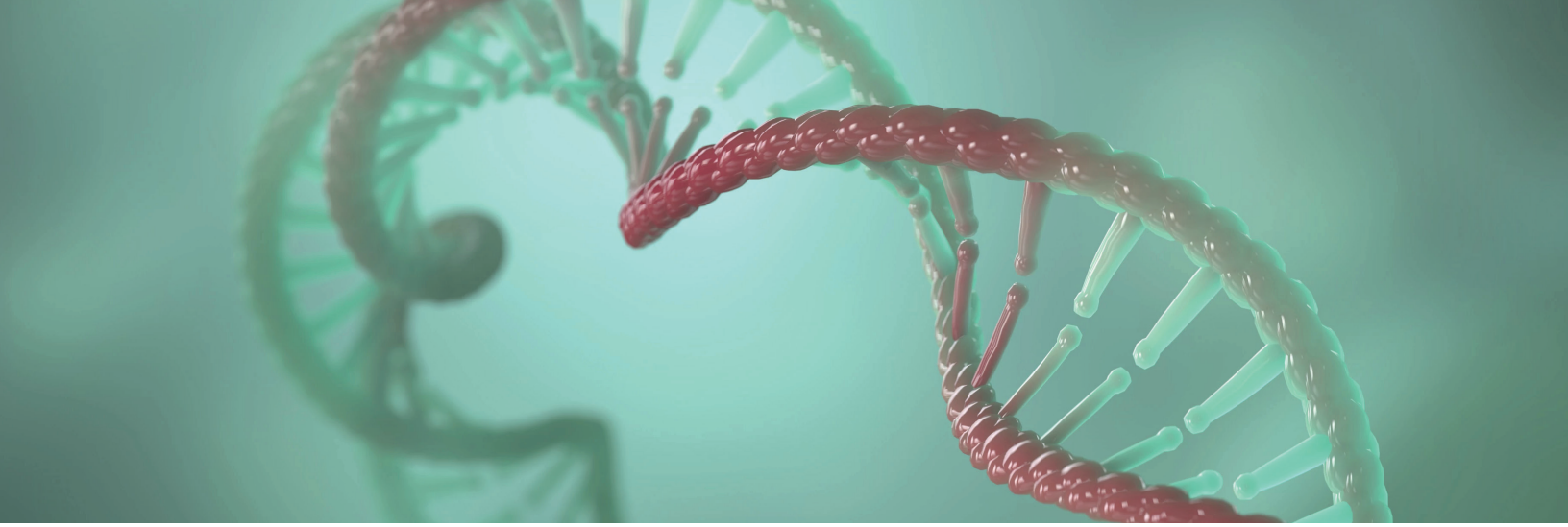


Shaping The Future Of Novel Therapy Development

Drug innovation has the potential to benefit everyone, but it cannot exist in a vacuum. Today's novel therapies are conceived and developed in a payer-, patient- and value-oriented environment, one in which the gap between ambition and uptake is wider than ever.

Yet biopharmaceutical innovation continues to flourish. A prime example is molecular and cell biology, where products such as cell and gene therapies are a growing commercial reality. Over the past decades, with the shift in interest from chemical synthesis to biologics and advanced therapy medicinal products (ATMPs) comes an increase in specificity and personalization, facilitated by more sophisticated diagnostic criteria.

There is also an increasing focus on underserved populations. Regulatory authorities have raised concerns about diversity and inclusion in R&D, explains Colin Orford, senior vice president, Drug Development Services at ICON. It recognizes disparities between highly controlled clinical trial populations and real-world drug use in which different nationalities or ethnicities may respond variably to the same drug.

Leveraging Synthetic Biology

Advances in synthetic biology, such as gene editing and molecular biology, have been key drivers of novel therapy development. Next-generation sequencing platforms have done much to open up genetic analysis and identify novel druggable targets.

Technologies such as the use of CRISPR-Cas9 have the potential to revolutionize gene editing, both for analysis and therapeutic intervention.

Biological regulators like microRNA are helping researchers to understand and intervene in gene transcription, and developing approaches such as exon skipping in rare diseases. Similarly, the ability to chemically stabilize peptides or mRNAs in the cellular environment can now extend their half-life, opening up endless possibilities for novel approaches for therapeutic interventions.

Much of this activity is RNA-driven. "Understanding genes is great, but the reality is more complex and we know they are spliced and then translated," Orford comments. "RNA is what does the work, really coding for the proteins." Messenger RNA was central to the development of novel vaccines against COVID-19. It is now being leveraged to other therapy areas.

As Orford observes, some companies, such as BioNTech, were already developing precision mRNA immunotherapies for oncology applications before COVID hit. There is also potential to extend mRNA applications into areas such as neuroscience. For the moment, though, and until understanding of underlying biology improves in these areas, cancer and rare disease remain the pathfinders for both mRNA and associated precision medicine, Orford says.

At the same time, he emphasizes, product developers are now thinking carefully about how best to deliver mRNA to cells without triggering immune responses, whether through lipid nanoparticles or viral vectors. There is growing interest in broadening the armory of delivery vehicles, by using approaches such as herpes simplex virus to increase the size of the mRNA payload and address more complex treatment modalities.

Colin Orford, *Senior Vice President, Drug Development Services, ICON*

At the discovery stage, novel analytical tools such as multi-omics are helping scientists to identify therapeutic targets in greater detail and determine whether they should be addressed with new chemical entities, biologics or ATMPs. Researchers can also use these technologies to investigate multiple biomarkers of biological engagement and ideally potential clinical benefit. Where feasible, combining 'wet' (e.g., tissue-based), imaging or emerging digital biomarkers "can build a lot of confidence around the way a drug is working", Orford points out.

Not all biomarkers will be predictive of a clinical outcome. By tracking biomarkers through the various phases of clinical development, though, researchers can inform novel approaches that feed back into discovery research. "You may see the biomarker response in a subset of the population, or you may see an unexpected change in a known biomarker response," Orford explains.

Widening The CGT Remit

If cell and gene therapies (CGTs) are at the forefront of novel therapy development, much of that activity remains focused on rare disease and oncology indications. As Orford highlights, most rare diseases are monogenic, and a single gene is less challenging to target than multiple genes.

Attention is shifting, however, to areas such as neurology and even type 1 diabetes using cellular based therapies. Researchers continue to pursue the "holy grail" of 'off-the-shelf' allogenic CGTs. For those products that do make it to market, issues such as pricing and reimbursement, as well as evidence of long-term safety, quality and effectiveness, continue to evolve.

As Orford notes, safety remains a key consideration when developing innovative therapies and is already front and center in CGT regulation. CAR-T and other therapies are habitually approved on condition of 15 years' follow-up, including registry-based observational studies. "At the moment, we're probably too early in the process to understand how well those post-marketing requirements are actually being managed," Orford adds.

At the same time, chemistry, manufacturing and controls (CMC) standards need to be developed and maintained in a similar manner to conventional therapeutics and there may even be a need for greater stringency. These are very complex products which come to market much faster than more conventional therapies, Orford notes. CGT developers need to show that their production methodologies are viable, sustainable and fully reproducible beyond the clinical trial arena and into the post-approval environment.

Finding the right price point for something potentially curative, and squaring it with the realities of health care utilization and budgeting, is another challenge. Companies should focus on evidence generation from early in the drug development paradigm, front-loading considerations such as cost management, value, broad-based outcomes, health care infrastructure and market access. "There will be many price-sensitive markets, like the UK at the moment, where reimbursement is always going to be very challenging," Orford warns.

Neurological Opportunities

While therapy areas such as cancer, rare diseases and immunology continue to dominate the novel therapy landscape, there has also been encouraging progress in once intractable neurological conditions. Notably, amyloid-targeting antibodies for early Alzheimer's disease, such as lecanemab (Leqembi; Eisai/Biogen) and donanemab (Eli Lilly), offer new hope to patients with few other treatment options.

> "While therapy areas such as cancer, rare diseases and immunology continue to dominate the novel therapy landscape, there has also been encouraging progress in once intractable neurological conditions."

Evidence from clinical trials that lecanemab and donanemab may slow cognitive decline by anything from 27% to 35% is welcome, Orford says, although Alzheimer's treatment still has a long way to go. "We really don't understand the biology well enough yet," he comments, noting that the amyloid hypothesis "is still a bit of a smoking gun".

There are also continuing problems with identifying and diagnosing early-Alzheimer's populations, then finding tools sensitive enough to measure cognitive decline in the milder stages of the disease. "You're recruiting a patient population that doesn't necessarily have a significant or consistently observable deficit, and the outcome is that they don't get something they don't already have," Orford comments.

> "Smaller companies work very well in rarer diseases: because of their nature you can get to a regulatory submission with a relatively small number of patients."

Lecanemab and donanemab employ slightly different amyloid-targeting strategies, and whilst not ATMPs, they represent innovative therapies, Orford notes. Ultimately, he believes that R&D for Alzheimer's will migrate towards multiple therapies, drawing on lessons from oncology. Even if you fully subscribe to the amyloid hypothesis, it stills begs the question of whether the real issue is over-production or clearance of amyloid.

Nor does Orford envisage any wholesale industry shift from niche indications towards broader population targets, as more progress is made with neurological diseases. "It depends on who you are and where you are" he says, pointing to the "massive" investment made by industry in CGTs. Biomedtracker data featured in reports by the American Society of Gene & Cell Therapy (ASGCT) and Citeline shows in just 2022, over $2.180bn was invested into CGT start-up financing.[1] "People are still going to focus on these much more precision-based areas, certainly in oncology, where we have a better understanding of biology," Orford continues.

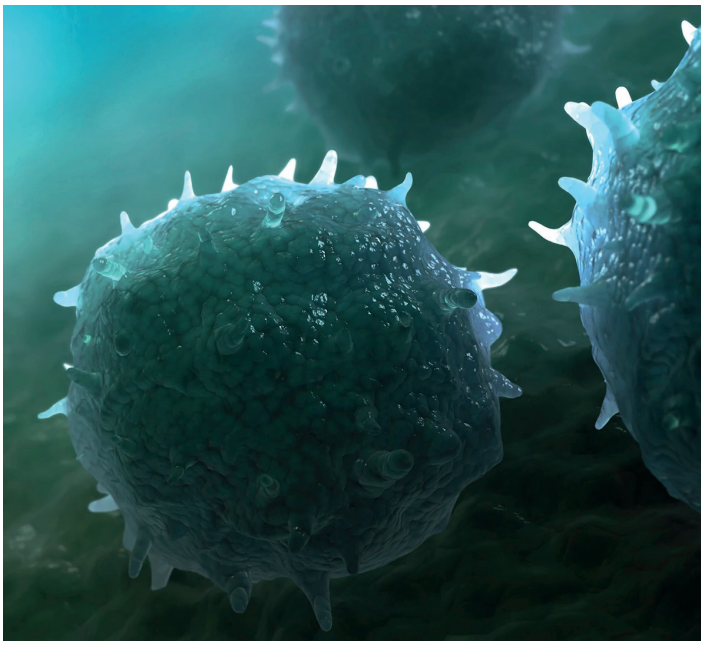
What may emerge is more divergence between R&D strategies at larger and smaller biopharmaceutical companies. "Smaller companies work very well in rarer diseases: because of their nature you can get to a regulatory submission with a relatively small number of patients," Orford explains. "Then you don't have the issues around marketing to a very large primary care population."

For many larger companies, though, broader-based disease populations remain an attractive proposition, both scientifically and commercially. "While there is one school of thought that we are getting more precise biomarkers and better understanding of diseases, there is another school saying we need polypharmacy and combination therapies," Orford says. "I think the industry is going to remain slightly undecided on this one."

Planning For Novel Therapies

With new treatment modalities presenting complex market access challenges for industry in a cost- and value-conscious environment, companies must ensure their development programs for novel therapies always "start with the end in mind", Orford stresses.

More and more, target product profiles need to incorporate issues such as payer positioning, patient access and meaningful differentiation. "You can have great science and be first-in-class, and you can get to market really quickly," Orford comments. "But unless your drug has a clinical effect better than a drug produced eight years ago, you're going to have a more difficult time in the marketplace."



Historically, industry has relied heavily on marketing machines that "can create a lot of noise around an asset's attributes". That impact is diluted as market access is determined increasingly by payers, demanding in-depth understanding of the reimbursement environment and its implications for drug development. "You are adding additional complexity in clinical trials when you start to do this," Orford notes.

"But I don't believe approval is the goal anymore," he adds. "That is a big shift, particularly where regulators and payers are developing their in-depth understanding of these new modalities as they emerge from company pipelines." Recent events such as the introduction of direct price negotiations for selected medicines under the US Medicare scheme will be crucial barometers for evolving R&D strategies and the pursuit of innovation, Orford predicts.

At the same time, he emphasizes, the patient voice is becoming more central to drug development. "We have seen this very much in rare diseases. There is a high level of advocacy and people understand their conditions extremely well." That calls for "something much more bespoke", Orford says. "Drug developers have to think far more now about patient access: the patient voice and what is the true unmet medical need. And you cannot be third, fourth or fifth to market to the same degree without some genuine differentiation."

Rethinking R&D strategies for novel therapies in today's marketplace may also mean deprioritizing, to some extent, traditional aspirations on speed to market. "We still hear a lot of people talking about speed," Orford comments. "At the same time, I think some companies now are actually saying, rather than focus on speed, let's just get it right first time."

References

1. Citeline & ASGCT, ASGCT/Citeline Quarterly Report: Q1 2023 (2023) https://pharmaintelligence.informa.com/asgct-report

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