A new wave of technology: Janet Lambert

Gene-edited therapies produce first clinical data

A new wave of therapies using gene-editing technologies is quickly approaching the market, with the potential to transform the standard of care for patients with a variety of serious diseases and disorders. While the COVID-19 pandemic has transformed the global healthcare landscape, therapeutic developers across the globe continue to drive progress in this promising area of medicine, all the while espousing the values for efficacy and patient safety laid out in a document last August by the Alliance for Regenerative Medicine (ARM), alongside a coalition of preeminent developers in the field[1].

This article is a review of the state of play in this highly innovative area of therapeutic development, which continues to progress despite the pandemic.

There are currently 66 companies worldwide developing therapies using gene-editing technologies, including 16 with clinical stage compounds. There are a total of 32 ongoing gene-editing clinical trials worldwide, all of which are at an early stage. The developers are looking to advance durable and potentially curative treatments for a wide variety of indications, including serious cancers, endocrine and metabolic disorders, bleeding disorders, HIV, and certain forms of inherited blindness. Innovative cell and gene therapies, including those using gene-editing technologies, have the potential to drastically improve upon the standard of care for these patients, who may have few or no treatment options available to them. In addition, these therapies can provide considerable cost savings to healthcare systems in the medium-to-long term[2].

One of the most notable trends in the past six to 18 months has been the progress of CRISPR-Cas9 technologies. Last summer, CRISPR (clustered regularly interspaced short palindromic repeats) entered the clinic for the first time in Europe and the US, joining ZFNs (zinc finger nucleases) and TALENs (transcription activator-like effector nucleases). CRISPR Therapeutics AG, Vertex Pharmaceuticals Inc, and Tmunity Therapeutics Inc made headlines last summer as they initiated their respective clinical trials – CRISPR and Vertex looking to test their product to correct mutations that cause sickle cell disease and beta thalassaemia, both serious diseases affecting red blood cell production that affect hundreds of thousands of patients globally, and Tmunity collaborating with Penn Medicine on a gene-edited immunotherapy for the treatment of severe cancers.

By the end of 2019, investigators had reported initial signs of efficacy and safety and CRISPR-based technologies have continued to advance in 2020. In March, Editas Medicine Inc and Allergan Plc announced that they had treated the first *in vivo* CRISPR patient with a product aimed at correcting a mutation resulting in blindness.

Another notable trend is the use of gene-editing technologies to create allogeneic cell-based immunotherapies. These therapies, which often build upon the strategies used to create first generation chimeric antigen receptor T cell (CAR-T) and T cell receptor (TCR) therapies, are intended to provide an 'off-the-shelf' option to patients and providers. While many current cell-based immunotherapies are autologous and must be manufactured on a patient-by-patient basis using an individual's own cells, these next generation allogeneic cell based immunotherapies would be able to be manufactured on a larger scale and administered as needed to patients. Theoretically, these treatments could help to lower costs and shorten timelines for the manufacture and administration of these therapies.

We're already beginning to see progress from the first wave of allogeneic gene-edited CAR-T therapies that have entered the clinic. At the American Society of Clinical Oncology (ASCO) virtual meeting in May, Allogene Therapeutics Inc provided an update on positive initial results from ALLO-501's Phase 1 study, showing the treatment to be well tolerated with no dose-limiting toxicities. Anti-tumour activity was observed across all dosage levels.

In April we saw data from Gracell Biotechnology Ltd on its first in human clinical trial for universal TruUCAR GC027 in certain lymphoblastic leukaemia patients. The data was presented during the American Association of Cancer Research (AACR) Virtual Annual Meeting, and showed promising initial results for five patients, all of whom achieved a complete remission with or without complete blood count recovery, and four having no minimal residual disease detected after treatment.

All five patients tolerated the single infusion of the CAR-T with no adverse neurotoxicity effects. Interim data from Precision BioSciences Inc in December of last year suggested a tolerable safety profile and encouraging early evidence of clinical activity for its gene-edited CAR-T therapy to treat non-Hodgkin lymphoma. Additional data from this new wave of therapies are expected throughout the year.

Researchers and scientists continue to look for methods to improve upon existing gene-editing technologies. The use of CRISPR, TALENs, and ZFNs revolutionised the field of gene editing because these technologies can be produced at a lower cost, are easier to use, and create more precise and efficient edits than earlier technologies. Continued refinement of these technologies will ensure that these therapies can be made on a commercial scale. And there is considerable interest in using new platforms, such as base editing, to increase efficiency, reduce off-target effects, and allow for a greater number of edits within the genome.

Finally, we're seeing the application of gene-editing technologies expand. While early clinical trials have primarily focused on difficult-to-treat cancers and inherited genetic diseases, it's possible that gene-editing technologies could be used to treat a much wider array of diseases and disorders in the future. Like the broader cell and gene therapy sector – where approximately one-third of clinical trials are targeting more prevalent disorders – researchers have begun to explore the applicability of gene-editing technologies to indications afflicting larger patient populations. Of particular interest this year was a study from Stanford University in the US

Table 1. Companies with clinical-stage gene edited therapies

Company	Location of clinical trials	Therapeutic indications
Allergan Plc	United States	Opthalmology
Allogene Therapeutics Inc	United States	Oncology
Cellectis SA	United States	Oncology
CRISPR Therapeutics AG	Australia, Belgium, Canada, Germany, Italy, United Kingdom, United States	Oncology, inherited blood disorders
Editas Medicine Inc	United States	Opthalmology
Guangzhou Anjie Biomedical Technology Company	China	Oncology
Les Laboratoires Servier SAS	France, Spain, United Kingdom, United States	Oncology
Chengdu MedGenCell Co Ltd	China	Oncology
Nanjing Bioheng Biotech Co Ltd	China	Oncology
PACT Pharma Inc	United States	Oncology
Precision BioSciences Inc	United States	Oncology
Sangamo Therapeutics Inc	United Kingdom, United States	HIV, inherited blood disorders, inherited metabolic disorders
Sanofi SA	United States	Inherited blood disorders
Shanghai Bioray Laboratory Inc	China	Inherited blood disorders
Tmunity Therapeutics Inc	United States	Oncology
Vertex Pharmaceuticals Inc	Belgium, Canada, Germany, Italy, United Kingdom, United States	Inherited blood disorders

which discussed the potential to use CRISPR to fight viruses like that which caused the COVID-19 pandemic[3].

All of the milestones we've seen in recent months show that gene editing, and advanced therapy medicinal products as a whole, remain one of the most exciting developments in medicine. As with all breakthrough biotechnologies, we need to exercise good stewardship in our research and development practices and ensure that work involving the genetic modification of cells takes place within a robust bioethical framework, such as the principles outlined last year by ARM.

The great news here is that, increasingly, these treatments are demonstrating safety and efficacy, and are therefore moving through the clinic rapidly towards the patients in urgent need. Now more than ever, in the unprecedented landscape of COVID-19, it's important not to lose sight of the end goal for these therapies: providing a profound and potentially curative outcome for patients. It's imperative that all advanced therapy stakeholders and supporters adapt and support each other amidst the new challenges we now face, in order to continue the exciting momentum that we've seen recently in the sector.

References:

1. Therapeutic Developers' Statement of Principles, *The Alliance for Regenerative Medicine*, 28 August 2019. This document, signed by 15 companies in the gene editing space, expresses a common commitment to high standards for patient safety and efficacy in somatic cell (non-heritable) genome editing. It also asserts that germline (heritable) genome editing is currently not appropriate in clinical settings. The full statement can be viewed at: https://bit.ly/3eJLNlD.

2. New Report Demonstrates Potential for Cell and Gene Therapies to Provide Cost Savings, *The Alliance for Regenerative Medicine*, https://bit.ly/3dsWJUu

3. Qi, Stanley, Can Crispr technology attack the coronavirus? Stanford University, Schools of Engineering & Medicine, 18 March 2020, https://stanford.io/3cqvyIK

This article was written by Janet Lambert, chief executive officer of The Alliance for Regenerative Medicine.