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A Peek At The Hand Of Cell, Gene And RNA Therapies

by Shardha Millington

With nearly 3,500 therapies in development globally, and almost $480m in start-up financing in Q1 of 2021 alone, the cell, gene and RNA therapy area is seeing a sharp rise in development and attention.

The world of cell, gene and RNA therapy, which at one time may have seemed like a thing of fiction, is not only reality, but a reality that is growing at speed. With nearly 3,500 therapies in preclinical and clinical development globally, and almost $480m in start-up financing in the first quarter of 2021 alone, it is seeing a sharp rise in development and attention. And with 77 therapies in Phase III clinical trials, the industry is also teetering on the potential of even more exciting regenerative medicines becoming available to patients.

Of course, it is well known that with great power comes great responsibility and with strong ethical considerations, high cost and safety concerns, there are some opportunities that can be taken advantage of to make this space more accessible and to add new strings to the industry's bow.

The Landscape

Despite being closely tied in nature, the dramatic growth in development of cell, gene and RNA therapies shows distinct patterns. The number of gene therapies, including genetically modified cell therapies, has grown exponentially since 2014, while non-genetically modified cell therapies have seen a more consistent rapid increase since 2015 and RNA therapies have grown more steadily since 2004 (*see Exhibit 1*).

A clear unifying feature across all three areas, however, when comparing the relative proportions of each stage of development, is that this pace of expansion is largely a reflection of preclinical development. The transition into the clinical development and beyond is not seeing the same dramatic increase over the years, suggesting a bottleneck at the point of entry into clinical trials.

Exhibit 1.

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For gene therapy products, oncology is the stand-out focus, with 997 out of around 1,700 therapies being developed for cancer indications, and out of the known cancer types the three most common are myeloma, acute lymphocytic leukaemia and acute myelogenous leukaemia. Solid cancer (unspecified) is also on top for non-genetically modified cell therapies and RNA therapies, however they both include a more mottled disease landscape (*see Exhibit 2*).

Exhibit 2.

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New And Upcoming Technologies

Hand-in-hand with the rise in development in these areas has come innovative technology and approaches that have provided potential breakthrough ideas. *Orna Therapeutics, Inc.*, a start-up that recently launched with an $80m series A financing deal, is leveraging circular RNA (also dubbed "oRNA" or "circRNA") for a spread of potential indications such as cancer, autoimmune disease, regenerative medicine and genetic disorders. The technology consists of a string of RNA coding for circularisation ribozyme, an expression element, a therapeutic protein, and a homology arm, which has neither cap nor tail and which autocatalyses into circular RNA. It is a simple one-step process which is a trump card in manufacturing terms, and results in higher levels of protein expression in cells compared to linear mRNA which has a knock-on benefit in terms of power per dose – a similar benefit to that of self-replicating/amplifying mRNA.

It could be said, however, that the golden ticket in this field is being able to produce a therapy that is non-immunogenic, and this is where a further crucial benefit of the therapy comes into play. Research conducted by Orna has shown that a cellular immune response is not induced by circRNA in RIG-I and TLR competent cells and is "effectively translated *in vivo* without provoking an RNA-mediated innate immune response," the company's co-founders note in their research.

Alongside immunogenicity, sustainability makes for an attractive therapy, particularly in the case of cellular therapies where manufacturing can be a long and complex process, often involving removing and manipulating the patient's own immune cells. *Notch Therapeutics* is an example of a company pioneering its own novel platform with sustainability in mind: the Notch Engineered Thymic Niche (ETN). The aim of the platform is to allow immune cells, including T-cells, to be produced from induced pluripotent stem cells (iPSCs) in a renewable fashion that

allows manufacturing of these immunotherapies to be scaled-up and to bypass the need for "animal components or feeder cell lines," the company says. Using a niche that is designed to recreate that of the human thymus, and proprietary bead-based expansion technique, these iPSCs can be ultimately differentiated, with a novel twist and in a precisely controlled manner, into "fully functional immune cells" that can be used as an off-the-shelf, universal treatment for patients.

Gaps In The Industry

While there is much innovation the field, there are key opportunities that can be taken advantage of to progress further. One of the key selling points of gene therapy is that it should theoretically cut the head off the snake and provide long-lasting treatments that target the condition at its source. Naturally, certain diseases have historically lent themselves to this treatment approach as, for example, bone marrow can be completely removed and replaced and therefore facilitates a clean-cut gene replacement technique. As shown in Exhibit 2, however, comparatively to oncology where the introduction of CAR-T technology has been revolutionary and climbed to a dominant 65% of genetically modified therapies (according to data from Pharmaprojects), many of these indications represent only a fraction of the development focus. There is a wealth of other life-long conditions that can be targeted that would otherwise require indefinite or daily, and in some cases invasive, treatment.

HIV/AIDS is a good example of this, and also represents an interesting overlap into the application of the highly innovative CAR-T technology outside oncology, for infectious diseases. One company venturing into this domain is Wuhan Bio-Raid Biotechnology with two preclinical HIV/AIDs CAR-T programs, A-1801 and A-1902. Miltenyi Biomedicine has also conducted research in the field, suggesting in an August 2019 publication that "CARs targeting multiple highly conserved sites on the HIV-1 envelope glycoprotein using a two-molecule CAR architecture, termed duoCAR" have potential to be the way to go.

These approaches raise a good question for the near-term future of cell and gene therapy: could we begin to see an expansion of typically oncology-orientated technology into other indications, including infectious disease?

Exhibit 3.

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Another particularly noticeable gap appears to be the use and development of gene therapies using non-viral vector technology, with only 22% of gene therapies in development leveraging this as a tool (*see Exhibit 3*). Despite being a popular and often effective choice, viral vectors have raised potential concerns with their safety. In February, bluebird bio halted clinical development

and roll-out of their beta-thalassemia treatment, Zynteglo, due to two instances of blood cancer reported from their Phase I/II trial, for which they are looking into a potential connection with the use of their lentiviral vectors.

Of course, on a more topical note outside of gene therapy, the Oxford/*AstraZeneca PLC* COVID-19 vaccine, Vaxzevria, has caused a stir with cases of rare blood clotting being reported and potentially linked to the use of a viral vector. Potential safety concerns such as these make a non-viral vector approach attractive in comparison. It also, perhaps more pertinently due to the limited cloning capacity and vector-targeted neutralizing antibodies associated with viral vectors, highlights gene therapy vectors as an Achille's heel that could be strengthened.

Bluebird's Latest Gene Therapy Stumble Will Help Vertex Close The Gap

By Andrew McConaghie

21 Apr 2021

Once the darling of biotech investors, Bluebird Bio's go-it-alone strategy with Zynteglo has not paid off as German launch plans stall.

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The DNA integration technology start-up, *SalioGen Therapeutics*, is focused on non-viral vectored gene therapies using a mammalian-derived enzyme, saliogase, to insert genetic codes *in vivo* with the aid of lipid nanoparticle delivery technology. The technology works by co-delivering a saliogase RNA sequence and a DNA sequence to target cells, allowing the saliogase enzyme to integrate "the supplied DNA into a precise, defined location in the recipient genome without the need for homologous recombination," the company says. Some of the professed benefits of this approach include the fact it simply requires an addition of genetic material, and no deletion, and that it is a more affordable alternative to viral vectors which are notoriously expensive to produce.

Regulatory Developments

Of course, a key question is: does a gap in the field exist as an opportunity if there is no-one there to fill it? Herein lies the need for incentives to encourage players in the market. The current major player is *Astellas Pharma, Inc.*with 23 candidates in preclinical development, followed by *Sarepta Therapeutics, Inc.*, *China Immunotech (Beijing) Biotechnology Co LTD* and *Taysha Gene Therapies, Inc.*, to name a few. A flow of new ideas and innovation, however, is important too.

In Q1 of 2021 nearly $480m in start-up financing was deployed across 13 companies throughout the gene, cell and RNA sector. This is an increase of approximately $224.5m since Q1 2020, however it represents a decrease since Q4 2020 (*see Exhibit 4*). A trend of increased financial injections into the field is not yet as clear as that observed for non-start-ups (*see Exhibit 5*) which

saw 98 financing deals in Q1 2021 – just shy of triple the number for Q1 2020.

Some of the largest start-up financings were the launch of *Lexeo Therapeutics*and the closing of Notch Therapeutics' financing to develop their pipeline of renewable stem cell-derived cancer immunotherapies, both of which were valued as $85m series A deals.

Exhibit 4.

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In addition to financing, the sharing of expertise needs to be encouraged. If there is anything the COVID-19 pandemic has taught us as a population as well as an industry, it is that collaboration is crucial, and this can come in the form of corporate alliances and acquisitions as well as government incentives and schemes.

In terms of acquisitions seen in Q1 2021, some of note include the acquisition of Myst Therapeutics by Turnstone Biologics and the merging of 9 biotechs into the newly-formed Centessa Pharmaceuticals which focusses on a "bottom-up" approach to research, placing the data at the centre of their operations.

Exhibit 5.

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In another vein, perhaps the most noticeable government-backed incentivisation scheme is the UK's Cell and Gene Therapy Catapult with which the UK Government "aims to build an £10bn industry." The Catapult scheme works with companies in areas such as clinical operations, regulatory, manufacturing and industrialization to help companies progress their development projects into "viable commercial products."

As an example of the work done by this scheme, one success story includes Purespring Therapeutics, a spin-out company of the University of Bristol, which was awarded £45m worth of investment from Syncona last year thanks to a preclinical development plan constructed and costed in collaboration with the Catapult scheme. The company expects to be able to progress a new gene therapy to a clinical development stage in 3 to 4 years. This is one of the largest single investments made to a new UK university biotech company.

Importantly, the Catapult scheme allows start-ups to work closely with the MHRA (as well as other regulatory partners including the EMA, the FDA and health technology appraisal bodies) to ensure compliance with government guidelines for a well-regulated transition through development – something that as shown from the tribulations of viral vectors, could be key in ensuring requirements are met sufficiently and efficiently.

The Cell and Gene Therapy Catapult scheme also works with the UK Regenerative Medicine Platform, which aims to produce research to encourage more regenerative therapies to enter the clinic through a collaboration of research hubs. This drive to jump the hurdles faced by regenerative medicines as they target entry into clinical trials could be a considerable help in tackling the bottleneck of these therapies in the preclinical stage (*see Exhibit 1*) and is an important consideration for cell, gene and RNA therapies. With all the activity that is currently evident, the question for industry is whether the momentum can be maintained in future quarters and whether we can leverage gaps in the field to encourage a higher turnover into more clinically advanced products.

This article is based on an April 2021 Analysis Field Report prepared by Ly Nguyen-Jatkoe, executive director, Americas, Informa Pharma Custom Intelligence, Amanda Micklus, senior pharma consultant, Informa Pharma Custom Intelligence and Doro Shin, senior director, content marketing, Informa Pharma Intelligence, in collaboration with the American Society of Gene + Cell Therapy. Access the full report here. If you have any questions about the themes discussed in this article, or would like to learn more about Pharma Intelligence's products and consulting offerings, please contact Ly, Amanda, or Doro.