CELL & GENE THERAPY INSIGHTS

SPOTLIGHT

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

COMMENTARY

The heart of market access: opportunities and challenges for cell and gene therapy development for orphan and prevalent cardiovascular diseases

Faraz Ali

Heart disease is the leading cause of death globally, and there is a need for better medicines. No cell and gene therapies (CGTs) for heart disease are approved, but a new generation of companies are advancing promising science. The pipeline of CGTs is mostly focused on *in vivo* AAV-based therapies for prevalent cardiovascular (CVD) conditions, in contrast to broader trends favoring an initial focus on rare diseases seen in other therapeutic areas. CGTs for orphan heart disease indications have relevant benchmarks that could be used to justify the value and price for a one-time, potentially curative therapy. Significant challenges stand in the way of the development, approval, pricing, and adoption of even highly effective CGTs for prevalent CVD indications. Overcoming these will require scientific breakthroughs; heavy investment in CGT manufacturing technology and capacity; commercial and financial sophistication; and a focus on the needs of patients.

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A HEART-BREAKING INTRODUCTION

Heart disease exacts a tremendous toll on global human health and is the leading cause of death in the world, more than all oncology combined [1]. In the USA, >30 million adults are diagnosed with heart disease (or 12% of all adults), and an adult dies from a cardiovascular (CVD)-related health condition such as a heart attack every 40 seconds, a gruesome statistic that translates to 31% of all US deaths each year [2,3]. The picture is equally bleak at the other end of the age spectrum, as ~35,000 children are born in the USA every year with congenital heart disease (CHD), and CHD is the leading cause of birth defect-related morbidity and mortality [4–6]. While standards of care have improved with time, it is not keeping up; recent analysis has shown that after decades of reduction in the mortality rate due to heart failure, it started to increasing again during the last decade [7–9]. And while there are >250 known genetically defined cardiomyopathies and monogenic disorders where the primary source of morbidity and mortality involves the heart, there are almost no approved products that target the underlying cause of such diseases [10].

There is clearly a need for improved treatments. Unfortunately, attempts at developing novel cell and gene therapies (CGTs) for heart disease have not been successful to date. Much effort was devoted to regenerative medicine approaches using autologous or allogeneic cell sources, but after >150 clinical studies involving thousands of patients over the last 2 decades those efforts have mostly ended in failure, and in some cases, scandal [11,12]. Of the original industry-driven cell therapy efforts, Revascor™ from Mesoblast – allogeneic mesenchymal precursor cells (MPCs) cell therapy for advanced chronic heart failure – is one of the few still ongoing and showing some promise in late stage trials [13,14].

There have been far fewer attempts at gene therapy for heart disease. The most well-known effort was advanced by Celladon, a company founded in 2000 to evaluate a one-time, intracoronary infusion of the gene therapy agent Mydicar® (AAV1 to deliver SERCA2a). After promising pre-clinical and early clinical results, this effort was discontinued in 2015 after an unsuccessful Phase 2b study (CUPID 2) [15]. Celladon was sold in March 2016.

HEART DISEASE GENE & CELL THERAPY VERSION 2.0

Soon after Celladon conceded defeat, a new crop of biopharma innovators emerged to advance the next generation of CGTs for heart disease. Table 1 captures important activities – company formation, financings, clinical and regulatory milestones – associated with a selected list of such companies in chronological order the last 4 years, starting with the founding of Tenaya Therapeutics in 2016.

Tenaya is advancing first-in-class product candidates from three separate platforms – Cellular Regeneration, Gene Therapy, and Precision Medicine. The Gene Therapy platform uses AAV vectors for the targeted delivery and expression of therapeutic payloads to specific cells in the heart, with an initial focus on the treatment of genetic cardiomyopathies. The Cellular Regeneration platform uses adeno-associated virus (AAV) vectors to deliver proprietary combination of transcription factors that can drive *in vivo* reprogramming of resident cardiac fibroblasts into cardiomyocytes, with an initial focus on chronic heart failure following a myocardial infarction. The Precision Medicine platform uses isogenic iPSC-derived cardiomyocytes as human disease models to identify and validate new heart failure targets and to screen for therapeutic compounds – including gene therapies and small molecules – with an initial focus on genetically-defined dilated cardiomyopathies (DCMs).

As Table 1 reveals, most of these CGT companies are using AAV-based approaches where the target organ is the heart. It is beyond the scope of this article to consider the scientific merit of the different approaches represented by these companies. However, it is worth

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TABLE 1

Selected companies advancing cell or gene therapies for cardiovascular disease.

Company	Modality	Target heart disease indication	Target organ	Population size	Recent milestones	Date
Tenaya Therapeutics	Gene therapy (AAV)	Genetic HCM Genetic DCM Ischemic heart failure	Heart Heart Heart	Orphan Orphan Prevalent	Founded	2016
BlueRock Therapeutics	Engineered cell therapy	Ischemic heart failure	Heart	Prevalent	Founded Bayer acquisition	2016 2019
REGENXBIO	Gene therapy (AAV)	Familial hyper-cho-lesterolemia (FH)	Liver	Orphan	First patient dosed	2017
Renova	Gene therapy (Ad5)	HFrEF	Heart	Prevalent	Fast track designation	2017
Xylocor	Gene therapy (Ad)	Refractory angina	Heart	Prevalent	Founded First patient dosed	2018 2020
Sana Biotechnology	Engineered cell therapy	Ischemic heart failure	Heart	Prevalent	Founded	2018
Precigen	Gene therapy (non-viral)	Heart failure	Heart	Prevalent	First patient dosed	2018
Verve Therapeutics	Gene therapy (LNP)	Coronary artery disease (CAD)	Liver	Prevalent	Founded Series B	2019 2020
Renovacor	Gene therapy (AAV)	Genetic DCM	Heart	Orphan	Founded	2019
DiNAQOR	Gene therapy (AAV)	Genetic HCM	Heart	Orphan	Founded BioMarin partnership	2019 2020
Rocket Pharmaceuticals	Gene therapy (AAV)	Danon disease	Heart	Orphan	First patient dosed	2019
AskBio	Gene therapy (AAV)	Congestive heart failure (CHF)	Heart	Prevalent	First patient dosed	2020

observing that while many have an early focus on orphan indications, a majority have an initial focus on prevalent indications (with Tenaya Therapeutics unique in its explicit pursuit of CGTs for both orphan and prevalent heart disease indications in parallel).

This reflects a broader trend: of the >1000 clinical studies evaluating regeneration medicines and advanced therapies, 45 are focused on cardiovascular indications, of which the majority are for prevalent forms of heart disease [16]. A recent analysis more specifically of *in vivo* gene therapies programs revealed that ~75% were focused on rare indications; of the remaining 25% focused on prevalent indications, cardiovascular programs were disproportionately represented, with programs intended to address atherosclerosis, coronary artery disease, angina, peripheral arterial disease, atrial fibrillation, and heart failure [17].

This insight is intriguing. In almost every other therapeutic area, the initial focus of CGTs has been on orphan conditions. Early clinical, regulatory, and commercial success in rare diseases has provided the necessary validation and risk reduction required to consider pursuing CGTs for more prevalent indications. The field of heart disease appears to be unique in that the pursuit of CGTs for prevalent conditions has not been de-risked by prior success in rare diseases.

These insights beg the question: what kind of payer environment can the current generation of CGT companies focused on heart disease expect (if and) when their therapies are approved?

CGT VALUE, PRICING & REIMBURSEMENT, MARKET ACCESS CONSIDERATIONS

Debates about the price and market access for CGTs have been raging since before

Glybera® – the first AAV-based *in vivo* gene therapy approved in West in 2012 – broke a conceptual barrier by setting the price for their one-time therapy at €1MM. The debate has since only intensified with commensurate and increasing high prices for subsequently approved CGT therapies including Luxturna® ($0.85MM) and Zolgensma® ($2.1MM). Before receiving a Complete Response Letter from the FDA, BioMarin had suggested the price for Roctavian™ – a one-time gene therapy for Hemophilia A – would be around $3MM, which would have made it one of the most expensive therapies in the world.

Debates about the appropriate value and price for CGTs for heart disease will also not be straightforward. The specifics will inevitably vary between products intended for orphan heart disease indications vs for more prevalent cardiac indications.

SCENARIO 1: CGTS FOR ORPHAN HEART DISEASE INDICATIONS

If a potentially curative, one-time CGT for a rare and severe genetic heart disorder was approved, there are several benchmarks that biopharma companies behind such a product could turn to support the value of their therapy and to attempt to justify a high, one-time price to recoup their investment. These benchmarks are captured in Table 2, and described below.

Heart transplants

Heart transplants are the only existing 'curative' therapy for individuals experiencing end-stage heart failure, whether due to a rare genetic disease or due to more traditional causes of heart disease associated with age and lifestyle. These procedures are very rare – mainly due to a severely limited supply of donor hearts – with only ~3500 procedures performed in the USA in 2019 [18]. At $1.6MM+ in total billed charged per procedure, heart transplants are also one of the most expensive medical treatments of any kind current covered by payers [19]. Long-term outcomes are variable, particularly for children who may require multiple transplants over their lifetime as they grow up. A CGT that could replace the need for a heart transplant and/or that had a magnitude of effect commensurate with a heart transplant with fewer long-term side effects would be well-positioned to use that as a justification for value – and therefore, price – that is similar or higher, and that could still be considered cost-effective.

LVADs

Implantation of left ventricular assist devices (LVADs) is the only option available to patients with end-stage heart failure who are not able to obtain a heart transplant. Data supports improved survival and quality of life, but these procedures are not considered cost-effective [20]. The total cost of a LVAD can be in the $250K–300K range when accounting for both the cost of the surgery and the device [21,22]. In situations where the LVAD provides a bridge to a heart transplant, the cost of the LVAD will be additive to that of the transplant. Long-term outcomes are variable and there are substantially increased lifetime costs because of frequent readmissions and costly follow-up care, including LVAD replacements. A CGT that could replace the need for a LVAD or that had a magnitude of effect and safety profile superior to several rounds of LVAD replacements would be well-positioned to use that as a justification for value – and therefore, price – in the $0.5MM–$1MM range or higher, and that could still be considered cost-effective.

Chronic therapies for orphan heart disease

Only a few therapies have been developed for orphan disease where the source of morbidity and mortality is primarily due to the heart.

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Of the more than 770 orphan therapies approved, only an estimated ~3% were for cardiac indications [23]. The most relevant example is the pair of therapies Vyndaqel® and Vyndamax™ (both from Pfizer) that were approved in recent years for transthyretin amyloid cardiomyopathy (ATTR-CM), an ultra-orphan genetic cardiomyopathy with less than 5K estimated patients eligible for treatment in the USA [24]. The annual cost for this lifetime therapy is approximately $225K/year [25]. A biopharma innovator commercializing an approved gene therapy for a genetic cardiomyopathy would make the case that a one-time, potentially curative therapy should be valued at levels similar to 3–5 years of therapy of chronic therapy for a similarly sized indication. Such a logic could translate to a price of $0.7MM–$1.1MM. It is worth acknowledging that the logic of this argument would not be as convincing to a payer or a Health Technology Assessment (HTA) agency as would be in the case if the gene therapy was truly displacing an expensive chronic therapy (e.g. as is the case for CGTs under development for hemophilia A and B, or for lysosomal storage disorders like MPS I, MPS II, and Pompe where the standard of care involves high cost protein replacement therapies).

Non-cardiac gene or cell therapies

Approved therapies for non-cardiac orphan diseases mentioned earlier are priced in the $1MM–$2MM range. It could be reasonable to assume that a future gene or cell therapy approved for a rare heart disease will follow the commercial and market access playbook already established by similar products for non-cardiac orphan indications. Such products would of course not be accepted by payers and HTA agencies as direct comparators for cost or value for a cardiac orphan disease product. But the fact that such agencies have increasingly had to consider and adopt value frameworks and innovative payment models (such as annuities and risk-sharing agreements) for other gene and cell therapies for orphan conditions presumably better prepares them to engage in such discussions with the biopharmaceutical innovators in Table 1 in the coming years.

Taken together, this suggest that CGTs for orphan heart disease could strive for prices in the $0.5MM–$2MM range, presuming high and durable efficacy and an overall strong health evidence and outcomes research (HEOR) package that includes analysis on cost offsets and comparative effectiveness vs relevant benchmarks.

SCENARIO 2: CGTS FOR PREVALENT HEART DISEASE INDICATIONS

The frame of reference changes dramatically for the potential value proposition, price, and adoption of CGTs for more prevalent heart disease indications. The challenges fall into three broad categories:

High product performance expectations & regulatory uncertainty

- Cardiovascular drug development has mostly been the realm of large outcome studies where a survival benefit must be demonstrated over and above standard of care, and where there is very low tolerance for safety risks. Endpoints focused on functional improvements – such as ejection fraction (EF), 6-minute walk tests (6MWT) – alone have generally not been acceptable for FDA approval. This translates to a need for very large, long, and expensive randomized and placebo-controlled clinical studies. To put this in perspective, one report found that the average size of a clinical study used to support recommendations for heart failure treatments involved more than 2,300 patients, with one study including as many

8,400 patients [26]. Studies for therapies intended to treat diabetes may require very safety trials involving 5,000–15,000 patients to rule out cardiovascular risk [27].

- This phenomenon at least in part explains why drug development in cardiovascular disease has been so challenging. Between 2000 and 2009, Food and Drug Administration (FDA) approvals for new cardiovascular drug therapies declined by approximately 33% compared with the prior decade [28]. Several studies have determined that the overall probability of successful drug development from Phase I through commercial launch is in the 4–7% range for CVD, among the lowest of all therapeutic areas [29,30]. A recent analysis demonstrated that, on average, biopharmaceutical companies spent $1B in clinical development per cardiovascular product approval, the highest ratio compared to any other therapeutic area [31]. Some experts believe that "clinical trials in cardiovascular medicine have grown in size, scope, and complexity … [resulting in] shifts away from the cardiovascular arena by some pharmaceutical companies" [32].

- The FDA – acknowledging these concerns – issued draft guidance on endpoints for drug development for heart failure in 2019 "to make it clear that an effect on symptoms or physical function, without a favorable effect on survival or risk of hospitalization, can be a basis for approving drugs to treat heart failure". Unfortunately for CGTs, this draft guidance also makes clear that "drugs with novel mechanisms of action are more likely to require mortality data" [33].

Low cost benchmarks for standard of care treatments

- First line therapies for heart failure has mostly been the realm of generic small molecules, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), beta blockers (BBs), aldosterone antagonists (AldA), and diuretics [34]. These medications are very well accepted as safe and effective, with proven long-term survival benefits. They are also very inexpensive. One of the most widely prescribed ACEi drugs (enalapril) has an annual cost of less than $500 per year, and this combination of generic first line therapies has a collective annual cost less than $2,000 per year [35,36]. These therapies are considered very cost effective, and in some scenarios these medications save costs (i.e. where heart-failure patients' lives were prolonged at lower costs to the healthcare system) [37].

High price sensitivity

- In addition to being the leading cause of death, heart failure is one of the largest and most expensive categories for payers. The USA spends $317 billion per year on CVD (including heart disease and stroke) – or nearly 17% of all US healthcare spending – representing the most expensive category of chronic diseases to treat [38]. The total direct and indirect costs of heart failure alone is expected to increase to $70 billion by 2030 [39]. This makes it a therapeutic area of very high focus for cost control for both private and public payers.

- When genetics or congenital defects is not the underlying cause, then heart failure is most common in individuals aged 65 or older, as aging can weaken the heart muscle, and older people also may have had diseases for many years that led to heart failure. This means that most heart failure patients in the USA are covered by Medicare, the primary public option.

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Indeed, heart failure is a leading cause of hospital stays among people on Medicare [40]. Many older adults live on an average income of less than $25,000 per year, and therefore are most price sensitive and less able to afford out-of-pocket (OOP) costs and co-pays associated with essential medicines. The effect of Medicare beneficiary price sensitivity on product utilization has been well documented, with one study demonstrating that even a $10 increase in monthly premiums translated to measurable differences in the market share of a plan [41,42].

LESSONS LEARNED FROM RECENT PRODUCT LAUNCHES FOR PREVALENT CVD INDICATIONS

The experience of the most recent product launches intended for broad use in prevalent heart disease indications – also captured as relevant cost benchmarks in Table 2 – are illustrative of the challenges that new CGTs in this category may encounter in the future:

PCSK9i therapies for hypercholesterolemia

Repatha® (Amgen) and Praluent® (Sanofi/Regeneron) were both approved in 2015 and launched at a price of $14,000 per year. Consensus sales estimates for peak sales were greater than $3 billion per year for each therapy [43,44]. But insurers imposed strict controls against their adoption; one study found that less than 50% of patients who were prescribed a PCSK9i received insurance approval for the therapy [45]. An analysis by the Institute for Clinical and Economic Review (ICER) in 2017 suggested Repatha® could not be considered cost effective unless priced 80–90% lower i.e. in the range of $1,700–2,200 per year [46]. Amgen riposted with their own cost–effectiveness analysis suggesting that number was more like $9,700; a number higher than ICER's but that nonetheless undercut their own sales price [47]. The same year, Amgen announced a first-of-its-kind risk-sharing agreement for Repatha® with Harvard Pilgrim Healthcare under which Amgen offered a rebate for the cost of Repatha® for an eligible patient who has a heart attack or stroke while on the product. However, this appears to have been a one-off

TABLE 2

Potential comparators for cell or gene therapies for heart disease.

Therapy	Modality	Indication	Provider	US price
Zolgensma®	Gene therapy (*in vivo* AAV)	Spinal muscular atrophy (CNS)	Novartis/AveXis	$2,100,000 (one time)
Heart transplant	Surgical procedure	End-stage heart failure	Heart transplant centers	$1,670,000 (per procedure)
Left ventricular assist device (LVAD)	Implantable device + surgical procedure	End-stage heart failure	Device: Medtronic, Abbott, etc. Surgery: heart failure Clinics	Device: $80,000–90,000 (per procedure) Surgery: $175,000 (per procedure)
Vyndaqel®/ Vyndamax™	Small molecule	Transthyretin amyloid cardiomyopathy (ATTR-CM)	Pfizer	$225,000/year
Repatha®/ Praluent®	Monoclonal antibody (PCSK9i)	Patients with high LDL that cannot be controlled by statins	Amgen/ Sanofi-Regeneron	$5,850/year
Entresto®	Small molecule (ARNi)	Patients with chronic heart failure and reduced ejection fraction	Novartis	$4,500/year
Enalapril	Small molecule (ACEi)	Patients with high blood pressure and/or congestive heart failure	Multiple (generic)	<$500/year

agreement as no other such agreements were announced [48]. The results of a large outcome study involving more than 27,000 patients demonstrated that Repatha® significantly reduced major adverse cardiovascular events (MACE) but unfortunately did not move the needle with payers and did not increase product adoption [49]. Amgen and Sanofi/Regeneron have been locked in a price war, with both products taking at 60% price reduction in 2018, bringing their prices to the $5,000–6,000 range [50]. Yet despite the positive clinical data, cost–effectiveness analysis, willing to share risk, and competitive forces at work, sales for both products have only modestly improved, and expectations for peak sales are dramatically less than they were 5 years ago.

ARNi therapy for heart failure with reduced ejection fraction (HFrEF)

Entresto® (Novartis) was also approved in 2015 and launched at a list price of $4,500 per year [51]. Analysis by ICER was mostly supportive of Entresto®'s value at this price, suggesting a modest 9% decrease would make it cost effective; however, the same analysis also focused on a potentially very high budget impact of $15 billion over a 5-year horizon if Entresto® uptake was 'unmanaged' [52]. Many payers indeed imposed control on the adoption of this product, including use of clinical criteria (e.g. cutoffs for treatment eligibility based on ejection fraction values) that were not supported by available clinical evidence [53]. To support adoption, Novartis entered into risk-sharing agreements with major insurers including Cigna and Aetna in 2016, but other payers and pharmacy benefit managers (PBMs) have been openly skeptical of such arrangements [54]. It has also emerged more recently that senior citizens who are on a Medicare Part D plan may have to pay $1600 year in OOP costs for Entresto®, making it unaffordable for some [55].

It is informative to note the differences in the way that payers approach the budget impact of therapies for prevalent vs orphan disorders. Pfizer's Vyndaqel® for ATTR cardiomyopathy is intended for an orphan heart disease, and by some estimates annual global sales could grow to $1.5 billion in 2021 and to $3.5 billion by 2025 [56]. At these levels, the budget impact of Vyndaqel® would be comparable to Entresto®'s $1.7 billion in sales in 2019 and would be greater than the <$1 billion in combined sales for Repatha® and Praluent® in 2019 [57–59]. While payers will undoubtedly try to impose some restrictions on the use of Vyndaqel®, those efforts will likely not rise to the level experienced by Repatha®, Praluent®, and Entresto®. This is possibly because the long-term budget exposure of unmanaged treatment is perceived to be far higher with products intended for more prevalent populations, even for cost-effective therapies. This is likely to be true for CGTs as well.

The clinical, regulatory, and commercial considerations described in this section represent important challenges at multiple level for the biopharmaceutical innovators advancing CGTs for prevalent heart disease conditions:

- Most, if not all, are working on product candidates with novel mechanism of actions (MOAs) that may require large outcome studies where a survival benefit must be demonstrated and where there will be very low tolerance for safety risks.
- Such clinical studies are likely to be long and expensive and will require considerable long-term financing needs from private and public investors.
- The expenses involved with such studies may be dramatically higher vs historical benchmarks considering the uniquely high cost of goods (COGs) for CGTs that can be in the range of hundreds of thousands of dollars for a single dose using current technology (vs pennies per dose of a small molecule) [60].
- The volume of drug required to support larger Phase 2 and registration clinical

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studies (and eventual commercial supply) will be orders of magnitude larger than what is required for orphan diseases. This would stretch the limits of the current manufacturing paradigm of dependence on CDMOs, many of which are already facing severe limitations on capacity to support the growth in CGTs for orphan drug development [61].

- Even if the COGs of CGTs were to decrease an order of magnitude from where they are today (i.e. in the range of tens of thousands of dollars), that may still translate to unacceptably high prices for such products vs generic small molecules that currently represent the standard of care. Such products may be unlikely to be considered cost-effective by ICER in the USA (or by HTAs ex-US).

- Considering the high and growing prevalence of heart failure, the budget impact of even modestly priced, cost-effective CGTs would be high and would face challenges to broad adoption by payers.

One limitation of the preceding analysis is that the data presented are US-centric. However, recommendations for pharmacological interventions to prevent and to treat heart failure are generally consistent between the US and EU [62]. The lower cost of healthcare spending and the higher sensitivity to drug prices outside the US is very well-documented. Therefore, it is likely that the value, pricing, and market access considerations documented here will be commensurately challenging ex-USA for novel CGTs intended for prevalent heart diseases.

PRESCRIPTIONS FOR CGT SUCCESS

Several recommendations follow from this analysis for biopharmaceutical companies contemplating development of innovative CGTs for heart disease:

Product selection

An initial product focus on orphan heart diseases may overall make more strategic sense for most companies, whether entrepreneurial start-ups or established biopharmaceutical companies, where technical hurdles and market access barriers are likely considerably lower vs for more prevalent heart conditions.

Product design

It is important to continue to invest in innovation to improve the risk-benefit ratio of CGTs intended for prevalent heart disease. What this means for AAV-based gene therapy products in particular:

- The field needs capsids with higher tropism for the heart (to reduce dose levels and COGs) and that also de-target other organs, especially the liver (to improve potential safety profile).

- While promotors already exist to limit the expression of proteins to the heart (e.g. for cardiomyocytes), these need to be improved to enable higher expression per cell, and to work in other abundant cell types (e.g. cardiac fibroblasts).

- There also needs to be more exploration of the use of delivery devices (e.g. direct injection and/or infusion-based catheters) that can provide therapy closer to where it is needed vs traditional IV infusion-based therapies. This can improve efficacy; reduce the potential off-target safety concerns associated with systemic administration; and lower the overall product (and COGs) required of a one-time dose.

Product profile

Gene and cell therapies for prevalent conditions must be prepared to demonstrate high

overall efficacy – including an overall survival benefit – on top of SOC therapies, plus very strong safety profiles. Companies working on such product candidates need to start with that end in mind even early in drug development. This needs to be formally factored into early thinking on Target Product Profiles (TPPs) and needs to be explored during non-clinical development.

Development strategy

Depending on the specific target and MOA of the gene or cell therapy product candidate, it may be advisable to first establish the efficacy and safety profile in a relevant rare condition or in a well-defined sub-population of heart disease patients first before expanding to more prevalent conditions. Such a strategy has potential to reduce development time and costs, and to 'de-risk' the investment in large outcome studies.

Manufacturing

For CGTs focused on prevalent heart conditions, it is critical for the field to invest in manufacturing technology breakthroughs and infrastructure early in drug development in order to reduce reliance on CDMOs, to achieve COGs at commercial scale that is dramatically lower than current benchmarks, to support commercially viable and societally responsible prices, and to ensure reliably consistent global supply.

Commercial models

CGT companies need to be prepared to address the price-sensitivity of future customers. While that is true in general, it is especially the case for products intended for prevalent heart diseases. Product innovation may need to be paired with innovative financial models to share risk and/or to address budget impact [63].

Partnerships

Strategic partnerships with large biopharmaceutical companies are already an area of focus for many biotech start-ups. Some early innovators in the field of gene and cell therapy – including Spark Therapeutics and bluebird bio – have demonstrated it is possible to become a fully-integrated company and commercialize their first products intended for rare diseases on their own. However, for products intended for prevalent heart disease indications, strategic partnerships with larger biopharmaceutical companies who have the experience with cardiovascular outcome studies; the resources to invest in manufacturing infrastructure; and the commercial know-how to navigate the complexity of global value, pricing and reimbursement and market access considerations may be essential for product launch and adoption.

CONCLUSION

Biopharmaceutical companies are often guilty of taking a 'build it and they well come' approach towards drug development for innovative therapies. This paper makes the case for a very different approach to drug development for CGTs for heart disease, particularly for therapies intended for prevalent heart conditions, where most biopharma innovator efforts appear to be currently focused.

As an emerging leader in next-generation gene therapies, regenerative medicines, and precision-medicine approaches for both rare and prevalent heart disease conditions, Tenaya Therapeutics has already been expending thought, effort, and investment in many of the areas described above, years before starting first-in-human studies. This is consistent with our mission to discover, develop, and deliver potential curative therapies that target the underlying causes of heart failure. We are motivated by a vision to transform the lives of individuals and families fighting heart disease and will keep the needs of these patients at the forefront as we navigate the challenges ahead and create the treatments that these patients urgently need.

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AFFILIATION

Faraz Ali
Chief Executive Officer, Tenaya Therapeutics

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