CHAPTER 1

Innovation S-Curves in Living Drugs Development and Their Commercialisation

Alain A. Vertès
Sloan Fellow, London Business School, London, United Kingdom

INTRODUCTION

Innovation proceeds in S-curves (Vertès and Dowden, 2015). S-curves can be defined as polynomials with an initial period of slow growth, starting, for example (if measuring innovation over time), when a breakthrough discovery is made until an inflection point around which dramatic improvements are made, thanks to accelerating returns, after which follows a period of diminishing returns in R&D efforts that occurs until an upper asymptote is reached, which signals that the technology maturity is itself reached. Exponential mathematical entities are typically extremely difficult to appreciate intuitively (Kurzweil, 2010); hence, due to this cognition bias, decision-making on exponential phenomena is extremely difficult. In mathematics and physics, the logarithmic scale that linearises exponential phenomena is a very useful tool to circumvent this cognitive limitation. Intuitively understanding the impact of exponential phenomena on R&D advances, certainly best exemplified by Moore's law for semiconductor electronics (Moore, 1965), remains challenging in conditions of decision-making on a new radical innovation, especially when the said radical innovation may require sustained investments of significant sizes under conditions of high uncertainty, a task further complexified by the need for the decision-maker to understand the corresponding opportunity costs of the new investment. Formal frameworks have been proposed to circumvent these cognitive limitations in business decision-making. These frameworks rely on an evaluation flowchart that comprises steps to (1) determine a technical domain of interest, (2) perform competition analyses to identify potential target technologies, (3) define the appropriate metrics for performance, (4) estimate or measure future technical improvement curves, (5) integrate a sensitivity analyses on the time variable and (6) iterate to further refine the assessment (Benson and Magee, 2018). Furthermore, other methods implementing, for example, a correlated geometric random walk with drift have been proposed to predict the pace of technological progress (Farmer and Lafond, 2016).

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S-CURVE PATTERNS IN INDUSTRIAL PRODUCT EMERGENCE

S-curve patterns are well-documented in historic accounts of the emergence of technology platform-to-products companies in virtually all industries, including biotechnology companies. In the arena of monoclonal antibodies, these companies comprise Genentech (South San Francisco, CA, USA) (now a Hoffman–La Roche, Basel, Switzerland, group company), Amgen (Thousand Oaks, CA, USA), Centocor Biotech Inc. (Philadelphia, PA, USA) (now Janssen Biotech Inc.), a Johnson & Johnson (New Brunswick, NJ, USA, group company) or Biogen (Cambridge, MA, USA), to name only a few; the main technology S-curves are progressing from murine antibodies (1980s) to chimeric antibodies (late 1980s), fully human antibodies (2000s), antibody fragments (late 1990s–2000s) and further on to multivalent antibodies, immunotoxins and synthetic antibodies (2010s and beyond) (Vertès and Dowden, 2015). Integrated, these discrete S-curves, or 'innovation chunks', constitute the 3-decade long aggregate innovation S-curve that took place in the field of monoclonal antibodies. The tipping point here was the capacity to 'humanise' the antibodies to overcome antiidiotypic foreign body HAMA (human antimurine antibody) responses. Despite the technology of cell therapeutics still being in its infancy (not discussed here are conventional vaccines), several elemental technology S-curves that will mark the technological revolution of cell-based therapies can already be identified based on technological comparables and bibliometric analyses, literature searches, grant proposals or intellectual property searches. These S-curves include (1) the possibility to therapeutically use a variety of cell types including haematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), pluripotent stem cells and their derivatives, T cells or natural killer (NK) cell and their engineered derivatives (e.g., CAR-T cells or CAR-NK cells), dendritic cells, macrophages, etc; (2) manufacturing; (3) enhancement of biological attributes; (4) combination with conventional drugs; (5) delivery devices and formulation and (6) solid organ transplantation (Vertès and Dowden, 2015). Similarly to the mathematical concept of integrals that assigns a number to infinitesimal quantities by combining them and its inverse, differentiation (Laugwitz, 1997), the CAR-T technology itself can be further differentiated into innovation chunks that are still required to make this platform approach a mature one. These innovation chunks are already apparent in the patent and scientific literature because, as highlighted above, radical innovation science typically progresses in 3-decade long increments. The ultimate goal here is to make the CAR-T cell technology and associated combination therapies sufficiently safe and efficacious for impacting the immunosuppressive tumour microenvironment and resolving solid tumours. From the foundation in 1993 to create a modular structure to leverage the healing potential of the native immune system (Stancovski et al., 1993), the first tipping point in the CAR-T approach was achieved in 1996 by enhancing the engineered T cell killing effect by including a co-stimulating functional group into the basic CAR-T construct (Alvarez-Vallina and Hawkins, 1996). As a result,

from this simple analysis, it comes four upcoming inflection points necessary for the technology to achieve its maturity: (1) enhanced safety on the one hand to prevent fatal cytokine release syndrome responses and debilitating neurotoxicities, (2) enabling the use of allogeneic off-the-shelf CAR-T living drugs, (3) deploying the curative potential of CAR-Ts in solid tumour oncology and (4) enabling precision oncology by taking into account not only intrinsic characteristics of individual patients but also the dynamics of the disease in a single patient.

THE BOTTOM-LINE IMPACT OF THE SUCCESSFUL ADOPTION OF A RADICAL INNOVATION

The deployment of successful radical innovations that bring new designs and paradigm-changing products to the market has dramatic positive impacts on financial indicators. Taking again the example of monoclonal antibodies, F. Hoffmann-La Roche (Roche) took a controlling equity stake in Genentech in 1990, remarkably coinciding with the first peak of maturity of that technology as measured by bibliometric analyses (Vertès, 2010). Interestingly, the links and active collaborations between the Basel Institute for Immunology (1971–2000) and Genentech (1976–2009) created a synergistic environment, where Basel-based Roche was on the one hand perceived as the best owner of the technology platform developed by the then still emerging Genentech, and Roche scientists and management having had the advantage of a deep hands-on exposure to the new technology, thus resulting in Roche being equipped with the required skills and talents (Melchers, 2012). A decade later, the worldwide sales of the blockbuster MabThera (rituximab) exceeded in 2001 the CHF 1 billion mark and the CHF 4 billion mark in 2005. This success significantly contributed to the Roche Group operating profit (excluding exceptional items) that grew by 25.4% in 2005 from 16.3% in 2001, with the Roche oncology pharmaceuticals sales growing 40% in the fiscal year 2005, as compared with 17% for the oncology market as a whole, and total sales growing 25% in that same year (Humer, 2005). What is more is the fact that in 2005 the pharmaceutical sales of Roche exceeded those of Merck & Co. (Kenilworth, NJ, USA) and it is only in 2011 that the pharmaceutical sales of Merck & Co. levelled up again with those of Roche (after the Remicade sales exceeded $2 billion in 2010), whereas in 2001 these were about double as those of Roche (Vertès, 2016a). In 2007, only Roche, Genentech and Amgen derived more than 10% of their pharmaceutical sales from monoclonal antibodies. Remarkably, 7 years later, 40% of all the biotechnological products in clinical development are conducted by, or in association with, large pharmaceutical companies, but the early entrants accessed technology platforms or efficient discovery engines, rather than licences to a discrete number of products (Vertès and Dowden, 2015). In 2008, the market share for monoclonal antibodies was estimated at $33 billion and Roche's share at $15 billion (Melchers, 2012). The market equivalent of Genentech's value at the time of Roche's full acquisition in 2009 was $64 billion (Vertès, 2016b).

BLACK SWAN RISK: THE CONSEQUENCES OF NONADOPTION OF A RADICAL INNOVATION

Radical innovation oftentimes echoes creative destruction, as typically observed when a paradigm-changing design or product reaches the market, exemplified by the digital industry, which led to the demise of silver halide film companies (with the notable exception of Polaroid Corporation (Minnetonka, MN, USA) given the unique attribute of its instant photography technology), or the Internet, which led to the demise of shops selling or renting movies, books or music on a solid support. This phenomenon can be directly ascribed to a dependence on a single technology, thus resulting in a 'black swan' risk, i.e., the risk for an unlikely but highly disruptive event to occur (here, the coming of age of a radical innovation). In the absence of a suitable hedge, for example, another technology platform at steady state or a quick turnaround to adapt to the new business reality, such black swan technology events typically result in a dwindling business and eventually in bankruptcy. Similarly, entire cities, regions or countries have failed economically or have been at high risk of failure when chiefly dependent on a single industry, for example, while lacking diversification and highly dependent on automobile manufacturing, banking or coal mining when these industries underwent devastating business changes, to cite only a few examples.

THE BIG PHARMAS AND RADICAL INNOVATION ADOPTION

In the 1980s, competitive success came mostly from achieving cost or quality advantages over rivals in existing markets. From the 1990s to this date, success originated from building and dominating fundamentally new markets. As discussed by Hamel (Hamel and Prahalad, 1991), "corporate imagination and expeditionary marketing" have been observed to be the keys that unlock such new markets. In the pharmaceutical industry, this is exemplified by the current tendency to develop personalised or precision medicines. Clearly, those options and others in conventional therapeutic modalities offer pharmaceutical companies a spectrum of business growth paths that might be rewarding enough and optically less risky than the adoption of radical innovation such as monoclonal antibodies in the 1990s, or nowadays cell- and gene-based therapies or nucleic acid therapies. Large firms in any industry have a tendency to favour investment in projects that represent incremental deviations from the status quo (Hamel and Prahalad, 1991; Prahalad and Hamel, 1990). In the context of the pharmaceutical business, this translates into large pharmaceutical firms favouring investment in projects with incremental deviations in small molecules or conventional biologics. These traits of corporate culture are reinforced by decades-long time periods between successive cycles of disruptive technology emergence, again, empirically measured in 25–30-year cycles (Vertès, 2016b). Given this tendency to not invest in high risk (but potentially high reward) radical innovation and their lack of cultural

agility against technology disruption risk, a question is why, as an asset class, large pharmaceutical companies do not fail more often?

An element of response lies in the fact that these companies exploit evergreen technology platforms (e.g., small molecules) and operate a number of different franchises, thereby spreading risk. For example, if Roche had not acquired a controlling stake in Genentech in 1990, it undoubtedly had several other strategic options for achieving growth rate goals. As a result, if a pharmaceutical company does not invest early in a radical innovation that will subsequently prove successful, it merely runs the risk of a decreased ranking and the need to reorganise or implement an M&A depending on its cash reserves but will still have some opportunity to jump in the bandwagon in the form of product in-licencing or partnerships, as was the case with the late monoclonal antibody adopters. Furthermore, as the fundamental of the nongeneric pharmaceutical business lies in patented products, i.e., in a temporary exclusivity for selling certain products before commodities can be launched by competitors, these companies have mastered the management of design cycles characterised by four main steps: (1) breakthrough, (2) commercialisation, (3) commercial maturity and (4) commercial obsolescence. This is reflected in the increasing tendency for large pharmaceutical firms to run efficient product life cycle teams and to divest R&D-stage or marketed compounds more than ever before (Gassmann et al., 2016).

Big and midsize pharmaceutical companies, as an asset class, still delay large-scale investments in cell- and gene-based therapies, i.e., until technological and market risks will have been further reduced (Vertès, 2014). This slow rate of adoption, and sometimes U-turns after investing, remains a vexing hurdle, given clinical progress achieved to this date with a variety of stem cell lineages (Vertès, 2014; Lawrence, 2016). Large pharmaceutical firms with their exquisite core competences in incremental innovation and broad sales network offer to the industry key elements of the regenerative medicine ecosystem and thus have the capabilities to accelerate the delivery of regenerative medicine products to the market, thereby helping answer clinical unmet needs faster. Nevertheless, all the major pharmaceutical corporations closely monitor progress in regenerative medicine, and some conduct clinical development programmes in advanced therapeutic medicinal products, as exemplified by GSK to build with the HSC-based Strimvelis new competence factors and infrastructures (Vertès, 2014, 2016c), or Novartis with CD19-CAR-T cells–based tisagenlecleucel-T (Lawrence, 2016; June et al., 2014). Having said that, both companies have implemented strategic changes, with GSK out-licencing its rare disease gene therapy portfolio to the biotechnology company Orchard Therapeutics (London, UK) only 2 years after the approval of Strimvelis (Al Idrus, 2018), and Novartis has disbanded its cell and gene therapy unit only 2 years after its founding (Lawrence, 2016). Furthermore, several regenerative medicine strategic alliance and licencing transactions have already been implemented, although most of these involve midsize firms (Vertès, 2014). The greatest difficulty is perhaps that the regenerative medicine industry, and

particularly for cell-based therapies, is at the time of writing only approaching the point of inflexion of its first-generation product S-curves, as numerous clinical trials will read out in 2020 (i.e., within the next 3 years) (Field, 2015; Ronfard et al., 2017) with optimism fuelled by the approvals in 2017 of two autologous CAR-T cell products in spite of broad applications remaining challenging because of acute lethal toxicities and uncertain long-term impacts: Kymriah (tisagenlecleucel) in August of that year for certain paediatric and young adult patients with a form of acute lymphoblastic leukaemia (ALL), and in October Yescarta (axicabtagene ciloleucel), a cell-based gene therapy to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment (Zheng et al., 2018). An efficient path to promote the broad adoption of regenerative medicine technologies by large pharmaceutical firms is to accelerate the full clinical translation and commercialisation of this first generation of products. In parallel, Alofisel (darvadstrocel) developed for treating complex perianal fistulas in Crohn's disease by Tigenix (Leuven, Belgium, now a Takeda (Osaka, Japan) group company) became in 2018 the first allogeneic MSC therapy to be approved in the European Union; it follows the approval in 2015 of TEMCELL HS Inj (remestemcel-L) for Graft-versus-Host-Disease (GvHD) in Japan received by Mesoblast's (Melbourne, Australia) partner JCR Pharmaceuticals Co. Ltd. (Ashiya, Japan).

POLICIES AND REGULATORY FRAMEWORKS AS ACCELERATORS OF TECHNOLOGY ADOPTION AND DEPLOYMENT

Breaking barriers to accelerate the pace of regenerative medicine is what has been achieved by Japan's 2014 PMDA Act (Azuma and Yamanaka, 2016). This regulatory change provided an accelerated conditional approval path for regenerative medicine products that have been demonstrated in humans to be well tolerated and for which appropriate indications of efficacy have been generated (*Sakigake* designation) (Kondo et al., 2017). It has de facto triggered a translational momentum in Japan, initiated by the approval in 2015 of the allogeneic stem cell product TEMCELL HS Inj and the autologous skeletal myoblast manufacturing kit HeartSheet, with Japanese pharmaceutical firms having been the most active at implementing cell-based therapy partnerships and foreign companies prioritising Japan in their developmental efforts (Vertès, 2014, 2016b; Azuma and Yamanaka, 2016). Similar evolutions are considered elsewhere, for example, in South Korea (Vertès, 2016c). In the United States, the 21st Century Cures Act enacted in December 2016 provides a similar mechanism through a legislation for an expedited approval path for cellular medicines designated as Regenerative Medicine Advanced Therapies (RMATs) (Messmer and Cumming, 2017). Under this legislation, cell-based therapies may be designated as RMATs if they are intended to treat, modify, reverse or cure a serious or life-threatening disease or condition, provided that there is preliminary clinical evidence indicating the potential to address the corresponding unmet medical need. In Europe, the European Medicines

Agency launched also in 2016 the PRIME scheme, which is similar to the US breakthrough therapy programme (Kondo et al., 2017). This voluntary scheme is designed to 'enhance support for the development of medicines that target an unmet medical need'; it is, as quoted from the EMA, 'based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier' (Anonymous, 2016).

PREDICTING TECHNOLOGICAL PROGRESS: CRITICAL INNOVATION CHUNKS OF THE CAR-T S-CURVE

A remarkable hybrid design to consider, at the interface of cell- and gene-based therapies and therapeutic monoclonal antibodies, is the technology of CAR-T cells, which was highlighted earlier in this Chapter. Building on the magic bullet concept of linking a toxin to a functional delivery group to generate a targeted immunotoxin (Strebhardt and Ullrich, 2008), a targeting antibody is linked to a T cell to combine the specificity of the antibody with the T cell function. The first double-chain chimeric antibody receptor (TCRaVH + TCRbVL) was created in 1989 and the first antitumour-specific CAR in 1993, whereas the first in human CAR-T cell trial was performed in the early 2000s, and pilot clinical trials using an improved architecture (comprising single-chain antibody fragment, TCR-derived signalling elements and co-stimulatory domains) showing a complete remission of liquid cancer patients was achieved from 2008 (Eshhar et al., 1996; Gross and Eshhar, 2016; June et al., 2015). Several major roadblocks nevertheless remain, including the observation that approximately 30% of the recipients of the new adoptive therapy are at risk of developing very severe cytokine release syndromes, the intensity of which has been observed to be linked to the tumour burden at the time of treatment (Lee et al., 2014; Teachey et al., 2015). Moreover, there are business model issues when the use of autologous cells results in the new therapy having a large service-based component as opposed to an off-the-shelf product for which economies of scale help keep production costs lower. Complex also are the pricing and reimbursement issues generated by the change of paradigm, from disease-modifying to high-cost curative medicines. While stunning efficacy has already been observed in the form of cases of complete remission of ALL, transformational future innovation chunks in CAR-T cell development include (1) achieving enhanced safety (on/off molecular switches, suicide switches, antidotes), (2) enhanced specificity and selectivity, (3) allogeneic T cells, (4) enhanced efficacy (armoured CARs, combination therapy, e.g., with checkpoint inhibitors), (5) enhanced persistence and relapse prevention, (6) improved manufacturing and expansion processes, (7) increased treatment simplicity and speed, (8) improved logistics, (9) predictive biomarkers, (10) combination therapies through parallel or sequential treatments, (11) enhanced solid tumour penetration and (12) increased impact on the immunosuppressive tumour microenvironment (Fig. 1.1).

The second wave of innovation here needs to progress from the safe treatment of liquid cancers (e.g., ALL) to the treatment of solid cancers. The cancer treatment market is currently worth $77 billion; it is the largest and fastest growing areas for new drug development and should grow to $144 billion by 2023 of which cancer immunotherapy is projected to represent a significant share (Anonymous, 2013, 2015). As a result, the level of adoption of CAR-T cell therapies is unparallelled among cell- or gene-based therapeutic platforms (Brower, 2015), albeit checkpoint inhibitors and immunooncology therapies in the long term could very well achieve complete remissions through combination therapies (Page et al., 2014).

Similarly, innovation chunks can be forecast for other cell-based therapies. For example, HSC transplantation – a procedure first performed 50 years ago and with more than 1 million patients already transplanted – can now be contemplated for the delivery of genetically engineered HSCs as a curative treatment for severe genetic diseases of the

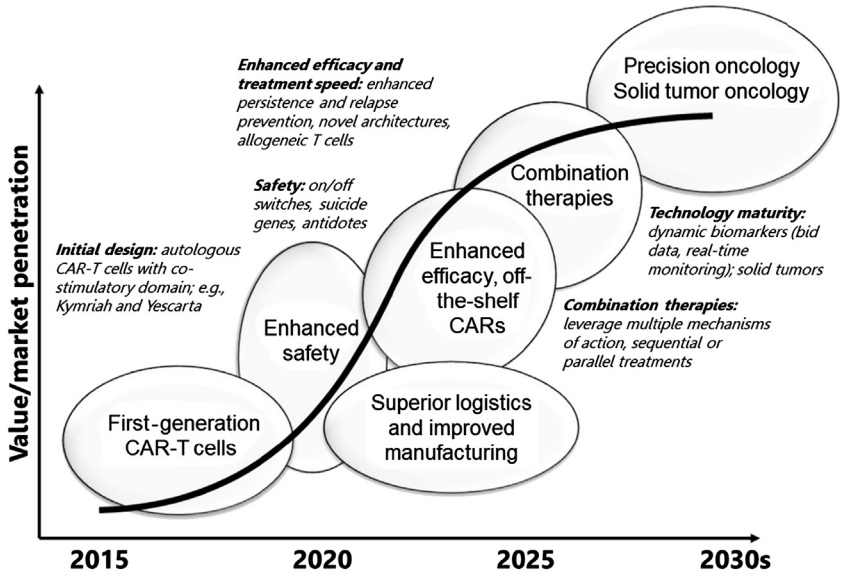

Figure 1.1 ***Innovation chunks in CAR-T cell technology development.*** Four major upcoming inflection points are necessary for the CAR-T cell technology to achieve its maturity: (1) enhanced safety to prevent fatal cytokine release syndrome responses and debilitating neurotoxicities, (2) enabling the use of allogeneic off-the-shelf CAR-T living drugs, (3) deploying the curative potential of CAR-Ts in solid tumour oncology and (4) enabling precision oncology by taking into account not only intrinsic characteristics of individual patients but also the dynamics of the disease in a single patient. Integrated together, the discrete innovation chunks presented here define the innovation S-curve of second-generation living drugs for oncology applications. The apex of the curve is defined by the combination of several therapeutic modalities either in parallel or in sequence, as well as patient population stratification tools to achieve safe and efficacious treatments for solid cancers.

blood such as β-thalassaemia major or sickle cell anaemia, and even AIDS (Vertès, 2015a,b). Moreover, allogeneic MSCs have been proven to be well tolerated in hundreds of independent clinical trials involving thousands of patients, with products already approved in several jurisdictions exemplified by remestemcel-L, as highlighted earlier (Vertès, 2015b). The inflexion point of the aggregate MSC innovation S-curve undoubtedly lies with enhanced efficacy custom-designed to the indication of interest: e.g., (1) using alternative manufacturing methods, (2) licencing of adoptive MSCs or recruitment of endogenous MSCs, (3) altered cell surface ligands to promote homing, novel MSC subtypes, (4) multiple mechanisms of action using genetically engineered MSCs, (5) cell-cell, (6) cell-biologics or (7) cell-small molecule combination therapies and (8) to develop appropriate biomarkers (Vertès and Dowden, 2015;Vertès, 2015b). Regarding pluripotent stem cell–derived products, novel treatments for metabolic diseases (synthetic capsules as insulation device) and for sensory losses, including notably, in ophthalmology (the eye is a naturally insulated and easily accessible organ), are likely to come to age first.

PERSPECTIVES

Putting all these perspectives together, the regenerative medicine industry is currently in a period of transition: the first-generation cell-based therapies as a whole is fast approaching the market, an advance that is signalled by a few advanced therapy medicinal products having already received marketing authorisations. Strong hurdles remain but powerful catalysts are at play to extend market access (Fig. 1.2). Regulatory approvals here will increasingly drive large pharmaceutical companies to adopt the new technology, as the opportunity cost with conventional pharmaceutical modalities will decrease in parallel. Moreover, the next wave, that is, genetically engineered cell-based therapies, including CAR-T cells, is already in the work. Large technology risk nonetheless remains, but the more mature MSC- and HSC-based products are poised to crystallise interest for the adoption of these emerging technologies. Last but not least, recent advances in developmental biology and stem cell biology make now more attractive than ever before the use of chemistry, a core competence of pharmaceutical companies, for drugging endogenous repair mechanisms, for example, leveraging endogenous pericytes or MSCs in the cardiac, inflammation or orthopaedics disease areas, akin in cancer to the blocking of negative immune modulators to unleash the fighting potential of T cells (Caplan and Hariri, 2015; Stephen et al., 2015). The second generation of cell-based products, engineered to confer superior clinical attributes to living drugs, represents the next S-curve in pharmaceutical care; these novel attributes that are notably, enabled by a synergy between different therapeutic modalities provide new hopes for patients afflicted by heretofore intractable diseases, comprising particularly various forms of solid tumour cancers, neurodegeneration and chronic diseases of ageing.

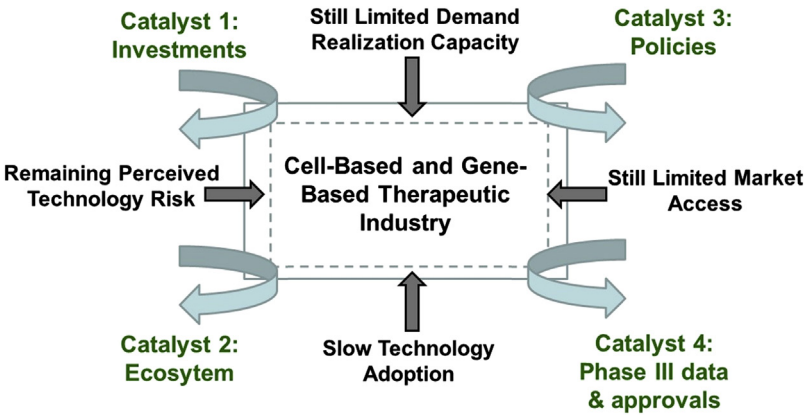

Figure 1.2 ***Hurdles and catalysts of market access in the cell- and gene-based therapy industry.*** The main issues that remain to be fully resolved for the cell- and gene-based therapy arena to reach its technology and commercial maturity include (1) the large-scale adoption by pharmaceutical firms, (2) enhanced demand realisation potential through improved logistics, standardisation worldwide manufacturing capacity and process economics, (3) market access through early dialogues regarding pricing, reimbursement and affordability of the new products that may require the implementation of a new business model to appropriately maintain incentives to invest in curative therapies while maintaining the sustainability of public healthcare and (4) reducing the remaining perceived technology risks. Several catalysts act in synergy to relieve the market from these market-shrinking forces: (1) robust levels of investments, (2) regulatory and policy changes, (3) building of the industry critical mass akin to total factor productivity and economies of learning, (4) metaanalysis of Phase II and Phase III clinical data and approvals in major markets: the United States, EU5 (Germany, France, Italy, United Kingdom, Spain) and Japan.

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