CHAPTER 24

Strategic Alliances in Cytotherapies and Gene Therapies: Funding the New Wave of Cell Therapeutics

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INTRODUCTION

Because cell- and gene-based therapies, also referred to as Advanced Therapeutic Medicinal Products (ATMPs), were first introduced 40 years ago, the promise of these therapies has been the ability to provide curative-like efficacy for patients (Murnaghan, 2018). There have been some years where hype created the promise of disease-modifying and curative therapies that was dashed by negative results of the initial clinical trials. While this promise has been around, the data to support the promise have been lacking, until recently. With the recent successes of cell-based therapies such as CAR-T (Kymriah by Novartis (Anonymous, 2018e) Basel, Switzerland, and Yescarta by Kite/Gilead (Anonymous, 2018b) Foster City, California, approved by FDA in August and October 2017, respectively), cell therapies (Alofisel approved by EMA in March 2018 by TiGenix/Takeda (Anonymous) Osaka, Japan, and approval by PMDA (Pharmaceuticals and Medical Devices Agency) in September 2015 in Japan of Prochymal by Mesoblast (Anonymous, 2015b) Mebourne, Australia) and gene therapies (Luxturna by Spark Therapeutics, Philadelphia, Pennsylvania approved by FDA in December 2017 (Anonymous, 2018d)) in the clinic and their subsequent approvals, there has been a renewed interest in the field by investors and large companies. In this chapter, we compare three different time periods – the 2000s, 2010s and today (2017) – to characterise the difference in type, number of partnerships and transactions that have been completed.

THE 2000s LANDSCAPE

The period of the late 1990s and early 2000s was characterised by several trends. There was the internet bubble, which pumped billions of dollars into near worthless companies, that had some carry over into the biotech industry and to cell and gene therapy. Several gene therapy trials were performed during this time period with very high expectations by investors. However, several patients contracted leukaemia in one clinical

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study due to the vector, while in another study a young patient died as a direct effect of the gene therapy (Raper et al., 2003). The combination of these two events effectively put the gene therapy industry in a decade-long trough (Somia and Verma, 2000) and effectively shuttered gene therapy from an industrial perspective with academic work ongoing to develop safer delivery vectors (Lewis, 2014). While gene therapy was suffering from negative clinical outcomes, cell therapy was riding high on the discovery of embryonic stem cells and other scientific achievements. However, with the popping of the internet bubble, biotech and cell therapy investment also declined driven by unsustainably high valuations of companies and a view from the US Government that genomic data should be freely available (Watson, 2017). This was also driven by the financial failure of several companies, including a company with an approved cell therapy, Advanced Tissue Sciences or ATS. ATS was unable to demonstrate a profit and eventually filed for bankruptcy despite having a marketed product, Transcyte (Pangarkar et al., 2010). The product was then sold to Smith and Nephew, who sold it to Advanced Biohealing in 2006, which was acquired by Shire in 2011. Shire then sold the product to Organogenesis in 2015 which becomes the fifth owner since product approval in 2001. The driver of Shire's exit was a significant shift in reimbursement of the product by Medicare (Anonymous, 2014a). Meanwhile, the few remaining cell therapy companies continued to limp along with low valuations, difficulty raising funds, while effectively being ignored by most investors. This Darwinian environment resulted in the selection of a handful of cell therapy companies that had potentially viable technologies, strong intellectual property, including patents with strong composition-of-matter claims, and highly skilled leadership teams. Companies such as Athersys (Cleveland, Ohio, USA), Mesoblast (Melbourne, Australia), Dendreon (Seattle, Washington, USA) were amongst these survivors.

THE 2010s LANDSCAPE

In 2010, there were several macroeconomics headwinds as the United States had recently experienced a housing bust that resulted in a severe recession essentially worldwide (Rich, 2012). This recession caused housing prices to drop, the stock market to plummet and as a result very limited investment in formation of new companies as well as limited investment in existing companies in the biotech sector. These macroeconomic woes also caused a great dip in investment in new companies from venture capital and limited interest in partnerships from large companies (McKernan et al., 2010). Nonetheless, several large pharmaceutical companies showed some interest in cell therapy during the 2005–10 period, with 25 transactions from large companies targeting cell-based therapies with most of the deal activity occurring with adult stem cell companies, although most of these transactions were very small research collaborations with very little money changing hands (McKernan et al., 2010). The highest profile transactions were Pfizer

(New York, USA)/Athersys, Cephalon (Frazer, Pennsylvania, USA)/Mesoblast, Genzyme (Cambridge, Massachusetts, USA)/Osiris (Columbia, Maryland, USA) and Shire (Dublin, Ireland)/Advanced BioHealing (Westport, Connecticut, USA) (Malik et al., 2015).

Pfizer took a licence to the Athersys product, Multistem, for inflammatory bowel disease in late 2009, and this was held up as a real breakthrough for the cell therapy industry as it was the most significant partnership transacted since the early 2000s in cell therapy (Anonymous, 2009). While the economic terms were relatively modest ($6M upfront + $105M in milestones), the prospect of a large pharmaceutical company sponsoring a large Phase II study in inflammatory bowel disease to test whether MSCs (Mesenchymal Stem Cells) can function as a therapy was an important milestone for the industry. Unfortunately, this trial was not positive when it read out, which followed a long string of failed clinical studies for MSCs during this time period (Athersys as part of Q1, 2015). However, Athersys, which regained full control of its asset, has continued to develop it and is currently in a partnership with Healios KK (Tokyo, Japan) evaluating Multistem in stroke where Phase II data were promising (Athersys, 2016).

Cephalon partnered in late 2010 with Mesoblast, a biotech developing MSC-based therapies in multiple disease areas. Mesoblast had a long history in cell therapy since the 1990s (Anonymous, 2011a). In the partnership, Cephalon had global rights to cardiac, transplantation and neurological indications. However, the partnership was viewed negatively by the investment community given the economic terms, which were viewed as being excessive, with Cephalon paying $130M upfront and purchasing just under a 20% stake in Mesoblast ($220M) for total upfronts of $350M (Anonymous, 2010). Subsequently, Teva Pharmaceutical Industries (Petah Tikva, Israel) acquired Cephalon and, hence, became the holder of these programmes. The clinical studies were underway when Teva pulled the plug on the investment, returned rights to Mesoblast and sold its stake in the company, while writing down $171M of its investment stake and $258M in the product stakes (Goodman, 2018). Mesoblast continues to push ahead with the clinical trials (Globes, 2017).

Genyzme and Osiris entered into an agreement in November 2008, whereby Genzyme gained commercialisation rights to Osiris' MSC product, Prochymal/Chondrogen. The product was in late clinical studies at the time for Graft versus Host Disease (GvHD). The terms of the agreement gave Genzyme global commercialisation rights (except the United States/Canada) in exchange for $130M upfront to Osiris as well as downstream development, regulatory and commercial milestones as much as $1.25B (Anonymous, 2012b). Sanofi subsequently purchased Genzyme in February 2011 and noted in an SEC (Securities And Exchange Commission) filing that they had terminated the Phase III programme in GvHD (Anonymous, 2012a). Osiris subsequently regained rights to the product at no cost to them, despite Genzyme having paid the large upfront. The product subsequently received conditional approval for paediatric GvHD in Canada and New Zealand, while used under an expanded access programme

in the United States. Despite this regulatory success in those two jurisdictions, Osiris struggled to commercialise the product in Canada and ultimately exclusively licenced the product to Mesoblast for $50M upfront as a mix of cash and stock with a potential $50M in milestones. Osiris is now focused on other areas in its pipeline (Carroll, 2013).

The final large transaction of the 2010 decade was the purchase of Advanced Biohealing by Shire in May 2011. Shire paid $750M for Advanced Biohealing to access its product, Dermagraft. Shire also created a Regenerative Medicine Division in parallel with Advanced Biohealing serving as the core of the division with a commitment to spend $100M building out a new research hub in San Diego (Anonymous, 2011b). However, in January 2014, Shire abruptly sold Dermagraft to Organogenesis for nothing upfront (including the manufacturing plant, technology, assets, etc.) and potentially $300M in milestones over a 4-year period. Shire wrote off $650M for the acquisition, halted work on its San Diego campus and closed its Regenerative Medicine Division (Anonymous, 2014b). This rapid turnabout was due to a change in Medicare reimbursement which makes the commercialisation of the product unsustainable for Shire which points out the challenges that can happen even after a product approval is achieved (Bigelow, 2014).

In this section, four large transactions have been highlighted between large companies and cell-based therapeutics companies. All four transactions were terminated, or the acquired assets were sold off within a few years of each of these transactions. The primary driver for the terminations was either insufficiency of the clinical data or commercial failure of the assets. In addition, changing strategies of the large company played a major role in the Osiris and Advanced Biohealing transactions. Nonetheless, while there were a few large transactions during this period, they were dismal failures with nothing to show for over $1B invested by large companies. These failures effectively ended interest by large Pharma in cell-based therapy companies that were founded in the 1990's. However, these transactions and the comfort level with large companies with these non-traditional platforms was a driver in the recent resurgence of regenerative medicine-based therapies.

THE LANDSCAPE IN 2017–2018

While the gene therapy arena was effectively in hibernation for most of the period 2000–10 from a corporate perspective, academic groups continued to pursue optimising the vectors and delivery approaches for viral-based therapies (Hastie and Samulski, 2015). For example, at the University of Pennsylvania, significant work was ongoing to generate safer viruses for delivery into patients (Wirth et al., 2013). These efforts paid off with the founding of multiple companies including Spark Therapeutics (Philadelphia, Pennsylvania, USA), Dimension Therapeutics (Cambridge, Massachusetts, USA) in 2013, while earlier efforts resulted in the founding of companies such as REGENXBIO (Rockville,

Maryland, USA) in 2008 (Yahoo, 2018). Many other gene therapy companies have been founded as well during the last few years capitalizing on the expanding science in this space. In addition to the greatly improved situation for gene therapy companies, there has been a significant interest in immunotherapies which are focused on using the body's immune system to destroy tumour cells. One of the early scientific papers which cemented this approach as a viable therapy demonstrated that two-third of the patients who had received the experimental treatment experienced a complete remission of their Acute Leukocytic Leukaemia which was a real breakthrough for this disease (Kalos et al., 2011). This CAR-T (chimeric antigen receptor T cells) approach really jumpstarted this type of cell therapy and precipitated the partnership between the University of Pennsylvania and Novartis to develop paradigm-changing approaches to treat liquid cancers. Other companies founded in this same time period comprise Bluebird (Cambridge, Massachusetts, USA), Cellectis (Paris, France), Kite Pharma (Los Angeles, California, USA) and Bellicum (Houston, Texas, USA) amongst others (Brower, 2015). These four biotechs all had successful IPOs (Initial Public Offering) in 2014–15. In addition to the Novartis deal, there were several other transactions completed in this time period for CAR-T cells. The major transactions are depicted in Table 24.1.

Beyond CAR-T, there was also significant activity in financing related to advanced therapies in the 2015–17 period. According to the Alliance for Regenerative Medicine, there has been over $2.5B raised in IPOs over the last 3 years with follow-ons adding another $7B in funding to these companies. In addition, another $4B in upfront payments via corporate partnerships was announced, as well as $4B in venture funding

Table 24.1 Deal Terms For CAR Therapies.

Licensee	Date	Licencor	Notes
University of Pennsylvania	2012	Novartis	Undisclosed terms but first deal in this space building off clinical data on small number of CLL (Chronic Lymphocytic Leukemia) patients
Bluebird bio	2013	Celgene	Unspecified upfront payment plus up to $225 million per product
Cellectis	2014	Pfizer	Allogeneic approach to CAR-T which promised low COGs (Cost of Goods) $80 million upfront plus up to $185 million per product and royalties
Kite Pharma	2015	Amgen	$60 million upfront and up to $525 million per product in milestone payments, plus royalties
MD Anderson	2015	Ziopharm, Intrexon	$100 million

Adapted from https://www.the-scientist.com/?articles.view/articleNo/42462/title/The-CAR-T-Cell-Race/.

(Alliance for Regenerative Medicine Quarterly, 2017). In aggregate, this is a total of $17.5B in funding into these advanced therapy companies with the bulk of the funds being invested to cell- and gene-based therapeutics companies. This funding is beginning to pay off with nearly 1000 clinical trials underway by companies in this sector that have led to several recent approvals including Strimvelis by GSK in the European Union (EU) on 27 May 2016 (Anonymous, 2016), Kymriah by Novartis in the United States on 30 August 2017 (Anonymous, 2017c) (Basel, Switzerland), Yescarta by Gilead/Kite in the United States on October 2017 (Anonymous, 2017h), Luxturna by Spark Therapeutics in the United States on 19 December 2017 (Anonymous, 2017d) and Alofisel by TiGenix/Takeda in the EU on 23 March 2018 (Anonymous, 2018a). The recent approvals of Spark Therapeutics treatment for blindness and two approvals in the CAR-T space have further excited investors about the opportunity in advanced therapies.

In addition to the above activity, there have been several acquisitions in the space that are driven by investor excitement in these new therapies during the 2-year period 2017–18. Two of the largest transactions in the ATMP arena to this date are the purchase by Celgene (Summit, New Jersey, USA) of Juno Therapeutics (Seattle, Washington, USA) in January 2018 for $9B for access to their late stage CAR-T therapies and the acquisition by Gilead acquisition of Kite Therapeutics for $12B for access to their approved CAR-T therapy (axicabtagene ciloleucel or Yescarta, a treatment for non-Hodgkin lymphoma that was approved in October, 2017) and a large pipeline of related therapeutics (Ramsey, 2018; Baum, 2017). Gilead has not stopped there, with a $567M acquisition of Cell Design Labs (Emeryville, California, USA) in December 2017 (Vinluan, 2017). Beyond these acquisitions over the last year, there have been some smaller, nonetheless, noteworthy acquisitions, including CSL's (King of Prussia, Pennsylvania, USA) acquisition of Calimmune (Sydney, Australia) (Anonymous, 2017b), Takeda's (Osaka, Japan) acquisition of TiGenix (Brussels, Belgium) (Anonymous, 2018c), Gamma Delta Therapeutics (London, England) by Takeda and Cell Medica (London, UK) purchase of Catapult Therapy TCR subsidiary (London, UK) from the UK Cell and Gene Therapy Catapult (Anonymous, 2017f).

Further driving the industry is the activity in the CDMO/CMO (Contract Development Manufacturing Organisation) industry as these companies position themselves to further drive the demand of these therapies to the clinic and to the market. It is clear that manufacturing is rapidly becoming a bottleneck in the industry, however, the CDMO/CMO industry is rapidly catching up (Brooks, 2017). As small companies have specialised and grown focused on cell and gene therapy manufacturing, larger CMOs have either built their own expertise or acquired the smaller players. Recent acquisitions by CMOs for increased biologics capabilities include the purchase by Catalent (Somerset Township, New Jersey, USA) of Cook Pharmica (Bloomington, Indiana, USA) ($950M), that by the Chinese pharmaceutical company 3SBio (Shenyang, China) of Therapure (Mississauga, Ontario, Canada) ($290M), What's more, the Carlyle group (Washington

DC, USA, private equity player rather than an industry player) purchased Albany Molecular Research (Holywell, UK) ($922M) and ThermoFisher Scientific's (Waltham, Massachusetts, USA) acquisition of Pantheon (Minneapolis, Minnesota, USA) ($7.2B). While these acquisitions were focused in the biologics realm, there have also been acquisitions in the cell and gene therapy CMO space. Lonza (Basel, Switzerland) acquired PharmaCell (Maastricht, Netherlands) in Europe for their speciality expertise in cell and gene therapy manufacturing (Lonza). Two other acquisitions of note include Hitachi Chemical's (Tokyo, Japan) acquisition of PCT (Anonymous, 2017g) (Allendale, New Jersey, USA) and KBI's (Durham, North Carolina, USA) purchase of Opexa's (Houston, Texas, USA) assets (Anonymous, 2017e). Hitachi was interested in the expertise that PCT had developed in cell therapy manufacturing. Meanwhile, KBI's purchase of Opexa's manufacturing assets enabled KBI to move into the cell- and gene-manufacturing space. Fuji Film (Tokyo, Japan) has also made inroads into the area with its purchase of Cell Dynamics Inc. in 2015 (CDI – Madison, Wisconsin, USA) (Anonymous, 2015a).

Finally, one of the other large companies providing a suite of contract research services (including manufacturing) which has moved rapidly into the cell and gene space is General Electric (GE – Boston, Massachusetts). GE has made multiple investments into the cell and gene industry as it builds up its capabilities and scale in this area and appears to be headed toward offering an integrated approach to cell therapy process development and manufacturing (Anonymous, 2017a). GE has purchased companies such as Asymptote (Cambridge, UK – cryopreservation technology), Biosafe Group (Geneva, Switzerland – integrated cell-processing systems), partnered with the Government of Canada to launch a bioproduction facility in Toronto (partnered with Centre for Commercialization of Regenerative Medicine – CCRM) and colaunched a new company with the Mayo Clinic (Rochester, Minnesota, USA) called Vitruvian Networks (San Francisco, California, USA) that provides software systems and services for cell and gene manufacturing. Wuxi (Shanghai, China) has been active in this space for years after its purchase of Apptec (Minneapolis, Minnesota, USA) in 2008 (Anonymous, 2008). As one can see, the last few years have been vastly different in the number of transactions and interest in cell therapy relative to the prior two-time periods examined.

IS THIS THE 'REAL' DEAL?

With all this recent activity and investment in cell therapies, one must ask if this industry is finally maturing to the point where it is in a position to spawn marketed products that are changing patients' lives and driving profitable therapies. The answer is a resounding yes. With the recent approvals since 2017 of new therapies combined with the strong product pipeline of cell- and gene-therapy companies, it appears that the industry is headed towards a multiyear period of success for cell and gene therapies as new products

are launched that provide lifesaving medications to patients. The ability demonstrated by several biotech's to deliver major product approvals in multiple indications is a clear sign of success for the industry.

PERSPECTIVES

Since cell- and gene-based therapies were first introduced 40 years ago, there has always been a promise that life-changing and commercially successful products would launch to revolutionise patient treatment. While this promise has always been tantalisingly close to those in the industry, this promise is becoming a reality. Much like monoclonal antibodies 25 years ago, cell and gene therapies are just coming of age. In another 20 years, they may well be a third modality that generates many billions of dollars in revenue a year, while, more importantly, changing patient lives.

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