Cell Stem Cell
Forum

Evolving Industry Partnerships and Investments in Cell and Gene Therapies

Devyn M. Smith,[1,*] Emily J. Culme-Seymour,[2] and Chris Mason[3,4]
[1]Sigilon Therapeutics, 100 Binney Street, Suite 600, Cambridge, MA 02142, USA
[2]Gene Therapy, Rare Diseases Unit, R&D, GSK, 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
[3]Advanced Centre for Biochemical Engineering, University College London, Bernard Katz building, London, WC1E 6BT, UK
[4]AVROBIO, One Kendall Square, Bldg 300, #201, Cambridge, MA 02139, USA
*Correspondence: devyn@sigilon.com
https://doi.org/10.1016/j.stem.2018.03.004

Cell and gene therapies hold the promise of providing significant and durable health gains to patients in many disease states and have recently elicited significant investor and partner interest. We cover the current state of industry partnerships and investments, highlight what makes a partnership advantageous, and discuss implications for stem cell therapies.

Cell and gene therapies hold the promise of bringing significant clinical benefits to patients by directly targeting the underlying cause of disease. Gene therapy drew large investor interest in the 1990s, but this vanished following an unexpected patient death and the occurrence of leukemia within clinical studies in the late 1990s and early 2000s (Rubanyi, 2001). Cell therapy also generated significant investor interest in the 1990s, but this likewise evaporated after a string of clinical and commercial failures (such as those that happened with the companies Organogenesis and Advanced Tissue Sciences; Pangarkar et al., 2010). Without substantial investment, academic laboratories nonetheless continued to advance their research and first-in-human clinical studies. As a result, significant progress was made on the underlying science required to develop a next generation approach to numerous indications. Large biopharmaceutical companies' interest in this field began to increase in the late 2000s as proof-of-concept clinical data began to emerge (McKernan et al., 2010). This initial interest was generally focused on cell-based therapies, primarily mesenchymal stem cells (MSCs), but has rapidly expanded in the last 5 or 6 years. Today, we see a reemergence of gene therapy and the evolution of new treatments, such as chimeric antigen receptor (CAR)-T cell therapies, which have been fueled by billions of dollars of private and public capital being invested in new companies. This Forum discusses the current state of partnering and investment across the fields of cell and gene therapy. In addition, we highlight advantages of the different types of partnerships with a view toward the future.

Overview of Large Company Investments

There has been an increase in the number of investments that large biopharmaceutical companies have made between 2010 and 2016 in advanced therapies (note: 50 transactions were evaluated in this analysis and tool- and technology-related investments are excluded; see Table S1). Nearly every major biopharma company has made investments, generally through partnerships with three types of external parties: (1) early-stage, pre-IPO companies (e.g., Transposagen and Precision Biosciences); (2) publicly listed advanced therapy asset and technology companies (e.g., Spark Therapeutics and Juno Therapeutics); and (3) academic institutes that can receive direct funding (e.g., University of Pennsylvania and University of Texas). These large company investments have included outright acquisition, traditional licenses that include the components listed above, and research agreements. In addition, the majority of these transactions were completed in 2014–2016 (Figure 1A).

Traditional partnerships can include four major components: an upfront amount of cash, payments for milestones (e.g., an IND filing or BLA approval), royalties (percentage of sales), and payments for sales milestones. "Biobucks" is a term used for the aggregate potential monetary amount of the partnership to the biotech if all milestones and royalties are successfully achieved.

There have been some interesting trends in the indication, modality, and mix of companies that have been involved in deals over this period. Specifically, there has been a clear focus on oncology and rare disease indications, as well as a marked shift away from MSC-like therapies to other modalities such as CAR-T cells, gene therapy, and gene editing. Undoubtedly, there has been much more deal-making activity direct from global biopharma in advanced therapies than seen previously (Figure 1). Each of these trends will be explored further here.

Trends in Transaction Type

A review of the transactions evaluated in this analysis has highlighted the shift to a more collaborative model instead of the traditional approach to build internally and/or acquire (Figure 1A). The benefits of maintaining a collaborative partnering approach are significant, including a capital sparing approach that leverages the links to the founding scientists and their institutions to help the biopharma learn how to optimize the development, manufacture, and clinical/regulatory aspects of the partnered assets. There have been several direct partnerships and collaborations with translationally focused academic centers (accounting for 12% of the evaluated transactions), which have proven to be a key innovation source for growing existing pipelines. This has created excitement within academic circles, where such transactions bring significant funding and enable translational expertise to develop. Since these transactions can in some instances create

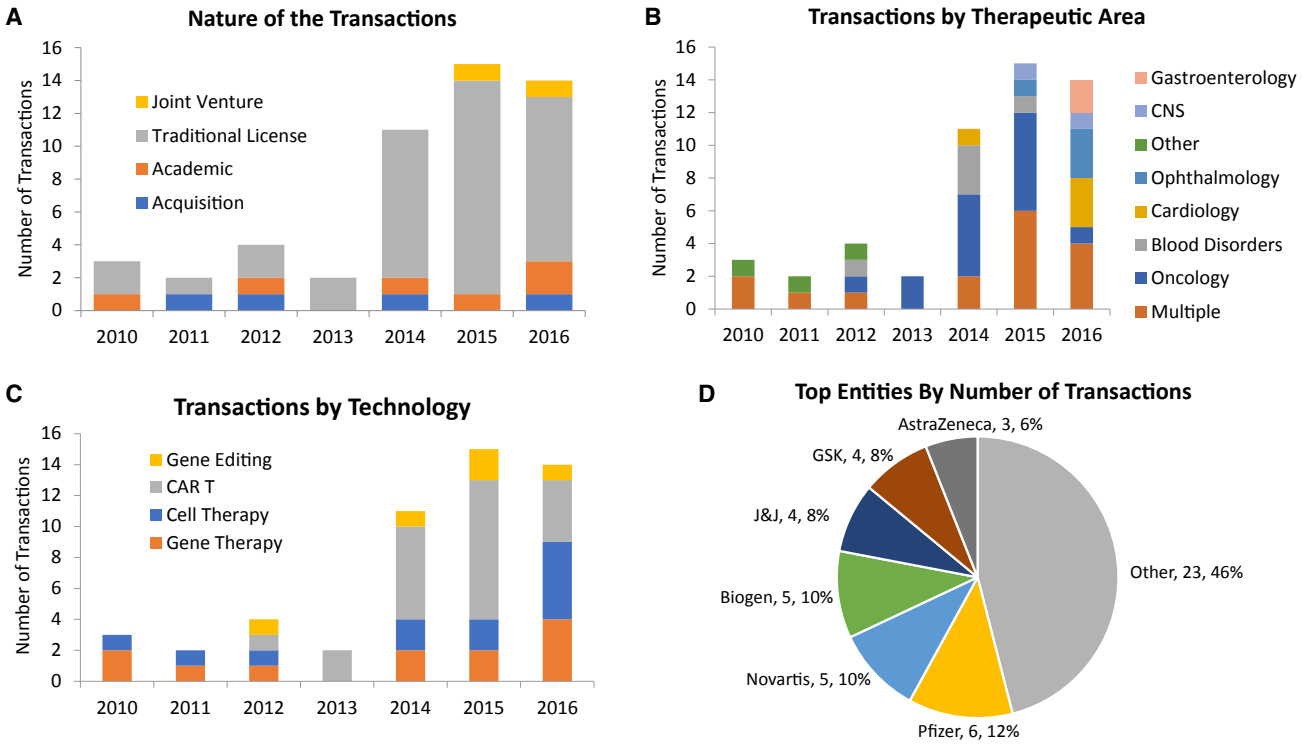

Figure 1. The Majority of the Public Transactions/Investments Made by Large Pharma Companies for Therapeutics in the Cell and Gene Therapy Space between 2010 and 2016

(A) Summary of the different transaction types, determined by the nature of the deal.
(B) Summary of the transactions by year by therapeutic area, determined by evaluating the targeted indications and placing them into relevant therapeutic areas.
(C) Summary of the transactions by year by technology type.
(D) Top entities that have performed the most transactions over the period.

conflicts of interest for institutions and investigators, these types of partnerships can on occasion result in decreasing openness and general unwillingness for the academic center to consider new collaborations. This is negated, however, when successful partnerships result in new medicine creation and development, which can demonstrate the value of the deal to both parties, and thus allow expansion in scope of the original partnership itself.

Trends in Indication Focus

As mentioned above, there has been a clear preference for partnering with biotech companies in the oncology (e.g., leukemia and other hematological malignancies) and rare disease (e.g., hemophilia and lysosomal storage diseases) spaces, which has been driven by the positive clinical data generated in these areas (Figure 1B). The bulk of the recent oncology-focused collaborations revolve around biopharma companies accessing core science and technology based on harnessing the patient's own immune system via gene modification to redirect it to destroy the patient's tumor cells. There has been huge success in numerous clinical studies deploying this approach, with autologous immune system redirection via modifications with genes encoding for efficacious T cell receptors (e.g., GSK and Adaptimmune in 2014) and CAR molecules (e.g., Novartis and the University of Pennsylvania in 2012 and Baxalta/Shire and Precision Medicine in 2016). These T cell therapy platforms have demonstrated dramatic clinical improvements in previously untreatable pediatric and adult hematological malignancies, albeit with some safety aspects remaining to be addressed (Rapoport et al., 2015; Gill and June, 2015).

One of the earliest partnerships in oncology was between Novartis and the University of Pennsylvania in 2012, with the parties forging a research and licensing agreement to work together to commercialize CD19 immunotherapies for oncology indications. The $20M upfront payment for this collaborative deal was unprecedented within the cell and gene therapy community at the time. This partnership has been successful given the approval of the first FDA-approved CAR-T cell therapy, Kymriah, in 2017 (as outlined in Fortune). One interesting challenge for the oncology space regarding the T cell-based therapies is the limited success in solid tumor indications to date, though significant efforts have been underway for a while to find new robust targets for CAR-T cells to efficaciously treat such indications (Guo et al., 2016).

There are many gene therapy deals that cover multiple therapeutic areas with a dominance in rare (orphan) diseases (Figure 1C). The strategy in rare diseases is predominantly focused on Mendelian-based orphan diseases, where a mutation in a single gene will give rise to the disease. Bayer and Dimension Therapeutics announced a collaboration in 2014 to develop and commercialize a gene therapy for the treatment of hemophilia A,

based on Dimension's adeno-associated virus (AAV)-based gene therapy platform. Pfizer and Spark Therapeutics also announced a collaboration in 2014 focused on developing AAV-based gene therapy for hemophilia B, which has recently shown highly promising clinical trial data (via Spark Therapeutics), and in 2017, Spark themselves received approval of the first FDA-approved gene therapy, Luxturna, an AAV-based gene therapy for a rare form of inherited vision loss. Another key collaboration in this field was the strategic alliance between GSK and the Telethon Institute for Gene Therapy (TIGET) to develop gene therapy treatments for rare genetic disorders, with the first asset from this partnership, an *ex vivo* gene therapy indicated for ADA-SCID, receiving marketing approval from the European Medicines Agency in 2016, under the brand name Strimvelis (Touchot and Flume, 2017). Finally, a recent deal between the University of Pennsylvania and Biogen (as outlined by Xconomy Boston), with notable financial terms involving an upfront payment of $20M and up to $2B in biobucks, highlights the amounts that companies are willing to spend to access potential step-change therapies.

Trends in Modality Focus

There has been a clear shift from first-generation cell therapies (e.g., MSC-like cells and pluripotent cells) to next generation approaches such as gene therapy, CAR-T cells, and gene editing (see Figure 1D). In the 2014–2016 period, there was significant activity in CAR-T cells, followed by gene therapy, with cell therapy having a surge in deals in 2016. This surge in deals over this 3 year period has likely been driven by the spate of positive clinical data from gene therapy and CAR-T clinical studies.

Gene editing is widely acknowledged to have the potential to radically change the safety proposition regarding gene insertion into patient cells, both *ex vivo* and *in vivo*, as well as the possibility to ameliorate a disease entirely, though undoubtedly there remain many unknowns yet to be clarified (Haas et al., 2017). Nonetheless, and despite the lack of clinical data available, many biopharmaceutical companies have solidified deals related to this technology. Bayer and CRISPR Therapeutics announced a collaboration in December 2015 with a joint venture named Casebia Therapeutics focused on a gene editing platform using the CRISPR/Cas9 system. The Cellectis collaborations initiated between Pfizer and Servier in 2014 have focused on developing allogeneic T cell therapies for various oncology targets using another gene editing platform, the TALEN system, with the goal of engineering T cells deficient in expression of their T cell receptors (Poirot et al., 2015). In terms of progress into the clinic, the phase I trial of the Cellectis product is already underway in the UK for B cell acute lymphoblastic leukemia. For the CRISPR/Cas9 system, it is likely that 2018 will see the initiation of the first USA clinical trial involving CRISPR-mediated gene editing for cancer, with another study already underway in China that treated the first patient in November 2016 (Cyranoski, 2016).

Trends in Company Mix

Many of the deals evaluated here were initially made with early-stage pre-IPO companies who have since become publicly traded (e.g., Spark, Juno, and Intellia). What is unique in this space is the number of deals that have been signed, despite the asset not yet being clinic-ready. This is quite unusual given that large biopharma companies often prefer asset deals that already have accompanying clinical data. In terms of geography of the non-pharma partner, most of the companies or groups have been USA based, though Europe is also strongly represented (e.g., TIGET, uniQure, and Oxford BioMedica).

The Ideal Partnership Model

There are important considerations when searching for a potential partner. For example, a small company will be looking for a partner to provide the essential capital required to fund the development of their therapy, as well as a partner who can bring development and commercial expertise to the table. Meanwhile, a larger company is looking for an asset within a current strategy/business focus, as well as scientific expertise in that modality/asset, and new talent that can bolster existing skillsets. Given these requirements, what are important considerations for a small company searching for a biopharma partner? These areas would include: talented scientists and management, complementary indications both clinically and commercially, and a sound manufacturing strategy.

A strong, experienced management team combined with skilled scientists is important for a small company to not only successfully close a deal, but also execute on the deal as well. Companies that focus on diseases with identified targets and known mechanisms of action, combined with a readily identifiable patient group and clear clinical endpoints in the specific indication, have proven to be highly sought after. This has fueled the interest in the rare disease space, where monogenic conditions are attractive indications for gene therapy development. A robust manufacturing strategy is another positive in terms of a deal, particularly since these new therapies require a dramatic change in thinking about manufacturing and supply, due to often onerous and complex process development steps, and unique challenges with regards to logistics and final administration. In addition, companies must drive down the cost of goods of their medicines to ensure profitability of the final product. This requires significant resources and an existing understanding of supply and logistics, something that a biopharma company can arguably bring to the table.

New opportunities will continue to be assessed by biopharma in the standard way: a combination of top quality science, a skilled team capitalizing on that science, and an overall fit in terms of strategy and capability with the existing portfolio. Long-term financial viability of the medicines arising from the opportunity are also one of the key drivers, and the multi-million-dollar deals in recent years certainly suggest that the bulk of the large biopharma companies believe that cell and gene therapies will provide real value to patients.

Implications for Stem Cell-Based Therapeutics

While the focus on *ex vivo* and *in vivo* gene and gene-modified cell therapies develops further, this impacts upon the stem cell therapy sector, at least in terms of those looking at stem cells as therapies. Following rapid developments in the isolation, culture, and differentiation of various stem cell types in the 1990s and 2000s, their potential as a viable, scalable source of therapies seemed

suitable for numerous indications, and large amounts of money were subsequently fed into the sector by public funding and private investment. This promise was by no means ignored by big pharma, many of whom set up key partnerships with small and medium-sized enterprises (SMEs) and early-stage developers, as well as those growing large in-house research and development offerings (e.g., Pfizer/Athersys). However, as some of the key trials designed to show efficacy did not reach their efficacy endpoints, the concern emerged that stem cell therapies may not materialize into the numerous transformational medicines promised. Next to efficacy, duration of effect and the ability to be disease-modifying beyond a temporary response remains to be seen in the ongoing clinical trials. This by no means has deterred new stem cell therapy-focused companies from commencing important programs that, if successful, would have tremendous impacts in many diseases. In addition, the regulatory environment across the world has shifted to view cell and gene therapies more favorably as demonstrated by the USA (21st Century Cures Act) and Japan (Pharmaceuticals and Medical Devices Agency, Japan). Separate from regulatory changes, there is significant need for new reimbursement approaches to cell therapies. There are many models being discussed and time will tell what models become viable.

A Look to the Future

From 2010 to 2016, substantial amounts of money have been invested in cell and gene therapy, from both the deals being completed and significant investment by the public and private sectors (as outlined by Business Insider). This investment has in turn enabled a growth in the number of clinical trials initiated (as outlined by Cell Trials), which should lead to new approved therapies. In fact, there are several potential new therapies involving CAR-T cells and gene therapy that are fast approaching submission for FDA approval, with Novartis' and Kite Pharma's CAR-T products and Spark's AAV gene therapy product already having been approved by the FDA in the last few months. New investment into the field as a whole has resulted in the formation of companies focused on delivering the next generation of therapeutics, with a focus on areas including new delivery routes and approaches to managing the host's immune system (e.g., Universal Cells and Sigilon Therapeutics), the engineering of other cell populations such as tumor- and marrow-infiltrating lymphocytes, and the growth of next generation gene therapy approaches (e.g., novel vector designs and non-viral technologies) and innovative bone marrow transplant approaches to regenerative therapy (e.g., Magenta Therapeutics). It is an exciting time for cell and gene therapy—a field whose time has finally come.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Table S1 and can be found with this article online at https://doi.org/10.1016/j.stem.2018.03.004.

DECLARATION OF INTERESTS

Devyn Smith is a shareholder of Sigilon Therapeutics and Emily Culme-Seymour is a shareholder of GlaxoSmithKline plc. Chris Mason is co-founder, Chief Scientific Officer, and shareholder of AVROBIO, Inc.; co-founder and shareholder of ORIbiotech Ltd.; and a member of the Cell & Gene Therapy Scientific Advisory Board, GlaxoSmithKline plc.

WEB RESOURCES

Business Insider, http://www.businessinsider.com/venture-capital-interest-in-regenerative-medicine-2017-4

Cellectis, http://www.cellectis.com/en/press/cellectis-announces-first-patient-treated-in-phase-1-trial-of-ucart19-in-pediatric-acute-b-lymphoblastic-leukemia-b-all

Cell Trials, http://celltrials.info/2017/05/06/analysis-publications-clinical-trial-results-regenerative-medicine/

Fortune, http://fortune.com/2017/08/30/fda-novartis-car-t-kymriah/

Magenta, https://www.magentatx.com/press-releases/magenta-therapeutics-advances-stem-cell-transplantation-strategy-with-50-million-series-b-financing-licensing-of-clinical-stage-stem-cell-expansion-program-and-strategic-partnership-with-be-the-matc/

Pharmaceuticals and Medical Devices Agency, Japan, https://www.pmda.go.jp/files/000211336.pdf

Spark Therapeutics, http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-presents-updated-interim-hemophilia-b-data

Xconomy Boston, https://www.xconomy.com/boston/2016/05/16/biogen-turns-to-upenn-gene-therapy-pioneers-in-wide-ranging-alliance/

REFERENCES

Cyranoski, D. (2016). CRISPR gene-editing tested in a person for the first time. Nature *539*, 479.

Gill, S., and June, C.H. (2015). Going viral: chimeric antigen receptor T-cell therapy for hematological malignancies. Immunol. Rev. *263*, 68–89.

Guo, Y., Wang, Y., and Han, W. (2016). Chimeric Antigen Receptor-Modified T Cells for Solid Tumors: Challenges and Prospects. J. Immunol. Res. *2016*, 3850839.

Haas, S.A., Dettmer, V., and Cathomen, T. (2017). Therapeutic genome editing with engineered nucleases. Hamostaseologie *37*, 45–52.

McKernan, R., McNeish, J., and Smith, D. (2010). Pharma's developing interest in stem cells. Cell Stem Cell *6*, 517–520.

Pangarkar, N., Pharoah, M., Nigam, A., Hutmacher, D.W., and Champ, S. (2010). Advanced Tissue Sciences Inc.: learning from the past, a case study for regenerative medicine. Regen. Med. *5*, 823–835.

Poirot, L., Philip, B., Schiffer-Mannioui, C., Le Clerre, D., Chion-Sotinel, I., Derniame, S., Potrel, P., Bas, C., Lemaire, L., Galetto, R., et al. (2015). Multiplex Genome-Edited T-cell Manufacturing Platform for "Off-the-Shelf" Adoptive T-cell Immunotherapies. Cancer Res. *75*, 3853–3864.

Rapoport, A.P., Stadtmauer, E.A., Binder-Scholl, G.K., Goloubeva, O., Vogl, D.T., Lacey, S.F., Badros, A.Z., Garfall, A., Weiss, B., Finklestein, J., et al. (2015). NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat. Med. *21*, 914–921.

Rubanyi, G.M. (2001). The future of human gene therapy. Mol. Aspects Med. *22*, 113–142.

Touchot, N., and Flume, M. (2017). Early Insights from Commercialization of Gene Therapies in Europe. Genes (Basel) *8*, E78.