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Global strategic partnerships in regenerative medicine

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The approach to research and development in biomedical science is changing. Increasingly, academia and industry seek to collaborate, and share resources and expertise, by establishing partnerships. Here, we explore the co-development partnership landscape in the field of regenerative medicine, focusing on agreements involving one or more private entities. A majority of the largest biopharmaceutical companies have announced strategic partnerships with a specific regenerative medicine focus, signifying the growth and widening appeal of this emerging sector.

Regenerative medicine: a unique challenge and opportunity

Regenerative medicine offers novel opportunities to address unmet medical needs, and incorporates a range of scientific disciplines. While acknowledging the potential of endogenous repair and tissue engineering, we restricted our analysis to approaches that seek to replace or regenerate human cells or tissues, as well as cell-based approaches for drug screening and toxicology applications. This focus was identified due to the novelty and unique challenges of living cellular products. Several cellular therapies have achieved market approval, with many more entering clinical trials, marking the emergence of a sustainable industry [1,2].

Despite significant scientific advances and high expectations of therapeutic potential, numerous barriers persist, many of which are unique to this novel class of therapies. Cell therapy faces issues of scale and automation in biomanufacturing, challenges in securing intellectual property (IP) protection, and a range of regulatory and reimbursement uncertainties. Additionally, investment has been limited due to the early developmental stage of the field, perceived risks, as well as scientific, clinical, regulatory, and market uncertainties [3,4]. Drug discovery and toxicology applications have been more widely investigated and, in some cases, adopted, but still face challenges of scale and standardization, as well as uncertainty regarding correlation with clinical relevance. Research and development (R&D) has predominantly occurred in an academic setting, where clinician-led efforts, mostly under the auspice of the 'art of medicine', have resulted in numerous clinical trials. However, in comparison to company-sponsored trials, translation of academic efforts has been primarily limited to autologous 'procedural' approaches [5]. By contrast, the small number of cell therapies that have achieved market approval have all occurred via company-led routes [1].

The limited experience of the major pharmaceutical companies with therapeutic regenerative medicine approaches, combined with the industry-wide trend of decreasing in-house R&D, has fostered the growth of creative innovation models; public–private, private–private and multi-institutional partnerships have all been established [6–9]. Such collaborative approaches may be even more integral for innovative break-through technologies, such as in the field of regenerative medicine [7]. Here, we focus on co-development partnerships that include one or more private organizations.

The landscape of co-development partnerships in regenerative medicine

An opinion frequently held is that the commercialization expertise and financial resources of the pharmaceutical industry will be required for the regenerative medicine field to mature effectively as a major therapeutic class. Over the past decade, the pharmaceutical industry has aligned itself with academic groups as well as with small and medium-sized enterprises (SMEs) to co-develop potential therapies (Table 1). In comparison to therapeutic classes, such as monoclonal antibodies, partnership activity remains

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Table 1. Co-development partnership agreements in regenerative medicine involving the top 22 pharmaceutical companies (ranked by 2012 revenue), (2004–2014)

No.	Company	Partnership
1	Johnson & Johnson (New Brunswick, NJ)	2005: invests in Tengion (Winston-Salem, NC) during Series A financing that resulted in US$39 million (Tengion, 2005)
		2012: partners with HSCI and Evotec (Hamburg) as part of the 'BetaCure' program to develop small molecule therapy for endogenous beta-cell generation for type 1 diabetes (HSCI, 2012)
		2014: partners with Capricor (Beverly Hills, CA), a deal that included a US$12.5 million initial payment for the development of allogeneic cardiac-derived cells for myocardial infarction (Capricor-Therapeutics, 2014)
NY	Pfizer (New York City, NY)	2009: Pfizer and UCL form collaboration to advance stem-cell based therapies for age-related macular degeneration (UCL, 2009)
		2009: forms an alliance with Athersys (Cleveland, OH) to co-develop MultiStem(R) (Pfizer, 2009)
		2012: Pfizer among other pharma companies invest a total of US$72.7 million for the creation of StemBANCC (Pfizer, 2012)
		2012: Pfizer Canada invests CA$500,000 in Centre for Commercialization of Regenerative Medicine (CCRM) to establish Pfizer-CCRM Innovation Fund that would accelerate regenerative medicine technologies for drug screening and therapeutic applications (CCRM, 2012)
3	Novartis (Basel)	2009: collaborates with HSCI on multi-year project to understand group of neuromuscular disorders (HSCI, 2009)
		2012: forms partnership with the University of Pennsylvania, including a US$20 million investment, to develop CAR-T cells for the treatment of leukemia (UPenn, 2012)
		2013: partners with Regenerex LLC (Louiseville, KT) to co-develop their Facilitating Cell Therapy Platform (FCRx) to promote immune tolerance (Novartis, 2013)
4	Sanofi (Paris)	2009: Sanofi-Aventis forms stem cell partnership with Salk Institute for 5 years (Salk, 2009)
		2012: Roche Pfizer, Sanofi establishes US$72.7 million Stem-cell bank through StemBANCC (Roche, 2012b)
5	Merck & Co (White house station, NJ)	N/A
6	GlaxoSmithKline (Brentford)	2008: enters into 5-year, US$25 million alliance with the Harvard Stem Cell Institute in stem cell science (GSK, 2008)
		2013: announces collaborative agreement with the UK Cell Therapy Catapult (Catapult, 2013)
7	Abbott (Abbott Park, IL)	2012: joins consortium of pharma companies for the creation of StemBANCC (Roche, 2012b)
8	Roche (Basel)	2008: partners with Stem Cells 4 Safer Medicines to generate stem cell repository for toxicology testing in high-throughput platforms
		2009: signs US$10.36 million 2-year collaboration with I-STEM (Institute for Stem Cell Therapy and Exploration of Monogenic Diseases) (I-Stem, 2009)
		2011: forms agreement with UCLA Stem Cell and Cancer Researchers to provide researchers with Roche's leading-edge technologies (UCLA, 2011)
		2012: Roche partners with HSCI to develop stem cell assays for autism spectrum disorders (Roche, 2012a)
		2012: spearheads StemBANCC initiative with IMI to generate 1500 iPS stem cell lines. US$72.7 million funded (Roche, 2012b)
9	Bayer (Leverkusen)	N/A
10	AstraZeneca (London)	2006: forms agreement with Cellartis (Paris) to develop improved safety screening systems based on human embryonic stem cell-derived liver and heart muscle cells, extended in 2009 (AstraZeneca, 2009)
		2010: forms research collaboration with Joslin Diabetes Center to understand the causes of type 2 diabetes by using stem cells (Joslin, 2010)
		2010: enters into a 3-year collaboration with UCL to develop regenerative medicines for diabetic retinopathy (UCL, 2010)
		2013: reaches agreement with Cellular Dynamics International, Inc. (Madison, WI) to develop new iPSC-derived cell types and screening applications (CDI, 2013b)
		2013: partners with the Wyss Institute, Harvard University to develop 'organ-on-a-chip' technologies (Wyss, 2013)
		2014: forms licensing and research collaboration with Immunocore (Abingdon) to codevelop 'Immune Mobilising Monoclonal T-Cell receptor against Cancer (AstraZeneca, 2014)
11	Eli Lilly (Indianapolis, IN)	2011: partners with Juvenile Diabetes Research Foundation to fund early-stage research that could enable patients with type 1 diabetes to regenerate insulin-producing cells (Lilly, 2011)
12	Teva (Petach Tikva)	2010: Mesoblast forms a strategic alliance with Cephalon Inc. (now owned by Teva) to develop and commercialize novel adult stem cell therapeutics (Teva, 2010)
13	Boehringer Ingelheim (Ingelheim am Rhein)	2012: invests in the US$72.7 million StemBANCC initiative along with Roche, Pfizer, and Sanofi (Roche, 2012b)
14	Bristol-Myers Squibb (New York City, NY)	2013: Bristol-Myers Squibb supports research conducted at the University of Edinburgh in which scientists generated liver cells using stem cell technology (Bristol-Myers, 2013)
15	Amgen (Thousand Oaks, CA)	N/A

Table 1 (*Continued*)

No.	Company	Partnership
16	Takeda (Osaka)	2011: makes strategic investment in Fate Therapeutics (San Diego, CA) to develop foundation in regenerative medicines (Takeda, 2011)
		2012: becomes strategic investor in Juventas Therapeutics (Cleveland, OH) in series B round of funding (Takeda, 2012)
		2014: partners with UCL to develop iPS cell technologies to treat muscular dystrophy (UCL, 2014)
17	Merck KgaA (Darmstadt)	2011: IntelliCell BioSciences (New York City, NY) validates technology used to generate fat, or adipose stem cells (IntelliCell, 2011)
		2012: collaborates with VeriStem Technologies Inc. (Singapore) to develop optimized technologies for removal of undifferentiated stem cells from pluripotent stem cell cultures (EMD-Millipore, 2012)
		2012: collaborates with Mittelhessen University of Applied Sciences to develop optimized cell culture and harvesting process for bioreactor-based stem cell cultures (Merck, 2012
		2013: teams up with PharmaCell (Maastricht) to develop optimized large-scale expansion and harvesting of HepaRG cells using bioreactor technology (EMD-Millipore, 2013)
18	Baxter (Deerfield, IL)	N/A
19	Astellas (Tokyo)	2013: in collaboration with Kyoto University's Center for iPS Cell Research and Application, discovers methods to promote kidney regeneration in human embryonic stem and induced pluripotent stem cells (Astellas, 2013)
20	Daiichi Sankyo (Tokyo)	N/A
21	Gilead Sciences (Foster City, CA)	N/A
22	Novo Nordisk (Bagsvaerd)	2008: invests EUR 100 million in cooperative project with Cellartis (Paris) and the Swedish Lund University Stem Cell Center to develop a cell therapy for treatment of insulin-dependent diabetes (Novo-Nordisk, 2008)
		2012: partners with Juvenile Diabetes Research and the European Foundation for the study of diabetes (JDRF, 2012)

modest yet increasing. Out of the top 22 pharmaceutical companies (ranked by 2012 revenues), 16 have formed co-development partnerships with a primary focus on regenerative medicine technologies. Pfizer (New York City, NY), Roche (Basel), and AstraZeneca (London) have been most active when measured by the number of deals announced (Table 1). Outside of the largest pharmaceutical companies, several private companies have formed alliances with academic institutions, in addition to numerous private–private co-development partnerships, which may prove to be vital for the future of the industry (Table 2).

Of the academic institutions that have formed alliances with the pharmaceutical industry or other private companies, Harvard University in the USA and University College London (UCL) in the UK are predominant (Table S1 in the supplementary material online). This trend mirrors that of the biomedical science field more broadly, with these two institutions demonstrating the highest number of academic–industry partnerships across the breadth of biomedical sciences [8]. Diabetes, neurological, and cardiovascular disorders were the therapeutic areas most frequently identified as the focus of strategic alliances in the sector (Figure S1 in the supplementary material online).

Combining strengths and eliminating deficiencies through co-development partnerships

Co-development partnerships in the field can be grouped around access to three key components: (i) production technology and/or technological expertise; (ii) commercialization, regulatory and/or clinical trial expertise; and (iii) financing.

The production process closely defines cell therapy products. The process is complex, with a limitless number of variations in source, reagents, and temporal considerations, which can all impact on the physiochemical and functional characteristics of the product. Thus, the production process creates a barrier for industry attempts to replicate published protocols. Therefore, co-development, as opposed to internal replication of published academic findings, is advantageous. Additionally, multiple technologies are frequently required to produce a cell therapy product, which may also involve the use of a scaffold or other biomaterial typically more familiar to medical device organizations. Thus, partnering can bundle technologies, increasing the likelihood of success and enable production of the clinical product. Servicing product pipelines through partnership, as opposed to inhouse R&D efforts, also provides private companies with the opportunity to view a wider range of research (born out of publicly visible findings and a broadly collaborative approach).

Although technological knowledge in the field is largely concentrated in academia, expertise in commercialization, regulation, and clinical trials is typically lacking in academia. Input from the pharmaceutical industry in these vital areas is required to better navigate the complex route from bench to bedside. This is a core motivation in partnership announcements, such as in the Pfizer–UCL agreement to develop embryonic stem cell-based technologies for the treatment of retinal diseases (Table S1 in the supplementary material online). The pharmaceutical industry does bring significant experience in these areas, but it should be acknowledged that the regulatory environment for cell therapies will differ from that of conventional products. Moreover, combinational products currently require an additional regulatory pathway, in which the pharmaceutical industry has limited experience. Furthermore, autologous cell therapies do not align with current pharmaceutical

Table 2. Co-development partnerships in regenerative medicine involving private companies, nonprofit companies, and academic institutions (2004–2014)[a]

Organization	Organization	Year	Press release
Advanced Cell Technology (Marlborough, MA)	Roslin Cells (Edinburgh)	2011	(ACT, 2011)
BD (Becton, Dickinson and Company) (Franklin Lakes, NJ)	Fate Therapeutics (San Diego, CA)	2010	(Fate-Therapeutics, 2010)
California Stem Cell, Inc. (Irvine, CA)	University of California, Irvine	2014	(Cell, 2014)
Cell Medica (London)	Baylor College of Medicine	2010	(Cell-Medica, 2010)
Cellectis (Paris)	Stemgent (Cambridge, MA)	2013	(Cellectis, 2013)
Cellular Dynamics International (Madison, WI)	Coriell Institute	2013	(CDI, 2013a)
Cellular Dynamics International (Madison, WI)	Life Technologies (Carlsbad, CA)	2012	(Life-Technologies, 2012)
Evotec (Hamburg)	Harvard Stem Cell Institute	2012	(Evotec, 2012, Evotec, 2013)
GE Healthcare (Pittsburgh, PA)	BGI (Beijing)	2012	(GEHealthcare, 2012a)
GE Healthcare (Pittsburgh, PA)	Karolinska University Hospital	2012	(GEHealthcare, 2012b)
Genzyme Corp. (now a Sanofi Company)	Osiris Therapeutics, Inc. (Columbia, MD)	2008	(Therapeutics, 2008)
Intrexon Incorporation (San Diego, CA)	Sanford-Burnham Medical Research Institute	2013	(Sanford-Burham, 2013)
iZumi Bio (now iPerian) (San Francisco, CA)	Kyoto University	2009	(University, 2009)
Kiadis Pharma (Amsterdam)	Technische Universitat Munchen	2014	(Pharma, 2014)
Life Technologies (Carlsbad, CA)	HSCI	2013	(Life-Technologies, 2013)
Lonza (Basel)	Roslin Cells (Edinburgh)	2010	(Roslin-Cells, 2010)
Mesoblast (Melbourne)	Cephalon (now a subsidiary of Teva)	2010	(Cephalon, 2010)
Neostem, Inc (New York, NY)	University of California	2013	(Neostem, 2013a)
Novocell Inc. (San Diego, CA)	Kyoto University	2008	(University, 2008)
New York Stem Cell Foundation (NYSCF)	Harvard Stem Cell Institute	2011	(NYSCF, 2011)
Paragon (Baltimore, MD)	University of Maryland Baltimore	2011	(UMB, 2011)
Pluristem Therapeutics Inc. (Haifa)	CHA Bio&Diostech (Seoul)	2013	(Pluristem, 2013)
Progenitor Cell Therapy (Allendale, NJ)	ATMI Inc (Danbury, CO)	2013	(Neostem, 2013b)
Q Therapeutics (Salt Lake City, UT)	Buck Institute	2008	(Institute, 2008)
Stem Cells Inc.	ALS Therapy Development Institute	2008	(CSC, 2008)
TAP Biosystems (Hertfordshire)	Loughborough University	2010	
TAP Biosystems (Hertfordshire)	International Stem Cell Corporation	2010	(TAP-Biosystems, 2010)
Tengion	Celgene Corporation	2013	(Tengion, 2013)
Viacyte (San Diego, CA)	Juvenile Diabetes Research Foundation (JDRF)	2011	(JDRF, 2011)

[a]Blue shading, private company; red shading, academic institution; gray shading, nonprofit.

business models and will require a new approach to commercialization. Such unique requirements have also led to the creation of several 'translation centers', such as the Canadian Centre for Regenerative Medicine (CCRM) and the UK Cell Therapy Catapult (see the press releases listed in the supplementary material online).

Financing is a clear motivation behind co-development partnerships, both for academia to benefit from the financial resources of the pharmaceutical industry, and for the industry to access alternative funding streams, such as government grants and support from disease foundations. Indeed, public–private–patient partnerships are becoming an increasingly prevalent and impactful component of this ecosystem. The California Institute of Regenerative Medicine (CIRM) has been a uniting force behind several collaborative agreements and provides financial backing to facilitate co-development projects. An additional motivation for public–private partnerships can be seen in the Pfizer-Athersys (Cleveland, OH) agreement, which extends the reach of MultiStem® into new indications, thus requiring additional capital for development and costly clinical trials (Table S1 in the supplementary material online). In the risk-adverse climate following the recent economic recession, co-development partnerships allow cash-poor organizations access to vital capital while reducing the investment risk of the pharmaceutical industry. This can be done through use of staged milestone payments, often linked to key clinical inflection points. Additional motivations for private companies to pursue partnerships result from challenges around licensing and access to primary human tissue samples [6,10]. Moreover, academic medical centers typically benefit from existing relations with key patient populations.

Impact of the evolving partnership model

The trend towards an increasing number of partnerships between the pharmaceutical industry, academia and SMEs (as well as amongst SMEs) will continue as technologies mature, as the regulatory environment becomes more established, and as the first wave of 'big wins' in the sector materializes. Expectations are high for: the curative potential of CAR-T cell technologies in a range of cancers; the phase II trial of Capricor (Beverly Hills, CA) for myocardial infarction; and the Advanced Cell Technologies (Marlborough, MA) trial with human embryonic stem cell-derived retinal pigment epithelial (RPE) cells for retinal disorders. Any increased activity in utilizing stem cell technologies for drug discovery will ultimately depend on the ability to standardize screening platforms as well as predictive potential. Tissue constructs on plug-and-play chips, including those that seek to link multiple different organ systems through fluid flow, are on the horizon and may further increase the ability to predict clinical outcomes. Indeed, partnerships in this arena have already developed, with AstraZeneca teaming with the Wyss Institute at Harvard University around their 'organs-on-a-chip' technology.

Closer academic-industry links foster a new breed of commercially minded research scientists, with a greater understanding of translation and the ability to communicate more effectively with industry. On the academic side, partnerships can bring a new approach to decision making in research, introducing criteria that industry have developed through an intimate familiarity with the translation pathway. On the industry side, interactions can promote alternative ways of explorative thinking and generate fresh ideas in research.

However, there are various potential pitfalls in academic–industry partnerships that may prevent a positive synergistic outcome. The demanding quarter-to-quarter productivity expectations of industry can be onerous when applied in an academic setting, and may also inhibit the exploratory nature of academic research. Potentially contentious areas in academic–industry partnerships include ownership and IP, publishing and confidentiality, and differences in 'culture' and incentives.

Pharmaceutical companies have increasingly begun to engage in co-development partnerships with both academic institutions and SMEs in the field of regenerative medicine, illustrative of a maturing industry and the development of technologies with the potential to deliver both commercial and clinical benefits. Such alliances allow the strategic building of complementary capacities and capability, uniting financial capital, expertise in process development, and commercialization pathways with novel therapeutic products.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tibtech.2014.05.007.

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