Cell-based Therapies: A Maturing Market Poised for Growth

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Scope

Recent advancements in cell-based therapy technology and FDA approvals have demonstrated the feasibility of treating difficult diseases. Given the progress, we examined recent market dynamics in a 3.5 year period starting in January 2015 by analyzing clinical trials, financing events, mergers and acquisition transactions (M&As) and initial public offerings (IPOs) to assess the overall activity of the sector and interest by venture capitalists and strategic players.

First Cell-based Therapy FDA Approvals

The regenerative medicine sector, and specifically cell-based therapies, is maturing as more clinical data is becoming available with consequent FDA approvals. Early interest in this sector was triggered when the FDA approved the first cultured cell therapy in 2000: Organogensis' Apligraf®, cultured skin cells and matrix for diabetic ulcers (Table 1).

Apligraf is allogeneic, also referred to as an allograft, where a donor's cells are cultured and used as treatment in a separate patient. This contrasts with autologous or an autograft when donor and patient are the same individual.

Over time, additional allografts were approved, the majority for dermatology indications. Recently, the sector has taken a tremendous leap as the FDA approved Novartis' Kymriah®, a cell-based gene therapy for leukemia, in October 2017. Shortly after, Kite, which was acquired by Gilead, gained approval for Yescarta®.

These represent the first FDA approvals for genetically modified autologous cells. Importantly, these approvals help pave a path for other therapies using genetically manipulated cells, allowing for development in novel indications where manipulation is necessary for efficacy.

Both Kymriah and Yescarta are indicated for rare cancers, a strategy that allows for premium pricing and an expedited FDA pathway. In addition, the FDA is supporting development by creating the regenerative medicine advanced therapy (RMAT) designation, which will include cell therapies, for serious or life-threatening diseases.[1]

Table 1

FDA Approved Cultured or Manipulated Cell Therapies

Sources: FDA & company websites

Company	Product	Indication	Description	Date Approved
Organogenesis	Apligraf	diabetic foot ulcers	allogeneic cultured keratinocytes and fibroblasts in a collagen matrix	20-Jun-2000
Shire (Organogenesis)	Dermagraft	diabetic foot ulcers	human fibroblasts, extracellular matrix, and bioabsorbable scaffold	01-Oct-2001
Dendreon	Provenge	prostate cancer	autologous antigen presenting cells incubated with prostatic acid phosphatase	29-Apr-2010
Fibrocell Technologies	laViv	nasolabial fold wrinkles	autologous cultured fibroblasts	22-Jun-2011
Organogenesis	Gintuit	gum tissue	allogeneic cultured keratinocytes & fibroblasts in bovine collagen	15-Mar-2012
Orthofix	Trinity Evolution	musculoskeletal defects	allograft of bone with osteogenic and osteoprogenitor cells	01-Jul-2013
Genzyme (Vericel)	Epicel	burns	autologous cultured keratinocytes in presence of mouse fibroblasts	18-Feb-2016*
Vericel	MACI	cartilage defects	autologous cultured chondrocytes on porcine collagen membrane	13-Dec-2016
Kite (Gilead)	Yescarta	refractory large B-cell lymphoma	genetically modified autologous T cells	18-Oct-2017
Novartis	Kymriah	non-Hodgkin lymphoma & B-cell acute lymphoblastic leukemia	genetically modified autologous T cells	01-May-2018

** previously marketed as unregulated product & device; Note: cord blood and transplant companies are not reported if no cell manipulation or culturing was required*

RMAT allows for actions to expedite review and guidance throughout development, in an effort to accelerate approval.[1,2]

The entry of Novartis and Gliead, coupled with the FDA's newly introduced RMAT designation indicate that the cell therapy segment is maturing, with the anticipation of a growing interest by strategic players.

Companies looking to enter the space should focus on serious or life-threatening diseases with currently limited treatment options to leverage this designation.

Additional Approvals Imminent

Assessment of active clinical trials is key in evaluating clinical progress and segment maturation. There are currently 346 active or recruiting cell-based therapy clinical trials. As shown, the oncology sub-segment dominates, primarily chimeric antigen receptor-T cells (CAR-T), with cardiology-focused therapies a distant second (Figure 1).

Several therapies have reached Phase 2/3 or 3, with some expected completion dates as early as 2019, including several oncology therapeutics. Other cell-based therapies in their pivotal trial include several cardiology indications (heart failure, ischemia, myocardial infarction), three therapies for orthopedic indications (cartilage defects and osteoarthritis), two for urinary incontinence, and an amyotrophic lateral sclerosis therapy.

Given the drug approval success rate from Phase 3 to approval,[3] we anticipate another cell-based therapy approval in the near-term. Interestingly, 70% of pivotal trials are conducted by public companies, indicating that public capital is often needed to fund these large and costly trials.

To gain an understanding of the major players, we examined the most prevalent sponsors of active and recruiting U.S. trials (Table 2). Most active clinical trial sponsors are regenerative medicine-specific companies with NantKwest, Bel-

licum Pharmaceuticals and Juno conducting most active trials.

Few large pharmaceutical companies are sponsoring large numbers of trials, indicating they are not currently the major segment drivers. Thus, big pharma has not fully embraced the space yet.

Due to the high cost of clinical development, small biotech companies should look to small- to mid-cap regenerative medicine-focused companies and big pharma to be acquired or partner to support clinical development.

More Than $1 Billion Invested in Private Placements in the Last 3.5 Years

Most active clinical trials focus on oncology and private placements follow a similar trend (Figure 2). As oncology attracts large amounts of capital (over $5 billion invested in the last few years[4]); it is anticipated that oncology will be dominating the cell-based therapy sub-sector in the coming years.

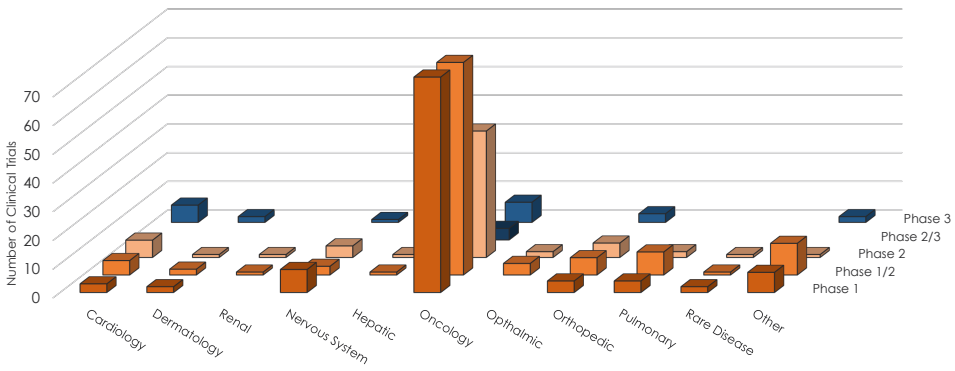
During the three-year time frame we evaluated, there were 67 private placements involving just over 50 companies, with several companies receiving multiple rounds of funding.

In contrast to the clinical trial analysis (Figure 1), rare diseases are the second most common indication for private placements. The majority (56%) of financed companies are targeting blood-based diseases, including hematological cancers, HIV and rare blood disorders.

A common strategy appears to be focusing on indications in which cells do not need to target a specific organ to illicit a therapeutic effect. An example is Orchard Therapeutics, whose first EMA-approved therapy was for the rare disease adenosine deminase severe combined immunodeficiency which is com-

Figure 1

Cell-based Therapy Clinical Trials Span Multiple Diseases



Source: Active and recruiting clinical trials were categorized from ClinicalTrials.gov on February 2018

Table 2

Most Active industry Sponsors of U.S. Active Trials

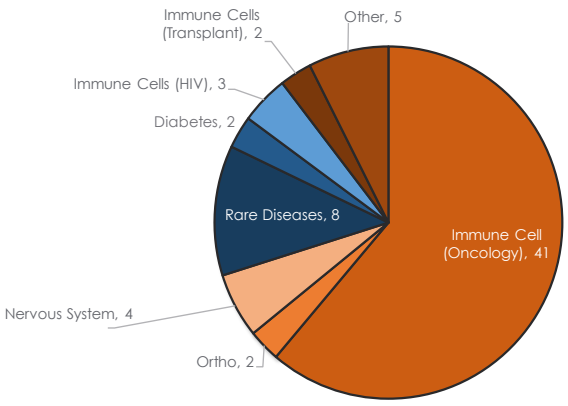
Industry Sponsor	Number of Active Trials	Number of Enrolling/Recruiting Trials
NantKwest	14	3
Bellicum Pharmaceuticals	9	6
Juno (Celgene)	8	8
Kite (Gilead)	6	6
Celgene	5	5
Merck Sharp & Dohme (6 total trials)	4	3
Iovance Biotherapeutics	4	4
Kiromic	4	4
Cook MyoSite	3	0
Longeveron	3	3
Mesoblast	3	2

Note: Some trials are co-sponsored

Source: Active and recruiting clinical trials were categorized from ClinicalTrials.gov on February 2018

Figure 2

Majority of Financed Cell-based Therapy Companies are Oncology-focused



Sources: Pitchbook and company websites

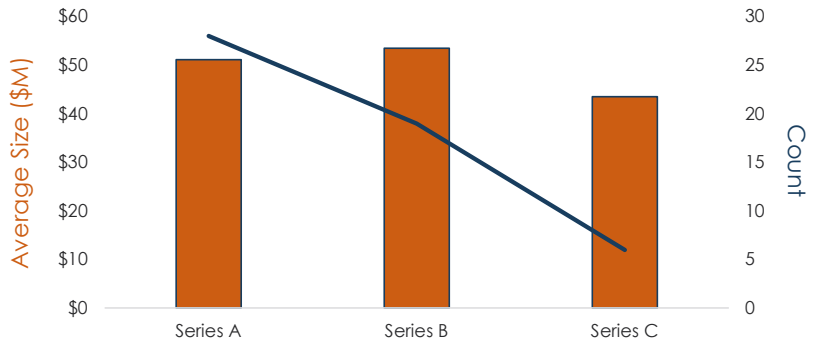
Note: Cell-based therapy financed companies were characterized based on most advanced asset indication. Financings <$5M were removed.

Figure 3

Cell-based Therapy Sector Draws Repeat Investors and Large Round Sizes

Source: Pitchbook

Frequent Investors	Number of Investments
F-Prime Capital Partners	5
ARCH Venture Partners	4
MPM Capital	4
Flagship Pioneering	4
GV	4
Amgen Ventures	3
Novo Holdings	3
SR One	3
Temasek Holdings	3
Novartis	3
Syncona	3



Note: Cell-based therapy financed companies were characterized based on most advanced asset indication. Financings <$5M were removed.

posed of gene-edited hematopoietic progenitor cells. This strategy likely helps to de-risk assets.

Few companies were financed in areas outside oncology and rare diseases, indicating a current narrow focus by the investment community.

Recent clinical approvals in oncology will further de-risk this specific sub-sector, encouraging additional investor appetite.

Many investors are taking multiple shots on goal within the cell-based therapy market (Figure 3 - Table), with several firms making 3 or more investments. Notably, 141 investors made ≤2 investments, indicating a diverse group of investors (data not shown). Several corporate venture arms have made multiple investments, including Novartis and Amgen, demonstrating early interest that suggests a future buyers universe.

Further, there were 28 Series A financing rounds at an average of $51.1 million, representing many early-stage companies raising large amounts of capital (Figure 3).

Series B rounds are expectedly larger at an average of $53.5 million. These round sizes are

encouraging to companies entering the space as securing a large financing will reduce the risk of undercapitalization in this capital-intensive sector.

While the Series C average size is lower than that of Series A and B, there were too few to draw conclusions (n=6).

Oncology Assets Drive the Largest Transaction Values

Of the 25 M&A transactions, the majority were of companies developing tools used by cell-based therapy companies ("tools") or oncology cell-based therapies (Figure 4). Tool companies are developing either a platform for contract work or a cell line/technology used to develop new cell therapies.

While some of these acquirers are expanding their service portfolio, others are therapeutics companies strategically looking to enter the cell-based therapy space. Examples include Astellas and Gilead making multiple acquisitions to enter a space with the promise of blockbuster drugs.

While there have been approvals in dermatology and oncology, there are no approvals in the other sub-sectors, likely reducing acquisitions in those sub-sectors given the uncertain regulatory path.

The average M&A transaction value was largely sub-sector specific (Table 3). Of note, Kite and Juno were acquired for large amounts ($12 and $9 billion, respectively) when they were in pivotal trials at the time of acquisition (Table 3). These assets were de-risked as the FDA path to clearance was defined and approval seemed imminent.

Oncology presents a clear dominance in the sector and it remains to be seen if follow on acquisitions will continue to obtain substantial returns. As deal numbers are limited, it is difficult to draw conclusions regarding deal value, but the data supports interest from strategic players garnered by recent approvals.

Oncology and tool companies were most acquired. Deal values will likely increase as other sub-sectors get first clinical approvals.

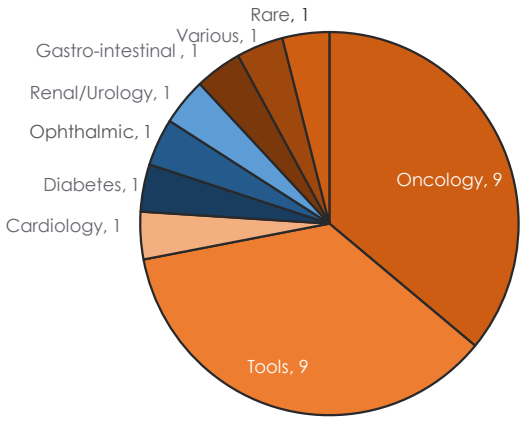
IPOs Cover a Variety of Diseases

Majority of the IPOs within the time frame occurred during 2015 (Table 4). To gain an estimation of return to shareholders, we examined the market cap 6-months after the IPO as an estimation of the valuation after the typical lock-up period.

While several had favorable market caps, including Adaptimmune Therapeutics, SanBio and Healios, the average was $273 million, suggesting a limited public market. This is further supported by the fact that there were only 13 successful IPOs over the 3.5-year span on a variety of exchanges. However, 2018 is proving to be an exciting year for biotech IPOs, which, coupled with recent FDA

Figure 4

Oncology Assets & Tool Companies are Sought After Through M&As



Sources: Pitchbook and company websites

Table 3

Oncology Assets Garner the Largest Deal Values

Sources: Pitchbook & company websites

Date	Target	Acquirer	Deal Value ($M)	Target Focus	Asset Description
21-Jan-2015	Celdara Medical (OnCyte)	Cardio3 BioSciences	161	Oncology	Portfolio of CAR-T candidates that use natural killer cell receptors
27-Feb-2015	Masthercell	Orgenesis	29	Tools	Industrialization of cell-based therapeutics further Orgenesis' Type 1 Diabetes treatment
06-Mar-2015	Tengion	RegenMedTX	22	Renal/Urology	Acquired assets out of bankruptcy, developing kidney/urology therapies
17-Mar-2015	T-Cell Factory	Kite Pharma	282	Oncology	Provides T cell receptor (TCR)-GENErator platform & manufacturing facilities
01-May-2015	Cellular Dynamics	FUJIFILM Holdings	307	Tools	Developer & manufacturer of fully functional human cells on industrial scale
11-May-2015	Stage Cell Therapeutics	Juno Therapeutics	233	Oncology	T cell isolation & expansion technology platforms
22-Jun-2015	VivaBioCell	VBC Holdings	-	Tools	Automated bioreactor
30-Jun-2015	Clio	Life Science Institute	21	Tools	Develops multilineage-differentiating stress-enduring cells
31-Jul-2015	Coretherapix	TiGenix	318	Cardiology	Lead asset: Allogeneic cardiac stem cells in Phase 2 for acute myocardial infarction
25-Sep-2015	Therakos	Mallinckrodt	1,325	Oncology	Extracorporeal photopheresis system that delivers autologous immune cells
18-Dec-2015	Janssen BetaLogics	ViaCyte	-	Diabetes	Both BetaLogics & ViaCyte focused on diabetes, improves ViaCyte's intellectual property
10-Feb-2016	Ocata Therapeutics	Astellas Pharma	379	Ophthalmic	Lead assets: Two Phase 2 cell therapies for macular degeneration diseases
18-Apr-2016	Cytonet	Promethera	-	Liver	Lead asset: Heparsc cell therapy with hepatocytes for urea cycle disorders
13-Jul-2016	Biosafe Group	GE Healthcare	-	Tools	Cell processing & banking devices
03-Jan-2017	Avapecia Life Sciences	Avagenesis	9	Various	Merger as both focused on commercializing cell isolation/therapy technologies
03-May-2017	PharmaCell	Lonza Group	-	Tools	Contract manufacturer focused on autologous cell therapy
18-May-2017	PCT	Hitachi Chemical	75	Tools	Cell therapy development & manufacturing services provider
20-Jun-2017	Catapult Therapy TCR	Cell Medica	-	Oncology	Lead asset: Genetically modified T cell therapy for oncology in Phase 1/2
07-Jul-2017	SynGen	Cesca Therapeutics	-	Tools	Cell processing platform used for treatments such as CAR-Ts
01-Sep-2017	Calimmune	CSL Behring	91	Rare Blood Diseases	Lead asset: Preclinical hematopoietic stem cell gene therapy for blood diseases & stem cell commercialization technologies
03-Oct-2017	Kite Pharma	Gilead Sciences	11,900	Oncology	Lead asset: CAR-T that was submitted to FDA and EMA for review
07-Dec-2017	Cell Design Labs	Gilead Sciences	567	Oncology	Lead asset: Preclinical therapy that targets multiple myeloma & multiple technologies platforms for gene expression & modulating activity
22-Jan-2018	Juno Therapeutics	Celgene	9,616	Oncology	Lead asset: CAR-T for refractory B cell acute lymphoblastic leukemia
13-Feb-2018	Universal Cells	Astellas Pharma	103	Tools	Technology to create cell therapies that do not require Human Leukocyte Antigen matching, reducing risk of rejection
07-Jun-2018	Quad Technologies	Bio-Techne	-	Tools	Technologies for cell separation & activation to be used in cell & gene therapy applications

Table 4

Limited Public Market for Cell-based Therapies

Sources: Pitchbook & company websites

Date	Company	Market Cap @ 6 months post-IPO ($M)	Lead Asset Focus	Description
06-Feb-2015	Bone Therapeutics (BRU: BOTHE)	162	Orthopedic	Cell therapies for spinal fusion (lead), delayed union and osteonecrosis of the hip
08-Apr-2015	SanBio (TKS: 4592)	376	Neurology	Cell therapies for stroke, traumatic brain injury & others
05-May-2015	Adaptimmune Therapeutics (NAS: ADAP)	929	Oncology	T-cell therapies for multiple cancers
12-Jun-2015	Idogen (SAT: IDOGEN)	Unavailable	Blood Disorders	Tolerogenic cell therapies for hemophilia A & organ transplantation
26-Jun-2015	Healios (TKS: 4593)	358	Ischemic Stroke	Developing multiple cell therapies including lead asset for ischemic stroke
15-Dec-2015	Kang Stem Biotech (KRX: 217730)	159	Various	Stem cell therapies for atopic dermatitis (lead), rheumatoid arthritis, Crohn's disease, also sells stem cell conditioned & culture media
22-Mar-2016	Xintela (STO: XINT)	12	Orthopedic	Developing cell therapy for cartilage damage & has a stem cell marker technology
29-Mar-2016	MaxCyte (LON: MXCT)	48	Tools	Tools used to engineer cells for cell therapies
11-May-2017	Qrons (PINX: QRON)	35	Neurology	Uses genetically modified mesenchymal stem cells for treatment of traumatic brain injuries
29-Mar-2018	UNUM Therapeutics (NAS: UMRX)	3289*	Oncology	Cell therapies using Antibody-Coupled T-Cell Receptor technology
21-Jun-2018	Avrobio (NAS: AVRO)	696*	Rare	Cell therapies using genetically modified stem cells for Fabry, Gaucher, Pompe Diseases & Cystinosis
22-Jun-2018	Autolus (NAS: AUTL)	970*	Oncology	T-cell therapies using proprietary viral vector and semi-automated cell manufacturing processes
27-Jun-2018	Neon Therapeutics (NAS: NTGN)	423*	Oncology	Personalized vaccines & Neoantigen T-cell therapies

**market cap at time of IPO*

approvals, is expected to drive more public interest in cell-based therapy companies.

Conclusions

While the cell-based therapy segment has not yet attracted significant interest by big pharma players, the segment is maturing as evidenced by venture capital investment as well early transactions. As such, we believe that it is poised for growth with an estimated CAGR of 10.6% (2017-2023).[5]

Several clear trends dictate the future for current companies in the space. Although over one third of the companies acquired were tool companies (Figure 4), the venture community and public market had limited interest in supporting these and instead focused on companies with a clear therapeutic indication (Figure 2 and Table 4).

While over $1 billion has been invested in the space, there has been limited M&A transactions, indicating that buyers are still wary of cell therapies, possibly due to safety concerns surrounding CAR-T cells.[6] In addition, the exceptionally high costs of therapy, a consequence of high development and production costs, presents a significant adoption challenge to all stakeholders.[7] However, the potential upside of multiple blockbuster drugs and the ability to treat diseases with no other foreseeable cure present a clear opportunity.

Oncology-focused cell therapies are currently the most sought after by both the venture community and strategic players and reach the highest deal valuations. However, we anticipate that advancement in manufacturing, pricing and therapeutic successes in the oncology sub-sector will likely translate to other subsectors in the coming years.

The cell-based therapy market will grow significantly, supported by recent clarity in the FDA pathway, improved clinical outcomes as well as market entry by big pharma.

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About Outcome Capital

Outcome Capital is a specialized life science and technology investment bank with a global reach, providing middle market group companies with a value-added approach to mergers and acquisitions, corporate finance and advisory services. The firm uses its proven 'strategy-led execution' approach to value enhancement by assisting boards and management teams in navigating both the financial and strategic markets and in implementing the best path for success. Outcome Capital's strength stems from its unique ability to draw on its wide range of operational, strategic and investment experience, its expertise across the value chain, and its broad industry relationships.

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