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Review article

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Commercialization of regenerative-medicine therapies

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Abstract

The clinical translation of regenerative-medicine products, including cell therapies, therapeutic tissue engineering products, and human cell and tissue products, remains limited because of the so-called 'valley of death', that is, the lack of resources necessary to move a product from early preclinical to clinical development. To advance more regenerative-medicine products into the clinic, academic researchers may benefit greatly from insights into the commercialization process, in particular, through academic startups. In this Review, we discuss key commercialization aspects, that is, protecting intellectual property, navigating regulatory pathways and obtaining funding, and highlight case studies of academic startups that have successfully developed US Food and Drug Administration-approved regenerative-medicine products and companies that have received Regenerative Medicine Advanced Therapy designations for their regenerative-medicine products in development.

Sections

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Key points

- Academic researchers interested in translating regenerative-medicine therapies to approved products may benefit from knowing about commercialization aspects early in research and development.
- Understanding the steps toward establishing intellectual property (IP) within academic institutions is key to conducting and disseminating IP-yielding research.
- Regenerative Medicine Advanced Therapy (RMAT) designations provide a pathway that can expedite the approval process of regenerative-medicine products.
- Grants and non-dilutive mechanisms can support preclinical studies, and dilutive mechanisms of funding and initial public offerings are the major sources of financial capital for clinical development phases.
- Academic institutions and funding agencies should implement policy changes to motivate and drive academic researchers toward the commercialization of regenerative-medicine technologies.

Introduction

Regenerative medicine is a burgeoning area of innovation[1,2]. Regenerative-medicine therapies, as defined in Section 506(g)(8) of the US Federal Food, Drug, and Cosmetic Act, include "cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service (PHS) Act (42 U.S.C. 264) and Title 21 of the Code of Federal Regulations Part 1271 (21 Code of Federal Regulations (CFR) Part 1271)". Based on interpretations of Section 506(g)(8) by the US Food and Drug Administration (FDA), which oversees their safety, regenerative-medicine therapies further include human gene therapy products as well as autologous, allogeneic and xenogeneic cell products. Specific regulations have been established in the USA, the European Union[3], Australia, Japan[4] and South Korea[5] to support, regulate and expedite the development of regenerative-medicine therapies[1,6]. For example, in the USA, the 21st Century Cures Act was enacted in 2016, and through the Act, the Regenerative Medicine Advanced Therapy (RMAT) designation was introduced, specifically to expedite the development and review of regenerative-medicine therapies[7].

Academic institutions, including universities, hospitals and research organizations, have greatly contributed to the development of the regenerative-medicine field[2]. Since the cellular immunotherapy product Provenge, originating from Stanford University, was approved in 2010, 20 cellular and gene therapy products (excluding eight haematopoietic stem-cell cord-blood products) have been approved by the FDA. Over the same period, however, over 1,000 new devices and 525 non-regenerative-medicine drugs[8] have received marketing authorizations in the USA. Thus, the number of FDA-approved regenerative-medicine products is limited in comparison to the number of approved medical devices and drugs. Of the 17 companies that originally developed the 20 FDA-approved regenerative-medicine products, 15 companies were associated with academic institutions and at least 12 of the 15 companies licenced regenerative-medicine technologies originating from academic institutions and researchers (Table 1). So far, the FDA has granted 86 RMAT designations, of which only 78 have been publicly announced (Table 2). These 78 RMAT designations have been granted to 60 companies and one academic institution, leading to three FDA-approved products. At least 40 of those companies used technologies that originated from academic institutions and researchers (Table 2). These numbers suggest that academic institutions serve as fertile ground for increasing the number of regenerative-medicine products that can benefit public health[9].

The low number of FDA-approved regenerative-medicine products is often attributed to the 'valley of death', that is, the lack of resources necessary to move a product from early preclinical to clinical development[9,10]. To traverse this 'valley of death', academic researchers, whose training typically focuses on concepts that drive basic discoveries, such as hypothesis-driven research, scientific presentations and publications, as well as grant writing, may benefit from learning about commercialization and regulatory considerations. The commercialization process encompasses the steps necessary to bring a regenerative-medicine product to market, which involve establishing intellectual property (IP), navigating the regulatory pathway, and obtaining funding for business development, infrastructure and FDA-sanctioned studies.

In this Review, we discuss key aspects of the commercialization pathway of regenerative-medicine therapies, including specific case studies and focusing on the US-based translational FDA framework; however, key considerations are also applicable to other countries and peripheral regenerative-medicine technologies. We first discuss the establishment of IP, outlining how to identify patentable technologies, develop patent strategies with domestic and international implications, prepare patent applications and develop licencing agreements. We then highlight relevant regulatory pathways specific to regenerative-medicine therapies, including steps for market approval of biologics, under which regenerative-medicine products are categorized. We also examine funding mechanisms and considerations of financial investments, not only for preclinical and clinical studies, but also for operating academic startups. Finally, we summarize financial exit strategies for regenerative-medicine companies. We conclude by discussing how academic institutions, funding agencies and governments can support the translation of regenerative-medicine therapies.

Establishing intellectual property

IP may be in the form of copyrights, trademarks, trade secrets or patents, which can protect aspects of a regenerative-medicine product. However, patents are the most common type of IP throughout the commercialization process. Patents, or patent claims that define the scope of the protection, preclude others from making, using or selling an invention for a limited period within the geographical region where they are granted (for example, 20 years from time of application in the USA)[11]. Patents de-risk the technology for assignees or licensees and build commercial value for attracting financial investments crucial to funding the research, development and clinical trials for translating regenerative-medicine therapies. Thus, establishing IP is an essential step toward commercialization. A case study illustrating how to establish IP is provided in Box 1.

Patentability and patent applications

As recognized by the US Patent and Trademark Office (USPTO), three types of patent exist: plant, design and utility patents. Plant patents

Table 1 | List of FDA-approved regenerative-medicine products

Trade name (year of first FDA approval)	Type of therapy	Current parent company	Original company to develop the technology	Academic institutions associated with original company that developed technology
Cellular immunotherapies				
Abecma (2021)	CAR–T cell therapy for the treatment of adult patients with relapsed/refractory multiple myeloma	Bristol-Myers Squibb	Bluebird Bio (founded as Genetix Pharmaceuticals)	Harvard University, Massachusetts Institute of Technology
Breyanzi (2021)	CAR–T cell therapy for the treatment of adult patients with different types of cancer of white blood cells	Bristol-Myers Squibb	Juno Therapeutics (founded as FC Therapeutics)	Fred Hutchinson Cancer Research Center, Memorial Sloan-Kettering Cancer Center, Seattle Children's Research Institute, St Jude Children's Research Hospital
Carvykti (2022)[39]	CAR–T cell therapy for the treatment of adult patients with relapsed/refractory multiple myeloma	Johnson & Johnson	Centocor	Wistar Institute Massachusetts Institute of Technology
Kymriah (2017)	CAR–T cell therapy for the treatment of B cell acute lymphoblastic leukaemia	Novartis	Novartis Pharmaceuticals	University of Pennsylvania
Provenge (2010)[40]	Autologous cellular immunotherapy for the treatment of prostate cancer	Sanpower	Dendreon Pharmaceuticals (founded as Activated Cell Therapy)	Stanford University
Tecartus (2020)	CAR–T cell therapy for the treatment of adult patients with relapsed/refractory mantle cell lymphoma	Gilead Sciences	Kite Pharma	University of California, Los Angeles Weizmann Institute
Yescarta (2017)	CAR–T cell therapy for the treatment of adult patients with large B cell lymphoma	Gilead Sciences	Kite Pharma	University of California, Los Angeles Weizmann Institute
Cellular therapies				
Gintuit (2012)[41]	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen for the treatment of surgically created vascular wound bed	Organogenesis	Organogenesis	Massachusetts Institute of Technology
Laviv (2011)[42,43]	Autologous cellular therapy for the improvement of the appearance of nasolabial fold wrinkles in adult patients	Castle Creek Pharmaceutical	Fibrocell Technologies (formerly Isolagen)	Hackensack University Medical Center
MACI (2016)	Autologous cultured chondrocytes on a porcine collagen membrane for the treatment of full-thickness cartilage defects of the knee	Vericel	Vericel (formerly Aastrom Biosciences)	NA
Rethymic (2021)	Allogeneic processed thymus tissue for the treatment of pediatric patients with congenital athymia	Sumitomo Pharma	Enzyvant Therapeutics	Duke University
StrataGraft (2021)	Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen for the treatment of adult patients with deep partial-thickness burns	Mallinckrodt Pharmaceuticals	Stratatech	University of Wisconsin — Madison
Gene therapies				
Adstiladrin (2022)	Adenovirus vector-based gene therapy for the treatment of adult patients with bladder cancer	Ferring Pharmaceuticals	FKD Therapies	University of Eastern Finland
Hemgenix (2022)	Adenovirus vector-based gene therapy for the treatment of adult patients with haemophilia B	CSL	UniQure (founded as Amsterdam Molecular Therapeutics)	University of Amsterdam
Imlygic (2015)	Genetically modified oncolytic viral therapy for the treatment of adult patients with melanoma	Amgen	BioVex	University College London
Luxturna (2017)	Adenovirus vector-based gene therapy for the treatment of child and adult patients with inherited retinal dystrophy	Roche Holding	Spark Therapeutics	Children's Hospital of Philadelphia University of Pennsylvania
Skysona (2022)	Autologous haematopoietic stem-cell-based gene therapy for the treatment of children with cerebral adrenoleukodystrophy	Bluebird Bio	Bluebird Bio (founded as Genetix Pharmaceuticals)	Harvard University Massachusetts Institute of Technology
Vyjuvek (2023)	Genetically modified herpes simplex virus for the treatment of patients six months of age and older with dystrophic epidermolysis bullosa	Krystal Biotech	Krystal Biotech	NA

Table 1 (continued) | List of FDA-approved regenerative-medicine products

Trade name (year of first FDA approval)	Type of therapy	Current parent company	Original company to develop the technology	Academic institutions associated with original company that developed technology
Gene therapies (continued)				
Zolgensma (2019)	Adenovirus vector-based gene therapy for the treatment of children less than two years old with spinal muscular atrophy	Novartis	AveXis	Nationwide Children's Hospital Ohio State University
Zynteglo (2022)	Lentiviral vector-based gene therapy for the treatment of adults and children with beta-thalassaemia	Bluebird Bio	Bluebird Bio (founded as Genetix Pharmaceuticals)	Harvard University Massachusetts Institute of Technology

This table was curated from publicly available information as of 30 June 2023. Academic institutions associated with the original company that developed the technology are defined as those that contributed to or licenced out regenerative-medicine technologies to companies at or shortly after company founding and/or those that had academic researchers as cofounders of the original companies. Every effort was made to search all information currently available. FDA, US Food and Drug Administration; CAR, chimeric antigen receptor; NA, not applicable.

cover certain newly discovered plants; design patents cover ornamental, non-functional features of an invention; and utility patents cover how an invention functions or how an invention is made. Roughly 90% of applications filed are utility patents, and most regenerative-medicine-related applications are of this type. Utility patents may relate to processes, machines, manufacturing or composition of matter. The patent claims that define the boundaries of the patent are often described in language such as "the process of…", "the method of…" or "the composition of…"[12]. In 2013, the USPTO and the European Patent Office adopted the Cooperative Patent Classification system for utility patents. The Cooperative Patent Classification code is often the most thorough way to search for utility patents. Regenerative-medicine products are typically protected by more than one utility patent because their development requires a complex array of discoveries that span the development and manufacturing process[13]. For example, StrataGraft, an FDA-approved regenerative-medicine product, is associated with a portfolio of patents that cover the cellular product[14], cryopreservation methods[15], tissue container systems[16] and methods of treatment[17].

To be patentable, the invention must be statutory, new, useful and non-obvious to a person skilled in the art[11,18]. 'Statutory' refers to meeting the requirements of the subject matter that can be patented. 'New' means that the invention must be new and that the important aspects of the invention have not been publicly disclosed. 'Useful' refers to whether the invention performs the intended purpose and has a practical utility and/or industrial application. 'Non-obviousness' or the 'inventive step' is the requirement for the invention to be non-obvious to someone of ordinary skill in a relevant field based on prior art. Patent examiners most often reject a patent application based on prior public disclosure or prior art.

Since 16 March 2013, the USA has switched from a 'first-to-invent' system to a 'first-inventor-to-file' system, under which all regions now operate[19]. Through the USPTO, two types of patent application exist for utility patents: provisional and non-provisional (Fig. 1a). A provisional application is a quick and inexpensive way to establish a US filing date, that is, the priority date. Filing a provisional patent application has the advantages of lower initial costs, a 12-month period to submit a full or non-provisional application, undisputed proof of the invention date, and the deferral of triggering the 20-year life of a utility patent. A non-provisional application is then examined by a patent examiner, and a patent may be issued if all the requirements of patentability are met. In addition, patent applications must meet the enablement requirement by disclosing enough information to enable a person skilled in the art to replicate the invention. US utility patent applications are published 18 months from the priority date.

To receive protection in multiple countries, separate patent applications may be filed simultaneously in all pertinent countries, or an international patent application under the Patent Cooperation Treaty (PCT) may be used to seek protection simultaneously in a large number of countries (Fig. 1a). The PCT application must be filed within 12 months from the priority date. An International Searching Authority then examines prior art, establishing a written opinion on patentability, and transmitting the written opinion within 16 months of the priority date. The international application is then published 18 months from the priority date. Typically, 30 months after the priority date, applicants pursue patents separately in each country, where they seek protection.

Prior public disclosure

Prior public disclosure is the act of disclosing, intentionally or unintentionally, the elements of an invention, meeting the enabling requirement prior to the patent filing date. Prior public disclosure may limit patentability by violating the 'new' criterion. This may include information published in scientific articles, for example, experimental methods[20], presentations and discussions in classrooms, corridors or any public space. Therefore, it is important for academic researchers to be cognizant of the ramifications of publicly disclosing information that has not been IP-protected. If an invention is publicly disclosed prior to patent filing, a grace period may exist in particular regions, for example, 12 months in the USA, that allows the invention to still meet the 'new' requirement (Fig. 1b). Japan, South Korea, Mexico, Argentina, China and Australia have also adopted grace periods, but the EU has not[21]. Thus, applying for foreign patents may become restricted. Guidance on public disclosure should therefore be sought early and frequently to ensure that academic researchers can disseminate scientific knowledge in a timely manner while navigating the complex IP process.

Prior art and freedom to operate

Prior art is any evidence that the invention is already known, which includes patents, existing products and publications[22]. Therefore, it is important to search for prior art, in addition to literature searches, to develop a patent strategy and meet patentability criteria for a technology. The patent examiner also performs a search for prior art after a non-provisional patent application is filed. Based on prior art, the patent examiner may then issue a 35 USC 102 rejection based on a single reference that the invention is not 'new' or a 35 USC 103 rejection

Table 2 | Regenerative-medicine companies that developed therapies receiving RMAT designations

Company name (year founded)	Announced date of RMAT designation (company's product development code)	Product description	Academic institutions associated with original company that developed technology	Year of IPO (amount raised in US dollars)	Year of M&A and type of M&A (financial details)
Abeona Therapeutics (1989)	1/29/2018 (EB-101) 4/23/2018 (ABO-102)	EB-101: gene-corrected autologous cell therapy for the treatment of recessive dystrophic epidermolysis bullosa ABO-102: adenovirus vector-mediated gene therapy for the treatment of Sanfilippo syndrome type A	Nationwide Children's Hospital	1989 (UD)	NA
Adaptimmune Therapeutics (2008)	12/3/2019 (ADP-A2M4) 11/8/2022 (ADP-A2M4CD8)	ADP-A2M4: autologous specific peptide enhanced affinity receptor T cell for the treatment of synovial sarcoma ADP-A2M4CD8: ADP-A2M4 cells also expressing the CD8a co-receptor for the treatment of platinum-resistant ovarian cancer	University of Oxford, University of Pennsylvania	2015 (US$191 M)	NA
Allogene Therapeutics (2017)[44]	4/21/2021 (ALLO-715) 6/8/2022 (ALLO-501A)	ALLO-715: allogeneic CAR–T cell therapy for the treatment of relapsed/refractory multiple myeloma ALLO-501A: allogeneic CAR–T cell therapy for the treatment of relapsed/refractory large B cell lymphoma	University of California, Los Angeles	2018 (US$373 M)	NA
Allovir (2013)	6/11/2019 (Posoleucel) 1/5/2022 (Posoleucel) 4/20/2022 (Posoleucel)	Posoleucel: allogeneic multi-virus specific T cell therapy for the prevention of clinically important infections and disease	Baylor College of Medicine	2020 (US$318 M)	NA
Angiocrine Bioscience (2011)	11/11/2020 (AB205)	AB205: human engineered cord endothelial cell therapy for the treatment of organ vascular niche injuries for the prevention of severe regimen-related toxicities in patients with Hodgkin lymphoma and non-Hodgkin lymphoma undergoing high-dose therapy and autologous haematopoietic stem-cell transplantation	Weill Cornell Medicine	NA	NA
Asterias Biotherapeutics (2012)	10/2/2017 (AST-OPC1)	AST-OPC1: oligodendrocyte progenitor population derived from embryonic stem cells for the treatment of spinal cord injury	University of California, Irvine	2015 (US$5.5 M)	2019 acquired by BioTime (UD)
Athersys (1995)	10/5/2017 (MultiStem) 9/23/2020 (MultiStem)	MultiStem: multipotent adult progenitor cells obtained from bone marrow for the treatment of ischaemic stroke and acute respiratory distress syndrome	University of Minnesota Case Western Reserve University	NA	2007 reverse merger (UD)
Audentes Therapeutics (2012)	8/21/2018 (AT132)	AT132: adeno-associated virus vector-based gene therapy for the treatment of X-linked myotubular myopathy	University of Florida	2016 (US$75 M)	2020 acquired by Astellas Pharma (US$3,000 M)
Autolus Therapeutics (2014)	4/25/2022 (Obe-cel)	Obe-cel: CD19-directed autologous CAR–T cell therapy for the treatment of relapsed/refractory B cell acute lymphocytic leukaemia	University College London	2018 (US$160 M)	NA
AxoGen (2002)	10/29/2018 (Avance Nerve Graft)	Avance Nerve Graft: allogeneic biologically active processed nerve graft for the repair of peripheral nerve discontinuities	University of Florida	NA	2011 reverse merger (UD)
BioMarin Pharmaceutical (1997)	3/8/2021 (valoctocogene roxaparvovec)	Valoctocogene roxaparvovec: adeno-associated virus vector-based gene therapy for the treatment of severe haemophilia A	NA	1999 (US$58 M)	NA
Bluebird Bio (1992)	10/1/2017 (LentiGlobin approved as Zynteglo for the treatment of beta thalassaemia)	LantiGlobin: gene therapy for the treatment of severe sickle cell disease	Harvard University Massachusetts Institute of Technology	2013 (US$116 M)	NA
Caladrius Biosciences (1980)	6/19/2018 (CLBS14)	CLBS14: autologous $CD34^+$ stem-cell therapy for the treatment of refractory angina	NA	1991 (UD)	2022 merger with Cend Therapeutics (UD)
Capricor Therapeutics (2005)	2/5/2018 (CAP-1002)	CAP-1002: allogeneic cardiosphere-derived cells for the treatment of Duchenne muscular dystrophy	Johns Hopkins University	NA	2013 reverse merger (UD)

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Caribou Biosciences (2011)	11/29/2022 (CB-010)	CB-010: allogeneic anti-CD19 CAR–T cell therapy for relapsed/refractory large B cell lymphoma	University of California, Berkeley	2021 (US$304 M)	NA
Carsgen Therapeutics (2014)	10/28/2019 (CT053) 1/10/2022 (CT041)	CT053: CAR–T cell therapy for the treatment of relapsed/refractory multiple myeloma CT041: CAR–T cell therapy for the treatment of advanced gastric or gastro-oesophageal junction adenocarcinoma with CLDN18.2^{+} tumour	NA	2021 (US$400 M)	NA
Cellerant Therapeutics (2003)	7/2/2018 (romyelocel-L)	Romyelocel-L: allogeneic myeloid progenitor cells for the prevention of serious infections in patients with de novo acute myeloid leukaemia	NA	NA	NA
Cellular Biomedicine (2013)	1/12/2022 (C-CAR039)	C-CAR039: autologous bi-specific CAR–T cell therapy for the treatment of relapsed/refractory diffuse large B cell lymphoma	NA	NA	2013 reverse merger (UD) 2021 acquired by consortium (US$411 M)
Cook Myosite (2002)	12/17/2020 (AMDC-USR)	AMDC-USR: autologous muscle derived cells for urinary sphincter repair for the treatment of persistent or recurrent stress urinary incontinence	NA	NA	NA
CRISPR Therapeutics (2013)	5/11/2020 (CTX001) 11/22/2021 (CTX110) 9/28/2022 (CTX130)	CTX001: autologous CRISPR gene-edited haematopoietic stem-cell therapy for the treatment of transfusion-dependent beta thalassaemia and sickle cell disease CTX110: allogeneic CAR–T cell therapy for the treatment of CD19^{+} B cell malignancies CTX130: allogeneic CAR–T cell therapy targeting CD70 for the treatment of mycosis fungoides and Sézary syndrome	Harvard University	2016 (US$56 M)	NA
Direct Biologics (2017)	4/12/2022 (Exoflo)	Exoflo: acellular bone- marrow mesenchymal-stem-cell-derived extracellular vesicle for the treatment of acute respiratory distress syndrome associated with COVID-19	NA	NA	NA
DiscGenics (2007)	1/26/2023 (rebonuputemcel)	Rebonuputemcel: injectable, allogeneic discogenic progenitor cell therapy for the treatment of symptomatic lumbar degenerative disc disease	NA	NA	NA
Enzyvant (2016)	4/17/2017 (RVT-802 approved as Rethymic)	RVT-802: allogeneic processed thymus tissue for the treatment of complete DiGeorge syndrome	Duke University	NA	2019 acquired by Sumitomo Dainippon Pharma (UD)
ExCellThera (2014)	4/23/2019 (ECT-001)	ECT-001: expanded cord blood cell therapy for the treatment of haematological malignancies	Université de Montréal University of Toronto	NA	NA
Fate Therapeutics (2007)	12/13/2021 (FT516)	FT516: gene-edited iPSC-derived natural killer cell therapy for the treatment of relapsed/refractory diffuse large B cell lymphoma	Harvard University University of Washington, Children's Hospital Boston Mass General Hospital for Children	2013 (US$40 M)	NA
Fibrocell Science (1995)	5/29/2019 (FCX-007)	FCS-007: genetically modified autologous fibroblast for the treatment of recessive dystrophic epidermolysis bullosa	Hackensack University Medical Center	2002 (UD)	2019 acquired by Castle Creek Pharmaceutical (US$63 M)
Fortress Biotech (2006)	11/8/2017 (CEVA101)	CEVA101: autologous bone-marrow-derived stem cells for the treatment of traumatic brain injury	NA	2011 (UD)	NA
Helixmith (1996)	May 2018 (VM-202)	VM-202: non-viral small-circular-DNA-molecule-based gene therapy for the treatment of diabetic peripheral neuropathy	Seoul National University	2005 (UD)	2022 acquired by Canaria Bio (UD)

Table 2 (continued) | Regenerative-medicine companies that developed therapies receiving RMAT designations

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Humacyte (2004)	3/20/2017 (Humacyl) 5/4/2023 (HAV)	Humacyl: human acellular vessel for providing vascular access to patients in need of life-sustaining haemodialysis HAV: human acellular vessel for the treatment of urgent arterial repair following extremity vascular trauma	Duke University, Massachusetts Institute of Technology	NA	2021 reverse merger (UD)
IASO Biotherapeutics (2017)	2/11/2023 (CT103A)	CT103A: B cell maturation antigen-targeted CAR–T cell therapy for the treatment of relapsed/refractory multiple myeloma	NA	NA	NA
Immunicum (2002)	5/6/2020 (Ilixadencel)	Ilixadencel: activated allogeneic dendritic cells for the treatment of metastatic renal cell carcinoma	NA	2013 (SEK 21 M)	NA
Intellia Therapeutics (2014)	3/21/2023 (NTLA-2002)	NTLA-2002: CRISPR-based gene-editing therapy for the treatment of hereditary angio-oedema	University of California, Berkeley	2016 (US$113 M)	NA
Iovance Biotherapeutics (2007)	10/11/2018 (lifileucel)	Lifileucel: autologous tumour-infiltrating lymphocyte cell therapy for the treatment of advanced melanoma	National Cancer Institute	2008 (UD)	NA
jCyte (2010)	5/2/2017 (jCell)	jCell: retinal progenitor cells for the treatment of developmental retinitis pigmentosa	University of California, Irvine	NA	NA
Juno Therapeutics (2013)	11/1/2017 (JCAR017–approved as Breyanzi)	JCAR017: autologous anti-CD19 CAR –T cell therapy for the treatment of relapsed/refractory aggressive large B cell non-Hodgkin lymphoma	Fred Hutchinson Cancer Research Center, Memorial Sloan-Kettering Cancer Center, Seattle Children's Research Institute, University of California San Francisco, St Jude Children's Research Hospital	2014 (US$265 M)	2018 acquired by Celgene (US$9,000 M)
Kiadis Pharma (1997)	9/20/2017 (ATIR101)	ATIR101: allogeneic T cell-enriched leukocytes devoid of alloreactive T cells for the restoration of lymphocyte levels after stem-cell transplantation	NA	2015 (US$36 M)	2021 acquired by Sanofi (US$358 M)
Krystal Biotech (2017)	6/24/2019 (KB103)	KB103: replication-defective, non-integrating viral vector for the delivery of functional human *COL7A1* genes for the treatment of dystrophic epidermolysis bullosa	NA	2017 (US$46 M)	NA
Magenta Therapeutics (2015)	9/4/2019 (MGTA-456)	MGTA-456: $CD34^+$ haematopoietic stem cells well matched with the patient for the treatment of multiple inherited metabolic disorders	Harvard University, Washington University in St Louis, Stanford University, San Raffaele Telethon Institute for Gene Therapy, University of Basel	2018 (US$100 M)	NA
Medeor Therapeutics (2012)	9/22/2020 (MDR-101)	MDR-101: single-dose cellular therapy manufactured from a living kidney donor's blood and peripheral stem cells to enable immune tolerance in kidney transplantation	Stanford University	NA	NA
Mesoblast (2004)	12/21/2017 (MPC-150-IM) 2/8/2023 (rexlemestrocel-L)	MPC-150-IM: mesenchymal precursor cell therapy for the treatment of heart failure patients with left ventricular systolic dysfunction and left ventricular assist devices Rexlemestrocel-L: bone-marrow-derived allogeneic mesenchymal precursor cell therapy for the treatment of chronic low back pain associated with disc degeneration	NA	2004 (US$21 M)	NA
MiMedx (2008)	3/9/2018 (AminoFix Injectable)	AminoFix Injectable: allogeneic micronized dehydrated amniotic membrane for the treatment of osteoarthritis of the knee	NA	NA	2008 reverse merger (UD)

Table 2 (continued) | Regenerative-medicine companies that developed therapies receiving RMAT designations

Company name (year founded)	Announced date of RMAT designation (company's product development code)	Product description	Academic institutions associated with original company that developed technology	Year of IPO (amount raised in US dollars)	Year of M&A and type of M&A (financial details)
Mustang Bio (2015)	8/22/2019 (MB-107)	MB-107: lentiviral gene therapy for the treatment of X-linked severe combined immunodeficiency	City of Hope National Medical Center, Fred Hutchinson Cancer Center, St Jude Children's Research Hospital	2017 (UD)	NA
Nightstar Therapeutics (2013)	6/14/2018 (NSR-REP1)	NSR-REP1: adeno-associated virus type 2 vector containing recombinant DNA for REP1 for the treatment of choroideraemia, a genetic retinal disorder that leads to blindness	University of Oxford	2017 (US$77 M)	2019 acquired by Biogen (US$800 M)
Novartis Pharmaceuticals (1996)	4/22/2020 (FDA-approved as Kymriah)	Kymriah: CD19-directed genetically modified autologous T cell immunotherapy for the treatment of relapsed/refractory follicular lymphoma	University of Pennsylvania	2001 (UD)	NA
Ocugen (2013)	5/24/2022 (NeoCart)	NeoCart: autologous chondrocyte-derived neocartilage for the treatment of full-thickness lesions of the knee cartilage	University of Colorado, University of Illinois at Chicago	NA	2019 reverse merger (UD)
Orca Bio (2016)	10/14/2020 (Orca-T)	Orca-T: allogeneic stem and immune cells with highly purified, polyclonal donor regulatory T cells for the enhancement of cell engraftment in haematopoietic stem-cell transplantation	Stanford University	NA	NA
Orchard Therapeutics (2015)	7/29/2019 (OTL-103)	OTL-103: autologous haematopoietic stem-cell-based gene therapy for the treatment of Wiskott–Aldrich syndrome	University College London San Raffaele-Telethon Institute for Gene Therapy	2018 (US$225 M)	NA
Organogenesis Holdings (1985)	1/11/2021 (ReNu)	ReNu: allogeneic cryopreserved amniotic suspension for the treatment of osteoarthritis of the knee	Massachusetts Institute of Technology	1986 (UD)	2018 reverse merger (UD)
PolarityTE (1998)	5/13/2022 (SkinTE)	SkinTE: autologous skin-tissue-based product for the treatment of chronic cutaneous ulcers	NA	NA	2017 reverse merger (UD)
Poseida Therapeutics (2014)	11/5/2018 (P-BCMA-101)	P-BCMA-101: autologous anti-B-cell maturation antigen CAR–T cell therapy for the treatment of relapsed/refractory multiple myeloma	NA	2020 (US$224 M)	NA
ProKidney (2015)	Oct 2021 (REACT)	REACT: renal autologous cell therapy for the treatment of diabetic chronic kidney disease	NA	NA	2022 SPAC merger (UD)
Regenxbio (2008)	5/24/2023 (RGX-121)	RGX-121: adeno-associated-virus-vector-based gene therapy for the treatment of mucopolysaccharidosis type II (Hunter syndrome)	University of Pennsylvania	2015 (US$159 M)	NA
Rocket Pharmaceuticals (2015)	11/27/2018 (RP-L102) 3/9/2021 (RP-L201) 2/7/2023 (RP-A501) 5/23/2023 (RP-L301)	RP-L102: lentiviral vector-based gene therapy for the treatment of Fanconi anaemia RP-L201: lentiviral-vector-based gene therapy for the treatment of leukocyte adhesion deficiency I RP-A501: adeno-associated-virus-based gene therapy for the treatment of Danon disease RP-L301: lentiviral vector-based gene therapy for the treatment of pyruvate kinase deficiency	NA	NA	2018 reverse merger (UD)
SanBio (2001)	9/20/2019 (SB623)	SB623: genetically modified and cultured adult bone marrow-derived mesenchymal stem cells for the treatment of chronic neurological motor deficits secondary to traumatic brain injury	NA	2015 (US$124 M)	NA
Sangamo Therapeutics (1995)	7/5/2019 (SB-525)	SB-525: adeno-associated virus serotype 6 vector-based gene therapy for the treatment of severe haemophilia A	NA	2000 (US$53 M)	NA
Stratatech (2000)	7/18/2017 (approved as StrataGraft)	StrataGraft: allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen for the treatment of deep partial-thickness burns	University of Wisconsin	NA	2016 acquired by Mallinckrodt (UD)

Table 2 (continued) | Regenerative-medicine companies that developed therapies receiving RMAT designations

Company name (year founded)	Announced date of RMAT designation (company's product development code)	Product description	Academic institutions associated with original company that developed technology	Year of IPO (amount raised in US dollars)	Year of M&A and type of M&A (financial details)
TiGenix (2000)	May 2019 (Alofisel)	Alofisel: allogeneic expanded adipose-derived mesenchymal stem cells for the treatment of complex perianal fistulas in patients with Crohn's disease	Katholieke Universiteit, Leuven Ghent University	2007 ($56 M)	2018 acquired by Takeda Pharmaceutical (US$608 M)
Talaris Therapeutics (2002)	4/18/2019 (FCR-001)	FCR-001: allogeneic stem-cell therapy to induce durable immune tolerance in living-donor kidney-transplant recipients	University of Louisville	2021 (US$150 M)	NA
Tessa Therapeutics (2012)	2/27/2020 (TT11)	TT11: autologous CD30 directed CAR–T cell therapy for the treatment of relapsed/refractory $CD30^+$ classical Hodgkin lymphoma	Baylor College of Medicine	NA	NA
TissueTech (2001)	4/16/2020 (TTAX02)	TTAX02: cryopreserved human umbilical cord for the treatment of spina bifida in utero	NA	NA	NA
University of California, San Francisco	2/14/2022 (AProArt)	AProArt: lentiviral gene therapy for the treatment of Artemis-deficient severe combined immunodeficiency	University of California, San Francisco	NA	NA
Vericel (1989)	5/10/2017 (Ixmyelocel-T)	Ixmyelocel-T: autologous expanded mesenchymal stromal cells and alternatively activated macrophages for the treatment of advanced heart failure due to ischaemic dilated cardiomyopathy	NA	1997 (US$20 M)	NA
Voyager Therapeutics (2013)	6/21/2018 (VY-AADC)	VY-AADC: adeno-associated-vector-based gene therapy for the treatment of Parkinson's disease in patients with motor fluctuations	University of Massachusetts, University of California San Francisco, Stanford University	2015 (US$81 M)	NA

This table was curated from publicly available information as of 30 June 2023. The FDA publishes the number of RMAT designations granted by year but does not maintain a publicly accessible database listing of each of the companies and products receiving RMAT designations. It should be noted that RMAT designation does not mean that the product has received FDA approval. Academic institutions associated with the original company that developed the technology are defined as those that contributed to or licenced out regenerative-medicine technologies to companies at or shortly after company founding and/or those that had academic researchers as cofounders of the original companies. Every effort was made to search all information currently available. RMAT, Regenerative Medicine Advanced Therapy; IPO, initial public offering; M&A, mergers and acquisitions; NA, not applicable; UD, undisclosed; M, million; CAR, chimeric antigen receptor; CRISPR, clustered regularly interspaced short palindromic repeats; COVID-19, coronavirus disease of 2019; SPAC, special purpose acquisition company.

based on the combination of one or more references that the invention is not 'non-obvious' to a person skilled in the art. Importantly, patent specifications (that is, background, drawings and detailed description) differ from scientific papers; for example, in a scientific paper, data is presented sequentially, accompanied by published literature to support gaps in the data and the conclusions. In contrast, a patent application highlights the novelty and inventiveness of the work; the drafting of a patent application typically requires collaboration with patent lawyers. Although it is difficult to predict the basis of these rejections, an initial and thorough prior art search can eliminate mistakes in the patent process and inform on the patentability of a technology prior to commencing commercialization.

Freedom to operate (FTO) analysis is also often conducted at key stages of commercialization[23]. We note that patents do not ensure that a regenerative-medicine product can be marketed freely without infringing upon other existing third-party IP. An FTO analysis is an expensive process that can help to determine whether a regenerative-medicine product can be made, used, sold or offered for sale without litigation risks for patent infringements. This analysis typically becomes the basis of a legal opinion from an IP attorney and is part of the due diligence process for obtaining financial investments. This difference between searching for prior art and an FTO analysis is important, because a prior art search does not ensure that FTO exists.

Patenting and licencing through an academic institution

IP can be established through the help of academic institutions. In most cases, upon employment, academic researchers sign an IP assignment agreement that grants academic institutions the sole ownership of IP. As a result, guidance on establishing IP is available at many academic institutions through a technology transfer office (TTO). In the process of establishing IP, an academic researcher submits a record of invention disclosure form to the TTO, which then determines whether the invention is worth patenting (Fig. 1b). The TTO evaluates whether the invention meets its own set of requirements, such as IP policy, market potential and budget. If the TTO decides to move forward, academic researchers work with the TTO to move a patent application forward. If the TTO decides not to pursue a patent application, the academic researchers have the option of pursuing a patent on their own, typically through their own legal counsel. In this case, academic researchers typically have ownership of the IP.

After a patent application is submitted, the technology may be licenced by the university (licensor) to an existing company or an academic startup (licensee). The process typically starts with a letter of intent, which is usually a non-binding document that explains the general terms that the potential licensor and licensee negotiate. A formal letter of agreement articulates more specific terms of a potential licensing agreement, such as license fees, milestone payments, royalties

Box 1

Intellectual property case study: Rethymic by Enzyvant Therapeutics

The technology for Rethymic, an allogeneic processed thymus tissue to treat congenital athymia, was developed at Duke University[45]. Results from the first clinical trial were published in 1999[46] and 2003[47]. However, public records indicate that the first patent application related to this technology was filed by Duke University in 2006 ("Parathyroid and thymus transplantation in DiGeorge syndrome subjects")[48,49], which added the transplantation of parathyroid tissue to the initial method of thymus transplantation used in the first clinical trial. The patent was granted by the European Patent Office in 2011[49] but not by the US Patent and Trademark Office (USPTO) so far. In 2017, Enzyvant Therapeutics licenced the technology from Duke University to commercialize the technology. In 2019, another related patent application was filed by Duke University ("Cultured thymus tissue transplantation promotes donor-specific tolerance to allogeneic solid organ transplants") and is currently pending[50]. In 2020, another related patent was filed by Duke University and Enzyvant Therapeutics ("Methods of determining the suitability of cultured thymus tissue for implantation into humans and associated methods of use")[51]. We note that it is not known why the initial patent was not granted by the USPTO, given that USPTO rejections or company strategies are not public knowledge. Subsequent patent applications continue to be filed to protect the intellectual property, illustrating the concept that intellectual property considerations are an ongoing process and that not having a US patent does not preclude one from obtaining US Food and Drug Administration approval.

and/or issuance of equity[24]. Next, a formal licencing agreement is drafted and signed by both parties, outlining final terms and conditions for the scope and rights of the IP. The terms of licencing agreements are open to negotiation and vary greatly depending on the country and academic institution. Some TTOs have their general terms publicly available; for example, the University of California San Diego (UCSD) has a standard US$500 nominal fee accompanied by a 5% equity stake in the company diluted after a typical first-round investment; however, the option of a royalty-bearing agreement also exists. For therapeutics, UCSD requires additional fees, such as milestone fees and maintenance fees. Licencing terms vary for each case and for each institution and require negotiations.

FDA regulatory pathway

Three centres regulate medical products within the FDA: the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) (Fig. 2). In the case of regenerative-medicine products, CBER is especially relevant because it oversees the approval of products with a biologic component, such as vaccines, cellular and gene therapy (CGT) products, and blood products. More complex products may be classified as combination products and assigned to multiple centres by the Office of Combination Products; the centre handling the primary mechanism of action also has primary jurisdiction[25]. The legal framework for translating medical products to market is outlined in CFR Title 21. The FDA has also developed guidance documents with non-binding information for specific areas (such as CGT products and cartilage repair products). For example, the guidance pertaining to CGT products is applicable to tissue-engineering products, T cell therapies, gene therapies and any other product that fits under the CGT umbrella. Furthermore, CGT therapies, in particular, human cell, tissue and cellular and tissue-based products (HCT/Ps), may also be regulated under either section 351 or section 361 of the PHS Act. Products that are minimally manipulated and for homologous use fall under section 361 with considerably less regulatory burden than for 351 HCT/Ps.

Several expedited programmes exist to help speed up the regulatory process. The RMAT designation is the most relevant to regenerative-medicine products and can be applied if the sponsor has obtained preliminary clinical data to show that a regenerative-medicine therapy can be used to "treat, modify, reverse or cure a serious or life-threatening condition". Advantages of the RMAT designation include close communication and guidance from the FDA, rolling review of applications, and eligibility for priority review and/or accelerated approval. Because no universal set of experiments can evaluate the safety and efficacy of all CGT products, the product's sponsor must determine the appropriate approach based on guidance documents and interactions with the FDA to provide sufficient justification for the selected approach. A case study describing the navigation of the FDA regulatory pathway by an academic startup is provided in Box 2.

Preclinical research toward an Investigational New Drug application

For 351 HCT/Ps, the first major milestone is to obtain approval to conduct clinical trials; an Investigational New Drug (IND) application demonstrating safety and establishing scientific support for clinical investigation must be authorized by the FDA[25] (Fig. 2). To obtain specific guidance related to these studies and to prepare for an IND submission, sponsors can optionally request an INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meeting and/or a pre-IND meeting with the FDA. Major parts of an IND package, as described by 21 CFR 312, include an introductory statement and general investigational plan, investigator's brochure, protocols, chemistry, manufacturing and control information, pharmacology and toxicology information, previous human experience with the investigational drug, additional information for specific applications such as paediatric studies, and relevant information requested by the FDA on a case-by-case basis. Central to obtaining data in the IND submission is the implementation of a quality management system (QMS), which includes the principles of Good Laboratory Practice (GLP) during the preclinical stage[26]. The conditions for GLP involve the setting of minimum basic requirements for study aspects, such as written protocols, operating procedures, study reports and personnel; alternatively, the sponsor can provide a reason for noncompliance in its IND submission. Once investigators submit an IND package, the FDA has 30 days to review the contents and authorize the investigational use of the proposed therapy in clinical trials.

Clinical research toward a Biologics License Application

Once the IND application is authorized, the sponsor may administer the product in clinical trials (Fig. 2). Phase I clinical trials assess safety

in a small group of participants, identify side effects, and determine the appropriate dose. Phase II trials are conducted to assess product efficacy and further evaluate safety in a larger group of participants. Finally, phase III trials are used to assess safety and efficacy in a large cohort. Trial phases may also be split into multiple studies (for example, phases IIa and IIb) to test specific research questions sequentially, or phases may be combined (for example, phase I/II) to streamline the studies. Between phases, 'end of phase' meetings with the FDA (for example, 'end of phase I') are used to discuss product development plans, adequacy of current studies, protocols for future clinical trials, issues of chemistry, manufacturing and control, and any other relevant topics (for example, paediatric study plans). Depending on the phase, indication and trial design, clinical trials may vary in blinding (for example, open-label or no blinding, patient- or single-blinded, patient- and researcher-blinded or double-blinded), controls (for example, uncontrolled or single-arm, controlled or multi-arm), and randomization (for example, randomization or no randomization). Throughout the preparation and execution of clinical trials, a QMS must be in place to ensure the quality of processes, data and documentation. QMS benefits include identification and resolution of quality issues, organization and efficiency of the execution of clinical trials, data integrity and standardization for regulatory authorities. As part of QMS, current good manufacturing practice (cGMP) regulations must be implemented. The cGMP regulations contain minimum requirements for the methods, facilities and controls used in the manufacturing process. We note that phase I trials may be exempt from some cGMP regulations.

Clinical trial data are then included in the submission of a Biologics License Application (BLA). The BLA typically contains applicant information, product and manufacturing information, preclinical studies, clinical studies and labeling. Sponsors should request a pre-BLA meeting, in which they acquaint FDA reviewers with the ongoing work to be submitted in the BLA, clarify issues of statistical analysis, discuss issues of chemistry, manufacturing and control readiness, and bring up any other relevant or unresolved issues. Upon submission, the FDA reviews the various components of the package and, if necessary, holds advisory committee meetings to obtain additional input from independent experts and the public. Standard review of the BLA occurs within 12 months of submission, including a 60-day filing review period[27]; however, sponsors may need to anticipate some back-and-forth with the FDA, adding more time to approval. Once a BLA is approved, the product may be marketed for clinical use.

Ongoing regulatory compliance

After approval, ongoing regulatory compliance is required. Post-marketing requirements and post-marketing commitments are defined by the FDA at approval. Post-marketing requirements include studies that must be conducted as required by law, whereas post-marketing commitments include studies that the sponsor has agreed to conduct but are not required by law. For example, phase IV trials (that is, post-marketing studies) may be necessary to collect additional safety, efficacy and optimal-use information. To market the product, manufacturing must continue to meet cGMP standards for the lifetime of the product. If a product has serious safety concerns, the FDA may require a Risk Evaluation and Mitigation Strategy programme to promote patient and provider compliance and ensure that adequate patient monitoring is conducted to mitigate adverse

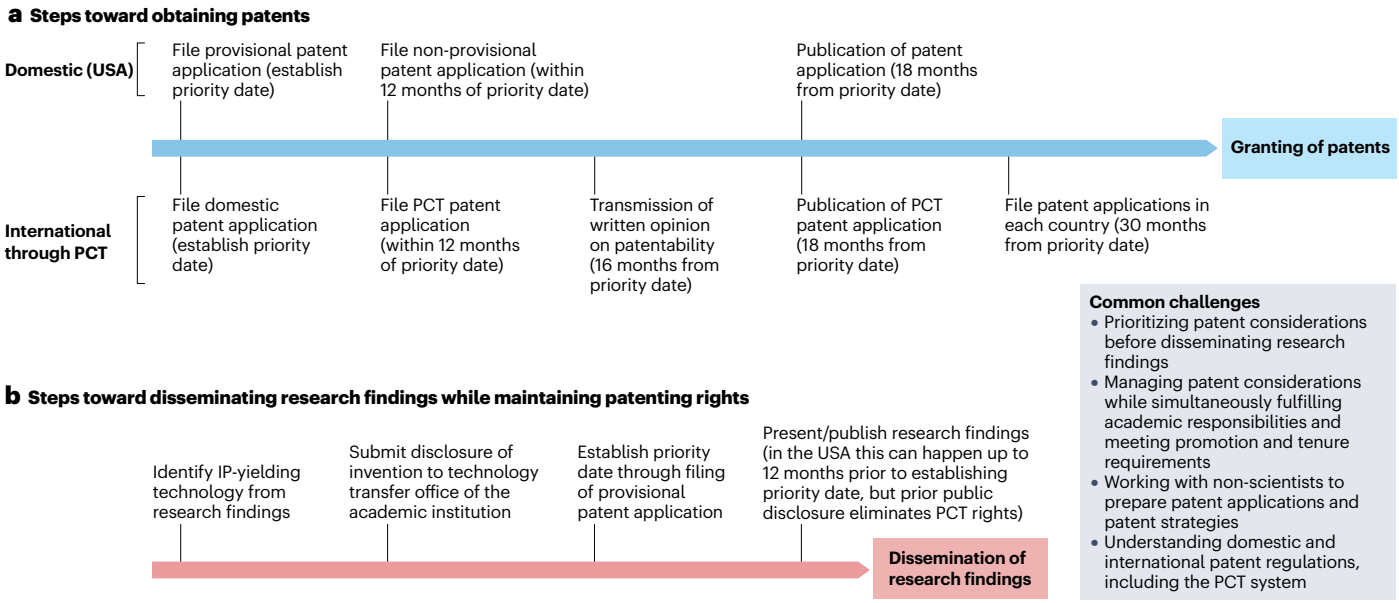

Fig. 1 | Steps toward obtaining patents and disseminating research findings while maintaining patenting rights. a, To apply for a US utility or plant patent, a provisional patent application is typically filed to establish a priority date. Subsequently, a non-provisional patent application is filed within 12 months of the priority date. To apply for international patents through the Patent Cooperation Treaty (PCT), a PCT patent application is filed within 12 months of the priority date. The applicants typically file patent applications in each country separately at 30 months from the priority date. **b**, At an academic institution, to establish intellectual property (IP) and publish research outcomes from identified IP-yielding technology, a disclosure of invention is first submitted to the technology transfer office. A provisional patent application is then filed to establish a priority date, which allows for research findings to be presented and/or published, that is, public disclosure. In the USA, public disclosure can happen up to 12 months prior to the priority date, but any such disclosure would eliminate PCT rights. Common challenges include prioritizing patent considerations before disseminating research outcomes as well as understanding domestic and international patent regulations.

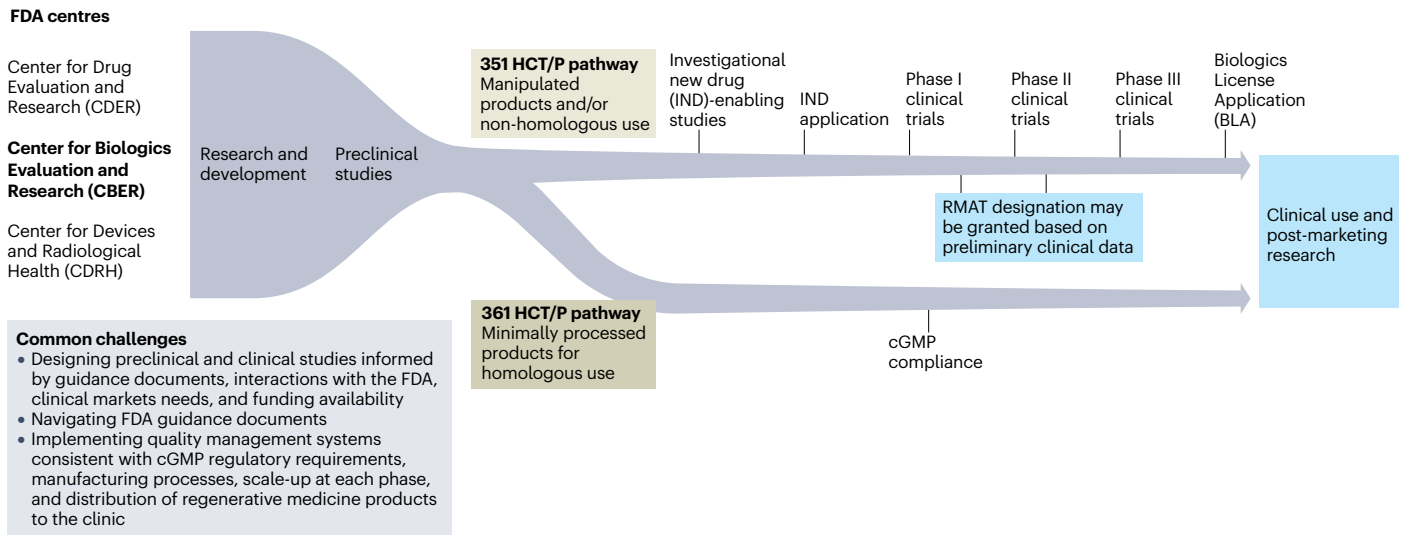

Fig. 2 | The FDA regulatory pathway for regenerative-medicine therapies. In the USA, regenerative-medicine therapies are primarily regulated by the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER). The 361 human cells, tissues, and cellular and tissue-based products (HCT/P) pathway may be considered for minimally processed products intended for homologous use; however, regenerative-medicine therapies, as defined by the FDA, fall under the 351 HCT/P pathway. Upon completing preclinical studies and Investigational New Drug (IND)-enabling studies, an IND application can be submitted to CBER to receive authorization for initial clinical trials. A regenerative-medicine advanced therapy (RMAT) designation may be granted on the basis of preliminary clinical data from early clinical trials. Upon completing the necessary phases of clinical trials, the sponsor submits a Biologics License Application (BLA) to receive market authorization for a regenerative-medicine product. Common challenges include designing preclinical and clinical studies, navigating FDA guidance documents and implementing quality management systems. cGMP, current good manufacturing practice.

events. Additionally, periodic adverse-drug-experience reports must be submitted to the FDA[28]. Therefore, even after approval, the product's sponsor must actively work to ensure ongoing regulatory compliance.

Mechanisms of funding

Funding mechanisms should match the development stage of the academic startup (Fig. 3). The appropriate fund-raising activities need to be determined according to real-time considerations, such as the availability of funding, stage of development and expected costs, including costs for legal work (for example, IP, company formation and compliance), regulatory consultants, research and administrative staff (for example, clinical research coordinators, clinical research associates, project managers), contract research organizations, contract manufacturing organizations, business personnel, insurance, milestone payments and licencing fees and expenses related to clinical trials. The completion of every milestone de-risks the commercialization process, leading to higher company valuation and, thus, different funding requirements. Dilution of equity (that is, company shares) also influences the selection of the funding mechanism. Through dilutive funding, a portion of the company's equity can be allotted to investors in exchange for their financial investments, leading to dilution of the original shareholders' stake (Box 3). By contrast, non-dilutive funding mechanisms do not involve equity dilution, although fees may be required.

Initial funding mechanisms

A number of initial funding mechanisms are available to academic startups in the transition from benchtop discoveries to early business development. Incubators, either external or academia-associated, may be available to help with the initial business development. Incubators usually require small fees in exchange for their space and resources, although they may also seek equity or royalties. Resources available at incubators may include office space, laboratory space, access to advisors, legal counsel, university technology transfer services and grant proposal assistance. For example, under the Genesis Seed Fund, Rutgers University offers up to US$40,000 in non-dilutive funding, on a matching financial contribution basis, to early-stage startups with university-licenced technologies. Aside from resources and expertise, incubators can provide an space independent of academic research laboratories, helping to decouple the startup from academia. Such a process may assist in managing real or apparent conflicts of interest, owing to the potential of financial gains which may influence the academic laboratories' research objectives[29].

However, academic incubators with the equipment, facilities and expertise required specifically for regenerative-medicine startups remain limited. Alternatively, external incubators may provide resources to regenerative-medicine startups; for example, JLABS, the innovation branch at Johnson & Johnson, provides an incubator for life-science companies, including those under the regenerative-medicine umbrella. UBI Global provides a list and ranking of incubators and accelerators worldwide. It is important to consider the specifications of each incubator to ensure it has the specific expertise and resources that a regenerative-medicine startup may require.

Initially, a company is owned entirely by its founders. A single founder or multiple founders coalesce to start the company, resulting in varying proportions of shares being distributed to the initial founders. Founders and/or friends and family may contribute to the initial funding to start the business. Typically, a company then seeks additional funding through individual investors or angel investor

groups (that is, groups of private individuals who finance small business ventures) through what is commonly referred to as a 'seed round'. The amount for a seed round may range between US$100,000 and US$5 million, averaging US$2.2 million. These initial funding mechanisms may allow a regenerative-medicine startup to form its initial structure; however, additional capital in the form of non-dilutive or dilutive funding may be required to advance the company.

Non-dilutive funding mechanisms

Non-dilutive funding mechanisms are typically offered by institutions that do not seek equity (that is, shared ownership) in the startup. Although dilutive funding may be available through venture capital (VC) firms, a regenerative-medicine startup may wish to consider non-dilutive funding mechanisms; these, however, may not be of the same magnitude. Non-dilutive funding includes state or federal grants, such as Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants, or loans, such as Small Business Administration (SBA) loans.

Funding mechanisms specific to regenerative medicine are also available through specific institutes, for example, the California Institute for Regenerative Medicine (CIRM)[30] and Regenerative Medicine Minnesota, which offer funding for basic scientific discoveries that enable regenerative-medicine-relevant technologies, for the building of infrastructure, such as manufacturing facilities or clinics, as well as for preclinical studies and clinical trials. Typically, these organizations do not seek equity in the startup; however, the funding mechanisms can be contingent on an agreement to provide a portion of the revenues upon full-scale commercialization and product approval. The funding of state-based institutes can vary greatly in amount and such grants are typically highly competitive.

Federal funding is a main source of capital for early regenerative-medicine startups; for example, through the SBIR and STTR programmes, over US$4 billion are provided in funding per year to a variety of technologies, including regenerative medicine. SBIRs and STTRs are phased grant mechanisms, offered by the National Institutes of Health (NIH), the National Science Foundation (NSF), the US Department of Defense and other governmental bodies. Phase I and II grants are most commonly awarded. Phase I grants are used to establish technical merit, feasibility and commercial potential of the proposed product, and last 6–12 months depending on the awarding body and proposed

Box 2

Regulatory pathway case study: StrataGraft by Stratatech

The technology for StrataGraft, an allogeneic cellularized scaffold product for the treatment of adults with thermal burns, was developed at the University of Wisconsin-Madison. In 2000, Stratatech was founded as an academic startup on the finding that an immortalized human keratinocyte cell line had been isolated and characterized[52]. Stratatech submitted its Investigational New Drug application in 2001. Because one of the cell lines used for manufacturing had originally been cultured in the presence of murine feeder cells, the product was designated as a xenotransplantation product. In 2016, Stratatech was acquired by Mallinckrodt Pharmaceuticals. In 2017, the treatment obtained Regenerative Medicine Advanced Therapy designation. A Biologics License Application (BLA) was submitted in 2020, and StrataGraft was approved in 2021.

A total of 18 studies were included in the BLA pharmacology/toxicology review of StrataGraft, including preclinical in vitro studies and in vivo murine studies. Preclinical pharmacology studies were not conducted, and so pharmacology studies were based on clinical data. One toxicology study was conducted in the form of a retrospective analysis of previously completed studies. No standalone developmental and reproductive toxicology studies or genotoxicity studies were required. A total of 14 carcinogenicity/tumorigenicity studies were conducted on cell lines, cell banks and implanted StrataGraft tissues. Three additional toxicology studies of components and cryopreservation agents were conducted. Potential drug interactions were included based on a literature review. Overall, it was concluded that no major safety concerns were generated from the preclinical studies.

During the BLA clinical review, four clinical trials were evaluated. A phase I/IIa trial assessed StrataGraft for the repair of full-thickness complex skin defects (open-label, controlled, randomized with total enrollment of 15 participants; start July 2006, completion April 2008)[53–55]. Next, a phase Ib trial was conducted as a dose-escalation study in deep partial-thickness wounds to assess the safety of increasingly larger product doses (open-label, controlled, randomized with total enrollment of 30 participants; start September 2011, completion October 2014)[56]. A phase II study was initiated for the use of StrataGraft to treat full-thickness complex skin defects and terminated in 2019 due to "protracted enrollment and limited wound closure in the first three subjects" (open-label, controlled, randomized with total enrollment of three participants; start April 2017, completion March 2019)[57]. In parallel, a pivotal phase III trial assessed the safety and efficacy of StrataGraft in treating deep partial-thickness burns (open-label, controlled, randomized with total enrollment of 71 participants; start May 2017, completion March 2020)[58]. Of these studies, only the phase Ib and phase III trials were considered for efficacy because they were the only two to investigate the intended indication of deep partial-thickness wounds. However, the US Food and Drug Administration (FDA) also considered safety data generated from the phase I/IIa and phase II trials for an alternate indication.

In addition to the four clinical trials included in the BLA review, four other clinical trials of StrataGraft are registered with ClinicalTrials.gov. Before FDA approval, an additional late-stage clinical trial was initiated to allow expanded access to patients with deep partial-thickness burns[59]. Additional clinical trials are currently ongoing to collect more information on scarring[60], to assess safety and efficacy in paediatric patients[61] or to use StrataGraft in conjunction with an autograft for full-thickness burns[62]. Therefore, although StrataGraft has been approved, research is ongoing and additional patient populations and indications may be further approved.

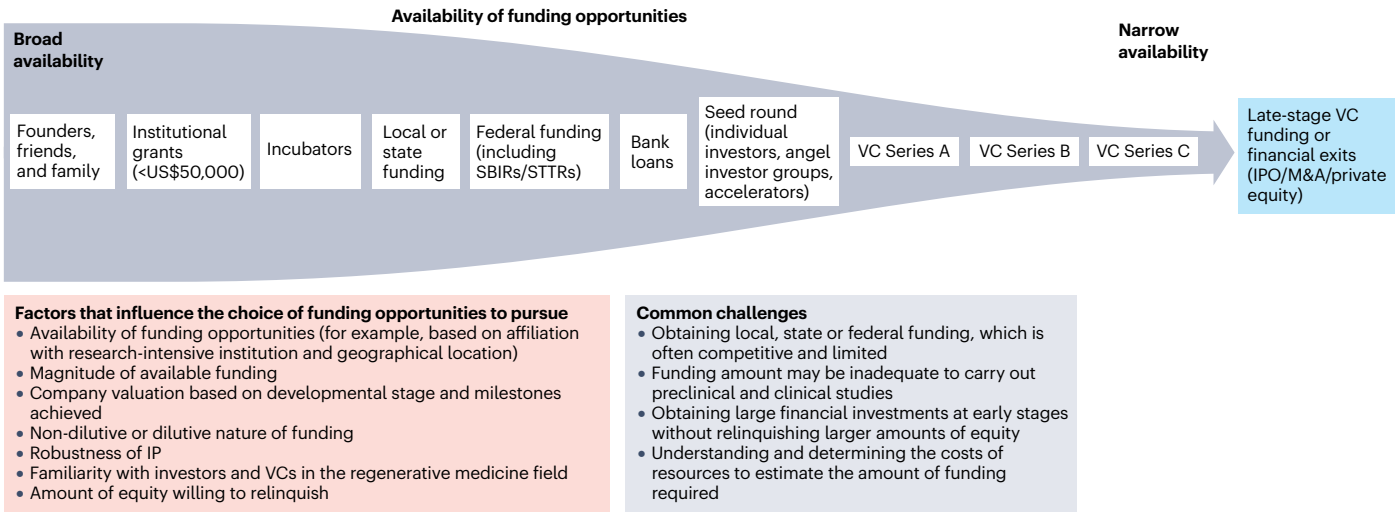

Fig. 3 | Funding mechanisms for academic startups. Academic startups may be funded by various funding mechanisms during the commercialization process. Not all startups make use of all funding opportunities or in the particular order depicted; however, many startups are founded through institutional grants, incubators and/or an initial seed round, prior to seeking federal funding (for example, Small Business Innovation Research, SBIR), accelerators, or local or state funding. Although infrequent, bank loans may be available to startups. Series A, B and C venture capital (VC) funding may be available as the company matures. As a startup progresses through this process, the availability of funding opportunities decreases. Upon maturing, a startup may issue an initial public offering (IPO), seek mergers with other companies, or become acquired by large pharmaceutical companies. Factors that influence funding type and magnitude include the availability and magnitude of funding opportunities, non-dilutive or dilutive nature of funding, and amount of equity the company is willing to relinquish. Common challenges include obtaining competitive and limited funding without relinquishing large amounts of equity and determining costs of resources to estimate the amount of funding required. STTR, Small Business Technology Transfer; M&A, mergers and acquisitions; IP, intellectual property.

research. Phase II grants are awarded to continue the research and development performed in phase I; however, these grants are funded based on a review of the results achieved in phase I, and the commercial potential of the project is more heavily weighed. Phase II grants are often only eligible to prior phase I awardees and can last up to 2 years. Toward preparation and generation of preliminary data for SBIR and STTR proposals, Phase 0 grants may be available to prepare for phase I or II grants. For example, New York, via the Western New York Incubator Network SBIR/STTR assistance programme, offers up to US$4,000 to support the development of phase I proposals. As of October 2022, the funding caps for the total cost of each phase I and phase II SBIR/STTR are US$295,924 and US$1,972,828, respectively. Additional increases are allowed under certain SBA-approved waivers or through SBA approval. For example, various institutes under the NIH allow costs for studies related to regenerative-medicine-based therapies to be funded in excess of these amounts. The startup submitting these grant proposals must ensure they comply with the federal government's administrative requirements, which should be considered if federal grant proposals are submitted with the assistance of an academic institute's sponsored programmes administration. We note that SBIR and STTR grants are highly competitive.

Founders may also seek bank loans to fund their work non-dilutively, which may, however, be challenging for startups without company assets for collateral. SBA loans, in contrast, may not require collateral, can be in excess of US$5 million, and provide competitive terms, rates and fees. Although loans may be appealing to regenerative-medicine startups, founders should be aware that the startup may make zero or very limited revenue, making it difficult to pay back loans on time. In addition, debts figure into company valuation.

Dilutive funding mechanisms

After an initial funding round, regenerative-medicine startups typically seek capital through various types of dilutive funding. Some institutions have accelerators for university-based startups to provide companies access to mentorship, investors and other support in exchange for equity. Dilutive funding also comes in the form of various rounds of VC funding, which may coincide with certain major milestones or de-risking steps in the regulatory pathway, such as pre-IND, IND filing, and commencement of a phase I, II or III clinical trial. These regulatory milestones often require large sums of money, which are typically not available through non-dilutive funding. Another form of dilutive funding mechanism is the convertible note, which is a loan that can be repaid in equity at a specified time or particular milestone.

Accelerators, much like incubators, can assist early startups but typically support later-stage startups that have a defined business model by providing, for example, assistance with the regulatory pathway. For example, Y Combinator Management consists of a variety of investments and companies, with the healthcare sector making up about 12%. In the case of Y Combinator, a standard agreement consists of US$125,000 in exchange for 7% of the startup.

As a regenerative-medicine startup progresses, there may be successive rounds of VC funding. VC funding for regenerative-medicine companies increased to new highs in 2020 and 2021, exceeding US$20 billion in 2021, according to the Alliance for Regenerative Medicine. To obtain the funds required for IND-enabling preclinical studies, for product manufacturing in a cGMP-compliant facility or for clinical trials, companies typically seek a series A round of VC funding. Successive rounds are commonly known as series B, series C and so on, often increasing in monetary amounts. For reference, in the medical

device industry, the averages for venture capital series A, B, and C were US$22 million, US$48 million and US$62 million in the first half of 2022, respectively. Prior to executing a round, the leading VC firm normally performs due diligence on behalf of the investors. This may include auditing of corporate records and analysis of the startup's IP and other assets to determine the value of the company. Upon reaching an agreement on company value and deal terms between the VC firm and the company, the deal is closed, and the startup receives the funds.

Financial exit strategies

Financial exit strategies are plans for selling ownership of the company to investors or another company primarily for the purpose of raising additional funds. Typical exits include initial public offerings (IPOs) and mergers and acquisitions (M&A) (Box 4). Exit decisions for regenerative-medicine companies depend on many factors, such as the outcome of clinical studies, meeting of milestones, cash-flow needs and market conditions. Investors may be motivated to realize timely returns on their investments, whereas academic researchers may be additionally motivated to see their research work translated to useful clinical products. Academic researchers may or may not stand to benefit financially from financial exits; however, financial exits are part of the commercialization process (Table 2).

Box 3

Funding case study: Luxturna by Spark Therapeutics

The technology for Luxturna, a gene-therapy product for the treatment of patients with biallelic *RPE65*-mediated inherited retinal disease, was developed at the Children's Hospital of Philadelphia with the underlying research and development being performed between 2004 and 2013[63]. The academic startup Spark Therapeutics was founded in 2013 initially to develop gene-therapy treatments for inherited retinal disease and haemophilia B[64]. To develop a pipeline of gene-therapy treatments, Spark Therapeutics went through a number of funding mechanisms.

During its founding, Spark Therapeutics was pledged a US$50 million commitment from the Children's Hospital of Philadelphia, receiving an initial investment of US$10 million in series A funding. This initial investment supported two gene-therapy clinical trials at the Children's Hospital of Philadelphia: a phase III study for inherited blindness caused by mutations in the *RPE65* gene and a phase I/II study for haemophilia B, a hereditary bleeding disorder caused by a lack of blood-clotting factor IX[63,64]. In 2014, the company raised an additional US$72.8 million in series B funding led by Sofinnova Ventures, which included additional investments by the Children's Hospital of Philadelphia. The series B funding advanced the ongoing clinical trials and funded the company's headquarters and manufacturing facility. The series B funding was sufficient for Luxturna to be approved by the US Food and Drug Administration in 2017, four years after the initial founding and three years after its series B funding. At the time, this was the first and only gene therapy indicated for a genetic disease.

Box 4

Financial exits case study: Zolgensma by AveXis

The technology of Zolgensma, an adeno-associated-virus-vector-based gene therapy indicated for the treatment of paediatric spinal muscular atrophy type 1, was developed by teams at the Research Institute at Nationwide Children's Hospital and Ohio State University. AveXis was founded in 2012 and received an exclusive licence from Nationwide Children's Hospital in 2013 to develop the technology. In 2014, AveXis raised US$8.5 million in series B1 to fund a phase I clinical trial, which was conducted from 2014 to 2017 (refs. 65,66). Additional funding of US$10 million in series C and US$65 million in series D was raised to further fund its phase I clinical trial and expand operational capabilities. In 2016, the company completed an initial public offering (IPO), offering 4,750,000 shares of common stock at a price of US$20 per share, raising US$95 million. The funds were intended for ongoing operations, including a phase I clinical trial and the establishment of its own manufacturing facility. The company was then acquired by Novartis in 2018 for US$8.7 billion. A Biologics License Application was filed in 2018, and Zolgensma was approved by the US Food and Drug Administration in 2019. The IPO provided an important mechanism for raising additional capital for the successful completion of the phase I clinical trial, leading to the acquisition.

Initial public offering

An IPO is the process of offering shares of a private company to the public through the issuance of new stock, transforming the privately held company to a public one. The typical IPO process takes over 6 months and is expensive, costing, for example, 7% in bank fees for a US$100 million IPO. The process, which includes a due diligence and valuation process, typically involves investment bankers, underwriters, lawyers, accountants and US Securities and Exchange Commission experts. Due diligence involves the full disclosure of finances, legal aspects, such as IP rights, commercial aspects, such as market competitiveness, and corporate governance. The valuation process involves the estimation of company value based on objective and subjective factors, such as the management team, capital structure, potential earnings, market value of assets and competitiveness. The offer price and number of shares to be sold are determined based on company valuation and funds to be raised.

Regenerative-medicine companies often raise financial capital through IPOs. According to publicly available data (Table 2), 38 of 63 (60.3%) companies granted RMAT designations have become publicly traded through IPOs. Thirty-three of those 38 (86.8%) companies reached IPOs before they were granted RMAT designations, suggesting that regenerative-medicine companies can generate enough public investor interest before completing all clinical phases. Specifically, in the US markets, regenerative-medicine companies with RMAT designations raised on average US$147 million (median US$115 million; range US$21–400 million) through their IPOs (Table 2).

Box 5

Overview case study: Breyanzi by Juno Therapeutics

The technology for Brenyanzi, a chimeric antigen receptor (CAR)–T cell immunotherapy, was developed at Memorial Sloan-Kettering Cancer Center, the Seattle Children's Research Institute, and Fred Hutchinson Cancer Research Center. Juno Therapeutics was founded in 2013 by cofounders, including seven academic researchers instrumental in developing CAR–T cell-related technologies. The cofounders held separate patents for key technologies developed at different academic institutions; however, the key patent for lisocabtagene maraleucel (JCAR017), or what eventually became Brenyanzi, was filed by St Jude Children's Research Hospital (with inventors Drs Campana and Imai) in November 2004. The patent was granted in March 2013 by the US Patent and Trademark Office (US8399645B2) and licenced exclusively to Juno Therapeutics in December of 2013. We note that Juno Therapeutics settled a legal dispute with Novartis Pharmaceuticals and the Trustees of the University of Pennsylvania concerning disputes partly involving the above patent. Novartis, developing therapies, one of which led to Kymriah, agreed to an initial payment of US$12.25 million to Juno Therapeutics plus future milestone payments and royalties from net sales in exchange for a licence to continue its development of therapies subject to the above patent.

In a series of venture capital funding, the company raised a total of US$310 million from December of 2013 to August of 2014. In December 2014, the company raised US$304 million through its initial public offering. The Investigational New Drug application (16506) for a single-arm, phase I, multicentre clinical study was authorized in June 2015. The clinical study commenced in January 2016 (ref. 67). JCAR017 received various designations from the US Food and Drug Administration (FDA) for the treatment of patients with relapsed or refractory large B cell lymphoma: orphan designation (April 2016), breakthrough designation (December 2016), and Regenerative Medicine Advanced Therapy designation (October 2017). A pre-Biologics License Application (BLA) meeting, followed by BLA submission, led to FDA approval of JCAR017 in February of 2021 as Breyanzi. Breyanzi was subsequently approved in Japan (March 2021), Switzerland (February 2022), Canada (May 2022), and the European Union (June 2022). Prior to the FDA approval, the company was acquired by Celgene for US$10.4 billion (March 2018), and Celgene was subsequently acquired by Bristol-Myers Squibb for US$74 billion (November 2019). Through additional clinical studies, the indications of Breyanzi are continuing to be expanded. The product revenue of Breyanzi was US$87 million for 2021 and US$182 million for 2022 with a peak sales forecast of US$1.3 billion in 2031.

Mergers and acquisitions

The term M&A refers to the consolidation of companies through financial transactions. In a merger, two or more companies may come together to form a single legal entity. In an acquisition, one company typically purchases another company.

A reverse merger is particularly relevant to regenerative-medicine companies, involving a private company purchasing the shares of an existing public company, thereby turning the private company into a public one. Companies often opt for reverse mergers to avoid the time, cost and complexities of IPOs, while increasing their access to capital and liquidity of stocks. Ten of 63 (15.9%) companies receiving RMAT designations have become publicly traded companies through reverse mergers (Table 2). Reverse mergers do not typically generate immediate capital, but rather open up new avenues of raising capital, such as through private equity or secondary public offerings. Private equity, much like VC funding, is a form of investment that historically focuses on investing in a public or private company and reshaping it (for example, through restructuring, cost reductions, mergers and/or inserting new leadership teams) to prepare for a financial liquidity event, such as resale of the company. Private equity is less common in the life sciences than in other industries, such as energy, consumer products or retail. A secondary public offering may come in two forms: investors may sell their shares to the general public to recoup investments, or the company may sell its shares to raise additional capital, also referred to as follow-on offerings.

Typically, more mature regenerative-medicine companies are acquired. Thirteen companies that received RMAT designations were acquired for an average of US$2.0 billion (median US$608 million; range US$63 million to US$9.0 billion) (Table 2). BioVex, Juno Therapeutics, Stratatech, AveXis and Spark Therapeutics, which are all academic startups that developed FDA-approved regenerative-medicine products, were acquired by large pharmaceutical companies for an average of US$5.9 billion (median US$6.8 billion; range US$1–9 billion), indicating the interest of large pharmaceutical companies in regenerative-medicine therapies (Table 1). With the exception of Spark Therapeutics, these academic startups were acquired prior to receiving FDA approval. Large pharmaceutical companies can not only provide the capital needed to fund clinical studies and establish manufacturing but also the network and expertise to deliver the products to the market through hospitals and clinics.

Outlook

Academic researchers interested in translating their regenerative-medicine therapies may benefit greatly from learning about the commercialization process. Collaboration with clinicians and patients further helps in identifying clinical utility, design parameters and value of regenerative-medicine technologies; for example, input from clinicians affects not only clinical trial designs but may also inform preclinical study designs and the directions or priorities of basic research. Clinicians may be able to explain the limitations of existing therapies, desired outcomes of new treatments, and the feasibility of deploying a regenerative-medicine product in the operating room. A vision of how a regenerative-medicine product may be used clinically can also reveal other product aspects that need to be developed, such as new methods or tools for product placement or delivery as well as surrogate markers for efficacy evaluation. Specific programmes, such

as the NSF-funded Innovation-Corps (I-Corps), that train scientists in assessing market potential using a customer discovery process, are also effective in identifying the needs of patients, clinicians and payers (for example, insurance companies or Medicare). Such programmes may also lead to interactions with the Value Analysis Committees, who are primarily responsible for deciding whether a product will be used within hospitals and healthcare systems[31]. Comparing the effectiveness of new and existing regenerative-medicine therapies, known as comparative effectiveness research, is also an important consideration because reimbursement (that is, payment by insurance companies for a treatment) may require the advantages of new regenerative-medicine therapies in comparison with existing therapies to be identified[32,33]. Therefore, working with clinicians and patients will help to identify product needs early to ensure that time and resources are allocated appropriately.

The difference in priorities between academic and commercialization endeavours may present a dilemma that requires consideration. University faculty members typically prioritize research, teaching and service, including publications and the training and graduation of students and other trainees, which may be delayed by IP considerations. However, universities can take steps to motivate faculty members to pursue commercialization; for example, the Promotion and Tenure-Innovation and Entrepreneurship (PTIE) coalition is a collection of universities that advocates in favour of recognizing innovation and entrepreneurship activities in the faculty promotion and tenure process. PTIE encourages rewarding faculty members for translational efforts, such as allowing commercialization impact to offset teaching or service responsibilities[34]. Furthermore, IP policies of universities often reward academic inventors through benefit-sharing of royalties and licence fees. Policies regarding financial incentives should be updated periodically to maintain alignment with developments in evolving fields, such as regenerative medicine. Academic researchers should also maintain compliance with their institutional conflicts of interest policies to manage any potential conflicts. Furthermore, academic researchers require the support of academic institutions in the management of career priorities and conflicts that may arise through the commercialization process. We encourage academic institutions to modernize traditional faculty personnel policies to facilitate the translation and commercialization of academia-based regenerative-medicine research.

Academic research resources may represent only a modest percentage of the overall commercialization effort, as numerous resources, including the TTO, legal counsel, investors, regulatory consultants, manufacturing experts and business professionals, must be accessed to commercialize regenerative-medicine products. Academic researchers must align themselves with non-science personnel and, at times, defer to the decisions of others with different areas of expertise. The required large financial investments may often lead to dilution (that is, of ownership and control) and/or financial exits (for example, acquisition by large pharmaceutical companies). Thus, academic researchers who developed the core technologies may be required to yield control to those with financial resources and business expertise. However, foundational research in the development of a regenerative-medicine product remains key, even if it represents only a fraction of the overall effort and resources required for commercialization.

Beyond SBIR and STTR mechanisms, governmental funding agencies should develop additional mechanisms to fund IND-enabling

Box 6

Obstacles to commercialization

Obstacles obstruct every step of the interdependent commercialization pathways, including intellectual property (IP) establishment, regulatory approval and funding. For example, academic researchers that disclose their inventions through publications prior to establishing a priority date may lose the chance to patent their technologies and, as a result, may have difficulties in obtaining funding. In addition, sufficient funding must be secured to meet regulatory requirements and to pursue patents, which may be delayed by failing to reach milestones. Moreover, received funds must be managed, while avoiding actual or perceived conflicts of interest. A case in point are two regenerative-medicine companies that did not reach US Food and Drug Administration (FDA) approval of their regenerative-medicine products.

StemCells received a US$20 million award from the California Institute for Regenerative Medicine (CIRM) in 2012 for its Alzheimer's disease therapeutic. In 2014, the company decided not to conduct clinical trials for this indication because of inconclusive results from preclinical studies, while still pursuing other clinical trials for spinal cord and macular degeneration. Analysts consider problems that plagued StemCells to include its overextended condition (that is, attempting to commercialize multiple products simultaneously), lack of funding, inconclusive data, unclear IP and conflicts of interest. The company was eventually acquired through a reverse merger, but no regenerative-medicine product has been commercialized.

Histogenics, founded in 2000, established IP and secured funding to take NeoCart, an autologous chondrocyte implant developed for the treatment of cartilage defects of the knee, eventually to phase III clinical trials[68]. NeoCart was developed in part at Brigham and Women's Hospital and received allowances for US patents in 2005 (US6949252B2) and 2009 (US7537780B2), along with international patents. The company's fundraising included US$13.1 million (2006), US$5.35 million (2008), US$9.0 million (2008), US$34 million (2011), US$49 million (2012), and US$65 million through an initial public offering in 2014. With regard to regulation, Histogenics received an Investigational New Drug authorization for NeoCart in 2003, conducted the first-in-human clinical trial of ten patients from 2004 to 2008, and conducted a phase II clinical trial of 30 patients from 2006 to 2009 to compare NeoCart to a standard-of-care treatment method (microfracture) at a ratio of 2:1[68]. The phase III study, started in 2010, was to include 170 patients across 40 clinical sites in the USA. However, NeoCart narrowly missed the one-year protocol assessment for superiority, leading to the termination of the trial in 2019[68]. Histogenics was acquired in a reverse merger in 2019, and NeoCart has not been commercialized.

studies, such as pivotal preclinical studies, manufacturing development and clinical trials to bridge the 'valley of death'. For example, new funding mechanisms may be created in the form of administrative supplements for federal grants to enable academic researchers to conduct market research or develop a regulatory strategy. For example, funding resources from federal government, such as NIH's Commercialization Readiness Pilot (CRP) programme, are specifically designed for late-stage research and development support. Similarly, federal investment funds could be established that specifically promote promising academic startups emanating from traditional (for example, NIH R01) scientific funding mechanisms. The mismatch in available versus necessary funding for commercialization should be examined at the governmental level.

Academic institutions and funding agencies should also help to reconcile the tension between commercialization and open science and innovation policies. The imperative to translate or commercialize university research is expressed in policy statements, TTO mandates, funding opportunities, IP support as well as in public funding agency requirements and agreements[35]. Simultaneously, open science policies, such as data sharing and open access, are promoted by the same entities through their data-sharing policies and guidelines, such as the most recently updated NIH Data Management and Sharing Policy (effective 25 January 2023). Data-sharing policies hope to maximize the value of research and indicate that both data generators and data users should act with integrity and transparency, especially through recognition of the contributions of researchers who generate, preserve and share datasets[35]. However, commercialization endeavours may require careful consideration of data ownership and licences. In 2022, the White House Office of Science and Technology Policy also updated the US policy guidance to make taxpayer-supported research results immediately available without an embargo or cost by the end of 2025. Ideally, the dual pressures of commercialization and open science will be balanced to benefit both science and society through the optimization of social value and economic benefit that emanates from university research[35].

In addition to IP, regulatory pathways, mechanisms of funding and financial exits considerations, the commercialization process includes the design of preclinical studies and clinical trials[25,36], reimbursement strategies[37,38], market analysis, business development, and international regulations and policies. Moreover, here, we discuss regenerative-medicine companies that developed FDA-approved regenerative-medicine products and/or received RMAT designations; however, to delineate the factors that lead to company successes or failures, academic startups at various clinical stages may need to be examined. For example, we stand to learn from both the successes of companies such as Juno Therapeutics (Box 5) as well as the obstacles to commercialization that other companies have faced in trying to obtain FDA approval of their regenerative-medicine products (Box 6).

Standardized pathways for the translation and commercialization of regenerative-medicine technologies have yet to be developed. Although each regenerative-medicine company may face distinct challenges, depending on the product, such limited precedence and standardization may impede the translation of regenerative-medicine technologies. In addition, an understanding of the commercialization process may allow academic researchers to develop commercialization strategies that match their regenerative-medicine technologies. To this end, the scientific community, academic institutions and governmental agencies need to work together to modify policies and develop new programmes to assist academic researchers with the objective of maximizing the public benefit of academic and translational research.

Citation diversity statement

We acknowledge that papers authored by scholars from historically excluded groups are systematically under-cited. Here, we have made every attempt to reference relevant papers in a manner that is equitable in terms of racial, ethnic, gender and geographical representation.

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References

1. Oberweis, C. V., Marchal, J. A., López-Ruiz, E. & Gálvez-Martín, P. A worldwide overview of regulatory frameworks for tissue-based products. *Tissue Eng. B* **26**, 181–196 (2020).
2. Jacques, E. & Suuronen, E. J. The progression of regenerative medicine and its impact on therapy translation. *Clin. Transl. Sci.* **13**, 440–450 (2020).
3. Goula, A. et al. Advanced therapy medicinal products challenges and perspectives in regenerative medicine. *J. Clin. Med. Res.* **12**, 780–786 (2020).
4. Sipp, D. & Okano, H. Japan strengthens regenerative medicine oversight. *Cell Stem Cell* **22**, 153–156 (2018).
5. Kim, D.-S. & Bae, S. Impact and challenges of enactment for advanced regenerative medicine in South Korea. *Front. Bioeng. Biotechnol.* **10**, 972865 (2022).
6. Qiu, T., Hanna, E., Dabbous, M., Borislav, B. & Toumi, M. Regenerative medicine regulatory policies: a systematic review and international comparison. *Health Policy* **124**, 701–713 (2020).
7. Hogle, L. F. & Das, A. The social production of evidence: regenerative medicine and the 21st Century Cures Act. *Regen. Med.* **12**, 581–586 (2017).
8. Brown, D. G. & Wobst, H. J. A decade of FDA-approved drugs (2010–2019): trends and future directions. *J. Med. Chem.* **64**, 2312–2338 (2021).
9. Butler, D. Translational research: crossing the valley of death. *Nature* **453**, 840–842 (2008).
10. Frederickson, R. M. Escaping the valley of death. *Mol. Ther.* **20**, 476–478 (2012).
11. Hinsenkamp, A., Benyó, Z. & Hornyák, I. Overview of tissue engineering patent strategies and patents from 2010 to 2020, including outcomes. *Tissue Eng. B* **28**, 626–632 (2022).
12. Allen-Hoffmann, L., Comer, A., Conrad, P. B., Hoffmann, M. & Ivarie, C. A.-R. Improved skin substitutes and uses thereof. Australian patent application 214639 B2 (2010).
13. Asano, S., Nakanishi, Y. & Sugiyama, D. Intellectual property in the field of regenerative medicine in Japan. *Clin. Ther.* **40**, 1823–1827 (2018).
14. Pirnstill, J. & Allen-Hoffmann, B. L. Cold storage of organotypically cultured skin equivalents for clinical applications. US patent 10743533 B2 (2022).
15. Allen-Hoffmann, B. L., Pirnstill, J. C., Gratz, K. R. & Comer, A. R. Cryopreservation of viable human skin substitutes. Australian patent 232795 B2 (2019).
16. Koepsel, J. & Gratz, K. Tissue container systems. US patent application 0330542 A1 (2022).
17. Smiell, J., Comer, A., Lokuta, M. & Allen-Hoffmann, B. L. Methods for treating acute wounds and improving outcomes. Australian patent application 353695 A1 (2020).
18. Wang, S.-J. Patent portfolios for biotech inventions. *Nat. Biotechnol.* **31**, 501–503 (2013).
19. Rachinsky, T. First-to-invent versus first-to-file: impact of the AIA. *Pharm. Pat. Anal.* **3**, 353–359 (2014).
20. Begley, C. G. & Ioannidis, J. P. A. Reproducibility in science. *Circ. Res.* **116**, 116–126 (2015).
21. Ozyhar, T., Barnabei, L. & Myrick, D. When speed matters: a discussion on the benefits of a grace period in patent law to accelerate pharmaceutical innovation in times of pandemic. *J. Law Biosci.* **9**, lsac004 (2022).
22. Sherkow, J. S. Preprint servers and patent prior art. *EMBO Rep.* **23**, e54439 (2022).
23. Armstrong, J. P. K. et al. A blueprint for translational regenerative medicine. *Sci. Transl. Med.* **12**, eaaz2253 (2020).
24. Crama, P., Reyck, B. D. & Degraeve, Z. Milestone payments or royalties? Contract design for R&D licensing. *Oper. Res.* **56**, 1539–1552 (2008).
25. Nordberg, R. C., Otarola, G. A., Wang, D., Hu, J. C. & Athanasiou, K. A. Navigating regulatory pathways for translation of biologic cartilage repair products. *Sci. Transl. Med.* **14**, eabp8163 (2022).
26. Zscharnack, M. et al. Preclinical good laboratory practice-compliant safety study to evaluate biodistribution and tumorigenicity of a cartilage advanced therapy medicinal product (ATMP). *J. Transl. Med.* **13**, 160 (2015).
27. Cox, E. M., Edmund, A. V., Kratz, E., Lockwood, S. H. & Shankar, A. Regulatory affairs 101: introduction to expedited regulatory pathways. *Clin. Transl. Sci.* **13**, 451–461 (2020).
28. Kulkarni, T. N. & Kulkarni, N. G. Authoring a periodic adverse drug experience report… here's what you need to know! *Perspect. Clin. Res.* **10**, 95–99 (2019).
29. Alapati, D., Egan, P. & Holcombe, J. Understanding conflict of interest for academic entrepreneurs. In *Academic Entrepreneurship for Medical and Health Scientists*. PubPub Edition (2021).
30. Collins, L. R. & Shepard, K. A. CIRM tools and technologies: breaking bottlenecks to the development of stem cell therapies. *Stem Cell Transl. Med.* **9**, 1129–1136 (2020).
31. Yuh, D. D. Value analysis committees: not just another committee to get out of. *J. Thorac. Cardiovasc. Surg.* **155**, 686–687 (2018).
32. Dang, A. & Kaur, K. Comparative effectiveness research and its utility in in-clinic practice. *Perspect. Clin. Res.* **7**, 9–14 (2016).

33. Westrich, K. D., Wilhelm, J. A. & Schur, C. L. Comparative effectiveness research in the USA: when will there be an impact on healthcare decision-making? *J. Comp. Eff. Res.* **5**, 207–216 (2016).
34. Carter, R. G. et al. Innovation, entrepreneurship, promotion, and tenure. *Science* **373**, 1312–1314 (2021).
35. Caulfield, T., Harmon, S. H. & Joly, Y. Open science versus commercialization: a modern research conflict? *Genome Med.* **4**, 17 (2012).
36. Tompkins, B. A. et al. IMPACT: Preclinical studies of cell therapy for human disease. *Circ. Res.* **122**, 1006–1020 (2018).
37. Ginty, P., Singh, P., Smith, D., Hourd, P. & Williams, D. Achieving reimbursement for regenerative medicine products in the USA. *Regen. Med.* **5**, 463–469 (2010).
38. Bubela, T. et al. Bringing regenerative medicines to the clinic: the future for regulation and reimbursement. *Regen. Med.* **10**, 897–911 (2015).
39. Marks, L. V. Collaboration — a competitor's tool: the story of Centocor, an entrepreneurial biotechnology company. *Bus. History* **51**, 529–546 (2009).
40. Cheever, M. A. & Higano, C. S. PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. *Clin. Cancer Res.* **17**, 3520–3526 (2011).
41. Schmidt, C. Gintuit cell therapy approval signals shift at US regulator. *Nat. Biotechnol.* **30**, 479–479 (2012).
42. Schmidt, C. FDA approves first cell therapy for wrinkle-free visage. *Nat. Biotechnol.* **29**, 674–675 (2011).
43. Boss, W. K. et al. Autologous cultured fibroblasts as cellular therapy in plastic surgery. *Clin. Plastic Surg.* **27**, 613–626 (2000).
44. Morrison, C. Boom: 2018's biotech IPOs. *Nat. Rev. Drug Discov.* **18**, 3–6 (2019).
45. Markert, M. L. et al. Successful formation of a chimeric human thymus allograft following transplantation of cultured postnatal human thymus. *J. Immunol.* **158**, 998–1005 (1997).
46. Markert, M. L. et al. Transplantation of thymus tissue in complete DiGeorge syndrome. *N. Engl. J. Med.* **341**, 1180–1189 (1999).
47. Markert, M. L. et al. Thymus transplantation in complete DiGeorge syndrome: immunologic and safety evaluations in 12 patients. *Blood* **102**, 1121–1130 (2003).
48. Markert, M. Parathyroid and thymus transplantation in DiGeorge syndrome subjects. US patent 0041854 A1 (2009).
49. Markert, M. L. Parathyroid and thymus transplantation in DiGeorge syndrome subjects. World patent application WO 107601 A3 (2006).
50. Markert, M. L. Cultured thymus tissue transplantation promotes donor-specific tolerance to allogeneic solid organ transplants. World patent application WO 165197 A1 (2019).
51. Markert, M. L. et al. Methods of determining the suitability of cultured thymus tissue for implantation into humans and associated methods of use. Canadian patent application 3150732 A1 (2021).
52. Allen-Hoffmann, B. L. et al. Normal growth and differentiation in a spontaneously immortalized near-diploid human keratinocyte cell line, NIKS. *J. Investig. Dermatol.* **114**, 444–455 (2000).
53. Schurr, M. J. et al. Phase I/II clinical evaluation of stratagraft: a consistent, pathogen-free human skin substitute. *J. Trauma. Acute Care Surg.* **66**, 866 (2009).
54. US National Library of Medicine. StrataGraft™ skin tissue (human donor skin) in the surgical management of complex skin defects. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT00618839 (2019).
55. Centanni, J. M. et al. StrataGraft Skin substitute is well-tolerated and is not acutely immunogenic in patients with traumatic wounds: results from a prospective, randomized, controlled dose escalation trial. *Ann. Surg.* **253**, 672 (2011).
56. US National Library of Medicine. StrataGraft® skin tissue as an alternative to autografting deep partial-thickness burns. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01437852 (2019).
57. US National Library of Medicine. StrataGraft® skin tissue as an alternative to autografting full-thickness complex skin defects. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03005054 (2016).
58. Gibson, A. L. F. et al. A phase 3, open-label, controlled, randomized, multicenter trial evaluating the efficacy and safety of StrataGraft® construct in patients with deep partial-thickness thermal burns. *Burns* **47**, 1024–1037 (2021).
59. US National Library of Medicine. StrataGraft skin tissue expanded access at specific study sites (StrataCAT). *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04123548 (2021).
60. US National Library of Medicine. Scarring in stratagraft-treated vs. autograft-treated burn wounds: a clinical and histological investigation. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04896346 (2022).
61. US National Library of Medicine. StrataGraft safety, tolerability and efficacy in pediatric subjects (StrataSTEPS). *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT05517902 (2023).
62. US National Library of Medicine. StrataGraft overlay of meshed autograft in full-thickness thermal Burns (StrataSOMA). *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04765202 (2023).
63. Russell, S. et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet* **390**, 849–860 (2017).
64. Walsh, C. E. & Batt, K. M. Hemophilia clinical gene therapy: brief review. *Transl. Res.* **161**, 307–312 (2013).
65. US National Library of Medicine. Gene transfer clinical trial for spinal muscular atrophy type 1. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02122952 (2022).
66. Mendell, J. R. et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N. Engl. J. Med.* **377**, 1713–1722 (2017).
67. US National Library of Medicine. Study evaluating the safety and pharmacokinetics of JCAR017 in B-cell non-Hodgkin lymphoma (TRANSCEND-NHL-001). *ClinicalTrials.gov* https://www.clinicaltrials.gov/ct2/show/NCT02631044 (2023).
68. Anderson, D. E., Gridley, A. & Crawford, D. C. Next generation cartilage repair and the pre-arthroplasty patient. *Oper. Tech. Sports Med.* **30**, 150956 (2022).

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Competing interests
R.P.D., J.C.H. and K.A.A. are cofounders of and hold equity in Cartilage Inc. The remaining authors declare no competing interests.

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4/17/2017 (RVT-802: https://enzyvant.com/enzyvant-receives-fda-designations/
5/2/2017 (jCell): https://www.biospace.com/article/jcyte-receives-regenerative-medicine-advanced-therapy-designation-/
5/10/2017 (Ixmyelocel-T): https://investors.vcel.com/news-releases/news-release-details/vericel-receives-fda-regenerative-medicine-advanced-therapy-rmat
7/18/2017 (approved as StrataGraft): https://www.prnewswire.com/news-releases/us-fda-designates-mallinckrodts-stratagraft-as-regenerative-medicine-advanced-therapy-300489200.html
2017 (UD): https://www.globenewswire.com/en/news-release/2017/08/22/1091116/0/en/Mustang-Bio-Commences-Trading-on-the-NASDAQ-Global-Market.html
9/20/2017 (ATIR101): https://www.businesswire.com/news/home/20170919006698/en/Kiadis-Pharma-Receives-FDA-Regenerative-Medicine-Advanced-Therapy-RMAT-Designation-for-ATIR101™
10/1/2017 (LentiGlobin approved as Zynteglo for the treatment of beta thalassaemia): https://www.raps.org/news-and-articles/news-articles/2019/5/regulatory-intelligence-update-on-regenerative-me
10/2/2017 (AST-OPC1): https://www.globenewswire.com/news-release/2017/10/02/1138619/0/en/Asterias-Announces-Two-Significant-Developments-for-Spinal-Cord-Injury-Program.html
10/5/2017 (MultiStem): https://seekingalpha.com/news/3299585-fda-designates-athersys-multistem-cell-therapy-for-accelerated-approval-shares-ahead-8
11/1/2017 (JCAR017): https://www.businesswire.com/news/home/20171101006552/en/Juno-Therapeutics-Reports-Third-Quarter-2017-Financial-Results
11/8/2017 (CEVA101): https://www.fortressbiotech.com/news-media/press-releases/detail/42/fortress-biotech-announces-cellvations-ceva101-granted
12/21/2017 (MPC-150-IM): https://www.globenewswire.com/news-release/2017/12/21/1268818/0/en/Mesoblast-Receives-FDA-Regenerative-Medicine-Advanced-Therapy-Designation-for-Its-Cell-Therapy-in-Heart-Failure-Patients-With-Left-Ventricular-Assist-Devices.html
1/29/2018 (EB-101): https://investors.abeonatherapeutics.com/press-releases/detail/109/abeona-receives-fda-regenerative-medicine-advanced-therapy
2/5/2018 (CAP-1002): https://www.globenewswire.com/news-release/2018/02/05/1333106/29467/en/Capricor-Receives-FDA-Regenerative-Medicine-Advanced-Therapy-RMAT-Designation-for-Duchenne-Muscular-Dystrophy-Therapy.html
3/9/2018 (AminoFix Injectable): https://mimedx.gcs-web.com/news-releases/news-release-details/amniofixr-injectable-granted-regenerative-medicine-advanced
4/23/2018 (ABO-102): https://investors.abeonatherapeutics.com/press-releases/detail/123/abeona-announces-fda-grants-rmat-designationto-abo-102

May 2018 (VM-202): https://www.raps.org/news-and-articles/news-articles/2019/5/regulatory-intelligence-update-on-regenerative-me
2000 (US$53 M): https://www.fool.com/investing/2018/05/17/sangamo-therapeutics-stock-history.aspx
6/14/2018 (NSR-REP1): https://www.globenewswire.com/en/news-release/2018/06/14/1524448/0/en/Nightstar-Therapeutics-Receives-Regenerative-Medicine-Advanced-Therapy-RMAT-Designation-for-NSR-REP1-in-Choroideremia.html
6/19/2018 (CLBS14): https://www.globenewswire.com/news-release/2018/06/19/1526396/18623/en/Caladrius-Receives-FDA-Regenerative-Medicine-Advanced-Therapy-Designation-for-CD34-Cell-Therapy-for-Treating-Refractory-Angina.html
6/21/2018 (VY-AADC): https://www.globenewswire.com/en/news-release/2018/06/21/1527729/36461/en/Voyager-Therapeutics-Announces-FDA-Regenerative-Medicine-Advanced-Therapy-RMAT-Designation-Granted-for-VY-AADC-for-the-Treatment-of-Parkinson-s-Disease.html
7/2/2018 (Romyelocel-L): https://www.businesswire.com/news/home/20180702005248/en/Cellerant-Therapeutics-Inc.-Announces-FDA-Grants-Regenerative-Medicine-Advanced-Therapy-RMAT-Designation-for-Romyelocel-L-to-Prevent-Infections-During-Neutropenia
8/21/2018 (AT132): https://www.prnewswire.com/news-releases/audentes-announces-regenerative-medicine-advanced-therapy-rmat-designation-granted-by-the-fda-to-at132-for-the-treatment-of-x-linked-myotubular-myopathy-300699224.html
10/11/2018 (Lifileucel): https://www.globenewswire.com/news-release/2018/10/11/1620273/0/en/Iovance-Biotherapeutics-Reports-Results-from-FDA-End-of-Phase-2-meeting-and-Provides-Updates-About-the-Company-s-Clinical-Program.html
10/29/2018 (Avance Nerve Graft): https://ir.axogeninc.com/press-releases/detail/849/avance-nerve-graft-receives-regenerative-medicine
11/5/2018 (P-BCMA-101): https://investors.poseida.com/news-releases/news-release-details/poseida-therapeutics-receives-regenerative-medicine-advanced/
11/27/2018 (RP-L102): https://ir.rocketpharma.com/news-releases/news-release-details/rocket-pharmaceuticals-receives-fda-regenerative-medicine/
4/18/2019 (FCR-001): https://talaristx.com/2019/04/talaris-therapeutics-inc-announces-promising-phase-2-data-of-novel-allogeneic-cell-therapy-in-living-donor-kidney-transplant-recipients/
4/23/2019 (ECT-001): https://www.globenewswire.com/news-release/2019/04/23/1807869/0/en/ExCellThera-s-lead-technology-ECT-001-receives-FDA-Regenerative-Medicine-Advanced-Therapy-RMAT-designation.html
May 2019 (Alofisel): https://www.takeda.com/newsroom/newsreleases/2022/alofisel-darvadstrocel-shows-clinical-remission-rate-at-six-months-in-the-real-world-inspire-study-interim-analysis-consistent-with-the-pivotal-clinical-admire-cd-study/
5/29/2019 (FCX-007): https://www.globenewswire.com/en/news-release/2019/05/29/1856272/33272/en/Fibrocell-Receives-FDA-Regenerative-Medicine-Advanced-Therapy-Designation-for-FCX-007-Gene-Therapy-for-the-Treatment-of-RDEB.html
6/11/2019 (Posoleucel): https://ir.allovir.com/news-releases/news-release-details/allovir-announces-viralym-m-granted-regenerative-medicine/
6/24/2019 (KB103): https://ir.krystalbio.com/news-releases/news-release-details/krystal-biotech-announces-positive-results-phase-2-clinical
7/5/2019 (SB-525): https://investor.sangamo.com/news-releases/news-release-details/sangamo-and-pfizer-announce-updated-phase-12-results-sb-525
7/29/2019 (OTL-103): https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-fda-regenerative-medicine/
8/22/2019 (MB-107): https://ir.mustangbio.com/news-events/press-releases/detail/68/mustang-bio-and-st-jude-childrens-research-hospital
9/4/2019 (MGTA-456): https://investor.magentatx.com/news-releases/news-release-details/magenta-therapeutics-announces-fda-regenerative-medicine/
9/20/2019 (SB623): https://www.pharmaceutical-business-review.com/news/sanbio-rmat-sb623-cell-therapy/
10/28/2019 (CT053): https://www.prnewswire.com/news-releases/carsgen-announces-investigational-car-t-therapy-ct053-granted-rmat-designation-by-the-us-fda-for-rr-multiple-myeloma-300945966.html
12/3/2019 (ADP-A2M4): https://www.adaptimmune.com/investors-and-media/news-center/press-releases/detail/11/regenerative-medicine-advanced-therapy-designation-granted
2/27/2020 (TT11): https://www.thepharmaletter.com/article/tessa-picks-up-rmat-designation-for-novel-car-t-cell-candidate
4/16/2020 (TTAX02): https://www.prnewswire.com/news-releases/tissuetech-receives-regenerative-medicine-advanced-therapy-rmat-designation-from-us-food-and-drug-administration-301042276.html
4/22/2020 (FDA-approved as Kymriah): https://www.novartis.com/news/media-releases/novartis-kymriah-receives-fda-regenerative-medicine-advanced-therapy-designation-follicular-lymphoma
5/6/2020 (Ilixadencel): https://www.globenewswire.com/news-release/2020/05/06/2028129/0/en/Immunicum-AB-publ-Receives-Regenerative-Medicine-Advanced-Therapy-Designation-from-FDA-for-Ilixadencel-in-Kidney-Cancer.html
5/11/2020 (CTX001): https://crisprtx.com/about-us/press-releases-and-presentations/crispr-therapeutics-and-vertex-pharmaceuticals-announce-fda-regenerative-medicine-advanced-therapy-rmat-designation-granted-to-ctx001-for-the-treatment-of-severe-hemoglobinopathies
9/22/2020 (MDR-101): https://www.medeortx.com/news/pr-2020-09-22.php
9/23/2020 (MultiStem): https://www.athersys.com/investors/press-releases/press-release-details/2020/FDA-Grants-RMAT-Designation-to-MultiStem-Cell-Therapy-for-the-Treatment-of-Acute-Respiratory-Distress-Syndrome/default.aspx
10/14/2020 (Orca-T): https://www.globenewswire.com/news-release/2020/10/14/2108307/0/en/Orca-Bio-Receives-Regenerative-Medicine-Advanced-Therapy-RMAT-Designation-for-Orca-T.html
11/11/2020 (AB205): https://angiocrinebioscience.com/news-events/news/
12/17/2020 (AMDC-USR): https://www.biospace.com/article/fda-grants-rmat-designation-for-cook-myosite-s-investigational-autologous-muscle-derived-cells-for-urinary-sphincter-repair/
1/11/2021 (ReNu): https://organogenesis.com/news-events/press-release-01112021.html
3/8/2021 (valoctocogene roxaparvovec): https://investors.biomarin.com/2021-03-08-BioMarin-Announces-FDA-Regenerative-Medicine-Advanced-Therapy-RMAT-Designation-Granted-to-Valoctocogene-Roxaparvovec-Investigational-Gene-Therapy-for-Hemophilia-A
3/9/2021 (RP-L201): https://ir.rocketpharma.com/news-releases/news-release-details/rocket-pharmaceuticals-receives-fda-regenerative-medicine-0/
4/21/2021 (ALLO-715): https://ir.allogene.com/news-releases/news-release-details/allogene-therapeutics-announces-fda-regenerative-medicine/
Oct 2021 (REACT): https://investors.prokidney.com/news-releases/news-release-details/prokidney-corroborates-mechanism-action-reacttm-cell-marker
11/22/2021 (CTX110): http://ir.crisprtx.com/news-releases/news-release-details/crispr-therapeutics-announces-fda-regenerative-medicine-advanced/
12/13/2021 (FT516): https://ir.fatetherapeutics.com/news-releases/news-release-details/fate-therapeutics-highlights-positive-durability-response-data
2022 SPAC merger (UD): https://medcitynews.com/2022/01/regenerative-med-biotech-prokidney-inks-825m-merger-to-back-ckd-cell-therapy/
1/5/2022 (Posoleucel): https://ir.allovir.com/news-releases/news-release-details/fda-grants-regenerative-medicine-advanced-therapy-rmat/
1/10/2022 (CT041): https://www.prnewswire.com/news-releases/carsgen-announces-ct041-car-t-cell-product-candidate-granted-rmat-designation-by-the-fda-301456859.html
1/12/2022 (C-CAR039): https://www.cellbiomedgroup.com/newsroom/fda-rmat?lang=en
2/14/2022 (AProArt): https://www.ucsf.edu/news/2022/02/422276/ucsf-gene-therapy-deadly-mutation-fast-tracked-fda-review
4/12/2022 (Exoflo): https://directbiologics.com/fda-grants-direct-biologics-regenerative-medicine-advanced-therapy-rmat-designation-for-the-use-of-exoflo-in-covid-19-related-ards/
4/20/2022 (Posoleucel): https://ir.allovir.com/news-releases/news-release-details/fda-grants-regenerative-medicine-advanced-therapy-rmat-0/
4/25/2022 (Obe-cel): https://autolus.gcs-web.com/news-releases/news-release-details/fda-grants-regenerative-medicine-advanced-therapy-rmat/
5/13/2022 (SkinTE): https://www.prnewswire.com/news-releases/polarityte-announces-fda-regenerative-medicine-advanced-therapy-designation-granted-to-skinte-301546677.html
5/24/2022 (NeoCart): https://ir.ocugen.com/news-releases/news-release-details/ocugen-announces-new-cell-therapy-program-following-fda/
6/8/2022 (ALLO-501A): https://ir.allogene.com/news-releases/news-release-details/allogene-therapeutics-announces-fda-granted-regenerative/
9/28/2022 (CTX130): https://crisprtx.com/about-us/press-releases-and-presentations/crispr-therapeutics-announces-fda-regenerative-medicine-advanced-therapy-rmat-designation-granted-to-ctx130-for-the-treatment-of-cutaneous-t-cell-lymphomas-ctcl
11/8/2022 (ADP-A2M4CD8): https://www.adaptimmune.com/investors-and-media/news-center/press-releases/detail/234/adaptimmune-reports-increased-response-rate-and-durability
11/29/2022 (CB-010): https://investor.cariboubio.com/news-releases/news-release-details/caribou-biosciences-announces-fda-granted-regenerative-medicine/
1/26/2023 (rebonuputemcel): https://www.discgenics.com/news-posts/2023/1/26/discgenics-announces-fda-regenerative-medicine-advanced-therapy-rmat-designation-granted-to-idct-for-degenerative-disc-disease
2/7/2023 (RP-A501): https://ir.rocketpharma.com/news-releases/news-release-details/rocket-pharmaceuticals-receives-fda-regenerative-medicine-1/
2/8/2023 (rexlemestrocel-L): https://www.globenewswire.com/en/news-release/2023/02/08/2604535/0/en/FDA-Grants-Regenerative-Medicine-Advanced-Therapy-Rmat-Designation-for-Rexlemestrocel-L-in-Chronic-Low-Back-Pain.html
2/11/2023 (CT103A): https://www.iasobio.com/phone/info.php?id=215
3/21/2023 (NTLA-2002): https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-fda-regenerative-medicine
5/4/2023 (HAV): https://www.globenewswire.com/news-release/2023/05/04/2661452/0/en/Humacyte-s-Human-Acellular-Vessel-HAV-Receives-FDA-s-Regenerative-Medicine-Advanced-Therapy-RMAT-Designation-for-Urgent-Arterial-Repair-Following-Vascular-Trauma.html
5/23/2023 (RP-L301): https://ir.rocketpharma.com/news-releases/news-release-details/rocket-pharmaceuticals-receives-fda-regenerative-medicine-2/
5/24/2023 (RGX-121): https://www.prnewswire.com/news-releases/regenxbio-receives-fda-regenerative-medicine-advanced-therapy-rmat-designation-for-rgx-121-gene-therapy-for-hunter-syndrome-301831944.html
1997 (US$20 M): https://investors.vcel.com/node/11886/html
1999 (US$58 M): https://www.bioworld.com/articles/392839-biomarin-completes-58m-ipo-as-first-product-nears-market?v=preview
2004 (US$21 M): https://www.intelligentinvestor.com.au/shares/asx-msb/mesoblast-limited/float
2007 (US$56 M): https://www.pehub.com/tigenix-ipo-prices-in-brussels/
2007 Reverse merger (UD): https://www.cleveland.com/business/2007/06/athersys_goes_public_in_revers.html

2008 (UD): https://roic.ai/company/IOVA
2008 Reverse merger (UD): https://www.biospace.com/article/mimedx-announces-post-split-name-change-/
2011 Reverse merger (UD): https://www.cfodive.com/news/reverse-merger-helped-recession-hit-axogen-regain-footing/602531/
2013 (SEK 21 M): https://www.marketscreener.com/quote/stock/MENDUS-AB-PUBL-17946401/news/Immunicum-AB-has-completed-an-IPO-in-the-amount-of-SEK-21-40-million-39111826/
2013 (US$116 M): https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-closing-initial-public-offering-and
2013 (US$40 M): https://www.fiercebiotech.com/r-d/fate-ipo-flop-raises-fresh-concerns-about-investors-appetite-for-biotech
2013 Reverse merger (UD): https://www.biospace.com/article/china-s-b-cellular-biomedicine-group-b-announces-reverse-merger-/
2013 Reverse merger (UD): https://www.businesswire.com/news/home/20131121005377/en/Capricor-and-Nile-Therapeutics-Complete-Merger-to-Form-Capricor-Therapeutics-Inc.
2014 (US$265 M): https://www.fiercebiotech.com/r-d/updated-juno-banks-a-265m-ipo-pushing-next-big-thing-oncology
2015 (US$124 M): https://www.businesswire.com/news/home/20150408005269/en/SanBio-Announces-Pricing-of-Initial-Public-Offering-on-Tokyo-Stock-Exchange
2015 (US$159 M): https://www.globenewswire.com/news-release/2015/09/22/770163/10150220/en/REGENXBIO-Announces-Closing-of-Initial-Public-Offering-and-Full-Exercise-of-Underwriters-Option-to-Purchase-Additional-Shares.html
2015 (US$191 M): https://www.nasdaq.com/articles/adaptimmune-therapeutics-prices-upsized-ipo-17-high-end-range-2015-05-05
2015 (US$36 M): https://www.fiercebiotech.com/r-d/kiadis-banks-36m-a-euro-ipo-to-fund-its-stem-cell-r-d
2015 (US$5.5 M): https://www.prnewswire.com/news-releases/asterias-biotherapeutics-completes-public-offering-and-private-placement-of-common-stock-300033976.html
2015 (US$81 M): https://ir.voyagertherapeutics.com/news-releases/news-release-details/voyager-therapeutics-announces-closing-initial-public-offering/
2016 (US$113 M): https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-closing-initial-public-offering
2016 (US$56 M): https://www.fiercebiotech.com/biotech/crispr-therapeutics-raises-a-56m-ipo-but-patent-battles-potential-stock-drops-loom
2016 (US$75 M): https://pitchbook.com/newsletter/audentes-raises-75m-in-ipo
2016 Acquired by Mallinckrodt (UD): https://www.fiercebiotech.com/medical-devices/mallinckrodt-acquires-regenerative-medicine-company-stratatech
2017 (US$46 M): https://www.globenewswire.com/en/news-release/2017/09/22/1131592/0/en/Krystal-Biotech-Announces-Closing-of-Initial-Public-Offering-and-Full-Exercise-of-Underwriters-Option-to-Purchase-Additional-Shares.html
2017 (US$77 M): https://www.globenewswire.com/en/news-release/2017/10/02/1139020/0/en/Nightstar-Announces-Closing-of-Initial-Public-Offering-and-Full-Exercise-of-Underwriters-Option-to-Purchase-Additional-American-Depositary-Shares.html
2017 Reverse merger (UD): https://www.globenewswire.com/news-release/2017/04/07/1052850/0/en/PolarityTE-TM-Inc-Announces-Completion-of-Merger-and-Acquires-Important-Intellectual-Property-for-Regenerative-Medicine-Programs.html
2018 (US$100 M): https://www.businesswire.com/news/home/20180625006210/en/Magenta-Therapeutics-Announces-Closing-of-Initial-Public-Offering
2018 (US$160 M): https://autolus.gcs-web.com/news-releases/news-release-details/autolus-announces-closing-initial-public-offering-and-full/
2018 (US$225 M): https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-closing-225-million-initial/
2018 (US$373 M): https://ir.allogene.com/news-releases/news-release-details/allogene-therapeutics-announces-closing-initial-public-offering/
2018 Acquired by Celgene (US$9,000 M): https://www.geekwire.com/2018/juno-therapeutics-acquired-celgene-9b-dramatic-deal-rising-biotech-star/
2018 Acquired by Takeda Pharmaceutical Company (US$608 M): https://www.pharmaceutical-technology.com/news/takeda-tigenix-acquisition-608m/
2018 Reverse merger (UD): https://endpts.com/gene-therapy-startup-rocket-pharma-reverse-merges-with-troubled-inotek-after-25m-raise/
2018 Reverse merger (UD): https://organogenesis.com/news-events/press-release-12102018.html
2019 Acquired by Biogen (US$800 M): https://investors.biogen.com/news-releases/news-release-details/biogen-completes-acquisition-nightstar-therapeutics
2019 Acquired by BioTime (UD): https://www.spglobal.com/marketintelligence/en/news-insights/trending/dgy96s7WowE7oCnW-Mu7KA2
2019 Acquired by Castle Creek Pharmaceutical (US$63 M): https://www.globenewswire.com/en/news-release/2019/09/12/1915187/33272/en/Castle-Creek-Pharmaceutical-Holdings-to-Acquire-Fibrocell.html
2019 Acquired by Sumitomo Dainippon Pharma (UD): https://enzyvant.com/sumitomo-dainippon-pharma-completes-the-formation-of-the-strategic-alliance-with-roivant-sciences/
2019 Reverse merger (UD): https://www.nbcphiladelphia.com/news/local/malvern-gene-therapy-company-completes-reverse-merger/219782/
2020 (US$224 M): https://investors.poseida.com/news-releases/news-release-details/poseida-therapeutics-announces-pricing-initial-public-offering/
2020 (US$318 M): https://www.globenewswire.com/en/news-release/2020/08/03/2072010/0/en/AlloVir-Announces-Closing-of-Upsized-Initial-Public-Offering-and-Full-Exercise-of-the-Underwriters-Option-to-Purchase-Additional-Shares.html
2020 Acquired by Astellas Pharma (US$3,000 M): https://www.spglobal.com/marketintelligence/en/news-insights/trending/VpqpVltOd5YKifSvTvBf2A2
2021 (US$150 M): https://ir.talaristx.com/news-releases/news-release-details/talaris-therapeutics-announces-closing-initial-public-offering/
2021 (US$304 M): https://www.businesswire.com/news/home/20210727006010/en/Caribou-Biosciences-Announces-Closing-of-Upsized-Initial-Public-Offering
2021 (US$400 M): https://www.bioworld.com/articles/508424-car-t-developer-carsgen-debuts-on-hkex-with-400m-ipo-targets-bcma-first?v=preview
2021 Acquired by consortium (US$411 M): https://www.prnewswire.com/news-releases/cellular-biomedicine-group-inc-announces-completion-of-merger-301231873.html
2021 Acquired by Sanofi (US$358 M): https://www.fiercebiotech.com/biotech/sanofi-inks-358m-kiadis-takeover-to-acquire-nk-cell-platform
2021 Reverse merger (UD): https://www.marketscreener.com/quote/stock/HUMACYTE-INC-126300449/news/Humacyte-Inc-completed-the-acquisition-of-Alpha-Healthcare-Acquisition-Corp-from-a-group-of-share-36263997/
2022 Acquired by Canaria Bio (UD): https://www.koreabiomed.com/news/articleView.html?idxno=20085
2022 Merger with Cend Therapeutics (UD): https://www.globenewswire.com/en/news-release/2022/09/15/2516989/18623/en/Caladrius-Biosciences-and-Cend-Therapeutics-Announce-Closing-of-Merger-and-the-Emergence-of-Lisata-Therapeutics.html
20 cellular and gene therapy products: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
21 CFR 312: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312
525 non-regenerative-medicine drugs: https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products
7% in bank fees for a US$100 million IPO: https://news.crunchbase.com/public/want-to-take-your-startup-public-heres-what-it-actually-costs-to-ipo/
86 RMAT designations: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cumulative-cber-regenerative-medicine-advanced-therapy-rmat-designation-requests-received-fiscal
a list and ranking of incubators and accelerators worldwide: https://www.andeglobal.org/publication/the-ubi-global-world-rankings-of-business-incubators-and-accelerators/
a US$20 million award from the California Institute for Regenerative Medicine (CIRM): https://www.fiercebiotech.com/biotech/stemcells-inc-awarded-20-million-from-california-institute-for-regenerative-medicine-for
Abecma (2021): https://www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-multiple-myeloma
Accelerators: https://www.feedough.com/accelerator-vs-incubator/
acquired by Celgene: https://www.geekwire.com/2018/juno-therapeutics-acquired-celgene-9b-dramatic-deal-rising-biotech-star/
acquired by Mallinckrodt Pharmaceuticals: https://www.fiercebiotech.com/medical-devices/mallinckrodt-acquires-regenerative-medicine-company-stratatech
acquired by Novartis: https://www.novartis.com/news/media-releases/novartis-enters-agreement-acquire-avexis-inc-usd-87-bn-transform-care-sma-and-expand-position-gene-therapy-and-neuroscience-leader
acquired in a reverse merger: https://www.businesswire.com/news/home/20190930005241/en/Ocugen-Announces-Completion-of-its-Merger-with-Histogenics-to-Create-Nasdaq-Listed-Clinical-Stage-Company-Developing-Novel-Ocular-Gene-Therapies-and-Biotherapeutics
acquired through a reverse merger: https://www.massdevice.com/stemcells-soars-on-reverse-merger-with-israels-microbot-medical/
Adstiladrin (2022): https://www.ferring.com/ferring-receives-approval-from-u-s-fda-for-adstiladrin-for-high-risk-bcg-unresponsive-non-muscle-invasive-bladder-cancer/
Amgen: https://sciencebusiness.net/news/74714/UCL-spin-out-sold-to-Amgen-in-%241-billion-deal
amount for a seed round: https://www.paddle.com/resources/guide-to-seed-funding-for-startups
Analysts consider: https://www.statnews.com/2016/06/01/stem-cell-company-shutters
approved as Breyanzi: https://news.bms.com/news/details/2021/U.S.-Food-and-Drug-Administration-Approves-Bristol-Myers-Squibbs-Breyanzi-lisocabtagene-maraleucel-a-New-CAR-T-Cell-Therapy-for-Adults-with-Relapsed-or-Refractory-Large-B-cell-Lymphoma/default.aspx
approved as Rethymic): https://endpts.com/after-three-decades-and-a-surprise-rejection-first-treatment-for-babies-born-without-a-thymus-secures-fda-approval/
approved by the US Food and Drug Administration: https://www.fda.gov/vaccines-blood-biologics/zolgensma
approved: https://www.fda.gov/vaccines-blood-biologics/stratagraft
AProArt: https://www.cirm.ca.gov/our-progress/awards/ex-vivo-transduction-human-artemis-dclre1c-cdna-lentiviral-vector-aproart-cd34
ATIR101: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/allodepleted-t-cell-immunotherapeutic-atir101
averages for VC series A, B, and C: https://www.evaluate.com/vantage/articles/insights/venture-financing-ipo/venture-financing-holds-steady-device-makers
AveXis: https://www.novartis.com/news/media-releases/novartis-enters-agreement-acquire-avexis-inc-usd-87-bn-transform-care-sma-and-expand-position-gene-therapy-and-neuroscience-leader
Baylor College of Medicine: https://elevate.bio/press-releases/elevatebio-announces-that-allovir-joins-its-portfolio-of-highly-innovative-cell-and-gene-therapy-companies/; https://www.tessacell.com/about-tessa-therapeutics/

BioVex: https://mergr.com/amgen-acquires-biovex-group
BLA clinical review: https://www.fda.gov/vaccines-blood-biologics/stratagraft
BLA pharmacology/toxicology review of StrataGraft: https://www.fda.gov/vaccines-blood-biologics/stratagraft
Bluebird Bio (founded as Genetix Pharmaceuticals): https://investor.bluebirdbio.com/news-releases/news-release-details/genetix-pharmaceuticals-renamed-bluebird-bio-announces
Breyanzi (2021): https://news.bms.com/news/details/2021/U.S.-Food-and-Drug-Administration-Approves-Bristol-Myers-Squibbs-Breyanzi-lisocabtagene-maraleucel-a-New-CAR-T-Cell-Therapy-for-Adults-with-Relapsed-or-Refractory-Large-B-cell-Lymphoma/default.aspx
California Institute for Regenerative Medicine (CIRM): https://www.cirm.ca.gov/
cartilage repair products: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preparation-ides-and-inds-products-intended-repair-or-replace-knee-cartilage
Carvykti (2022): https://www.jnj.com/u-s-fda-approves-carvykti-ciltacabtagene-autoleucel-janssens-first-cell-therapy-a-bcma-directed-car-t-immunotherapy-for-the-treatment-of-patients-with-relapsed-or-refractory-multiple-myeloma
Case Western Reserve University: https://case.edu/medicine/about/newsroom/our-latest-news/case-western-reserve-center-stem-cell-and-regenerative-medicine-and-athersys-receive-1m-third-frontier-grant-support-research-spinal-cord-injury
cellular immunotherapy product Provenge: https://stanmed.stanford.edu/pioneering-cancer-drug-provenge-fresh-look
CFR Title 21: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
CGT products: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preclinical-assessment-investigational-cellular-and-gene-therapy-products
Children's Hospital of Philadelphia University of Pennsylvania: https://www.chop.edu/news/childrens-hospital-philadelphia-celebrates-fda-approval-gene-therapy-inherited-blindness
City of Hope National Medical Center: https://www.cityofhope.org/news/phase-1-clinical-trial-of-mb-101
clinical trials: https://www.fda.gov/patients/clinical-trials-what-patients-need-know/what-are-different-types-clinical-research
completed an initial public offering (IPO): https://www.globenewswire.com/en/news-release/2016/02/11/809635/0/en/AveXis-Announces-Pricing-of-Initial-Public-Offering.html
considered safety data generated from the phase I/IIa and phase II trials for an alternate indication: https://www.fda.gov/vaccines-blood-biologics/stratagraft
convertible note: https://www.investopedia.com/terms/s/senior-convertible-note.asp
Cooperative Patent Classification system: https://www.cooperativepatentclassification.org/about
current Good Manufacturing Practice (cGMP) regulations: https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations
Dilution of equity: https://www.svb.com/startup-insights/startup-equity/startup-equity-dilution
Duke University, Massachusetts Institute of Technology: https://wraltechwire.com/2021/02/18/a-blooming-success-the-rise-of-humacyte-from-humble-beginnings-to-1-1b-valuation/
Duke University: https://endpts.com/after-three-decades-and-a-surprise-rejection-first-treatment-for-babies-born-without-a-thymus-secures-fda-approval/
Duke University: https://endpts.com/after-three-decades-and-a-surprise-rejection-first-treatment-for-babies-born-without-a-thymus-secures-fda-approval/
'End of Phase' meetings: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-ind-milestone-type-b-meetings
Enzyvant Therapeutics GmbH licenced the technology from Duke University: https://www.prnewswire.com/news-releases/enzyvant-to-develop-novel-biologic-therapy-for-complete-digeorge-syndrome-300386922.html
established IP: https://patents.justia.com/assignee/histogenics-corporation
exceeding US$20 billion in 2021: https://alliancerm.org/sector-report/2021-annual-report/
excess of these amounts: https://grants.nih.gov/grants/guide/notice-files/NOT-HL-22-065.html
FDA approval of JCAR017: https://news.bms.com/news/details/2021/U.S.-Food-and-Drug-Administration-Approves-Bristol-Myers-Squibbs-Breyanzi-lisocabtagene-maraleucel-a-New-CAR-T-Cell-Therapy-for-Adults-with-Relapsed-or-Refractory-Large-B-cell-Lymphoma/default.aspx
Ferring Pharmaceuticals: https://ferringusa.com/?press=ferring-and-blackstone-life-sciences-invest-over-570-million-usd-in-novel-gene-therapy-for-bladder-cancer-patients
Financial exit strategies: https://www.investopedia.com/terms/b/business-exit-strategy.asp
founded in 2013: https://www.prnewswire.com/news-releases/spark-therapeutics-launched-with-50-million-in-financing-to-advance-late-and-mid-stage-gene-therapy-programs-with-clinical-proof-of-concept-228752221.html
Fred Hutchinson Cancer Center, St Jude Children's Research Hospital: https://ir.mustangbio.com/news-events/press-releases/detail/68/mustang-bio-and-st-jude-childrens-research-hospital
Fred Hutchinson Cancer Research Center Memorial Sloan-Kettering Cancer Center Seattle Children's Research Institute: https://www.forbes.com/sites/matthewherper/2014/08/05/why-this-cancer-fighting-company-has-raised-300-million-in-just-12-months/
Fred Hutchinson Cancer Research Center Memorial Sloan-Kettering Cancer Center Seattle Children's Research Institute University of California, San Francisco St Jude Children's Research Hospital: https://www.businesswire.com/news/home/20171101006552/en/Juno-Therapeutics-Reports-Third-Quarter-2017-Financial-Results
funding caps: https://www.sbir.gov/about
Genesis Seed Fund: https://research.rutgers.edu/researcher-support/commercialize-your-innovation/launch-startup/new-ventures/genesis-seed-fund
Gilead Sciences: https://www.gilead.com/news-and-press/company-statements/kite-pharma
Harvard University, Massachusetts Institute of Technology: https://news.mit.edu/2001/sicklecell
Harvard University, Washington University in St Louis, Stanford University, San Raffaele Telethon Institute for Gene Therapy, University of Basel: https://investor.magentatx.com/news-releases/news-release-details/magenta-therapeutics-announces-485m-series-financing-transform/
Harvard University: https://hsci.harvard.edu/company-startups
Harvard University: https://hsci.harvard.edu/company-startups
Hemgenix (2022): https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treat-adults-hemophilia-b
highly competitive: https://grantengine.com/sbir-sttr-paylines-by-nih-institute/
Imlygic (2015): https://www.amgen.com/newsroom/press-releases/2015/10/fda-approves-imlygic-talimogene-laherparepvec-as-first-oncolytic-viral-therapy-in-the-us
INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meeting: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-interact-meeting
interpretations of Section 506(g)(8) by the US Food and Drug Administration (FDA): https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/resources-related-regenerative-medicine-therapies
'inventive step': https://www.wipo.int/pct/en/texts/ispe/13_01_02.html
Investigational New Drug application: https://www.fda.gov/vaccines-blood-biologics/stratagraft
IPO: https://pitchbook.com/blog/ipo-process-explained
JLABS: https://jnjinnovation.com/home
Johns Hopkins University: https://www.sdbj.com/technology/capricor-therapeutics-relocates-la-jolla/
Johnson & Johnson: https://johnsonandjohnson.gcs-web.com/news-releases/news-release-details/johnson-johnson-announces-completion-merger-centocor-inc/
Juno Therapeutics (founded as FC Therapeutics): https://pitchbook.com/profiles/company/60580-27#overview
Juno Therapeutics: https://www.geekwire.com/2018/juno-therapeutics-acquired-celgene-9b-dramatic-deal-rising-biotech-star/
Katholieke Universiteit Leuven Ghent University: https://www.flandersinvestmentandtrade.com/invest/en/news/tigenix-raise-20-million-euro-product-trials
Kymriah (2017): https://www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriahtm-ctl019-children-and-young-adults-b-cell-all-refractory-or-has-relapsed-least-twice
Kymriah: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel
Luxturna (2017): https://sparktx.com/press_releases/fda-approves-spark-therapeutics-luxturna-voretigene-neparvovec-rzyl-a-one-time-gene-therapy-for-patients-with-confirmed-biallelic-rpe65-mutation-associated-retinal-dystrophy/
Luxturna to be approved by the US Food and Drug Administration: https://sparktx.com/press_releases/fda-approves-spark-therapeutics-luxturna-voretigene-neparvovec-rzyl-a-one-time-gene-therapy-for-patients-with-confirmed-biallelic-rpe65-mutation-associated-retinal-dystrophy/
M&A: https://www.sba.gov/business-guide/grow-your-business/merge-acquire-businesses
MACI (2016): https://investors.vcel.com/news-releases/news-release-details/fda-approves-maci-treatment-symptomatic-cartilage-defects-knee
Mallinckrodt Pharmaceuticals: https://mallinckrodt.gcs-web.com/news-releases/news-release-details/mallinckrodt-announces-us-fda-approval-stratagraftr-allogeneic/
Massachusetts Institute of Technology: https://organogenesis.com/about-us/
Massachusetts Institute of Technology: https://organogenesis.com/about-us/
MGTA-456: https://investor.magentatx.com/news-releases/news-release-details/magenta-therapeutics-announces-updated-phase-2-data-mgta-456/
National Cancer Institute: https://www.stocktitan.net/news/IOVA/iovance-biotherapeutics-announces-first-patient-randomized-in-phase-1fnhlejx69wn.html
Nationwide Children's Hospital Ohio State University: https://www.nationwidechildrens.org/newsroom/news-releases/2013/10/avexis-biolife-licenses-spinal-muscular-atrophy-sma-patent-portfolio-from-nationwide-childrens
Nationwide Children's Hospital: https://www.prnewswire.com/news-releases/abeona-therapeutics-and-nationwide-childrens-hospital-receive-prestigious-global-genes-champions-of-hope-award-for-patient-advocacy-227092241.html
NIH Data Management and Sharing Policy: https://oir.nih.gov/sourcebook/intramural-program-oversight/intramural-data-sharing/2023-nih-data-management-sharing-policy
NIH's Commercialization Readiness Pilot (CRP) programme: https://seed.nih.gov/support-for-small-businesses/commercialization-enhancement-programs/crp
no major safety concerns were generated from the preclinical studies: https://www.fda.gov/vaccines-blood-biologics/stratagraft
NSF-funded Innovation-Corps (I-Corps): https://beta.nsf.gov/funding/initiatives/i-corps/about-i-corps
obtained Regenerative Medicine Advanced Therapy designation: https://www.prnewswire.com/news-releases/us-fda-designates-mallinckrodts-stratagraft-as-regenerative-medicine-advanced-therapy-300489200.html
only the phase Ib and phase III trials were considered for efficacy: https://www.fda.gov/vaccines-blood-biologics/stratagraft
Orca-T: https://ashpublications.org/blood/article/140/Supplement1/654/487614/Precision-Engineered-Cell-Therapy-Orca-T
OTL-103: https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-fda-regenerative-medicine/

over 1,000 new devices: https://www.fda.gov/about-fda/center-devices-and-radiological-health/cdrh-reports
University of Oxford, University of Pennsylvania: https://www.adaptimmune.com/our-company
Patent Cooperation Treaty (PCT): https://www.wipo.int/pct/en/faqs/faqs.html
peak sales forecast: https://www.europeanpharmaceuticalreview.com/news/179320/cd19-car-t-agents-to-boost-blood-cancer-market/
Phase 0 grants: https://www.sbir.gov/sites/default/files/SBIR-Table_StateMatchingPhase0_Sept2020.pdf
pledged a US$50 million commitment from the Children's Hospital of Philadelphia: https://www.prnewswire.com/news-releases/spark-therapeutics-launched-with-50-million-in-financing-to-advance-late-and-mid-stage-gene-therapy-programs-with-clinical-proof-of-concept-228752221.html
pre-IND meeting: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-pre-ind-meetings
private equity (PE): https://www.investopedia.com/terms/p/privateequity.asp
product revenue of Breyanzi: https://bioprocessintl.com/bioprocess-insider/therapeutic-class/bms-sees-car-t-sales-rocket-in-line-with-increased-capacity/
Promotion and Tenure-Innovation and Entrepreneurship (PTIE) coalition: https://ptie.org/
Provenge (2010): https://stanmed.stanford.edu/pioneering-cancer-drug-provenge-fresh-look/
quality management system: https://www.nidcr.nih.gov/sites/default/files/2017-12/quality-management-of-clinical-research-brief-overview.doc
raised a total of US$310 million: https://www.crunchbase.com/organization/juno-therapeutics/company_financials
raised an additional US$72.8 million in series B funding: https://www.prnewswire.com/news-releases/spark-therapeutics-raises-728-million-in-oversubscribed-financing-260806381.html
raised US$304 million through its initial public offering: https://www.nasdaq.com/articles/juno-therapeutics-prices-upsized-ipo-24-largest-2014-biotech-ipo-22-billion-market-cap
reason for noncompliance: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1
Regenerative Medicine Advanced Therapy (RMAT) designation: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation
Regenerative Medicine Minnesota: https://www.regenmedmn.org/
Rethymic (2021): https://enzyvant.com/enzyvant-receives-fda-approval-for-rethymic-allogeneic-processed-thymus-tissue-agdc-a-one-time-regenerative-tissue-based-therapy-for-pediatric-congenital-athymia/
reverse merger: https://www.investopedia.com/terms/r/reversetakeover.asp
Rexlemestrocel-L: https://go.drugbank.com/drugs/DB17606
Risk Evaluation and Mitigation Strategy programme: https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems
Roche: https://technical.ly/startups/spark-therapeutics-acquired-roche-bill-marrazzo-university-city-science-center-gene-therapy/
Roughly 90% of applications filed are utility patents: https://www.uspto.gov/web/offices/ac/ido/oeip/taf/data/patdesc.htm
San Raffaele-Telethon Institute for Gene Therapy: https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-fda-regenerative-medicine/
SBA loans: https://www.sba.gov/funding-programs/loans
SBIR and STTR programmes: https://www.sbir.gov/node/2120519
secondary public offerings: https://www.cbinsights.com/research-what-is-a-secondary-offering
section 361: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271
Section 506(g)(8) of the United States (US) Federal Food, Drug, and Cosmetic Act: https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.htm
Seoul National University: https://www.koreabiomed.com/news/articleView.html?idxno=20085
settled a legal dispute: https://www.wsj.com/articles/juno-therapeutics-settles-patent-dispute-with-novartis-1428326691
Several expedited programmes: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
SkinTE: https://www.woundsource.com/product/skinte
Skysona (2022): https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-receives-fda-accelerated-approval-skysonar-gene
Spark Therapeutics: https://sparktx.com/press_releases/spark-therapeutics-enters-into-definitive-merger-agreement-with-roche/
Stanford University: https://orcabio.com/who-we-are/
Stanford University: https://www.medeortx.com/about-us.php
StrataGraft (2021): https://mallinckrodt.gcs-web.com/news-releases/news-release-details/mallinckrodt-announces-us-fda-approval-stratagraftr-allogeneic/
StrataGraft: https://www.stratagraft.com/
Stratatech: https://www.fiercebiotech.com/medical-devices/mallinckrodt-acquires-regenerative-medicine-company-stratatech
subsequently approved: https://www.ns-healthcare.com/news/breyanzi-large-b-cell-lymphoma/
Sumitomo Pharma: https://endpts.com/after-three-decades-and-a-surprise-rejection-first-treatment-for-babies-born-without-a-thymus-secures-fda-approval/
Tecartus (2020): https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/us-fda-approves-kites-tecartus-the-first-and-only-car-t-treatment-for-relapsed-or-refractory-mantle-cell-lymphoma
technology for Brenyanzi: https://www.forbes.com/sites/matthewherper/2014/08/05/why-this-cancer-fighting-company-has-raised-300-million-in-just-12-months/?sh=449f6d8b50d5
technology for StrataGraft: https://pathology.wisc.edu/2021/06/21/stratagraft-approved-by-fda/
technology of Zolgensma: https://www.nationwidechildrens.org/newsroom/news-releases/2013/10/avexis-biolife-licenses-spinal-muscular-atrophy-sma-patent-portfolio-from-nationwide-childrens
three FDA-approved products: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cber-regenerative-medicine-advanced-therapy-rmat-approvals
three types of patent: https://www.uspto.gov/patents/basics/general-information-patents
"treat, modify, reverse, or cure a serious or life-threatening condition": https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation
TT11: https://www.tessacell.com/pipeline/
UniQure (founded as Amsterdam Molecular Therapeutics): https://www.biopharmadive.com/news/hemophilia-gene-therapy-fda-approval-hemgenix-csl-uniqure/636999/
Université de Montréal University of Toronto: https://www.signalsblog.ca/catching-up-with-excellthera-and-co-founder-guy-sauvageau/
University College London: https://www.uclb.com/portfolio/our-spinouts/orchard-theapeutics-plc/
University of California San Diego (UCSD): https://innovation.ucsd.edu/commercialize/licensing.html
University of California, Berkeley: https://ipira.berkeley.edu/caribou-biosciences-inc
University of California, Berkeley: https://ipira.berkeley.edu/intellia
University of California, Irvine: https://innovation.uci.edu/2016/11/20161129special-feature-stem-cell-strides-asterias-biotherapeutics/
University of California, Irvine: https://innovation.uci.edu/2020/06/uci-startup-company-jcyte-partners-with-santen-pharmaceutical/
University of California, Los Angeles: https://labusinessjournal.com/news/arie-belldegrun/
University of California, Los Angeles: https://www.biopharmadive.com/news/Kite-Pharma-UCLA-tcell-allogeneic/423263/
University of California, San Francisco: https://www.ucsf.edu/news/2022/02/422276/ucsf-gene-therapy-deadly-mutation-fast-tracked-fda-review
University College London: https://www.autolus.com/about-us/
University of Colorado University of Illinois at Chicago: https://www.fiercebiotech.com/biotech/eye-specialist-ocugen-looks-east-for-second-round-fundraising
University of Eastern Finland: https://www.uef.fi/en/article/university-of-eastern-finland-and-ferring-ventures-to-continue-collaboration-in-gene-and-cell
University of Florida: https://ir.axogeninc.com/press-releases/detail/811/axogen-inc-receives-david-j-gury-company-of-the-year
University of Florida: https://news.drgator.ufl.edu/2013/09/26/uf-teams-with-company-to-advance-gene-therapy-treatments/
University of Louisville: https://www.uoflnews.com/post/uofltoday/uofl-born-company-secures-100-million-to-advance-cell-therapy/
University of Massachusetts University of California, San Francisco Stanford University: https://www.umassmed.edu/es/news/news-archives/2014/02/voyager-therapeutics-targets-novel-gene-therapies-to-combat-diseases/
University of Minnesota: https://www.nytimes.com/2002/12/11/business/technology-politically-correct-stem-cell-is-licensed-to-biotech-concern.html
University of Oxford: https://www.ox.ac.uk/news/2015-11-09-£23-million-boost-oxford-spinout-company
University of Pennsylvania: https://pci.upenn.edu/regenxbio-receives-fda-fast-track-designation-for-its-novel-gene-therapy-candidate/
University of Pennsylvania: https://www.novartis.com/news/media-releases/novartis-kymriah-receives-fda-regenerative-medicine-advanced-therapy-designation-follicular-lymphoma
University of Pennsylvania: https://www.pennmedicine.org/news/news-releases/2019/september/university-pennsylvania-announces-exclusive-alliance-novartis-development-new-focused-relationship
University of Washington, Children's Hospital Boston Mass General Hospital for Children: https://iscrm.uw.edu/fate-therapeutics-a-company-started-in-seattle-with-intellectual-property-from-iscrm-has-announced-its-first-clinical-trials/
University of Wisconsin: https://pathology.wisc.edu/2021/06/21/stratagraft-approved-by-fda/
University of Wisconsin — Madison: https://news.wisc.edu/gov-evers-state-leaders-tour-uw-biotech-spinoff-stratatech/
updated the US policy guidance: https://www.whitehouse.gov/ostp/news-updates/2022/08/25/ostp-issues-guidance-to-make-federally-funded-research-freely-available-without-delay/
US$10 million in series C: https://www.wsj.com/articles/DJFVW00120150109eb19ozrd9
US$13.1 million: https://www.pehub.com/histogenics-adds-131-million/
US$34 million: https://www.massdevice.com/histogenics-raises-34-million-after-prochon-biotech-merger/
US$49 million: https://www.fiercebiotech.com/biotech/histogenics-closes-49-million-series-a-fundraising-to-support-commercial-development-of-0

US$5.35 million: https://www.prweb.com/releases/2008/05/prweb908944.htm/
US$65 million in series D: https://www.fiercebiotech.com/biotech/avexis-secures-65-million-financing
US$65 million through an initial public offering: https://www.bizjournals.com/boston/blog/bioflash/2014/12/with-65m-offering-histogenics-becomes-states-17th.html
US$9.0 million: https://www.fiercebiotech.com/biotech/histogenics-secures-9-million-second-round-of-financing
Vyjuvek (2023): https://www.fda.gov/vaccines-blood-biologics/vyjuvek
Weizmann Institute: https://www.haaretz.com/israel-news/2017-08-31/ty-article/kite-pharmas-success-is-nothing-compared-to-tevas-failure/0000017f-dbae-df9c-a17f-ffbef7f70000
Weill Cornell Medicine: https://angiocrinebioscience.com/about-us/our-story/
Western New York Incubator Network SBIR/STTR assistance programme: https://www.wnyincubators.com/sbir-sttr-assistance
Y Combinator Management: https://www.ycombinator.com/
Yescarta (2017): https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/us-fda-approves-kites-tecartus-the-first-and-only-car-t-treatment-for-relapsed-or-refractory-mantle-cell-lymphoma
Zolgensma (2019): https://www.novartis.com/news/media-releases/avexis-receives-fda-approval-zolgensma-first-and-only-gene-therapy-pediatric-patients-spinal-muscular-atrophy-sma
Zynteglo (2022): https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-fda-approval-zynteglor-first-gene-therapy