The state of cell and gene therapy in 2023

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Progress in the understanding of human diseases has coincided with the advent of precision medicine, whereby the underlying genetic and molecular contributors can be used as diagnostic and therapeutic biomarkers. To address these, drug developers have designed a range of different treatment strategies, including gene therapy, which the American Society of Gene and Cell Therapy defines as the use of genetic material to treat or prevent disease. A number of approaches exist, including the delivery of genetic material *in vivo* or *ex vivo*, as well as the use of RNA species to alter gene expression in particular disease states. Through the end of the first quarter of 2023, there were more than 100 different approved gene, cell, and RNA therapies throughout the world, with over 3,700 more in clinical and preclinical development. This review comprehensively captures the landscape for such advanced therapies, including the different genetic technologies used and diseases targeted in clinical trials.

INTRODUCTION

Gene, cell, and RNA therapies, collectively called cell and gene therapies (CGTs) in this review, represent the cutting edge of drug discovery (Figure 1). Owing to their precise nature, targeted against the genetic and molecular drivers of disease, these therapeutic approaches are the embodiment of precision medicine. CGTs may provide patients with a given disease, in which the causation is well known and characterized, a therapy specifically designed to correct the root genetic cause. Identifying a need to accurately report on the state of clinical and preclinical development of these therapies, the American Society of Gene and Cell Therapy (ASGCT) initiated a partnership with Citeline in 2021. The purpose of the partnership is for Citeline and ASGCT to jointly acquire, develop, and maintain relevant industry corporate, financial, and clinical data that can be used to report regularly on the performance of the gene, cell, RNA, and regenerative medicine sectors.

CGTs may provide patients with certain diseases, in which the root genetic causation is well known and characterized, a therapy specifically designed to correct such causes, by delivering genetic material that modifies the expression of the target gene. Recent advances for the treatment of spinal muscular atrophy (SMA), an autosomal recessive disease, have yielded two examples of new advanced genetic therapies. Nusinersen (Spinraza; Biogen) is an antisense oligonucleotide (ASO), a single-stranded nucleic acid matched to a specific sequence in intron 7 of *SMN2* pre-mRNA. This mechanism causes splicing correction and production of full-length functional SMN protein, with accompanying clinical benefit for SMA patients of all ages.[1] Pe-

diatric patients younger than 2 years now also have the gene therapy onasemnogene abeparvovec (Zolgensma; Novartis) as a one-time, potentially curative treatment option. Onasemnogene abeparvovec is an adeno-associated virus (AAV) vector-based gene therapy that delivers a functional copy of the SMN1 gene encoding SMN protein to motor neuron cells.[2] This restores SMN levels and reverses skeletal muscle atrophy, with clinical benefits demonstrated for up to 7.5 years thus far.[3]

Cell therapies, the so-called living drugs, can harness similar genetic engineering techniques to enhance or modify their natural capabilities. Currently, such reprogramming is commonly applied to white blood cells or hematopoietic stem cells, creating powerful therapeutic strategies in oncology and immunology settings. The most prevalent example of genetically engineered cell therapies is chimeric antigen receptor T cells (CAR-Ts). In the classic design of first-generation autologous CAR-T therapies such as tisagenlecleucel (Kymriah; Novartis) and axicabtagene ciloleucel (Yescarta; Gilead), a patient's own T cells are harvested and engineered to express CAR constructs that target CD19.[4] These are powerful agents that have produced high response rates in clinical trials of patients with advanced B cell malignancies.[5] As the technology evolves, alternative CAR constructs are being explored alongside allogeneic, or "off the shelf," T cells with multiple genetic changes, and expressing CARs on other types of immune cells such as natural killer (NK) cells and macrophages. The full potential of cell therapies is being extrapolated broadly to the field of regenerative medicine, aided by the ability to precisely control gene expression. Pharmaceutical and biotechnology companies have active cell therapy programs in diseases as diverse as diabetes, heart failure, and multiple sclerosis.

As the intermediate species between genes and proteins in the central dogma of biology, RNA has an incredibly versatile potential. This includes gene silencing and activation via complementary base pairing to pre-mRNA in the form of ASOs and short interfering RNA (siRNA). More recently, mRNA has been used to produce the antigenic severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) Spike protein in the hundreds of millions of individuals who have received coronavirus disease 2019 (COVID-19) vaccines designed by Moderna and BioNTech. The same concept can be applied for the *in vivo* production of therapeutic proteins and
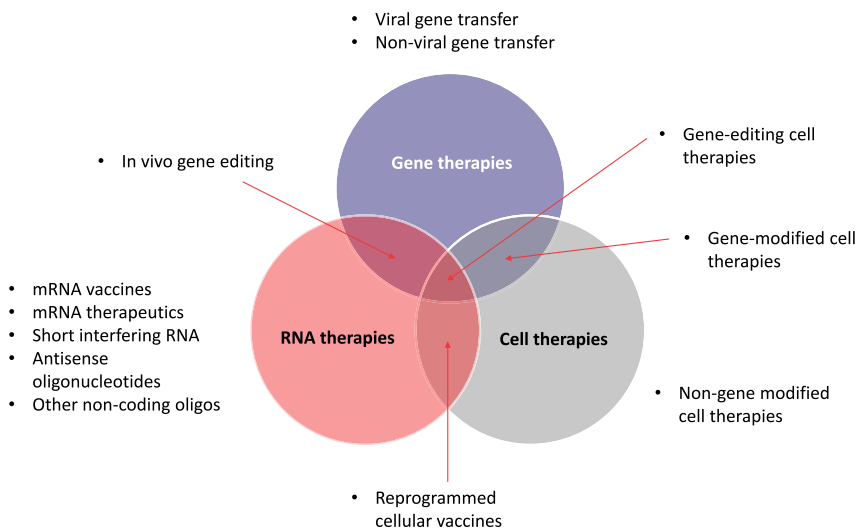
Figure 1. Current universe of advanced therapies, including areas of overlap.

monoclonal antibodies, although this approach is more experimental. RNA can also enable the creation of gene and cell therapies when it is used as a precursor for the proteins and enzymes required for genetic engineering mechanisms. The areas of overlap between gene, cell, and RNA therapies offer the potential for incredibly powerful and targeted drugs.

Gene editing is one such example that came to the fore in 2021 following the proof-of-concept data for NTLA-2001 in transthyretin (TTR) amyloidosis.[6] NTLA-2001 is a CRISPR-based drug designed to halt the expression of misfolded TTR, which causes neuropathy and cardiomyopathy in affected patients. NTLA-2001 comprises oligonucleotides encapsulated within lipid nanoparticles (LNPs), taking the form of a guide RNA (gRNA) sequence that directs the gene editing machinery to the correct location, as well as mRNA, which encodes Cas9 protein for DNA cutting. In interim data from a Phase I trial, patients receiving NTLA-2001 achieved a 92% reduction in serum TTR protein at the highest dose at day 28, showing the powerful potential of *in vivo* gene editing.[7] The potential also exists for *ex vivo* editing of cell therapies using RNA scaffolds, thereby combining all three novel drug modalities in a single treatment.

APPROVED THERAPIES WORLDWIDE

Globally, there are now 111 different gene, cell, or RNA therapies that have been approved in at least one country globally (Tables 1, 2, and 3). The majority of these (73) are cell-based therapies (Tables 1 and 2), 11 of which involve genetic modification, referred to in this paper as "genetically modified cell therapies." There are a further 14 approved gene therapies that act through gene transfer. The remaining 24 approvals are for RNA-based drugs, which include 16 noncoding oligonucleotides and 8 mRNA-based COVID-19 vaccines (Table 3).

In 2022, 12 first approvals across gene, cell, and RNA therapies occurred, 5 of which were for gene transfer/genetically modified cell therapies. This makes 2022 a milestone year for gene transfer therapies

in particular. Notably, these approvals introduced the first gene therapy options for both hemophilia A and B patients, in the form of valoctocogene roxaparvovec (Roctavian; BioMarin) and etranacogene dezaparvovec (Hemgenix; CSL Behring and uniQure), respectively. Both are examples of AAV5 gene therapies using a liver-specific promoter; however, although Roctavian delivers and expresses a B-domain-deleted human factor VIII coding sequence,[8] Hemgenix delivers and expresses a hyperactive factor IX transgene.[9] Besides gene therapies, first approvals in 2022 also included tabelecleucel (Tab-cel; Atara Biotherapeutics), the first-approved allogeneic T cell immunotherapy, and a continuation of the response to the COVID-19 pandemic with the approval (including emergency use authorizations) of 4 new mRNA vaccines.

Moving into 2023, 6 first-time approvals were granted in the first 5 months: 1 gene transfer therapy, 2 nongenetically modified cell therapies, and 3 RNA therapies. Tofersen (Qalsody; Ionis Pharmaceuticals and Biogen), the first treatment to target the genetic cause of amyotrophic lateral sclerosis, is an ASO that induces Rnase H-mediated degradation of SOD1 mRNA, reducing the synthesis of the SOD1 protein.[10] Also approved this year was beremagene geperpavec (Vyjuvek; Krystal Biotech). Not only is this the first gene therapy for the treatment of wounds in patients with dystrophic epidermolysis bullosa but it is also the first-ever topical gene therapy to be approved. Beremagene geperpavec is a herpes simplex virus 1 (HSV-1)-based gene therapy that delivers COL7A1 with the aim of reducing C7 protein.[11]

STATE OF THE DRUG PIPELINE

As of June 2023, there were 3,771 advanced genetic therapies under active development in the biopharmaceutical industry pipeline (Figure 2), according to the global research and development database Pharmaprojects. This number includes 2,070 drugs (55%) with a gene therapy classification, 1,989 (53%) that are cell therapies, and a further 910 (24%) that belong to the RNA class. As previously noted, the gene, cell, and RNA therapy classifications are not mutually exclusive and so these totals do not sum, but rather 1,192 (32%) of these drugs have at least 2 qualifying classifications. Gene-modified cell therapies is the most common example of this, with a total of 1,150 programs in active development.

A majority of the industry pipeline is in the preclinical stages and has not yet advanced to human clinical trials. Of all 3,771 disclosed drug candidates, only 1,083 (29%) are in clinical development. The ratio is similar across all 3 advanced drug modalities. This emphasis toward

Table 1. All approved gene therapies, including genetically modified cell therapies, as of June 2023

Product name	Generic name	Originator company	Modality	Disease(s)	Year first approved	Locations approved
Vyjuvek	Beremagene geperpavec	Krystal Biotech	HSV-1 gene therapy	Epidermolysis bullosa	2023	USA
Adstiladrin	Nadofaragene firadenovec	Merck	Adenoviral gene therapy	Bladder cancer	2022	USA
Hemgenix	Etranacogene dezaparvovec	uniQure	AAV5 gene therapy	Hemophilia B	2022	USA, EU, UK
Roctavian	Valoctocogene roxaparvovec	BioMarin	AAV5 gene therapy	Hemophilia A	2022	EU, UK
Upstaza	Eladocagene exuparvovec	PTC Therapeutics	AAV2 gene therapy	Aromatic L-amino acid decarboxylase deficiency	2022	EU, UK
Carvykti	Ciltacabtagene autoleucel	Legend Biotech	CAR-T	Myeloma	2022	USA, EU, UK, Japan
Skysona	Elivaldogene autotemcel	Bluebird Bio	Genetically modified autologous CD34+ hematopoietic stem cells	Adrenoleukodystrophy	2021[a]	USA
Delytact	Teserpaturev	Daiichi Sankyo	Oncolytic virus	Cancer, brain	2021	Japan
Benoda	Relmacabtagene autoleucel	JW Therapeutics	CAR-T	Cancer, lymphoma, B cell, diffuse large; cancer, lymphoma, follicular	2021	China

EU, European Union; UK, United Kingdom.
[a]Approved in the EU, but then was withdrawn.

preclinical assets is a common observation for any drug class because the biopharmaceutical industry prioritizes drug candidates and invests in a decreasing number of assets through each sequential stage of development. It is also likely that this is a notable underestimate of the true total, because a sizable number of preclinical candidates will not be disclosed in publicly available sources.

Gene therapies

Within the gene therapy pipeline, the major classification is whether the gene therapy is the drug or whether gene modification creates the drug. This is equivalent to *in vivo* gene therapy (via transfer or editing of genetic material) versus *ex vivo* gene-modified cell therapies. These broad groups are totaled separately in Figure 2; genetically modified cell therapies are the most common type of gene therapy, with a total of 1,150 in active development (56% of total gene therapies). Gene therapies that involve the transfer of new genetic material are the next most common (719; comprising 35% of all gene therapies), ahead of the emerging class of *in vivo* gene editors (201; 10% of total gene therapies).

Gene therapies can be delivered in a number of different ways, including viral vectors, nonviral vectors, and physical methods such as electroporation (Figure 3). These each have their own advantages and limitations, and the diversity in delivery approaches is used to create gene therapies with different characteristics. Considerations when choosing the optimal delivery vehicle include packaging capacity, genome integration, duration of expression, target specificity, and safety.

Viral vectors are by far the most common, accounting for over 90% of gene therapies with a known delivery method. Among these, AAVs are the most studied because they have a very limited ability to integrate into the patient genome, with lower innate immunogenicity.[12] AAV is therefore the predominant choice for *in vivo* gene therapy, with considerable investigation into different serotypes with discrete tropisms for particular cell types. Nearly half (49%) of all of the viral gene therapies under active development use AAV as the vector of choice (Figure 3). Lentiviruses are also commonly used as vectors in *ex vivo* applications in which genome integration is desired, thereby allowing continued gene expression following cell division. One such example is gene-modified hematopoietic stem cells expressing hemoglobin for the treatment of β-thalassemia and sickle cell disease, the most advanced example being betibeglogene autotemcel (Zynteglo; Bluebird Bio).[13] Lentiviral vectors account for 26% of disclosed viral gene therapies, well ahead of less prevalent vectors such as adenovirus (9%), retrovirus (5%), and HSV (2%).

Nonviral and physical methods for delivering gene therapies into cells are in the minority. Early approaches involved electroporation to transiently increase cell membrane permeability, while newer enhancements include the design of virus-like particles and LNPs. LNPs in particular are preferentially used for gene editing approaches because their larger packaging capacity enables the delivery of the necessary gRNA and endonuclease machinery.

Cell therapies

Biopharmaceutical companies are strongly embracing gene modification technologies to potentiate or create therapeutic activities for a range of cell types (Figure 3). Such gene-modified cell therapies now outnumber unmodified cell therapies by 1,150 (58%) to 839

Table 2. All approved nongenetically modified cell therapies as of June 2023

Product name	Generic name	Originator company	Modality	Disease(s)	Year first approved	Locations approved
Omisirge	Omidubicel	Gamida Cell	Hematopoietic progenitor stem cells	Stem cell engraftment	2023	USA
Vyznova	Corneal endothelial cell therapy	Aurion Biotech	Corneal endothelial cells	Corneal dystrophy	2023	Japan
Tab-cel	Tabelecleucel	Atara Biotherapeutics	T cell immunotherapy	Posttransplant lymphoproliferative disorder	2022	EU, UK
Sakracy	Autologous cultured oral mucosal epithelium	Hirosaki Lifescience Innovation	Mucosal epithelium	Limbal stem cell deficiency	2022	Japan
Trinity ELITE	Cellular allograft	Orthofix	Mesenchymal stem cells, osteoprogenitor cells, and demineralized cortical bone	Musculoskeletal disease	2021	USA
Stemedyne-MSC	Mesenchymal bone marrow–derived stem cells	Stemedica	Mesenchymal stem cells	Infarction, myocardial	2021	Kazakhstan
CardioRel	Autologous mesenchymal stem cell therapy	Reliance Life Sciences	Mesenchymal stem cells	Infarction, myocardial	2021	India
Rethymic	Allogeneic processed thymus tissue-agdc	Sumitomo Dainippon Pharma	Thymus tissue-agdc	DiGeorge syndrome	2021	USA
Ocural	Autologous cultured oral mucosal epithelium	Teijin Pharma	Mucosal epithelium	Limbal stem cell deficiency	2021	Japan
Stratagraft	Allogenic skin tissue cells	Mallinckrodt	Dermal and epidermal cells	Wound healing	2021	USA
Kaloderm	Allogeneic keratinocyte therapy	Tego Science	Keratinocytes	Burns; ulcer, diabetic	2020	South Korea, Indonesia, Mongolia
Nepic	Autologous corneal epithelium cells	Teijin Pharma	Epithelial cells	Limbal stem cell deficiency	2020	Japan
StemSpine	Autologous stem cell therapy	Creative Medical Technologies	Bone marrow aspirate	Pain, musculoskeletal; regeneration, cartilage, intervertebral disc	2019	USA
FemCelz	Female sexual dysfunction stem cell therapy	Creative Medical Technologies	Stem cells, including hematopoietic and mesenchymal stem cells	Sexual dysfunction, female	2019	EU, UK, USA
CartiLife	Autologous chondrocytes	Biosolution Co.	Chondrocytes	Arthritis, osteo	2019	South Korea
Cellistem	Umbilical cord mesenchymal stem cells	Cells for Cells	Mesenchymal stem cells	Arthritis, osteo; heart failure	2018	Chile
Epicel	Cultured epidermal autograft	Vericel Innovative Cellular Therapeutics	Epidermal cells	Burns	2018	USA
Stemirac	Stemirac	Nipro	Mesenchymal stem cells	Spinal cord injury	2018	Japan
Kyslecel	Minimally manipulated autologous pancreatic islets	Orgenesis	Pancreatic islet cells	Pancreatitis	2018	USA
Alofisel	Darvadstrocel	Takeda	Adipose-derived stem cells	Anal fistula, Crohn disease	2018	EU, Israel, Japan, UK

Table 2. Continued

Product name	Generic name	Originator company	Modality	Disease(s)	Year first approved	Locations approved
Spherox	Spheroids of human autologous matrix-associated chondrocytes	co.don	Chondrocytes	Regeneration, cartilage, orthopediac lesion	2017	EU, UK
Keraheal-Allo	Allogeneic keratinocytes	Biosolution Co.	Keratinocytes	Burns	2017	South Korea
Keraheal	Autologous keratinocytes	Biosolution Co.	Keratinoyctes	Burns	2017	South Korea
Apceden	Autologous dendritic cells	APAC Biotech	Dendritic cell immunotherapy	Colorectal cancer, non-small cell lung cancer, ovarian cancer, prostate cancer	2017	India
Chondron	Autologous chondrocytes	Sewon Cellontech	Chondrocytes	Regeneration, cartilage, orthopediac lesion	2017	China, India, Malaysia, Singapore, EU, South Korea, UK
Chondroseal	Chondroseal	Theracell Advanced Biotechnology	Adipose-derived stem cells	Regeneration, cartilage, orthopediac lesion	2016	UK
Cartil-S	Cartil-S	Theracell Advanced Biotechnology	Adipose-derived stem cells	Arthritis, osteo	2016	UK
AlloStem	Allogeneic adipose-derived mesenchymal stem cells	AlloSource	Mesenchymal stem cells	Regeneration, bone	2016	USA
Stempeucel	Allogeneic mesenchymal stem cells	Stempeutics	Mesenchymal stem cells	Ischemia, limb	2016	India
NeuroNata-R	Lenzumestrocel	Corestem	Mesenchymal stem cells	Amyotrophic lateral sclerosis	2015	South Korea
CureSkin	CureSkin	S.Biomedics	Skin cell therapy	Wound healing	2015	South Korea
TCD-51073	Autologous myoblast cell therapy	Precigen	Myoblasts	Heart failure	2015	Japan
Holoclar	Autologous corneal epithelial cells	Holostem Terapie Avanzate	Corneal epithelial cells	Limbal stem cell deficiency	2015	EU, UK
Novocart 3D	Autologous chondrocyte transplantation system	Aesculap Biologics	Chondrocytes	Regeneration, cartilage, orthopediac lesion	2014	Germany, Switzerland
Ortho-ATI	Autologous tenocyte implantation	Orthocell	Tenocytes	Regeneration, ligament; regeneration, tendon	2014	Australia, China, New Zealand
Ortho-ACI	Autologous chondrocyte implantation	Orthocell	Chondrocytes	Regeneration, cartilage	2014	Australia
HiQCell	HiQCell	Regeneus	Adipose tissue stem cells	Arthritis, osteo; tendinitis	2014	Australia
Cupistem	Autologous adipose-derived stem cell therapy	Bukwang Pharmaceutical	Adipose-derived stem cells	Anal fistula	2014	South Korea
Carticel	Autologous cultured chondrocytes	Sanofi	Chondrocytes	Regeneration, cartilage, orthopediac lesion	2014	USA
Carticel II	Matrix-induced autologous chondrocyte implantation	Sanofi	Chondrocytes	Regeneration, cartilage, orthopediac lesion	2013	USA
Ryoncil	Remestemcel-L	Smith & Nephew	Mesenchymal stromal cells	Graft-versus-host disease	2012	Japan
Gintuit		Organogenesis			2012	USA

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Table 2. Continued

Product name	Generic name	Originator company	Modality	Disease(s)	Year first approved	Locations approved
	Allogeneic keratinocytes/ fibroblasts/collagen		Dermal fibroblasts/ keratinocytes/collagen	Regeneration, soft tissue, gingival		
Cartistem	Human umbilical cord blood–derived mesenchymal stem cells	Medipost	Mesenchymal stem cells	Arthritis, osteo; regeneration, cartilage, orthopediac lesion	2012	South Korea
JACC	Autologous cultured cartilage	Teijin Pharma	Chondrocytes	Regeneration, cartilage, orthopediac lesion	2012	Japan
Hearticellgram-AMI	Autologous mesenchymal stem cell therapy	Pharmicell	Mesenchymal stem cells	Infarction, myocardial	2011	South Korea
Ossron	Autologous osteoblasts	Sewon Cellontech	Osteoblasts	Osteonecrosis; regeneration, bone, cancer-related bone loss; regeneration, bone, fracture healing	2011	South Korea
Provenge	Sipuleucel-T	Dendreon	Autologous dendritic cell vaccine	Prostate cancer	2010	USA
MPCs, autologous, bone repair	MPCs, autologous, bone repair	Mesoblast	MPCs	Regeneration, bone, fracture healing	2010	Australia
CreaVax-RCC	CreaVax-RCC	CreaGene	Dendritic cell vaccine	Renal cancer	2010	South Korea
De Novo NT	*De novo* natural tissue graft	Zimmer Biomet	Chondrocytes	Regeneration, cartilage, orthopediac lesion	2007	USA
Immuncell-LC	Autologous CIK cells and activated cytotoxic T lymphocytes	GC Biopharma	T cell immunotherapy	Liver cancer	2007	South Korea
Holoderm	Autologous keratinocyte therapy	Tego Science	Keratinocytes	Burns	2007	South Korea
Jacemin	Autologous cultured keratinocytes	Teijin Pharma	Keratinocytes	Burns, epidermolysis bullosa, melasma, vitiligo	2007	Japan
OsteoCel	OTI-050	Smith & Nephew	Osteocytes derived from mesenchymal stem cells	Regeneration, bone, cancer-related bone loss; regeneration, bone, craniomaxillofacial; regeneration, bone, dental; regeneration, bone, spinal fusion	2005	USA
M-Vax	Dinitrophenyl-modified autologous tumor vaccine	AVAX Technologies	Tumor cell vaccine	Melanoma	2005	EU
EpiDex	HEALIVA 001	Integra LifeSciences	Epidermal keratinocytes	Ulcer, diabetic	2002	EU
OrCel	Bilayered cellular matrix	Forticell Bioscience	Bilayered cellular matrix	Burns, epidermolysis bullosa	2001	USA
Melacine	Melanoma vaccine	GlaxoSmithKline	Melanoma cell vaccine	Melanoma	1999	Canada
TransCyte	Dermagraft-TC	Advanced Tissue Sciences	Dermal and epidermal cells	Burns	1997	USA
Dermagraft	ABH-001	Advanced Tissue Sciences	Dermal fibroblasts	Ulcer, diabetic	1997	Australia, Canada, EU, China, New Zealand, UK, USA, Israel, Singapore
Apligraf	Apligraf	Organogenesis	Epidermal keratinocytes and dermal fibroblasts	Ulcer, diabetic; ulcer, venostasis; wound healing	1997	Canada, USA, Saudi Arabia, Switzerland
ProChon	Autologous chondrocyte tissue implant	Ocugen	Chondrocytes	Regeneration, cartilage, orthopediac lesion	Unknown	EU, Israel

MPCs, mesenchymal precursor cells.

Table 3. All approved RNA therapies, including emergency authorizations for COVID-19 vaccines, as of June 2023

Product name	Generic name	Originator company	Modality	Disease(s)	Year first approved	Locations approved
Qalsody	Tofersen	Ionis Pharmaceuticals	Antisense therapy	Amyotrophic lateral sclerosis	2023	USA
ARCT 154	COVID-19 mRNA vaccine	Arcturus Therapeutics	mRNA vaccine	Infection, coronavirus, novel coronavirus prophylaxis	2023	Japan
Amvuttra	Vutrisiran	Alnylam	RNAi	Amyloidosis, TTR-related hereditary	2022	EU, USA, UK
ARCoV	COVID-19 mRNA vaccine	Suzhou Abogen Biosciences	mRNA vaccine	Infection, coronavirus, novel coronavirus prophylaxis	2022	Indonesia
Spikevax Bivalent Original/Omicron	Bivalent COVID-19 vaccine	Moderna	mRNA vaccine	Infection, coronavirus, novel coronavirus prophylaxis	2022	UK, Australia, EU, Canada, Japan, Singapore, South Korea, China, USA
COVID-19 vaccine	Bivalent COVID-19 vaccine	BioNTech	mRNA vaccine	Infection, coronavirus, novel coronavirus prophylaxis	2022	UK, USA
	SYS6006; COVID-19 mRNA vaccine	CSPC Pharmaceutical	mRNA vaccine	Infection, coronavirus, novel coronavirus prophylaxis	2022	China
Nulibry	Fosdenopterin	Orphatec	Oligonucleotide-derived therapy	Molybdenum cofactor deficiency	2021	USA, EU, Israel, UK
Gemcovac	COVID-19 mRNA vaccine	Emcure Pharmaceuticals	mRNA vaccine	Infection, coronavirus, novel coronavirus prophylaxis	2021	India
Comirnaty	Tozinameran	BioNTech	mRNA vaccine	Infection, coronavirus, novel coronavirus prophylaxis	2020	Australia, EU, Brazil, Canada, Ghana, Israel, Japan, Kuwait, Malaysia, Mexico, New Zealand, Rwanda, Singapore, South Africa, South Korea, UK, UAE, USA, China, Bahrain, Chile, Colombia, Indonesia, Oman, Sri Lanka, Thailand, Vietnam, Egypt, Indonesia
Oxlumo	Lumasiran	Alnylam	RNAi	Hyperoxaluria	2020	EU, USA, Brazil, UK
Leqvio	Inclisiran	Alnylam	RNAi	Atherosclerosis, heterozygous familial hypercholesterolaemia, hypercholesterolaemia	2020	EU, USA, Australia, UK
Amondys 45	Casimersen	Sarepta Therapeutics	Antisense therapy	Dystrophy, Duchenne muscular	2020	USA
Spikevax	2019-nCoV vaccine	Moderna	mRNA vaccine	Infection, coronavirus, novel coronavirus prophylaxis	2020	Canada, EU, Israel, Nigeria, UK, USA, Japan, South Korea, Australia, Botswana, Brunei, Indonesia, India, Vietnam, Thailand, China, Singapore, Saudi Arabia, Qatar, Paraguay, Mexico, Philippines
Waylivra	Volanesorsen	Ionis Pharmaceuticals	Antisense therapy	Hypertriglyceridaemia, lipoprotein lipase deficiency	2019	EU, UK, Brazil, Canada,
Viltepso	Viltolarsen	Nippon Shinyaku	Antisense therapy	Dystrophy, Duchenne muscular	2019	Japan, USA
Vyondys 53	Golodirsen	Sarepta Therapeutics	Antisense therapy	Dystrophy, Duchenne muscular	2019	USA
Givlaari	Givosiran	Alnylam	RNAi	Porphyria	2019	Canada, EU, UK, USA, Israel, Brazil, Japan

Table 3. Continued

Product name	Generic name	Originator company	Modality	Disease(s)	Year first approved	Locations approved
Onpattro	Patisiran	Alnylam	RNAi	Amyloidosis, TTR-related hereditary	2018	EU, Canada, Israel, Japan, Brazil, USA, UK, China
Tegsedi	Inotersen	Ionis Pharmaceuticals	Antisense therapy	Amyloidosis, TTR-related hereditary	2018	EU, Canada, UK, USA, Brazil
Ampligen	Rintatolimod	AIM ImmunoTech	Mismatched double-stranded RNA	Chronic fatigue syndrome	2016	Argentina
Spinraza	Nusinersen	Ionis Pharmaceuticals	Antisense therapy	Muscular atrophy, spinal	2016	Australia, EU, USA, Canada, China, Israel, South Korea, UK, Japan, Argentina, Brazil, Colombia
Exondys 51	Eteplirsen	Sarepta Therapeutics	Antisense therapy	Dystrophy, Duchenne muscular	2016	USA
Kynamro	Mipomersen sodium	Ionis Pharmaceuticals	Antisense therapy	Homozygous familial hypercholesterolaemia	2013	Argentina, South Korea, USA, Mexico

(42%). Among these, CAR-T approaches are the most prevalent, representing 30% of active pipeline cell programs in the industry. CD-19-targeting CAR-Ts provided the proof-of-concept that autologous T cells could be retrained and harnessed to treat certain hematological malignancies. Programs against a wide range of different antigens are under development, including B cell maturation antigen, CD22, mesothelin, and many others. Buoyed by the early clinical successes of tisagenlecleucel and axicabtagene ciloleucel, and reflecting the opportunities to improve upon patient safety and manufacturing processes, a large cohort of next-generation CAR-Ts is under investigation. The first CAR-T therapies are limited by the occurrence of serious adverse events relating to cytokine release syndrome and neurotoxicity, which necessitates continuous monitoring postinfusion.[14] Furthermore, CAR-T manufacturing is a multistep process that requires 3–4 weeks for the "vein-to-vein" time (from first extraction of the patient's own blood cells to the reinfusion of the patient's genetically modified T cells) of current autologous therapies.[15] Accordingly, follow-on CAR-Ts and other gene-modified cell therapies for oncology are designed to make improvements in these areas. One major strategy is through allogeneic CAR-T cells, whereby the T cells are produced from healthy donors and undergo multiple gene engineering steps to express CAR and mitigate the risk of immunogenicity. There are currently 142 active allogeneic CAR-T programs in development, the most advanced of which are in Phase II development.

Beyond CAR-Ts, the most common gene-modified cell therapies include T cell receptor (TCR) T cells and CAR-natural killer (CAR-NK) cells. As of June 2023, there are 146 TCR-T therapies in development and a further 88 CAR-NKs. Both are less mature drug classes than CAR-Ts, although the TCR class achieved a notable milestone with its first US Food and Drug Administration approval in January 2022 for the metastatic uveal melanoma drug tebentafusp (Kimmtrak; Immunocore).[16] TCRs are notably differentiated from CAR-Ts because they are not limited to antigens expressed on the cell surface but rather can extend to intracellular antigens, and therefore the treatment of solid tumors. However, TCRs require the involvement of major histocompatibility complex in recognizing these antigens and thus faces the challenge of allelic diversity in human leukocyte antigen (HLA) genes.[17] CAR-NK is an emerging modality with three proposed advantages over CAR-Ts, namely, with lower potential for tumor antigen escape and improved safety profile and without the requirement for HLA matching, improving amenability for allogeneic delivery.[18]

RNA therapies

RNA is the least commonly investigated advanced genetic modality, with a pipeline under half the size of that for gene- and cell-based drugs. There are 910 RNA-based therapeutics under active development, the majority of which (576; 63%) use RNA to regulate the translation and effect of proteins (Figure 3). Such noncoding oligomers are diverse in their design, either as single- or double-stranded species that are sequence matched to a corresponding genetic sequence, or that form tertiary structures with varying pharmacological effects. The remainder (334; 37%) are direct coding
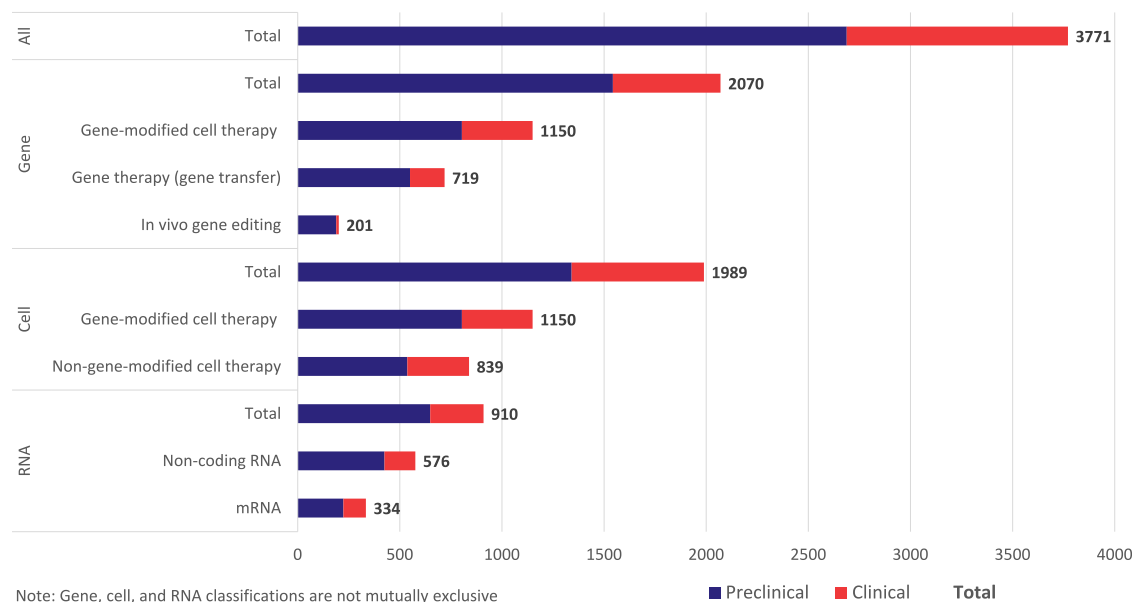
Note: Gene, cell, and RNA classifications are not mutually exclusive

Figure 2. Biopharmaceutical industry pipeline of gene, cell, and RNA-based drugs under active development.

sequences of mRNA that are translated *in vivo* by the ribosome into proteins. This is commonly used as a vaccination strategy, in which the resulting protein is antigenic such as in the design of mRNA-based SARS-CoV-2 vaccines. Of the 334 mRNA-based products in the pipeline, 199 are designed in such a way as to raise an immune response, whereas the remaining drugs are designed to produce a therapeutic protein or whose mechanism is not disclosed.

Within the noncoding cohort of RNA therapies, RNAi therapies outnumber the second of the 2 most prominent subcategories, ASOs, by 277 to 191. The rate at which new RNAi assets are being created is greater. ASO is the more mature technology and relies upon single-stranded nucleic acids that are sequence matched to a target length of pre-mRNA. ASO binding triggers a range of outcomes such as alternative processing and target degradation. By contrast, RNAi relies upon double-stranded sections of siRNA to harness the RNA-induced silencing complex, which has a natural and essential role in gene expression, to induce RNA cleavage.[19] Depending on the target pre-mRNA, both approaches can yield a range of outcomes, from gene silencing or activation to modification of splicing.

Outside of these two main noncoding classes, there are myriad other uses for RNA at the experimental stage. These include microRNA, short activating RNA, circular RNA, and tRNA, among others. As discussed previously, there is another use of RNA therapeutically in the form of gRNA, an essential part of CRISPR-based gene editing.

CLINICAL DEVELOPMENT LANDSCAPE

As the pipeline for gene, cell, and RNA therapies expands, the rate of new clinical trial initiation is generally increasing. However, in 2022 a 20% decrease from the record number of new trials and the percent increase observed in 2021 occurred. As shown in Figure 4, the recent

growth has been driven most notably by clinical trials of mRNA-based drugs, primarily in response to the SARS-CoV-2 pandemic.[20] A total of 195 mRNA clinical trials were initiated in 2022, which is just over 10 times higher than the corresponding prepandemic number in 2019, but half the corresponding number in 2021. There were more trials initiated of non-gene-modified cell therapies than any other class in 2022 (391), although the consistent growth of gene-modified cell therapies has closed the gap considerably, with 325 trials initiated in 2022.

There are relatively few clinical trials for *in vivo* gene therapies compared to the size of the drug pipeline described earlier in this review. Thirteen such studies for *in vivo* gene editing initiated in 2022, including first-in-human studies of EBT-101 (CRISPR therapy; Excision BioTherapeutics) in HIV-1 infection, SNIPR-001 (CRISPR-based therapy; SNIPR Biome) for *Escherichia coli* infection, and HMI-103 (nuclease-free gene editing therapy; Homology Medicines) for phenylketonuria. A total of 77 clinical trials for gene transfer therapies began in 2022, which is a decrease since the record 97 that were initiated in 2021. A similar trajectory can be plotted for noncoding RNA approaches, noting a strong uptick in 2021 to 141 studies initiated, followed by a drop in 2022 to 119.

In total, there are 5,572 clinical trials for advanced genetic therapies currently active. This number includes trials that are ongoing (open for enrollment, closed, or temporarily closed) as well as those planned by sponsors but not yet initiated. These active clinical trials account for 31% of all of the clinical development recorded so far within Trialtrove for gene, cell, and RNA therapies, with the total landscape containing 18,185 known clinical trials. The remainder of this review focuses on active clinical trials within each drug modality.

As shown in Figure 5, there are more active cell therapy trials (4,163) than either gene (2,233) or RNA therapy (930). For both cell and gene
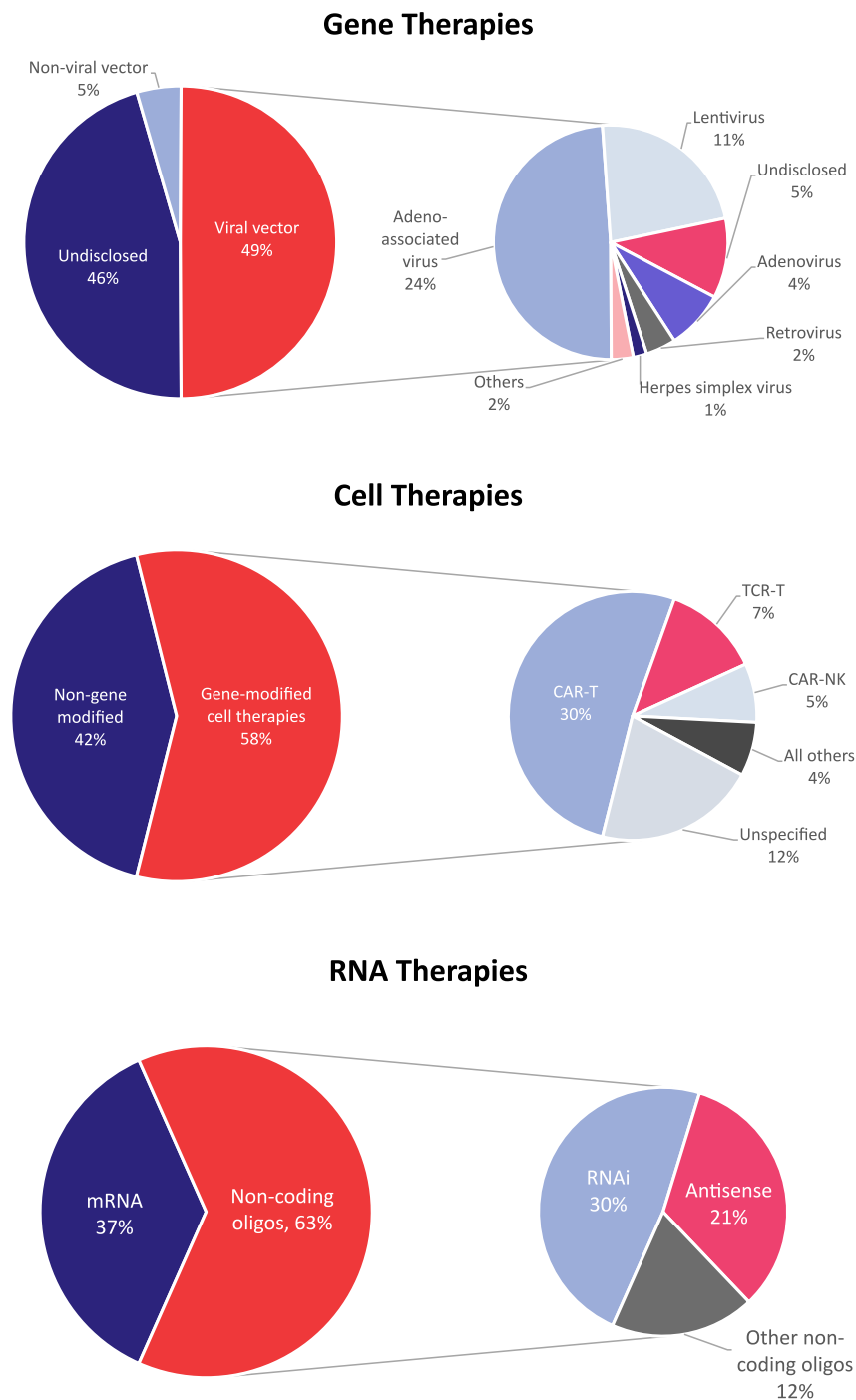
Gene Therapies

Cell Therapies

RNA Therapies

inflammation, CNS, metabolic/endocrinology, and cardiovascular. All of these represent minority areas of investigation behind oncology.

Gene therapies

The concentration of gene therapy trials in oncology is intense, accounting for 1,776 of 2,233 (80%, Figure 6). The main reason for this is the predominance of gene-modified cell therapies in cancer indications, in particular CAR-Ts being studied for hematologic malignancies. Such cell therapies are only very rarely studied clinically in nononcology indications. For *in vivo* gene therapy approaches, there is greater diversity across the range of therapy areas, reflecting the wide number of monogenic diseases and broad symptomatology that may result. Nevertheless, oncology is still the most common clinical setting for *in vivo* gene transfer therapies, ahead of CNS, metabolic and endocrinology, and cardiovascular conditions. Ophthalmology, in particular, rare inherited retinal disorders, is also a prevalent area of clinical investigation; these trials are included within the "Other" grouping.

Cell therapies

As noted above, gene-modified cell therapies are almost exclusively studied in oncology indications (Figure 6). However, for the group of non-gene-modified cell therapies, the breadth of therapeutic areas is notable. Although oncology is in the lead overall, there are large numbers of active cell therapy trials within autoimmunity and inflammation (475), CNS (257), and infectious diseases (213). These include diseases such as graft-versus-host disease, osteoarthritis, pain, and a large cohort of COVID-19 trials involving stem cell therapies.

RNA therapies

The distribution of active clinical trials for RNA drugs is highly variable, depending on whether the therapy is an mRNA-based vaccine or therapeutic, or a noncoding oligonucleotide-based drug such as RNAi or antisense. There are slightly fewer active trials of noncoding RNA-based drugs (421) compared to mRNA (509), and these trials are spread across a wider range of therapeutic areas (Figure 6). Again, the lead setting for noncoding RNA drugs is oncology (105 trials), although development in CNS (89), cardiovascular diseases (76), and infectious diseases (64) is not far behind. Similar to gene therapy approaches, this reflects the broad nature of diseases that

therapy, oncology is the leading therapy area under investigation, accounting for 80% of all gene therapy trials and 68% of cell therapies. Oncology is only the second most common clinical setting for RNA therapies (18%), behind infectious diseases (53%). For the combined total of active advanced genetic therapy trials, the remaining therapy areas by decreasing number of studies are infectious diseases, autoimmune/
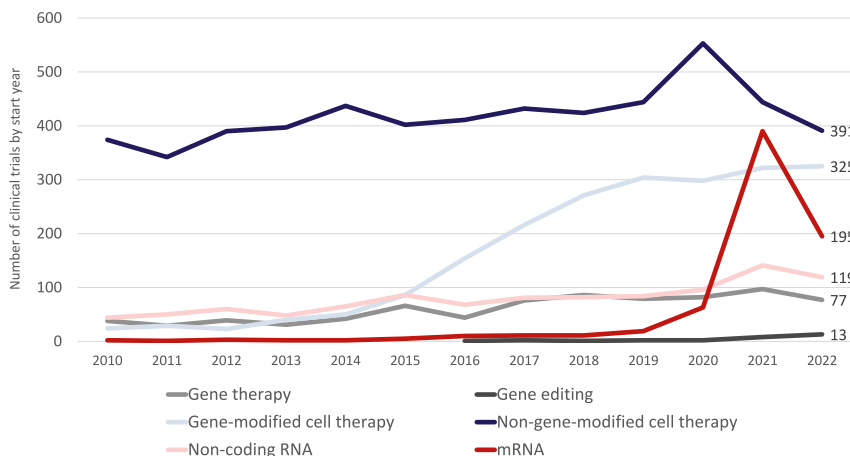
Figure 4. Number of clinical trials initiated each year for gene, cell, and RNA therapies.

are amenable to treatment via silencing or modification of the expression of single genes. A large majority of active mRNA drug trials are for the treatment or prevention of infectious diseases (429), of which COVID-19 is almost exclusively the focus (384). Beyond the current pandemic, the clinical investigation of mRNA in other infectious diseases includes influenza, cytomegalovirus, and HIV. There are also 62 active clinical trials for mRNA-based drugs in oncology, largely in the vaccination setting for personalized neoantigens or tumor-associated antigens. These span a range of different solid tumors, with non-small cell lung cancer, head and neck cancer, melanoma, and breast cancer being the most common indications.

FUTURE PERSPECTIVES

Standing at over 3,700 developmental candidates, the pipeline for advanced genetic therapies is both growing and diversifying. Gene and cell therapies are expanding well beyond their original proof-of-concept indications, and the COVID-19 pandemic has validated the potential of RNA vaccines. In particular, the areas of overlap between these technologies offers the promise of highly sophisticated and targeted new drugs. This enables the treatment of an increasing number of diseases,

particularly for patients with rare inherited monogenic diseases or biomarker-defined cancers. Encouragingly, the biopharmaceutical industry is making the transition between scientific discovery and clinical advances at scale and pace, as evidenced by the acceleration in new clinical trials for advanced genetic therapies. At the start of 2023 there were just under 5,600 active trials for such agents, and with more than 1,000 new trials initiating each year, therapeutic breakthroughs are beckoning. This momentum is carrying forward into new approvals and broader commercial availability, with the approval of 12 new therapies in 2022, and the landscape now totaling 111 different approved gene, cell, or RNA therapies as of June 2023. Looking ahead, this proliferation will continue because gene, cell, and RNA therapies occupy an increasing influence in and share of the wider biopharmaceutical research and development landscape.
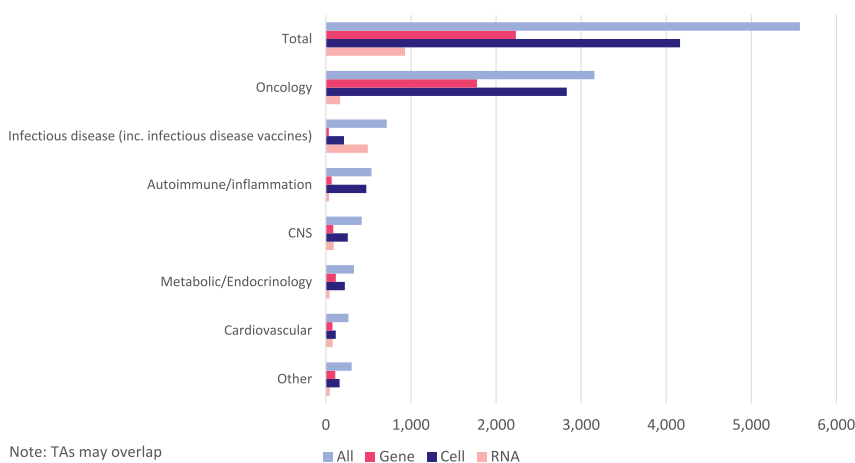
ACKNOWLEDGMENTS

Figure 5. Breakdown of active gene, cell, and RNA therapy clinical trials by status and therapy area (TA).
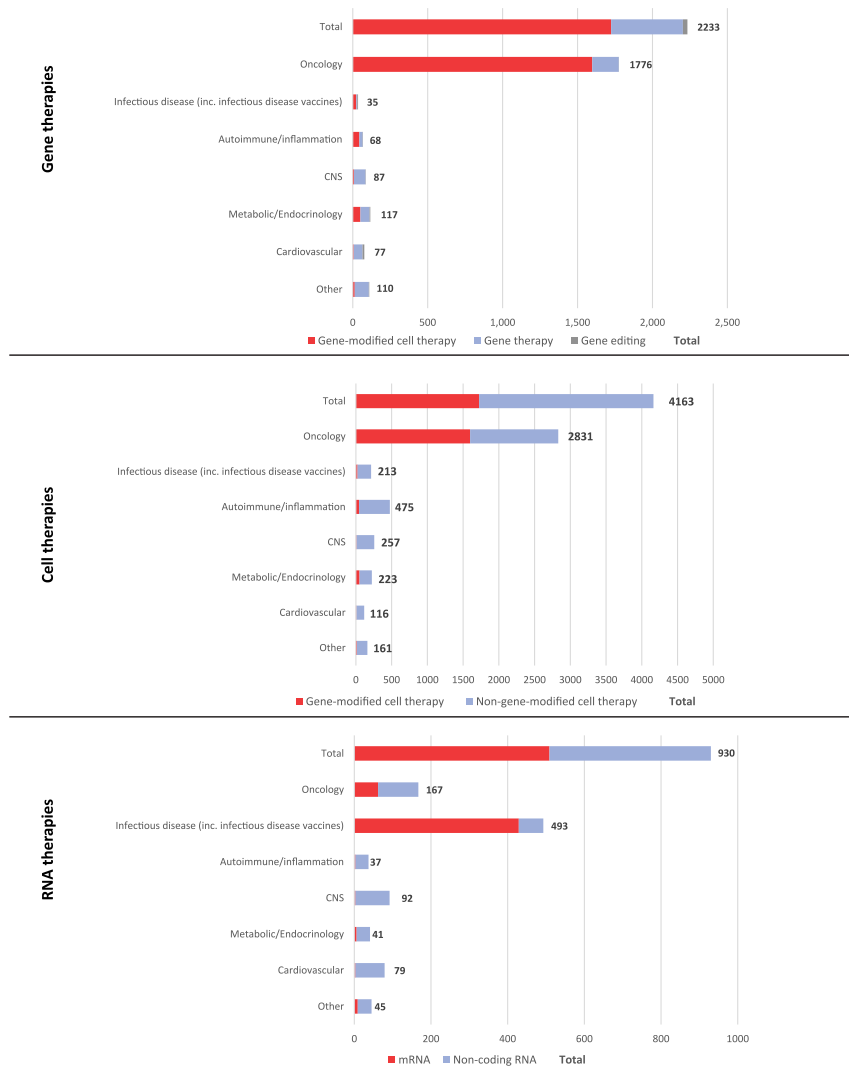
Figure 6. Therapy area concentration for active clinical trials of gene, cell, and RNA therapies
Please note that therapeutic areas may overlap.

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AUTHOR CONTRIBUTIONS

The project was conceptualized and administered by D.B. The paper was written, reviewed, and edited by S.M., D.C., L.N.-J, and F.E. The paper was reviewed and edited by D.B.

DECLARATION OF INTERESTS

D.B. is an employee of ASGCT. S.M., D.C., and F.E. are employees of Citeline. L.N.-J. is a former employee of Citeline. ASGCT and Citeline are partners in the development of the underlying data, which is derived from Citeline products and made available in the Gene, Cell & RNA Therapy Landscape quarterly data report.

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