Gene, Cell, & RNA Therapy Landscape

Q1 2023 Quarterly Data Report

American Society of Gene + Cell Therapy

CITELINE
formerly Pharma Intelligence

About the authors

The American Society of Gene & Cell Therapy (ASGCT) is the primary professional membership organization for scientists, physicians, patient advocates, and other professionals with interest in gene and cell therapy.

Our members work in a wide range of settings including universities, hospitals, government agencies, foundations, biotechnology and pharmaceutical companies. ASGCT advances knowledge, awareness, and education leading to the discovery and clinical application of gene and cell therapies to alleviate human disease to benefit patients and society.

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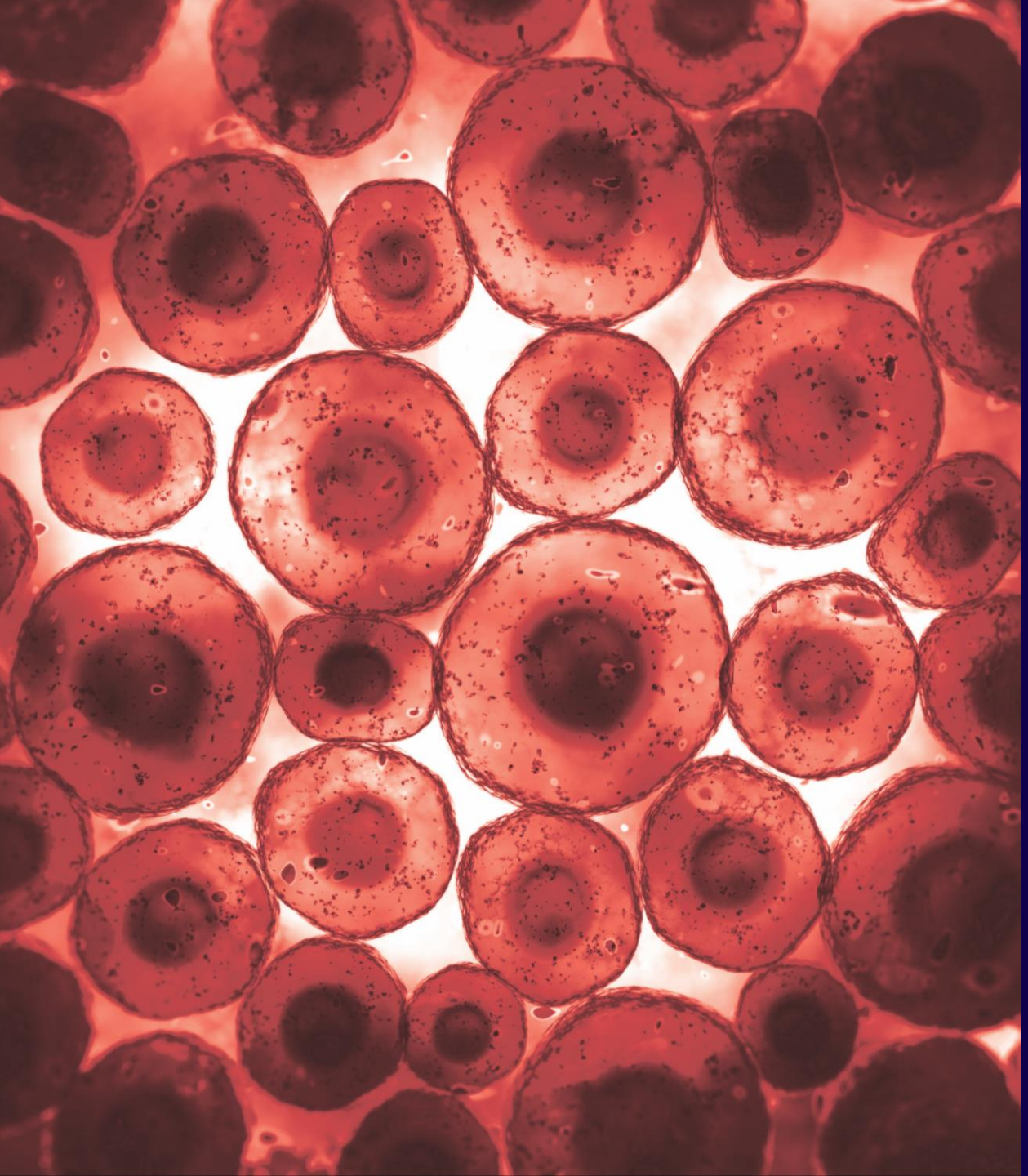

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American Society of Gene + Cell Therapy

Introduction

Welcome to the latest quarterly report from ASGCT and Citeline! In the first quarter of 2023, an mRNA vaccine was approved for COVID-19 prophylaxis in China, bringing the number of RNA therapy approvals to 22. In Japan, Vyznova was approved for corneal dystrophy, bringing the total non-genetically modified cell therapies to 61. No new gene therapies were approved in Q1, but Hemgenix was approved for hemophilia B in the EU and the UK.

The past quarter saw a decrease in gene therapy products in Phase I and II clinical trials, continuing a trend from Q4 2022. One therapy, exagamglogene autotemcel, or exa-cel, for people with transfusion-dependent beta thalassemia (TDT) or severe sickle cell disease (SCD), filed for approval in the first quarter. Also in the gene therapy pipeline, oncology and rare diseases remain the top areas of development both overall and in the clinic. Those two areas remain top areas of development in the pipeline of non-genetically modified cell therapies as well. In the RNA pipeline, rare diseases remain the top targeted therapeutic area, while anticancer therapies are the second most targeted area.

In Q1 2023, companies signed 110 deals — slightly fewer than the opening quarter of 2022 but similar compared to the previous two quarters. Series A and seed financings rebounded in Q1, reaching 17 transactions at a total of $615.2 million. This represents nearly double the volume and value of Q4 2022.

Key takeaways from Q1 2023

For the first time since Q2 2022, there were no new first approvals for gene therapies; however, Q1 2023 did see new RNA therapy and non-genetically modified cell therapy approvals

- CSPC Pharmaceutical's COVID-19 vaccine was granted emergency use authorization in China
- Aurion Biotech's Vyznova was approved for corneal dystrophy in Japan

Anticancer and rare diseases are the top two targeted therapeutic areas for pipeline gene, non-genetically modified, and RNA therapies

- Since Q4 2022, anticancer therapies overtook anti-infective therapies as the second most targeted therapy area for RNA therapies
- For all non-genetically modified cell therapies and RNA therapies, non-oncology indications dominate pipeline rare disease development; however, for gene therapies 54% of pipeline rare disease development occurs in oncology

Overall dealmaking by advanced molecule companies in Q1 2023 was virtually flat vs. Q4 2022, but start-up financing rebounded

- In Q1 2023, advanced molecular companies signed 110 total deals, just ahead of the 106 in Q4 2022, but slightly behind pace of the 123 done in the opening quarter of 2022
- Start-up financing saw big increases in Q1 compared with the previous quarter, doubling in volume and value to 17 Series A and seed financings together worth $615.2 million
- Active areas of investment for start-ups in Q1 were non-viral gene delivery via nanoparticles and lentiviral manufacturing
- Next-generation CAR-T developer Cargo had the top Series A round with $200 million

Key highlights in Q1 2023

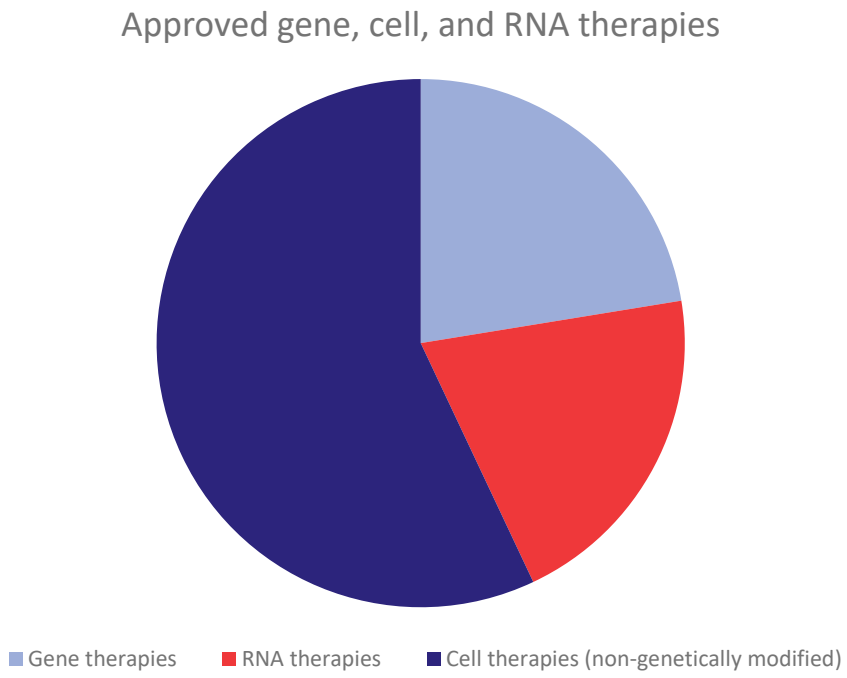
Q1 2023

American Society of Gene + Cell Therapy

Approved gene, cell, and RNA therapies

Globally, for clinical use:

- 24 gene therapies are approved (including genetically modified cell therapies)
  - There were no new gene therapy approvals in Q1 2023
- 22 RNA therapies are approved
  - In Q1 2023, an mRNA vaccine developed by CSPC Pharmaceutical was approved for COVID-19 prophylaxis in China
- 61 non-genetically modified cell therapies are approved
  - In Q1 2023, Vyznova was approved for corneal dystrophy in Japan



Source: Pharmaprojects | Citeline, April 2023

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Approved gene therapies as of Q1 2023 (1/2)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Gendicine	recombinant p53 gene	2004	Head and neck cancer	China	Shenzhen SiBiono GeneTech
Oncorine	E1B/E3 deficient adenovirus	2005	Head and neck cancer; nasopharyngeal cancer	China	Shanghai Sunway Biotech
Rexin-G	mutant cyclin-G1 gene	2006	Solid tumors	Philippines	Epeius Biotechnologies
Neovasculgen	vascular endothelial growth factor gene	2011	Peripheral vascular disease; limb ischemia	Russian Federation, Ukraine	Human Stem Cells Institute
Imlygic	talimogene laherparepvec	2015	Melanoma	US, EU, UK, Australia	Amgen
Strimvelis	autologous CD34+ enriched cells	2016	Adenosine deaminase deficiency	EU, UK	Orchard Therapeutics
Kymriah	tisagenlecleucel-t	2017	Acute lymphocytic leukemia; diffuse large B-cell lymphoma; follicular lymphoma	US, EU, UK Japan, Australia, Canada, South Korea, Switzerland	Novartis
Luxturna	voretigene neparvovec	2017	Leber's congenital amaurosis; retinitis pigmentosa	US, EU, UK, Australia, Canada, South Korea	Spark Therapeutics (Roche)
Yescarta	axicabtagene ciloleucel	2017	Diffuse large B-cell lymphoma; non-Hodgkin's lymphoma; follicular lymphoma	US, EU, UK, Japan, Canada, China	Kite Pharma (Gilead)
Collategene	beperminogene perplasmid	2019	Critical limb ischemia	Japan	AnGes
Zolgensma	onasemnogene abeparvovec	2019	Spinal muscular atrophy	US, EU, UK, Japan, Australia, Canada, Brazil, Israel, Taiwan, South Korea	Novartis
Zynteglo	betibeglogene autotemcel	2019	Transfusion-dependent beta thalassemia	US	bluebird bio

Source: Pharmaprojects | Citeline, April 2023

Text highlighted in yellow represents new approvals during Q1 2023

Approved gene therapies as of Q1 2023 (2/2)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Tecartus	brexucabtagene autoleucel	2020	Mantle cell lymphoma; acute lymphocytic leukemia	US, EU, UK	Kite Pharma (Gilead)
Libmeldy	atidarsagene autotemcel	2020	Metachromatic leukodystrophy	EU, UK	Orchard Therapeutics
Breyanzi	lisocabtagene maraleucel	2021	Diffuse large B-cell lymphoma; follicular lymphoma	US, Japan, EU, Switzerland, UK, Canada	Celgene (Bristol Myers Squibb)
Abecma	idecabtagene vicleucel	2021	Multiple myeloma	US, Canada, EU, UK, Japan	bluebird bio
Delytact	teserpaturev	2021	Malignant glioma	Japan	Daiichi Sankyo
Relma-cel	relmacabtagene autoleucel	2021	Diffuse large B-cell lymphoma; follicular lymphoma	China	JW Therapeutics
Skysona	elivaldogene autotemcel	2021	Early cerebral adrenoleukodystrophy (CALD)	US	bluebird bio
Carvykti	ciltacabtagene autoleucel	2022	Multiple myeloma	US, EU, UK, Japan	Legend Biotech
Upstaza	eladocagene exuparvovec	2022	Aromatic L-amino acid decarboxylase (AADC) deficiency	EU, UK	PTC Therapeutics
Roctavian	valoctocogene roxaparvovec	2022	Hemophilia A	EU, UK	BioMarin
Hemgenix	etranacogene dezaparvovec	2022	Hemophilia B	US, EU, UK	uniQure
Adstiladrin	nadofaragene firadenovec	2022	Bladder cancer	US	Merck & Co

Source: Pharmaprojects | Citeline, April 2023

Text highlighted in yellow represents new approvals during Q1 2023

Approved RNA therapies as of Q1 2023 (1/2)

Product name	Generic name	Year first approved	Disease(s)	Locations approved*	Originator company
Kynamro	mipomersen sodium	2013	Homozygous familial hypercholesterolemia	US, Mexico, Argentina, South Korea	Ionis Pharmaceuticals
Exondys 51	eteplirsen	2016	Dystrophy, Duchenne muscular	US	Sarepta Therapeutics
Spinraza	nusinersen	2016	Muscular atrophy, spinal	US, EU, UK, Canada, Japan, Brazil, Switzerland, Australia, South Korea, China, Argentina, Colombia, Taiwan, Turkey, Hong Kong, Israel	Ionis Pharmaceuticals
Ampligen	rintatolimod	2016	Chronic fatigue syndrome	Argentina	AIM ImmunoTech
Tegsedi	inotersen	2018	Amyloidosis, transthyretin-related hereditary	EU, UK, Canada, US, Brazil	Ionis Pharmaceuticals
Onpattro	patisiran	2018	Amyloidosis, transthyretin-related hereditary	US, EU, UK, Japan, Canada, Switzerland, Brazil, Taiwan, Israel, Turkey	Alnylam
Vyondys 53	golodirsen	2019	Dystrophy, Duchenne muscular	US	Sarepta Therapeutics
Waylivra	volanesorsen	2019	Hypertriglyceridemia; Lipoprotein lipase deficiency	EU, UK, Brazil, Canada	Ionis Pharmaceuticals
Comirnaty	tozinameran	2020	Infection, coronavirus, novel coronavirus prophylaxis	UK, Bahrain, Israel, Canada, US, Rwanda, Serbia, United Arab Emirates, Macao, Taiwan, Mexico, Kuwait, Singapore, Saudi Arabia, Chile, Switzerland, EU, Ghana, Colombia, Philippines, Indonesia, Australia, Hong Kong, Peru, South Korea, New Zealand, Japan, Brazil, Sri Lanka, Vietnam, South Africa, Thailand, Oman, Egypt, Malaysia	BioNTech
Moderna COVID-19 vaccine*	COVID-19 vaccine, Moderna	2020	Infection, coronavirus, novel coronavirus prophylaxis	US, Canada, Israel, EU, Switzerland, Singapore, Qatar, Vietnam, UK, Philippines, Thailand, Japan, South Korea, Brunei, Paraguay, Taiwan, Botswana, India, Indonesia, Saudi Arabia, Mexico, Australia, Nigeria, Colombia	Moderna Therapeutics

*For COVID-19 vaccines, this includes emergency use authorization and full approvals

Note that molnupiravir was previously included in this list; however, it has now been removed as it is no longer considered to fall under the category of RNA therapeutics

Source: Pharmaprojects | Citeline, April 2023

Text highlighted in yellow represents new approvals during Q1 2023

Approved RNA therapies as of Q1 2023 (2/2)

Product name	Generic name	Year first approved	Disease(s)	Locations approved*	Originator company
Givlaari	givosiran	2020	Porphyria	US, EU, UK, Canada, Switzerland, Brazil, Israel, Japan	Alnylam
Oxlumo	lumasiran	2020	Hyperoxaluria	EU, UK, US, Brazil	Alnylam
Viltepso	viltolarsen	2020	Dystrophy, Duchenne muscular	US, Japan	NS Pharma
Leqvio	inclisiran	2020	Atherosclerosis; Heterozygous familial hypercholesterolemia; Hypercholesterolemia	EU, UK, Australia, Canada, Israel, US	Alnylam
Amondys 45	casimersen	2021	Dystrophy, Duchenne muscular	US	Sarepta Therapeutics
Nulibry	fosdenopterin	2021	Molybdenum cofactor deficiency	US, EU, UK, Israel	Orphatec
Gennova COVID-19 vaccine	COVID-19 vaccine, Gennova Biopharmaceuticals	2022	Infection, coronavirus, novel coronavirus prophylaxis	India	Gennova Biopharmaceuticals
Amvuttra	vutrisiran	2022	Amyloidosis, transthyretin-related hereditary	US, EU, UK	Alnylam
Moderna Spikevax Bivalent Original/Omicron vaccine	COVID-19 Bivalent Original/Omicron vaccine, Moderna	2022	Infection, coronavirus, novel coronavirus prophylaxis	UK, Canada, Taiwan, Switzerland, Japan, EU, Australia, South Korea, Singapore, US	Moderna Therapeutics
ARCoV	COVID-19 vaccine, Suzhou Abogen Biosciences	2022	Infection, coronavirus, novel coronavirus prophylaxis	Indonesia	Suzhou Abogen Biosciences
Pfizer & BioNTech's Omicron BA.4/BA.5-adapted bivalent booster vaccine	Omicron BA.4/BA.5-adapted bivalent booster vaccine	2022	Infection, coronavirus, novel coronavirus prophylaxis	US, UK	BioNTech
CSPC Pharmaceutical COVID-19 vaccine	COVID-19 vaccine, CSPC Pharmaceutical	2023	Infection, coronavirus, novel coronavirus prophylaxis	China	CSPC Pharmaceutical

*For COVID-19 vaccines, this includes emergency use authorization and full approvals

Note that molnupiravir was previously included in this list; however, it has now been removed as it is no longer considered to fall under the category of RNA therapeutics

Source: Pharmaprojects | Citeline, April 2023

Text highlighted in yellow represents new approvals during Q1 2023

Key highlights in Q1 2023

Noteworthy events that happened in Q1 2023

Drug	Event Type	Indication	Molecule	Event Date
Carvykti	Filing for Approval (China)	Multiple Myeloma (MM)	Cellular	02 January 2023
VX-522	Fast Track Status	Cystic Fibrosis (CF)	mRNA (messenger RNA)	09 January 2023
NTLA-2002	Innovative Licensing and Access Pathway (ILAP) (UK)	Hereditary Angioedema (HAE)	Non-Viral Gene Therapy	11 January 2023
FBX-101	PRIME Designation (Europe)	Krabbe Disease (Globoid Cell Leukodystrophy)	Viral Gene Therapy	17 January 2023
KB407	Orphan Drug Designation (Europe)	Cystic Fibrosis (CF)	Viral Gene Therapy	18 January 2023
AOC-1020	Fast Track Status	Muscular Dystrophy	siRNA/RNAi	18 January 2023
Exa-cel	EMA Validation of Approval Application	Sickle Cell Anemia and Transfusion-Dependent Beta Thalessemia	Non-Viral Gene Therapy	25 January 2023
Injectable Discogenic Cell Therapy	Regenerative Medicine Advanced Therapy (RMAT) Designation	Musculoskeletal Conditions	Cellular	26 January 2023
Ryoncil	Response Submitted to Complete Response Letter (CRL)	Graft vs. Host Disease (GVHD) - Treatment	Cellular	31 January 2023
Leqvio	Filing for Approval (China) and J-NDA Filing (Japan)	Dyslipidemia / Hypercholesterolemia	siRNA/RNAi	01 February 2023
RP-A501	Regenerative Medicine Advanced Therapy (RMAT) Designation	Glycogen Storage Disease (GSD)	Viral Gene Therapy	07 February 2023
MPC-06-ID	Regenerative Medicine Advanced Therapy (RMAT) Designation	Chronic Low Back Pain (CLBP)	Cellular	08 February 2023
Equecabtagene	Fast Track Status and Regenerative Medicine Advanced Therapy (RMAT) Designation	Multiple Myeloma (MM)	Cellular	12 February 2023
AOC-1020	Orphan Drug Designation (US)	Muscular Dystrophy	siRNA/RNAi	13 February 2023
LION-101	Orphan Drug Designation (Europe)	Muscular Dystrophy	Viral Gene Therapy	15 February 2023
Hemgenix	Conditional Marketing Authorization (Europe)	Hemophilia B	Viral Gene Therapy	20 February 2023
PBGM01	Advanced Therapy Medicinal Product (ATMP) Classification	GM1 Gangliosidosis	Viral Gene Therapy	24 February 2023
GNT0003	PRIME Designation (Europe)	Crigler-Najjar Syndrome	Viral Gene Therapy	07 March 2023
Eplontersen	NDA/BLA Accepted	Hereditary Transthyretin (hATTR) Amyloidosis With Polyneuropathy (Familial Amyloid Polyneuropathy)	Antisense	07 March 2023
ARO-APOC3	Fast Track Status and Orphan Drug Designation (Europe)	Familial Chylomicronemia Syndrome (FCS)/Lipoprotein Lipase Deficiency (LPLD)	siRNA/RNAi	20 March 2023
NTLA-2002	Regenerative Medicine Advanced Therapy (RMAT) Designation	Hereditary Angioedema (HAE)	Non-Viral Gene Therapy	21 March 2023
DYNE-251	Orphan Drug Designation (US)	Duchenne Muscular Dystrophy (DMD)	Antisense	21 March 2023
CSPC Pharmaceutical COVID-19 vaccine	Emergency Use Approval (China)	COVID-19 Prophylaxis	mRNA vaccine	22 March 2023
Vyznova	Regulatory - Approval (Japan)	Corneal Dystrophy	Cellular	23 March 2023
LN-144	Rolling NDA/BLA Completed	Melanoma	Cellular	24 March 2023
DB-OTO	Orphan Drug Designation (Europe)	Hearing Loss - General	Viral Gene Therapy	30 March 2023

Source: Biomedtracker | Citeline, April 2023

Pipeline overview

Q1 2023

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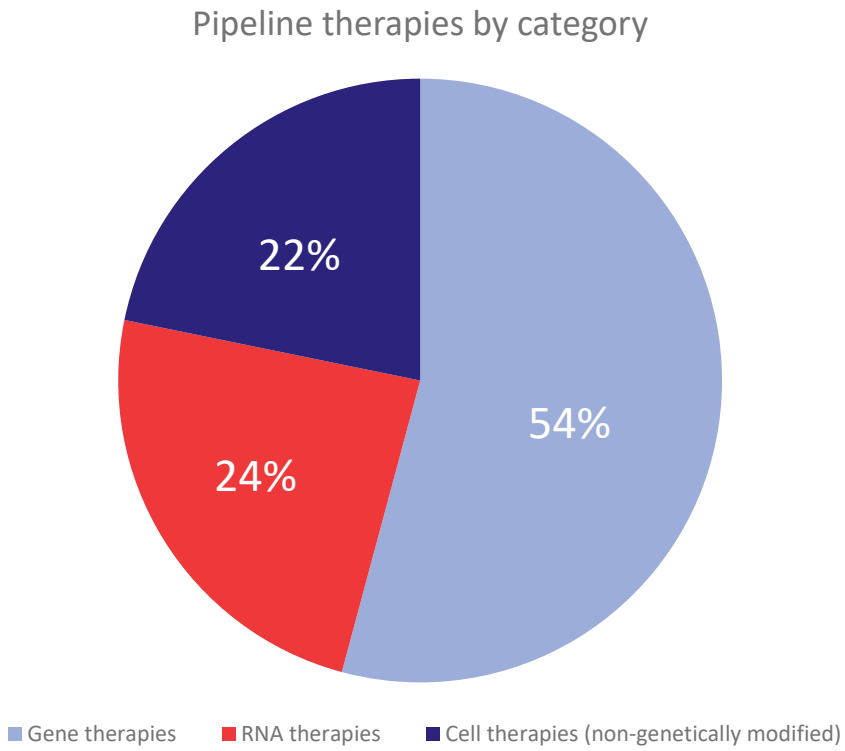
Pipeline of gene, cell, and RNA therapies

3,689 therapies are in development, ranging from preclinical through pre-registration

- 2,022 gene therapies (including genetically modified cell therapies such as CAR T-cell therapies) are in development, accounting for 54% of gene, cell, and RNA therapies
- 813 non-genetically modified cell therapies are in development, accounting for 22% of gene, cell, and RNA therapies



Source: Pharmaprojects| Citeline, April 2023

American Society of Gene + Cell Therapy

Gene therapy pipeline

Gene therapy and genetically modified cell therapies

Q1 2023

American Society of Gene + Cell Therapy

Gene therapy pipeline: Quarterly comparison

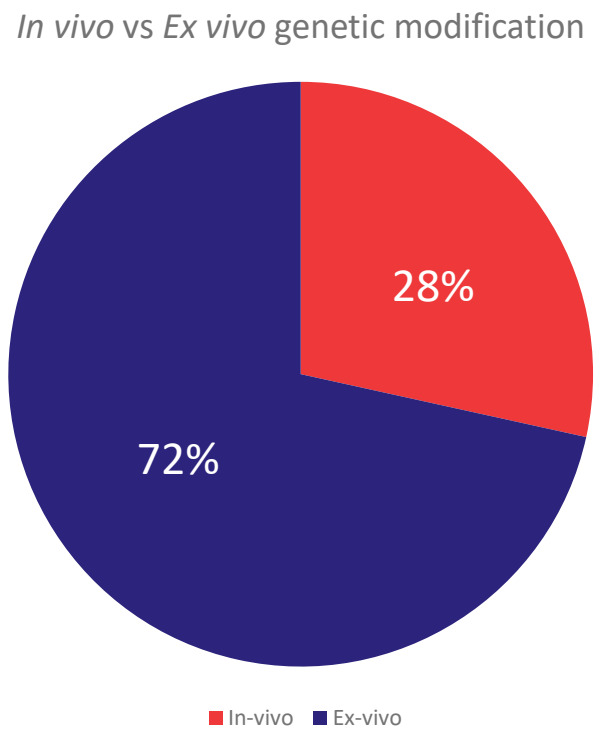
- Q1 2023 has continued last quarter's trend of seeing a decrease in Phase I and II gene therapy products, and also sees a decrease in preclinical stage programs
- One new therapy, exagamglogene autotemcel in sickle cell anemia and transfusion-dependent beta thalassemia, filed for approval in Q1 2023. Therapies currently in pre-registration are:
  - lenadogene nolparvovec (Genethon, GenSight Biologics)
    - In the EU and UK
  - beremagene geperpavec (Krystal Biotech)
    - In the US, EU, and UK
  - equecabtagene autoleucel (Nanjing IASO Biotherapeutics, Innovent)
    - In China
  - delandistrogene moxeparvovec (Sarepta Therapeutics)
    - In the US
  - zevor-cel (CARsgen Therapeutics)
    - In China
  - inaticabtagene autoleucel (CASI Pharmaceuticals, Juventas Cell Therapy)
    - In China
  - exagamglogene autotemcel (CRISPR Therapeutics, Vertex Pharmaceuticals)
    - In the EU and UK

Global Status	Q1 2022	Q2 2022	Q3 2022	Q4 2022	Q1 2023
Preclinical	1,451	1,482	1,480	1,515	1,493
Phase I	248	258	264	254	245
Phase II	250	248	249	248	247
Phase III	31	28	32	30	30
Pre-registration	6	8	6	6	7
Total	**1,986**	**2,024**	**2,031**	**2,053**	**2,022**

Source: Pharmaprojects| Citeline, April 2023

Genetic modification: *In vivo* vs. *Ex vivo*

- *Ex vivo* genetic modification is more widely used for gene therapies in pipeline development
- In Q1 2023, *in vivo* delivery techniques were used in 28% of gene therapies, 1% higher than the proportion has been for over 1 year



Source: Cell and Gene Therapy dashboard | Citeline, April 2023

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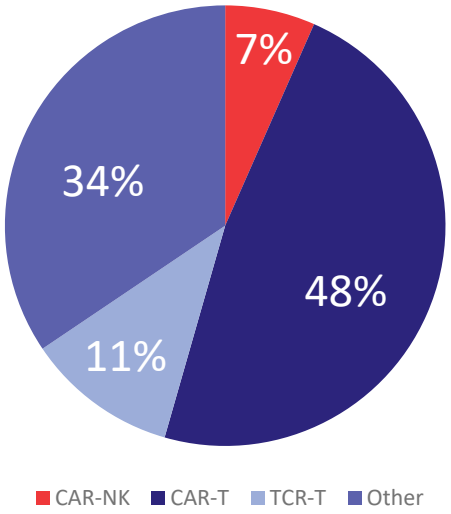
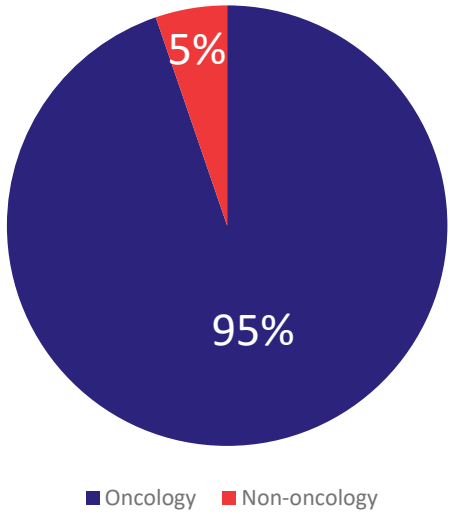
Gene therapy breakdown: CAR-Ts continue to dominate pipeline

- CAR T-cell therapies remain the most common technology used in the pipeline of genetically modified cell therapies (preclinical through to pre-registration), representing 48%, followed by the “other” category at 34%, which includes a list of less commonly used technologies including TCR-NK, CAR-M, and TAC-T
- 95% of CAR T-cell therapies are in development for cancer indications. The remaining non-oncology indications include scleroderma, HIV/AIDS, and autoimmune disease (unspecified).

Genetically modified cell therapy breakdown



CAR-T breakdown

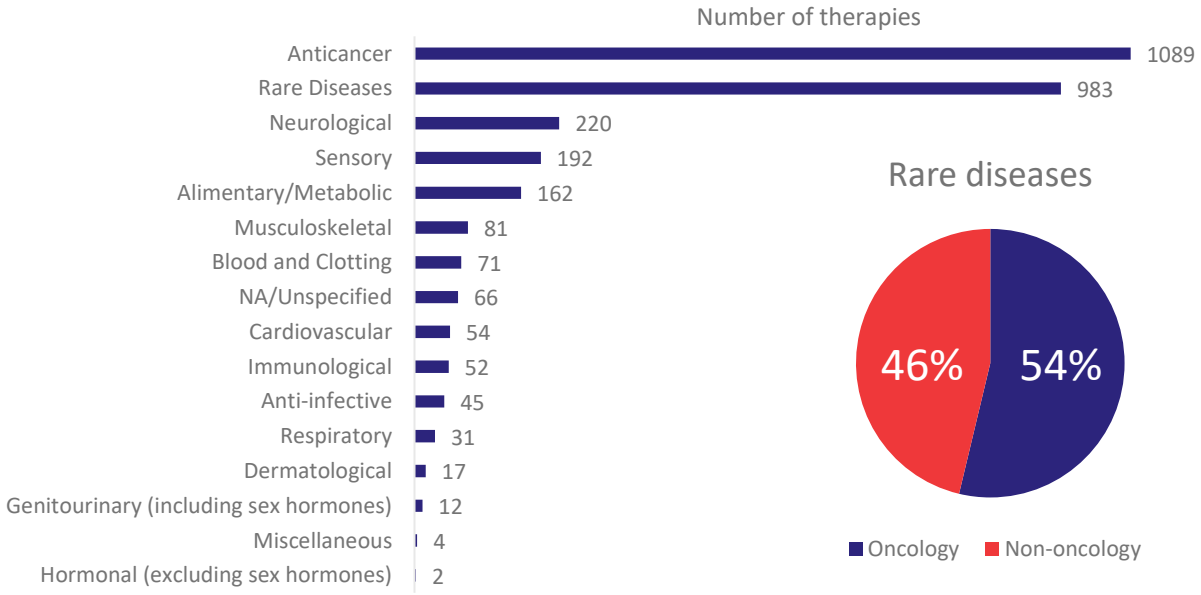


Source: Cell and Gene Therapy dashboard | Citeline, April 2023

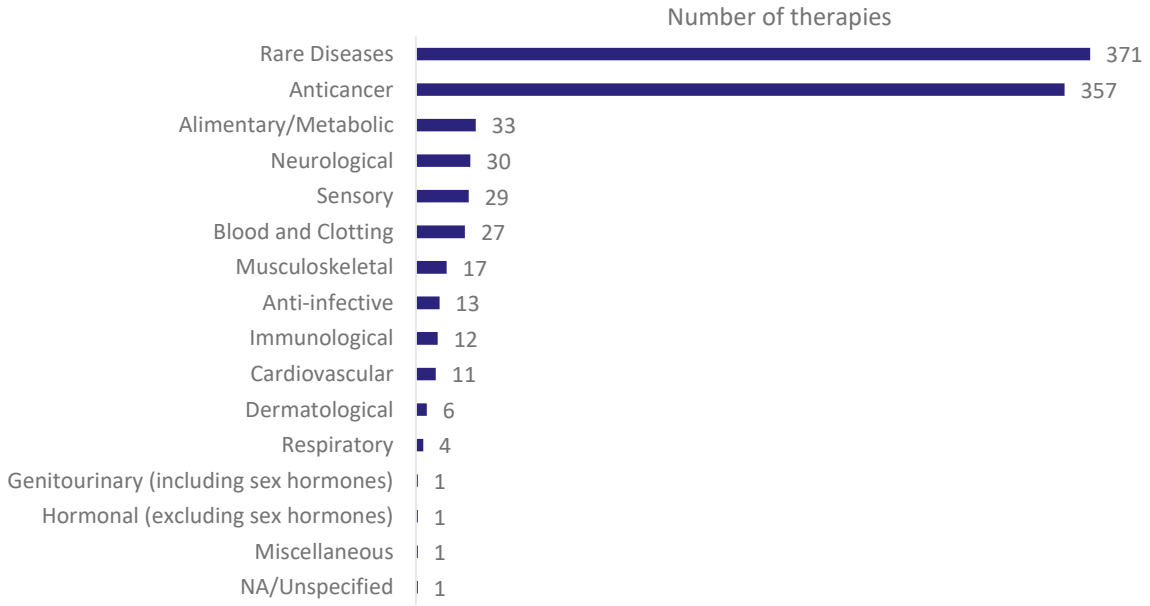
Gene therapy pipeline: Most commonly targeted therapeutic areas

- Oncology and rare diseases remain the top areas of gene therapy development in both the overall pipeline (preclinical to pre-registration) and in the clinic (Phase I to pre-registration)
- Development for rare diseases most commonly occurs in oncology, representing a majority of 54% compared to non-oncology rare disease gene therapy pipeline development

Number of therapies from preclinical through pre-registration



Therapies in the clinic (excludes preclinical development)



Source: Pharmaprojects| Citeline, April 2023

Note: figures based on indications in pipeline development only for each therapy

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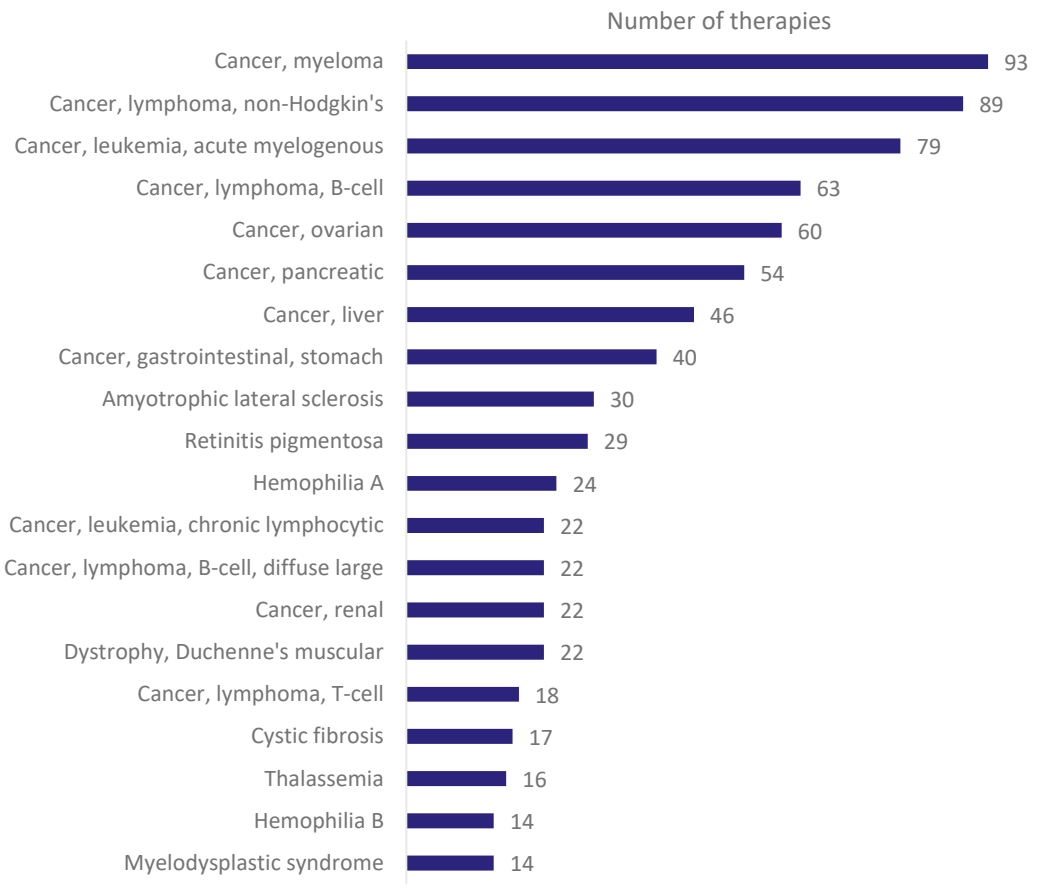
Gene therapy pipeline: Most common rare diseases targeted

- For the 983 pipeline (preclinical to pre-registration) gene therapies which are being developed for rare diseases, eight out of the top 10 rare diseases are oncological, as seen all throughout 2022
- In the same order as the previous six quarters, the top five rare diseases for which gene therapies are being developed are:
  1. Myeloma
  2. Non-Hodgkin’s lymphoma
  3. Acute myelogenous leukemia
  4. B-cell lymphoma
  5. Ovarian cancer



Source: Pharmaprojects| Citeline, April 2023

Note: figures based on indications in pipeline development only for each therapy

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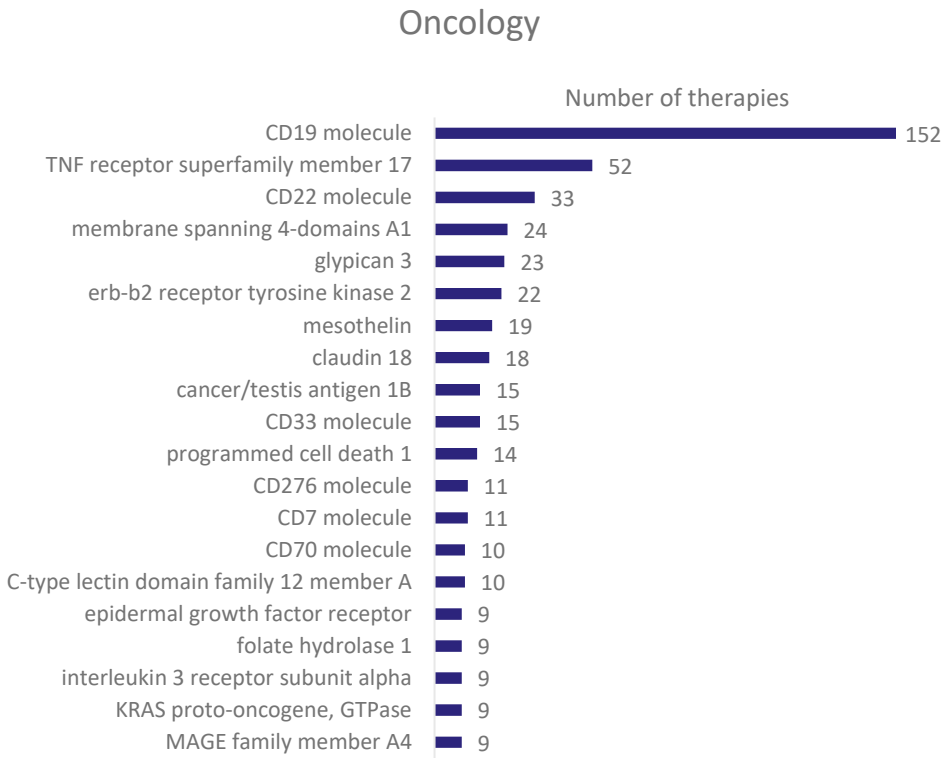
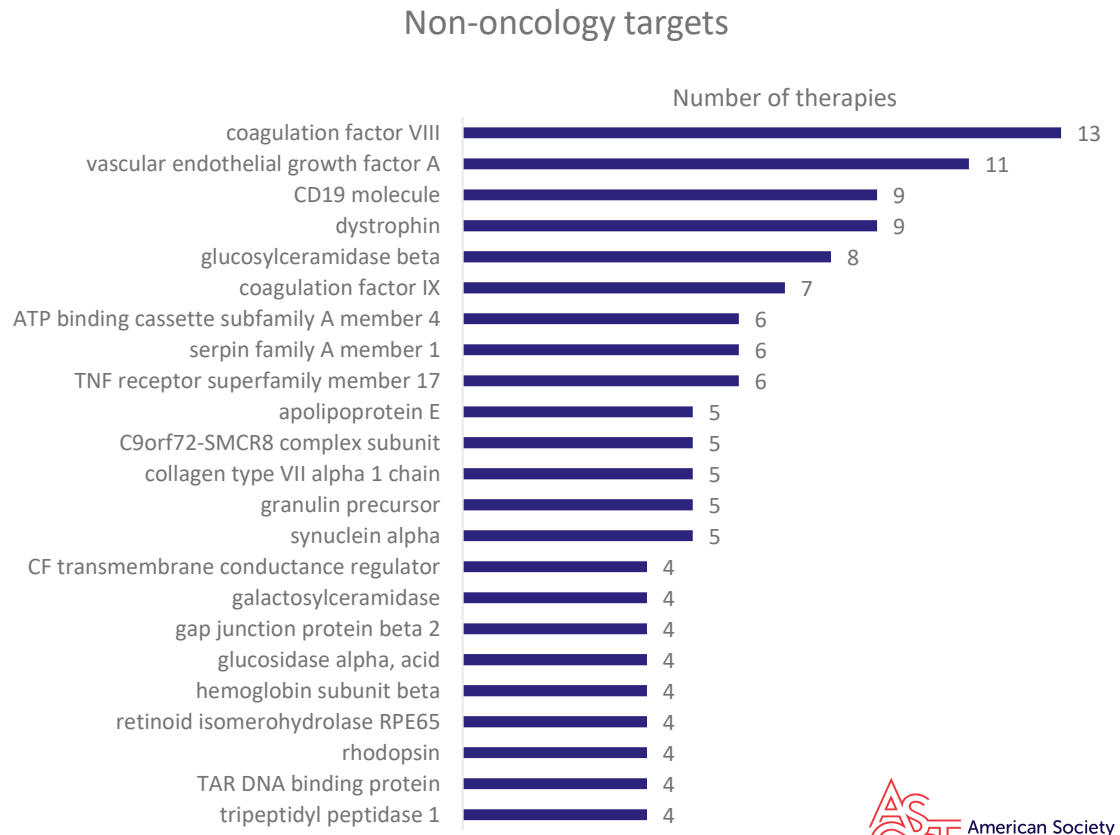
Gene therapy pipeline: Most common targets

Of the gene therapies in preclinical trials through pre-registration for which targets are disclosed:

- CD19, B-cell maturation antigen (BCMA), also known as TNF receptor superfamily member 17, and CD22 molecule continue to be the top three most common targets for oncology indications
- Coagulation factor VIII remains the most common target for non-oncology indications, while vascular endothelial growth factor A becomes the second most common in Q1 2023





Source: Pharmaprojects| Citeline, April 2023

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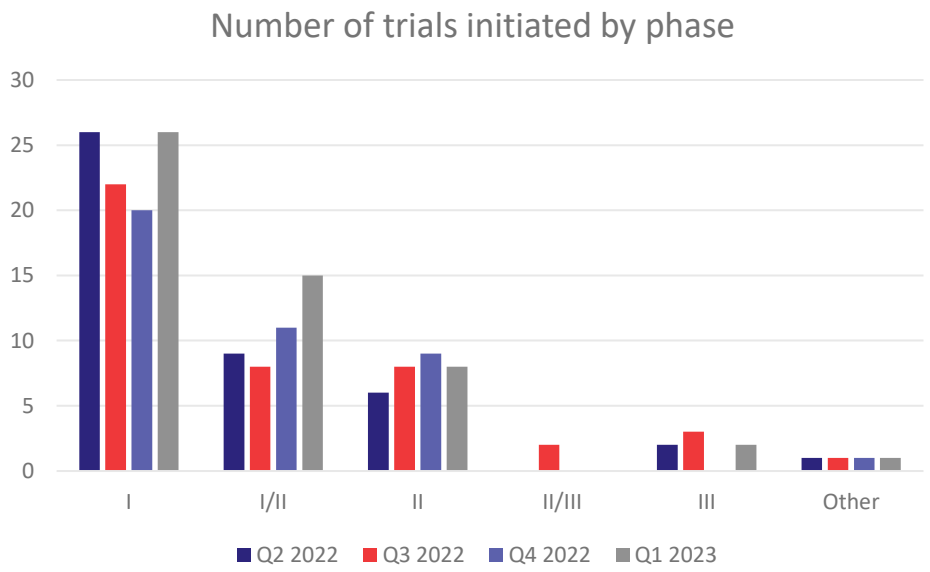
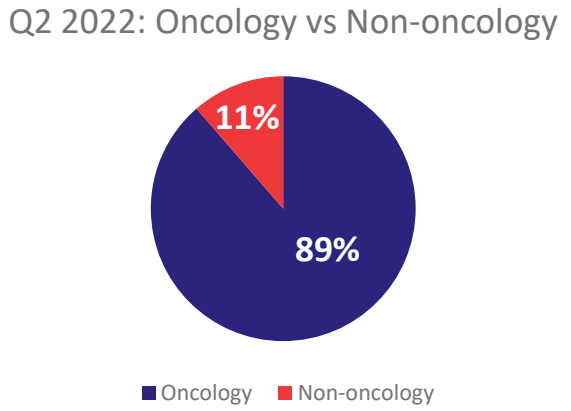
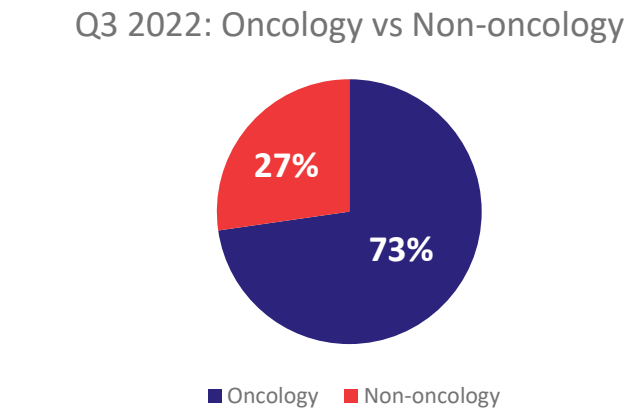
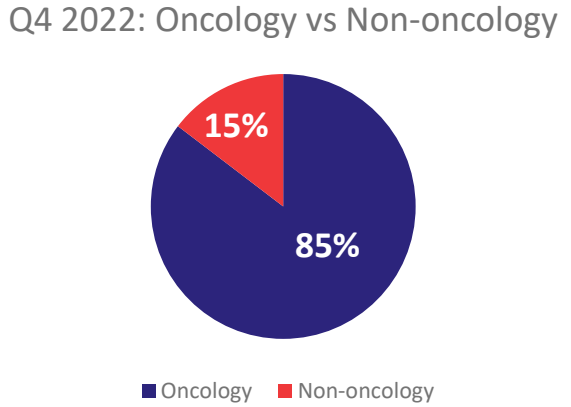
Gene therapy clinical trial activity

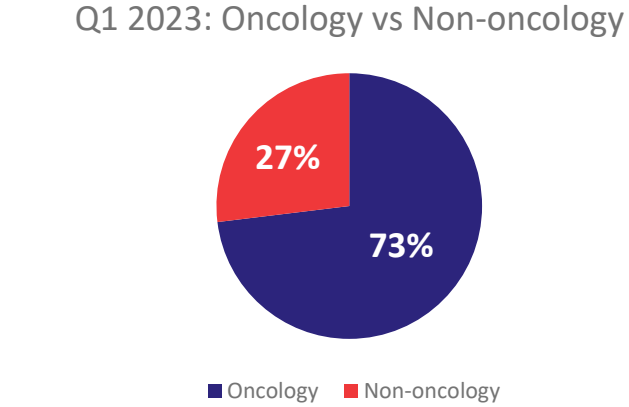
- 52 trials were initiated in Q1 2023 for gene therapies
- The proportion of gene therapy trials for non-oncology indications has increased by 12 percentage points since the previous quarter, to 27%, matching the proportion seen in Q3 2022











Source: Trialtrove| Citeline, April 2023

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Non-genetically modified cell therapy pipeline

Q1 2023

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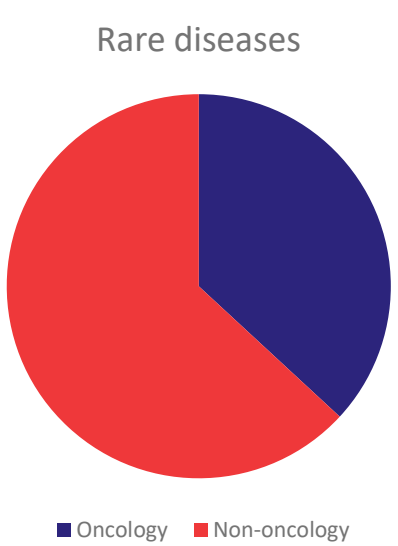
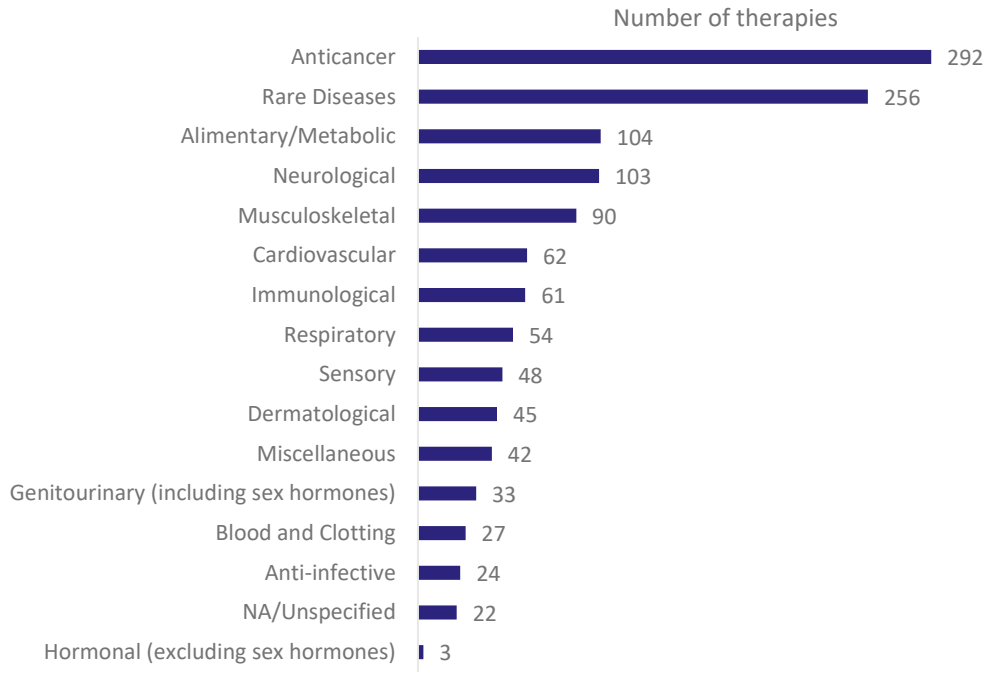
Non-genetically modified cell therapy pipeline: Most common therapeutic areas targeted

Of the cell therapies in development (preclinical through pre-registration):

- Oncology and rare diseases remain the top areas of non-genetically modified cell therapy development
- Of the non-genetically modified cell therapies in preclinical to pre-registration stages for rare diseases, 65% are in development for non-oncology rare diseases, a decrease of one percentage point from the previous quarter





Source: Pharmaprojects| Citeline, April 2023

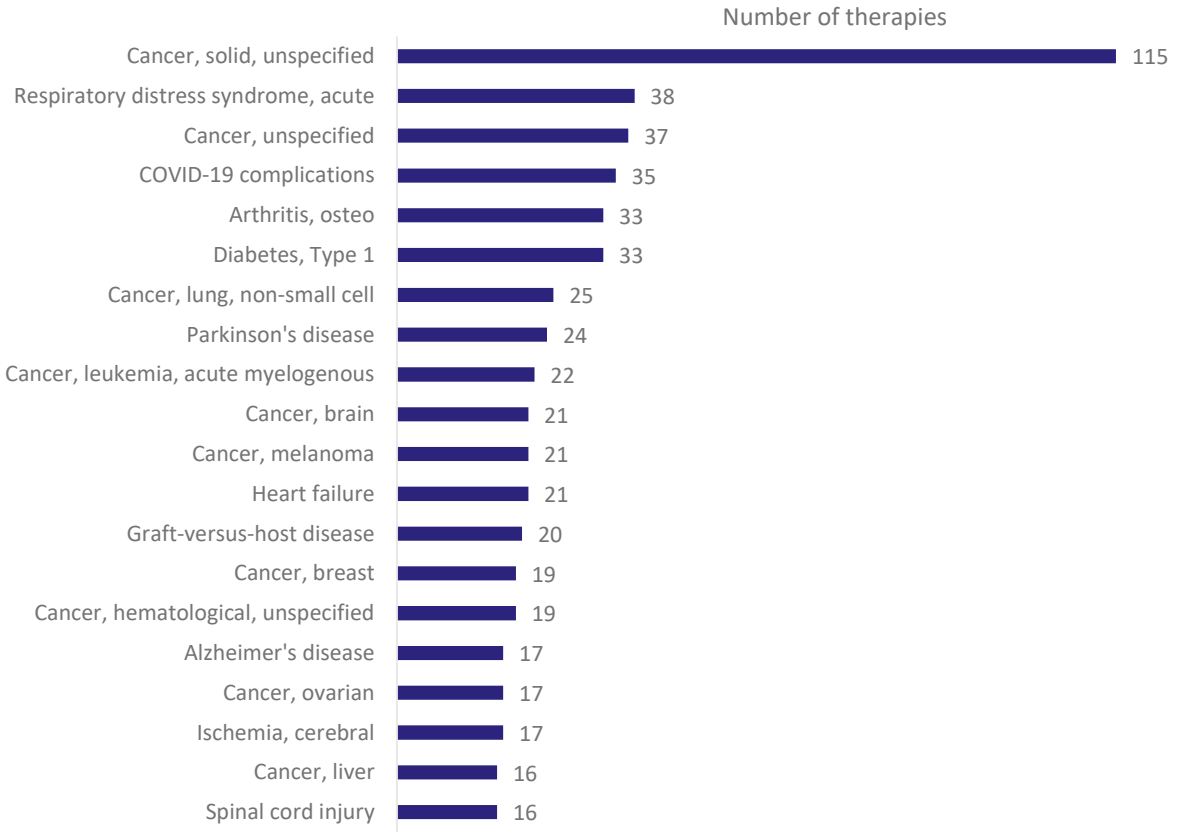
Note: figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

Non-genetically modified cell therapy pipeline: Most common diseases targeted

Of the therapies for which indications are specified, the top three indications remain the same as in Q4 2021 and throughout 2022:

1. Acute respiratory distress syndrome
2. COVID-19 complications
3. Osteoarthritis



Source: Pharmaprojects| Citeline, April 2023

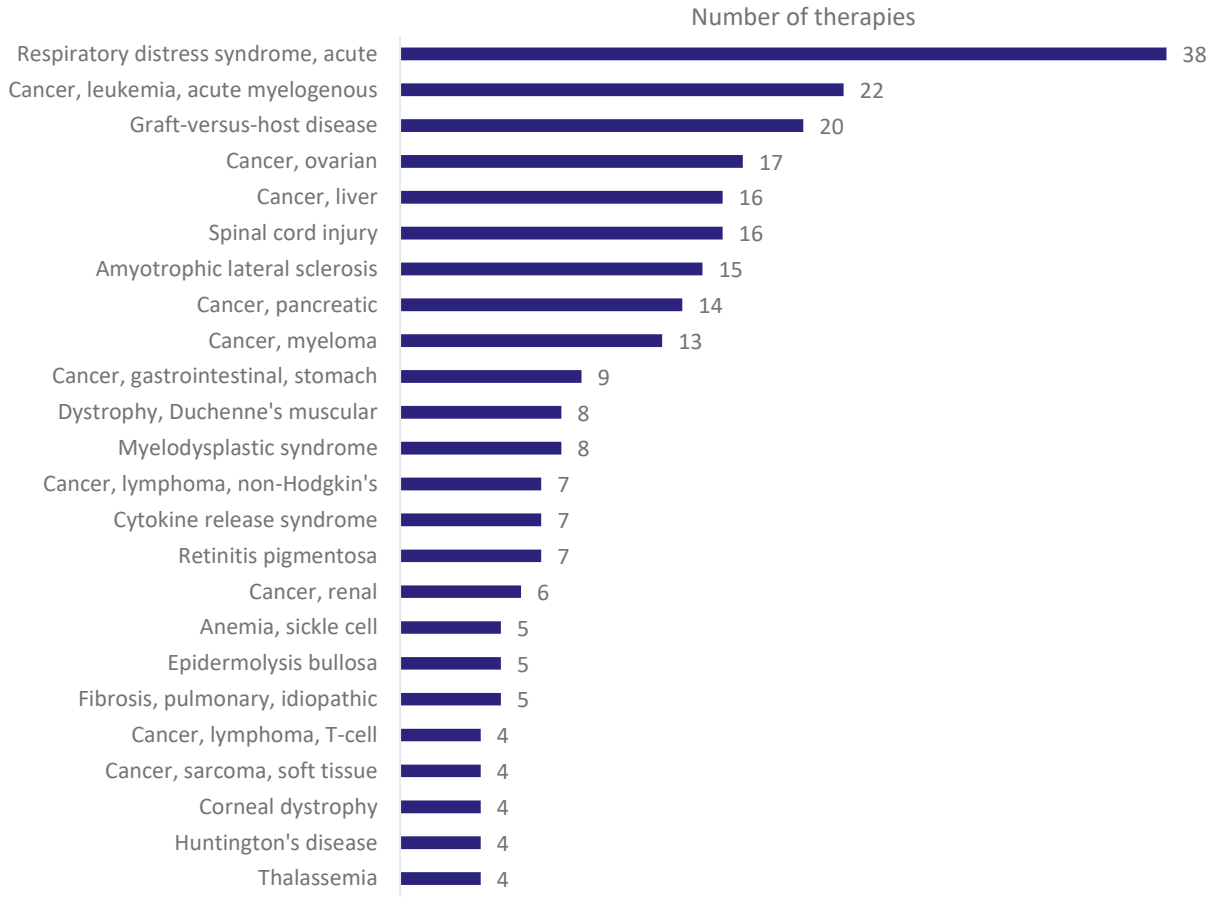
Note: figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

Non-genetically modified cell therapy pipeline: Most common rare diseases targeted

Of the therapies in development (preclinical through pre-registration) for rare diseases:

- The top three oncology indications are acute myelogenous leukemia, ovarian cancer, and liver cancer
- The top three non-oncology indications are acute respiratory distress syndrome, graft-versus-host disease, and spinal cord injury



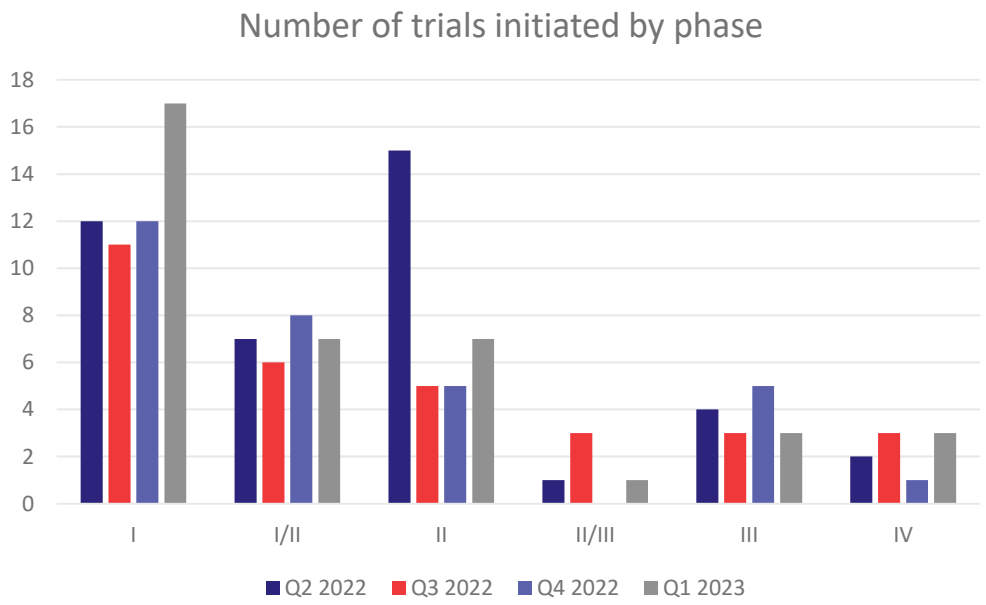
Source: Pharmaprojects| Citeline, April 2023

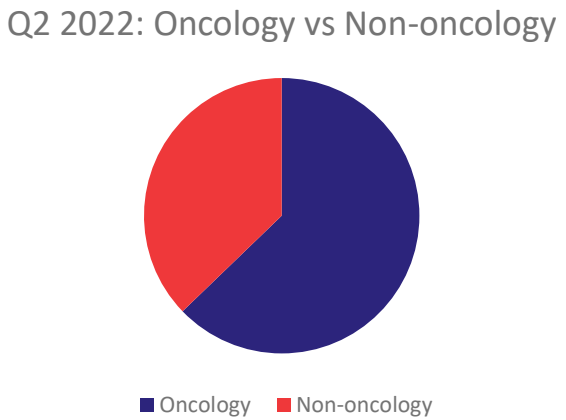
Note: figures based on indications in pipeline development only for each therapy

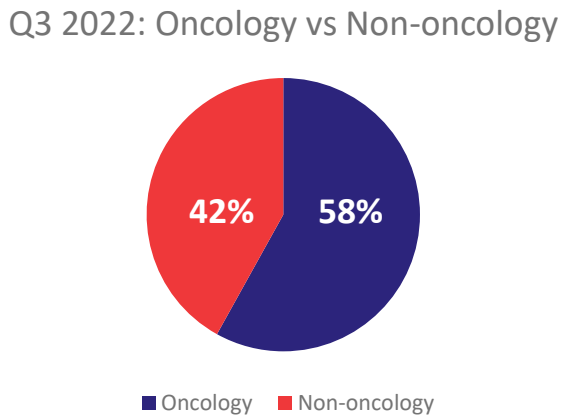
American Society of Gene + Cell Therapy

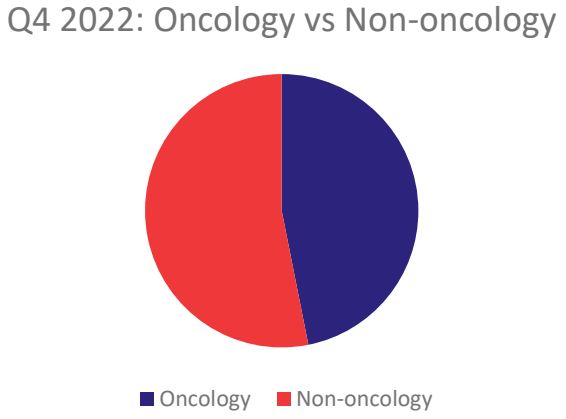
Non-genetically modified cell therapy trial activity

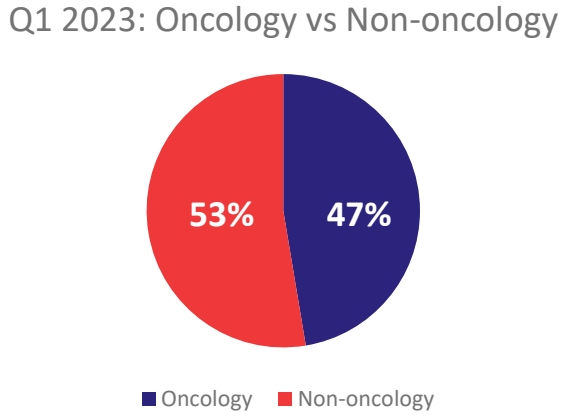
- 38 trials were initiated for non-genetically modified cell therapies in Q1 2023, 7 more than the previous quarter
- Of these 38, 53% are for non-oncology indications, a decrease of 2 percentage points from Q4 2022











Source: Trialtrove| Citeline, April 2023

American Society of Gene + Cell Therapy

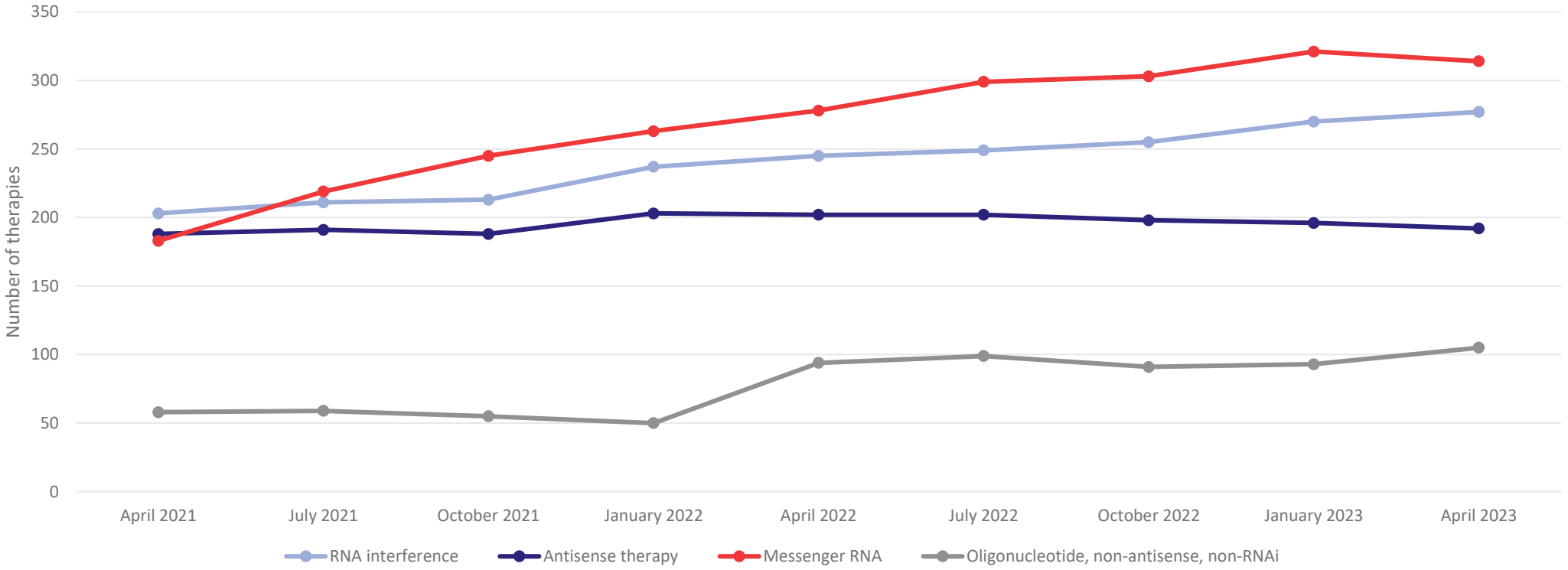
RNA therapy pipeline

Q1 2023

American Society of Gene + Cell Therapy

RNA therapy pipeline: Most common modalities

- Of RNA therapies in the pipeline, messenger RNA (mRNA) and RNA interference (RNAi) continue to be the preferred RNA modalities for research

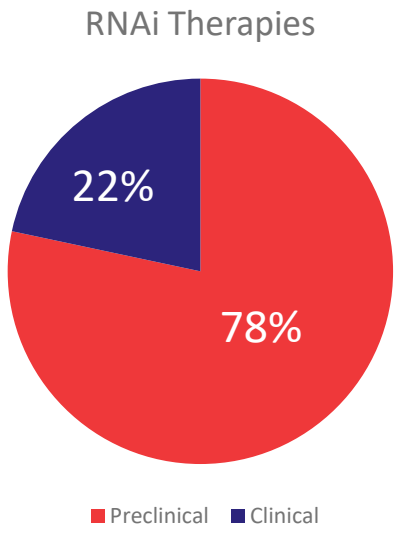


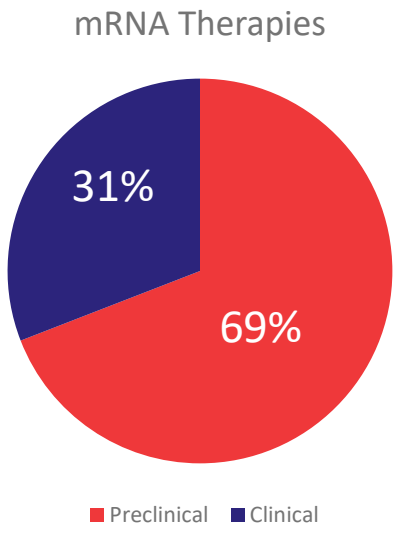
Source: Pharmaprojects| Citeline, April 2023

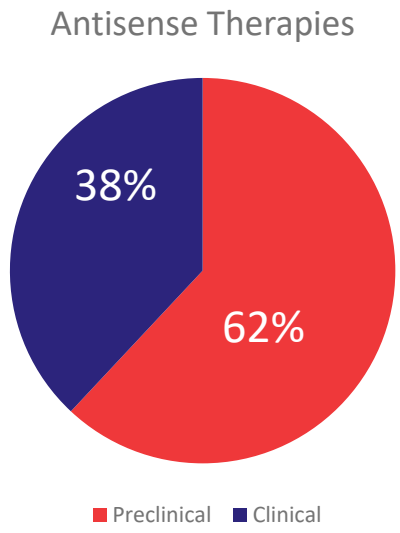
American Society of Gene + Cell Therapy

RNAi, mRNA, and antisense oligonucleotides: Preclinical vs. clinical

- The majority of RNAi, mRNA, and antisense therapeutics in development are in preclinical development, representing 78%, 69%, and 62% of their respective pipelines





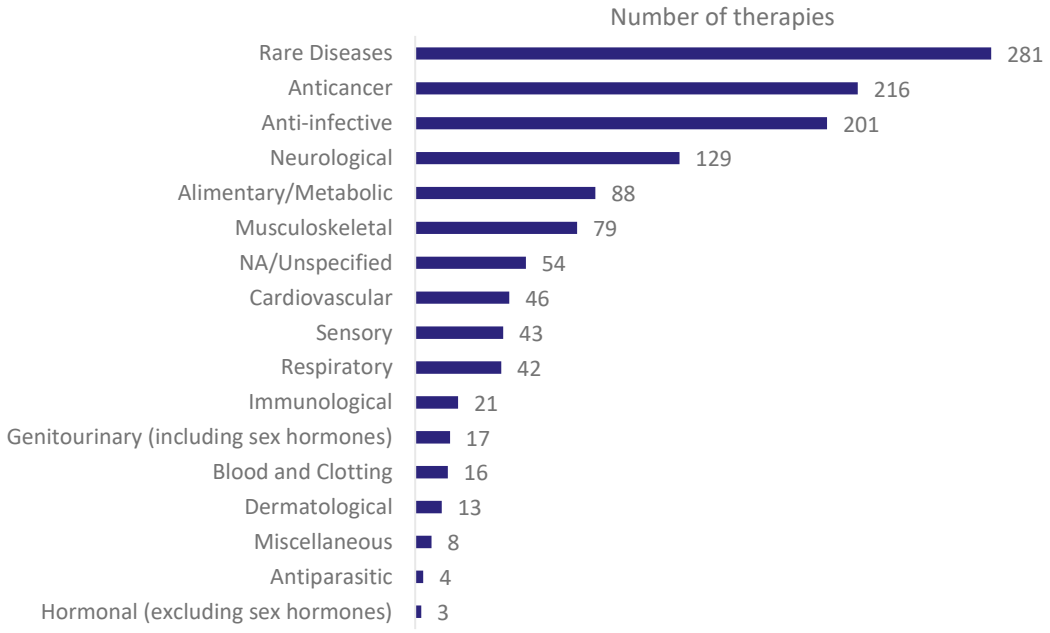


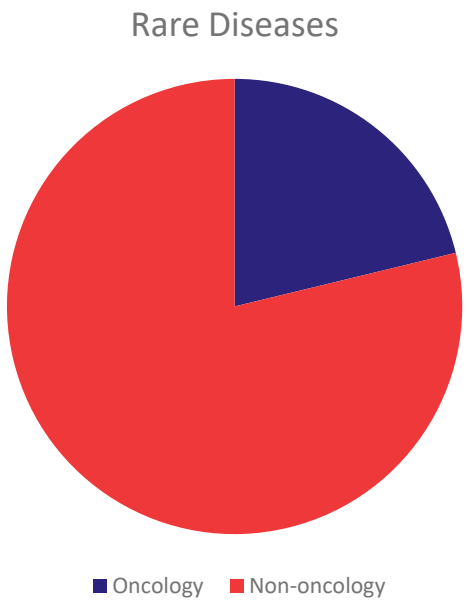
Source: Pharmaprojects| Citeline, April 2023

RNA therapies: Most commonly targeted therapeutic areas

Of the 897 RNA therapies currently in the pipeline (from preclinical through pre-registration):

- Rare diseases remains the top targeted therapeutic area by RNA therapies, while anticancer therapies replace anti-infective therapies as the second most targeted since Q4 2022
- Non-oncology indications continue to be the most targeted rare diseases by RNA therapies, representing a majority of 83%





Source: Pharmaprojects| Citeline, April 2023

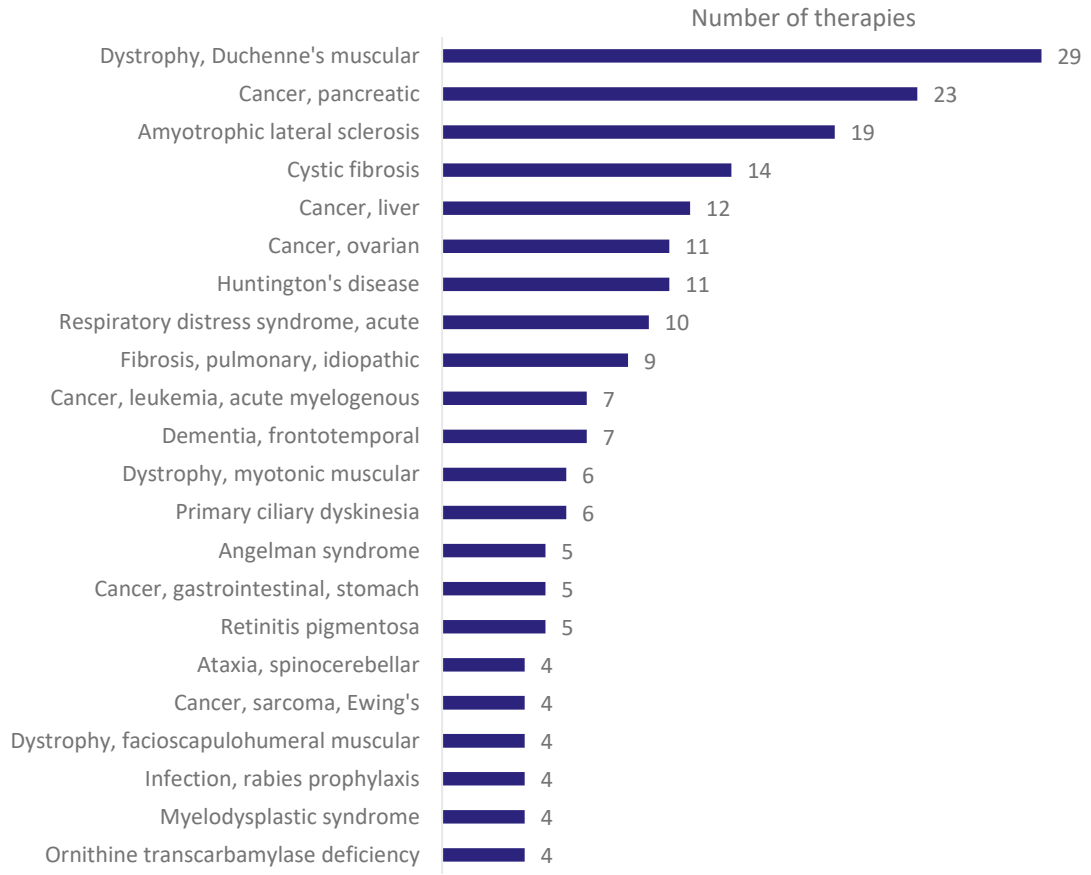
Note: figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

RNA therapies: Most common rare diseases targeted

Of the RNA therapies currently in the pipeline (from preclinical through pre-registration):

- Top specified rare oncology indications are pancreatic, liver, and ovarian cancer
- For non-oncology rare diseases, Duchenne's muscular dystrophy, amyotrophic lateral sclerosis, and cystic fibrosis are the most commonly targeted indications



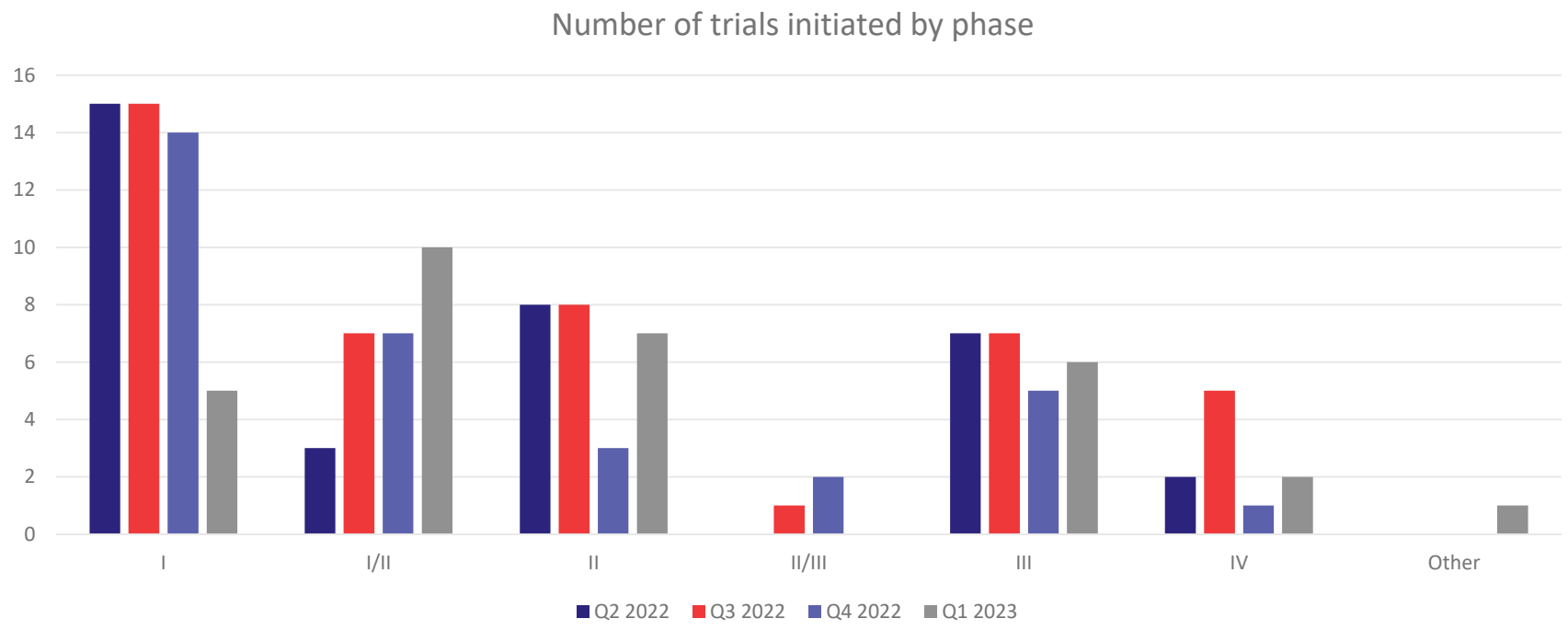
Source: Pharmaprojects| Citeline, April 2023

Note: figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

RNA therapy pipeline: Clinical trial activity

- 31 RNA trials were initiated in Q1 2023, compared to 32 in Q4 2022, 87% of which were for non-oncology indications



Source: Trialtrove| Citeline, April 2023

American Society of Gene + Cell Therapy

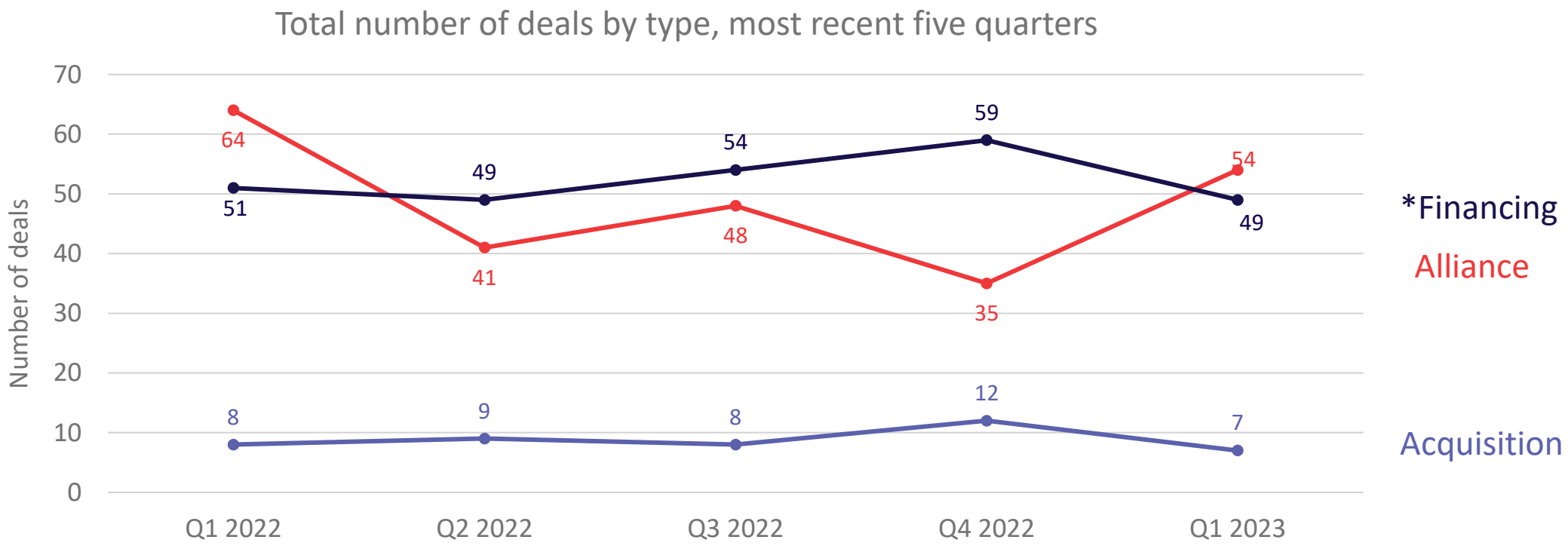
Overview of dealmaking for gene, cell, and RNA therapy companies

Q1 2023

American Society of Gene + Cell Therapy

Alliance, acquisition, and financing in gene, cell, and RNA therapy

- Advanced molecular therapy companies signed a total of 110 deals in Q1 2023, nearly flat compared with the previous two quarters
- Slightly fewer deals were done in Q1 2023 compared with the opening quarter of 2022, which featured 123 transactions
- The biggest increase in Q1 2023 was seen with alliances, which rose by 54% from 35 to 54 partnerships in Q4 2022 vs Q1 2023



Source: Biomedtracker| Citeline, BioSciDB| Evaluate, April 2023

*Financings include public financings (IPOs and follow-ons) plus privately raised funding through venture rounds, debt offerings, or private investment in public equity

American Society of Gene + Cell Therapy

Q1 2023 acquisitions in gene, cell, and RNA therapy

- Acquisition volume in Q1 2023 was at a quarterly low in the past year, with a total of 7 transactions signed, compared with the 12 done in Q4 2022, but closer to the 8–9 range seen during previous quarters
- Q1 2023 featured two billion-dollar takeovers: Chiesi's acquisition of Amryt, worth up to $1.5 billion, includes a preclinical non-viral gene therapy for epidermolysis bullosa; and Sartorius paid €2.4 billion for Polypus, which makes transfection agents and plasmid DNA for viral vector manufacturing

Deal Date	Deal Title	Potential Deal Value (USD $)
01/04/2023	Moderna to Acquire OriCiro Genomics for $85M	85,000,000
01/05/2023	Ensoma to Acquire Twelve Bio; Acquisition Closed	Undisclosed
01/08/2023	Chiesi Farmaceutici to Acquire Amryt Pharma for up to $1.48B	1,475,000,000
01/17/2023	Elicio Therapeutics and Angion Enter into Definitive Merger Agreement	Undisclosed
03/02/2023	Flamingo Therapeutics and Dynacure Merge to Develop RNA-Targeting Cancer Therapies	Undisclosed
03/06/2023	Adaptimmune and TCR² Therapeutics Announce Strategic Combination	Undisclosed
3/31/2023	Sartorius Acquires Viral Vector Manufacturing Company Polypus for €2.4B	2,600,000,000

Source: Biomedtracker| Citeline, BioSciDB| Evaluate, April 2023

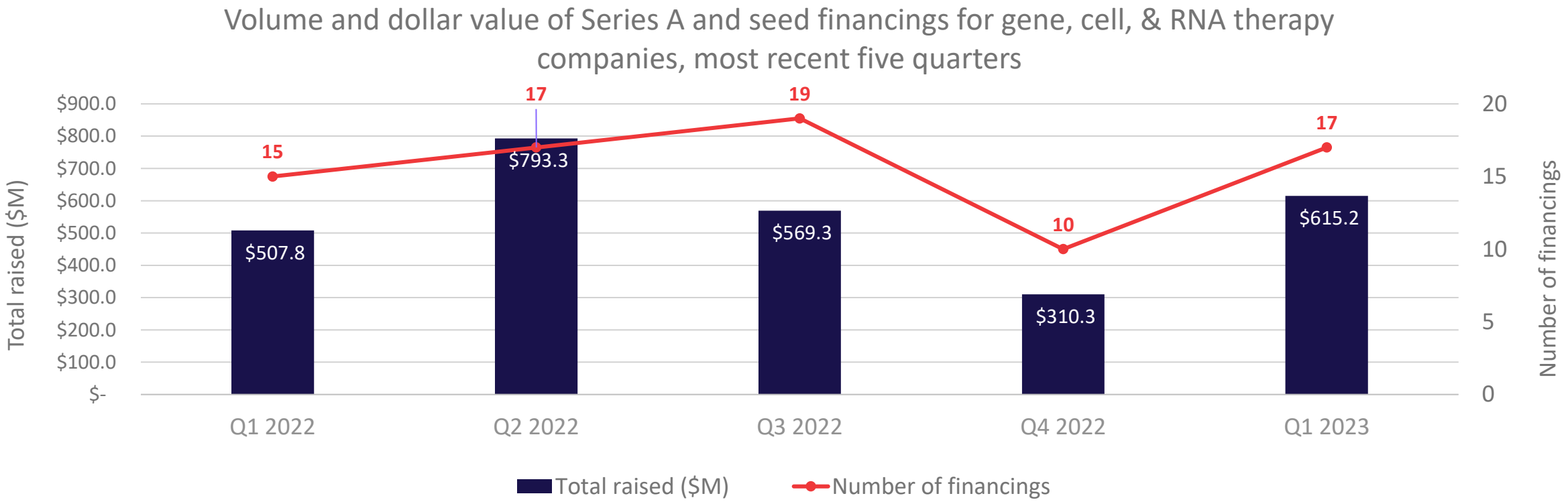
Start-up funding for gene, cell, and RNA therapy companies

Q1 2023

American Society of Gene + Cell Therapy

Start-up financing for gene, cell, and RNA therapy companies

- Series A and seed financings for advanced molecular companies rebounded in Q1 2023, reaching 17 transactions at an aggregate $615.2 million, representing nearly double the volume and value of Q4 2022
- Among the fundraisers were several companies investigating non-viral gene delivery, including using nanoparticles, and two new CDMOs focused on lentiviral vector production
- Note: The Q1 2023 totals include Aera Therapeutics' combined Series A and B fundraise of $193 million



Source: Biomedtracker| Citeline, April 2023

American Society of Gene + Cell Therapy

Q1 2023 start-up financing for gene, cell, and RNA therapy companies (1/2)

Deal Date	Deal Title	Modality Type	Company Location	Academic Source	Potential Deal Value (USD, $M)
01/11/2023	MPC Therapeutics Closes Seed Round	Small molecules that enhance performance and durability of CAR-T therapy	Switzerland, Plan-les-Ouates	University of Geneva	1.6
01/12/2023	Tiba Biotech Gets $2M in Seed Funding from CEPI	mRNA vaccines and therapeutics	United States, Massachusetts, Cambridge	MIT; Whitehead Institute	2
01/25/2023	Atomic AI Closes $35M Series A	AI platform to identify functional binders to RNA targets	United States, California, San Francisco	Stanford University	35
01/25/2023	Myosana Gets $5M in Seed Funding	Non-viral gene therapy	United States, Washington, Seattle	University of Washington	5
01/26/2023	iVexSol Raises $23.8M in Series A-3 Financing	CMDO producer of lentiviral vectors	United States, Massachusetts, Lexington	Undisclosed	23.8
01/31/2023	Vector Biomed Raises $15M in Series A Financing	CMDO producer of lentiviral vectors	United States, Maryland, Gaithersburg	Undisclosed	15
01/31/2023	Sichuan Zhishanweixin Biotechnology (Zhi Shan Wei Xin) Raises $29.61 Million in Series A+ Financing	AAV gene therapy	China, Sichuan	Undisclosed	29.61
02/15/2023	Nanite Raises $6M in Seed Round; Adds $2M	Programmable polymer nanoparticles for non-viral gene therapy	United States, Massachusetts, Boston	University of Minnesota	8

Source: Biomedtracker| Citeline, April 2023

Q1 2023 start-up financing for gene, cell, and RNA therapy companies (2/2)

Deal Date	Deal Title	Modality Type	Company Location	Academic Source	Potential Deal Value (USD, $M)
02/16/2023	Aera Therapeutics Launches with $193M Combined Series A and B Financings	Proprietary protein nanoparticle delivery system for genetic medicine	United States, Massachusetts, Boston	Broad Institute of MIT and Harvard University; University of Utah	193
02/22/2023	Resalis Therapeutics Announces Seed Financing of €10M	Non-coding RNA therapy	Italy, Torino	Aalborg University's Center for RNA Medicine	10.7
02/28/2023	Verismo Therapeutics Raises $7M in Pre-Series A Round	KIR (killer immunoglobulin-like receptor)-CAR T therapy	United States, Pennsylvania, Philadelphia	University of Pennsylvania	7
03/01/2023	CARGO Therapeutics Raises $200M in Oversubscribed Series A Round	CAR-T therapy	United States, California, San Mateo	Stanford University's Center for Cancer Cell Therapy	200
03/01/2023	Thymmune Gets $7M in Seed Funding	Thymic cell therapy	United States, Massachusetts, Cambridge	Harvard University	7
03/13/2023	Shennon Biotechnologies Closes $13M Seed Round	Immune cell profiling to create cell therapy	United States, California, San Francisco	Undisclosed	13
03/14/2023	Switch Therapeutics Raises $52M in Series A Funding	siRNA therapy	United States, California, San Francisco	Caltech; Harvard University; City of Hope	52
03/15/2023	Inspire Biotherapeutics Launches with Pre-seed Investment	Gene therapy	Canada, Toronto	Ottawa Hospital Research Institute	Undisclosed
03/16/2023	Seamless Therapeutics Launches with $12.5M Seed Round	Gene editing	Germany, Dresden	Technische Universität Dresden's University Cancer Center	12.5

Source: Biomedtracker| Citeline, April 2023

Notable Q1 2023 start-up gene, cell, and RNA therapy companies

	Company details	Academic source	Financing type/amount raised	Lead investor(s)	Therapy areas of interest
CARGO THERAPEUTICS	Next-generation CAR-T therapies using STASH/GAS technology addressing resistance and relapse with current CAR-T therapies	Stanford University's Center for Cancer Cell Therapy	Series A/$200M	Third Rock Ventures, RTW Investments, LP, Perceptive Xonto-geny Venture Fund	Cancer (hematological, including large B-cell lymphoma)
ERA THERAPEUTICS	Protein nanoparticle for delivery of gene therapy and gene editing systems	Broad Institute of MIT and Harvard University; University of Utah	Series A + Series B/$193M	ARCH Venture Partners, GV, Lux Capital	Unspecified
SWITCH THERAPEUTICS	Conditionally Activated siRNA (CASi) molecules for cell selective knockdown of targets	Caltech; Harvard University; City of Hope	Series A/$52M	Insight Partners, UCB Ventures	CNS and systemic indications

Source: Biomedtracker| Citeline, April 2023

Upcoming catalysts

Q1 2023

American Society of Gene + Cell Therapy

Upcoming Catalysts

Below are noteworthy catalysts (forward-looking events) expected in Q2 2023

Therapy	Generic Name	Disease	Catalyst	Catalyst Date
BIIB-067	tofersen	Amyotrophic Lateral Sclerosis (ALS)	PDUFA for NDA - First Review	25 Apr 2023 - 25 Apr 2023
Libmeldy	atidarsagene autotemcel	Metachromatic Leukodystrophy	Meeting with FDA	10 Jan 2023 - 30 Apr 2023
Amvuttra	vutrisiran	Hereditary Transthyretin (hATTR) Amyloidosis With Polyneuropathy (Familial Amyloid Polyneuropathy)	Japanese Approval Decision	1 Oct 2022 - 30 Apr 2023
Tab-cel	tabelecleucel	Hematologic Cancer	Approval Decision (UK)	8 Feb 2023 - 30 Apr 2023
NiCord	omidubicel	Bone Marrow Transplant and Stem Cell Transplant	PDUFA for BLA - First Review	1 May 2023 - 1 May 2023
Vyjuvek	beremagene geperpavec	Epidermolysis Bullosa	PDUFA for BLA - First Review	19 May 2023 - 19 May 2023
SRP-9001	delandistrogene moxeparvovec	Duchenne Muscular Dystrophy (DMD)	PDUFA for BLA - First Review	29 May 2023 - 29 May 2023
SRP-9001	delandistrogene moxeparvovec	Duchenne Muscular Dystrophy (DMD)	FDA Advisory Panel Meeting and Brief	16 Mar 2023 - 29 May 2023
Roctavian	valoctocogene roxaparvovec	Hemophilia A	PDUFA for BLA - Second Review	30 Jun 2023 - 30 Jun 2023
Libmeldy	atidarsagene autotemcel	Metachromatic Leukodystrophy	Approval Decision - Swissmedic	1 Jan 2023 - 30 Jun 2023
SB623	vandefitemcel	Traumatic Brain Injury (TBI)	Approval Decision (Japan)	1 Dec 2022 - 30 Jun 2023
Oxlumo	lumasiran	Hyperoxaluria	Supplemental Approval Europe (PH1)	31 Mar 2023 - 30 Jun 2023
Lantidra	allogeneic Islets of Langerhans	Diabetes Mellitus, Type I	PDUFA for BLA - First Review	21 Dec 2022 - 30 Jun 2023
Honedra	autologous CD34+ cells	Peripheral Arterial Disease (PAD)	Japanese Approval Decision	1 Jan 2023 - 30 Jun 2023
AT-132	resamirigene bilparvovec	X-linked Myotubular Myopathy	Meeting with FDA	29 Mar 2023 - 31 Jul 2023
Lumevoq	lenadogene nolparvovec	Leber's Hereditary Optic Neuropathy (LHON) (Ophthalmology)	European Approval Decision	1 Dec 2022 - 30 Nov 2023
Exa-cel	exagamglogene autotemcel	Sickle Cell Anemia	Approval Decision (UK)	31 Dec 2022 - 31 Dec 2023
Exa-cel	exagamglogene autotemcel	Thalassemia	Approval Decision (UK)	31 Dec 2022 - 31 Dec 2023
HPC-Cord Blood Therapy	Umbilical cord blood mononuclear stem cell therapy	Ischemic Stroke	PDUFA for BLA - First Review	1 Jan 2023 - 31 Dec 2023

Source: Biomedtracker| Citeline, April 2023

Appendix

Methodology, sources, and glossary of key terms

Q1 2023

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Methodology: Sources and scope of therapies

Sources for all data come from Citeline (formerly Pharma Intelligence)

Pipeline and trial data

- Data derived from **Pharmaprojects and Trialtrove**
- Therapeutic classes included in report categorizations:
  - Gene therapies: Gene therapy; cellular therapy, chimeric antigen receptor; cellular therapy, T cell receptor; lytic virus
  - Cell therapies: Cellular therapy, other; cellular therapy, stem cell; cellular therapy, tumor-infiltrating lymphocyte
  - RNA therapies: Messenger RNA; oligonucleotide, non-antisense, non-RNAi; RNA interference; antisense therapy

Deal, financing, and catalyst data

- Data derived from **Biomedtracker**. The following industry categorizations of deals are included: Gene therapy, cell therapy; antisense, oligonucleotides
- Additional alliance and acquisition deals data from **BioSciDB**, part of **Evaluate Ltd.** The following industry categorizations of deals are included: Cell Therapy - Stem Cells/Factors, oligonucleotides, antisense/triple helix, gene therapy, RNAi

Glossary of Key Terms

Therapy Type Definitions

Gene therapy is the use of genetic material to treat or prevent disease. For the purpose of this report, the following terms shall mean the following:

Gene therapy	Therapies containing an active ingredient synthesized following vector-mediated introduction of a genetic sequence into target cells *in-* or *ex-vivo*. Used to replace defective or missing genes (as in cystic fibrosis) as well as to introduce broadly acting genetic sequences for the treatment of multifactorial diseases (e.g. cancer). Direct administration of oligonucleotides without using vectors is covered separately in the antisense therapy class; RNA interference class; or oligonucleotide, non-antisense, non-RNAi class. Platform technologies for gene delivery are covered separately in the gene delivery vector class.
Cellular therapy, chimeric antigen receptor **Falls under gene therapy in this report*	Cellular therapy consisting of T cells that have been modified to express a chimeric antigen receptor (CAR) – this is a cell surface receptor that gives the T cells the ability to target a specific protein and fight the targeted cells.
Cellular therapy, T cell receptor **Falls under gene therapy in this report*	Cellular therapies whereby natural T cells collected for the patient are engineered to express artificial receptors (usually through viral transfections) that would target specific intracellular antigens (as peptides bound to proteins encoded by the major histocompatibility complex, MHC).
Lytic virus **Falls under gene therapy in this report*	Therapies which have a replication-competent virus, that lyse pathogenic cells directly. These are normally genetically modified to render them harmless to normal tissues. Examples include oncolytic viruses which specifically attack cancer cells.

Glossary of Key Terms

Therapy type definitions, cont.

Cell therapy includes the following therapeutic classes:

Cellular therapy, stem cell	Regenerative therapy which promotes the repair response of injured tissue using stem cells (cells from which all other specialized cells would originate).
Cellular therapy, tumor infiltrating lymphocyte	Adoptive cellular transfer of tumor resident T cells from tumor material, their expansion *ex vivo,* and transfer back into the same patient after a lymphodepleting preparative regimen.
Cellular therapy, other	Cellular therapies that do not fall under the categories of cellular therapy, stem cell; cellular therapy, CAR; cellular therapy, TIL; cellular therapy, TCR; or the specific cellular therapy are unspecified.

Glossary of Key Terms

Therapy type definitions, cont.

RNA therapy includes the following therapeutic classes:

Messenger RNA	Therapies that carry the desired mRNA code to overcome genetic mutations. The mRNA sequence will replace the defective mRNA in a patient and starts producing the desired protein.
Oligonucleotide, non-antisense, non-RNAi	Synthetic therapeutic oligonucleotides which operate by a mechanism other than antisense or RNA interference (RNAi). This includes ribozymes, aptamers, decoys, CpGs, and mismatched and immunostimulant oligonucleotides. Sequences delivered using vectors (gene therapy) are covered separately in "gene therapy." Antisense and RNAi oligonucleotides are covered separately in "antisense therapy" and "RNA interference," respectively.
RNA interference	Includes products which act therapeutically via an RNA interference (RNAi) mechanism, including small interfering RNAs (siRNAs). These may be synthetic oligonucleotides, or RNAi sequences may be expressed from a vector as a form of gene therapy (see "gene therapy" therapeutic class). *In vivo*, these sequences block the expression of a specific protein by forming an RNA-induced silencing complex, which then specifically binds to and degrades a complementary mRNA encoding the target protein. The use of RNAi purely as a drug discovery tool (e.g., in transgenic animal model production or in target validation) is not covered in this section.
Antisense therapy	Antisense compounds under development as potential therapeutics. These may be synthetic oligonucleotides, or antisense RNA may be expressed from a vector as a form of gene therapy. They may prevent the expression of a specific protein *in vivo* by binding to and inhibiting the action of mRNA, since they have a specific oligonucleotide sequence which is complementary to the DNA or RNA sequence which codes for the protein.

Glossary of Key Terms

Development status definitions

Pipeline	Drugs that are in active development
Preclinical	Not yet tested in humans
Phase I	Early trials, usually in volunteers, safety, PK, PD
Phase II	First efficacy trials in small numbers of patients
Phase III	Large-scale trials for registrational data
Pre-registration	Filing for approval made to regulatory authorities
Approved	Approval from relevant regulatory authorities for human use

Unspecified indications

Cancer, unspecified	Indications for which the specific tumor type is not specified
Cancer, hematological, unspecified	Indications for which the specific hematological cancer is not specified
Cancer, solid, unspecified	Indications for which the specific solid tumor is not specified

Deal type categories

Alliances	Co-marketing, co-promotion, disease management, joint venture, manufacturing or supply, marketing-licensing, product or technology swap, product purchase, R&D and marketing-licensing, reverse licensing, trial collaborations
Financing	Convertible debt, FOPO, IPO, nonconvertible debt, financing/other, private investment in public equity, private placement, royalty sale, special-purpose financing vehicle, spin-off
Acquisitions	Buy-out, divestiture, spin-out, full acquisition, partial acquisition, reverse acquisition

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