Gene, Cell, & RNA Therapy Landscape

Q3 2022 Quarterly Data Report

Q3 2022

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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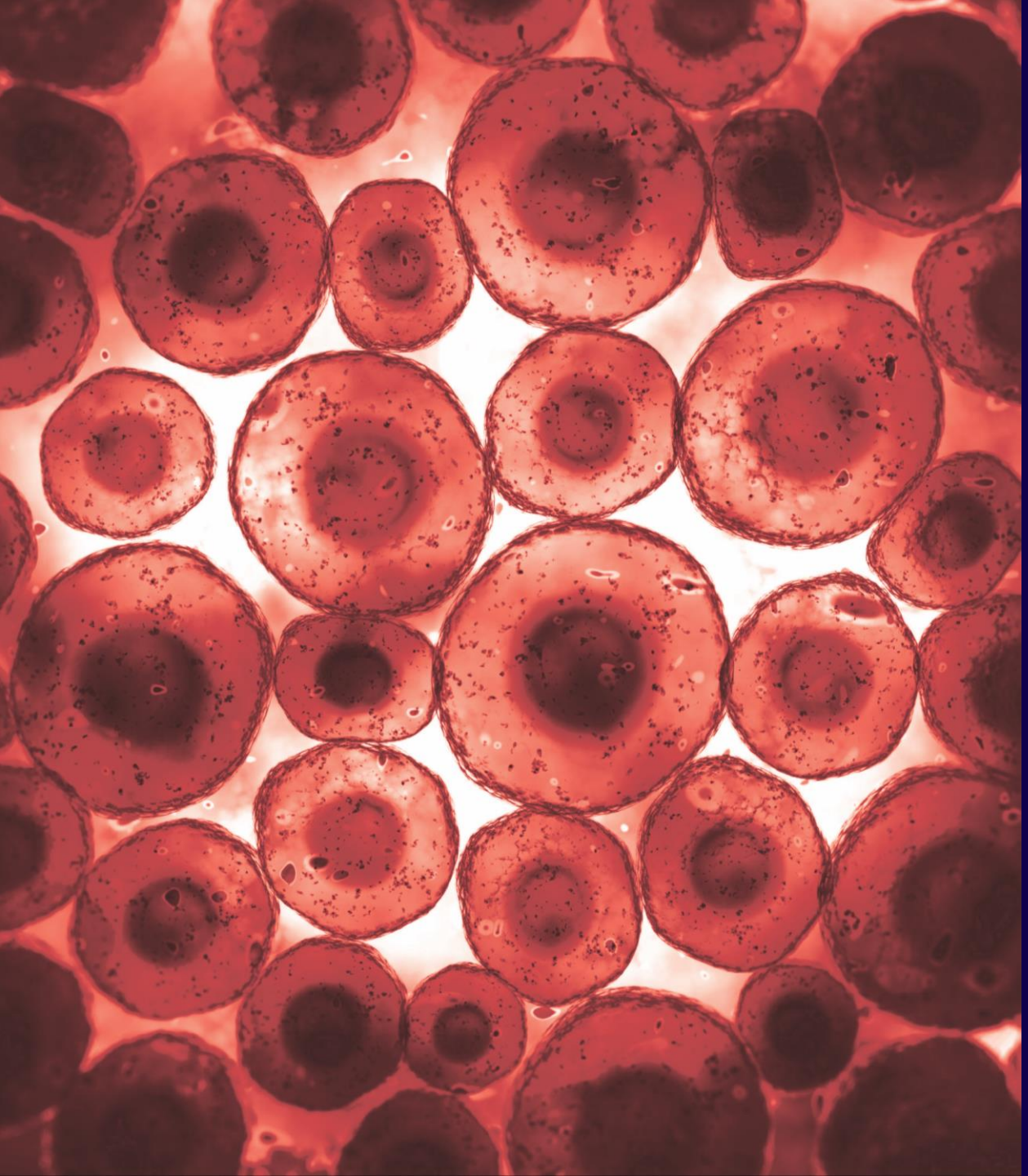
Our global teams of analysts, journalists and consultants keep their fingers on the pulse of the pharmaceutical, biomedical and medtech industries, covering it all with expert insights: key diseases, clinical trials, drug R&D and approvals, market forecasts and more. For more information on one of the world's most trusted life science partners, visit Citeline.



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American Society of Gene + Cell Therapy

Introduction

Welcome to the latest quarterly report from ASGCT and Citeline! This quarter, gene therapies Upstaza and Roctavian were approved in the EU for AADC deficiency and hemophilia A, respectively. Two more gene therapies were approved in the U.S.—Zynteglo and Skysona—for beta thalassemia and cerebral adrenoleukodystrophy (CALD), respectively, though they aren't first approvals. Three new RNA therapies for COVID-19 prophylaxis were also approved in multiple countries. More gene and RNA therapies were approved in Q3 than in each of the previous quarters for over a year.

Currently there are 3,649 therapies in development from preclinical through pre-registration. In the pipeline of genetically modified cell therapies, CAR T-cell therapies continue to dominate at 49 percent—98 percent of which are in development for cancer indications. Of the non-genetically modified cell therapies in development for rare diseases, 63 percent are for non-oncology rare diseases, including acute respiratory distress syndrome, graft-versus-host disease and amyotrophic lateral sclerosis. On the gene therapy side, oncology and rare diseases remain the top areas of development overall and in the clinic. Contrary to the previous three quarters, the proportion of gene therapy trials for non-oncology indications has increased by 16 percent since Q2, to 27 percent.

This quarter saw an 11 percent increase in dealmaking and jumps in partnerships and fundraising. Combined seed and Series A financing for 19 gene, cell, and RNA companies totaled $569.3 million, down significantly from $907.9 million one year ago.

Key takeaways from Q3 2022

Q3 2022 saw multiple first approvals for gene and RNA therapies

- More gene and RNA therapies have been approved in the past quarter than in each of the previous quarters for over a year, with two new gene therapy approvals and three new RNA vaccine approvals
- Zynteglo and Skysona were also both approved in the US in this quarter, but are not considered as new approvals as both therapies were previously approved in, and subsequently withdrawn from, the EU

The non-genetically modified cell therapy pipeline has remained consistent with the previous quarter

- Overall, pipeline development is focused mostly on anticancer indications, followed by rare diseases
- Within rare diseases, development is dominated by non-oncology indications, representing 63% of rare disease development for this therapy type

Companies obtaining start-up funding continue to increase

- The trend of increasing volume of start-up financing continued in Q3 2022, with 19 companies bringing in seed or Series A financing, up from 17 in Q2
- Various gene editing technologies were prominent among the top fundraisers, led by Capstan Therapeutics, which raised $102 million in its Series A round to support work on mRNA-encoded CARs and mRNA-encoded gene editing
- Dealmaking in general for advanced molecular therapy companies was up in Q3 over Q2, with solid increases in alliances and all financing types

Key highlights in Q3 2022

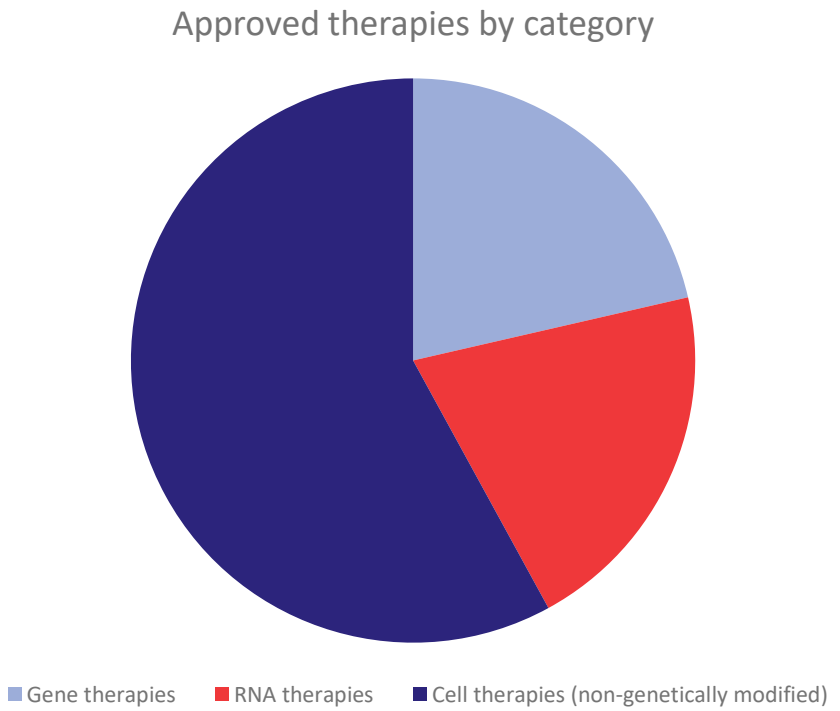
Q3 2022

American Society of Gene + Cell Therapy

Approved gene, cell, and RNA therapies

Globally, for clinical use:

- 22 gene therapies are approved (including genetically modified cell therapies)
  - In Q3 2022, there were two new gene therapy approvals: eladocagene exuparvovec (Upstaza) for AADC deficiency, and valoctocogene roxaparvovec (Roctavian) for hemophilia A, both in the EU
- 21 RNA therapies are approved
  - In Q3 2022, three new RNA therapies were approved, all for COVID-19 prophylaxis:
    - Moderna's Omicron-containing bivalent booster vaccine in the UK, Switzerland, Canada, Japan, Singapore and Taiwan
    - Pfizer & BioNTech's Omicron BA.4/BA.5-adapted bivalent booster vaccine in the UK and US
    - Suzhou Abogen Biosciences' ARCoV vaccine in Indonesia
- 59 non-genetically modified cell therapies are approved



Source: Pharmaprojects | Citeline, October 2022

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Approved gene therapies as of Q3 2022 (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

*As Zynteglo and Skysona had been approved in the EU and UK in 2019 and 2021 respectively (but have since been withdrawn), the new approvals in the US are not considered as first approvals

Source: Pharmaprojects | Citeline, October 2022

Text highlighted in yellow represent new approvals during Q3 2022

Approved gene therapies as of Q3 2022 (2/2)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Tecartus	brexucabtagene autoleucel	2020	Mantel 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	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

*As Zynteglo and Skysona had been approved in the EU and UK in 2019 and 2021 respectively (but have since been withdrawn), the new approvals in the US are not considered as first approvals

Source: Pharmaprojects | Citeline, October 2022

Text highlighted in yellow represent new approvals during Q3 2022

Approved RNA therapies as of Q3 2022 (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	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

†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, October 2022

Text highlighted in yellow represent new approvals during Q3 2022

Approved RNA therapies as of Q3 2022 (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	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	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	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

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

†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, October 2022

Text highlighted in yellow represent new approvals during Q3 2022

Key highlights in Q3 2022

Noteworthy events that happened in Q3 2022

Drug	Event Type	Indication	Molecule	Event Date
CAR-T Therapy Program (WUGEN)	Rare Pediatric Disease (RPD) Designation and Fast Track Status	Hematologic Cancer	Cellular	07/19/2022
Upstaza	Approval (Europe)	Neurology - Other	Viral Gene Therapy	07/20/2022
TX-200	Orphan Drug Designation (Europe)	Kidney Transplant Rejection	Cellular	07/21/2022
Amvuttra	CHMP (European Panel) Results (Positive)	Hereditary Transthyretin (hATTR) Amyloidosis With Polyneuropathy (Familial Amyloid Polyneuropathy)	siRNA/RNAi	07/21/2022
IONIS-SOD1Rx	Priority Review	Amyotrophic Lateral Sclerosis (ALS)	Antisense	07/26/2022
ABX1100	Orphan Drug Designation (U.S.)	Pompe Disease	siRNA/RNAi	08/01/2022
Omidubicel	Priority Review	Bone Marrow Transplant and Stem Cell Transplant	Cellular	08/01/2022
Zynteglo	Approval (U.S.)	Thalassemia	Viral Gene Therapy	08/17/2022
B-VEC	Priority Review	Epidermolysis Bullosa	Viral Gene Therapy	08/18/2022
Roctavian	Approval (Europe)	Hemophilia A	Viral Gene Therapy	08/24/2022
LN-144	Rolling NDA/BLA Initiated	Melanoma	Cellular	08/25/2022
Lomecel-B	Fast Track Status	Cardiovascular Disease	Cellular	08/31/2022
CAR T-Cell Therapy Program (AbbVie/Caribou)	Orphan Drug Designation (U.S.)	Follicular Lymphoma (FL)	Cellular	09/01/2022
NTLA-2002	Orphan Drug Designation (U.S.)	Hereditary Angioedema (HAE)	Non-Viral Gene Therapy	09/01/2022
Etranacogene Dezaparvovec	Orphan Drug Designation (Australia)	Hemophilia B	Viral Gene Therapy	09/08/2022
ABX1100	Rare Pediatric Disease (RPD) Designation	Pompe Disease	siRNA/RNAi	09/15/2022
Skysona	Accelerated/Conditional Approval (U.S.)	Adrenoleukodystrophy	Viral Gene Therapy	09/16/2022
Amvuttra	Approval (Europe)	Hereditary Transthyretin (hATTR) Amyloidosis With Polyneuropathy (Familial Amyloid Polyneuropathy)	siRNA/RNAi	09/20/2022
AVR-RD-04	Rare Pediatric Disease (RPD) Designation	Cystinosis	Cellular	09/20/2022
Carvykti	Approval (Japan)	Multiple Myeloma (MM)	Cellular	09/26/2022
Roctavian	Response Submitted to Complete Response Letter (CRL)	Hemophilia A	Viral Gene Therapy	09/29/2022
SRP-9001	NDA/BLA Filing	Duchenne Muscular Dystrophy (DMD)	Viral Gene Therapy	09/29/2022

Source: Biomedtracker | Citeline, October 2022

Pipeline overview

Q3 2022

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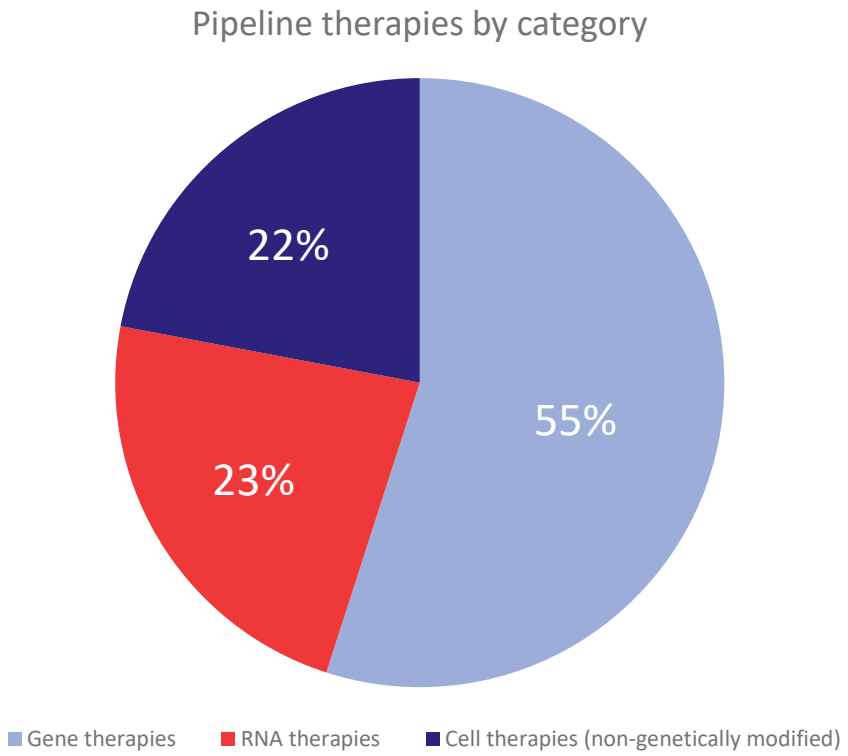
Pipeline of gene, cell, and RNA therapies

3,649 therapies are in development, ranging from preclinical through pre-registration

- 2,031 gene therapies (including genetically modified cell therapies such as CAR T-cell therapies) are in development, accounting for 55% of gene, cell, and RNA therapies
- 814 non-genetically modified cell therapies are in development, accounting for 22% of gene, cell, and RNA therapies



Source: Pharmaprojects| Citeline, October 2022

American Society of Gene + Cell Therapy

Gene therapy pipeline

Gene therapy and genetically modified cell therapies

Q3 2022

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Gene therapy pipeline: Quarterly comparison

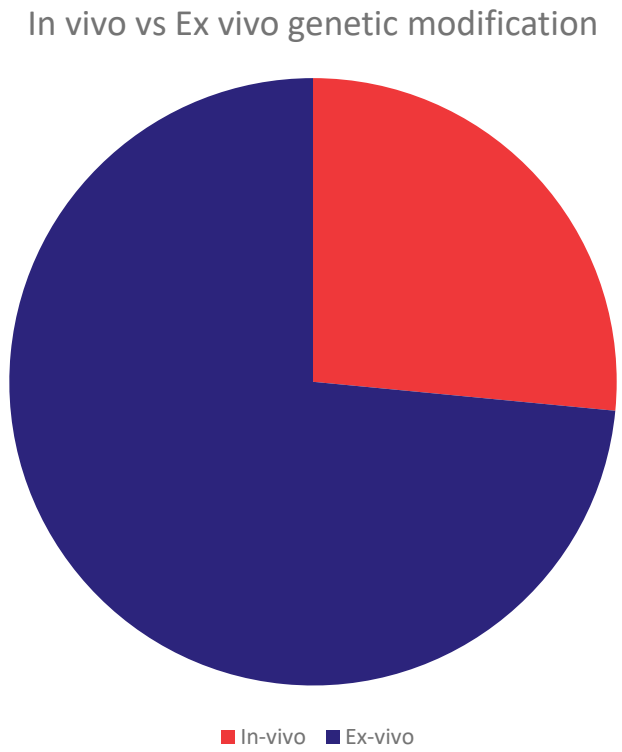
- For the first time in over a year, the number of drugs in Phase I, Phase II, and Phase III have all increased since the previous quarter
- One new gene therapy has filed for approval in Q3 2022. Therapies currently in pre-registration:
  - lenadogene nolparvovec (Genethon, GenSight Biologics)
    - In the EU and UK
  - nadofaragene firadenovec (Ferring, FKD Therapeutics, Trizell)
    - In the US
  - etranacogene dezaparvovec (uniQure, CSL Behring)
    - In the EU, UK, and US
  - beremagene geperpavec (Krystal Biotech)
    - In the US
  - equecabtagene autoleucel (Nanjing Iaso Biotherapeutics, Innovent)
    - In China
  - delandistrogene moxeparvovec (Sarepta Therapeutics)
    - In the US

Global Status	Q3 2021	Q4 2022	Q1 2022	Q2 2022	Q3 2022
Preclinical	1,353	1,412	1,451	1,482	1,480
Phase I	264	248	248	258	264
Phase II	239	244	250	248	249
Phase III	29	32	31	28	32
Pre-registration	5	5	6	8	6
Total	**1,890**	**1,941**	**1,986**	**2,024**	**2,031**

Source: Pharmaprojects| Citeline, Oct 2022

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

- *Ex vivo* genetic modification is more widely used for gene therapies in pipeline development
- In Q3 2022, *in vivo* delivery techniques were used in 27% of gene therapies, the same proportion as in Q4 2021 and H1 2022



Source: Cell and Gene Therapy dashboard | Citeline, October 2022

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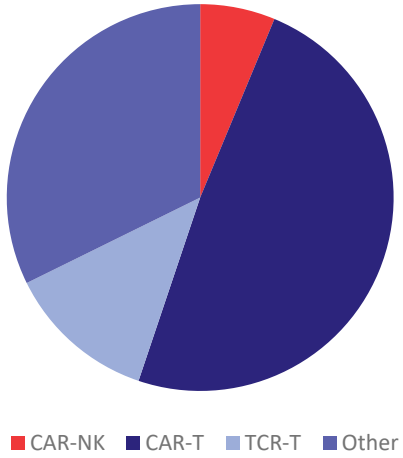
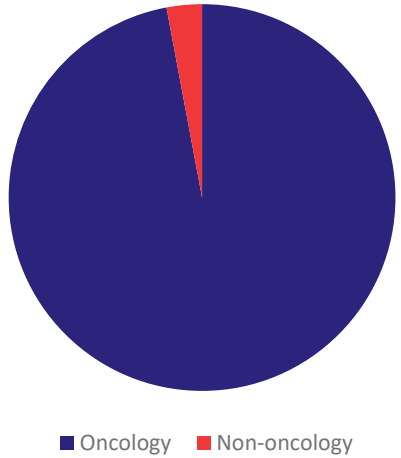
Gene therapy breakdown: CAR-Ts continue to dominate pipeline

- CAR T-cell therapies remain the most common technology used in the pipeline of genetically modified cell therapies (preclinical through to pre-registration), representing 49%, followed by the “other” category at 32%, which includes a list of less commonly used technologies including TCR-NK, CAR-M, and TAC-T
- As found in Q4 2021 and H1 2022, 98% 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

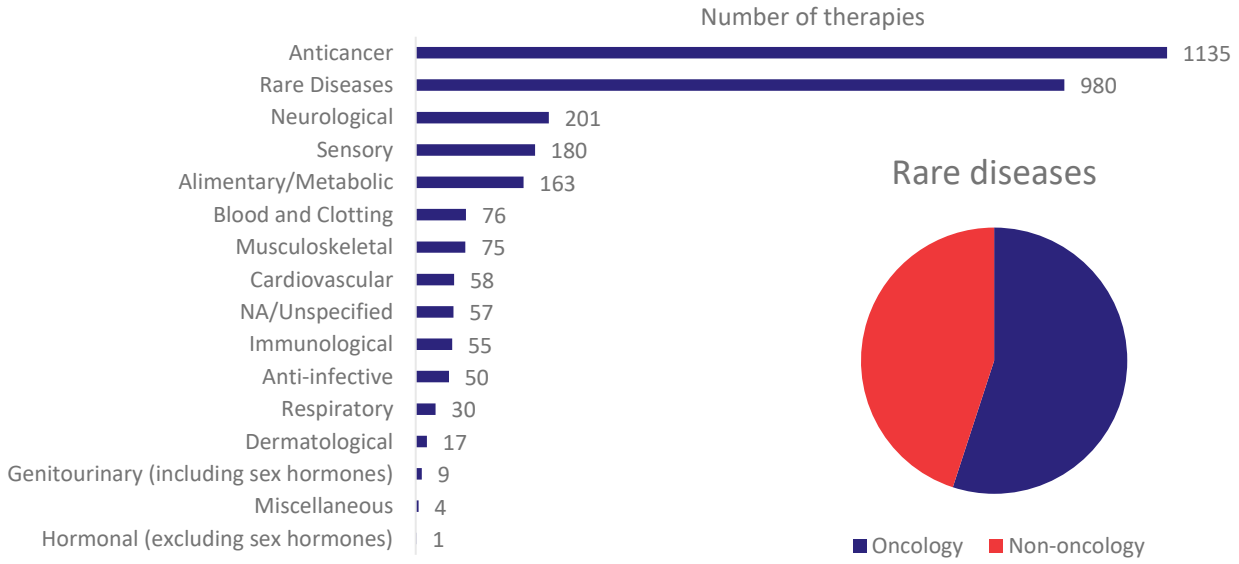


Source: Cell and Gene Therapy dashboard | Citeline, October 2022

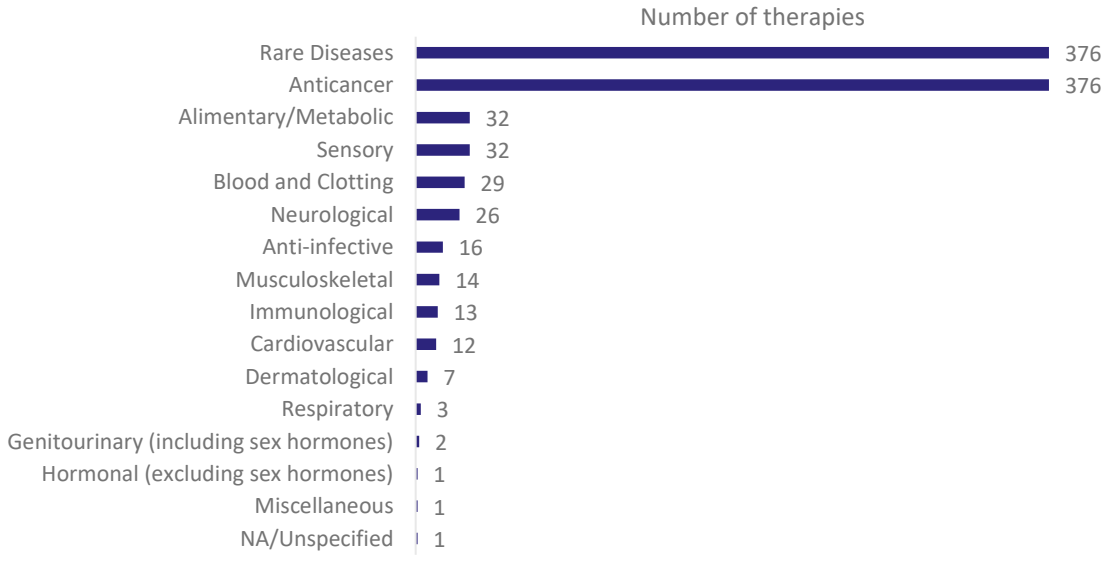
Gene therapy pipeline: Most commonly targeted therapeutic areas

- 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 55% 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, October 2022

*figures based on indications in pipeline development only for each therapy

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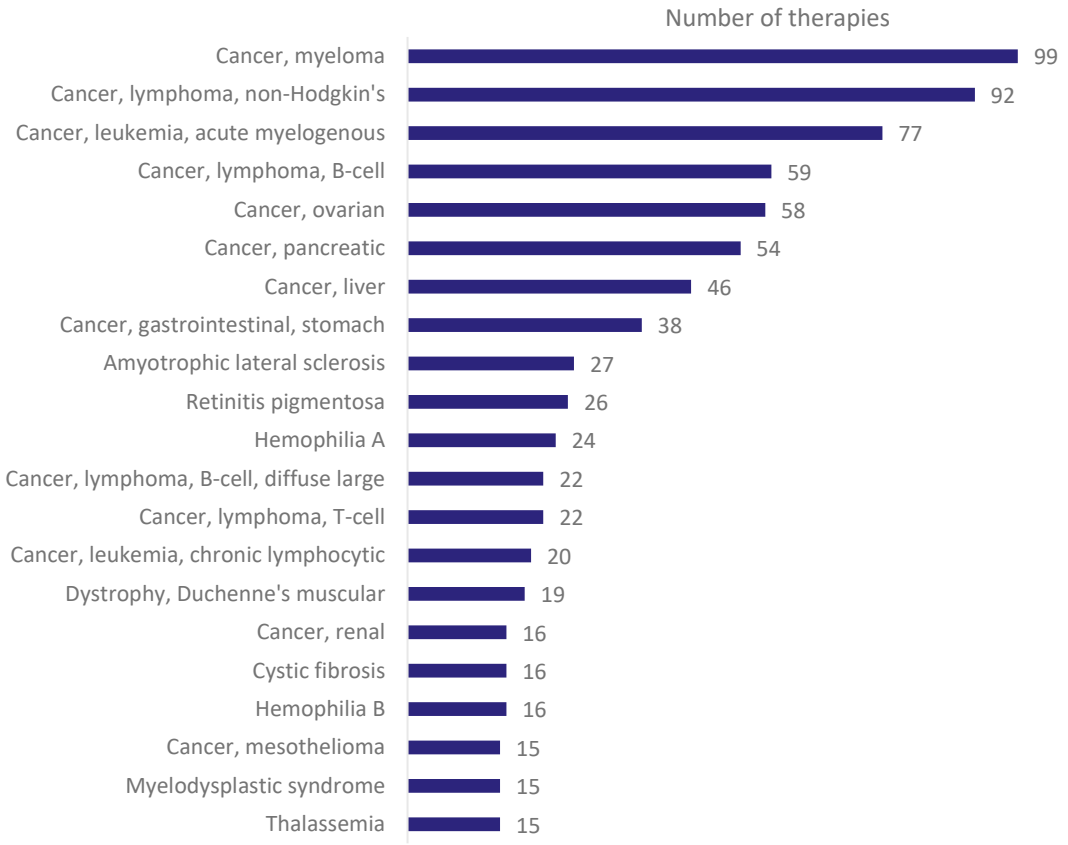
Gene therapy pipeline: Most common rare diseases targeted

- For the 980 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 in H2 2022
- In the same order as the previous four 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, October 2022

*figures based on indications in pipeline development only for each therapy

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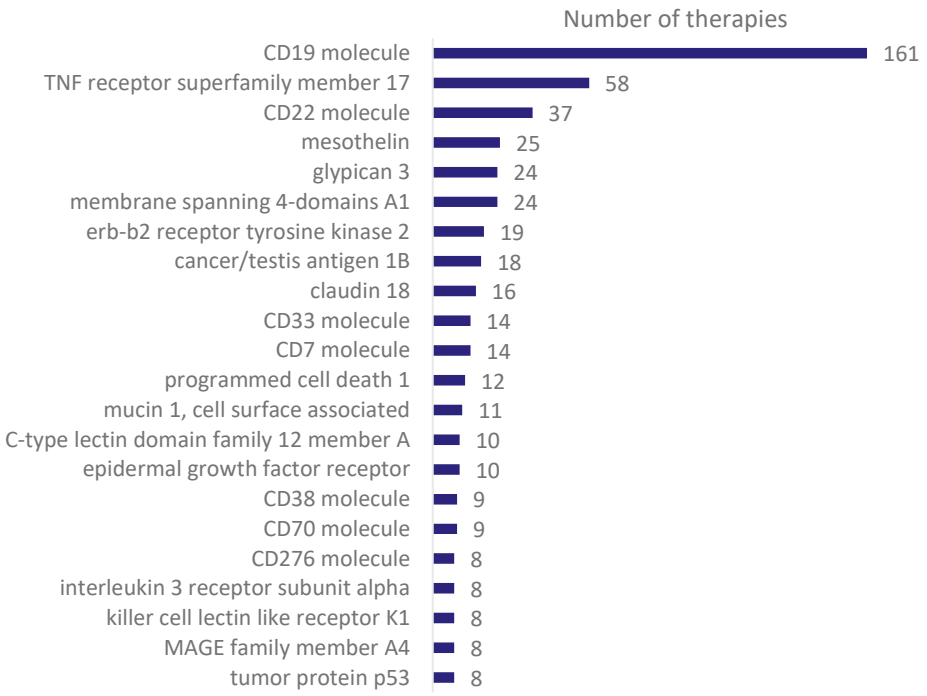
Gene therapy pipeline: Most common targets

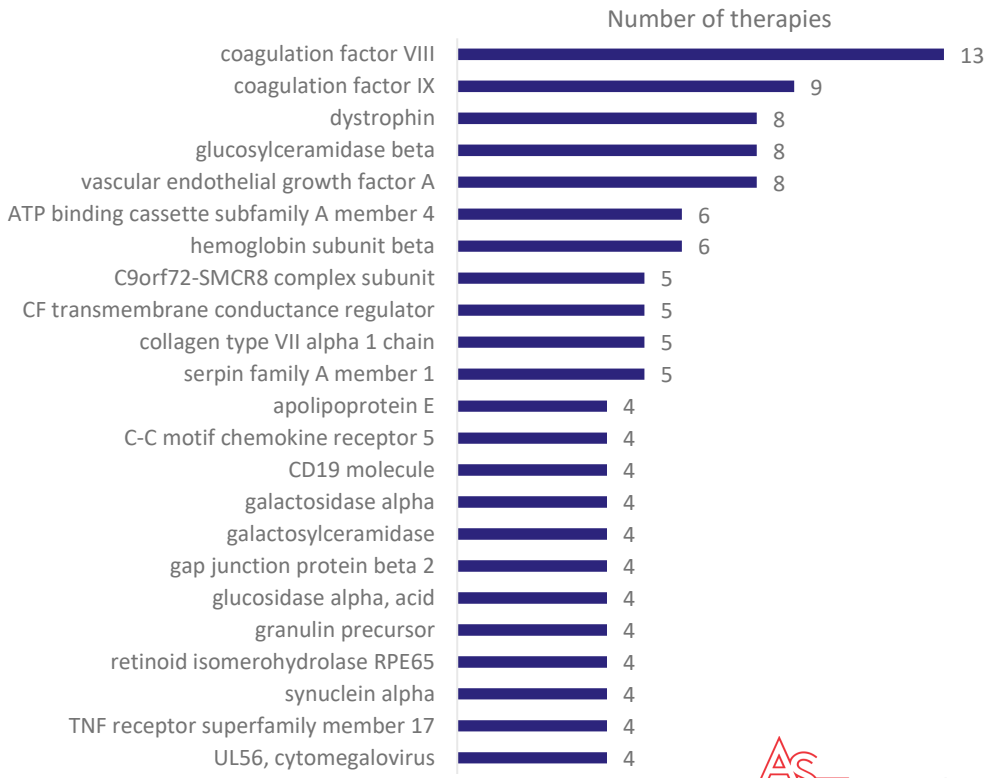
Of the gene therapies in preclinical trials through pre-registration in which targets are disclosed:

- 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 and coagulation factor IX remain the most common targets for non-oncology indications since Q1 2022

Oncology targets



Non-oncology targets



Source: Pharmaprojects| Citeline, October 2022

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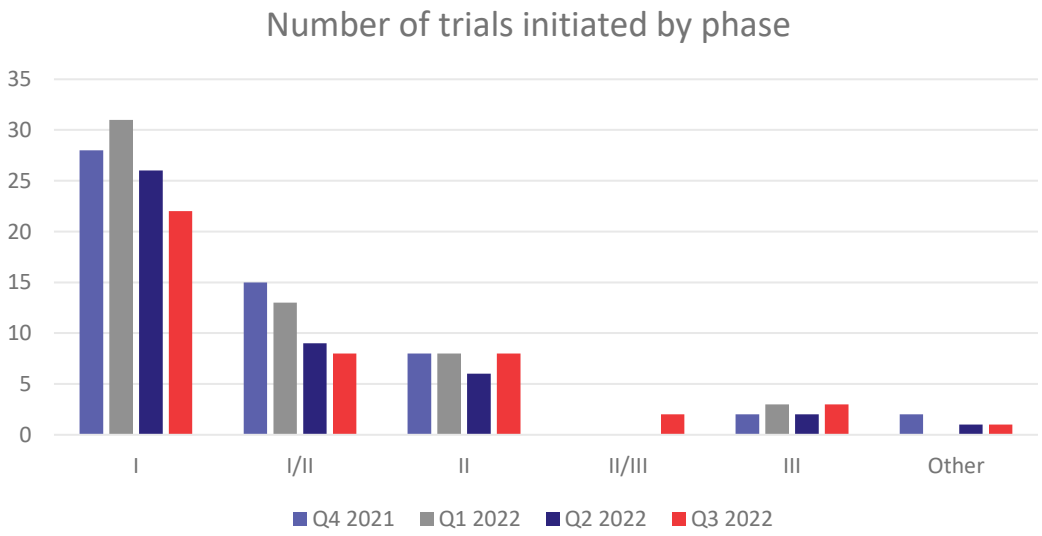
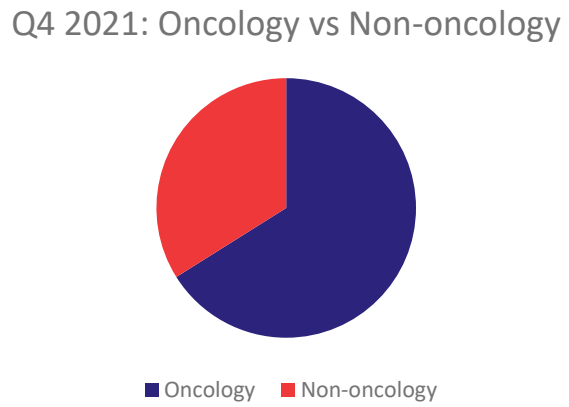
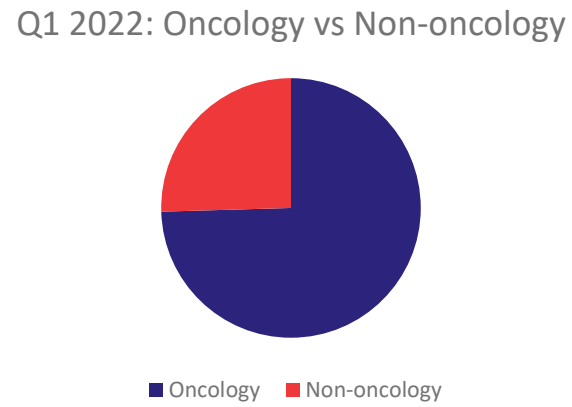
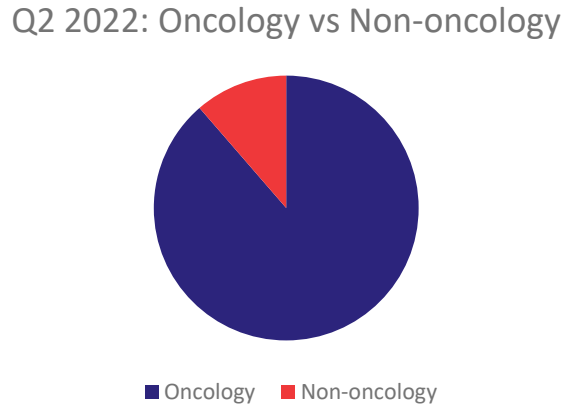
Gene therapy clinical trial activity

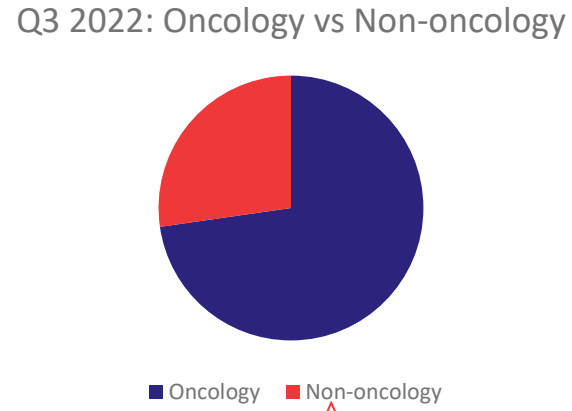
- 44 trials were initiated in Q3 2022 for gene therapies
- Contrary to the trend of the previous three quarters, the proportion of gene therapy trials for non-oncology indications has increased by 16% since Q2 2022, to 27%











Source: Trialtrove| Citeline, October 2022

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Non-genetically modified cell therapy pipeline

Q3 2022

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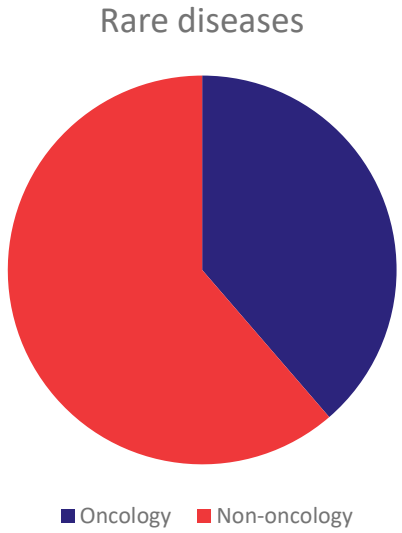
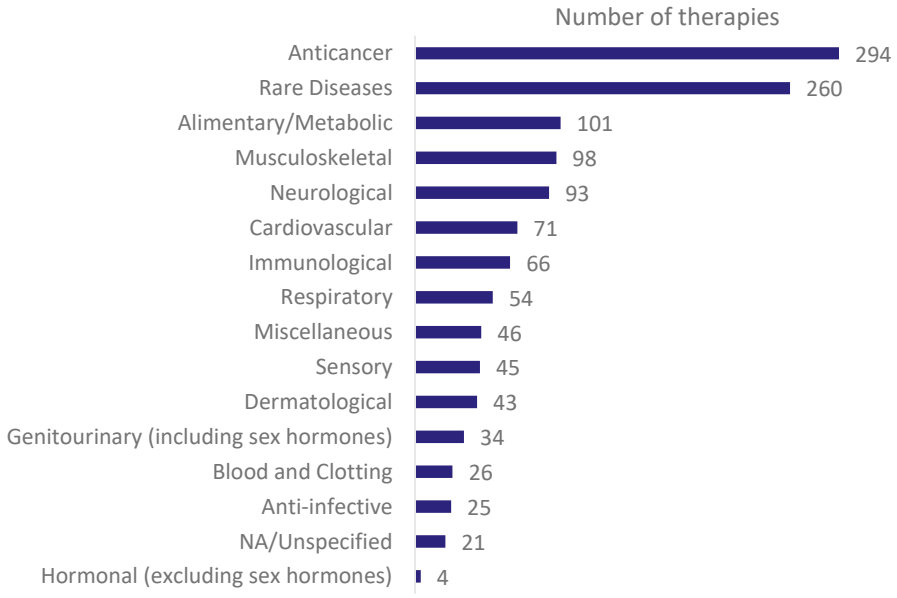
Non-genetically modified cell therapy pipeline: Most common therapeutic areas targeted

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, 63% are in development for non-oncology rare diseases, the same proportion as found in H1 2022





Source: Pharmaprojects| Citeline, October 2022

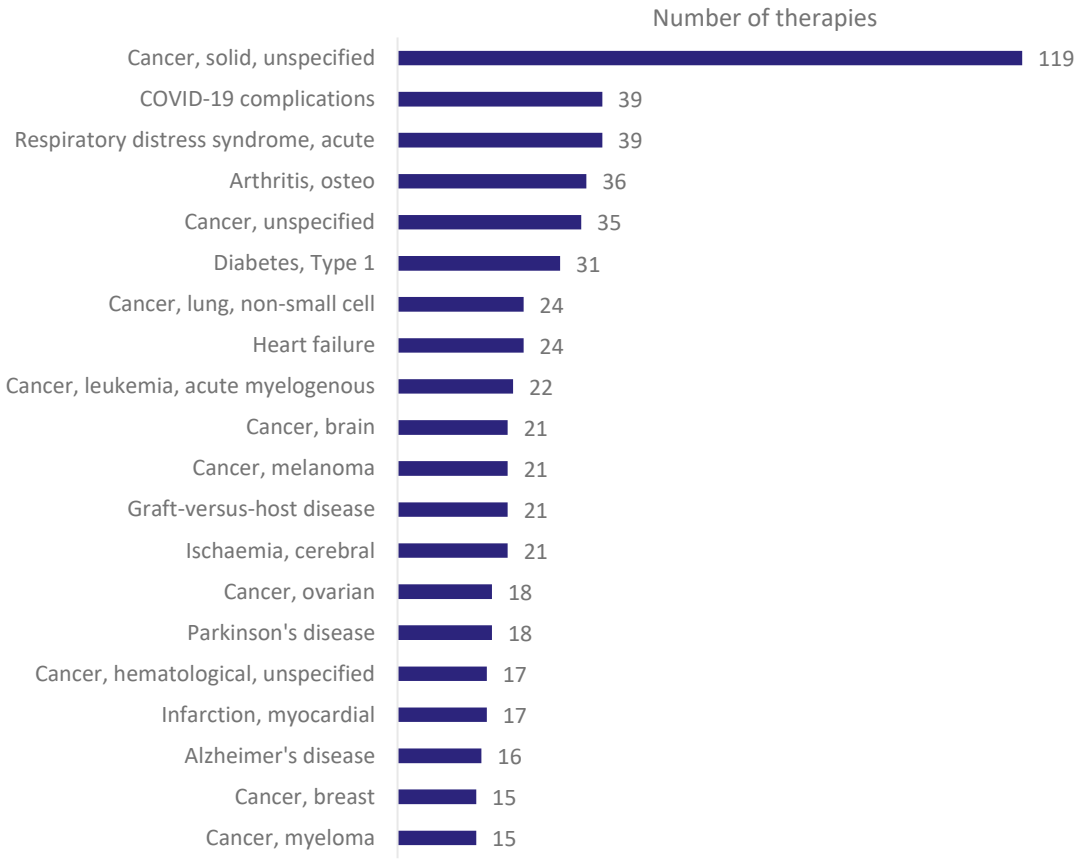
*figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

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

Of the diseases for which indications are specified, the top three indications remain the same as in Q4 2021 and H1 2022, and in the same order as in Q2 2022:

1. COVID-19 complications
2. Respiratory distress syndrome
3. Osteo arthritis



Source: Pharmaprojects| Citeline, October 2022

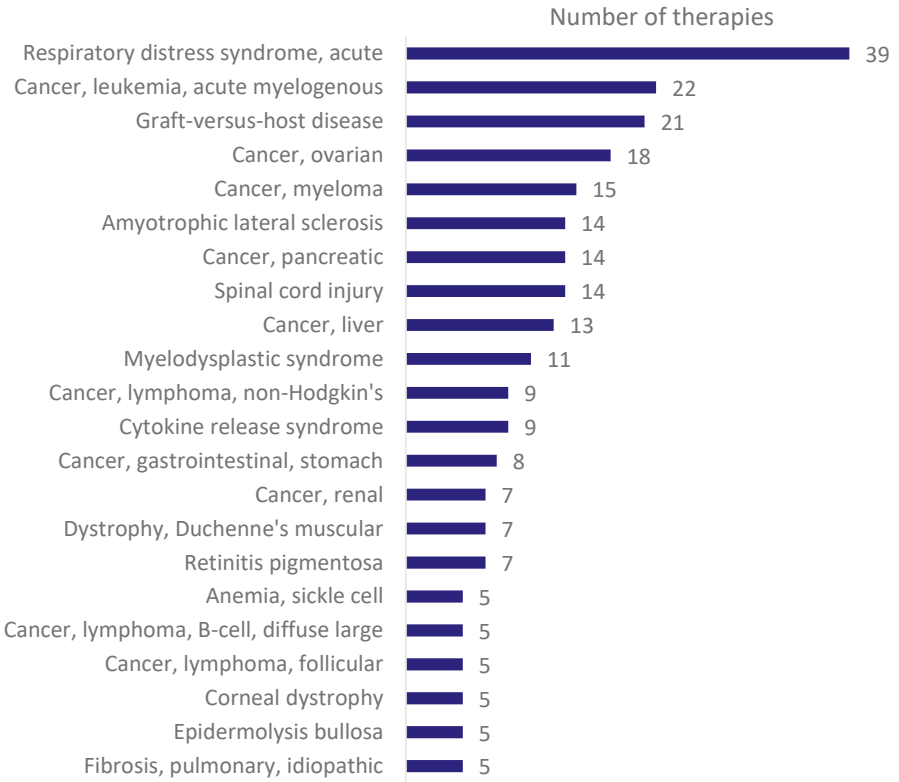
*figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

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

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

- The top three oncology indications are acute myelogenous leukemia, ovarian cancer and myeloma
- The top three non-oncology indications remain to be acute respiratory distress syndrome, graft-versus-host disease and amyotrophic lateral sclerosis



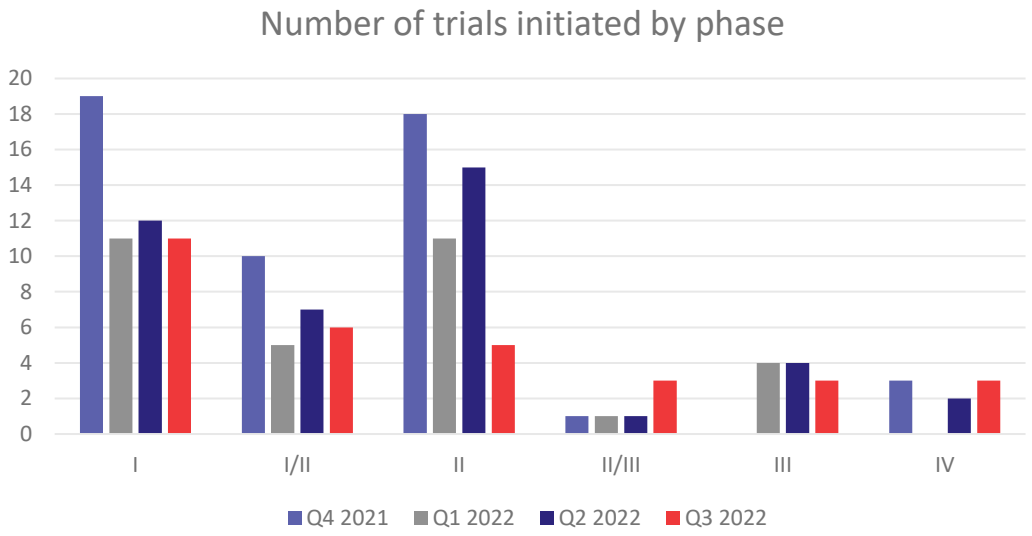
Source: Pharmaprojects| Citeline, October 2022

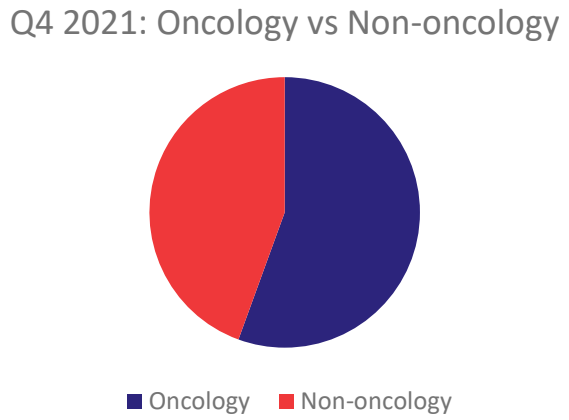
*figures based on indications in pipeline development only for each therapy

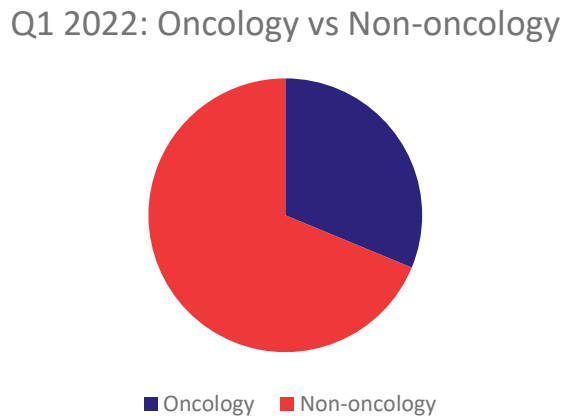
American Society of Gene + Cell Therapy

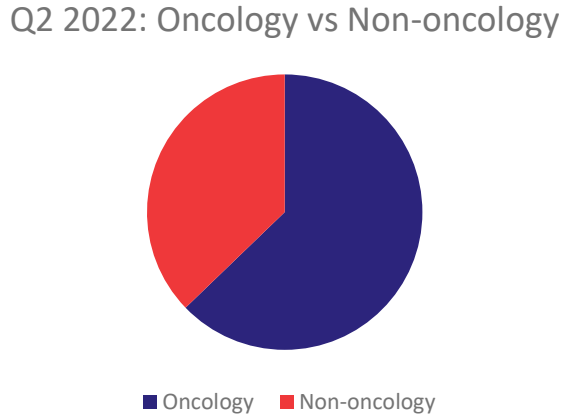
Non-genetically modified cell therapy trial activity

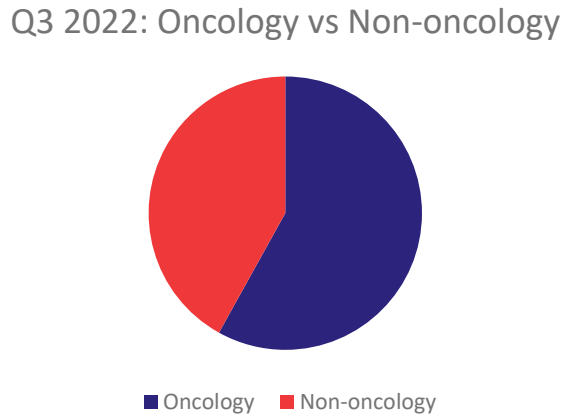
- 31 trials were initiated for non-genetically modified cell therapies in Q3 2022, and of these 42% are for non-oncology indications, an increase of 3% since Q2 2022











Source: Trialtrove| Citeline, October 2022

American Society of Gene + Cell Therapy

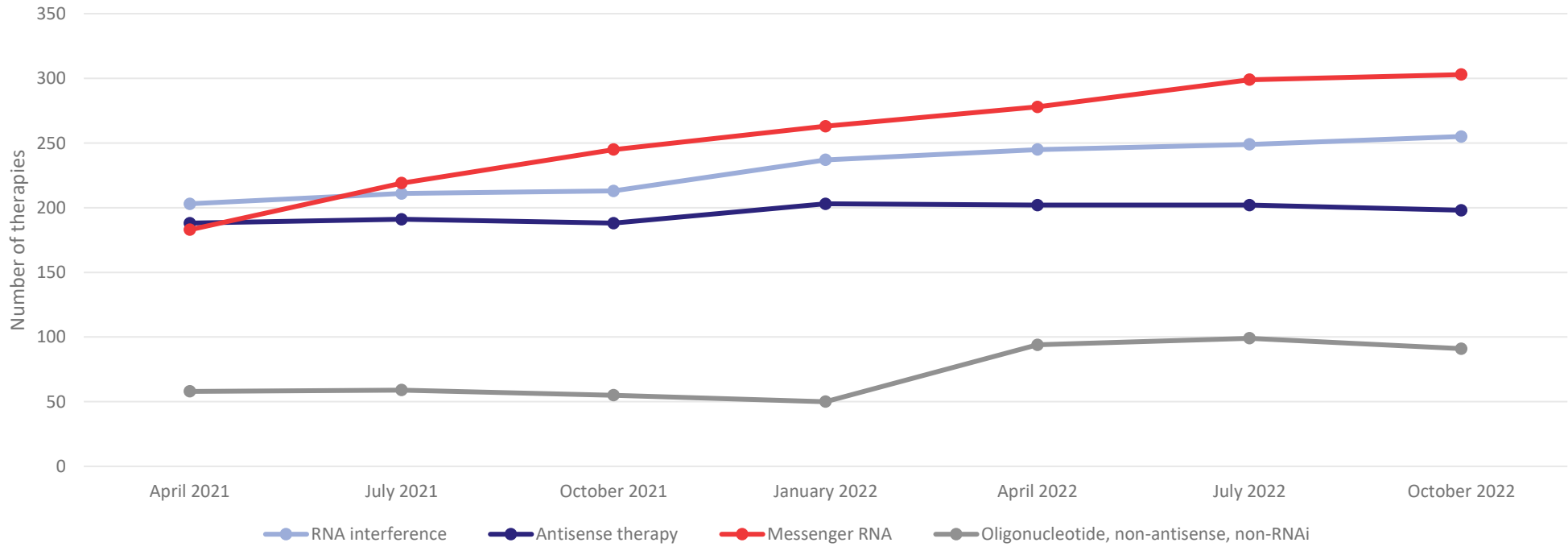
RNA therapy pipeline

Q3 2022

American Society of Gene + Cell Therapy

RNA therapy pipeline: Most common modalities

- Q3 2022 has seen a slight uptick in the number of RNA interference and messenger RNA therapies, while the numbers of antisense and oligonucleotide (non-antisense, non-RNAi) therapies have done down by four and eight respectively

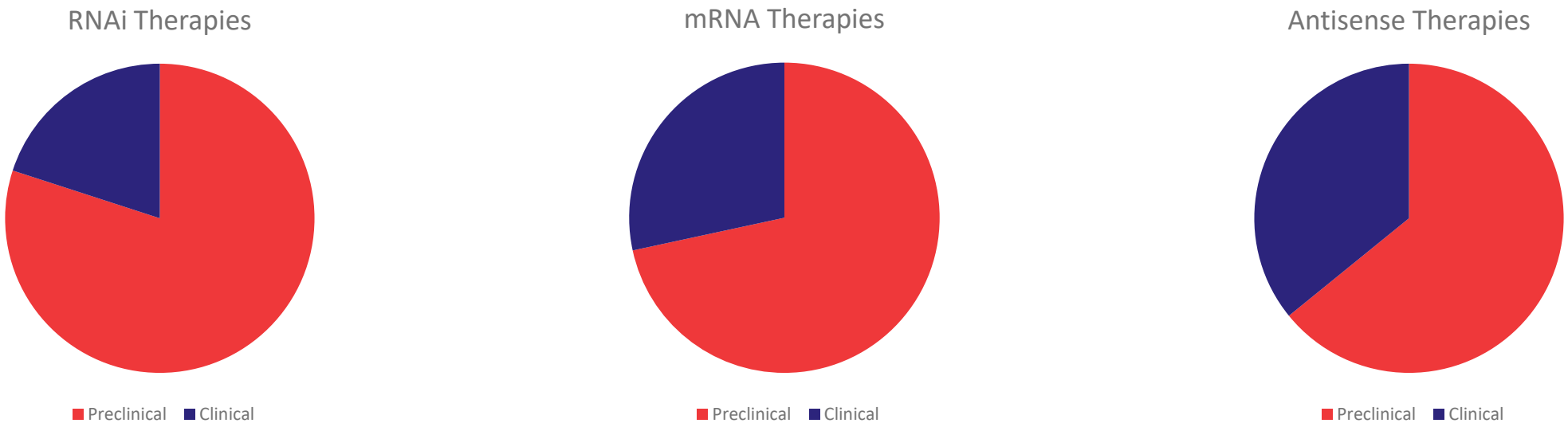


Source: Pharmaprojects| Citeline, October 2022

American Society of Gene + Cell Therapy

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

- Preclinical development continues to dominate RNAi, mRNA and antisense therapeutic development, representing 80%, 72% and 64% of development respectively



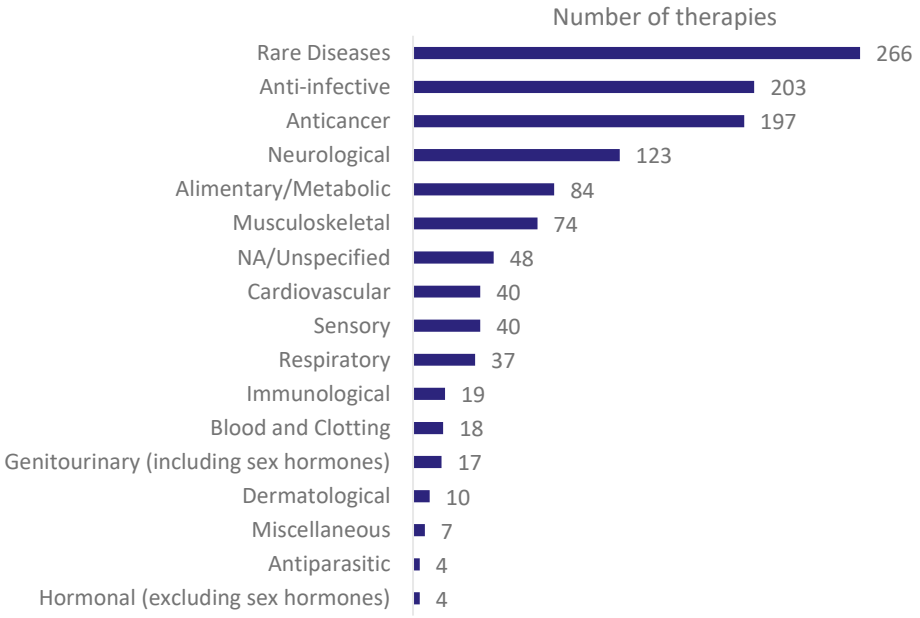
Source: Pharmaprojects| Citeline, October 2022

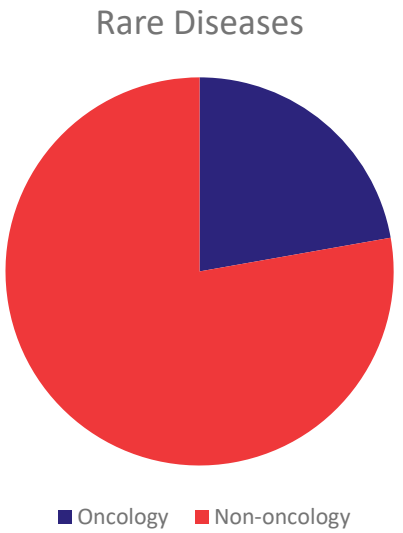
American Society of Gene + Cell Therapy

RNA therapies: Most commonly targeted therapeutic areas

Of the 850 RNA therapies currently in the pipeline (from preclinical through pre-registration):

- Rare diseases and anti-infective therapies remain the top two targeted therapeutic areas by RNA therapies
- Non-oncology indications continue to be the most targeted rare diseases by RNA therapies, representing a majority of 79%





Source: Pharmaprojects| Citeline, October 2022

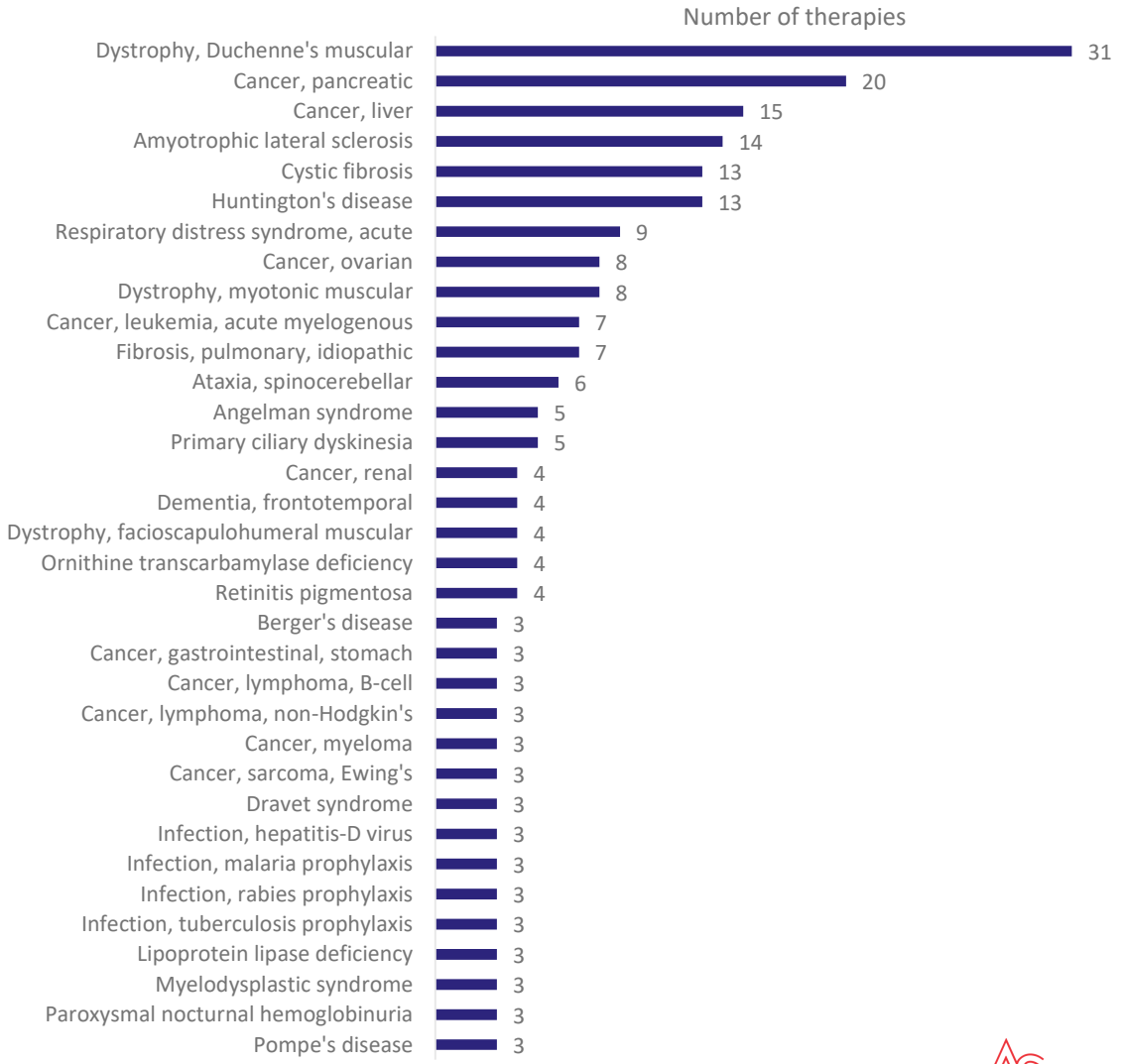
*figures based on indications in pipeline development only for each therapy

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, similar to H1 2022
- For non-oncology rare diseases, Duchenne's muscular dystrophy, amyotrophic lateral sclerosis and cystic fibrosis are the most commonly targeted indications

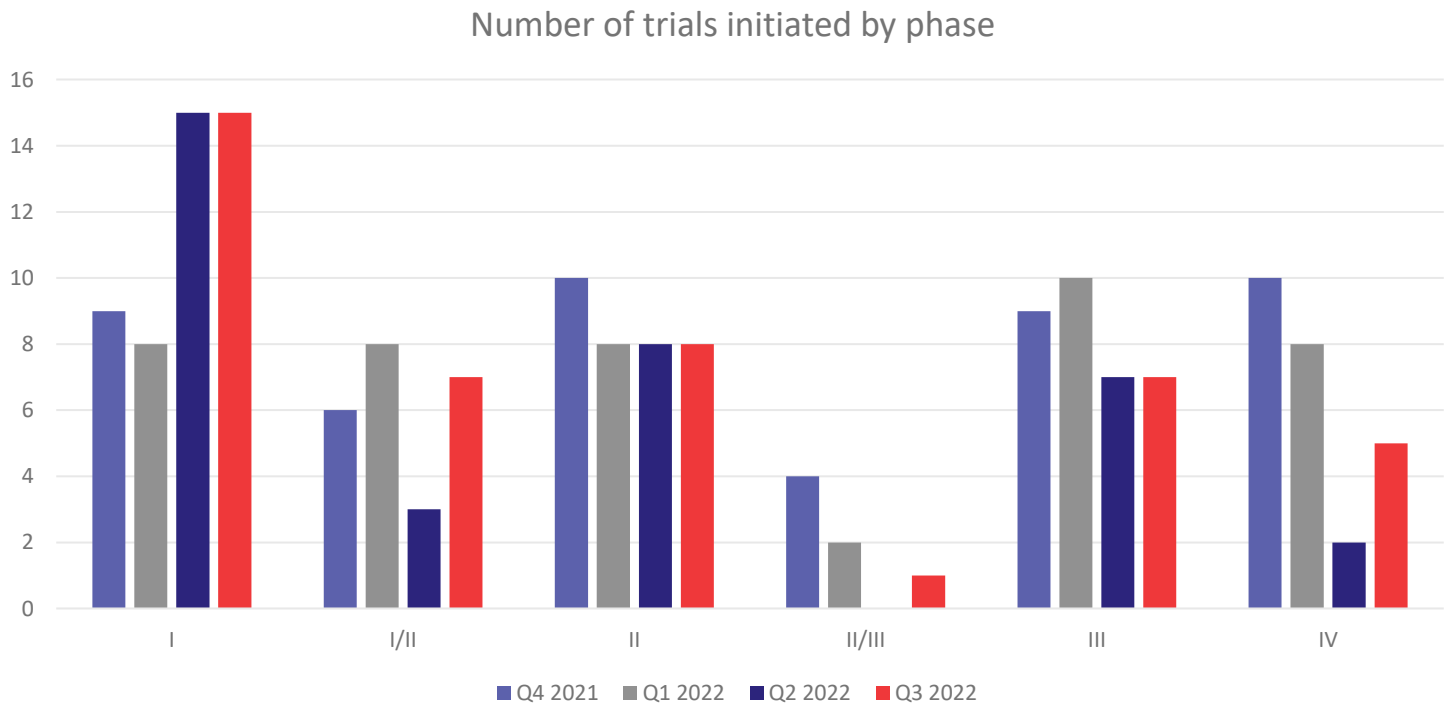


Source: Pharmaprojects| Citeline, October 2022

*figures based on indications in pipeline development only for each therapy

RNA therapy pipeline: Clinical trial activity

- 43 RNA trials were initiated in Q3 2022, compared to 36 in Q2 2022, 91% of which were for non-oncology indications



Source: Trialtrove| Citeline, October 2022

American Society of Gene + Cell Therapy

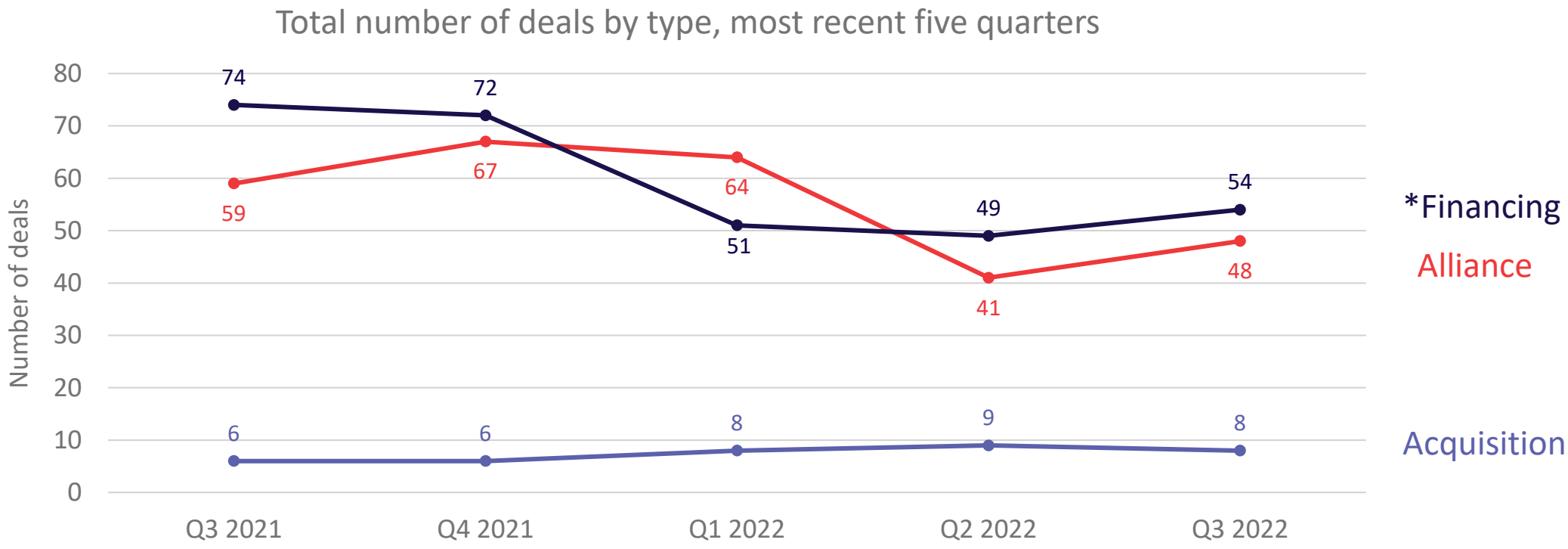
Overview of dealmaking for gene, cell, and RNA therapy companies

Q3 2022

American Society of Gene + Cell Therapy

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

- In Q3 2022, the volume of advanced molecular therapy dealmaking reached 110 deals, an 11% increase over the 99 transactions in Q2
- The greatest increase was in the number of partnerships, which jumped from 41 to 48 alliances; fundraising was also on the rise, from 49 to 54 financings done
- Acquisition activity in Q3 was ahead of the volume one year ago, but decreased from Q2



Source: Biomedtracker| Citeline, October 2022

*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

Q3 2022 acquisitions in gene, cell, & RNA therapy

- With eight acquisitions in the advanced molecular therapy space, Q3 2022 was just one deal shy of Q2's volume
- Following up its 2019 acquisition of Semma Therapeutics, Vertex made another deal in the area of cell therapies for diabetes by acquiring ViaCyte for $320 million
- The second-largest deal of the quarter saw Ultragenyx exercising an option it received in 2019 for GeneTx, which is developing an antisense oligonucleotide for Angelman syndrome

Deal Date	Deal Title	Potential Deal Value (USD $)
07/11/2022	Vertex to Acquire ViaCyte for $320M in Cash	320,000,000
07/18/2022	Ultragenyx Exercises Option to Acquire GeneTx	190,000,000
09/20/2022	Rocket Pharmaceuticals to Acquire Renovacor	53,000,000
09/21/2022	Sesen Bio and Carisma Therapeutics Announce Merger Agreement	Undisclosed
09/26/2022	CBI to Acquire Exicure	5,400,000
09/27/2022	Direct Biologics Signs Letter of Intent to Go Public via SPAC Merger	Undisclosed
09/30/2022	PACT Pharma Announces Agreement to Sell Select Assets to AmplifyBio	Undisclosed
09/30/2022	Solid Biosciences to Acquire AavantiBio	Undisclosed

Source: Biomedtracker| Citeline, October 2022

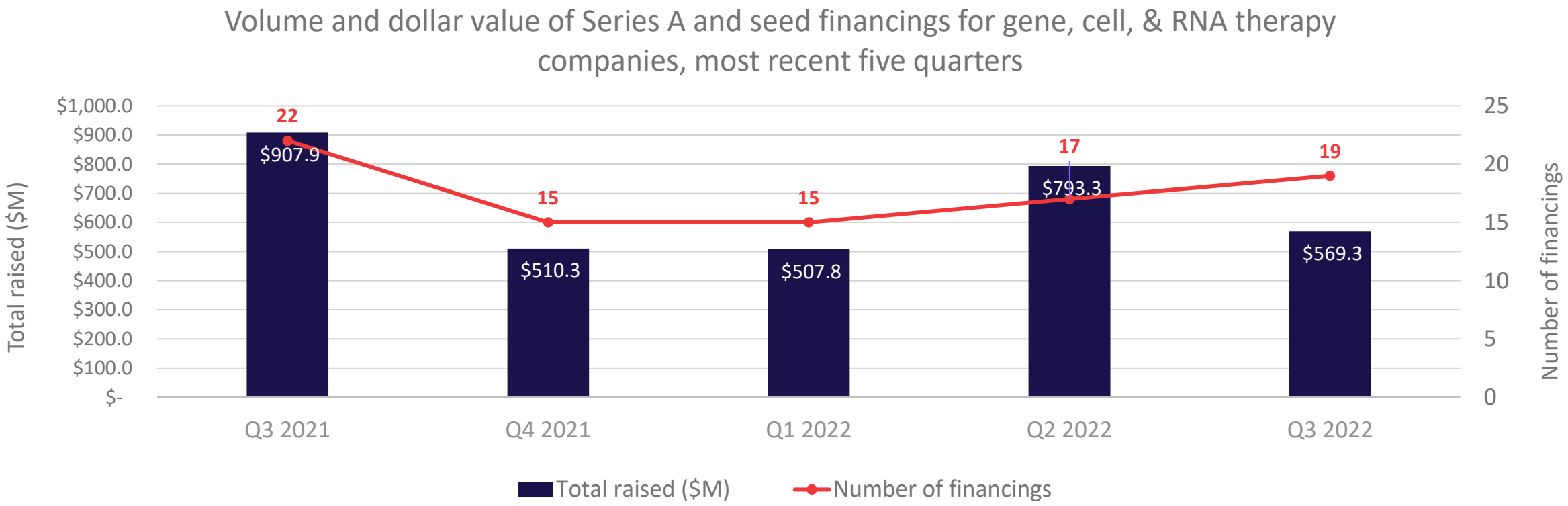
Start-up funding for gene, cell, & RNA therapy companies

Q3 2022

American Society of Gene + Cell Therapy

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

- Combined seed and Series A financing for 19 gene, cell, and RNA companies totaled $569.3 million in Q3 2022
- Q3's figures represented a decrease in aggregate value from Q2, but an increase, by two companies, in volume
- Compared with one year ago, the number of start-ups raising funds is down slightly, and the total dollar amount raised is substantially down, from $907.9 million in Q3 2021



Source: Biomedtracker| Citeline, October 2022

American Society of Gene + Cell Therapy

Q3 2022 start-up financing for gene, cell, & RNA therapy companies (1/3)

Deal Date	Deal Title	Modality Type	Company Location	Academic Source	Potential Deal Value (USD, $M)
07/07/2022	Kernal Biologics Raises $25M in Series A Financing	mRNA therapeutics	United States, Massachusetts, Cambridge	Co-founded by Yusuf Erkul and Burak Yilmaz	25
07/12/2022	Epic Bio Raises $55M Series A Financing	Epigenetics-level gene editing	United States, California, San Francisco	Stanford University	55
07/25/2022	Replay Launches with $55 Million Seed Financing	Genomic medicine technologies (high payload HSV vector, off-the-shelf iPSC cells, genome writing)	United States, California, San Diego	Co-founded by Adrian Woolfson, Lachlan MacKinnon, David Knipe, and Ron Weiss	55
07/28/2022	Core Biogenesis Raises $10.5m Series A Financing	Plant-based bioproduction for cell therapy	France, Strasbourg	Co-founded by Chouaib Meziadi and Alexandre Reeber	10.5
08/02/2022	Eleven Therapeutics Raises $18M in Seed Funding	AI-driven siRNA	United Kingdom, Cambridge	Co-founded by Yaniv Erlich, Shaul Ilan, and Greg Hannon	18
08/04/2022	Immunis Raises $10M Series A Financing	Stem cell therapy	United States, California, Irvine	Undisclosed	10
08/10/2022	Vector BioPharma Launches with $30M Series A Financing	Non-viral gene delivery	Switzerland, Basel	University of Zürich	30
08/15/2022	Remedium Bio Raises $2.3M in an Expanded Seed Round	Gene therapy	United States, Massachusetts, Needham	Undisclosed	2.3

Source: Biomedtracker| Citeline, October 2022

Q3 2022 start-up financing for gene, cell, & RNA therapy companies (2/3)

Deal Date	Deal Title	Modality Type	Company Location	Academic Source	Potential Deal Value (USD, $M)
08/25/2022	3T Biosciences Debuts with $40M Series A Financing	T-cell receptor therapy	United States, California, San Francisco	Stanford University	40
08/31/2022	Laverock Therapeutics Debuts with Seed Funding	Gene editing-induced gene silencing	United Kingdom, Stevenage	Technology licensed from Tropic Biosciences.	Undisclosed
09/02/2022	Neukio Biotherapeutics Completes $50M Series A-1 Financing	CAR-NK cell therapy	China, Shanghai	Founded by Richard Wang	50
09/07/2022	Arpeggio Biosciences Raises $17M in Series A Funding	Machine learning analysis of RNA profiles to discover modulators (small molecules, biologics, or antisense oligonucleotides) of transcriptome	United States, Colorado, Boulder	Technology developed by founders from University of Colorado	17
09/08/2022	Innervace Secures Up to $40M in Series A Funding	Implantable biofabricated neural pathway	United States, New York, New York	University of Pennsylvania's Perelman School of Medicine; UC San Diego	40
09/12/2022	Pretzel Therapeutics Launches with $72.5M Series A Financing	Gene editing	United States, Massachusetts, Waltham	University of Gothenburg; University of Cambridge; Karolinska Institutet	72.5
09/13/2022	WhiteLab Genomics Raises $10M in Series A Funding	Vector and payload development in silico	France, Paris	Co-founded by David Del Bourgo and Julien Cottineau	10
09/14/2022	Capstan Therapeutics Raises $102M in Series A to Develop Precision In-Vivo Cell Engineering	In vivo cell engineering	United States, California, San Diego	University of Pennsylvania	102

Source: Biomedtracker| Citeline, October 2022

Q3 2022 start-up financing for gene, cell, & RNA therapy companies (3/3)

Deal Date	Deal Title	Modality Type	Company Location	Academic Source	Potential Deal Value (USD, $M)
09/15/2022	Carver Biosciences Launches with Seed Financing	Gene editing	United States, Massachusetts, Boston	Princeton University	Undisclosed
09/29/2022	NeuShen Therapeutics Closes $20M Pre-A Financing	AAV gene therapy	China, Shanghai	Undisclosed	20
09/30/2022	EnPlusOne Biosciences Launches Enzymatic RNA Synthesis Platform with $12M in Seed Financing	RNA oligonucleotides	United States, Massachusetts, Watertown	Wyss Institute for Biologically Inspired Engineering at Harvard University	12

Source: Biomedtracker| Citeline, October 2022

Notable Q3 2022 start-up gene, cell, & RNA therapy companies

Company details	Academic source	Financing type/amount raised	Lead investor(s)	Therapy areas of interest
In vivo cell engineering via mRNA-encoded CARs and mRNA-encoded gene editing	University of Pennsylvania	Series A/$102M	Pfizer Ventures	Oncology, fibrosis, inflammation, and monogenic blood disorders
Gene editing tools to silence mutated mitochondrial DNA	University of Gothenburg; University of Cambridge; Karolinska Institutet	Series A/$72.5M	ARCH Venture Partners	Mitochondrial disorders, and diseases in metabolism, oncology, and neurodegeneration
In vivo gene editing using CasMINI, the smallest Cas protein to date	Stanford University	Series A/$55M	Horizons Ventures	Rare diseases in musculoskeletal, cardiovascular, metabolic, and ophthalmic
synHSV vector platform; uCell off-the-shelf iPSCs; DropSynth genome writing; and LASR protein rewriting	Undisclosed	Seed/$55M	KKR and OMX Ventures	Ophthalmic, neurology, dermatology, and musculoskeletal

Source: Biomedtracker| Citeline, October 2022

Upcoming catalysts

Q3 2022

American Society of Gene + Cell Therapy

Upcoming Catalysts

Below are noteworthy catalysts (forward-looking events) expected in Q4 2022

Therapy	Generic Name	Disease	Catalyst	Catalyst Date
Oxlumo	lumasiran	Hyperoxaluria	PDUFA for sNDA (PH1) - First Review	6 Oct 2022 – 6 Oct 2022
Oxlumo	lumasiran	Hyperoxaluria	CHMP Supplemental Opinion	1 May 2022 – 31 Oct 2022
EtranaDez	etranacogene dezaparvovec	Hemophilia B	CHMP Opinion	1 Sep 2022 – 30 Nov 2022
Lantidra	allogeneic Islets of Langerhans	Diabetes Mellitus, Type I	PDUFA for BLA - First Review	11 Aug 2022 – 31 Dec 2022
EtranaDez	etranacogene dezaparvovec	Hemophilia B	PDUFA for BLA - First Review	1 Nov 2022 – 31 Dec 2022
Oxlumo	lumasiran	Hyperoxaluria	Supplemental Approval Europe (PH1)	1 Jul 2022 – 31 Dec 2022
EtranaDez	etranacogene dezaparvovec	Hemophilia B	European Approval Decision	1 Nov 2022 – 31 Jan 2023
Tab-cel	tabelecleucel	Hematologic Cancer	CHMP Opinion	1 Aug 2022 – 28 Feb 2023
Spikevax	COVID-19 vaccine, Moderna	COVID-19 Prevention	CHMP Supplemental Filing Results	1 Oct 2022 – 31 Mar 2023
Spikevax	COVID-19 vaccine, Moderna	COVID-19 Prevention	Supplemental Approval Decision (Europe) - Children Under 6 Years	1 Nov 2022 – 30 Apr 2023
Roctavian	valoctocogene roxaparvovec	Hemophilia A	Approval Decision (U.S.)	29 Sep 2022 – 30 Jun 2023
Lumevoq	lenadogene nolparvovec	Leber's Hereditary Optic Neuropathy (LHON)	European Approval Decision	1 Dec 2022 – 30 Nov 2023

Source: Biomedtracker| Citeline, October 2022

Appendix

Methodology, sources & glossary of key terms

Q3 2022

American Society of Gene + Cell Therapy

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

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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