oligonucleotide-based drugs

Which kind of drugs are they???

Oligonucleotide-based drugs and RNA related words

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Codice evento

IMTGRO

FDA approvals 2025

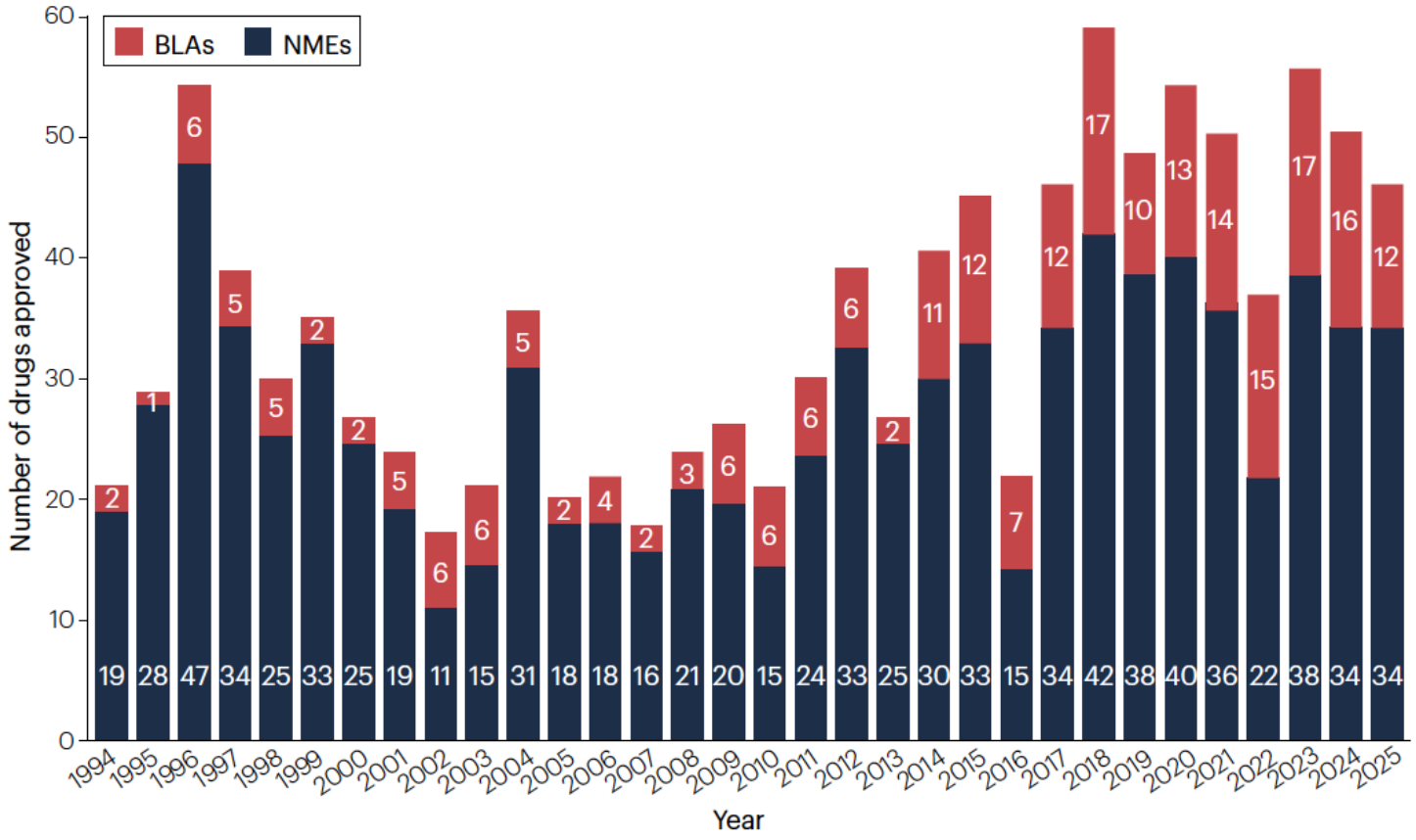


Fig. 1 | Novel FDA approvals since 1993. Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's CDER. See Table 1 for new approvals in 2025. Products approved by CBER, including vaccines and gene therapies, are not included in this drug count (Table 2). Source: FDA.

FDA approvals 2025

Table 1 | CDER approvals in 2025

Drug (brand name)	Sponsor	Properties	Indication
Datopotamab deruxtecan (Datroway)[a]	Daiichi Sankyo	TROP2-targeted ADC; topoisomerase inhibitor payload	HR-positive, HER2-negative breast cancer
Treosulfan (Grafapex)	Medexus	DNA alkylating drug	Preparative regimen for haematopoietic stem cell transplantation for cancers
Suzetrigine (Journavx)	Vertex	$Na_v1.8$ inhibitor	Acute pain
Mirdametinib (Gomekli)	SpringWorks/Merck KGaA	MEK1/2 kinase inhibitor	Neurofibromatosis type 1
Vimseltinib (Romvimza)	Deciphera/Ono	CSF1R kinase inhibitor	Tenosynovial giant cell tumours
Gepotidacin (Blujepa)	GSK	Triazaacenaphthylene bacterial type II topoisomerase inhibitor	Uncomplicated urinary tract infections
Fitusiran (Qfitlia)	Genzyme/Sanofi	Antithrombin-targeted siRNA	Bleeding episodes in haemophilia A or B
Atrasentan (Vanrafia)	Novartis	Endothelin receptor antagonist	Proteinuria in adults with primary IgAN
Penpulimab (Penpulimab)[a]	Akeso Biopharma	PD1-targeted mAb	Nasopharyngeal carcinoma
Nipocalimab (Imaavy)[a]	Janssen/J&J	Neonatal Fc receptor-targeted mAb	Generalized myasthenia gravis
Avutometinib plus defactinib (Avmapki Fakzynja Co-Pack)	Verastem	MEK1 inhibitor plus FAK kinase inhibitor	KRAS-mutated recurrent low-grade serous ovarian cancer
Telisotuzumab vedotin (Emrelis)[a]	AbbVie	c-Met-targeted ADC; microtubule inhibitor payload	Non-squamous NSCLC with high c-Met protein overexpression
Acoltremon (Tryptyr)	Alcon Labs	TRPM8 thermoreceptor agonist	Dry eye disease
Clesrovimab (Enflonsia)[a]	Merck & Co.	RSV fusion protein-targeted mAb	RSV lower respiratory tract disease prevention in neonates and infants
Taletrectinib (Ibtrozi)	Nuvation	ROS1 kinase inhibitor	ROS1-positive NSCLC
Garadacimab (Andembry)[a]	CSL Behring	Activated factor XII-targeted mAb	Hereditary angioedema prevention
Linvoseltamab (Lynozyfic)[a]	Regeneron	BCMA × CD3 bispecific T cell engager	Multiple myeloma
Sunvozertinib (Zegfrovy)	Dizal Jiangsu	EGFR kinase inhibitor	NSCLC with EGFR exon 20 mutations
Sebetralstat (Ekterly)	KalVista	Plasma kallikrein inhibitor	Hereditary angioedema attacks
Delgocitinib (Anzupgo)	Leo Pharma	Janus kinase inhibitor	Hand eczema
Sepiapterin (Sephience)	PTC	Phenylalanine hydroxylase activator	Hyperphenylalaninemia
Aceclidine (Vizz)	Lenz	Cholinergic agonist	Presbyopia
Dordaviprone (Modeyso)	Chimerix/Jazz	ClpP protease activator	Diffuse midline glioma with H3 K27M mutations
Zongertinib (Hernexeos)	Boehringer Ingelheim	HER2 kinase inhibitor	Non-squamous NSCLC with HER2 activating mutations
Brensocatib (Brinsupri)	Insmed	DPP1 inhibitor	Non-cystic fibrosis bronchiectasis
Donidalorsen (Dawnzera)	Ionis	Prekallikrein-targeted ASO	Hereditary angioedema prevention
Rilzabrutinib (Wayrilz)	Genzyme/Sanofi	BTK kinase inhibitor	Immune thrombocytopenia
Pembrolizumab plus berahyaluronidase alfa (Keytruda Qlex)[a]	Merck & Co.	PD1-targeted mAb and an endoglycosidase to enable subcutaneous delivery	Solid tumours approved for the intravenous formulation of pembrolizumab
Elamipretide (Forzinity)	Stealth	Mitochondrial cardiolipin binder	Muscle strength in Barth syndrome
Imlunestrant (Inluriyo)	Eli Lilly	Selective oestrogen receptor degrader	ER-positive, EGFR2-negative, ER1-mutated breast cancer
Paltusotine (Palsonify)	Crinetics	Somatostatin receptor agonist	Acromegaly
Remibrutinib (Rhapsido)	Novartis	BTK kinase inhibitor	Spontaneous urticaria
Nerandomilast (Jascayd)	Boehringer Ingelheim	PDE4 inhibitor	Idiopathic pulmonary fibrosis
Elinzanetant (Lynkuet)	Bayer Healthcare	NK_1 and NK_3 receptor antagonist	Vasomotor symptoms due to menopause
Doxecitine plus doxribtimine (Kygevvi)	UCB	Pyrimidine nucleosides	Thymidine kinase 2 deficiency
Ziftomenib (Komzifti)	Kura	Menin inhibitor	AML with a susceptible NPM1 mutation
Plozasiran (Redemplo)	Arrowhead	ApoC-III-targeted siRNA	Triglycerides in familial chylomicronemia

Therapeutic area 2025

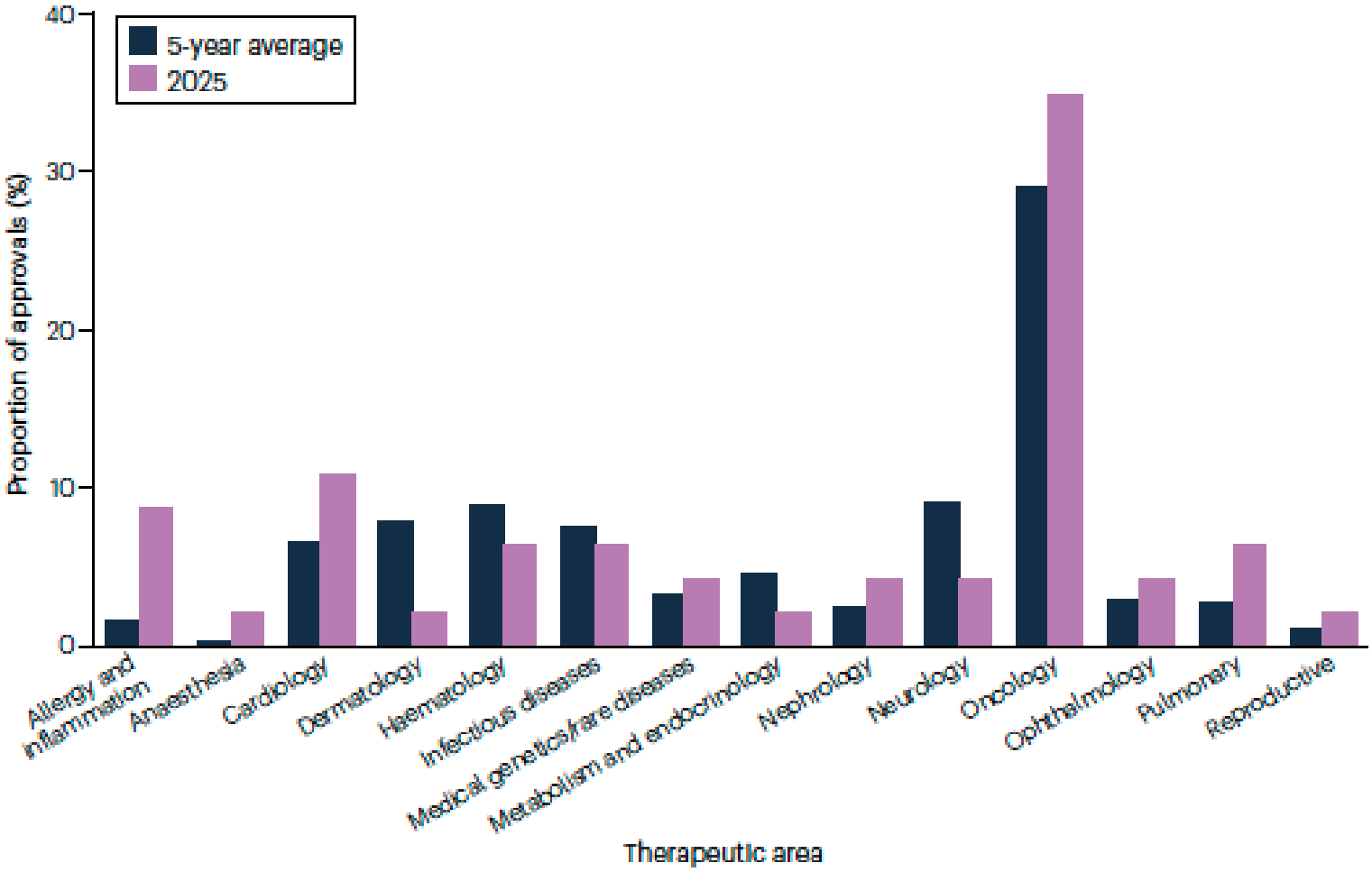


Fig. 2 | CDER approvals by therapeutic areas. Indications that span multiple disease areas are classified under only one, based on which FDA office and division reviewed the approval application. Source: *Nature Reviews Drug Discovery*, FDA.

Drug's modality

2025

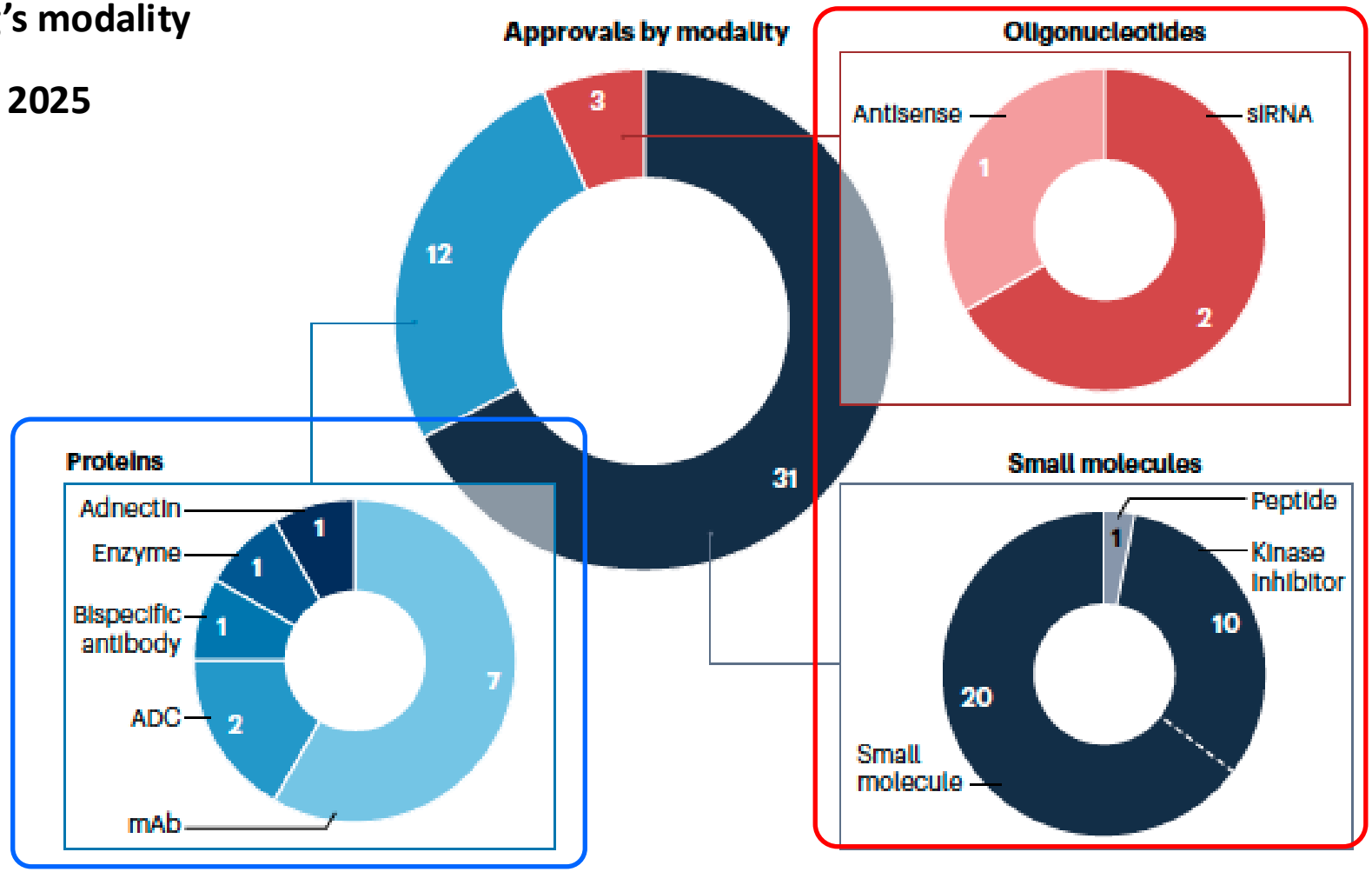


Fig. 3 | CDER approvals by modality. Small molecules, including peptides of up to 40 amino acids in length, and oligonucleotides are approved as new molecular entities. Protein-based candidates are approved through biologics license applications. ADC, antibody–drug conjugate; mAb, monoclonal antibody; siRNA, small interfering RNA. Source: *Nature Reviews Drug Discovery*.

Drug's modality

2023

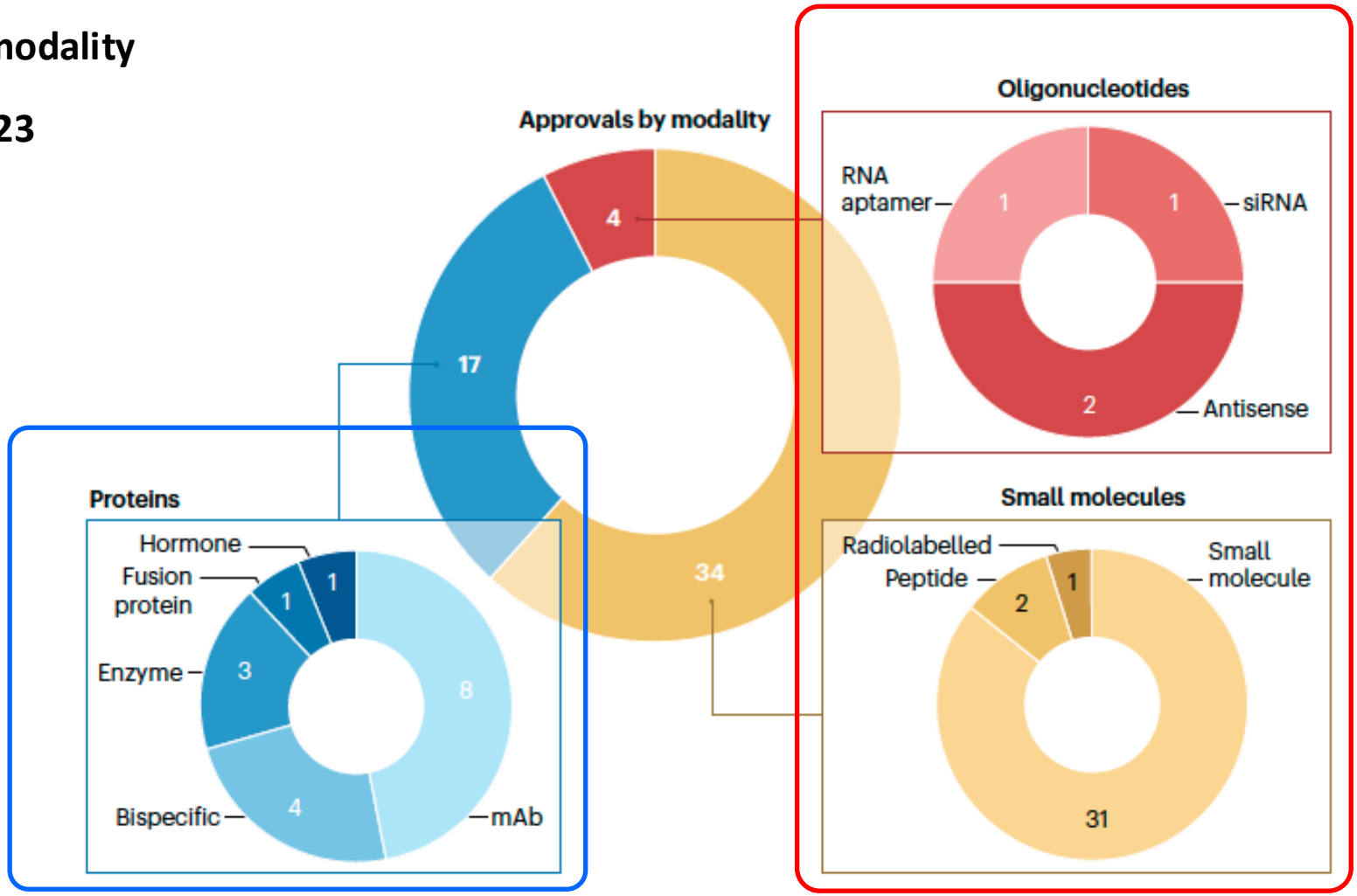


Fig. 3 | CDER approvals by modality. Small molecules, including peptides of up to 40 amino acids in length, and oligonucleotides are approved as new molecular entities (NMEs). Protein-based candidates are approved through biologics license applications (BLAs). mAb, monoclonal antibody; siRNA, small interfering RNA. Source: *Nature Reviews Drug Discovery*.

FDA approvals 2021

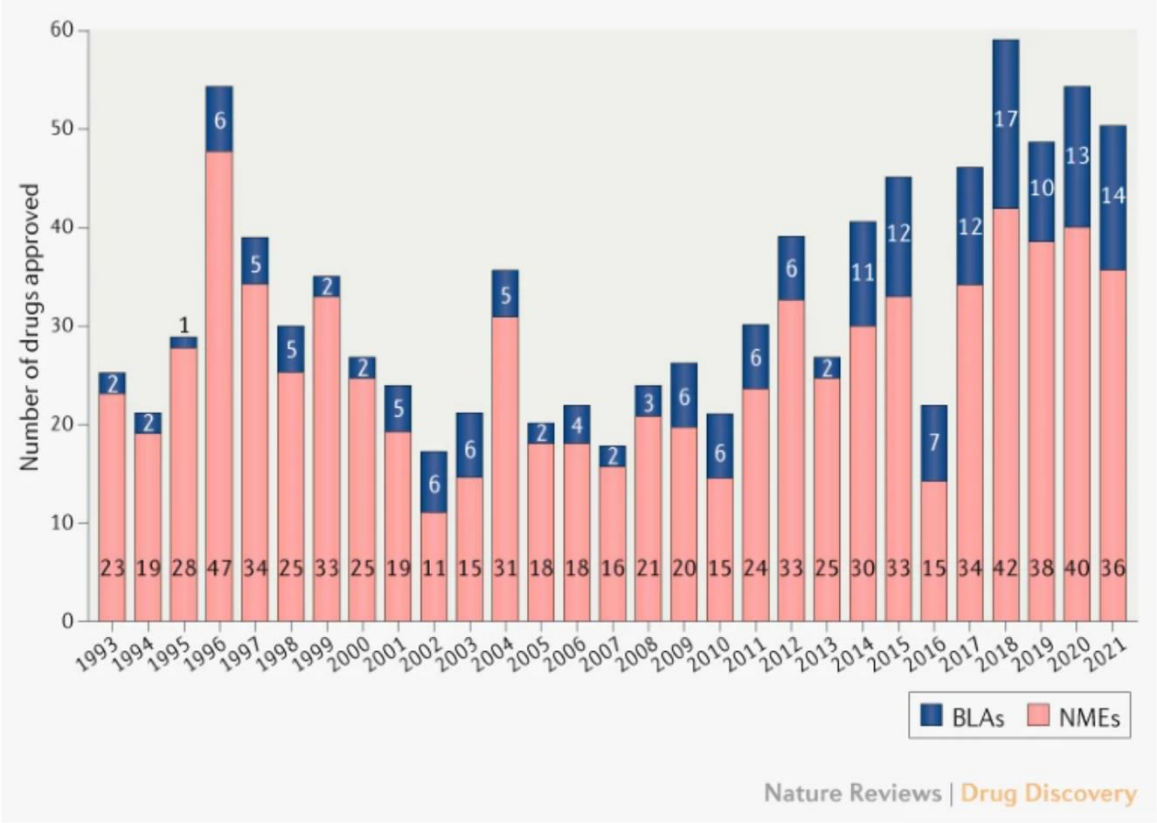
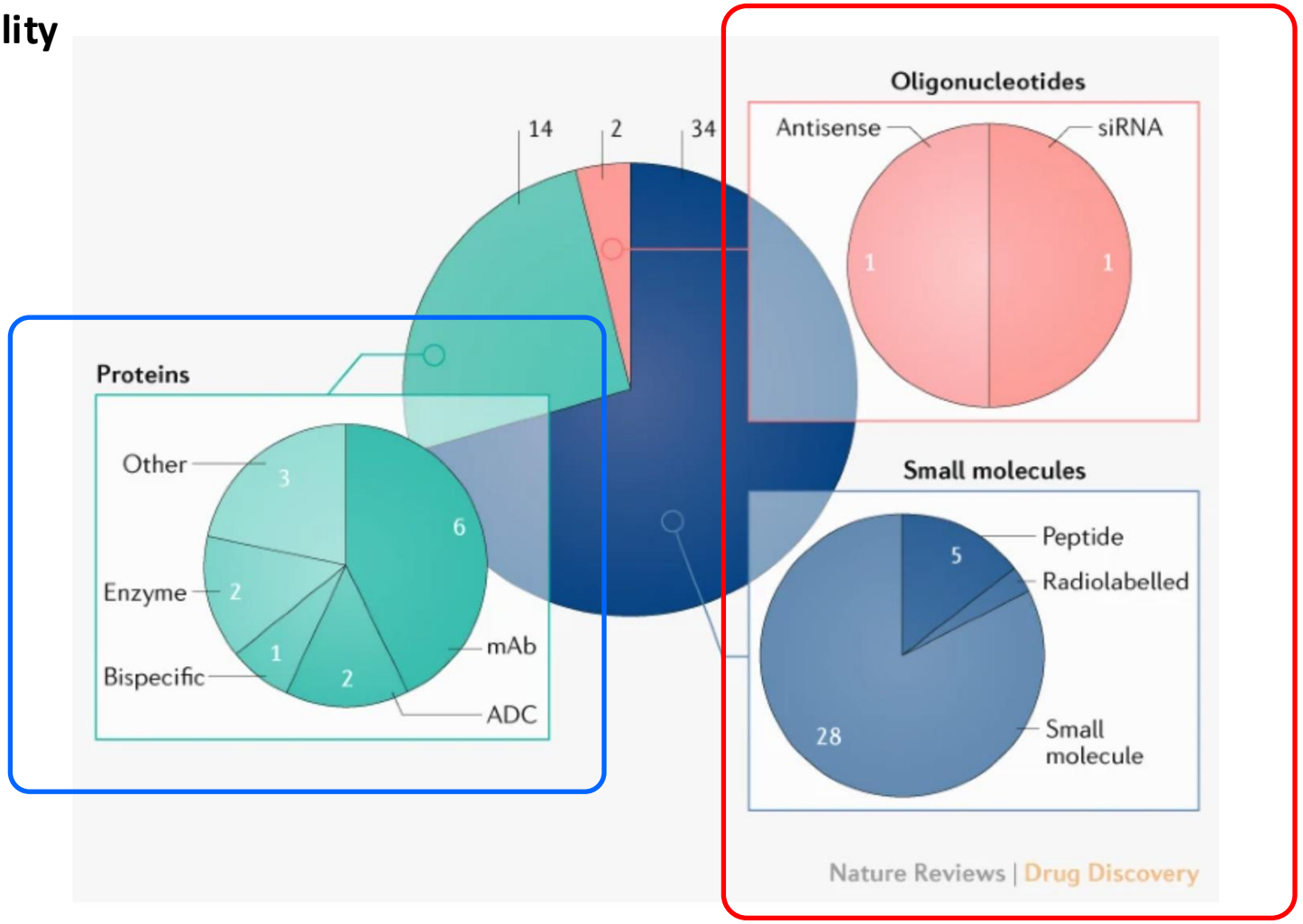


Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2021. Approvals by the Center for Biologics Evaluation and Research (CBER), for products such as vaccines and gene therapies, are not included in this drug count (see Table 2). Source: FDA.

Drug's modality



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FDA approvals 2020

Drug's modality

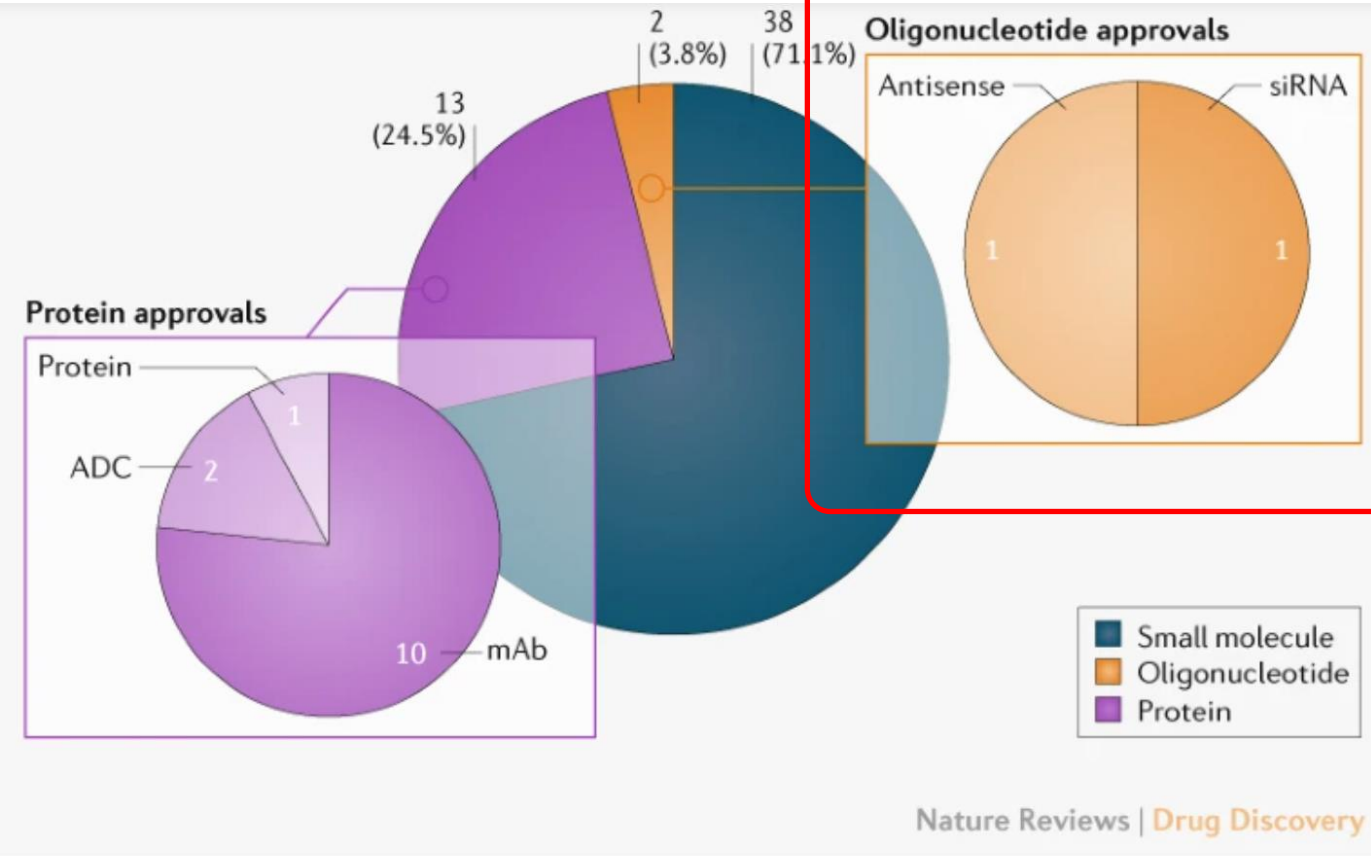

Fig. 3 | **CDER approvals by modality.** 'Small molecules' includes all peptides of up to 40 amino acids in length. Small molecules and oligonucleotides are approved as new molecular entities (NMEs). Protein-based candidates are approved through biologics license applications (BLAs). ADC, antibody–drug conjugate; mAb, monoclonal antibody. Source: *Nature Reviews Drug Discovery*.

FDA approvals 2019

Drug's modality

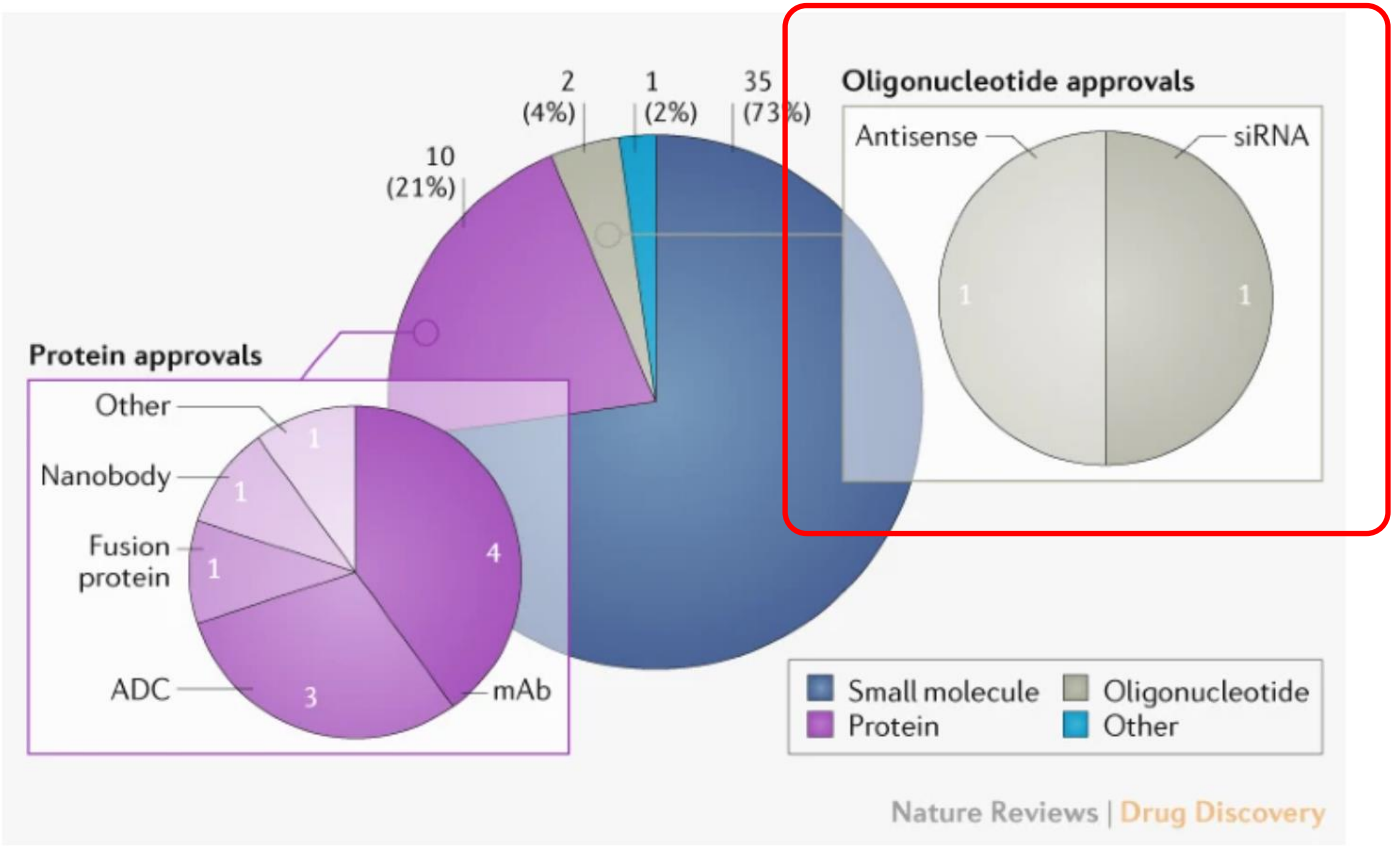

Fig. 4 | **CDER approvals by modality.** 'Small molecules' includes all peptides of up to 40 amino acids in length. Small molecules and oligonucleotides are approved as new molecular entities (NMEs). Protein-based candidates are approved as biologics license applications (BLAs). ADC, antibody–drug conjugate; mAb, monoclonal antibody. Source: *Nature Reviews Drug Discovery*.

FDA approvals 2018

This bumper approval crop follows on the heels of a few fruitful years for drug developers.

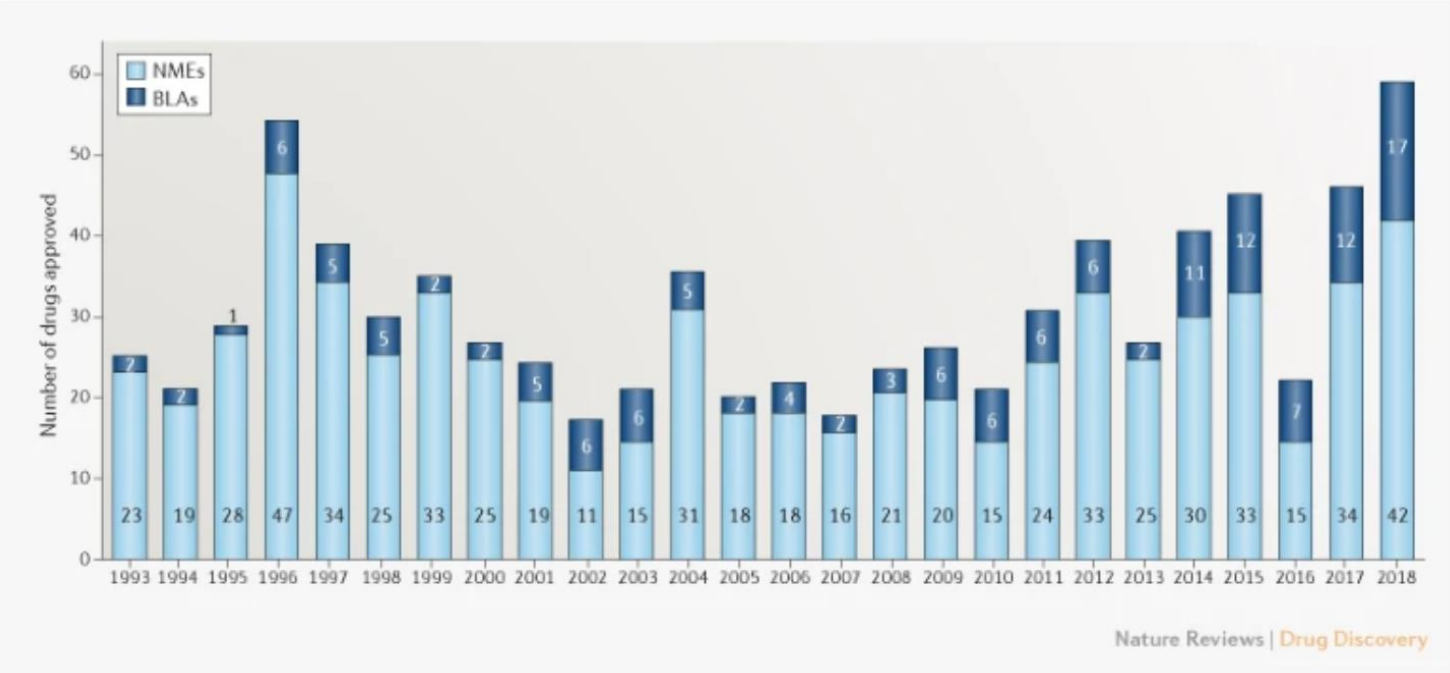

Fig. 1 | **Novel FDA approvals since 1993**. Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2018. Approvals of products such as vaccines by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count (see Table 2). Source: Drugs@FDA.

FDA approvals 2018

Table 4 | **Potential first approvals in 2018**

Drug name	Sponsor	Properties	Indication	Expected PDUFA date
Tezacaftor[a]	Vertex	CFTR corrector	Cystic fibrosis	February
Ibalizumab[a]	Theratechnologies	Anti-CD4 mAb	HIV	April
Fostamatinib	Rigel Pharmaceuticals	SYK inhibitor	Immune thrombocytopenic purpura	April
Andexanet alfa[a]	Portola Pharmaceuticals	Universal factor Xa inhibitor	Anticoagulant reversal	May
Erenumab	Amgen	Anti-CGRP receptor mAb	Migraine	May
Plazomicin[a]	Achaogen	Novel aminoglycoside antimicrobial	Antibacterial indications	June
Fremanezumab	Teva	Anti-CGRP mAb	Migraine	June
Tafenoquine[a]	GlaxoSmithKline	Antiparasitic DNA synthesis inhibitor	Malaria	July
Patisiran[a]	Alnylam Pharmaceticals	First RNAi drug	TTR-mediated amyloidosis	August
Galcanezumab	Eli Lilly	Anti-CGRP mAb	Migraine	September
Oliceridine[a]	Trevena	Biased μ-opioid receptor agonist	Acute pain	November
Larotrectinib[a]	Loxo Oncology	TRK inhibitor	NTRK-fusion solid tumours	NA (NDA completion in early 2018)

Source: BioMedTracker. CFTR, cystic fibrosis transmembrane conductance regulator; CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; NA, not applicable; NDA, new drug application; RNAi, RNA interference; TRK, tropomyosin receptor kinase; TTR, transthyretin. [a]Drug has breakthrough therapy designation.

FDA approvals 2018

From a scientific novelty perspective, 2018 saw the landmark approval of Alnylam's Patisiran as **the first small interfering RNA (siRNA) drug**, which uses RNA interference (RNAi) to downregulate protein expression.

Researchers first discovered the **RNAi pathway in 1998**, and a Nobel prize was awarded for this work in 2006. RNAi-based drugs harness the RNA-induced silencing complex to neutralize the expression of mRNA transcripts. Alnylam's patisiran is a double-stranded siRNA oligonucleotide that downregulates the expression of transthyretin (TTR), a transport protein that can misfold and aggregate to cause hereditary TTR-mediated amyloidosis.

The agency also approved Ionis Pharmaceuticals' Inotersen for the treatment of hereditary TTR-mediated amyloidosis in 2018. Inotersen is a single-stranded oligonucleotide that uses an **antisense mechanism** to lower TTR expression. It is the **fifth antisense drug** to gain approval.

Table 5.2 List of aptamers tested in clinical trials.

Aptamer	Target	Chemistry	Target class	Dissociation constant	Clinical indication	Clinical trial stage
NX1838	VEGF165	Modified RNA, PEGylated	Circulating	200 pM	AMD	FDA-approved
NX1975	PDGF	Modified DNA, PEGylated	Circulating	0.1 nM	AMD	Phase III
NOX-E36	CCL2	Spiegelmer, PEGylated	Circulating	1.4 nM	Type 2 diabetes mellitus	Phase II
NOX-A12	CXCL12	Spiegelmer, PEGylated	Circulating	200 pM	Multiple myeloma	Phase II
NU172	Thrombin	Unmodified DNA	Circulating	Not published	Surgical anticoagulation	Phase II
ARC1779	vWF	Modified DNA/RNA hybrid, PEGylated	Circulating	2 nM	von Willebrand disease	Phase II
REG1 system	FIXa	Modified RNA, PEGylated	Circulating	2.83 ± 0.4 nM	Surgical anticoagulation	Phase III
BAX499	TFPI	Modified DNA/RNA hybrid, PEGylated	Circulating	2.8 ± 0.3 nM	Hemophilia	Phase I
ARC1905	Human complement C5	Modified RNA, PEGylated	Circulating	2–5 nM	AMD	Phase II
AS1411	Nucleolin	Unmodified DNA	Intracellular	54.8 ± 7.3 nM	Acute myeloid leukemia	Phase II

First aptamer was approved in 2004.

NEWS IN BRIEF | 06 September 2023

FDA approves second RNA aptamer

UNIVERSITÀ DEGLI STUDI DI PADOVA

REVIEW ARTICLE OPEN

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RNA-based therapeutics: an overview and prospectus

Yiran Zhu[1], Liyuan Zhu[1], Xian Wang[2] and Hongchuan Jin[1]✉

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The growing understanding of RNA functions and their crucial roles in diseases promotes the application of various RNAs to selectively function on hitherto "undruggable" proteins, transcripts and genes, thus potentially broadening the therapeutic targets. Several RNA-based medications have been approved for clinical use, while others are still under investigation or preclinical trials. Various techniques have been explored to promote RNA intracellular trafficking and metabolic stability, despite significant challenges in developing RNA-based therapeutics. In this review, the mechanisms of action, challenges, solutions, and clinical application of RNA-based therapeutics have been comprehensively summarized.

Cell Death and Disease (2022)13:644; https://doi.org/10.1038/s41419-022-05075-2

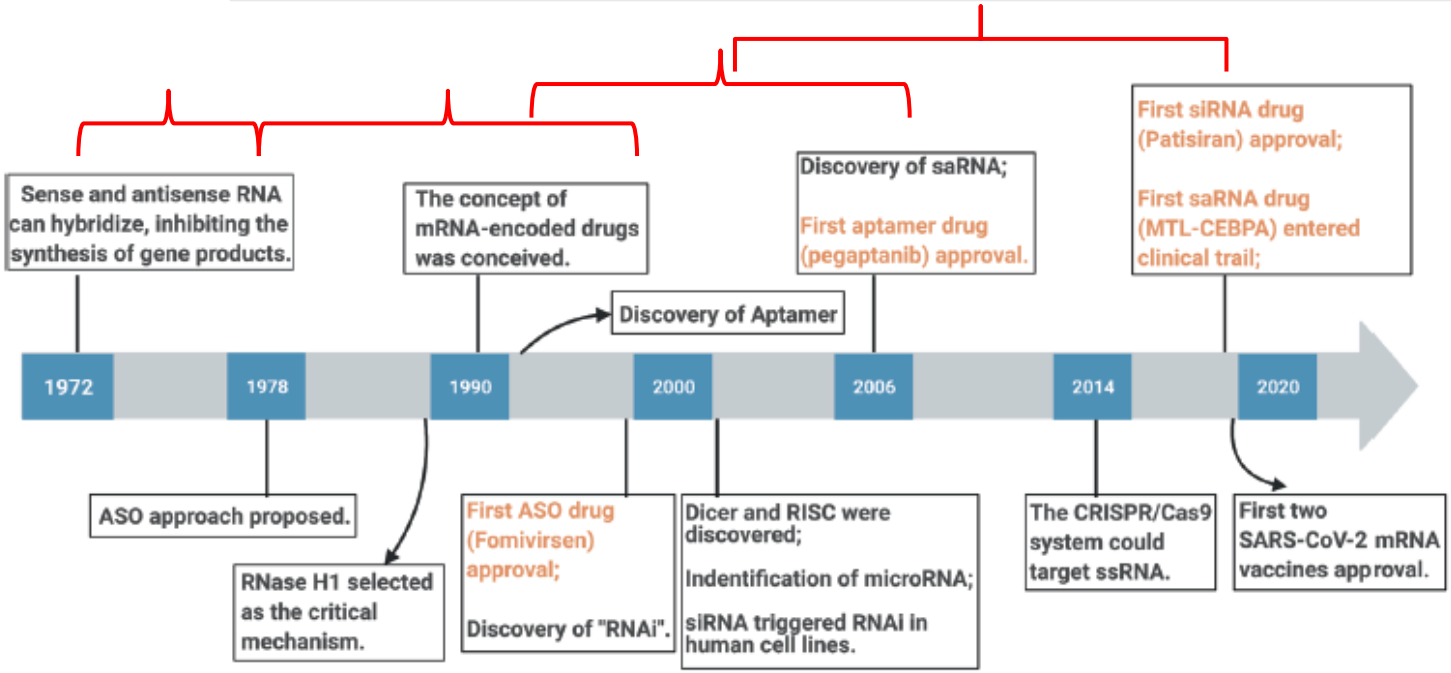


Fig. 1 An overview of major developments in the RNA-targeting field. A timeline of RNA-based technological advances, drug approvals and other important events are highlighted. Rapid development in the RNA-targeting field has been applied to treat rare and common diseases. ASOs antisense oligonucleotides, RNAi RNA interference, RISC RNA-induced silencing complex, siRNA small interfering RNA, saRNA small activating RNAs, ssRNA single-stranded RNA.

Table 2. RNA-based drugs with either FDA approval or in late phase 3 clinical trials.

RNA class	Drug	Alternative name	Sponsor	Indication	Target gene	Target organ	Chemical modifications or delivery method	Administration route	Updated states	Comments	References
ASO	Fomivirsen	Vitravene, ISIS 2922	Ionis Pharmaceuticals	Cytomegalovirus Retinitis, HIV Infections	*Immediate early region 2 (IE2)* mRNA	Eye	2′-H	Intravitreal	Completed NCT00002187, NCT00002355	The first FDA-approved ASO medication (1998), withdrawal in Europe and USA in 2002	[118, 119]
	Mipomersen	Kynamro™, ISIS 301012	Kastle and IonisTherapeutics	Hypercholesterolemia, Atherosderosis, Coronary Artery Disease	*Apolipoprotein B (ApoB)* mRNA	Liver	2′-MOE	Subcutaneous	Completed NCT01598948 NCT00607373 NCT01475825 NCT00770146 NCT00694109 NCT00794664 NCT00706849	The second-generation of ASOs ("Gapmers" ASO)	[120]
	Inotersen	ISIS 420915, Tegsedi, AKCEA-TTR-LRx	Ionis Pharmaceuticals	Hereditary ATTR Amyloidosis (hATTR)	*Hepatic transthyretin (TTR)* mRNA	Liver	2′-MOE	Subcutaneous	Completed NCT01737398		
	Nusinersen	ISIS 396443, Sprinraza, IONIS-SMN Rx, BIIB058	Ionis Pharmaceuticals and Biogen	Spinal Muscular Atrophy (SMA)	*Survival of motor neuron 2(SMN2)* pre-mRNA splicing (exon 7 inclusion)	Central nervous system	2′-MOE, Fully modified	Intrathecal	Completed NCT02292537	Approved in 2016	[18, 121]
	Eteplirsen	AVI-4658, EXONDYS 51®	Sarepta Therapeutics	Duchenne Muscular Dystrophy (DMD)	*DMD* pre-mRNA splicing (exon 51 skipping)	Muscule	2′-MOE, PMO	Intravenous	Completed NCT02255552	The third-generation of ASO medications with advanced chemical modifications	[17, 121]
	Golodirsen	SRP-4053,Vyondys 53™	Sarepta Therapeutics	Duchenne Muscular Dystrophy (DMD)	*DMD* pre-mRNA splicing (exon 53 skipping)	Muscle	2′-MOE, PMO	Intravenous	Recruiting NCT02500381		[122]
	Viltolarsen	Viltepso, NS-065, NCNP-01	NS Pharma	Duchenne Muscular Dystrophy (DMD)	*DMD* pre-mRNA splicing (exon 53 skipping)	Muscle	2′-MOE, PMO	Intravenous	Recruiting NCT04768062 NCT04687020 NCT04060199		[123]
	Casimersen	SRP-4045, Amondys 45™	Sarepta Therapeutics, Inc.	Duchenne Muscular Dystrophy (DMD)	*DMD* pre-mRNA splicing (exon 45 skipping)	Muscle	PMO	Intravenous	Recruiting NCT03532542 NCT02500381		[124]
RNAi	Patisiran	ALN-TTR02, ONPATTRO™	Alnylam Pharmaceuticals	hATTR	*TTR* mRNA	Liver	PS, 2′-O-Me, 2′-F (LNP)	Intravenous	NCT03862807, NCT01960348	The first siRNA drug approved by FDA (2018)	[129]
	Givosiran	ALN-AS1, GIVLAARI	Alnylam Pharmaceuticals	Acute Hepatic Porphyria	*Aminolevulinate synthase 1(ALAS1)* mRNA	Liver	PS, 2′-O-Me, 2′-F GalNAc	Subcutaneous	NCT03338816	The second siRNA drug approved by FDA (2019)	[134]
	Lumasiran	ALN-GO1, OXLUMO	Alnylam Pharmaceuticals	Primary Hyperoxaluria Type 1 (PH1)	*Hydroxyacid oxidase 1 (HAO1)* mRNA	Liver	PS, 2′-O-Me, 2′-F GalNAc	Subcutaneous	Phae III active; NCT03905694 NCT03681184 NCT04152200	The third siRNA drug approved by FDA (2020)	[135]
	Inclisiran	ALN-PCSSC, LEQVIO	Alnylam and Novartis Pharmaceuticals	Hypercholesterolemia, Atherosderotic Cardiovascular disease, Renal impairment	Proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA	Liver	PS, 2′-O-Me, 2′-F GalNAc	Subcutaneous	Phase III completed; NCT03399370 NCT03400800 NCT03397121	Expand siRNA's clinical portfolio beyond just orphan diseases.Provide sustained reductions in low-density lipoprotein (LDL) cholesterol levels with infrequent dosing (every 6 months).	
	Vutrisiran	ALN-TTRSC02	Alnylam Pharmaceuticals	hATTR	*TTR* mRNA	Liver	PS, 2′-O-Me, 2′-F GalNAc	Subcutaneous	Phae III active; NCT04153149 NCT03759379	May prove to be a more clinically utilize, effective treatment	

Table 2. continued

RNA class	Drug	Alternative name	Sponsor	Indication	Target gene	Target organ	Chemical modifications or delivery method	Administration route	Updated states	Comments	References
										option for hATTR than patisira	
	Fitusiran	ALN-AT3SC	Alnylam Pharmaceuticals and Sanofi Genzyme	Hemophilia A / B	*Antithrombin* mRNA	Blood	PS, 2′-O-Me, 2′-F GalNAc	Subcutaneous	Phase III completed; NCT03974113 NCT03417102		
	Nedosiran	DCR-PHXC	Dicerna Pharmaceuticals	Primary Hyperoxaluria	*Hepatic lactate dehydrogenase* mRNA	Liver	GalNAc	Subcutaneous	Phase III enrolling by invitation; NCT04042402	Compare with Lumasiran,it will have a potentially wider scope, since it is not limited to just PH1 patients.	
	Teprasiran	QPI-1002	Quark Pharmaceuticals	Cardiac surgery	*p53* mRNA	Kidney	2′-O-Me	Intravenous	Phase III completed; NCT02610296	The first systemically administered siRNA drug to enter human clinical trials	
	QPI-1007		Quark Pharmaceuticals	Primary angle-closure glaucoma	*Caspase 2* mRNA	Eye	2′-O-Me	Intravitreal	Phase II/III terminated: NCT02341560		
	Tivanisiran	SYL-1001	Sylentis, S.A.	Dry eye disease	*Transient receptor potential cation channel subfamily V member 1 (TRPV1)* mRNA	Eye	Unmodified	Topical eye drop	Phase III completed; NCT03108664		
Aptamer	Pegaptanib	Macugen®	Pfizer	Diabetic Macular Edema	VEGF (165 isoform)	Eye	Pegylated, all PO, 2′-F, and 2′-OMe; G and A methylated	Intravitreal injection	Phase IV Completed; NCT01486238 NCT01486238 NCT00406107 NCT00324116		[146]
mRNA vaccine	BNT162b2	Comirnaty®	BioNTech and Pfizer	Coronavirus disease 2019 (COVID-19)	Encodes the SARS-CoV-2 spike protein	Immune system	Nucleoside-modifed, lipid nanopartide-formulated	Interventional	Completed NCT04816669 NCT04887948 NCT04713553 NCT05030974	The first two FDA-approved SARS-CoV-2 vaccines with >94% effectiveness in phase III clinical trial	[147]
	mRNA-1273		Moderna Therapeutics	COVID-19	Encodes the SARS-CoV-2 spike protein	Immune system	Lipid nanopartide-formulated	Interventional	Completed NCT05030974		[148]

Approved at the moment:

14 ASOs
6 siRNAs
2 aptamers

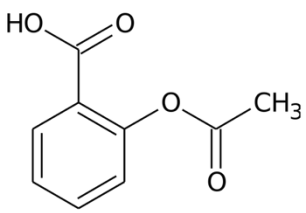
Scoperta e sviluppo del farmaco

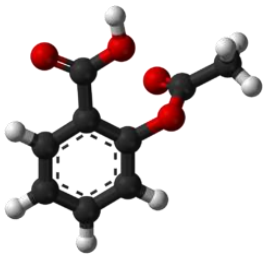
Vintage drugs

NME (Nuove Entità Molecolari)

Es. aspirina

- Piccola molecola
- 180 Da
- 21 atomi
- non immunogenica
- Chimicamente stabile



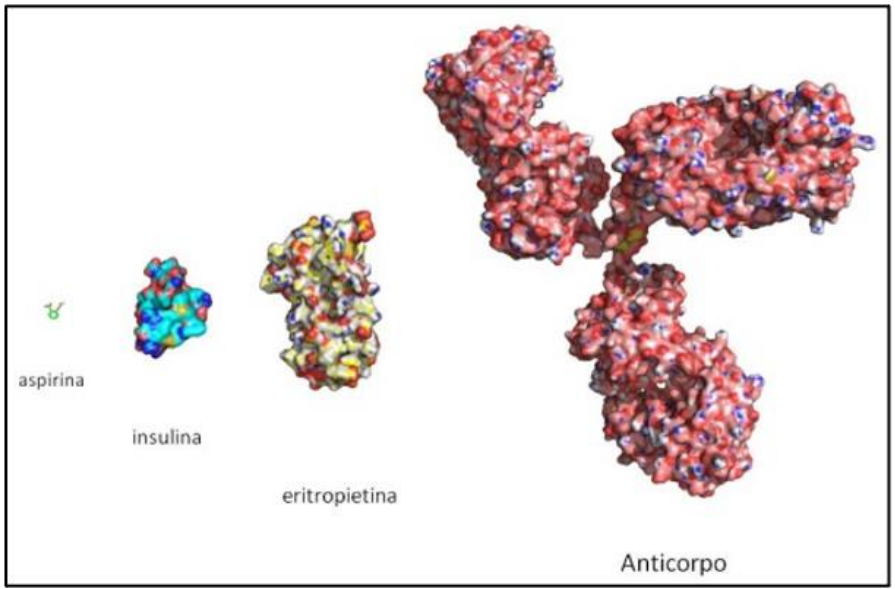


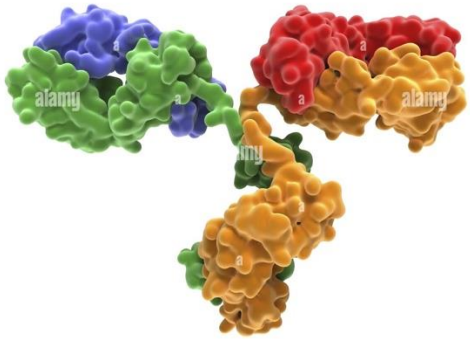
New age drugs

BLA (farmaci biotech)

Es. anticorpo monoclonale (mAb)

- Macromolecola
- 150 000 Da
- 20 000 atomi
- Immunogenica
- Chimicamente instabile





Scoperta e sviluppo del farmaco

Vintage drugs

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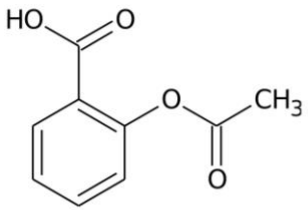
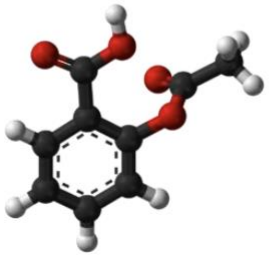
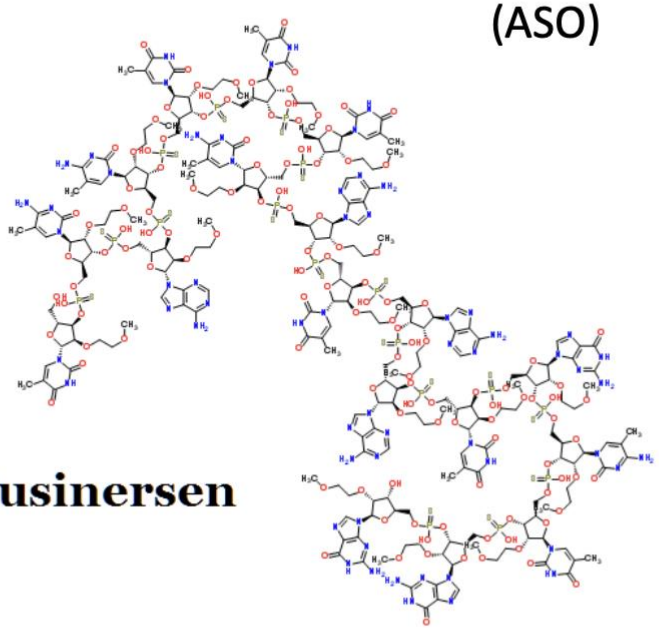




New age drugs

NME (Nuove Entità Molecolari)

Oligonucleotide AntiSenso (ASO)



Nusinersen

Small molecules
can be considered
"**vintage drugs**"



Synthetic molecules

Known and well characterized chemical structure

New generation chemical entities !!!

Protein-based biologics

Oligonucleotides:

- **Aptamers**
- **Antisense oligonucleotides (ASOs)**
- **Small interfering (siRNAs)**