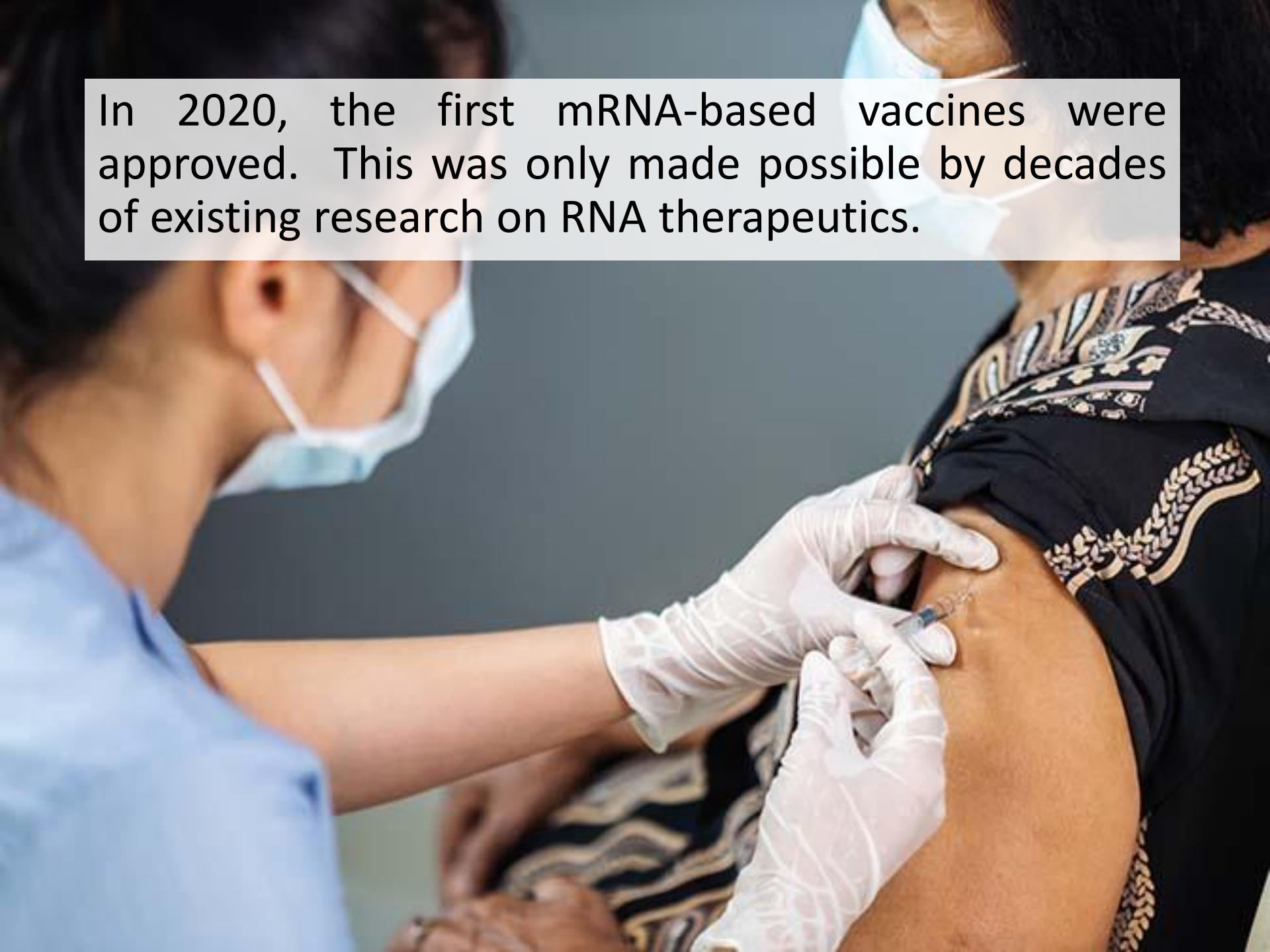
The limitless world of RNA therapeutics

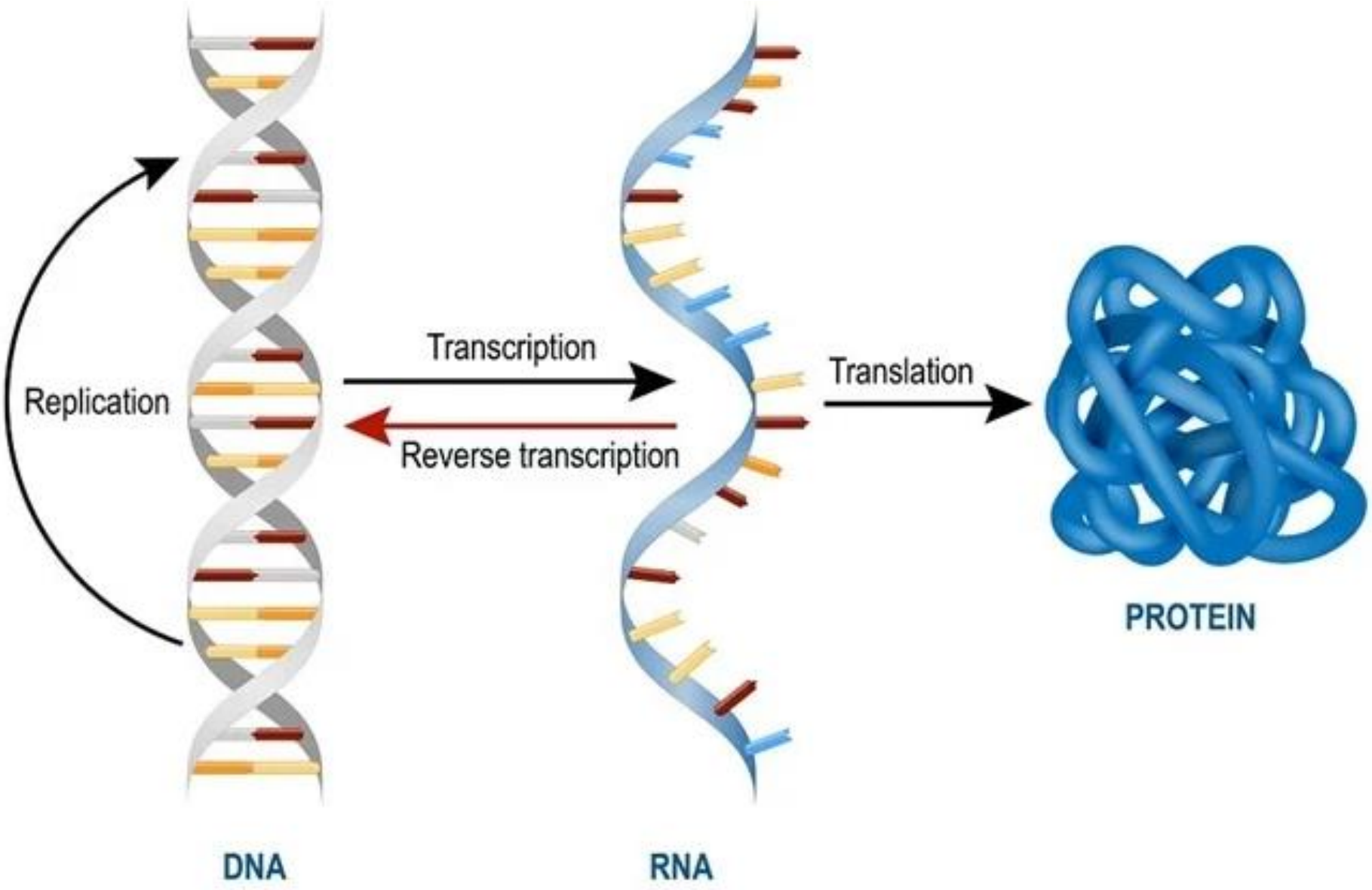
Karen Anthony
@Weekademia



In 2020, the first mRNA-based vaccines were approved. This was only made possible by decades of existing research on RNA therapeutics.

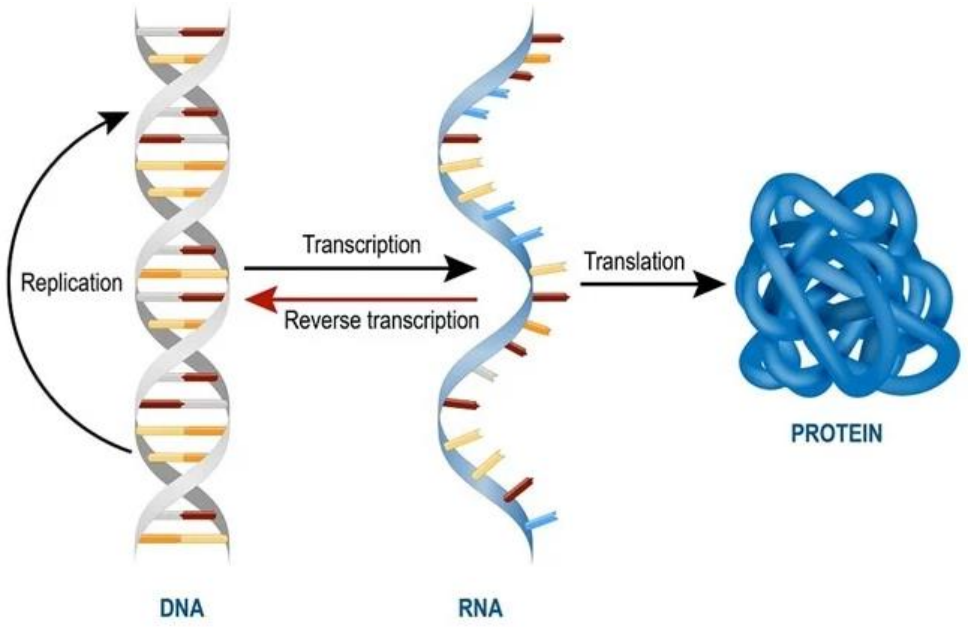
- What is RNA?
- A brief history of RNA therapeutics
- Highlight their use to treat rare genetic diseases

You will learn that RNA drugs are being developed for just one person, n=1 therapy

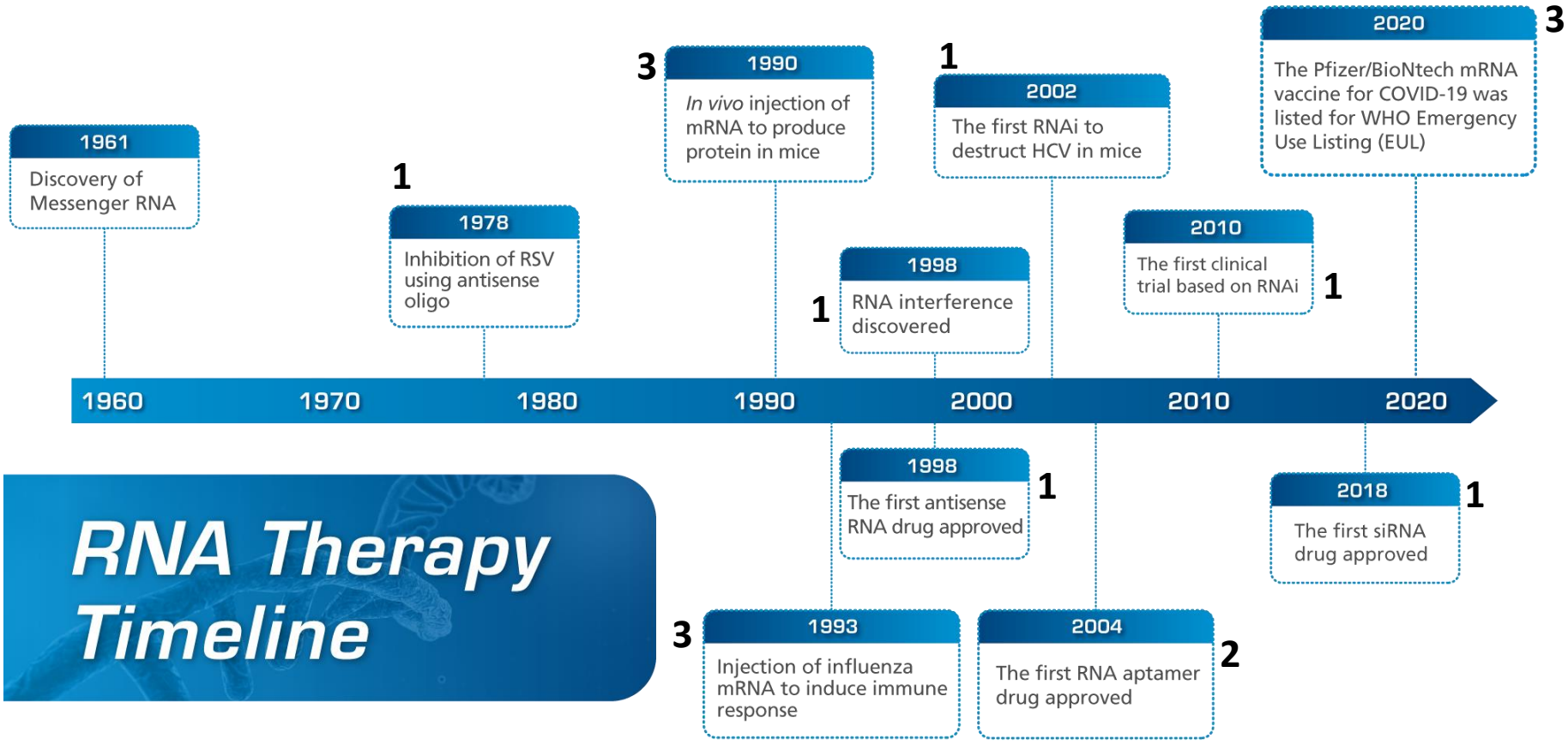

Replication
Transcription
Reverse transcription
Translation
PROTEIN
DNA
RNA

Three types of RNA drugs

1. Target nucleic acid
2. Target protein
3. Make proteins



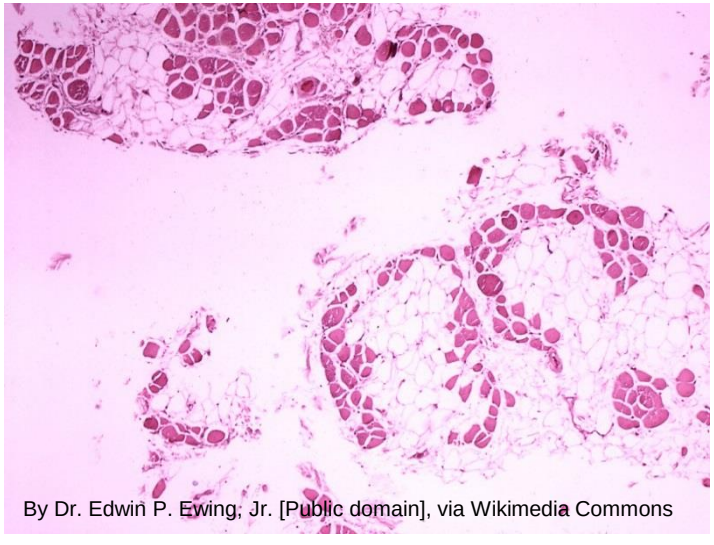
RNA drugs are not new



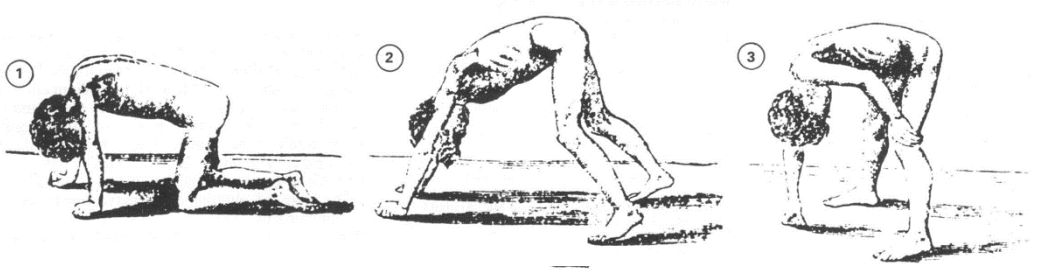
1. Target nucleic acid (13 drugs approved since 1998, four for Duchenne muscular dystrophy)
2. Target protein (one drug approved since 2004)
3. Make proteins (two drugs approved since 2020)

Duchenne muscular dystrophy (DMD)

- Fatal X-linked neuromuscular disorder
- Caused by mutations in the *DMD* gene resulting in a lack of dystrophin in skeletal muscles
- Patients progressively develop muscle weakness in the early years of life
- Boys lose ambulation by 10-12 years and typically die in their 20-40s
- 30% have learning difficulties

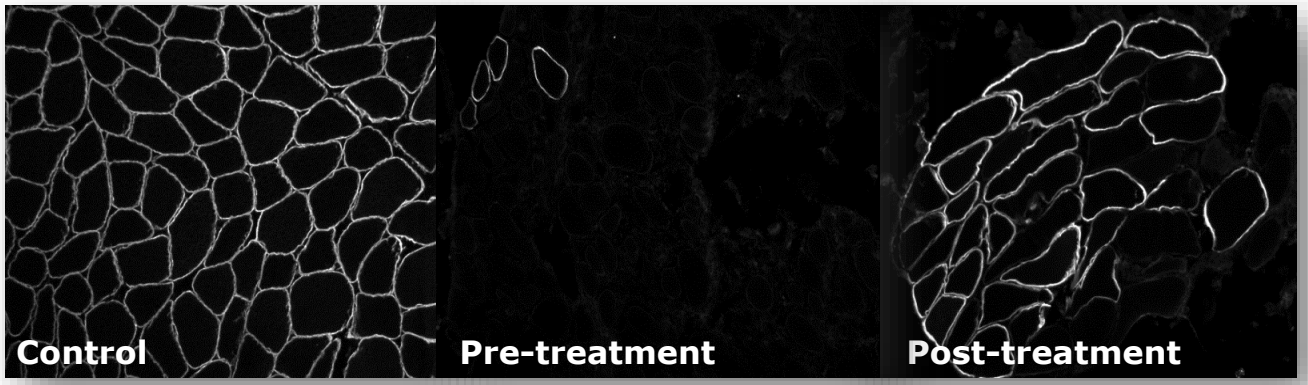


By Dr. Edwin P. Ewing, Jr. [Public domain], via Wikimedia Commons



Gowers WR. Clinical lecture on pseudohypertrophic muscular paralysis. Lancet 1879;ii,73-5.

Antisense Oligonucleotides for DMD



Lancet: **378**, 595–605 (2011)

Mutation specific approach for 13% of DMD patients

UCL GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

SAREPTA THERAPEUTICS

THE LANCET

Volume 378, Issue 9791, 13–19 August 2011, Pages 595–605

Articles

Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study

Sebahattin Cirak, MD[a, ‡], Virginia Arechavala-Gomeza, PhD[a, ‡], Michela Guglieri, MD[b], Lucy Feng, PhD[a], Silvia Torelli, PhD[a], Karen Anthony, PhD[a], Stephen Abbs, PhD[c], Prof Maria Elena Garralda, MD[d], John Bourke, MD[b], Prof Dominic J Wells, VetMB PhD[e], Prof George Dickson, PhD[f], Matthew JA Wood, [illegible] PhD[g], Prof Steve D Wilton, PhD[h], Prof Volker Straub, MD[b], Prof Ryszard Kole, PhD[i], Stephen B Shrewsbury, MD[j], Prof Caroline Sewry, PhD[a, j], Jennifer E Morgan, PhD[a], Prof Kate Bushby, MD[b],

Show more

MUSCLE BOOST: A drug that bypasses faulty genes has given new hope to children with a muscle-wasting disease. The treatment [illegible]cts of Duchenne [illegible]y (DMD) by repairing research shows. The [illegible]tential to reduce the [illegible] DMD enough to prevent severe disability throughout the body. [illegible]nts aged five to [illegible]injected drug in [illegible]ls in London, The [illegible]l reports today.

‘He was like a different child’

‘Today we can say with confidence that we’re going to win the battle’

THE TIMES | Monday July 25 2011 2GM

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News

Genetic patch ‘slows progress of killer muscular dystrophy’

HEALTH

Duchenne drug ‘breakthrough’

By Steve Connor
SCIENCE EDITOR

Scientists have claimed a “significant breakthrough” in the fight against Duchenne muscular dystrophy, a progressive muscle-wasting disease affecting 1,500 boys in Britain.

Those with the disorder carry gene mutations and are unable to produce a key muscle protein, dystrophin.

A clinical trial of a drug called AVI-4658 showed it was possible to boost dystrophin levels by 18 per cent – and at high doses about 80 per cent of patients responded to treatment.

More trials will show if it prevents muscle degeneration and deterioration.

Anecdotes are great – if they convey data accurately

Ben Goldacre

Channel 4 reported that a study in the Lancet showed a new drug had reduced the symptoms of Duchenne's muscular dystrophy. Unfortunately, the study shows no such thing

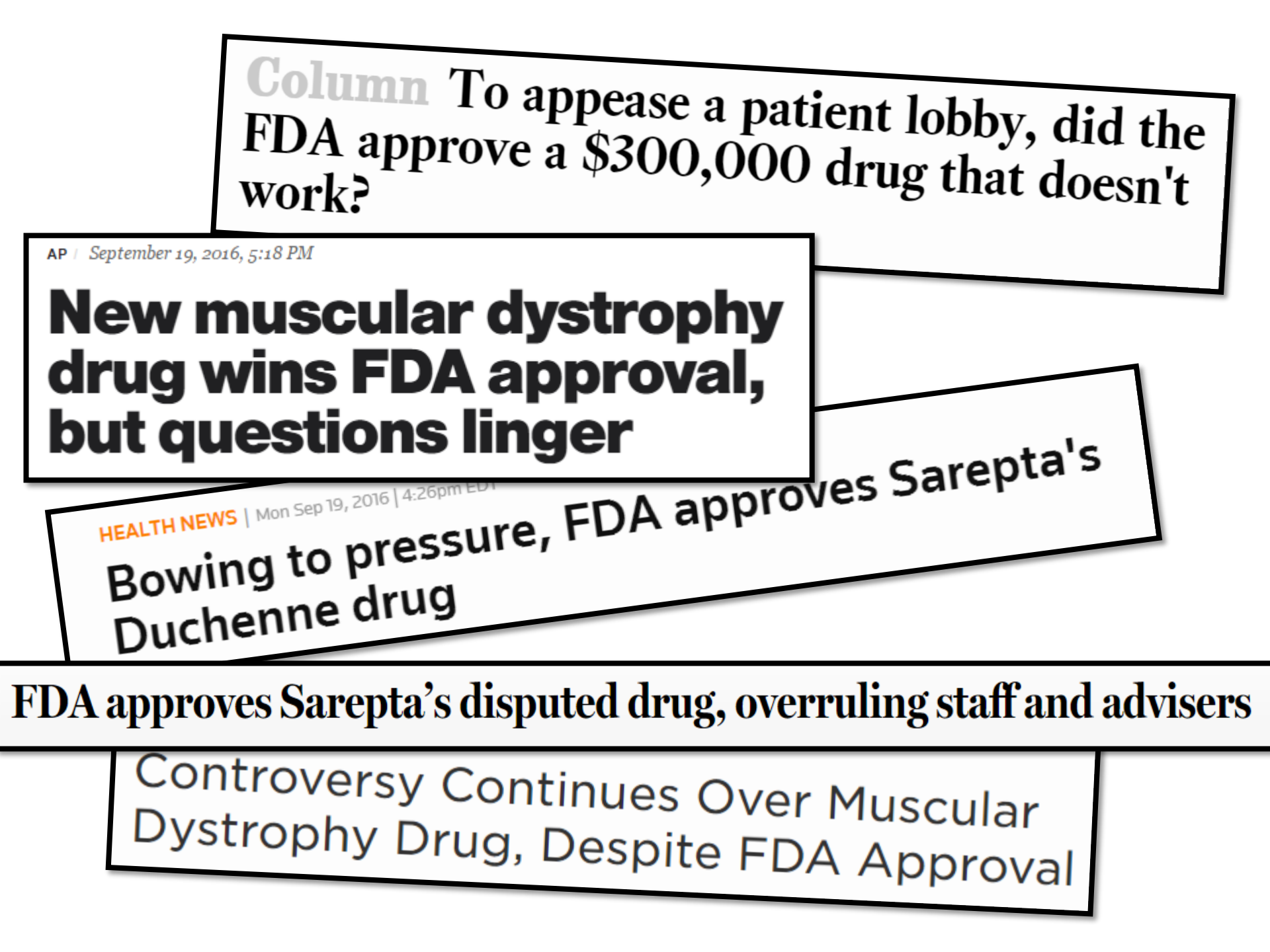
In 2016 FDA approved the first therapy for Duchenne muscular dystrophy (DMD)

EXONDYS 51™ (eteplirsen)

The 4th RNA therapeutic to be approved

“Has the Applicant provided substantial evidence from adequate and well controlled studies that Eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit?”

Advisory committee voted 6-7 against


Column To appease a patient lobby, did the FDA approve a $300,000 drug that doesn't work?
AP / September 19, 2016, 5:18 PM
New muscular dystrophy drug wins FDA approval, but questions linger
HEALTH NEWS | Mon Sep 19, 2016 | 4:26pm EDT
Bowing to pressure, FDA approves Sarepta's Duchenne drug
FDA approves Sarepta's disputed drug, overruling staff and advisers
Controversy Continues Over Muscular Dystrophy Drug, Despite FDA Approval

jenn mcnary
@jennmcnary
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Boys gripping their speeches in their hands, waiting for their turn - what I'll remember most #makeduchennehistory

1980s-era advocacy likened to AIDS/HIV crisis

PP MD
Parent Project MD
@ParentProjectMD
Following

#MakeDuchenneHistory The UK parents speak - we have traveled this far for .9% dystrophin. This small amount matters

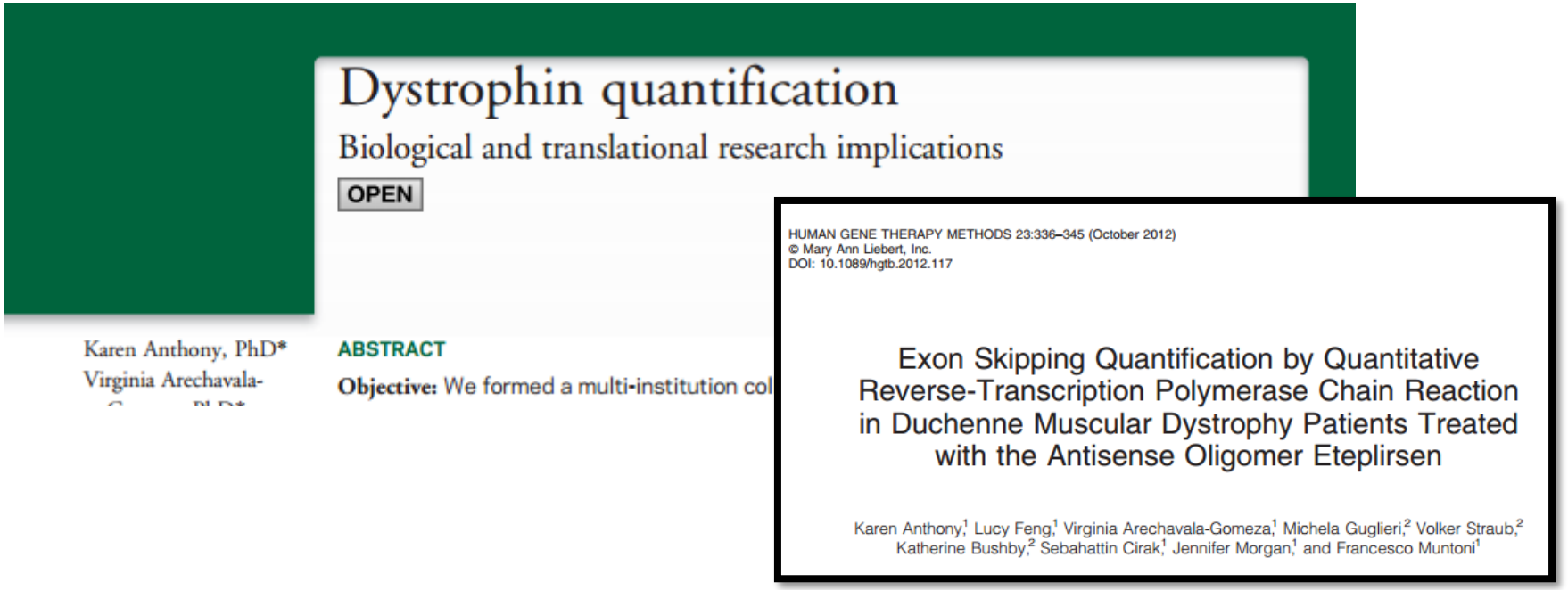
Dr. Mendell– 3900 injections. Not a single case of adverse side effects. #eteplirsen #MakeDuchenneHistory

THE RACE TO YES
The Race To Yes @TheRacetoYes · Apr 25
"You should approve #eteplirsen. @US_FDA please don't let me die early." - Billy #MakeDuchenneHistory

https://www.statnews.com/pharmalot/2016/05/24/senators-urge-fda-approve-sarepta-drug-duchenne/ via @statnews

Accelerated approval hinges on the accurate quantification of low levels of dystrophin

Neurology. 2014 Nov 25; 83(22): 2062–2069.



Multi-institution collaborations

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

Compared, standardised and validated dystrophin quantification methods to reach a consensus FDA happy with

Presented to FDA and heavily cited in FDA review documents

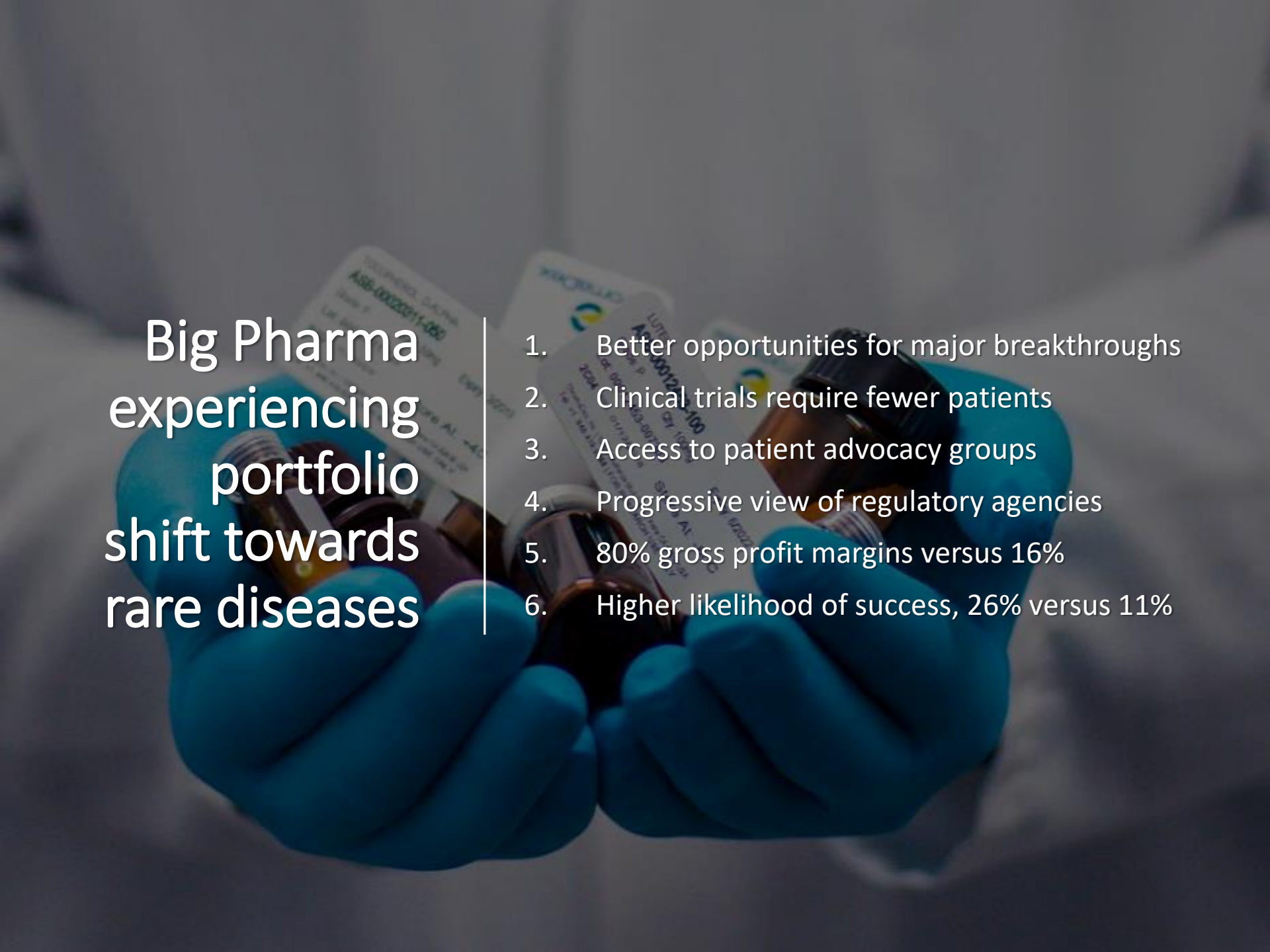
2016 13%

2019 8%

2020

2021 8%

~30% of DMD patients in total



Big Pharma experiencing portfolio shift towards rare diseases

1. Better opportunities for major breakthroughs
2. Clinical trials require fewer patients
3. Access to patient advocacy groups
4. Progressive view of regulatory agencies
5. 80% gross profit margins versus 16%
6. Higher likelihood of success, 26% versus 11%

Patients do not always have the same mutation, for some diseases this matters

Disease	Do patients have the same mutation?	One antisense RNA drug can treat…
Spinal muscular atrophy	No	90%
Duchenne	No	2-13%
Others	Yes/no	One person!

IS IT WORTH IT?

Milasen: idea to injection in 10 months

https://www.milasmiracle.org/milasen

1. Genetic diagnosis
2. Drug design
3. Test in patient cell lines
4. Toxicity check in rats
5. Treat

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

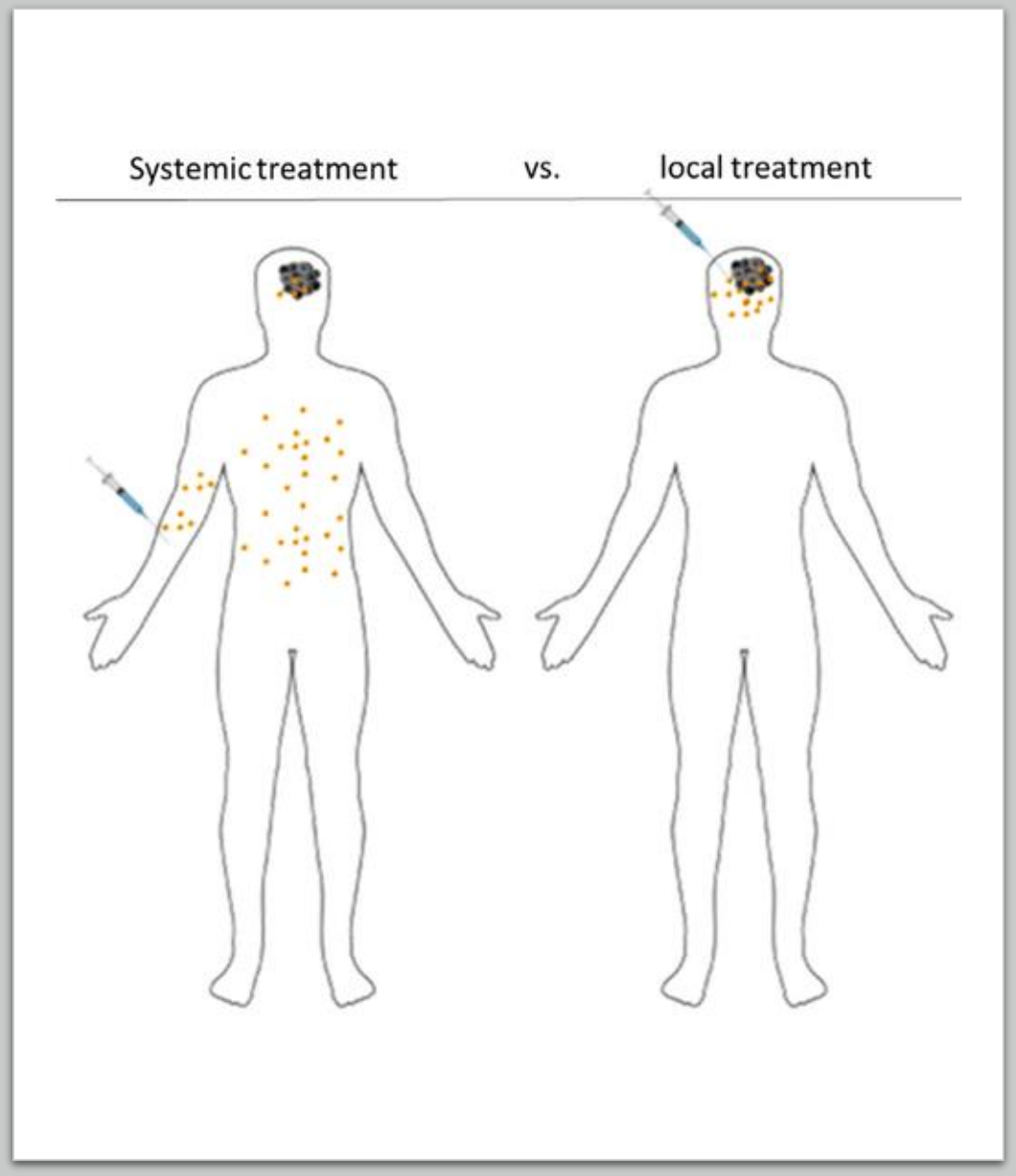
J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkovska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, and T.W. Yu

SUMMARY

Genome sequencing is often pivotal in the diagnosis of rare diseases, but many of these conditions lack specific treatments. We describe how molecular diagnosis of a rare, fatal neurodegenerative condition led to the rational design, testing, and manufacture of milasen, a splice-modulating antisense oligonucleotide drug tailored to a particular patient. Proof-of-concept experiments in cell lines from the patient served as the basis for launching an "N-of-1" study of milasen within 1 year after first contact with the patient. There were no serious adverse events, and treatment was associated with objective reduction in seizures (determined by electroencephalography and parental reporting). This study offers a possible template for the rapid development of patient-customized treatments. (Funded by Mila's Miracle Foundation and others.)

Eye and brain diseases provide opportunity

- Local treatment
- Low treatment frequency



Dutch Centre for RNA therapeutics

LUMC

Radboudumc

Erasmus MC
Universitair Medisch Centrum Rotterdam

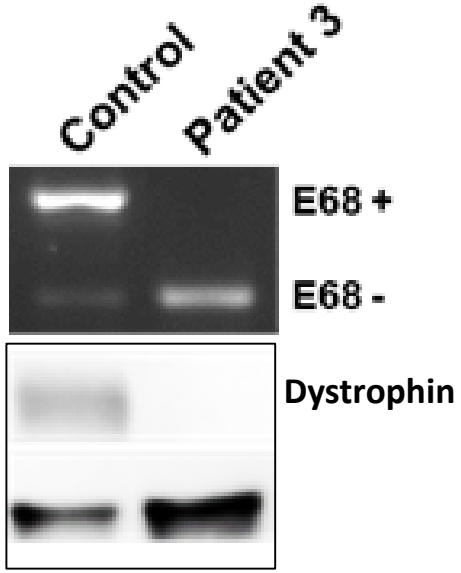
DCRT
Dutch
Center for
RNA
Therapeutics

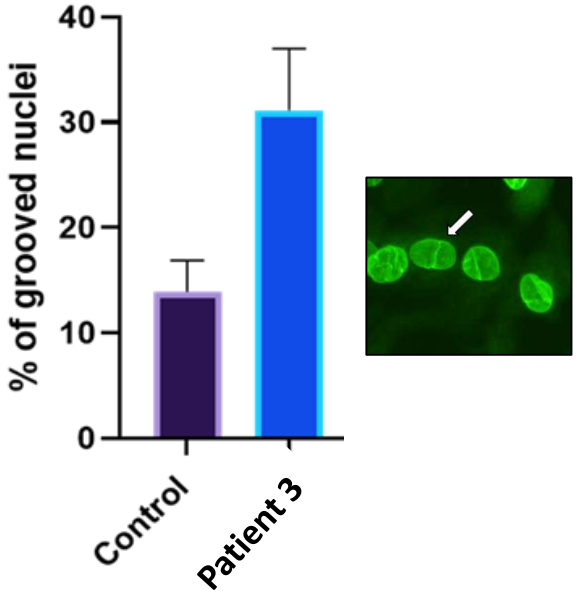
Annemieke Aartsma-Rus, Willeke Roon-Mom, Rob Collin, Linda van der Graaf and Ype Elgersma

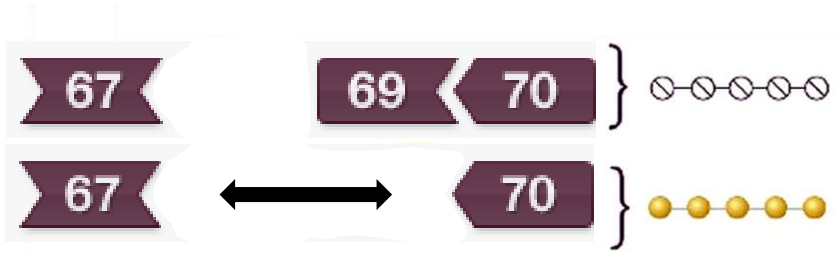
- Non-profit consortium
- "Academic Pharma"
- Develop tailor-made RNA therapy for patients with ultra rare genetic mutations focusing on eye and the central nervous system
- Develop therapies in-house and deliver to patients at cost
- https://www.rnatherapy.nl/

Relevant work at UoN

- 1st characterisation of ultra rare DMD mutation(s)







AFMTÉLÉTHON
CURE THROUGH INNOVATION

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Acknowledgements

- Centre for Physical Activity and Life Sciences (PALS)
  - Molecular Bioscience Research Group

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- **Amanda Ash**
- **Dr Lee Machado**

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University of Northampton

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MRC Centre for Neuromuscular Diseases