Leiden University Medical Center

ERICA

A roadmap to tailored genetic interventions in patients with neurodegenerative disorders

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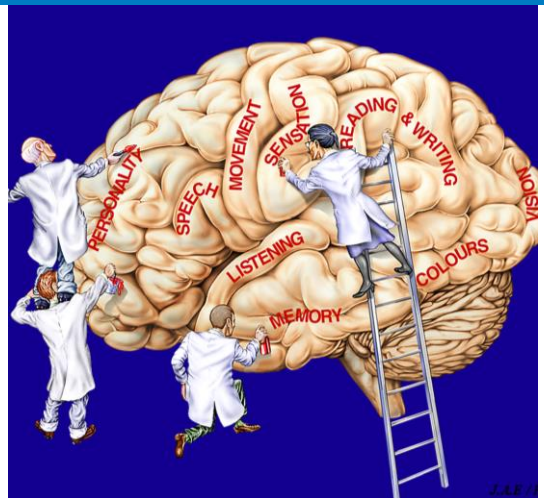
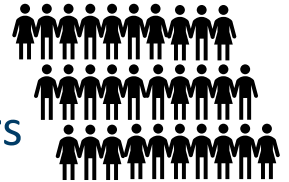
Leiden University Medical Center
Dutch Center for RNA Therapeutics
The Netherlands



Development an RNA targeting therapy ….

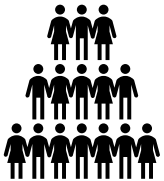
How will you develop this towards the first in human studies????

From rare to nano-rare diseases it gets more difficult



Outline drug development pipeline

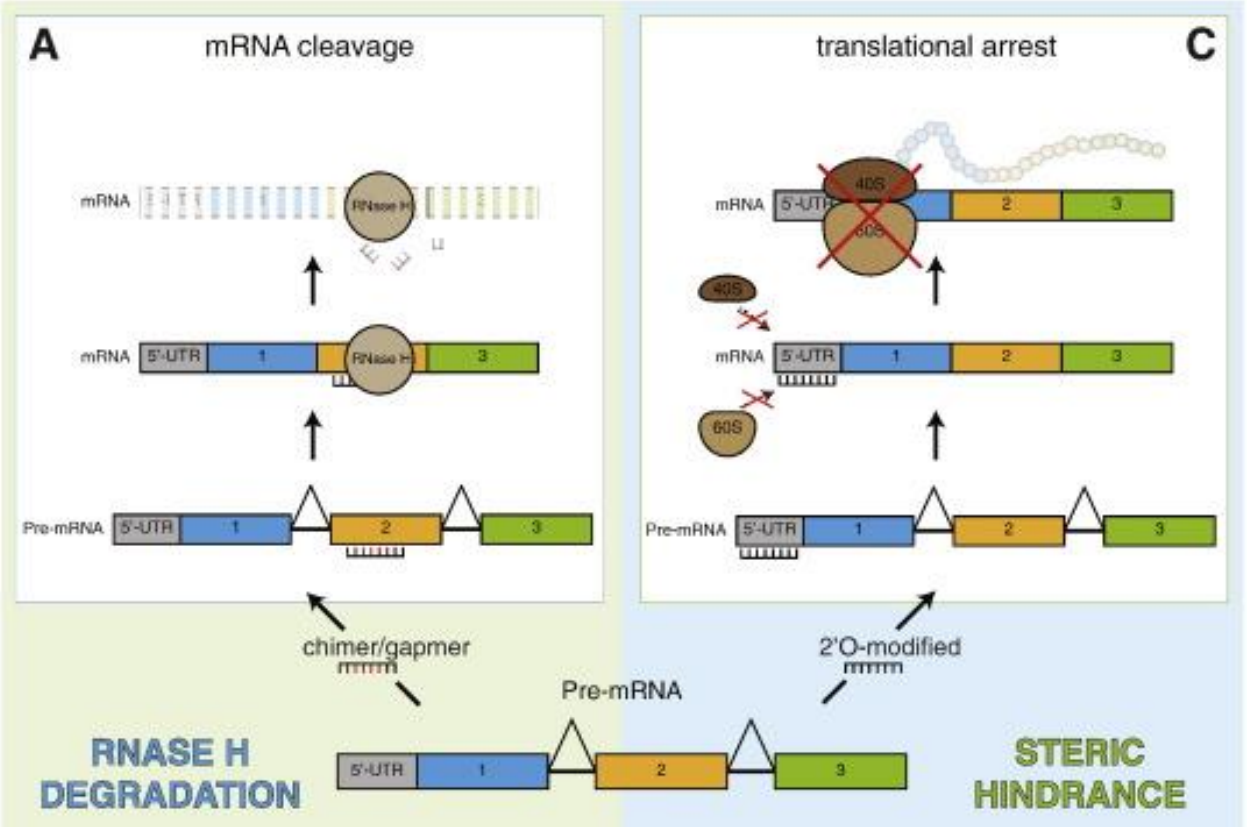
- Example of a trial that combines 3 neurodegenerative PolyQ disorders
- Example of SCA3 ASO program in the US under the Right to Try Act



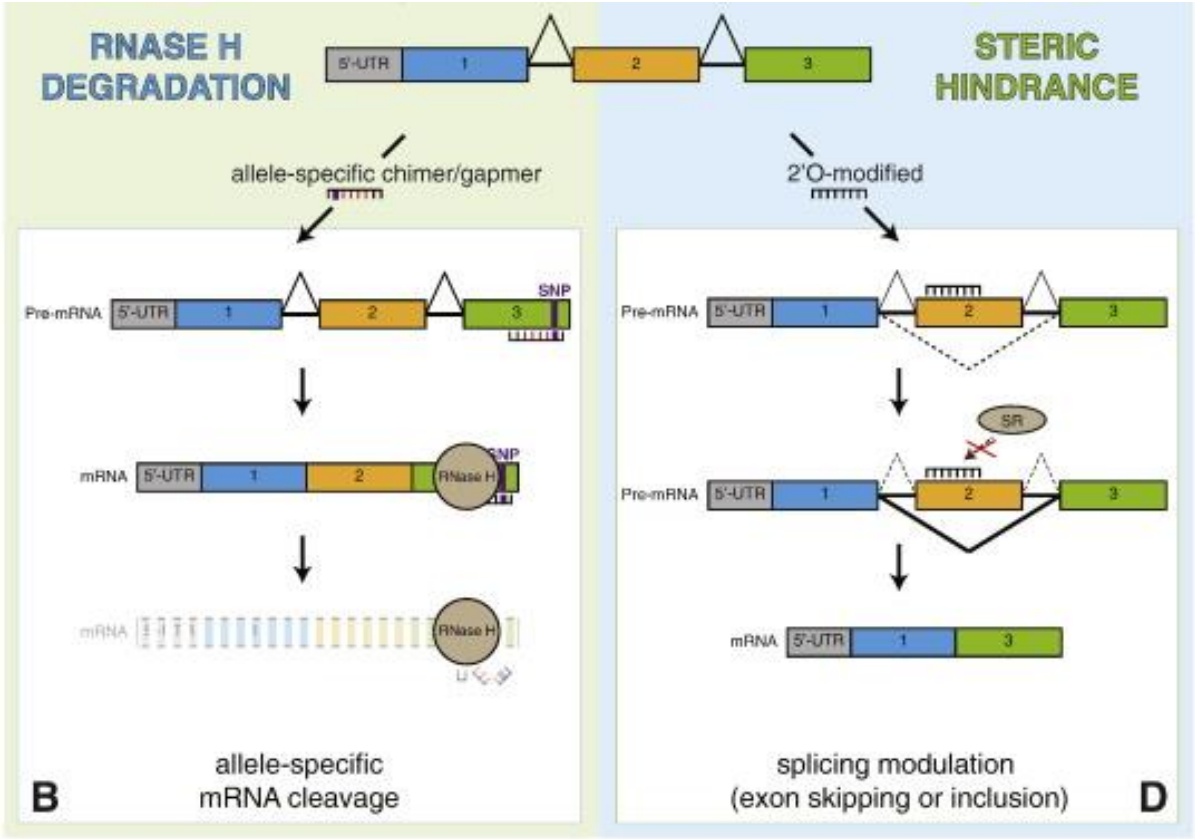
- USA n=1 pipeline from lab to patient

- EU/NL n=1 pipeline from lab to patient

Antisense oligonucleotide mechanism of action



Antisense oligonucleotide mechanism of action



Evers *et al.* 2015 ADDR

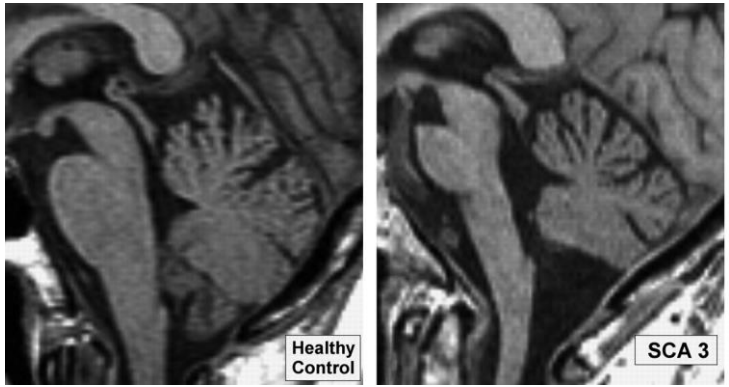
Spinocerebellar ataxia type 3 (SCA3)

SCA3:

- Autosomal dominant
- Prevalence ~ 1 : 100.000
- Onset age: 37 years
- Neurodegenerative

Symptoms:

- Ataxia
- Distal muscular atrophy
- Paralysis

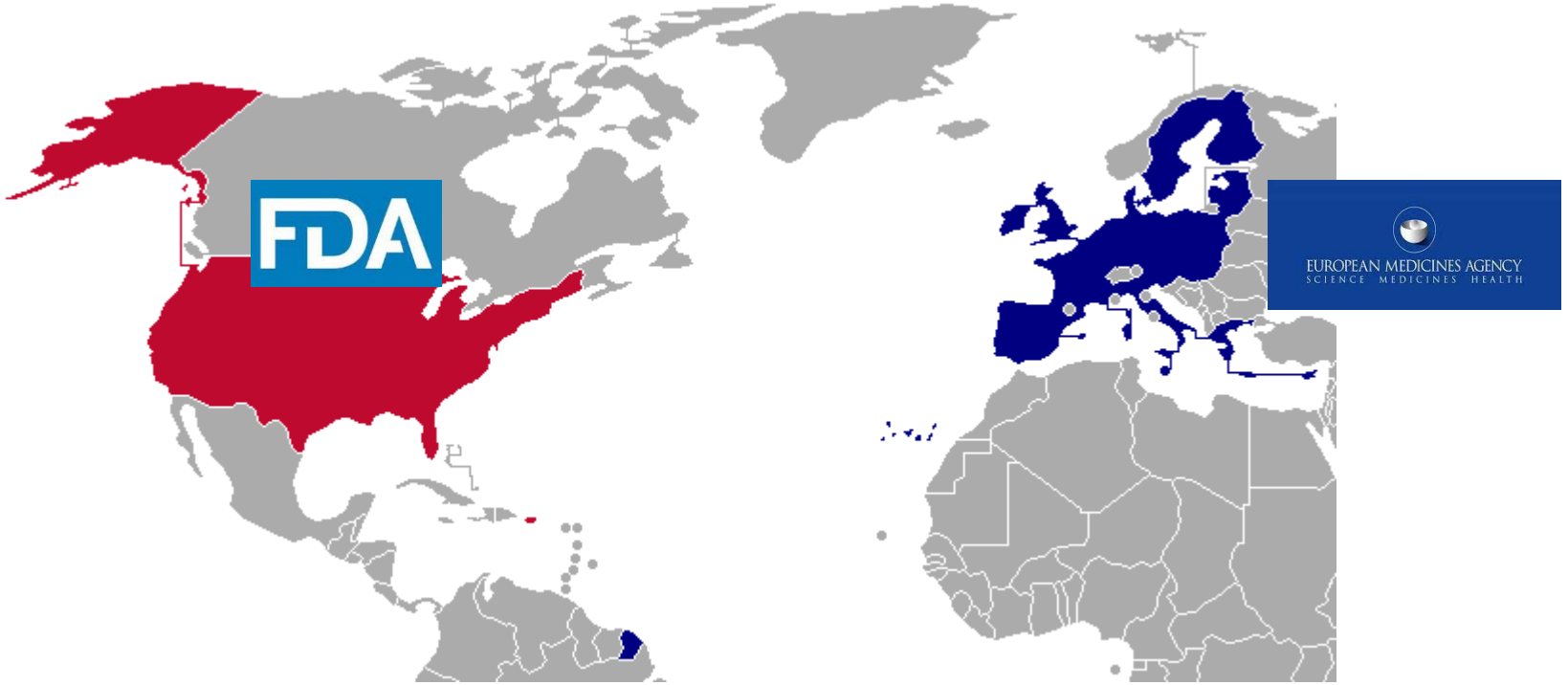


Eichler L et al. Am J Neuroradiol (2011)

Cause:

- CAG expansion in *ATXN3* (>50 repeats)
- PolyQ expansion in ataxin-3 protein

Different continents – different legislation



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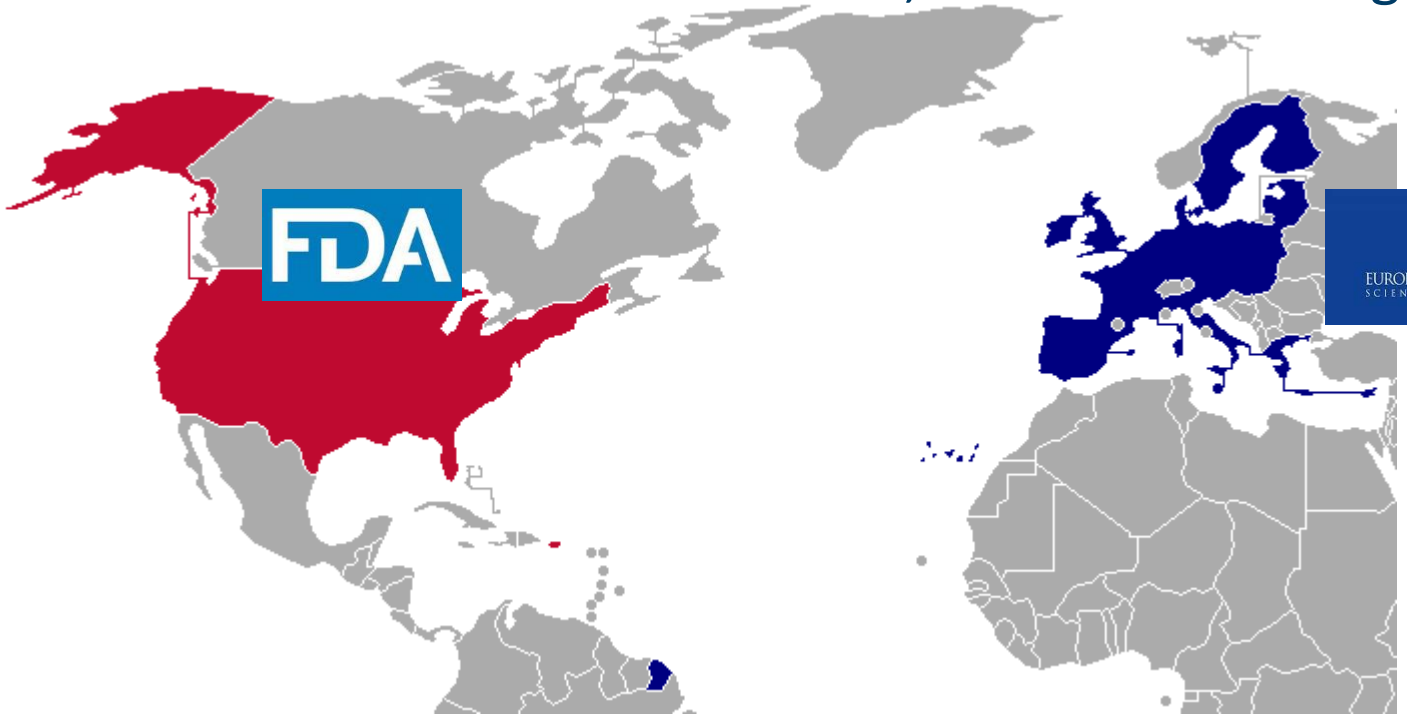
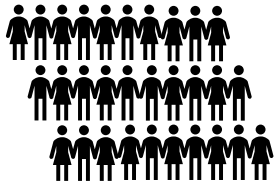
Different continents – different legislation

SCA1, SCA3 and Huntington disease





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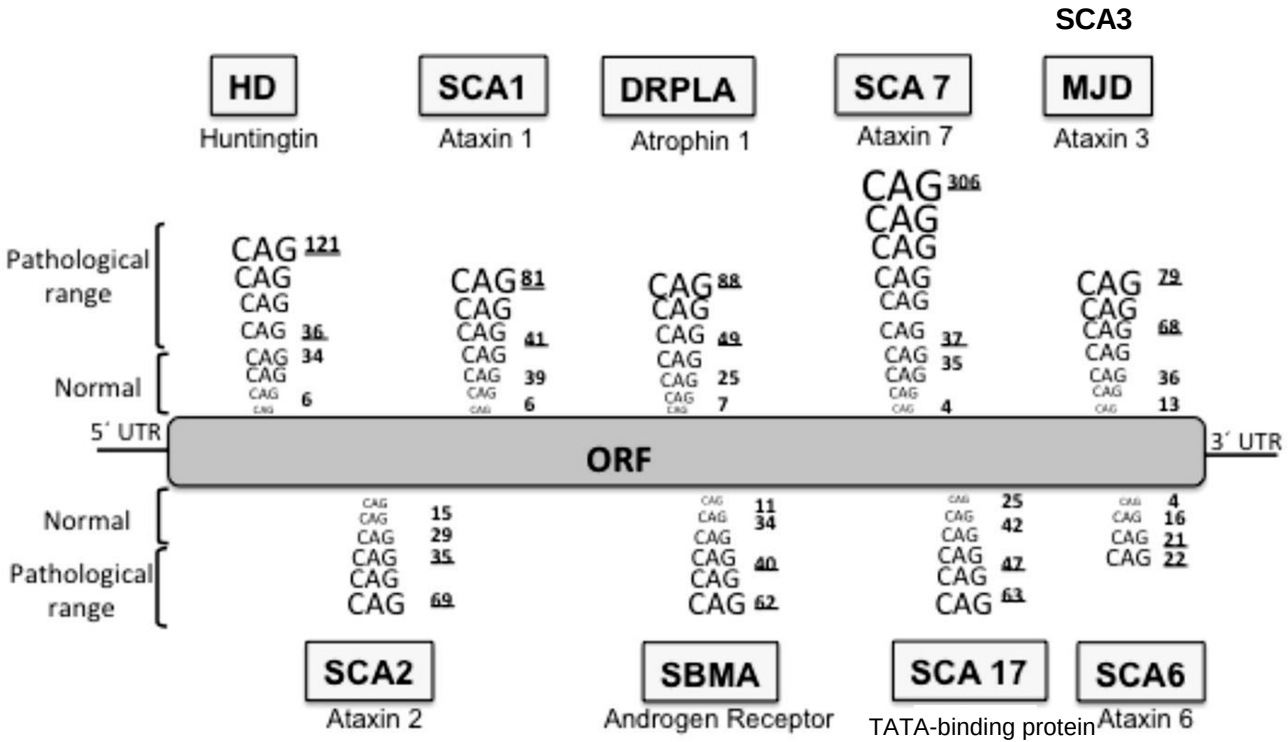
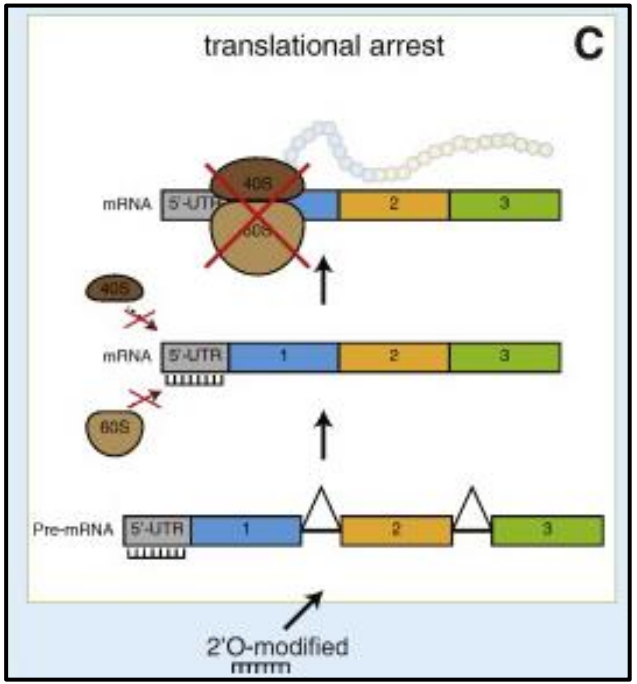
Polyglutamine disorders



Allele ‘preferential’ reduction of mutant protein



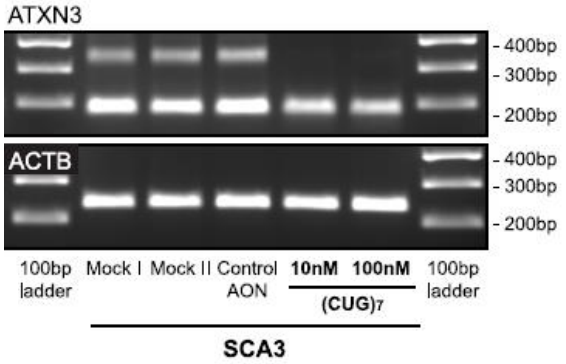
OPEN ACCESS Freely available online

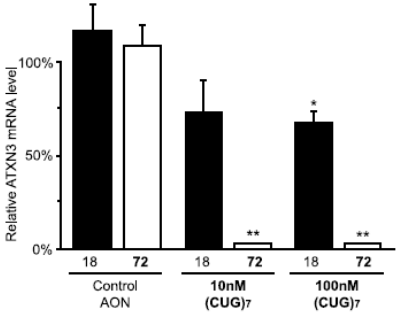
PLoS one

Targeting Several CAG Expansion Diseases by a Single Antisense Oligonucleotide

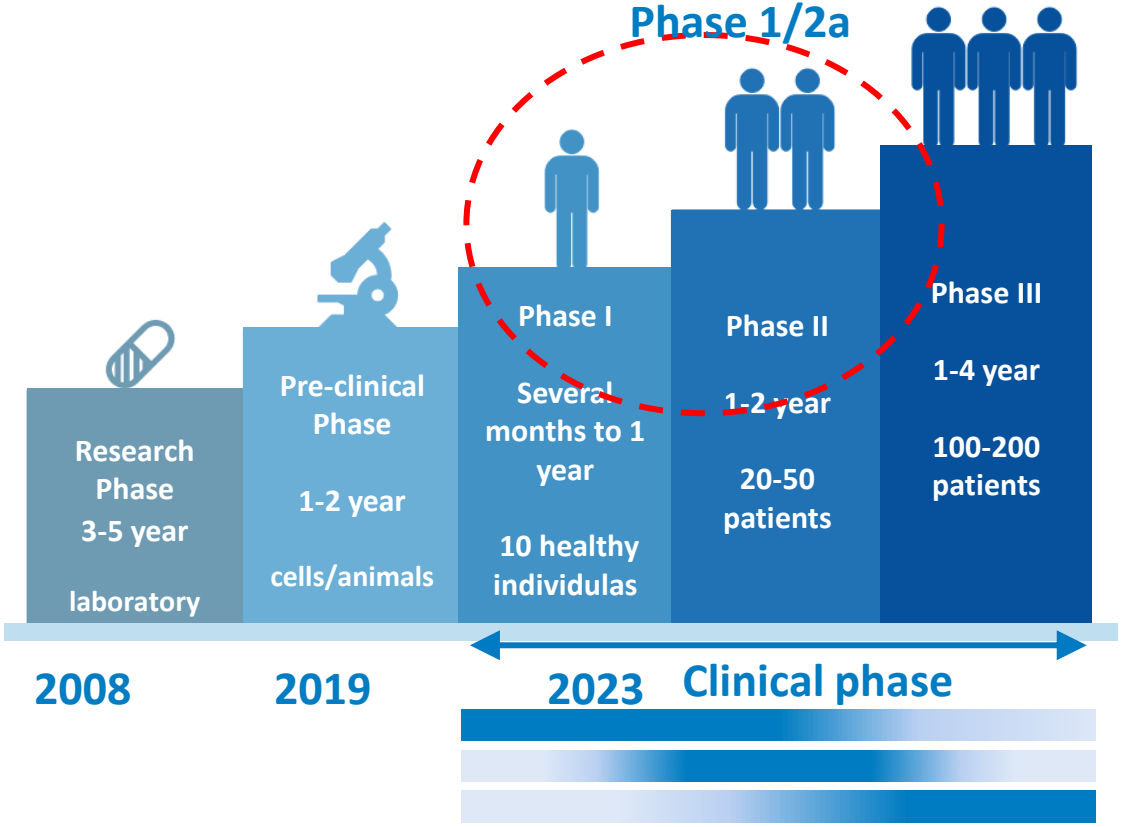
Melvin M. Evers[1], Barry A. Pepers[1], Judith C. T. van Deutekom[2], Susan A. M. Mulders[2], Johan T. den Dunnen[1,3], Annemieke Aartsma-Rus[1], Gert-Jan B. van Ommen[1], Willeke M. C. van Roon-Mom[1]*

1 Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands, **2** Prosensa Therapeutics B.V., Leiden, The Netherlands, **3** Leiden Genome Technology Center, Leiden University Medical Center, Leiden, The Netherlands

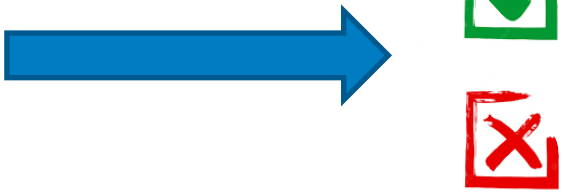




Phase 1/2a – safety study



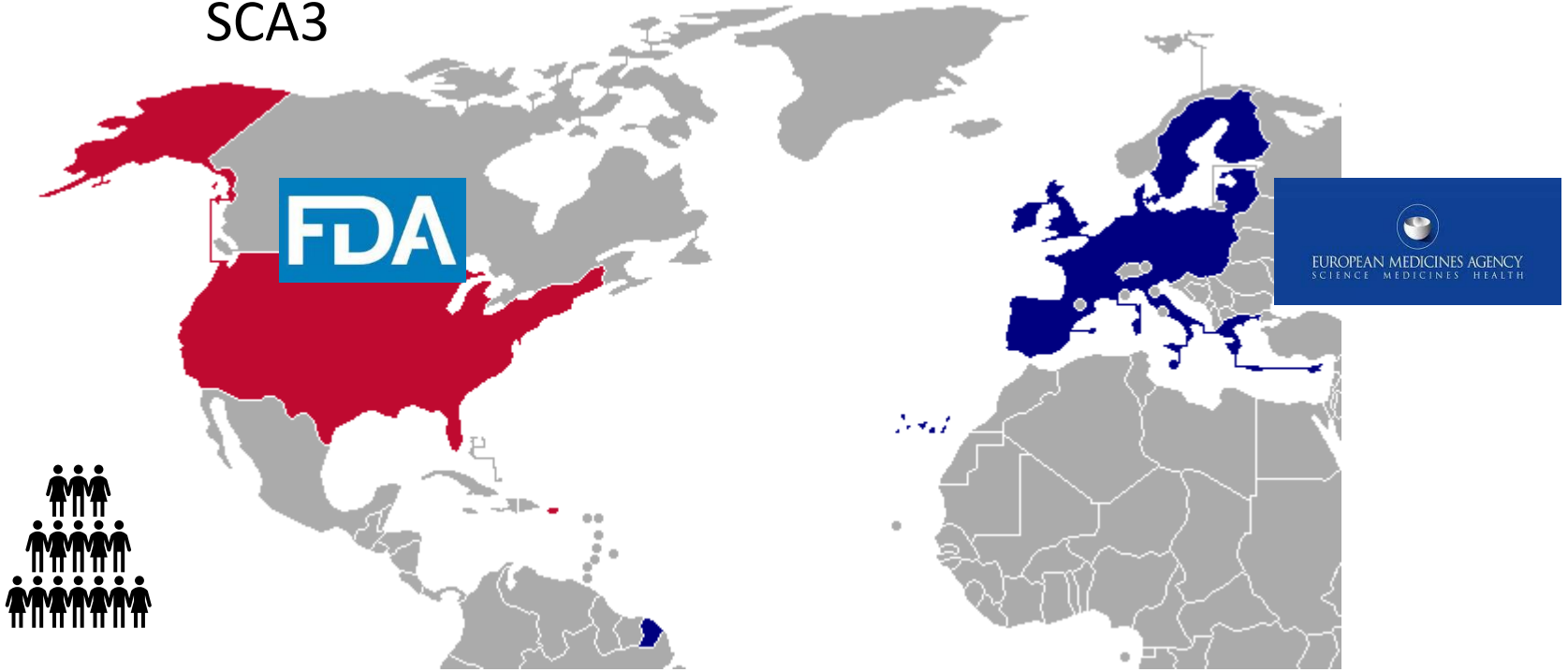
European Medicines Agency (EMA)



Different continents – different legislation

How can we develop more appropriate preclinical pipelines for rare diseases

SCA3



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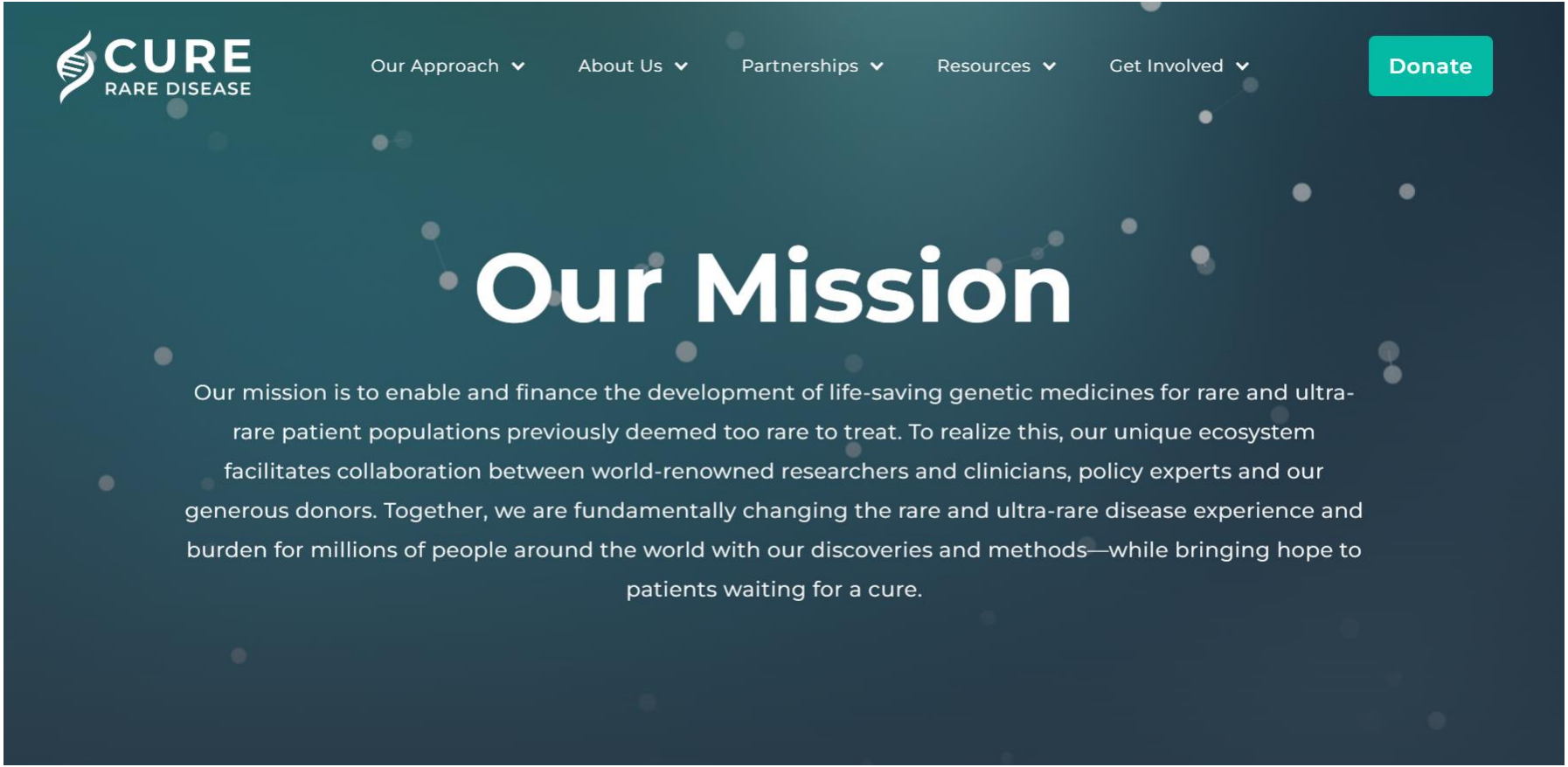
Cure Rare Disease



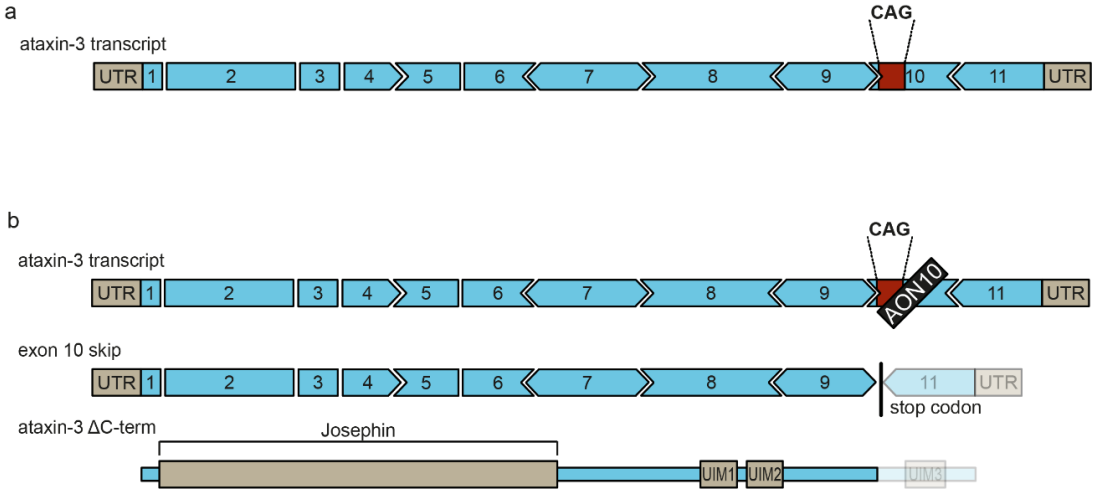
Ataxin-3 protein – exon skipping to remove polyQ repeat

Ataxin-3 protein:

- 42 kDa
- Highly conserved
- PolyQ repeat in C-terminus

Function:

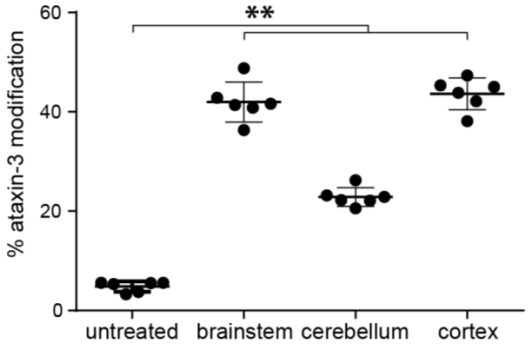
- Involved in proteasomal protein degradation
- Cleavage ubiquitin chains
- Many protein interactors + transcriptional activity
- Essential protein for cellular function?



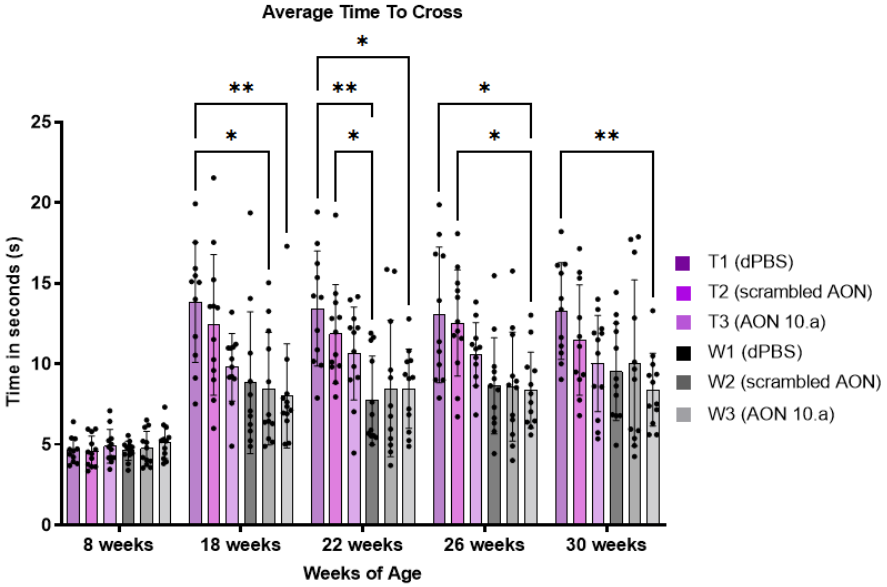
Toonen et al 2017 Mol Ther Nucleic Acids

Preclinical work in MJD84.2 mouse model

Around 40% modified ataxin-3 protein



Behavioral improvement



N of few – IND application FDA (Investigational New Drug)

CURE RARE DISEASE

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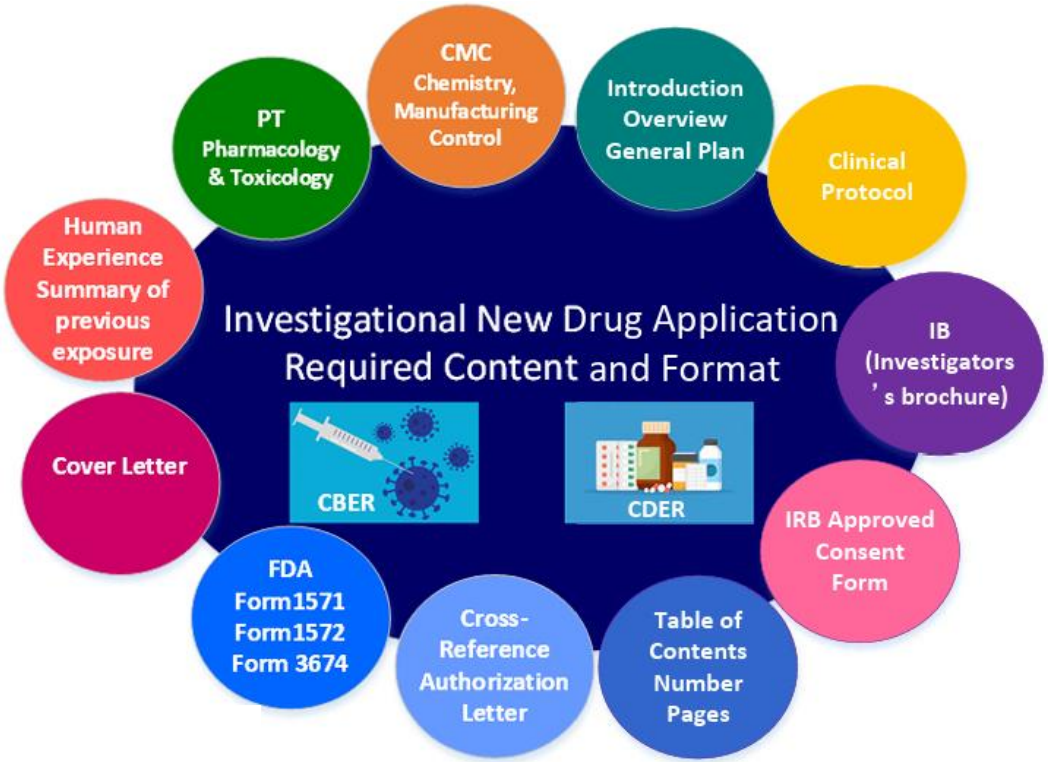
Spinocerebellar Ataxia Type 3

Spinocerebellar ataxia type 3 (SCA3) is caused by a mutation in the ATXN3 gene, which codes for the enzyme ataxin-3. Ataxin-3 is found in cells throughout the body and is involved in the process that destroys and removes damaged or extra proteins. It is believed that ataxin-3 is also involved in transcription, the first stage of protein synthesis. The disease has a prevalence of 1 to 5 in 100,000 people.

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Characterize Mutation	Prototype & Optimize	Test Efficacy	Manufacture & Test Safety	Clinical Trial	Ready for Out-Licensing

Pre-IND filing – safety and tolerability study

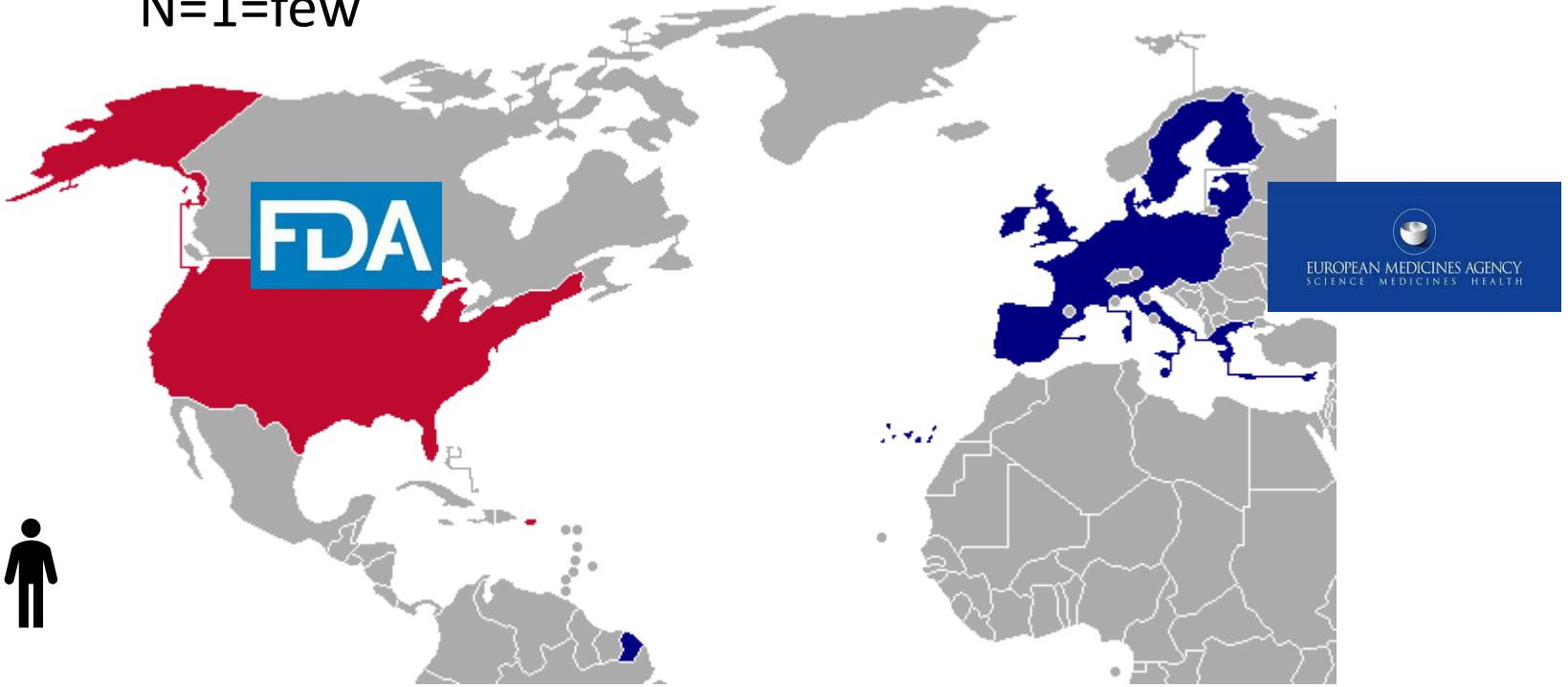


Pre-IND Briefing document

- Disease background – indication
- Product, dosage, route of administration
- Chemistry, Manufacturing and Controls
- Safety studies
- Toxicology studies
- Large animal studies
- Target engagement assay CSF/blood
- Study design
- Inclusion-exclusion criteria
- Primary, secondary endpoints
- Exploratory objectives
- Placebo controlled study

Different continents – different legislation

N=1=few



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A unique patient - a unique treatment

DCRT Dutch Center for RNA Therapeutics

Milasen

Kim et al 2019

ATIpeksen

Kim et al 2023

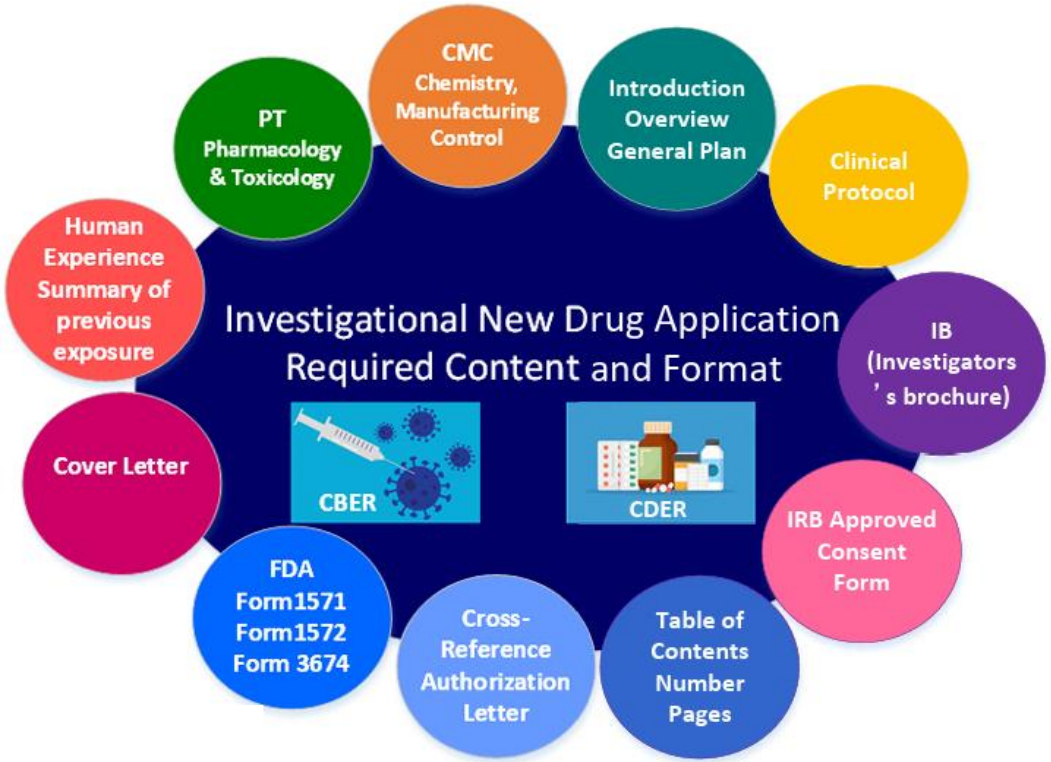
Valeriasen

Burbano et al 2022

JaciFUSen

Korobeynikov et al 2022

IND filing – safety and tolerability study



IND document

- Disease background – indication
- Product, dosage, route of administratio
- Chemistry, Manufacturing and Controls
- Safety studies
- Toxicology studies
- ~~Large animal studies~~
- ~~Target engagement assay CSF/blood~~
- Study design
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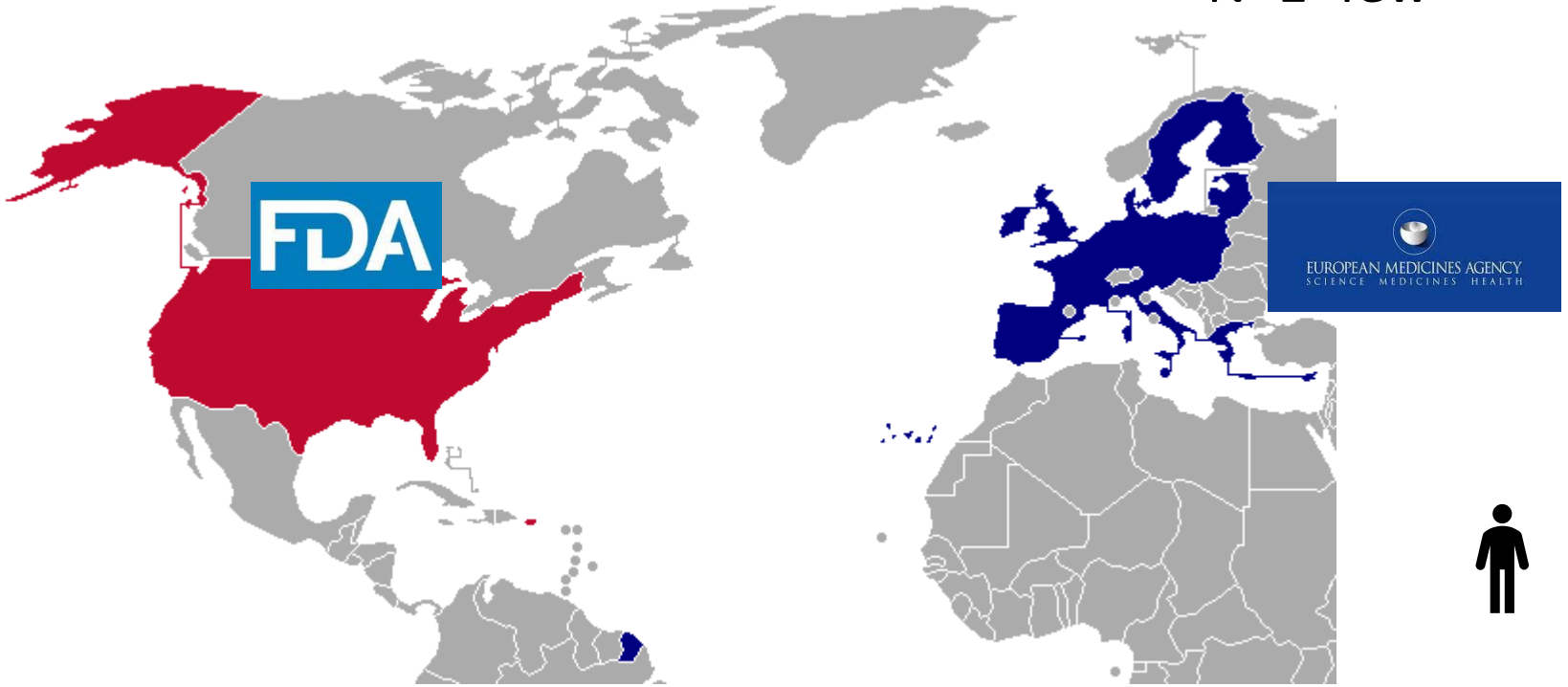
Different continents – different legislation

N=1=few



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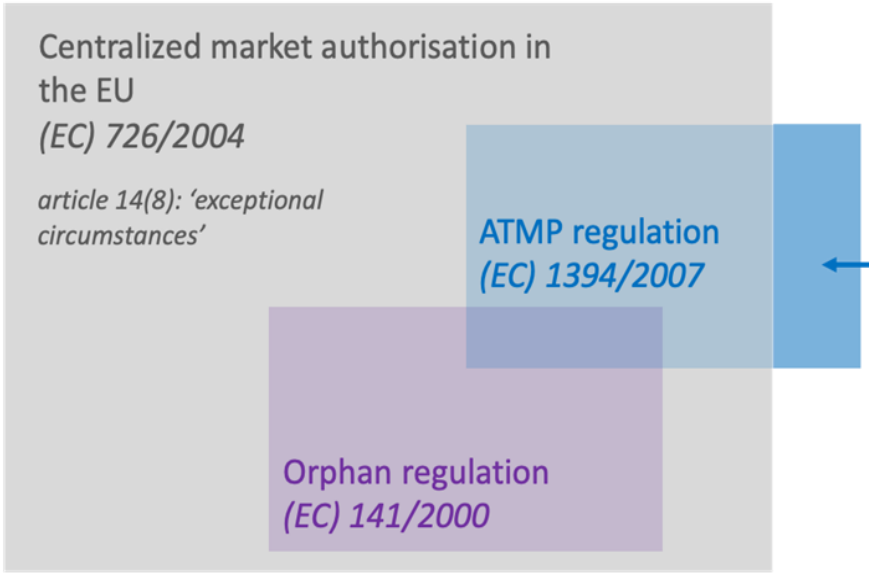
Access options for mutation-specific ASOs

Unlicensed access options for groups of patients

Clinical trial
(EC) 2001/83 Article 3(3)

Compassionate use
(EC) 726/2004 Article 83

- groups of patients with chronically or seriously debilitating or life-threatening disease
- medicinal product is undergoing clinical trial or subject of a marketing authorization application



Unlicensed access options for single patients

Hospital exemption
(EC) 1394/2007 Article 28(2)

- ATMP custom-made for an individual patient; not routinely produced
- administered in a hospital setting under exclusive responsibility of a medical practitioner
- produced and administered in the same member state
- manufacturing authorised by a competent authority of the member state
- quality standards equivalent to (EC) 726/2004

Named patient use
(EC) 2001/83 Article 5(1)

- to fulfill special needs
- purely therapeutic considerations

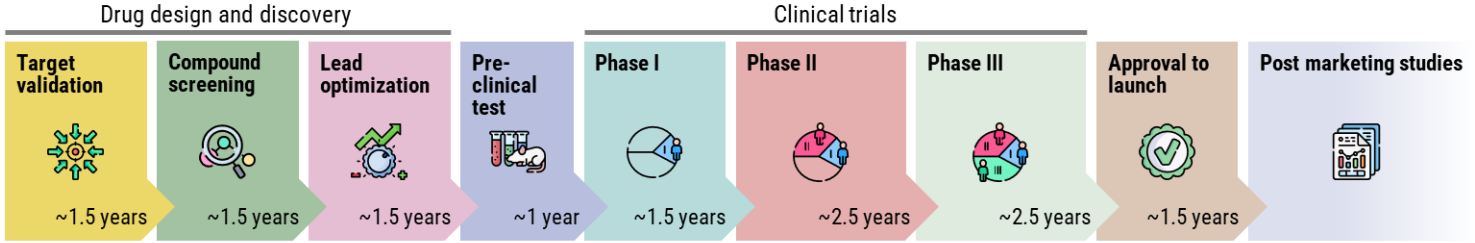
European laws and regulations

- Named-patient setting: no regulatory approval
- Approval from local ethical committees
- Hospital pharmacy preparation of GMP-compliant or GMP-like compound
- Preclinical studies and safety studies as much as possible *in-house*
- Likely differences between the EU countries

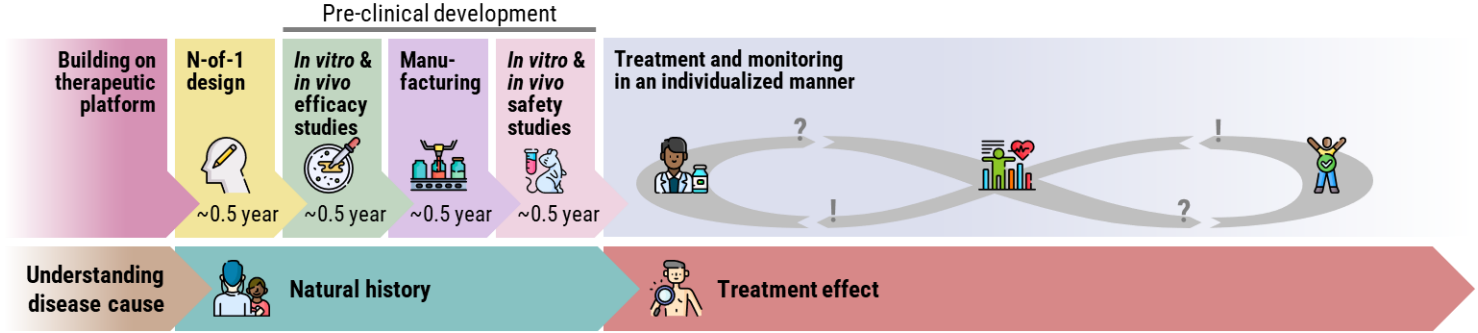
Rare diseases – thinking outside the box

DCRT Dutch Center for RNA Therapeutics

Traditional drug approval process



Patient specific N-of-1 treatment



Slide courtesy of IRDIRC N of 1+ task force

Pathway towards individual patient selection and treatment decisions

1. Case Dossier

Patient data sufficient for gene group?

- Submitted by clinician
- Completeness check secretariat UT

2. Gene Group Meeting

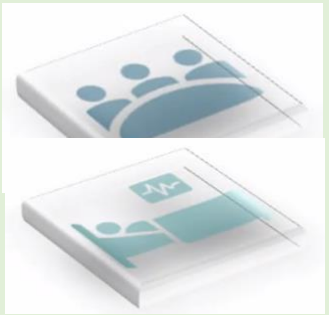
Patient and disease information enough to decide on treatment readiness?

Meeting with

- Submitting clinician
- Clinical and research leads UT & LUMC
- Clinical disease experts
- ASO biologists
- Ad hoc domain experts as needed
- 1M1M secretariat UT

3. Treatment Board meeting

Decide on start/stop development
Decide on start/stop treatment



Yes/
No

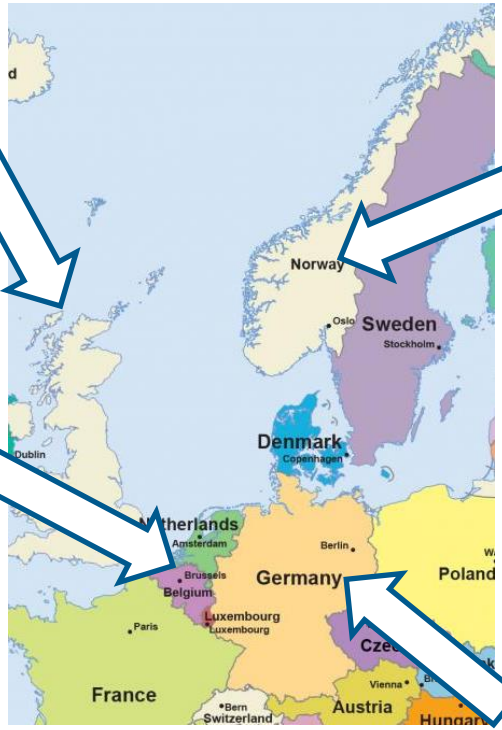
Meeting with

- Submitting clinician
- Clinical and research leads UT & LUMC
- PI representatives of gene group (1-2)
- External experts (N1C)
- Patient organisation representative
- Ethicist
- Disease domain experts as needed
- Independent clinical experts as needed
- ASO biologists as needed
- 1M1M secretariat UT

PRIME program – 4 countries – *ATM* gene
2 mutations – 2 ASOs - 8 patients

Bart van de Warrenburg

Rita Horvath



Asbjørg Stray-Pedersen

DCRT
Dutch
Center for
RNA
Therapeutics

Annemieke Aartsma-Rus

Rebecca Schüle Matthis Synofzik Holm Graessner

Dutch developments - formalizing the pipeline

Exploratory meeting with Centrale Commissie Mensgebonden Onderzoek (CCMO)(Central Committee on Research Involving Human Subjects)

- How to anticipate on future developments?
- Local ethical committees do not have expertise knowledge
- Make a national Master Protocol with experts and ccmo
- For each individual patient – file an amendment
- Can this master/amendment protocol be used throughout the EU

Acknowledgements

LUMC – Neuro-D group
- Barry Pepers
- Linda van der Graaf
- Tom Metz
- Elsa Kuijpers
- Hannah Bakels
- Ronald Buijsen
- Linde Bouwman
- Bas Voesenek
- Bas Rottgering
- Laurie Kerkhof
- Mariana Guimarães Ramos

DCRT -LUMC
- Annemieke Aartsma-Rus
- Anouk Spruit
- Marlen Lauffer
- Pauline van der Graaf
- Bianca Zardetto
- Redmar van den Berg
- Jack Morgan
- Iris Ensink
- Raul Andres Santamaria

1M1M
- Holm Graessner
- Annemieke Aartsma-Rus
- Rebecca Schule
- Matthis Synofzik

https://www.1mutation1medicine.eu/

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