Leids Universitair Medisch Centrum

Antisense oligonucleotides
Towards platform development for individualized ASOs

DCRT Dutch Center for RNA Therapeutics

1M 1M

N=1

Annemieke Aartsma-Rus

Disclosures (past 5 years)

- Employed by Leiden University Medical Center (LUMC), which has patents on exon skipping technology, some of which are licensed to BioMarin and sublicensed to Sarepta. As co-inventor, I am entitled to a share of royalties

- Ad hoc (past) consultant for: (AstraZeneca); BioMarin Pharmaceuticals; Dyne; (Eisai); (Eli Lilly); (Galapagos), Grunenthal, Wave; PTC Therapeutics; REGENXBIO; Sarepta Therapeutics; SpliSense; Takeda & Italfarmaco. Remuneration paid to LUMC

- Member of scientific advisory boards of (past): (Hybridize Therapeutics); Sarepta Therapeutics; Silence Therapeutics & Sapreme. Remuneration paid to LUMC

- Research funding received from (unrestricted grants): Sarepta, Entrada

- LUMC received speaker honoraria: Alnylam; BioMarin; Pfizer; Italfarmaco

Antisense oligonucleotide therapies

- Small, synthetic chemically modified DNA or RNAs
- Work in antisense manner (Watson-Crick base pairing)
- Target gene transcripts (RNA)
    - **Modulate splicing**
    - Cleave target transcripts
- NOT ATMPs

- Opportunity to intervene in an individualized way

Milasen example

1 year

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

- Genetic diagnosis
- AON design
- Tests in fibroblasts
- FDA discussion: rat tox
- Investigational new drug application
- First treatment
- Leveraged information nusinersen

Kim *et al. N.Engl.J.Med.* 2019

Current state of the art

- 19 nucleic acid therapies approved by FDA and EMA to treat thousands of individuals with rare genetic and acquired diseases
- >30 individualized antisense oligonucleotides used to treat >40 patients

  Mainly in USA (N-Lorem, Tim Yu, others)
- Currently more individualized ASOs than commercial ASO
- Leveraging information from approved ASOs (same modality and chemistry, route of administration etc)
- In USA INDs to initiate treatment for each individualized ASO (often for up to 5 patients)

European situation

- Treatment possible under named patient setting
- Rules/implementation differs per EU country
- EMA approval not needed (but advice appreciated)
- 1 mutation 1 medicine: facilitate development and access of individualized ASO treatments for eligible patients with neurological diseases
- ASOs developed in academic setting, e.g. DCRT
- DCRT: ITF feedback
- 1M1M: Scientific advice

1M1M – 1 mutation, 1 medicine

Academically driven European platform to develop and implementat RNA Therapies for ultra-rare diseases

Annemieke Aartsma-Rus

Willeke van Roon-Mom

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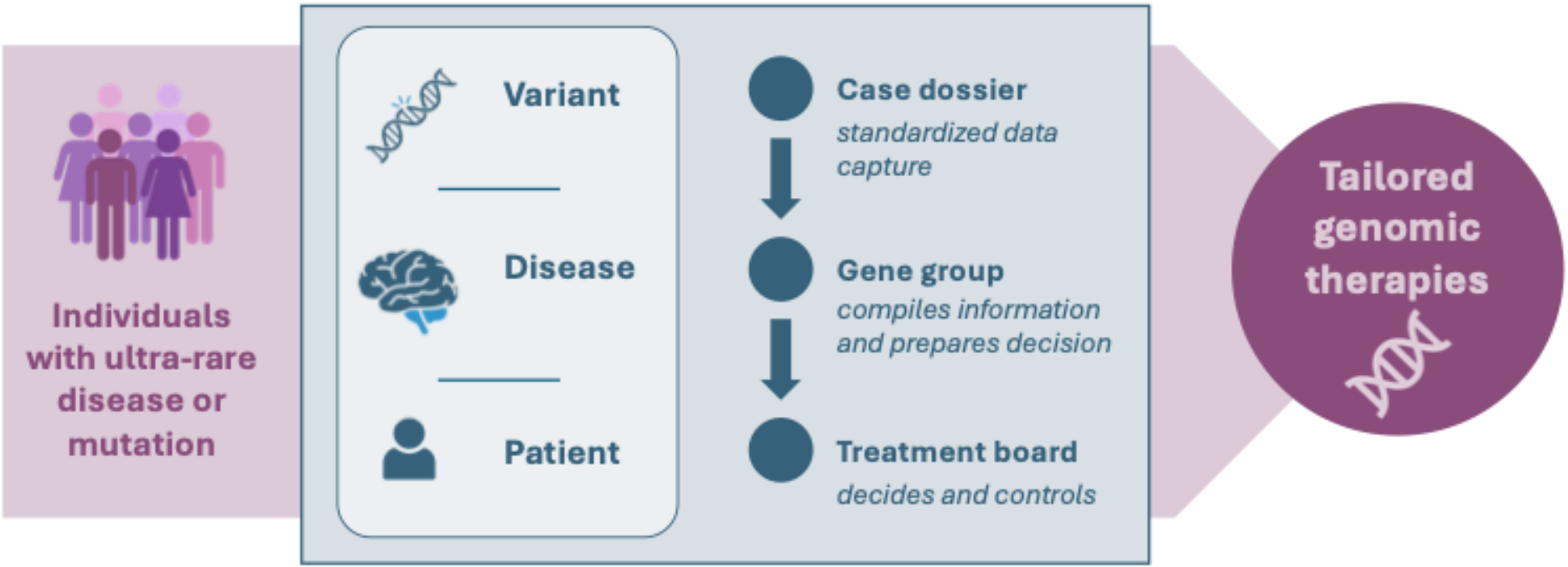
Matthis Synofzik

Rebecca Schüle

Goal:

- Make **indidividualized ASO therapies available**
- For eligible patients with **severely debilitating or life-threatening (SDLT) rare neurological diseases**
- In a **sustainable, scalable, time-critical and safe manner**

1M1M Best Practice Framework for Patient Evaluation



Case study AT (atipeksen)


Tim Yu

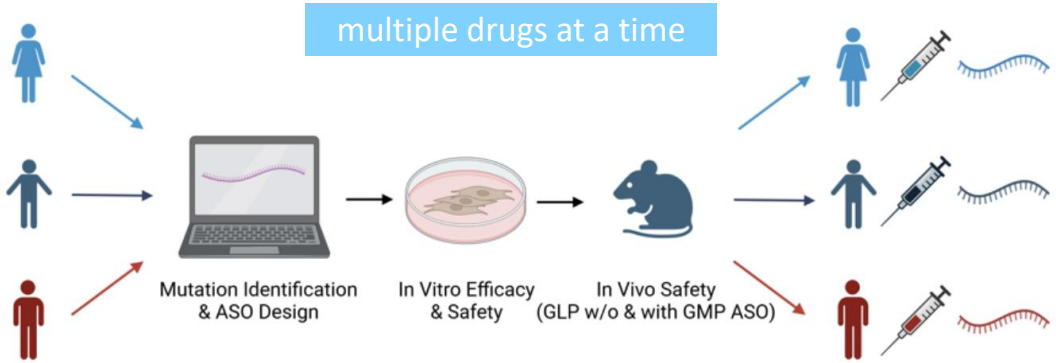

Matthis Synofzik


Rebecca Schüle

- Ipek treated in Boston‘s children hospital since 2018
- PK 4 years, transferred from Tübingen to Boston in 2021 for treatment, ASO dose escalation phase, treatment continuation in Tübingen from Sept 2022

Ataxia Telangiectasia use case

- *ATM* gene loss of function variants (autosomal recessive)
- Cryptic splicing variants common
- Eligible for splice modulating ASOs to restore production full-length protein
- Same disease, same approach, different ASOs



Ataxia Telangiectasia: fixed parameters

- Target gene: *ATM*
- Patient eligibility: 1M1M processes
- ASO type: splice modulating
- ASO chemistry: MOE PS (nusinersen)
- Route of administration: intrathecal
- Dose and regimen: leveraging from atipeksen

Masterprotocol ATM ASOs pt 1

Variable	Step 1	Future flexibility?
ASO sequence	Variable	Variable
ASO design	Guidelines	Improvement (efficiency & safety)
In vitro efficiency	RNA and protein effect, protein function, atipeksen reference	Reverse translation eg dosing (more reference ASOs)
In vitro toxicity	BJAB, neurotox in house (academic platform); CRO validation selected candidates (GLP-like)	Only in house? Improved models Reverse translation safe and toxic ASOs
Production	CRO, fill & finish in house	All in house (academic platform)
In vivo safety	In house, CRO validation (GLP-like)	Only in house Skip completely?

Masterprotocol ATM ASOs pt 2

Variable	Step 1	Future flexibility/improvement
Dose escalation, regimen	Based on atipeksen, ‘plan as you go’	Start higher dose? Guided by in vitro results and reversed translation
Monitoring safety	Based on known ASO IT side effects	More targeted (learning from more individualized and commercial ASOs)
Monitoring clinical OM	Patient specific, based on disease stage SARA score	More optimized based on treatment responsive outcomes
BioMarkers	NFl in CSF	Others?

Towards the future

- Platformizing per transcript and disease
  - Comfortable / low risk
  - Slow
  - Good first step but…
- Other diseases? Other ASO types?
  - One at the time will be very slow and still labour intensive (many platforms)

Other gaps/challenges

- Individualized ASO development leverages information other ASOs
  - Toxicity information often not shared
  - Information about failed developments often not shared
  - Academic developers can share better, but need to capture quality data
  - Natural history data lacking for many (ultra)rare diseases
- Reimbursement
  - Normal HTA system challenging for N=1/few
  - Often takes years to obtain evidence of treatment effects…
  - Named patient difficult to scale up