Hertie-Institut
für klinische Hirnforschung

A scalable platform approach for preclinical and clinical development of patient-customized ASOs for brain diseases

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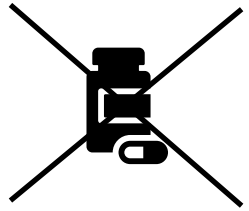
platform approaches:
a genuine opportunity for rare neurological disorders

1. thousands of RNDs, majority of them genetic (80%) and ultrarare

➔ despite increase in RND drug developments, treatment options will remain absent for the majority of RNDs

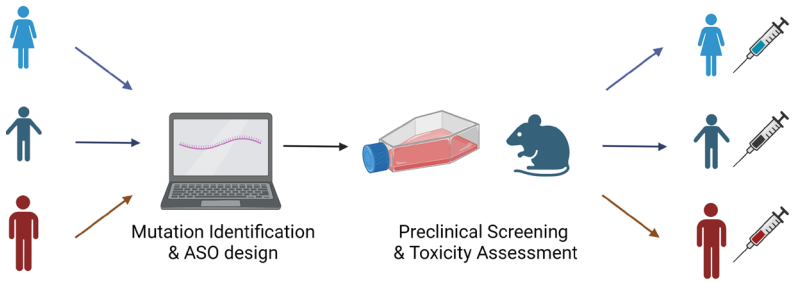
2. current drug development & regulatory paradigms in medicine not apt for ultra-rare diseases



➔ required number of patients not existing (often not even for a phase 1/2 trial)

platform approach

- a **systematic, scalable approach**
- applicable to **many RNDs alike**
- **targeting a shared biological principle**
- **potentially even approvable (?)**



concept: the main components of drug development can be *ultra-individualized* – and the same time *streamlined* ☺

1M1M – 1 mutation, 1 medicine

academically driven European platform

for the development and implementation of RNA Therapies for ultra-rare diseases

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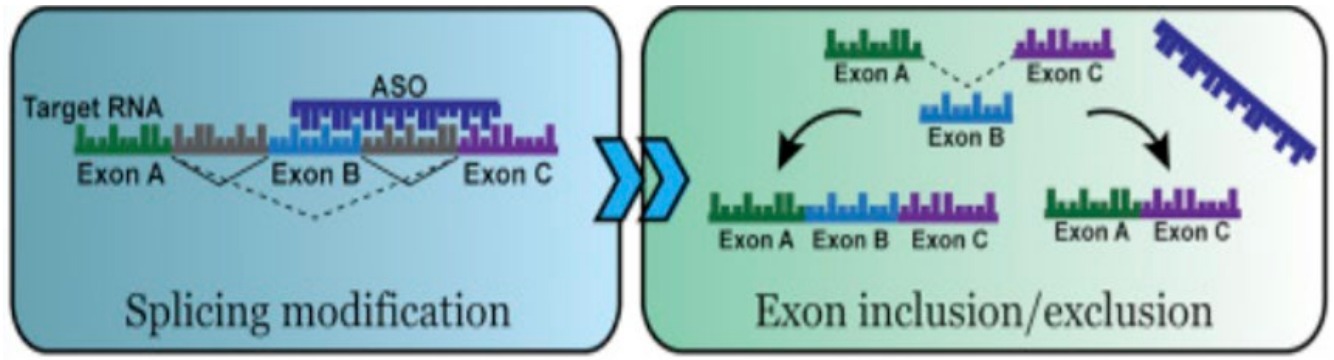
goal:

- to make **patient-customized ASO therapies available**
- to eligible patients with **severely debilitating or life-threatening (SDLT) rare neurological diseases**
- in a **sustainable, scalable, time-critical and safe manner**

the shared biological target of the platform:
mutations targetable by splice modulation ASOs

splice modulation ASOs = splice an exon in or out



applicable to <u>many different mutation *classes*</u>:

- **cryptic splice mutations** (deep-intronic or exonic) ➔ prevent inclusion of a pseudo-exon
- **canonical splice mutations** ➔ restore canonical splicing
- **missense/frameshift mutations** ➔ splice out the respective exon

Synofzik lab:
- works on *all* of these targeting strategies
- by example of Ataxia telangiectasia (A-T)

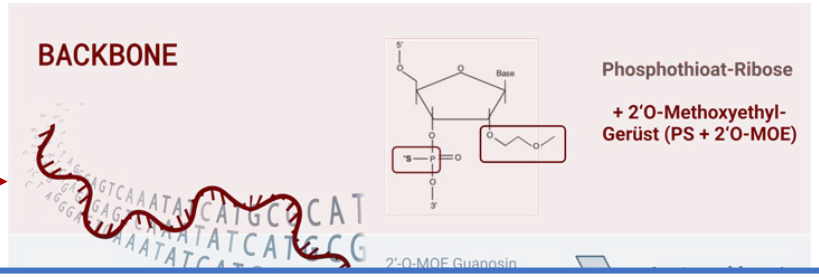
applicable to <u>manifold diseases</u> - and even <u>small groups and single patients</u>

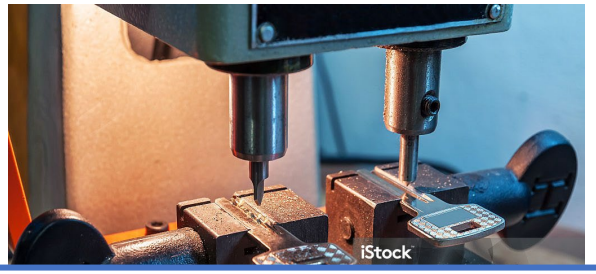
- **"*common*" *rare neurogenetic* diseases**: spinal muscular atrophy (SMA)
- **common *sporadic* neurological diseases**: ALS & FTD (TDP-43 diseases; several phase 1 trials)
- **>40 (!) *ultra-rare* neurological diseases and single patients** (academia, n-lorem)

the platform for patient-customized ASO drugs: a platform *drug* - embedded in a platform *process*

- **platform technology #1: the drug itself** = fixed (proven safe & effective) + pre-defined variable component

- FDA & EMA- approved (2016)
- PK/PD & toxicity well known
- CNS active & well tolerated (>14.000 patients)





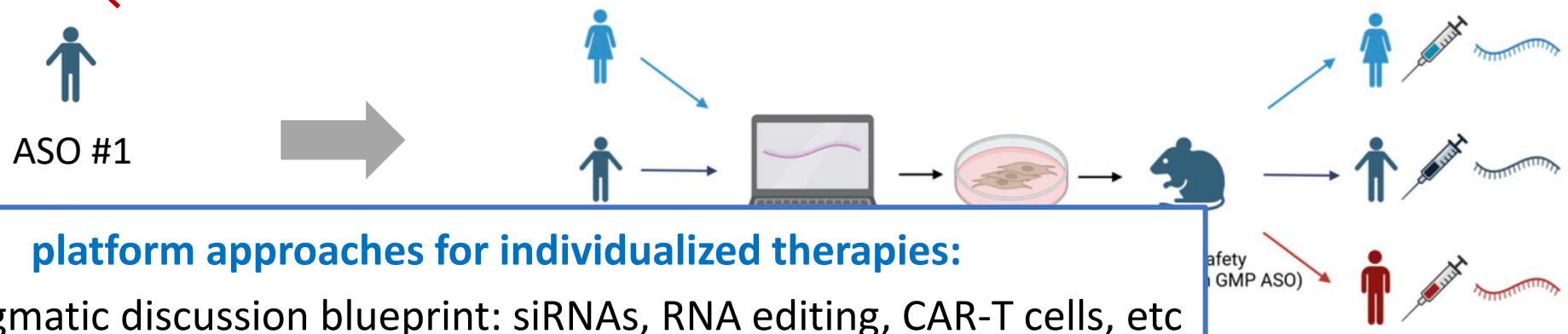
oligonucleotide backbone+sequence

➔ paradigmatic discussion blueprint : later also expand e.g to gapmer ASOs (here: Tofersen as approved backbone)

- **platform technology #2: the *process*** = fixed (standardized, streamlined) + pre-defined variable component

~~one drug at a time~~

multiple drugs at a time



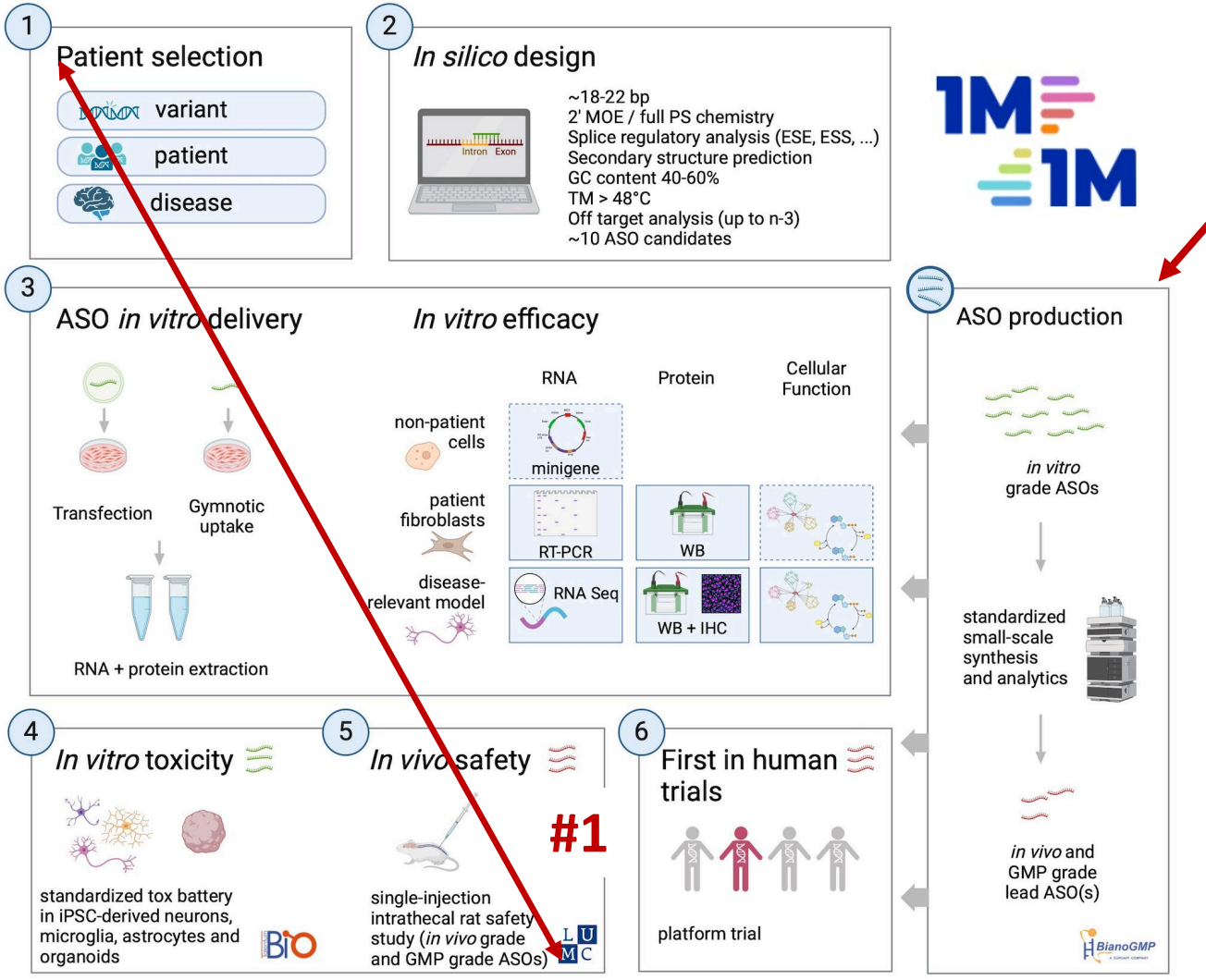
platform approaches for individualized therapies:

➔ paradigmatic discussion blueprint: siRNAs, RNA editing, CAR-T cells, etc

the platform for patient-individualized ASO drugs:
covering all steps from *in vitro screening* to *first-in-human treatments*

cross-disease & cross-mutation

SAME, STANDARDIZED:



ASO development for >10 brain diseases by 1M1M:

- *CSF1R*
- *POLR3A*
- *TRIT1*
- *NDUFAF6*
- *DARS2*

based on this example, how should we best categorize a "platform":

1. as *end-to- end (E2E)* process?
2. as *modular approach*: by each module?

- *SPG15*
- *A-T (Ataxia teleangiectasia)*

  > 20 mutations ➔ 20 ASOs

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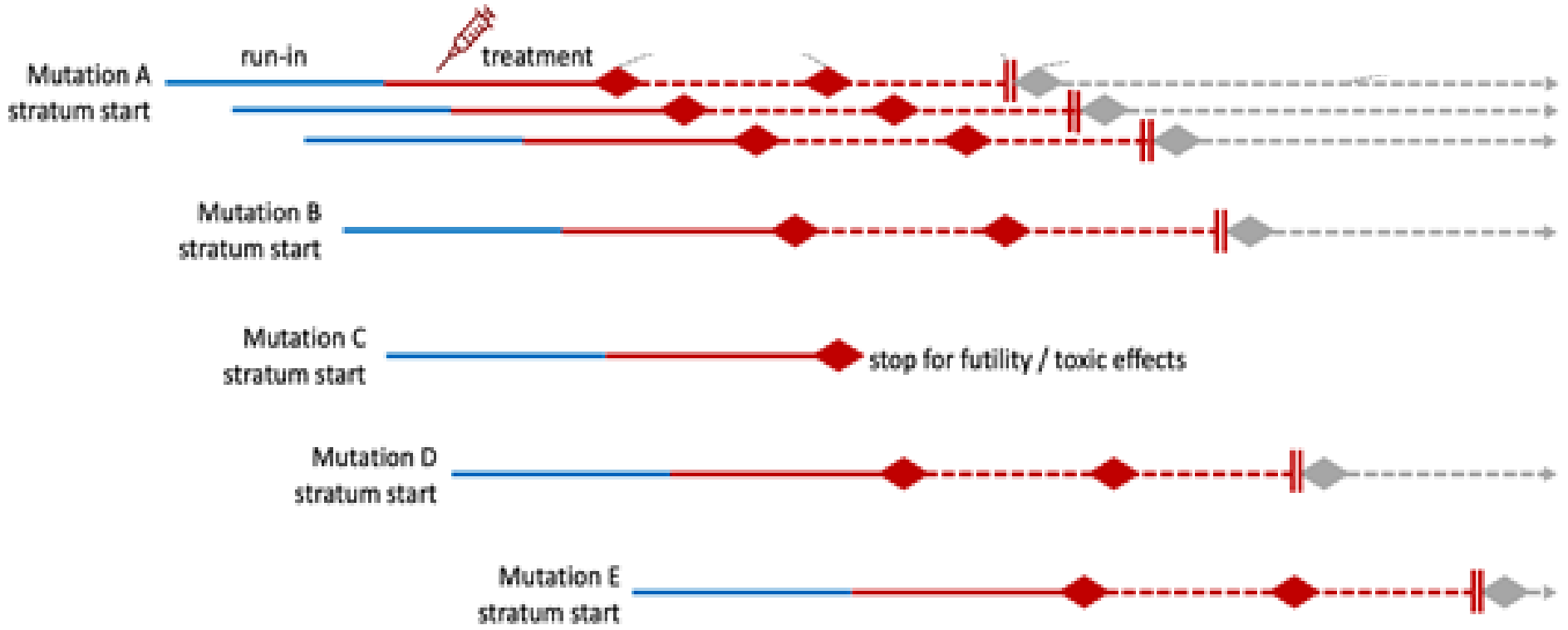
- CHMP 2022
- ITF 2021

Thank you!

demonstrating efficacy and safety for a platform of patient-customized therapies:

a platform trial design - for *very small groups*



- each arm = 1 ASO; for very small group of patients (e.g n=2-10)
- primary endpoint + top secondary endpoints: shared across arms
- efficacy & safety: *across* arms and *per* arm

platform for patient-customized ASOs:
a use case example to pioneer a blueprint for platform regulation

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SCIENCE MEDICINES HEALTH

- ITF, CHMP
- PRIME

a platform approach which offers a a strong opportunity to discuss/develop:

1. **blueprint** for regulatory assessment of ***RNA therapy platforms***
   - RNA therapies = programmable therapies ➔ *inherently platform technologies* ➔ many requests to come for EMA

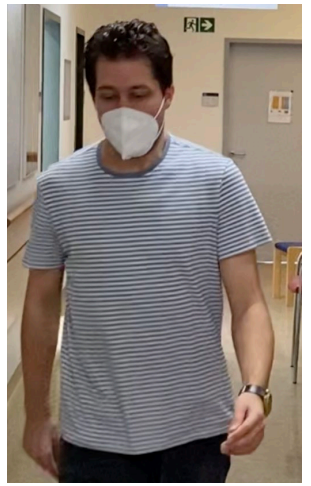
2. **blueprint** for regulatory assessment of ***platforms for individualized drug developments***
   - many requests to come in the future for EMA

3. regulatory pathways for **marketing authorization** not only of a ***platform drug***; but also of a ***platform process***
   - allows differences in products under a *single* MA
   - dramatically accelerates therapy development & reduces regulatory burden

4. treatments & their regulatory assessment for the **large number of (otherwise unreached) ultra-rare diseases**
   - a *scalable* platform of programmable therapies – might lead to *MA even for n-of-1/n-of-few medicines*
   - rapid access for so far untreatable diseases to highly innovative, targeted disease-modifying treatments
   - opens a whole field of medicine so far inherently been out of scope for regulatory agencies (and patient treatments)

5. **blueprint trial design** for a **master protocol** for a **platform trial with *very small group-arms***
   - might allow to generate regulatory sufficient evidence of efficacy and safety for MA even for *ultra-rare diseases*

first personalized ASO treatments for neurological disease in Europe



ASO #1 Boston Children's Hospital ASO #2 ASO #3 ASO #4

- with **baseline data + already month 30 data on maintenance dose**
- additional FU data every 3 months

"get your personal ASO"

Thank you!