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Nano-rare Patient Colloquium 2025

Why Science Matters: Building a Scalable and Unmatched ASO Discovery Engine

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The n-Lorem Research mission in context

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Balancing Urgency and Excellence in Nano-Rare Drug Discovery

- For the first time, we are going from *in vitro* data to patients, without *in vivo* pharmacology.
- We need to:
  - Deliver individualized ASOs rapidly and safely for pre-clinical development.
  - Innovate to help and reach more nano-rare patients that are currently left behind.
- **Question:** How do we ensure both speed and scientific rigor for the most urgent unmet needs?

Main Goals of ASO Discovery and Research at n-Lorem

- **Goal 1:** Identify the most optimal ASOs per case with precision and certainty.

- **Goal 2**: Advance the technology to reach more patients, faster, more efficiently and more safely.

What makes our platform unique

- Our unmatched experience across millions of ASOs, together with a scalable, industrialized process, delivers both efficiency and uncompromising scientific rigor.
- Today's progress stands on three miracles of science: genomics, ASOs, and the power of iPSCs; advances that together make possible what was impossible just ten years ago.
  - Genomics: we can now pinpoint the exact genetic change causing disease, giving every patient a precise starting point for treatment.
  - ASOs: we can create personalized medicines that treat the root cause of the patient's disease
  - iPSCs: we can test and deliver these therapies faster and at a lower cost

What makes our platform unique

- Our platform is based on:
  - Purpose-built for scale, speed, and scientific excellence.
  - Unparalleled ASO expertise
  - Correct and data-driven AI Integration, based on millions of ASOs: AI accelerates and streamlines discovery, guided by our unique datasets and deep expertise.
  - Continuous learning: Every patient teaches us something new: about biology, about ASO mechanisms and about health and disease.

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Scientific Rigor at the Core

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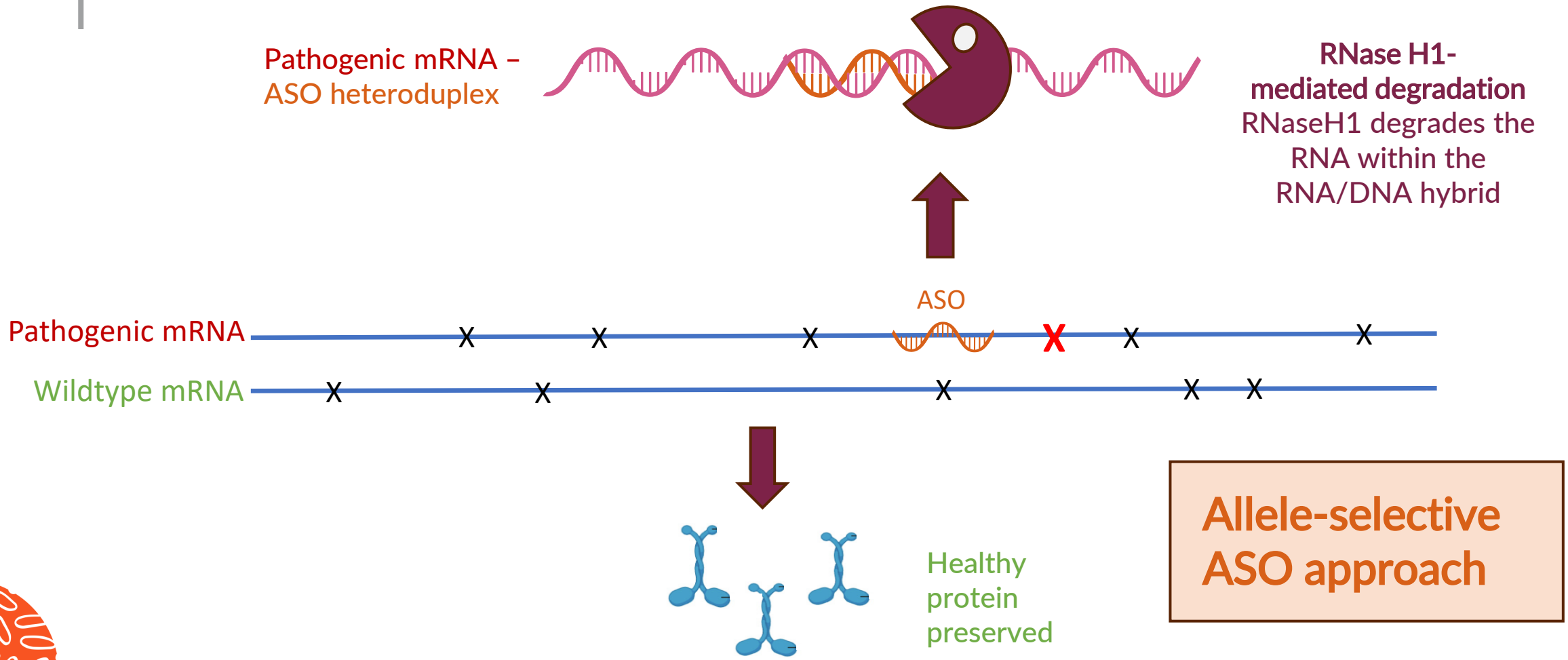
90% Success in ASO Discovery: Safe, Potent, and Effective

- High standards for efficacy, potency, and safety, even with compressed timelines
- 90% success rate in ASO discovery:
  - Non-allele-selective
  - Allele-selective
  - Splicing-modulating ASOs

Case study Ion Channels: The Electrical Switches of Our Bodies

- We are electrical machines: Every thought, heartbeat, and movement depends on the flow of ions: charged particles that generate and control electrical currents in our cells.
- Ion channels are the gatekeepers: These complex proteins finely regulate how ions move in and out, ensuring proper signaling in the brain, heart, muscles and beyond.
- Tightly controlled roles: Because ion channels sit at the center of such delicate processes, even small disruptions can cause serious disease.
- Precision and excellence matter: Identifying allele-selective ASOs for ion channel genes requires exceptional expertise and rigor; getting it wrong risks severe toxicity.

RNase H1 ASO Triggers Degradation of Mutant While Preserving Wildtype mRNA

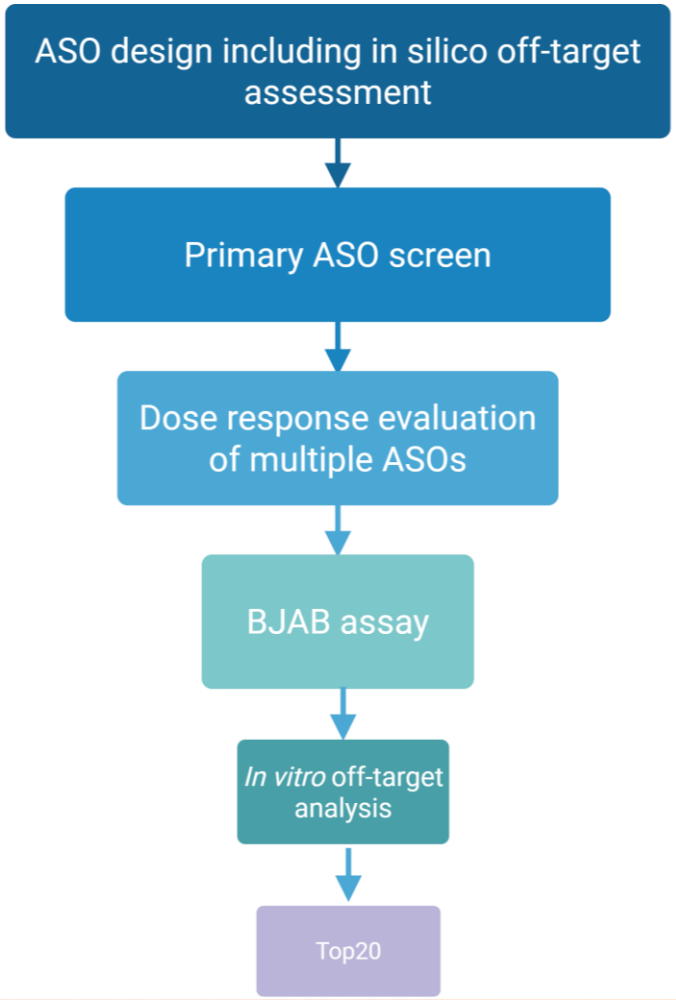


Unparalleled Expertise in Allele-Selective ASOs for Ion Channels

ION CHANNEL GENE	GENE FUNCTION	MUTATION	TYPE OF MUTATION
SCN2A	Sodium channel	c.2558G>A	TGOF /LOF
SCN2A	Sodium channel	c.5645G>A	TGOF/LOF
SCN8A	Sodium channel	c.649T>C	TGOF
CACNA1A	Calcium channel	c.4177G>A	TGOF
CACNA1E	Calcium channel	c.5159C>G	TGOF
KCNQ2	Potassium channel	c.841G>A	TGOF
KCNQ2	Potassium channel	c.634G>T	TGOF
KCNQ2	Potassium channel	c.683A>G	TGOF
KCNB1	Potassium channel	c.934C>G	TGOF
KCNB1	Potassium channel	c.1108T>C	TGOF
KCNH1	Potassium channel	c.1678C>T	TGOF
KCNT2	Potassium channel	c.800T>A	TGOF
CLCN7	Chloride channel	c.2144A>G	TGOF
NALCN	Sodium / Calcium channel	c.1639A>G	TGOF
NALCN	Sodium / Calcium channel	c.1798G>C	TGOF
GRIA1	Glutamate Receptor 1	c.1906 G>A	TGOF
SLC12A6	Sodium / Calcium transporter	c.2971A>G	TGOF
SLC37A4	Sodium / Calcium transporter	c.126C>T	TGOF

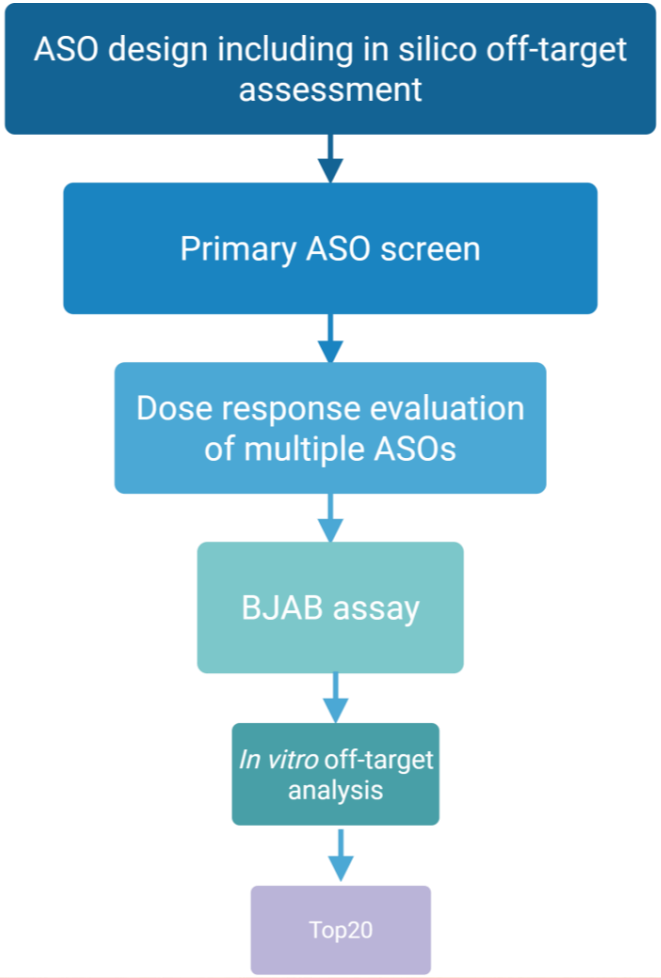
- **n-Lorem's strength:** Our deep ASO experience enables us to design safe, potent and efficacious ASOs that target the mutant allele while preserving critical channel function.
- We have multiple patients mutations in critical ion channel genes currently in the n-Lorem pipeline. All mutations are TGOF, rendering an allele-selective ASO approach the optimal therapeutic strategy

Our Discovery Engine



- Scalability
- Rigor
- Decision-making

Scalability



Minimum number of ASOs

Scan entire pre-mRNA

~500 or more

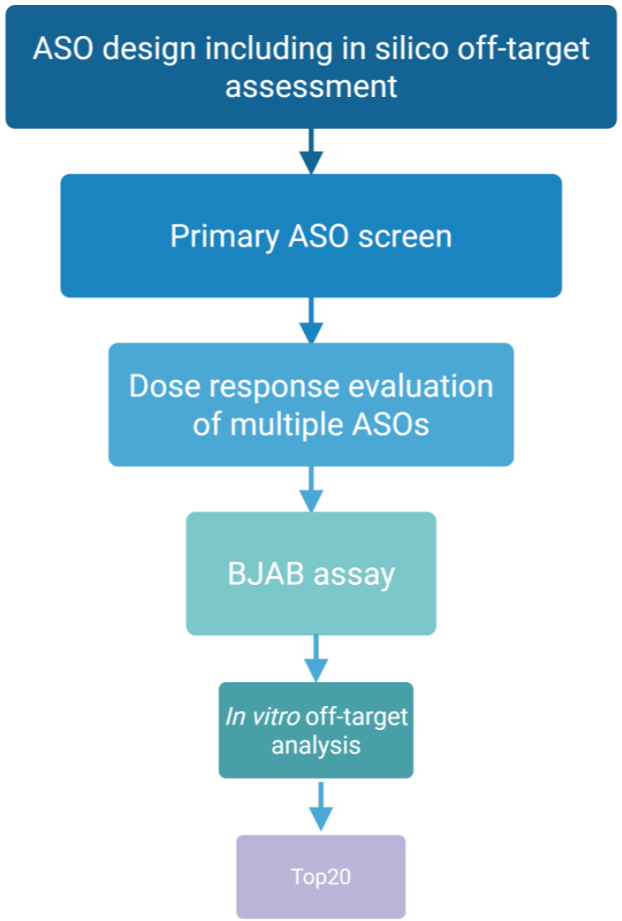
~50 -75

~50 -75

As many as necessary

20

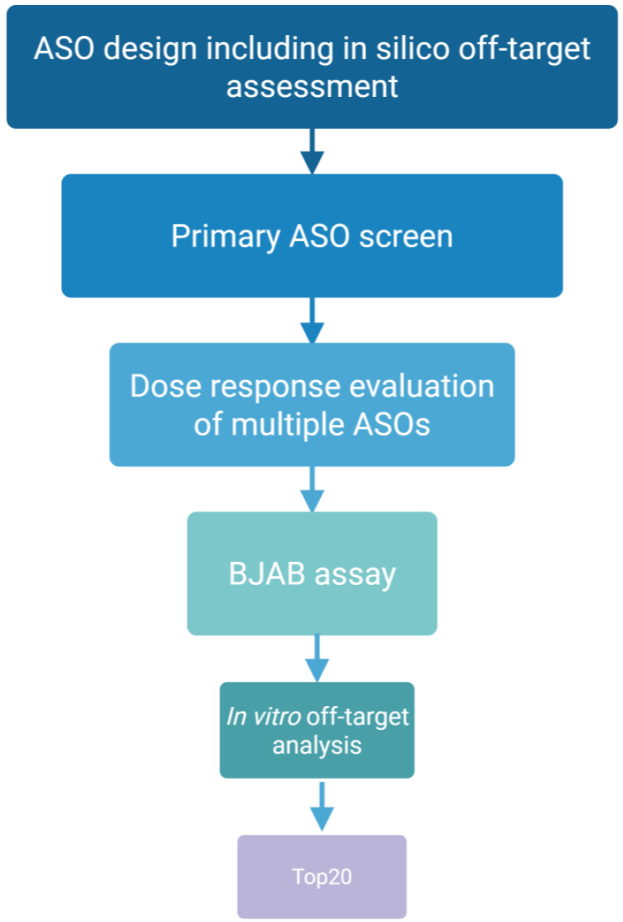
Scientific Rigor



Minimum criteria of ASOs moving to the next Discovery stage
Maximum Quality at Every Step

- All important attractive motifs included, unattractive excluded
- >80% target reduction
- High potency demonstrated by a low IC50 and high allele-selectivity by >5- to 10-fold
- Less than 2-fold increase in TNF-alpha surrogate CCL22 at high ASO concentrations
- >10-fold difference in IC50s for target RNA vs. off target and expression in CNS
- Select the most optimal ASOs

Decision-making



GO/No GO points

1. Is long read WGS sufficient for Design?
2. : Does patient have enough SNPs to enable ASO Design?

3: Do the patient cells meet QC requirements to initiate screening?
4: Do we have optimal efficacy with the ASOs tested?

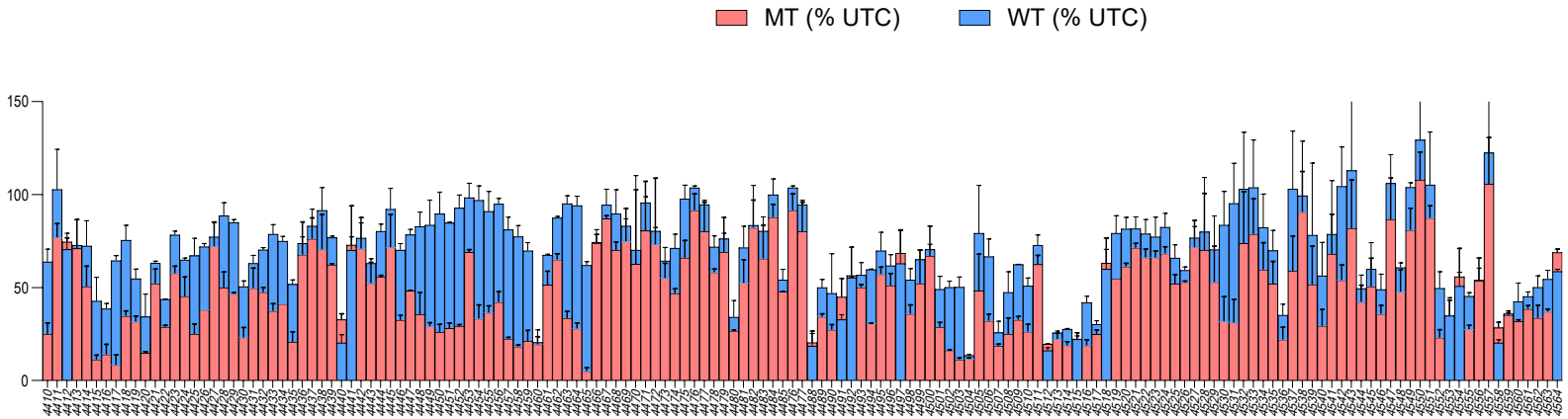
5: Do we have optimal allele-selectivity, potency and efficacy with the ASOs tested?
6: Do we have optimal ASOs after redesign (if necessary from D5)?

7: Do we have safe ASOs that are optimal from Dose response step?

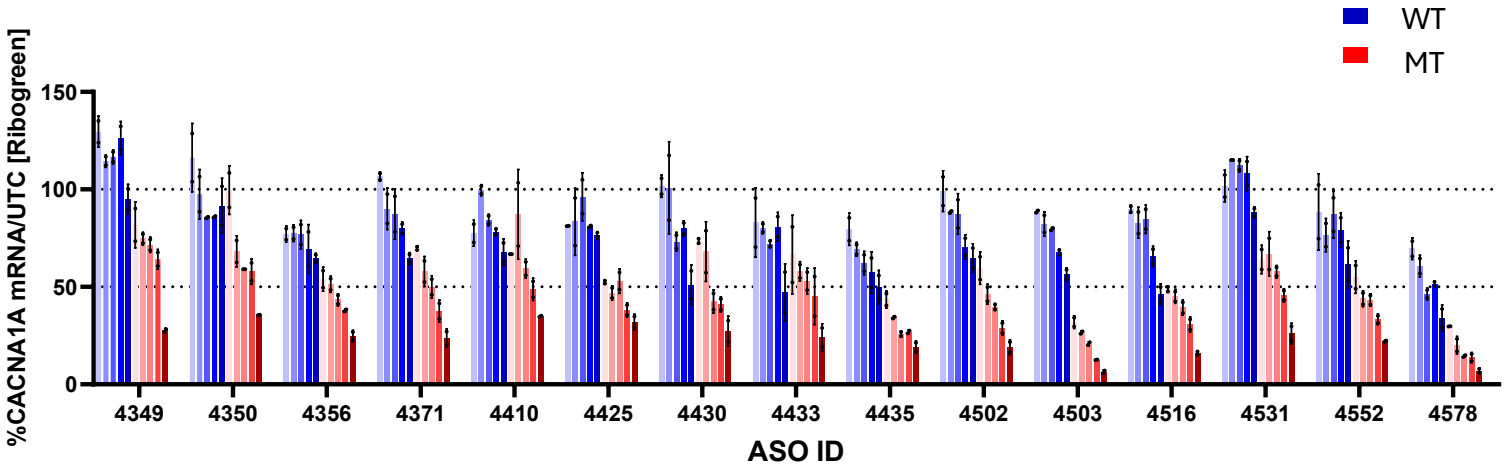
8: Do we have any worrisome off-targets?

9: Do we have efficacious, potent, allele-selective and safe ASOs?

Building Efficacious, Potent and Safe RNase H1 ASOs for Ion Channels



Single dose screening



Top20 candidates of two CACNA1A cases (same ASOs could be used for both patients)

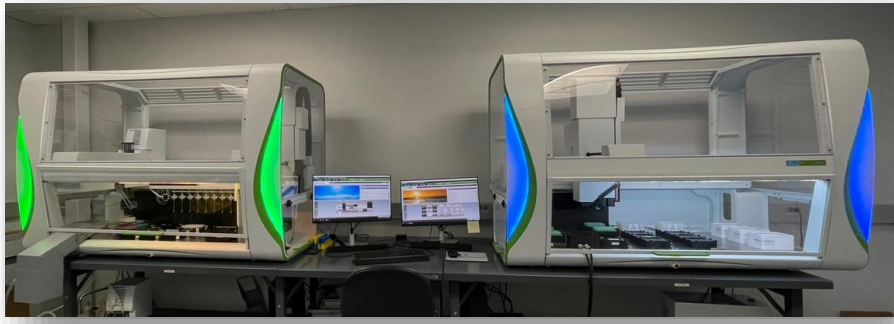
ASO Discovery Across Many Gene Classes and Therapeutic Areas

- **Across gene classes:** Our platform enables ASO discovery across diverse gene classes, including ion channels, enzymes, structural proteins, and noncoding RNAs
- **Broad therapeutic reach:** The same rigorous process can be applied to neurological, hepatic, and other disease areas, expanding impact across patients.

Gene Target	Therapeutic Area	Clinical Consequence	Route of Administration
CLCN7	Liver and Kidney target and disease, Motor disorder, Neurodegenerative	Liver failure, motor dev delays, delayed myelination, GI dysfunction	Subcutaneous
GARS1	Liver target and disease, Motor Disorder	Motor dev delays, GI dysfunction, hypotonia, pulmonary complications, dysautonomia	Intrathecal
GBE1	Glycogen Storage	Peripheral neuropathy, progressive muscle weakness, spasticity, neurogenic bladder, fatigue, cognitive difficulties	Intrathecal
PRPH2	Eye	Progressive vision loss to complete blindness	Intravitreal
SCN8A	Seizure Disorder	Intractable epilepsy, infantile spasms, multifocal seizures	Intrathecal
TARDBP	Motor Disorder, Neurodegenerative	Rapidly progressing and fatal ALS	Intrathecal

From Cases to Impact: Turning Science into Treatments Fast

- Fully automated, high-capacity ASO screening
  - Rapid and cost-effective
- Team productivity stat: 8-9 patient cases cleared per quarter by just 10 scientists -> translates to 10–15 INDs/year.
  - Perspective: this translates into >one IND/person/year. More productive than any other organization or drug modality
- Fully scalable systems and laboratory facilities sufficient to support more INDs per year



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Enabling Innovation: Where Science becomes Solutions

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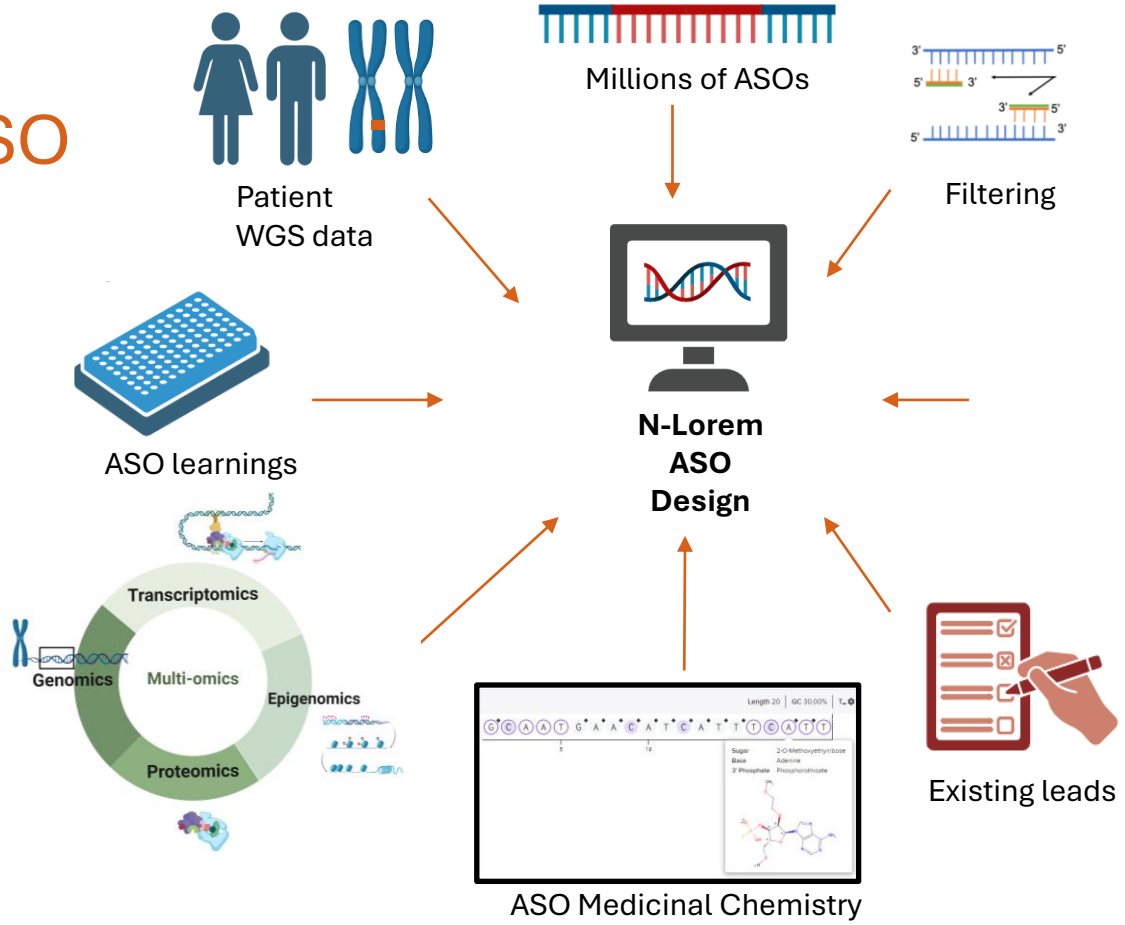
Proprietary AI-Driven ASO Design Platform

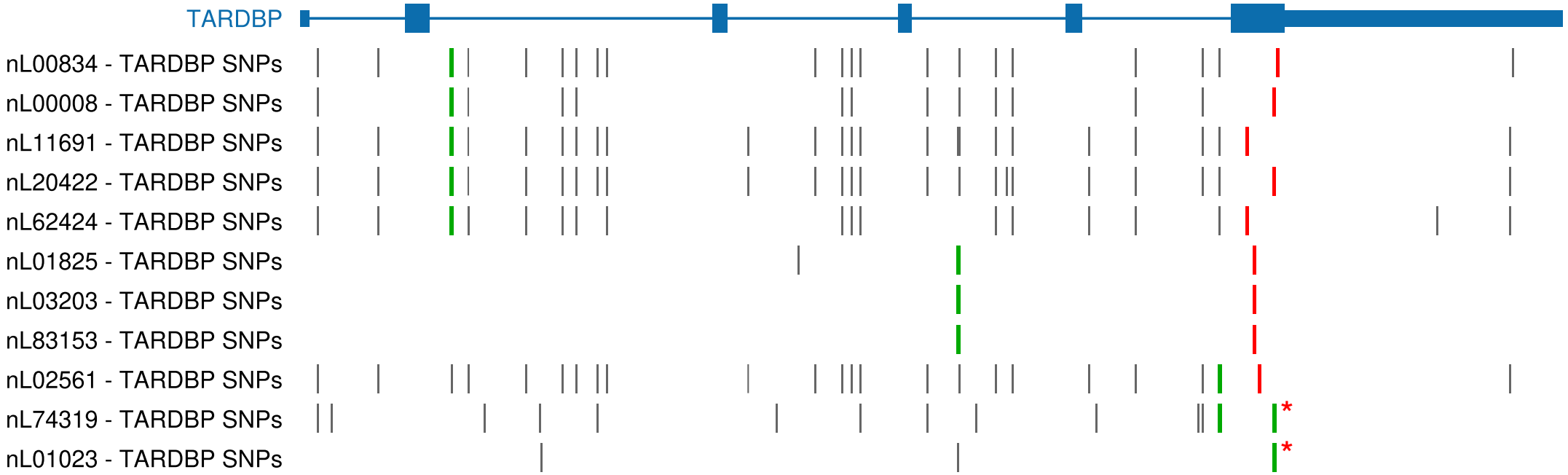
- Built from 35+ years of foundational ASO expertise and millions of ASOs
- Continuously refined using:
  - n-Lorem's high quality data
  - Multi-omics integration
  - Published datasets



Rapid, error-free SNP identification and design, enabling shared ASO solutions across patients

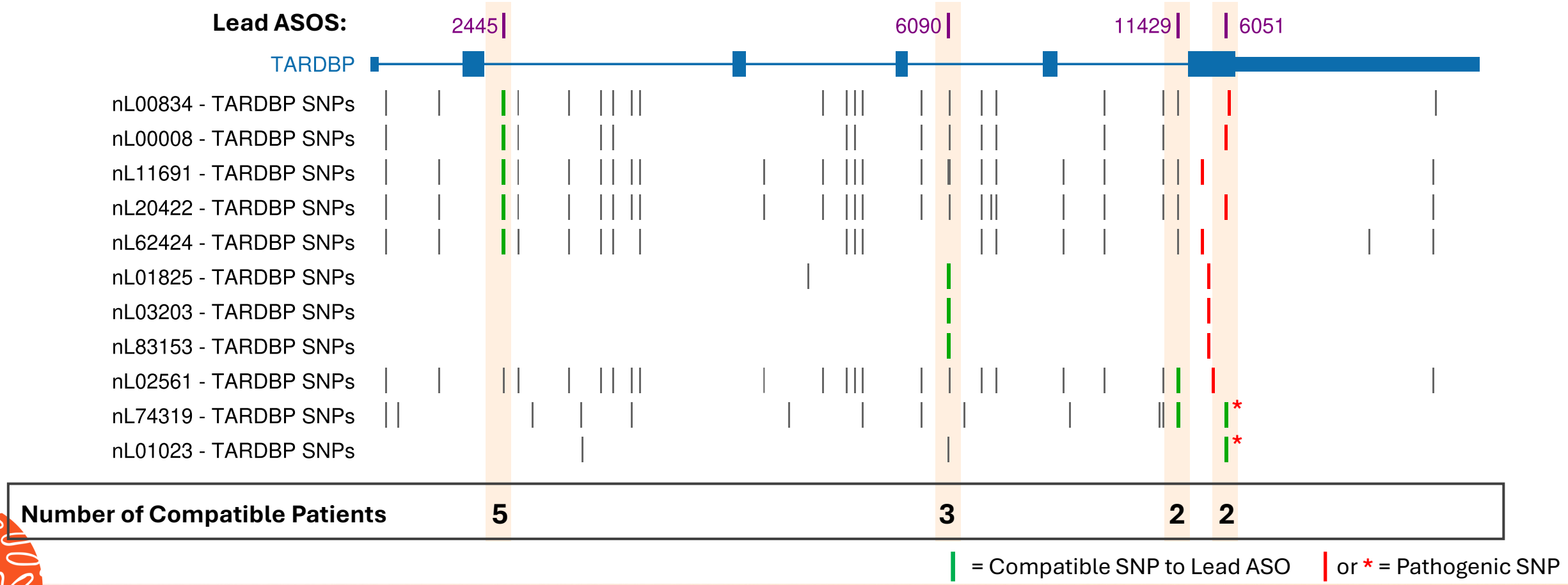
- We have built internal capabilities to enable ASO design that can treat multiple patients with the same allele-selective ASOs (KIF1A, SPTLC1, DHDDS, CACNA1A).
- We have built SNP – ASO maps to allow for rapid, error-free identification of how many patients in the pipeline can benefit from an existing ASO
- This means we can treat patients faster and cheaper.

Rapid, error-free SNP identification and design, enabling shared ASO solutions across patients



= Compatible SNP to Lead ASO | or * = Pathogenic SNP

Rapid, error-free SNP identification and design, enabling shared ASO solutions across patients



Pushing Boundaries: Research-Driven Innovation at the Forefront to help patients today

We are continuously tackling frontier problems in ASO discovery via advancing ASO technology to reach more patients in a safer, better way today

Some areas of ASO Research

we are focused on:

Impact Areas we are focused on: Next-Generation ASO Solutions

- **Novel approaches to allele-selectivity, including single SNP cases**
  - Treat more patients by enabling therapies for patient cases currently declined.
- **Designing ASOs for small, structured and heavily modified RNAs**
  - Essential genes that have crucial roles throughout our bodies.
- **Selectively increasing protein levels for loss of function mutations**
  - Expand to treat many of the patients we currently have to decline
- **Minimizing innate immune activation**
  - Create safer ASOs for central nervous system and peripheral administration
- **Understanding of molecular and cellular pathology of nano-rare mutations**
  - Could enhance drug discovery for many diseases
- **Resolving controversies and Clarifying the impact of nano-rare mutations on cell function**
  - When data don’t add up, we dig deeper, ensuring science drives the solution, not assumptions.

What is the nature of the mutation and is it ASO amenable? Case study JIP3

Mutation and Biology

MAPKI8P3 (JIP3) R578C missense mutation is a TGOF

- Alters interactome
- Disrupts axonal transport
- Overactivates JNK -> apoptosis
- Disrupts dopamine D1 signaling

Pathophysiology

Neuronal dysfunction

- Dystonia
- Developmental Delay
- Seizures
- A new cause of Parkinson's disease?

ASO Intervention

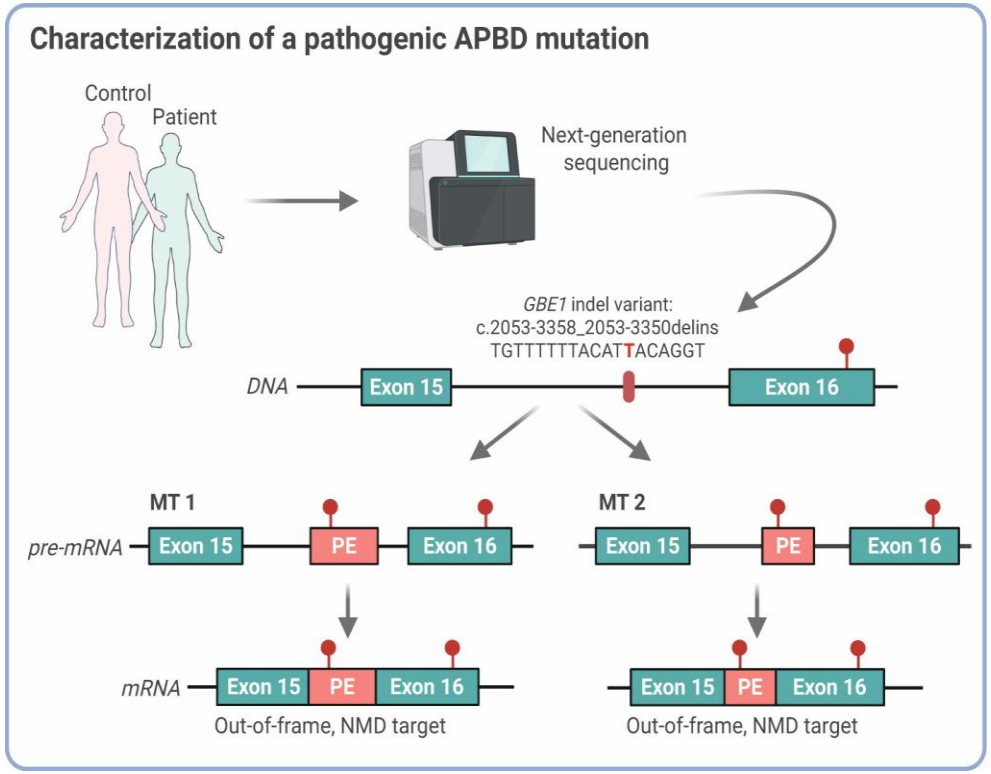
RNase H1 ASOs:

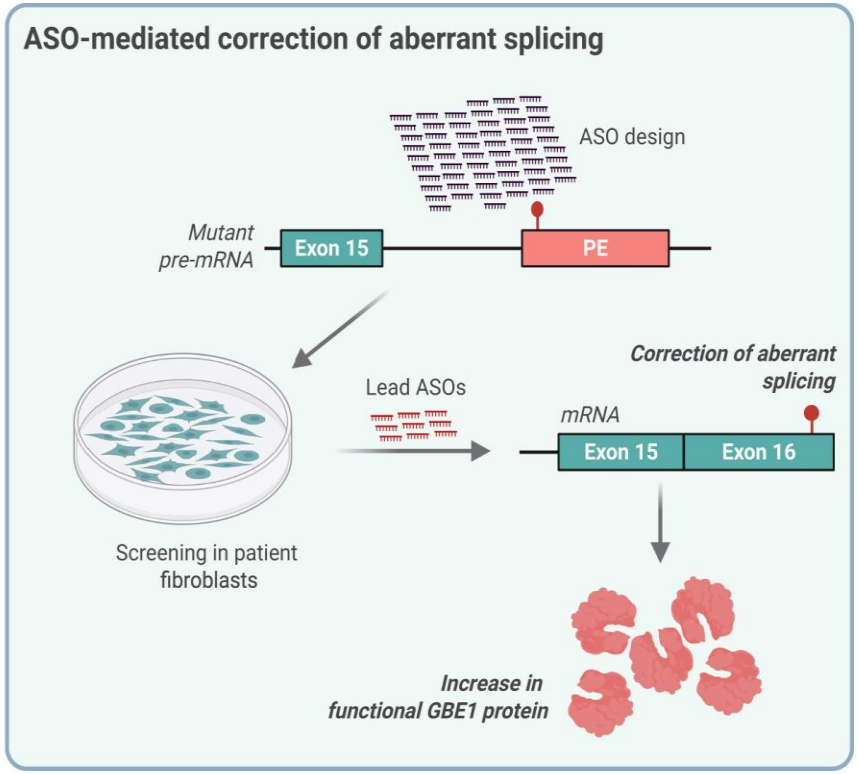
- Lower MT JIP3 80%
- Restored endosomal mobility
- Rescued neuronal viability
- Normalized dopamine D1 signaling

Allele-selective ASOs are the optimal therapeutic strategy for a TGOF mutation

Zhang et al. 2025 JCI Insights

When we need to go back and interrogate the science: Case study GBE1





Thomas et al. 2025 NAR

Minimizing innate immune activation: Delivering safer ASOs

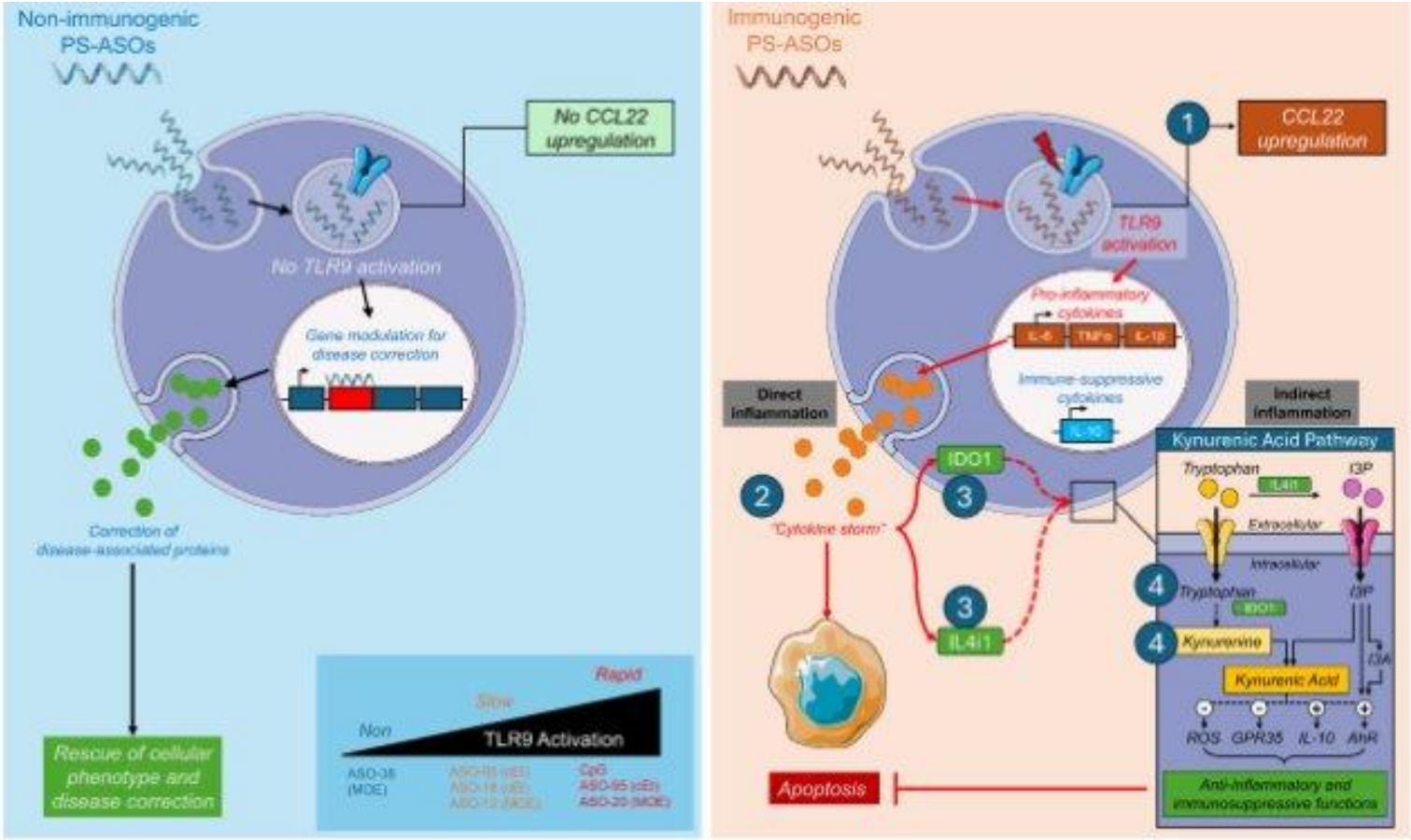
The Risk

- PS-ASOs can trigger **innate immune activation** (TLR9)
- Response is unpredictable: ASOs can be agonist, partial agonist, or not induce activation
- Risks: toxicity, burden of screening, **loss of therapeutic opportunity**

The Goal

- Determine **how** PS ASO-induced innate immune activation is **terminated**
- Determine **which metabolites** are terminators and if they can be **appropriate excipients** of IT or other routes of administration

When we need to minimize innate immune activation



Pytte et al. *submitted for publication*

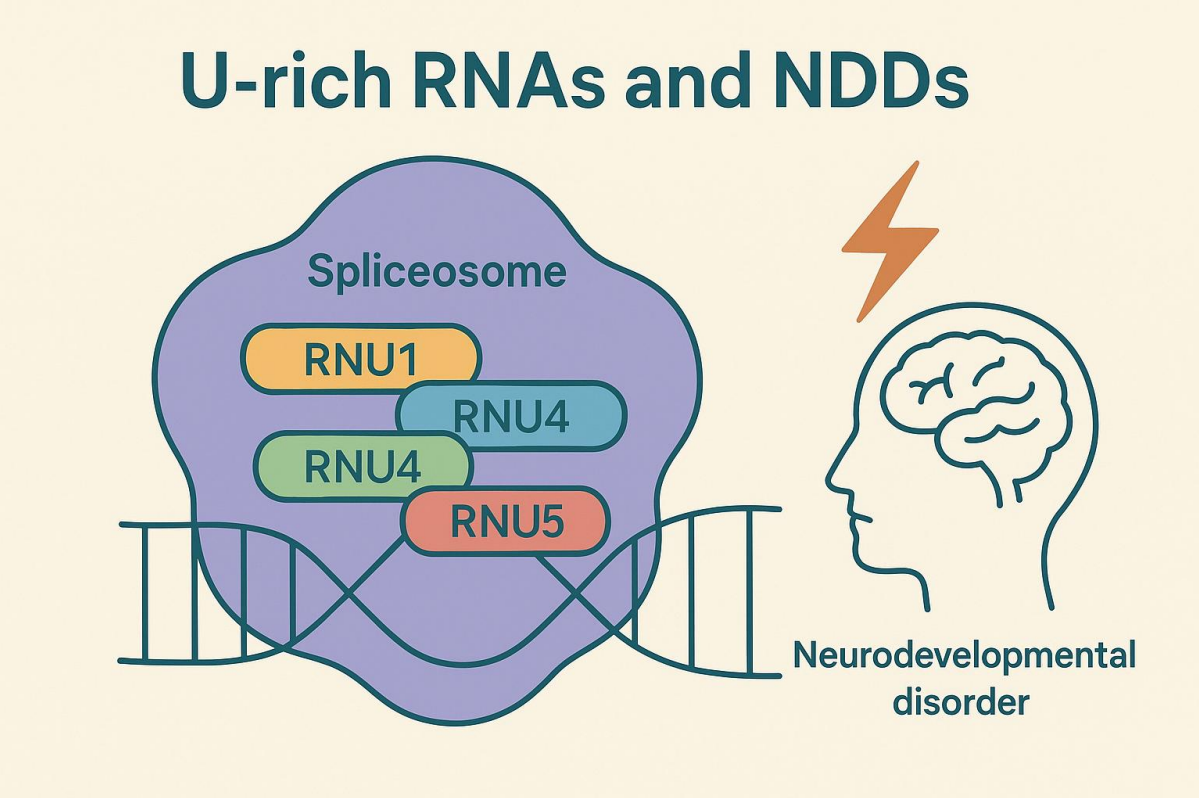
Refining the Most Complex Challenge in ASO Design

- Millions of patients have heterozygous mutations that require allele-selective ASOs
- **>50% of n-Lorem's patients require allele-selective ASOs**
- **Current approach is traditional brute screening around SNPs** = inefficient, limited potency, risk of cytotoxicity or immune activation
- **The balance**: precision determines both patient safety and therapeutic success

Leaders in Allele-Selective ASO Technology

- **Deep understanding of RNase H1 enzymology:** exploit unique cleavage patterns for true selectivity
- **High-throughput cleavage assays** to rapidly identify optimal cleavage sites
- **Integration of methyl-seq and RNA modifications** (2’-methoxy, m6A) to guide smarter ASO design
- **Novel chemistries** (mesyl-phosphoramidate, wing modifications) to minimize toxicity and immune activation
- An **integrated, data-driven approach:** replacing lengthy, sometimes inefficient screening with precision design

When we need to refine allele-selectivity: Case study RNU4-2



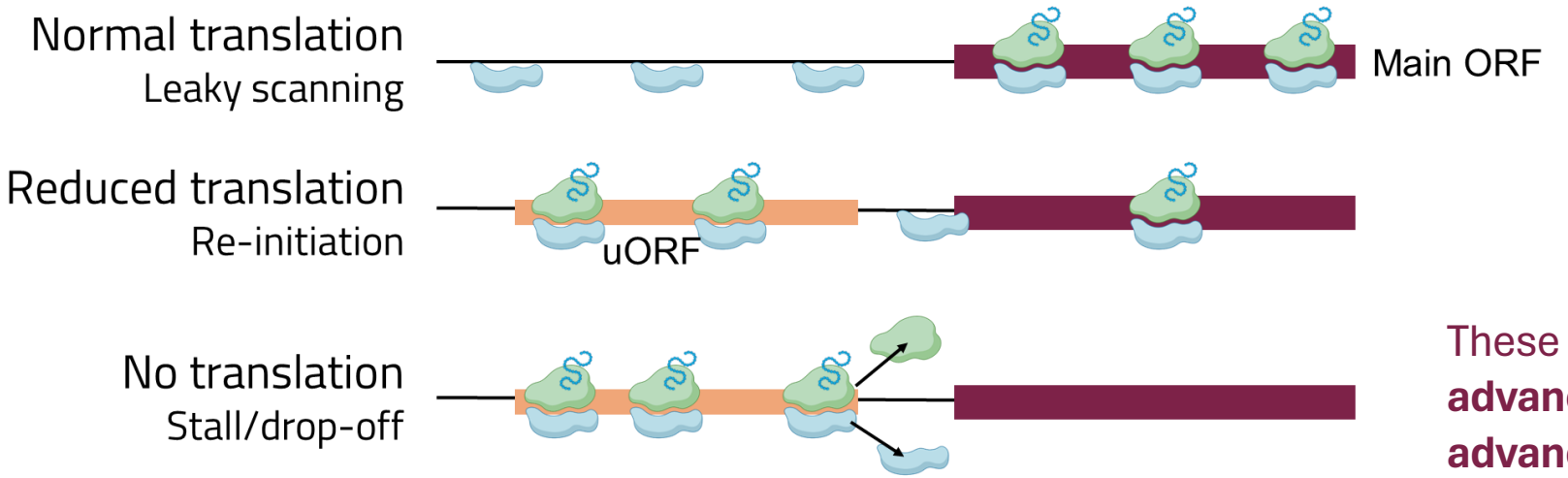
- Mutations in U-rich small nuclear RNAs are now recognized as a previously hidden but widespread cause of neurodevelopmental disorders. This is a **rapidly exploding field**.
- The ReNU syndrome**(RNU4-2)** currently appears to be the **most prevalent** and **best-characterized U-rich snRNA-related NDD**, with clear splicing defects shown.
- The mutation in RNU4-2 is not well-characterized: **we now know it's a TGOF**
- Due to the RNU4-2 length and structure, designing allele-selective ASOs is challenging: **we now have promising ASO candidates**

Zhang et al. *in preparation*

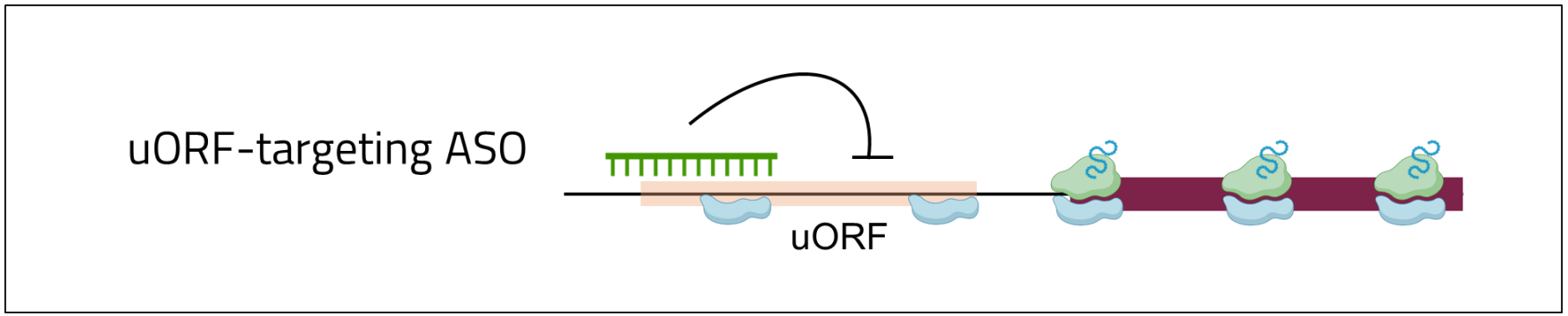
Selectively Increasing Protein levels for LOF mutations: Treating more patients

- **40% of drugs today are agonists** but many diseases need the opposite: more of the missing protein.
- n-Lorem is **pioneering ASO strategies** to *boost gene expression* in haploinsufficiency diseases.
- Previous, **proof-of-concept established** across multiple mechanisms by the Crooke lab:
  - Alternative splicing
  - PolyA site switching
  - uORFs (upstream open reading frames)
  - Translation inhibitory elements (TIEs)
  - Blocking inhibitory miRNA sites
- **We are unlocking treatment possibilities for diseases once thought untreatable**

When we need to treat LOF mutations



These solutions would represent a **major advance in the technology and major advance in the therapeutics landscape**



Vu et al. *in preparation*

Expanding the Boundaries of ASO Technology

Now

- Potent, efficacious and safe ASOs
- 90% discovery success
- Treating more patients today than yesterday

Next

- Improving allele-selectivity
- Expanding upregulation efforts and splicing tools
- Minimizing immunogenicity risks

Beyond

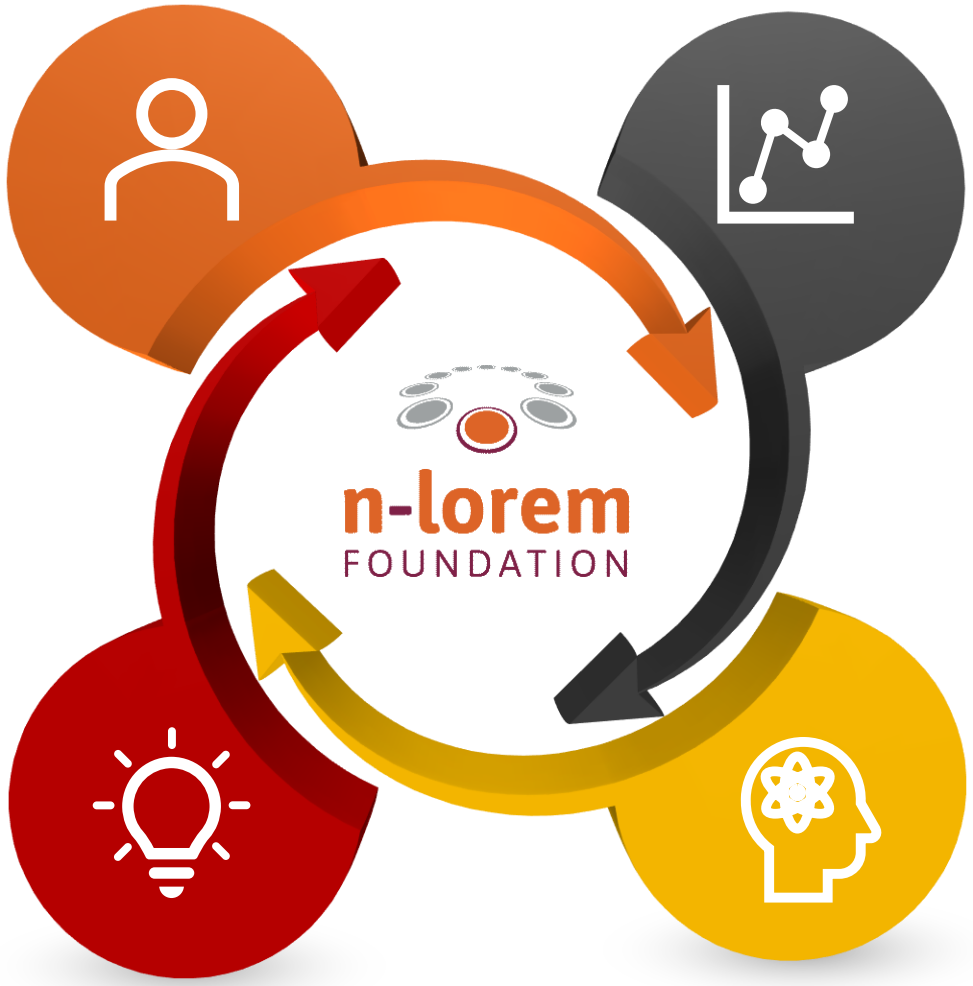
- Single SNP cases
- Small, structured RNAs
- Haploinsufficiencies
- Expanding reach across diseases

At n-Lorem, the next chapter in ASO advancement is already underway

Every Patient Advances the Science: From Patient to Knowledge to Hope

Patient

Data



Better Solutions

Knowledge

Delivering Impact, Advancing Knowledge

- Our ASOs are **potent, efficacious and safe**
- We can treat **more patients today than we treated yesterday**
- **Creating lasting knowledge** that we share with the community: Multiple peer-reviewed publications and patent filings emerging from this work
- Our work demonstrates that **efficiency and quality are not trade-offs**, they're mutually reinforcing when the platform is right.

Conclusions

- **Built for urgency**: We operate at the intersection of patient need and scientific possibility.
- **Built for scale**: The discovery platform is robust, adaptive, and continually learning
- **Built for hope**: Every ASO we make is a shot at a better life for someone with no other options.
- Industrialized approach, scientific rigor and deep ASO experience assure that we provide **optimal safe ASOs**
- And we are not satisfied: we are advancing the technology to be able to treat **more patients better, faster**

Thank you!

For believing in Science and what it can do for patients

- Anahid Foroughishafei
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- Julia Pytte
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- Lesley Saldana
- Andrew Sanginario
- Mike Taylor
- Anthony Vu
- Wei Zhang