



**n-lorem**  
FOUNDATION

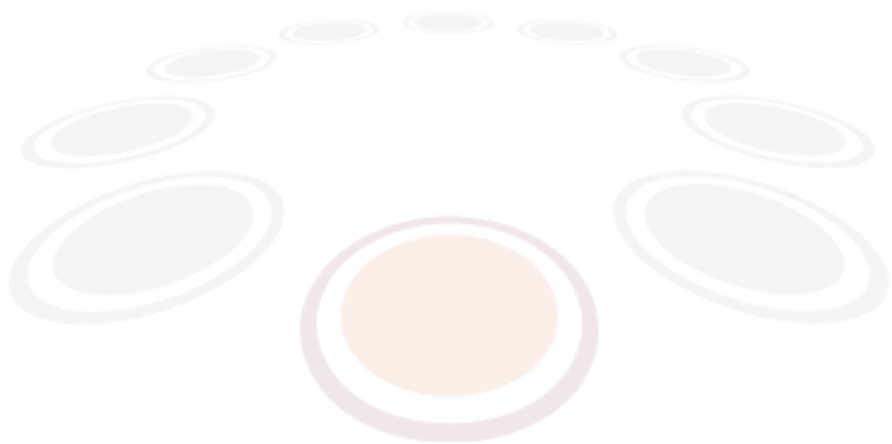
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# Introduction

September 2023

# mission

n-Lorem's mission is to apply the efficiency, versatility and specificity of antisense technology to charitably provide experimental antisense oligonucleotide (ASO) medicines to treat patients with nano-rare diseases (<30 patients worldwide).



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# n-LoREM Summary of Progress

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- Demand greatly exceeds expectation and continues to increase
- Fraction of applications approved for ASO treatment also substantially exceeds expectations
  - >225 submissions with ~100 patients approved for ASO treatment
  - 9 INDs filed, 5 patients on treatment
- Highly supportive FDA guidance unique to ASO treatment
- Quality systems established and functioning well
- Outstanding senior management team assembled and working well
- Established as the site of industrialized non-profit personalized experimental ASO provider
- Accumulating data provide encouraging evidence of personalized ASO benefit
- New laboratory facility established that increases capacity by 2 to 3 fold
- Systems and infrastructure to support expansion to treat thousands of patients
- Partnering greatly exceeded expectations



# Nano-rare: (1-30 Patients in the World)

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## Isolated and Desperate

Most nano-rare patients are never diagnosed

Average time to diagnosis is 6 years

Though each patient is unique, there may be millions worldwide

## Limited to No Options

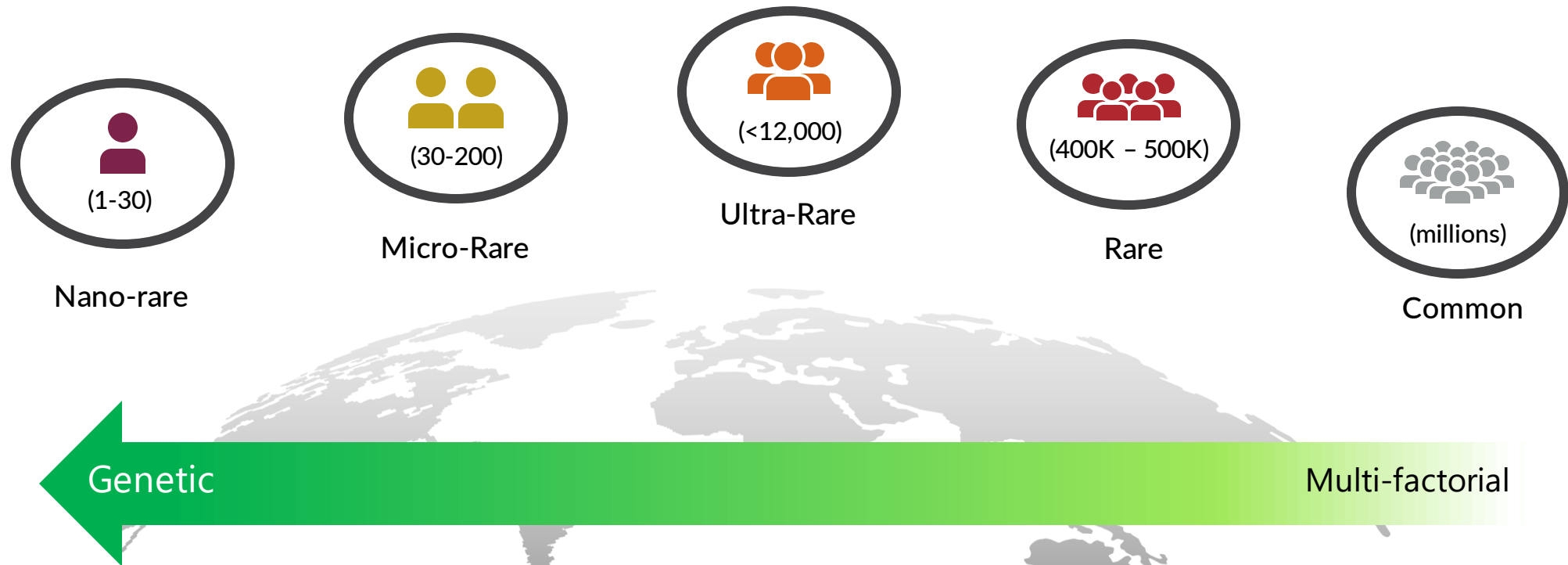
Mutation-driven drug discovery and development

Standard commercial model cannot work for nano-rare patients

Novel nonprofit model required



# Nano-rare: 1 to 30 Patients Worldwide



# Conceptual Framework

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- A drug discovery platform rapid and efficient enough to discover, develop and provide a **novel personalized** medicine to 1 patient
- Industrialization of the process to assure
  - Highest quality at each step
  - Meeting the needs of many nano-rare patients
- A non-profit model
  - Discover, develop and provide experimental treatments as a public service
  - Develop holistic patient support systems
- Maximize and disseminate learnings



# Nano-rare Patients Present Unprecedented Challenges to the Entire Health Care System

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- Identification and genetic characterization
  - Most nano-rare patients are never diagnosed
  - For the fortunate few patients who are diagnosed the journey is perilous and long
- Personalized patient-by-patient treatment is required
  - Rapid response
  - Life-long commitment
- Though each patient is unique, millions of nano-rare patients are thought to exist



# Anna's Story of Hope and Help



**Early 2020**

Symptomatic

**Oct 2020**

Diagnosed with ALS

**Dec 2020**

Treatment begins

**Aug 2021**

Dysphagic event requiring resuscitation and rehospitalization and induced coma

**Oct 2021**

Walking a few steps, fine motor skills returning

**During 2022 Continued Gains**

Stairs without support, independent breathing progressively longer

**December 2020: Treatment Begins :**

**Dec 2020**

Feeding tube, ventilator at night and can no longer hold her head up

**July 2021**

Symptoms improved including Regaining ability to walk up stairs

**Sept 2021**

Anna goes home

**Dec 2021**

Breathing on own for 1 hour, able to walk up stairs assisted

**Jan. 2023**

More rapid stair climbing and greater stamina  
Breathes on own for >12hrs/day  
Voice returns

**2004: Newborn**

All appearances, a healthy baby





# Anna's Story of Hope and Help

Anna: Oct. 2020  
Age 15 at diagnosis of ALS

Making the impossible possible – today



## Kelley and Connor Dalby

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(Click  to watch)

# Patient YouTube Video

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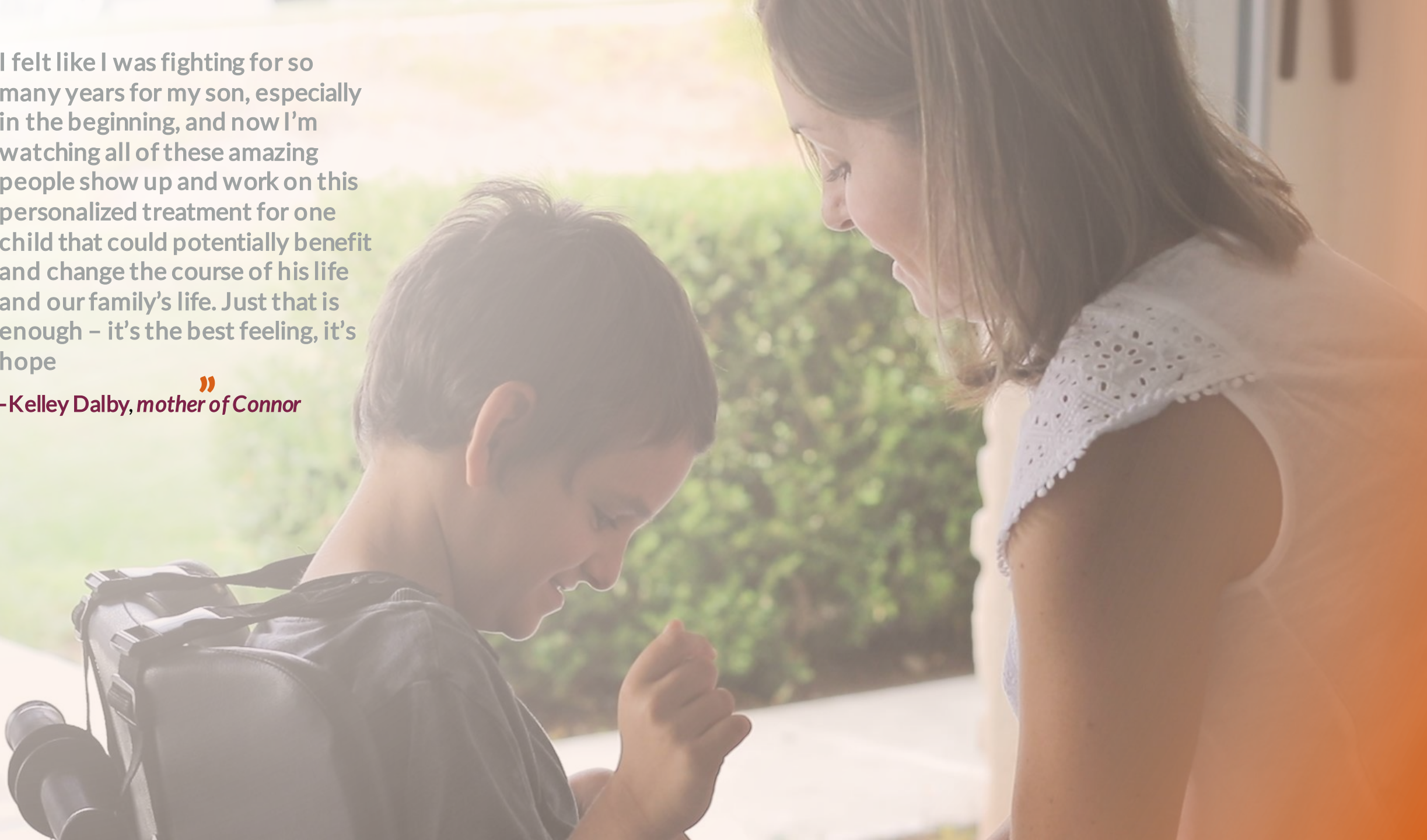


(Click image to watch)



“ I felt like I was fighting for so many years for my son, especially in the beginning, and now I’m watching all of these amazing people show up and work on this personalized treatment for one child that could potentially benefit and change the course of his life and our family’s life. Just that is enough – it’s the best feeling, it’s hope

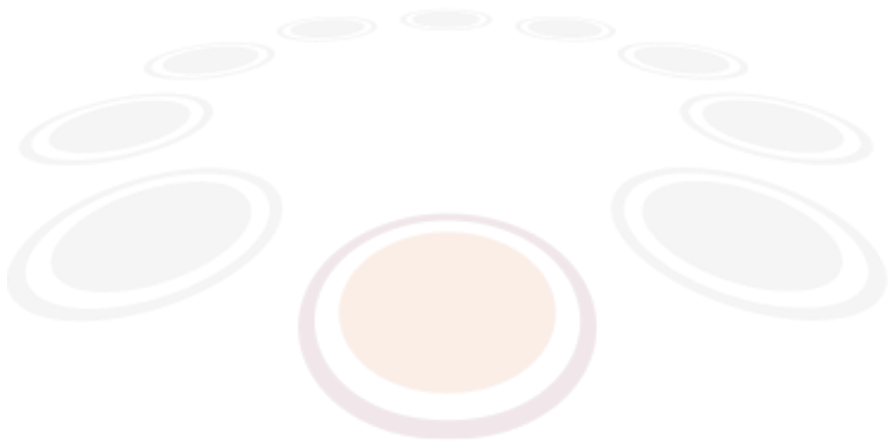
”  
-Kelley Dalby, *mother of Connor*



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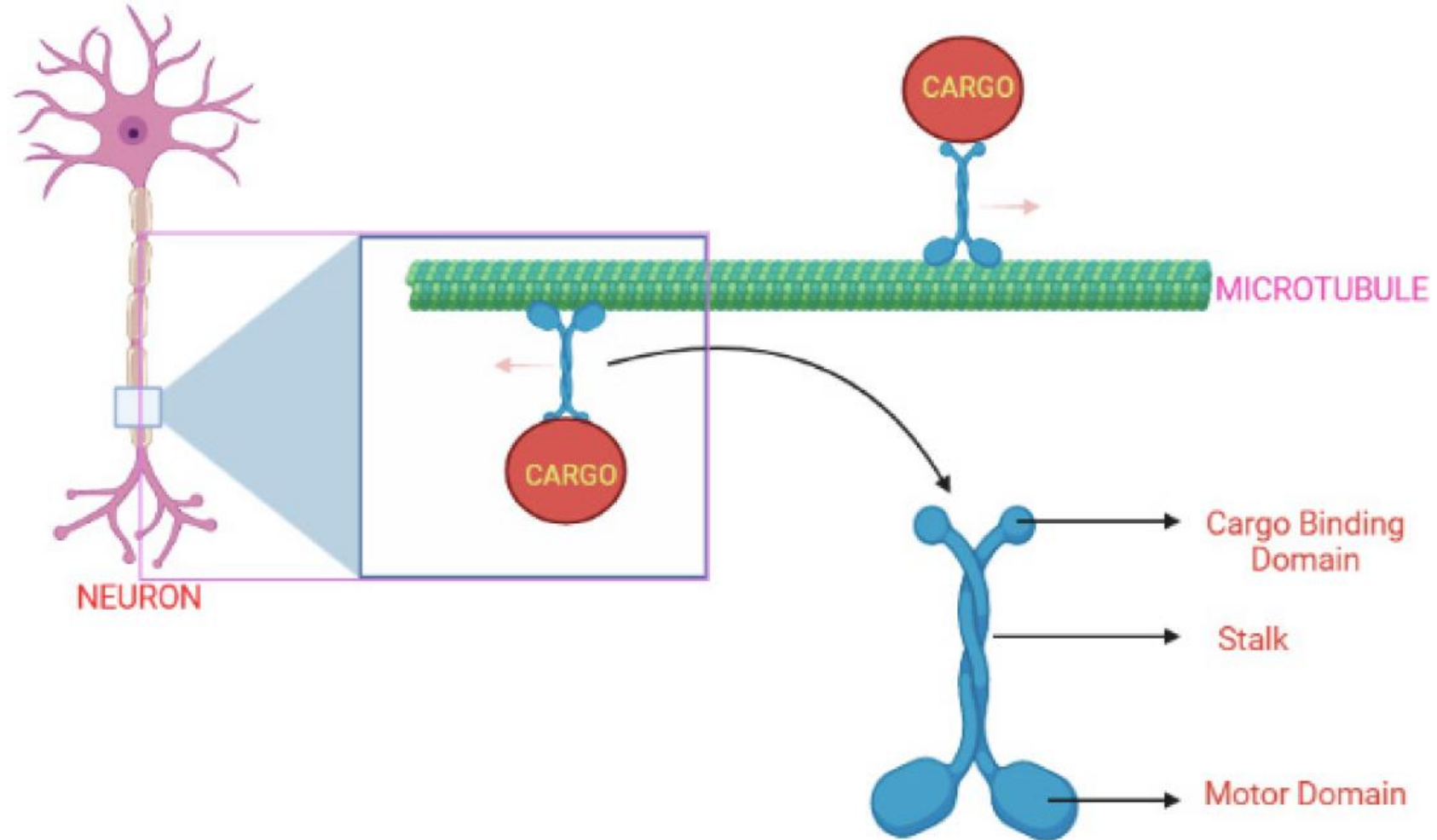
# KIF1A : An Allele-Selective Approach

## Susannah's Program



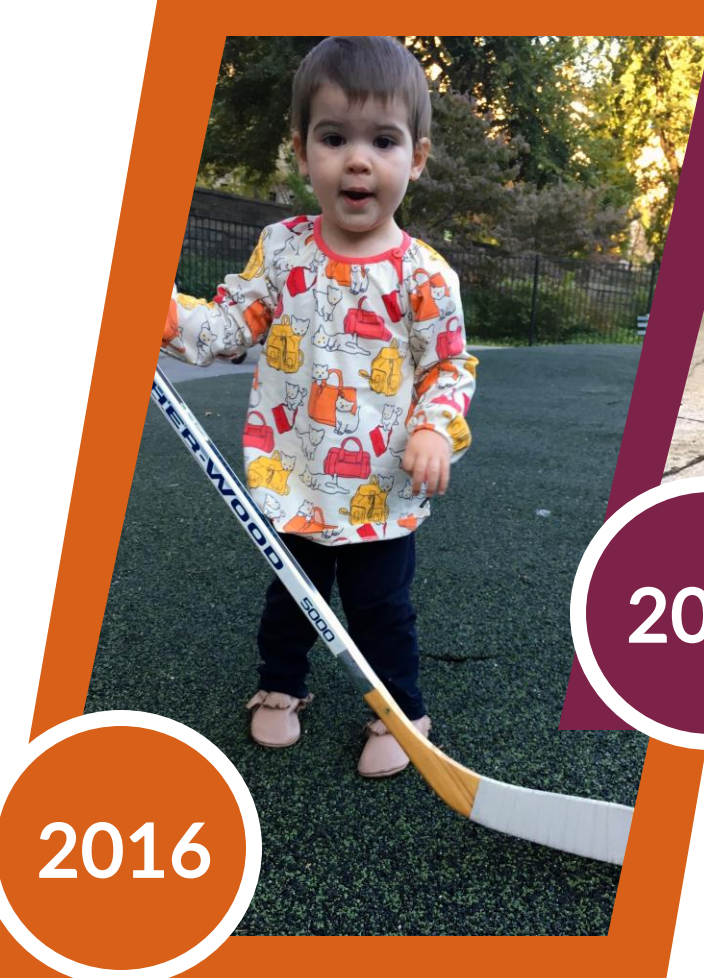
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# KIF1A Protein's Typical Shape and Movement Along the Microtubule Surface



Nair, A. *et al.* (2023)





2016

2018



2020



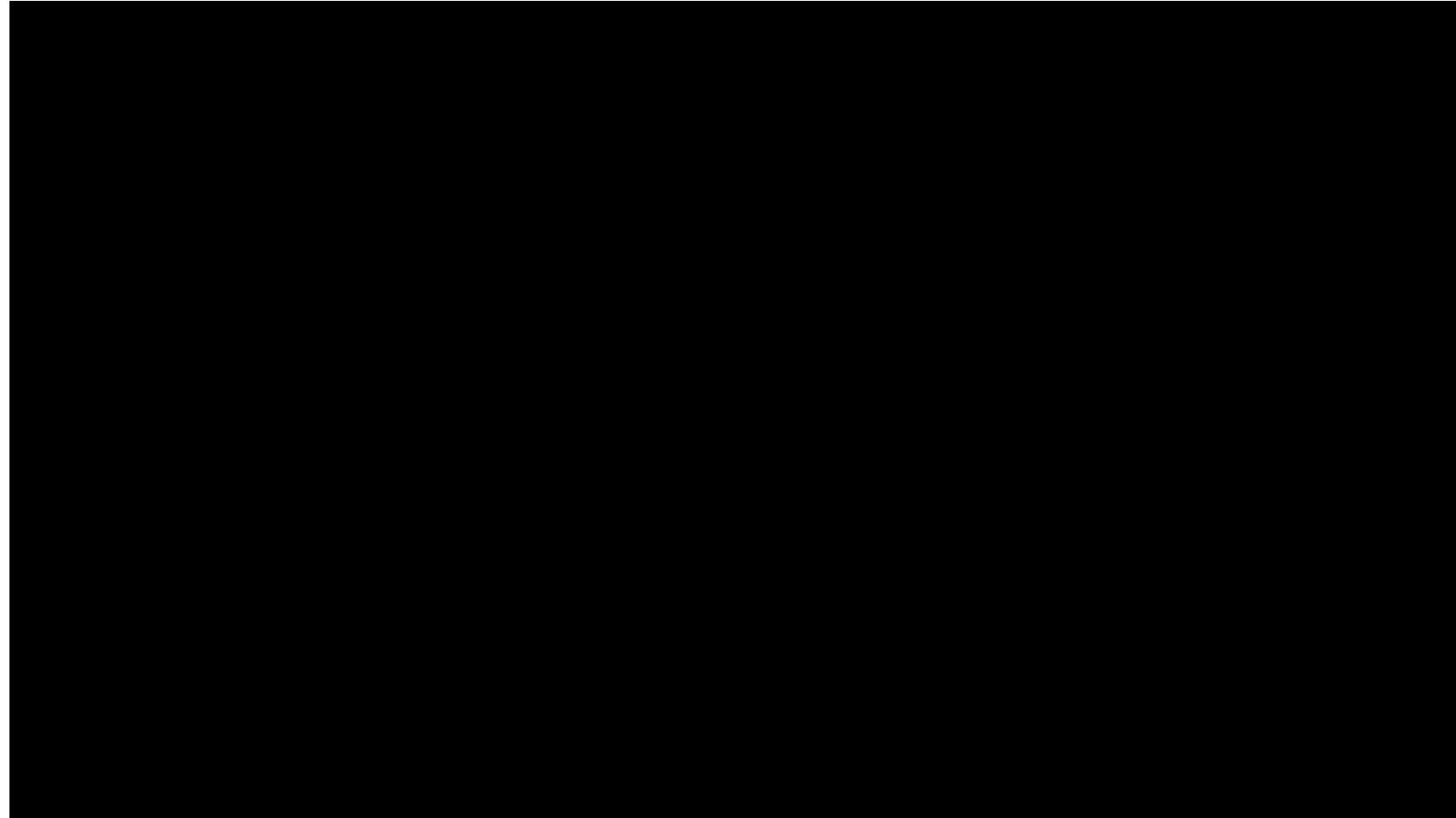
2021



“ I want Susannah to grow up and not know the meaning of the word degenerative. ”

-Luke, father of Susannah

# Susannah's Story of Hope and Help



**Making the impossible possible – today!**



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# Roles of n-Lorem



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# Roles of n-Lorem

**Treat**

Treat those patients who can be treated today

**Assure quality at every step**

Quality systems/Quality ASOs

**Leverage All Stakeholders to Maximize Value**

Establish broad network of collaborations

**Maximize Learning**

Individualized natural history & clinical trial plans

**Share Learnings**

Annual publication of results, investigator and patient meetings

**Play a Lead Role in Establishing Holistic Solutions**

Create pathway and model for others to follow

**Patient Support**

Nano-rare podcast series, patient advocacy support, website



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# Necessary Components to Meet The Needs of Nano-rare Patients



# Meeting The Needs of Nano-rare Patients

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- A solution to:
  - Insufficient health care funding to provide quality care for all patients
  - The inability of the nano-rare patient to compete for funding in any health economic-based investment approach
- Key Partners for Diagnosis and Treatment of Nano-rare Patients
- Supportive regulatory environment
- Technological feasibility



# A Non-Profit Solution – The Only Viable Approach Today

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- In the US and in most developed economies, investment in health care is inadequate to provide **quality care** to all patients
  - The gap in investment in health care vs. demand is likely to worsen
  - **nano-rare patients** are unlikely to compete well for **limited health care dollars** in any medical economics-based analysis
- Currently **no path** to **commercial** approval for single patients or patient populations of 1-30 worldwide
- ASO guidelines **apply** only to **nonprofit** efforts
  - Both pre-commercial and commercial regulatory demands and costs would be substantial
- The logistics of a clinical trial for a population of 30 or less patients make such a trial virtually impossible to conduct



# Key Partners for Diagnosis and Treatment of Patients



UDN and other personalized medicine centers are critical to diagnosis and treatment of nano-rare patients

- Diagnosis
- Genomic and phenotypic characterization
  - Nature of mutation
  - Gene function (target risk)
  - Genotype and phenotype
- Organs affected
- Main complaint
- Secondary issues
- Investigator capable of filing and managing an investigator-initiated IND
- Institution capable of managing an investigator-initiated IND



# Regulatory Support Established - ASO Guidance Issued



- FDA response to n-Lorem concept supportive
- n-Lorem posed questions that require policy decisions, but progress toward policies evident
- In the meantime, experience facilitating ASOs for individuals provides real-life guidance
- Initial FDA guidance for ASO for patients with diseases caused by ultra-ultra-rare mutations: [Jan. 4, 2021](#)
- Pre-clinical requirements: Detailed guidance April 2021
- CMC guidance [Dec 2021](#)
- Clinical guidance [Dec 2021](#)



# Some Recent Reviews on RNA-Targeted Drug Discovery

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- **Crooke, S.T., Baker, B.F., Crooke R.M., Liang, X.H.** Antisense Technology: An Overview and Prospectus. *Nature Review Drug Discovery*, 2021, 1-27.
- **Crooke, S.T., Baker, B.F., Crooke R.M., Liang, X.H.** Antisense technology a broadly enabling drug discovery technology? Molecular mechanisms. *J Biological Chemistry* 2021. 296:1-39.
- **Crooke, S.T., Liang, X.H., Crooke R.M., Baker, B.F., Geary, R.S.** Antisense Drug Discovery and Development Technology Considered in a Pharmacological Context. *Biochemical Pharmacology* 2020 ;114196.
- **Crooke, S.T., Seth., P.P., Vickers, T.A., Liang, X.H.** The Interaction of Phosphorothioate Containing RNA Targeted Drugs with Proteins is a Critical Determinant of The Therapeutic Effects of These Agents. *J. Am. Chem. Soc.* 2020, 142, 35, 14754–14771
- **Crooke, S.T., Vickers, T.A., Liang, X.H.** Phosphorothioate modified oligonucleotide–protein interactions. *Nucleic Acids Research*, 48(10):5235–5253, 2020.
- **Crooke, S.T., Witztum, J.L., Bennett, C.F., Baker, B.F.** RNA-Targeted Therapeutics. *Cell Metabolism* 29(2):231-54, 2018.
- **Seth, P.P, Cooke, S.T., Anderson, B.A., et al.** Towards Next Generation Antisense Oligonucleotides: Mesylphosphoramidate Modification Improves Therapeutic Index and Duration of Effect of Gapmer ASO. *Nucleic Acids Research*, 49(16) 9026 – 9041.





# RNA-Targeted Drugs Have Arrived

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- 15 RNA-targeted drugs approved
- First 'Blockbuster': Spinraza
- Expect approval of Ionis' ASO: eplontersen
- Multiple Ionis ASOs targeting large cardiovascular, metabolic and neurological diseases in advanced clinical development
- >250,000 patients treated
- >20,000 patient treated intrathecally
- Multiple chemical classes of PS ASOs studied thoroughly in man
- Multiple safety databases for Ionis ASOs published



# ASO Technology Makes n-Lorem Feasible

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- **Rapid and efficient**
- **Versatile**
  - Multiple post-binding mechanisms
  - Multiple routes of administration
  - Multiple organs
- **Validated and well understood**
  - Potent
  - Pharmacokinetics
  - Integrated safety databases
- **Cost effective**
  - Sophisticated automation: rapid, inexpensive, optimal ASO discovery
  - Potent and long-lasting ASO effects
  - Low manufacturing cost
- **Scalable**
- **Supported** by regulatory authorities



# Safety Databases That Integrate All Safety Observations

NUCLEIC ACID THERAPEUTICS  
Volume 27, Number 3, 2017  
Mary Ann Liebert, Inc.  
DOI: 10.1089/nat.2016.0650

## Original Articles

### The Effects of 2'-O-Methoxyethyl Containing Antisense Oligonucleotides on Platelets in Human Clinical Trials

Stanley T. Crooke,<sup>1</sup> Brenda F. Baker,<sup>1</sup> Joseph L. Witztum,<sup>2</sup> T. Jesse Kwoh,<sup>1</sup> Nguyen C. Pham,<sup>1</sup> Nelson Salgado,<sup>1</sup> Bradley W. McEvoy,<sup>1</sup> Wei Cheng,<sup>1</sup> Steven G. Hughes,<sup>1</sup> Sanjay Bhanot,<sup>1</sup> and Richard S. Geary<sup>1</sup>

NUCLEIC ACID THERAPEUTICS  
Volume 28, Number 1, 2018  
Mary Ann Liebert, Inc.  
DOI: 10.1089/nat.2017.0693

## Original Articles

### The Effects of 2'-O-Methoxyethyl Oligonucleotides on Renal Function in Humans

Stanley T. Crooke, Brenda F. Baker, Nguyen C. Pham, Steven G. Hughes, T. Jesse Kwoh, Danlin Cai, Sotirios Tsimikas, Richard S. Geary, and Sanjay Bhanot

Official journal of the American Society of Gene & Cell Therapy

*MTOpen*

*original article*

### Integrated Safety Assessment of 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides in NonHuman Primates and Healthy Human Volunteers

Stanley T Crooke<sup>1</sup>, Brenda F Baker<sup>1</sup>, T Jesse Kwoh<sup>1</sup>, Wei Cheng<sup>1</sup>, Dan J Schulz<sup>1</sup>, Shuting Xia<sup>1</sup>, Nelson Salgado<sup>1</sup>, Huynh-Hoa Bui<sup>1</sup>, Christopher E Hart<sup>1</sup>, Sebastien A Burel<sup>1</sup>, Husam S Younis<sup>1,2</sup>, Richard S Geary<sup>1</sup>, Scott P Henry<sup>1</sup> and Sanjay Bhanot<sup>1</sup>

NUCLEIC ACID THERAPEUTICS  
Volume 29, Number 1, 2019  
Mary Ann Liebert, Inc.  
DOI: 10.1089/nat.2018.0753

## Original Articles

### Integrated Assessment of the Clinical Performance of GalNAc<sub>3</sub>-Conjugated 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides: I. Human Volunteer Experience

Stanley T. Crooke, Brenda F. Baker, Shuting Xia, Rosie Z. Yu, Nicholas J. Viney, Yanfeng Wang, Sotirios Tsimikas, and Richard S. Geary



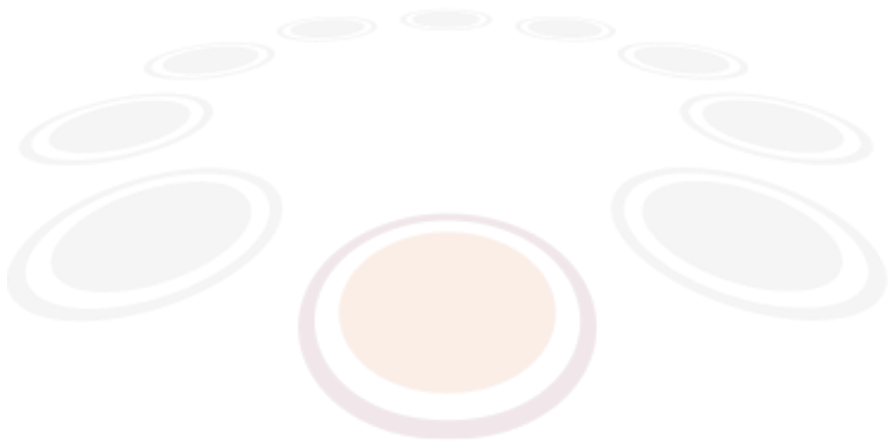
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**The n-Lorem Approach To Assure  
That Each Patient Is Treated With  
The Optimal Personalized ASO**

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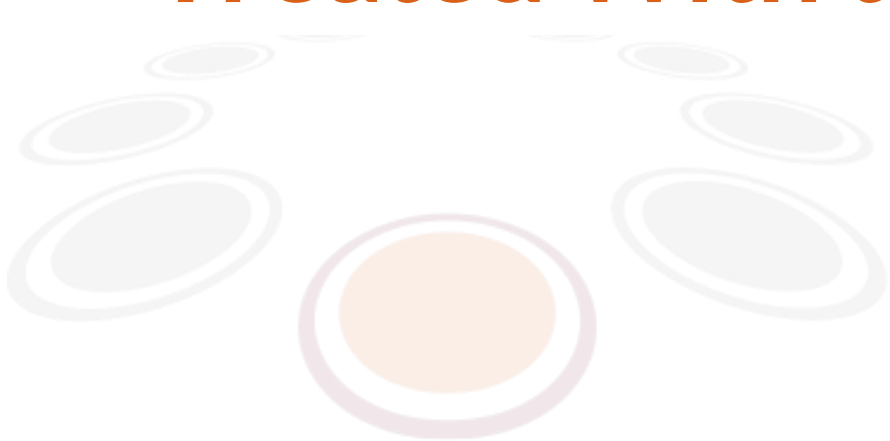
# All ASOs Are Not Created Equal



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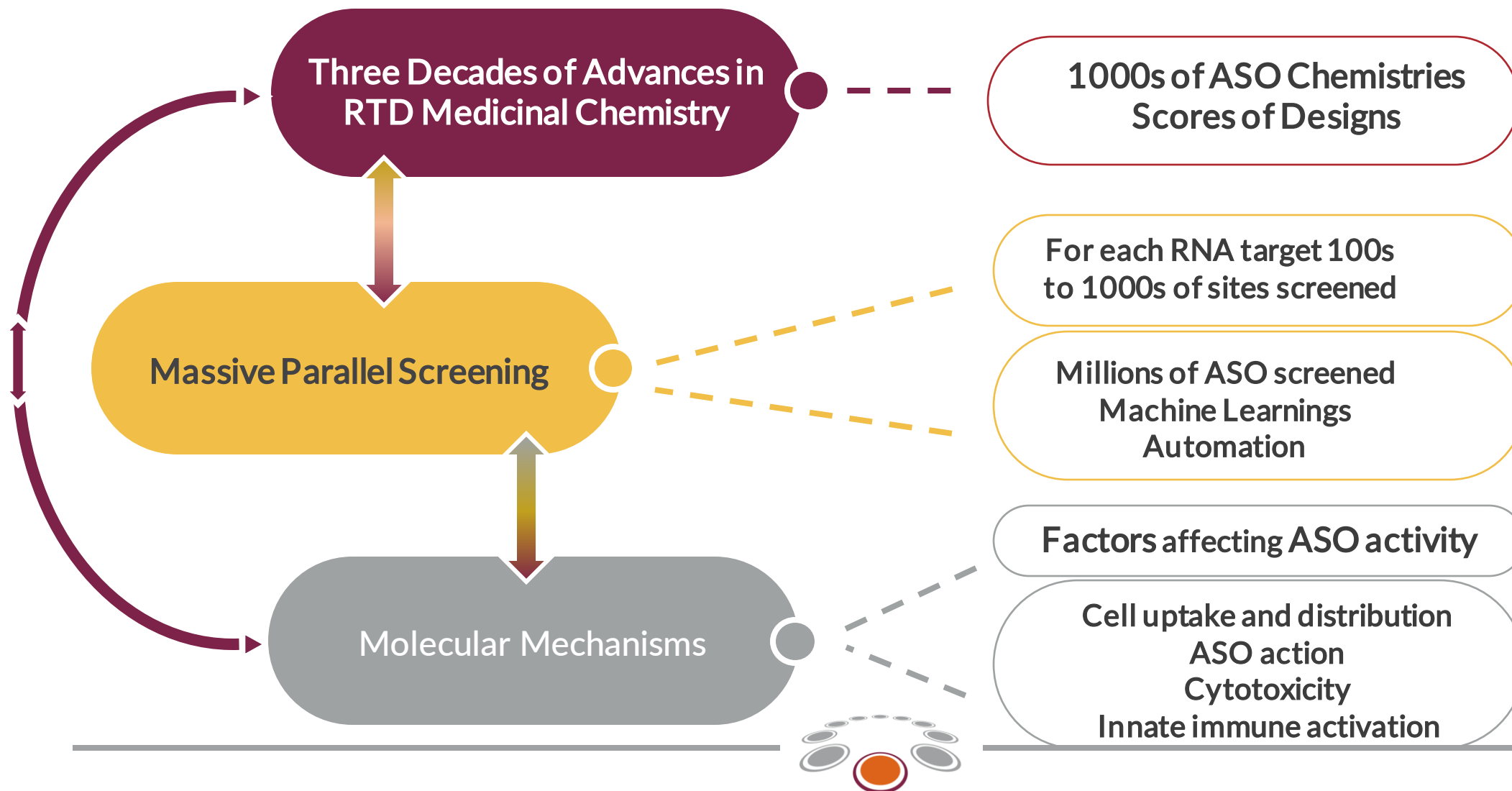
**n-Lorem Benefits From More Than 30 Years  
of Basic Research In Advancing ASO  
Technology to Assure Each Patients is  
Treated With the Best ASO Possible**



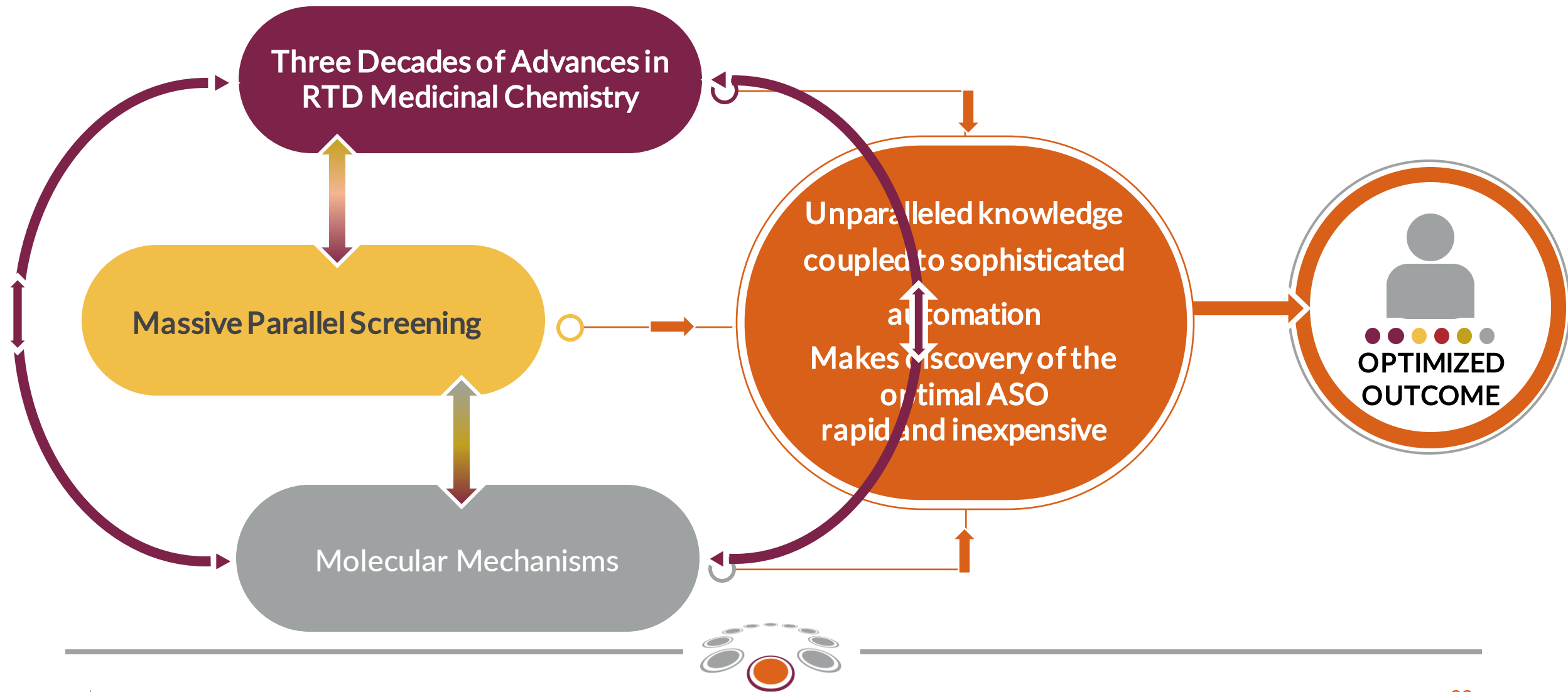
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# More Than 3 Decades Of Innovation

## Optimal ASOs for Nano-rare Patients







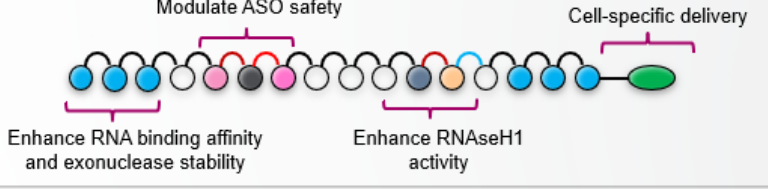


# More Than 3 Decades Of Innovation Optimal ASOs for Nano-rare Patients





# More Than 3 Decades Of Advances In The Medicinal Chemistry of RNA Targeted Drugs

Current Designs	Class	Mechanism
	Gen1	RNaseH1
	Gen2	RNaseH1
	Gen2 LICA	RNaseH1
	Gen2	Splicing/Other
	Gen 2*	ssRNAi
	Gen2.5; LICA	RNaseH1
Near Future Design		
	Gen3, LICA	RNaseH1

DNA ○ MOE ● cEt ● RNA ● 2'-OMe ● MOP/Other ● PS ○ New Linker ● PO<sub>4</sub> Analog ● Cell-targeting moiety ●

Crooke, S.T., et al. (2021) JBC, in press

- Hundreds of ASO chemistries
- Scores of designs
- Scores of cell lines including human cells

Migawa, M.T., *NAR* 2019, 47(11): 5465-5479; Crooke ST et al., *Nature Review Drug Discovery*, 2021, 1-27; Crooke ST et al., *JBC*, 2021. 296:1-39; Anderson, B.A., *NAR* 2021, 49(16): 9026-9041;



# Validated Routes of Administration for PS ASOs

## SYSTEMIC

- Intravenous
- Intramuscular
- Subcutaneous
- Oral

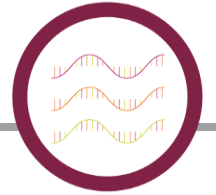
## LOCAL

- Intravitreal
- Intrathecal
- Aerosol
- Rectal

Crooke ST et al., *NAR*, 2020, 48(10):5235-5253; Crooke ST et al., (2020) *JACS* 142(35):14754-14771, Crooke ST et al., *Nature Review Drug Discovery*, 2021, 1-27, Crooke ST et al., *JBC*, 2021. 296:1-39; Crooke ST et al., *Biochem Pharm*, 2021 Jul;189:114196.



# Potency of Modern ASOs in Select Organs



Organs	Routes	Total ANNUAL dose
CNS	IT	500 mg
Liver	SQ	200 mg
Lung*	Aerosol	3 gm
Kidney	SQ	5-10 gm
Eye	Intravitreal	<50 mg

Low dose and long duration of effect make manufacturing costs of ASO very low

\*aerosol delivery to be introduced



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# n-Lorem Is Off To An Extraordinary Beginning



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# N-Lorem Founding Donors

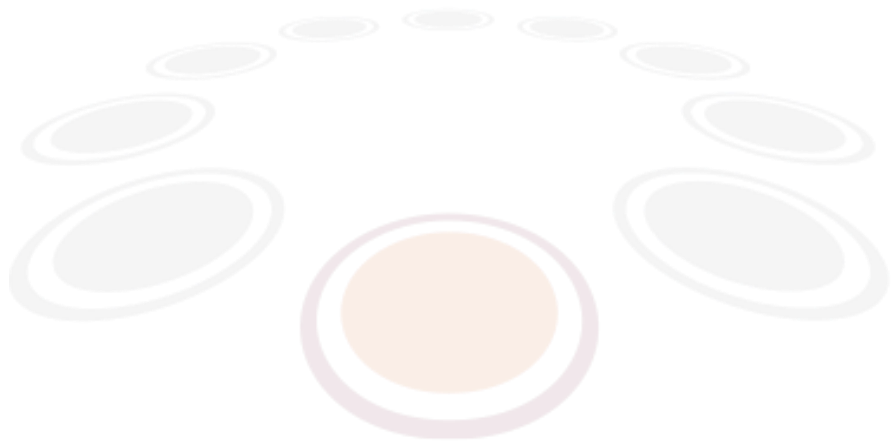
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- Ionis Pharmaceuticals, Inc.
- Biogen Inc.
- Stanley T. Crooke, MD, PhD & Rosanne M. Crooke, PhD



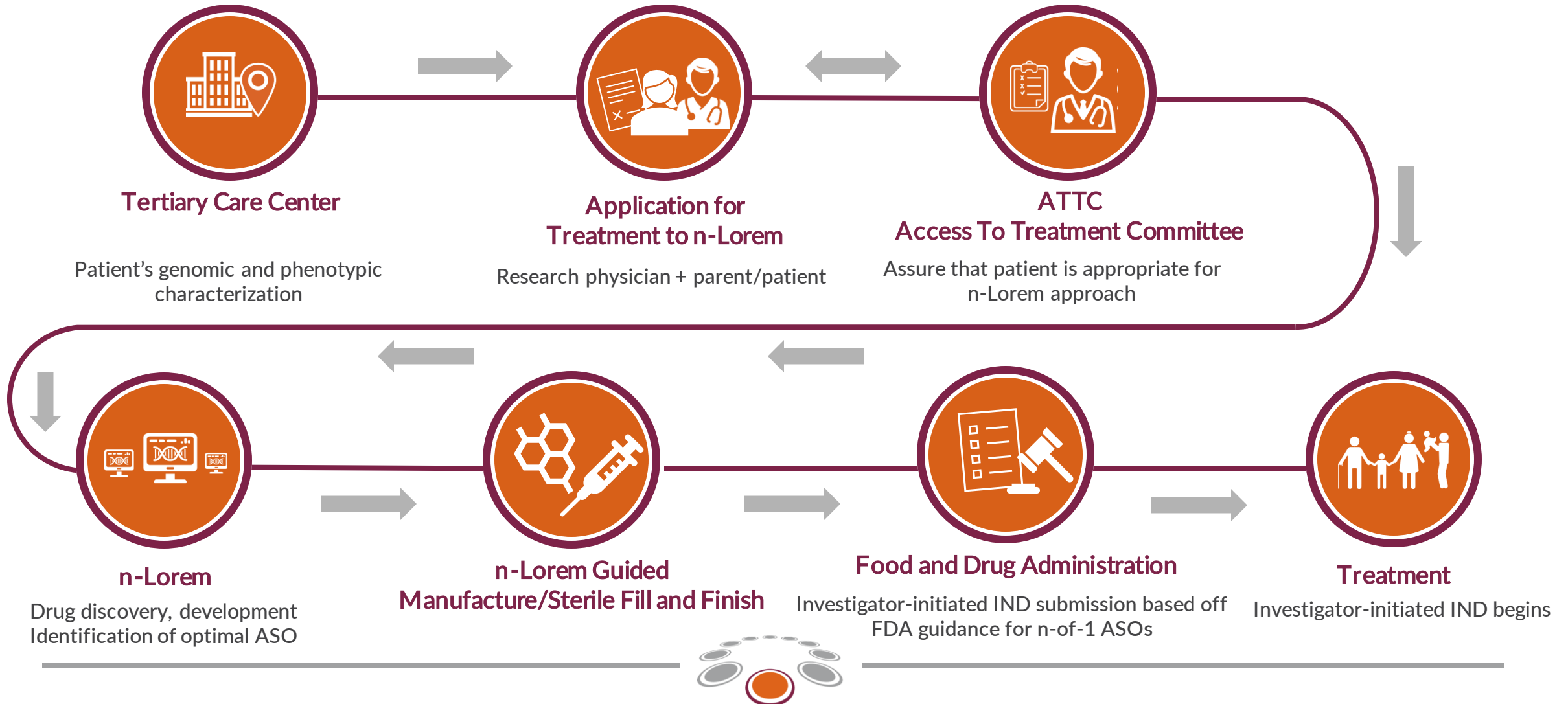
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**Novel Systems Assure the Highest Quality  
Possible At Each Key Step In The Treatment  
Process**



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# Overview Of n-Lorem Quality Processes To Identify An Optimal ASO



# Determining the Value of ASO Treatment One Patient at a Time

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## Novel n-Lorem process

### ● Goals:

- To assure that all involved understand why n-Lorem is treating patients and that if ASOs treatments are effective, patients will receive tangible benefits that matter
- To assure maximal learning from each patient and aggregate experience is possible

### ● Key Steps:

- Working with the investigator and patient/parent pre-define primary, secondary and exploratory endpoints and the clinical measures to be used
- There are no specific FDA requirements to assess performance of experimental treatments in nano-rare patients
- During the 15-18 mos. required to discover and develop the ASO, conduct a natural history study in that patient
- During the first year of treatment, using the measures assessed during natural history study to assess changes in the agreed upon endpoints





# Maximizing Learnings of Each Patient and Total Experience

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## n-Lorem can apply learnings of each patient to maximize opportunities

- The true prevalence of each “unique” mutation
- The natural history of multiple nano-rare diseases
- Human proof that a mutation in a specific gene causative of disease
- Assessing the plasticity of the human brain
  - How correctable are developmental delays?
  - How correctable are cognitive losses?
  - What are the contributions of seizures to developmental delays cognitive losses?
- Evaluation of novel mechanisms of ASO action that are not conserved in other species



# Assessing The Patient's Wellbeing

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n-Lorem case reports ask only for the clinical results that the investigator uses

- Only clinically validated biomarkers evaluated
- Test frequency defined by the investigator and consistent with best medical practices
- Developing solutions to minimize data entry
  - Ideally data will be transferred directly from the patient records
- For patients with neurological diseases, IT injection is required
  - Most non-neurological patients will receive subcutaneous injections in the physician's office



## Sharing Learnings Broadly

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**n-Lorem is committed to maximizing learnings and to share those learnings broadly**

- Investigators are strongly encouraged to publish case reports
- n-Lorem will analyze aggregate performance and publish in peer reviewed journals annually
- n-Lorem and investigators will share experiences in annual meetings of investigators and patients/parents



# Supporting Nano-rare Patients: n-Lorem's Approach

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- Conduct annual meetings focused on nano-rare patients
- Continue n-Lorem podcast series
- Enhance n-Lorem website with specified patient/investigator targeted information



# Demand For Treatment Greatly Exceeds Expectations

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- Applications for treatment >225 substantially exceeding expectations
- Approvals for treatment ~100, again substantially exceeding expectations
- Preponderance of CNS patients, but beginning to receive applications related to other organs
- To respond to the demand n-Lorem has expanded rapidly
  - ✓ Broadened senior leadership
  - ✓ Additional laboratory scientists
  - ✓ Multiple partners



# ~100 Patient Programs in Development

Patient Baseline/ Standard of Care Data Collection



>10

~60

>10

>5

9

Documentation collected  
Feasibility review  
ATTC review  
n-Lorem decision

WGS/ Obtain Cells  
ASO Design/ Synthesis  
ASO Discovery  
ASO Tolerability Screening

GLP Toxicology  
GMP Manufacturing  
Sterile Fill and Finish

IND-drafting  
IND-submission  
FDA meetings

5 patients on treatment  
2 pending IRB approval  
2 IND under review at FDA



# Clinical Safety of Personalized ASOs

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- To date, no ASO-related **severe** adverse events have been reported
- To date, no ASO-related adverse events have been reported



# Extraordinary Beginning

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- ✓ Quality systems established and working
  - ✓ Risk/Benefit decisions (ATTC)
  - ✓ Natural History and clinical trial plans
  - ✓ Systems to maximize learnings
- ✓ Initial clinical trials initiated in 2022
- ✓ Very high-quality core team recruited and working well
- ✓ Significant contributions from volunteers
- ✓ “Partners in Excellence” established





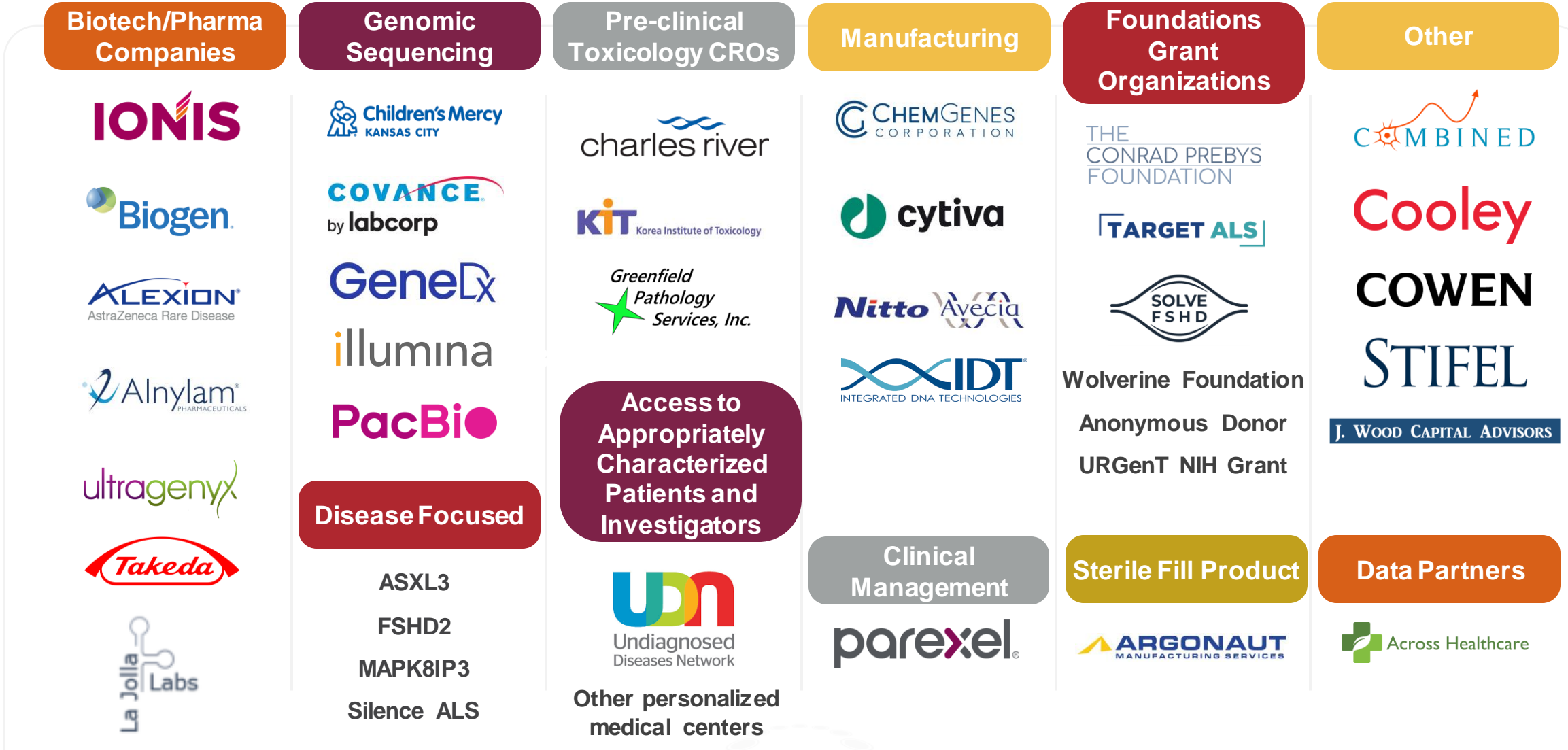
# Collaborations Between All Stakeholders

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- Enhance access to experimental ASO treatments for all nano-rare patients
- Enhance the quality of care
- Reduce the cost per patient
- Reduce the time from application to treatment
- Enhance the evaluation of the ASO performance in treated patients



# Support From Leaders Across All Areas of Drug Discovery, Development and Manufacturing *More than 30 Partners Supporting Nano-rare Patients*



# Recent Publications n-Lorem, n-Lorem Programs

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- Crooke, S.T., Kim-McManus., Dalby, K. A way forward for diagnosis of patients with extremely rare genetic mutations. *Nature Biotechnology*, 2023.
- Crooke, S.T. Meeting the needs of patients with ultrarare disease. *Trends in Molecular Medicine*, 2022. 28:87-96.
- Mittal, S., Tang, I., Gleeson, J.G. Evaluating human mutation databases for 'Treatability' using personalized antisense oligonucleotides, *bioRxiv*, 2022. 3(11): 740-759.
- Korobeynikov, V.A., Lyashchenko, A.K., Blanco-Redondo, B., Jafar-Nejad, P. Shneider, N.A. Antisense oligonucleotide as a therapeutic approach in amyotrophic lateral sclerosis, *Nature Medicine*. 28: 104-116.
- Crooke, S.T. Harnessing novel technology and a non-profit model to meet the needs of patients with ultra-rare disease. *The Scientist*, 2021.
- Crooke, S.T. Addressing the needs of patients with ultra-rare mutations one patient at a time: the n-Lorem approach. *Nucleic Acid Therapeutics*, 2021.
- Crooke, S.T. A call to arms against ultra-rare diseases. *Nature Biotechnology*, 2021, 39, 671-677.



# Conclusion

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- n-Lorem is off to a spectacular start, however there are many challenges ahead
  - Buoyed by response to date and optimistic that we can demonstrate model is sustainable
- Substantial need for nano-rare patients, while we have made significant progress, there is a lot more that we need to do
  - Demand 20-fold greater than expected
  - 9 INDS filed with more projected before year end
- Although we have significant in committed cash and in-kind support, we need hundreds of millions to continue to meet demand
  - Need more partners, more support





We can do this, and the **IMPACT** on  
**FAMILIES** can be  
**EXTRAORDINARY**



With your **HELP** we can  
serve more Families.

Make a tax-deductible charitable donation today at [www.nlorem.org/donate](http://www.nlorem.org/donate)

