n-lorem FOUNDATION

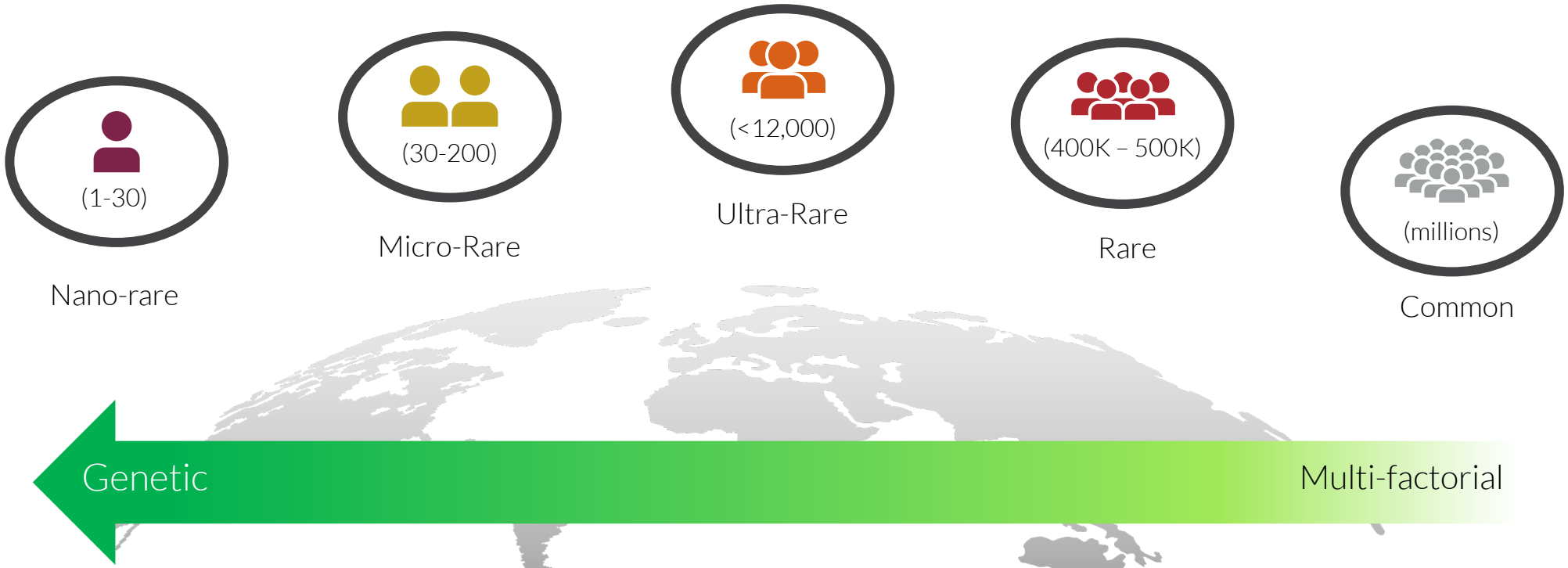
Introduction

February 2022

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).

Nano-rare: 1 to 30 Patients Worldwide



Conceptual Framework

- 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

- 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

“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

Roles of n-Lorem

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

Necessary Components to Meet The Needs of Nano-rare Patients

Meeting The Needs of Nano-rare Patients

- 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

- 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

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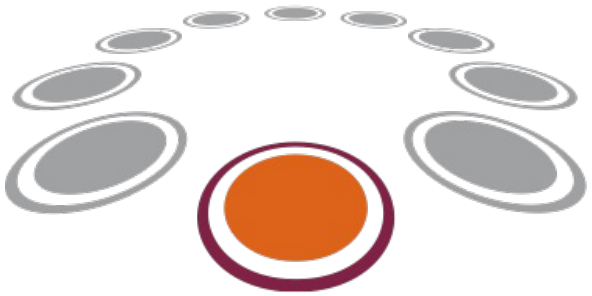
- FDA response to n-Lorem concept supportive
- n-Lorem posed questions that require policy decisions, but progress toward policies evident
- In the meantime, experience facilitating ASOs for individuals provides real-life guidance
- Initial FDA guidance for ASO for patients with diseases caused by ultra-ultra-rare 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

- ***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.

ASO Technology Makes n-Lorem Feasible

- 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



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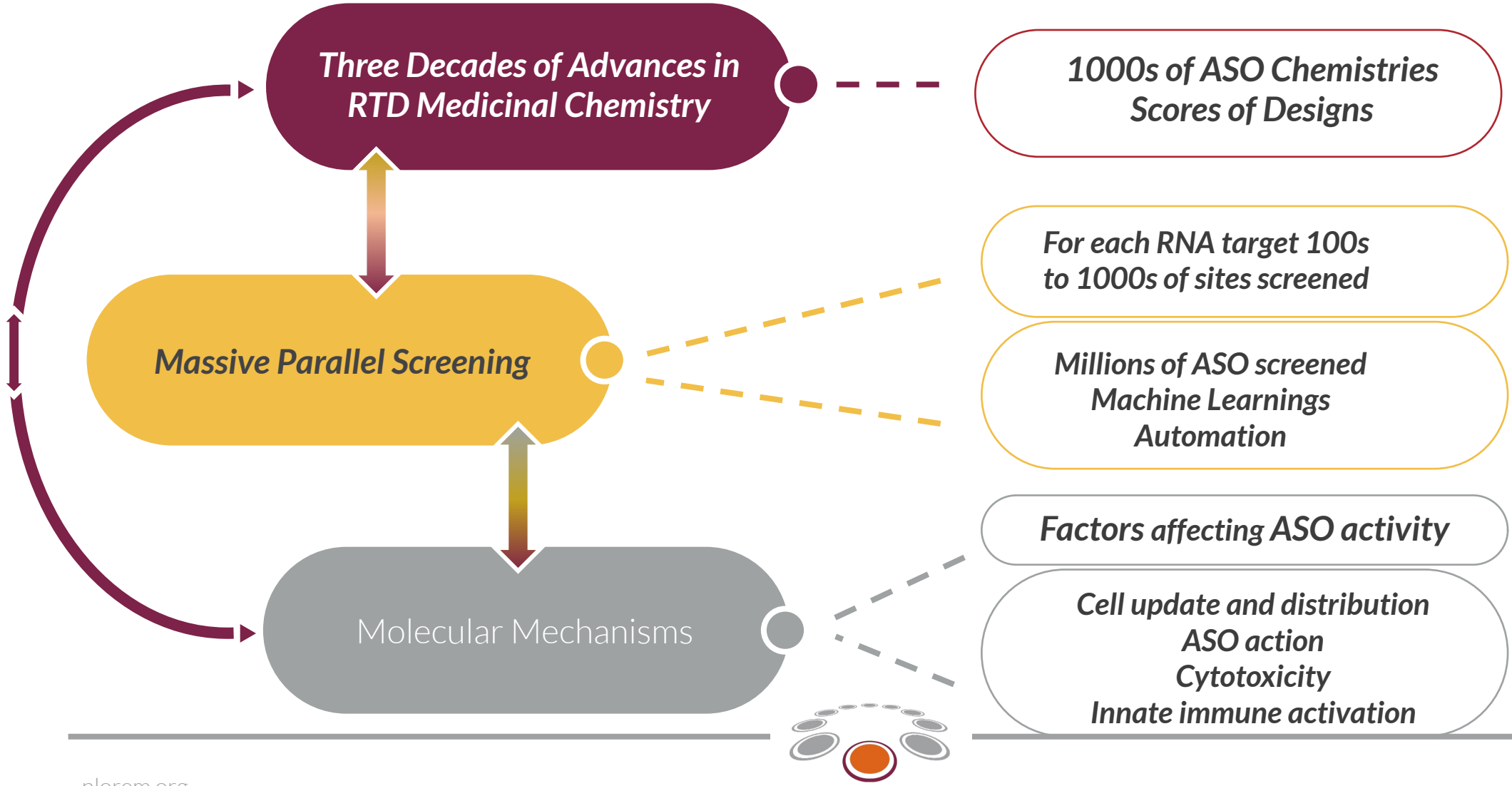
The n-Lorem Approach To Assure That Each Patient Is Treated With The Optimal Personalized ASO

All ASOs Are Not Created Equal

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

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



More Than 3 Decades Of Innovation
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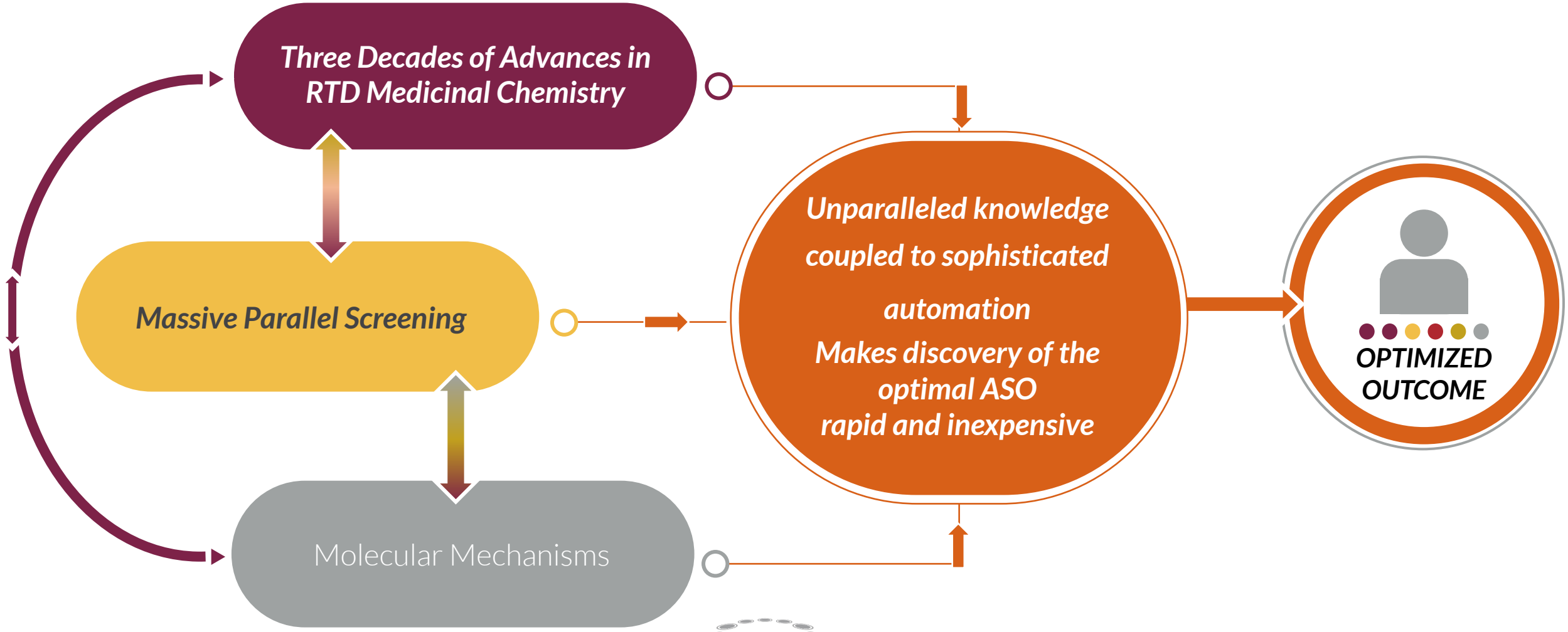
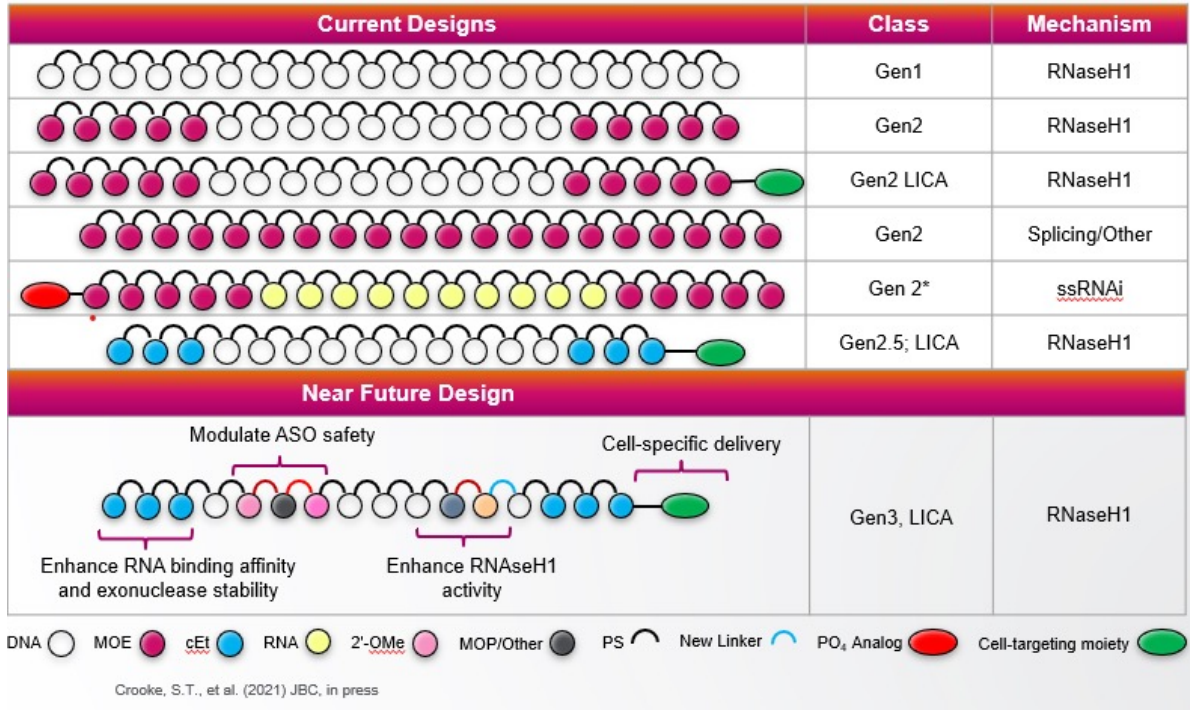


More Than 3 Decades Of Advances In The Medicinal Chemistry of RNA Targeted Drugs



- 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	LOCAL
Intravenous	Intravitreal
Intramuscular	Intrathecal
Subcutaneous	Aerosol
Oral	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

n-Lorem Is Off To An Extraordinary Beginning

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N-Lorem Founding Donors

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

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

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

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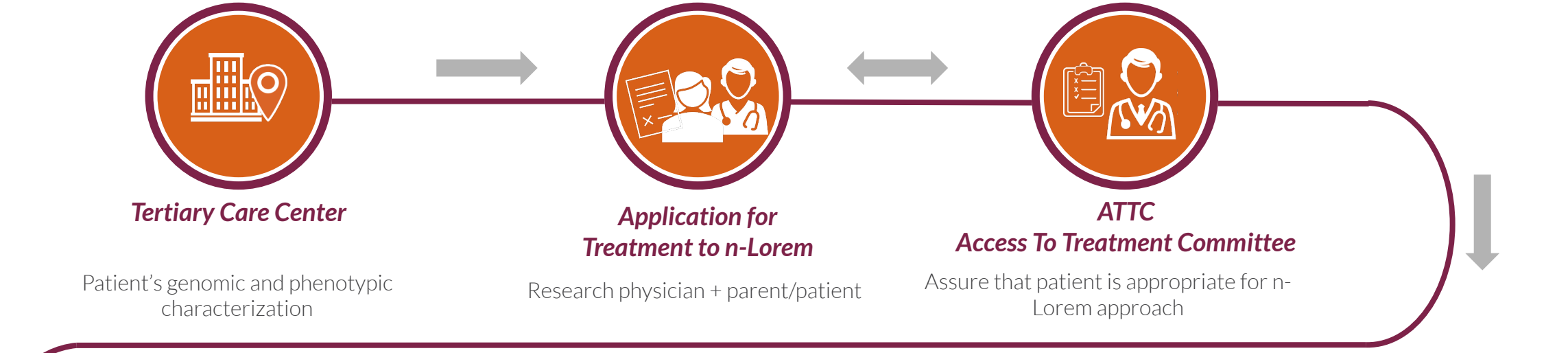

Tertiary Care Center

Patient's genomic and phenotypic characterization

Application for Treatment to n-Lorem

Research physician + parent/patient

ATTC Access To Treatment Committee

Assure that patient is appropriate for n-Lorem approach

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Drug discovery, development
Identification of optimal ASO

n-Lorem Guided Manufacture/Sterile Fill and Finish

Food and Drug Administration

Investigator-initiated IND submission based off FDA guidance for n-of-1 ASOs

Treatment

Investigator-initiated IND begins

Determining the Value of ASO Treatment One Patient at a Time

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 time 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

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

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

Recent Publications n-Lorem, n-Lorem Programs

- ***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*, Jan. 6, 2022.
- ***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.

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

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

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

Biotech/Pharma Companies

IONIS

Biogen

ALEXION AstraZeneca Rare Disease

Alnylam PHARMACEUTICALS

ultragenyx

La Jolla Labs

Genomic Sequencing

Children's Mercy KANSAS CITY

COVANCE by labcorp

GeneDx

illumina

PacBio

Disease Focused

ASXL3

FSHD2

MAPK8IP3

Silence ALS

Pre-clinical Toxicology CROs

charles river

KIT Korea Institute of Toxicology

Access to Appropriately Characterized Patients and Investigators

UDN Undiagnosed Diseases Network

Other personalized medical centers

Manufacturing

ChemGenes Corporation

cytiva

Nitto Avecia

Clinical Management

parexel

Foundations

The Conrad Prebys Foundation

TARGET ALS

SOLVE FSHD

Wolverine Foundation

Anonymous Donor

Sterile Fill Product

ARGONAUT MANUFACTURING SERVICES

Other

COMBINED

Cooley

COWEN

STIFEL

J. Wood Capital Advisors

Data Partners

Across Healthcare

Unipr

With your HELP we can serve more Families.

Make a tax-deductible charitable donation today at www.nlorem.org/donate