Resources for Rare Disease Organizations

The Jackson Laboratory Rare Disease Translation Center

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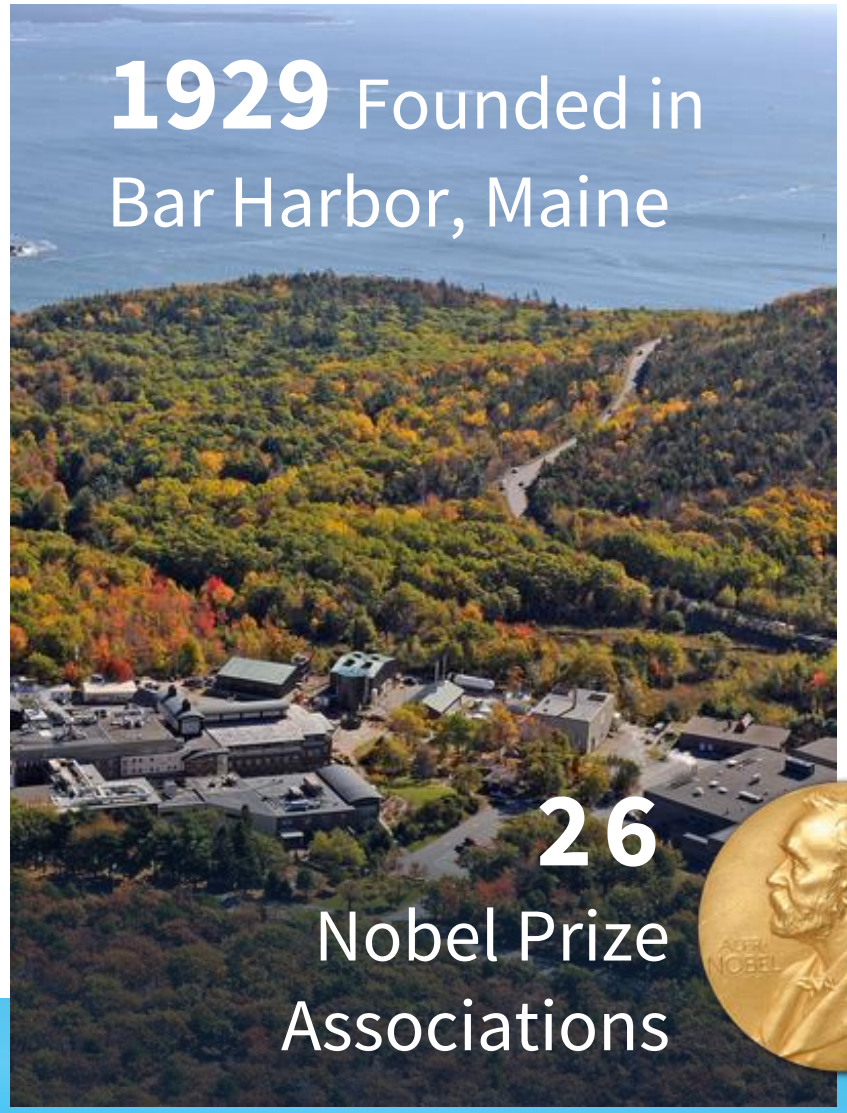
1929 Founded in Bar Harbor, Maine

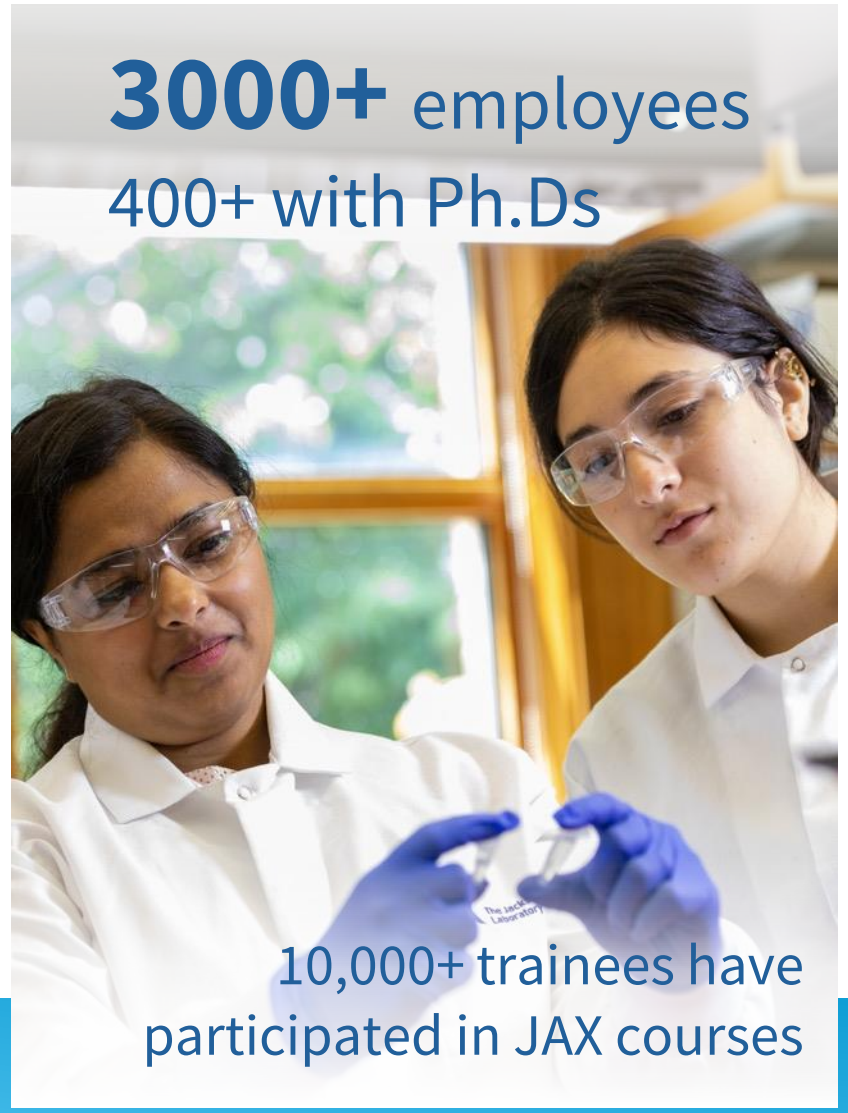


26 Nobel Prize Associations

12 JAX locations globally

3000+ employees

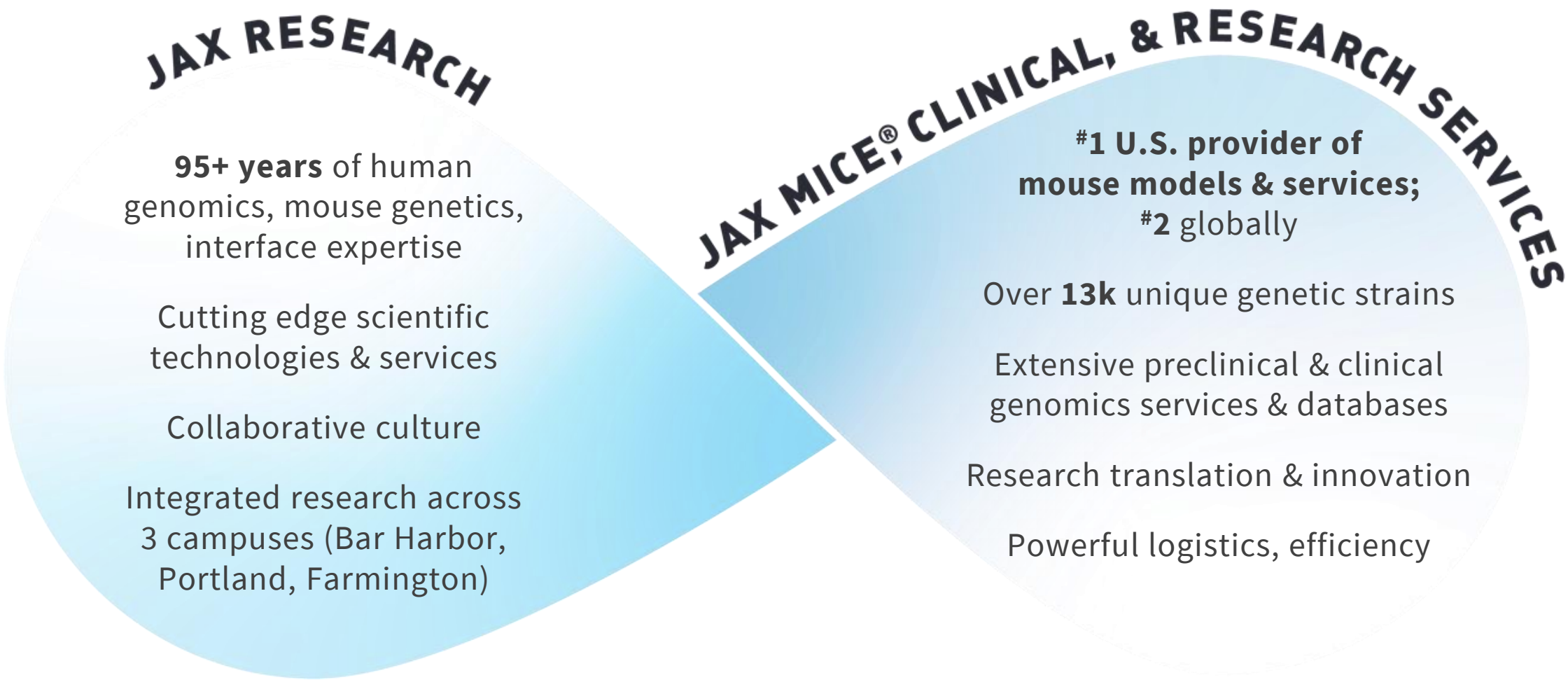
400+ with Ph.Ds



10,000+ trainees have participated in JAX courses

About The Jackson Laboratory

The JAX Distinction



DISCOVER

EMPOWER

JAX Rare Disease Translational Center

OUR MISSION

For and with rare disease families, foundations, researchers and clinicians, the JAX RDTC **innovates patient-relevant models and preclinical strategies** to deliver targeted therapies from **lab to clinic** swiftly and effectively.

Cat Lutz, Ph.D., MBA,
Vice President RDTC

JAX CARES ABOUT RARE

Mouse as an Avatar & Accelerator

Why the mouse?

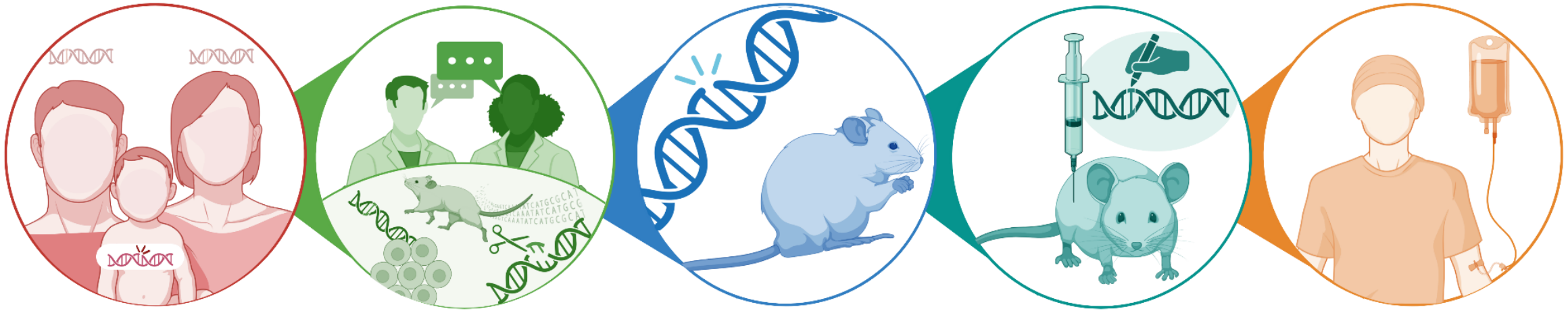
- Similar genetics, physiology, health
- 2.5 year lifespan
- Change the DNA to mirror human variants, disorders
- Whole body system complements cell lines
- For mechanistic proof of concept
- Important long term for new hypotheses and next-gen therapeutics
- Share openly to enable parallel studies
- Preclinical data for INDs

Provides answers

- What does the gene do?
- What does the variant impact?
- Which therapeutics are effective?
- Which readouts are modulated, are most informative?
- Is it safe?
- When to dose?
- Which route of administration?
- How well do drugs work in combination?

Our Approach

Translation begins with the end in mind: The Anticipated Therapy



Causative patient mutations

Scope project and therapeutic approach, and devise overall modeling strategy

Engineer the mouse model

Phenotype and test therapeutics

Preclinical data supports IND

Foundations, Researchers, Clinicians & Industry Partners

JAX's growing influence on rare disease

Neurodevelopmental

- Cornelia de Lange syndrome (CdLS) (HDAC8)
- Alternating hemiplegia of childhood (AHC) (ATP1A3)
- HNRNPH2-related disorder
- MED13L-related disorder
- PURA-related disorder
- Cockayne syndrome (ERCC6/XPA)
- CHOPS syndrome (AFF4)
- Schuurs-Hoeijmakers syndrome (PACS1)
- PACS2-related disorder
- Temple-Baraister syndrome (KCNH1)
- SHINE syndrome (DLG4)
- Wieacker-Wolff syndrome (ZC4H2)
- CACNA1A-related disorder
- Ogden syndrome (Naa10)
- MAPK8IP3-related disorder
- CDKL5 deficiency disorder (CDD)
- DDX3X-related disorder
- Dravet syndrome
- FAM177A1-related disorder
- KCNT1-related epilepsies
- Multiple sulfatase deficiency (MSD) (SUMF1)
- Rett syndrome (MECP2)
- SLC6A1-related disorder
- SYNGAP1-related disorder

Neurodegenerative

- KIF1A-associated neurodevelopmental disorder (KAND)
- Amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD) (UNC13A, CHMP2B, C9orf72, TARDBP)
- Metachromatic leukodystrophy (ARSA)
- Charcot-Marie-Tooth disorder (CMT) (ITPR3, SBF1, FIG4)
- Alzheimer's disease (KNG1)
- Infantile neuroaxonal dystrophy (PLA2G6)
- Leukoencephalopathy (CSF1R)
- Hereditary spastic paraplegia (HSP) (ALT1)
- Spastic paraplegia (SPG56)

Hematopoietic

- Schwachman-Diamond syndrome (SBDS)

Musculoskeletal/ Muscular Dystrophy/ Glycosylation defects

- Multicentric carpotarsal osteolysis syndrome (MAFB)
- Congenital muscular dystrophy (COL6A1)
- DHDDS-related disorder
- PGAP3-congenital disorder of glycosylation
- NGLY1-congenital disorder of glycosylation

Mitochondrial Disorders

- Friedreich ataxia (FXN)
- POLG-related disorder

Metabolic Disorders

- Glycogen storage disease (SLC37A4)
- Zellweger syndrome (PEX1)
- Nonketotic hyperglycinemia (GLDC)

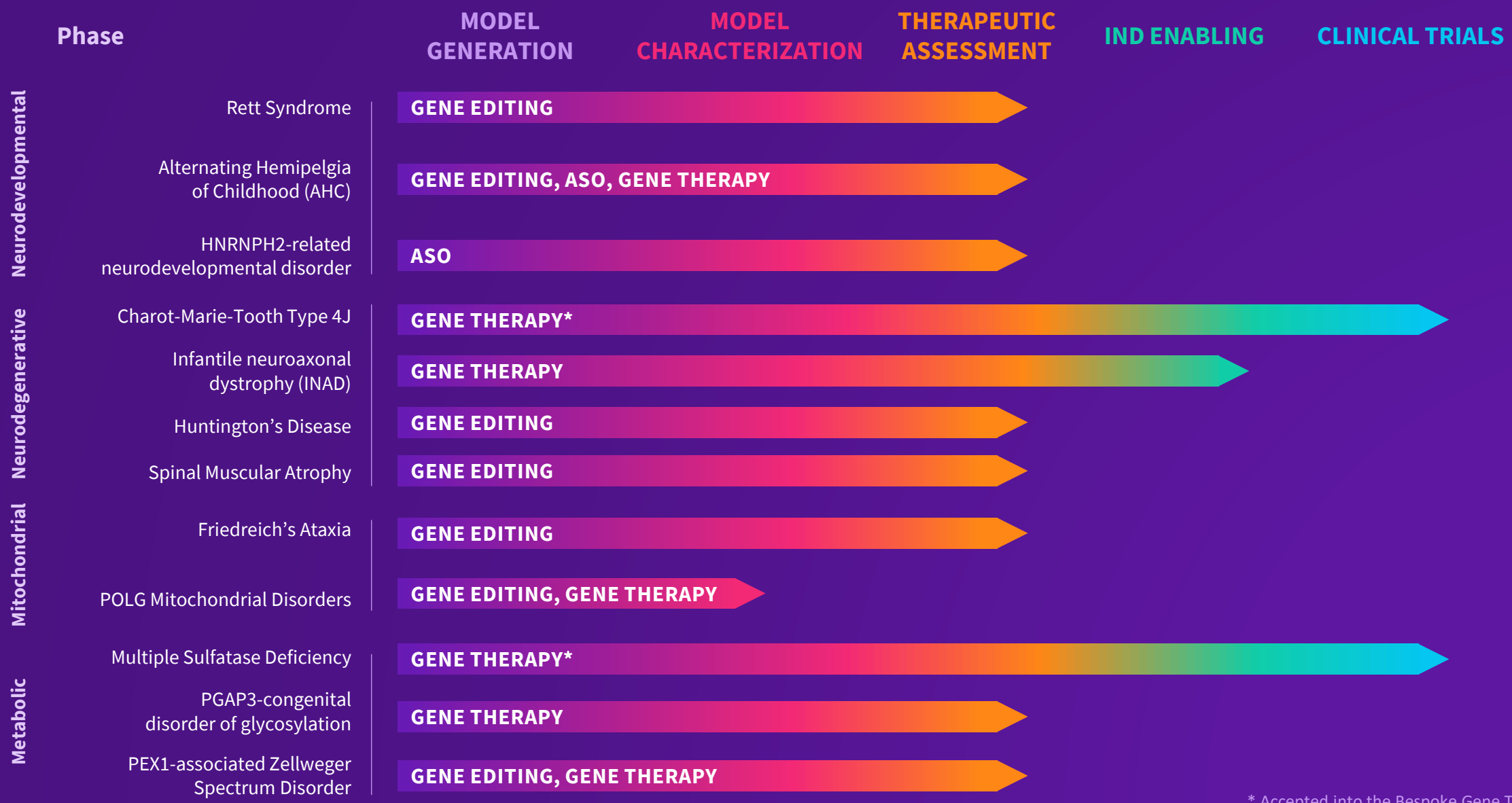
Other

- Dyskinesia (ADCY5)
- Chronic kidney disease (TRPC6)
- SPEEC1L-related disorder
- TMEM192-related disorder
- Olmsted syndrome (TRPV3)

60+
Distinct genetic diseases

35+
therapies being tested in mouse models

RDTC’s lead programs



* Accepted into the Bespoke Gene Therapy Consortium

Charcot Marie Tooth type 4J Gene Therapy

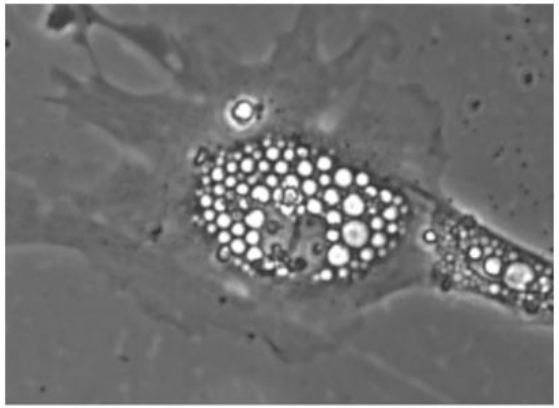
- Severe form of CMT neuropathy. Ultra-rare.
- Progressive profound muscle weakness in legs, arms or both with loss of motor capabilities.
- Autosomal recessive, caused by loss of function mutations in gene ***FIG4*.**

CURE CMT4J
ADVANCING GENE THERAPY FOR RARE DISEASES

Jocelyn Duff
Executive Director

UT Southwestern Medical Center

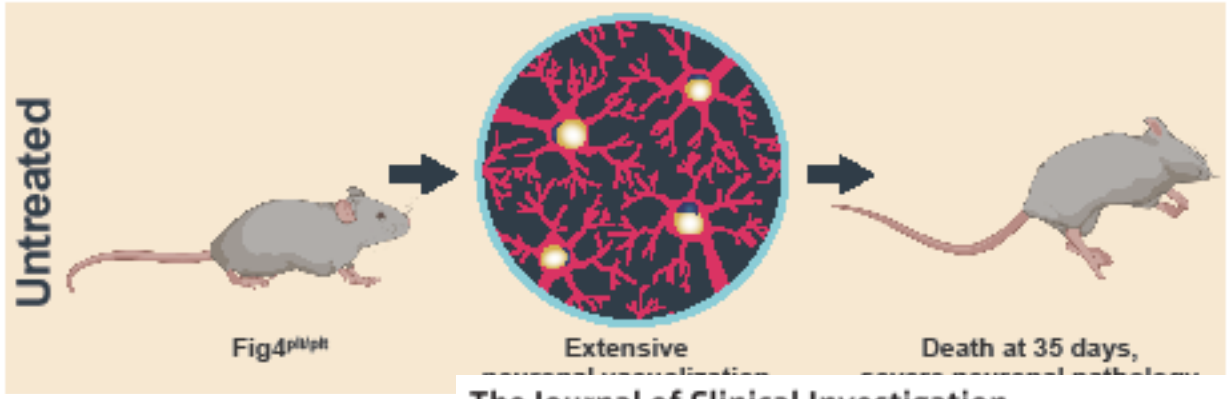
Steven Gray, Ph.D.
Rachel Bailey, Ph.D.

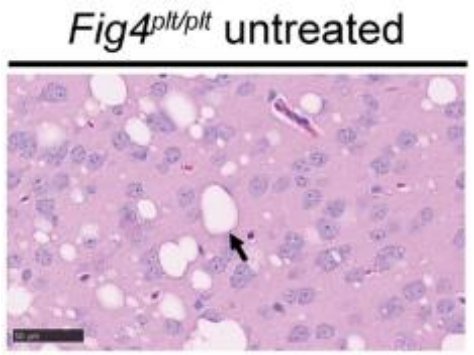


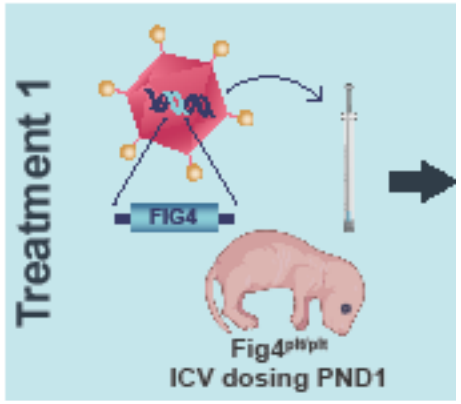
Vacuolation phenotype

Maximiliano Presa, Ph.D.
JAX Rare Disease Translational Center (RDTC)

CMT4J Gene therapy summary







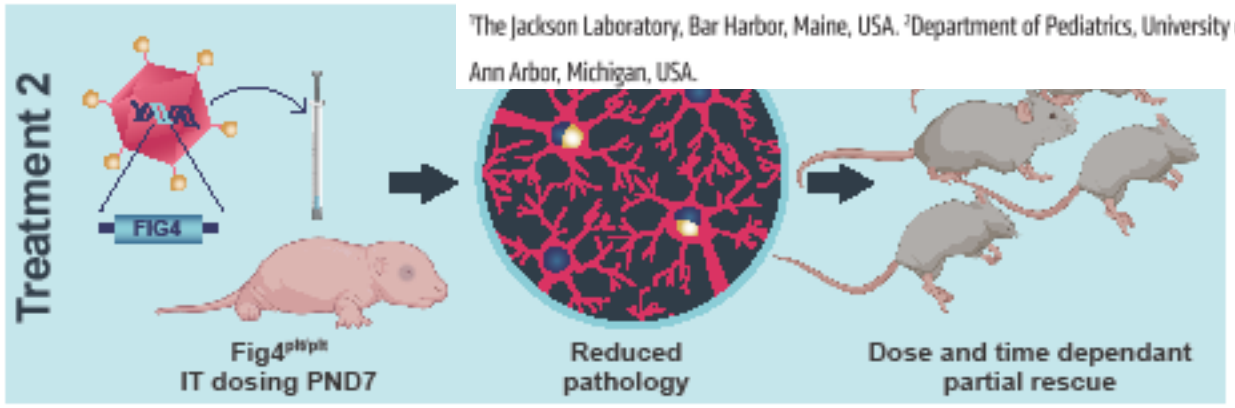
The Journal of Clinical Investigation

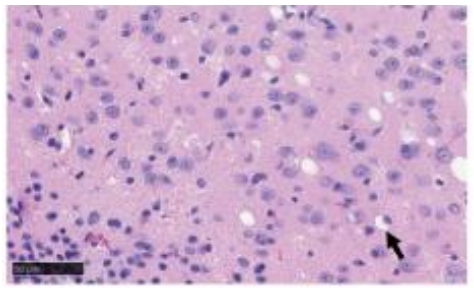
RESEARCH ARTICLE

AAV9-mediated FIG4 delivery prolongs life span in Charcot-Marie-Tooth disease type 4J mouse model

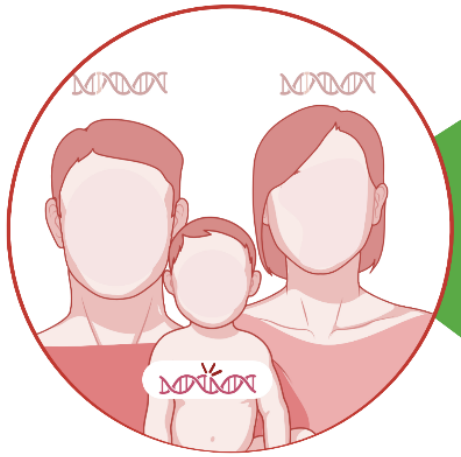
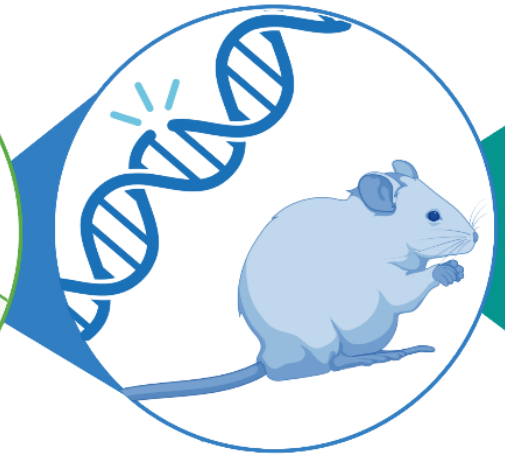
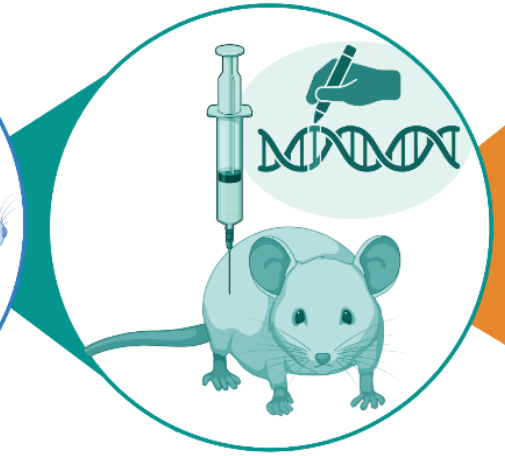
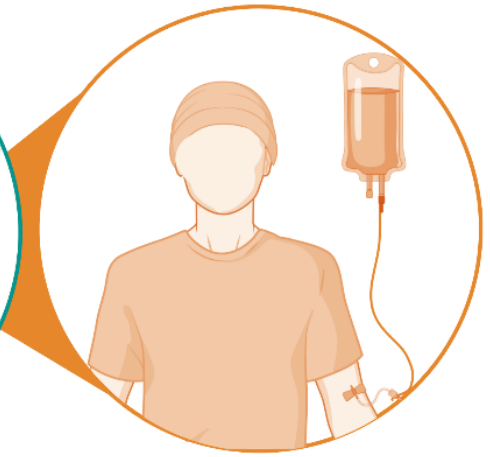
Maximiliano Presa,[1] Rachel M. Bailey,[2] Crystal Davis,[1] Tara Murphy,[1] Jenn Cook,[1] Randy Walls,[1] Hannah Wilpan,[1] Laurent Bogdanik,[1] Guy M. Lenk,[3] Robert W. Burgess,[1] Steven J. Gray,[2] and Cathleen Lutz[1]

[1]The Jackson Laboratory, Bar Harbor, Maine, USA. [2]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas, USA. [3]Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA.





The CMT4J Journey

Patient Variants	Anticipated therapies	Mouse engineering	Phenotype and testing	Pre-clinical test and IND
				
Talia's mouse	Gene Therapy	Fig4 gene knockout Fig4 mutation I41T	Gene Therapy Drug repurposing?	AMP Bespoke Gene Therapy Consortium

How it Works

rarediseases@jax.org

1

Nominate Your Disease

Use the NIH grant-funded JAX Center for Precision Genetics (JCPG)

rarediseases@jax.org

2

Committee Research & Acceptance Criteria

What do we know about the biology?

Does a mouse exist, does it work?

Feasibility and potential — will it work, advance goals?

Humanization approach?

Aiming for which clinical features?

Fits with the intended therapeutics?

Who will use it once built?

3

Let's Get to Work!

Grant funding available for initial model development

Expert team develops new mouse model, with genetic engineering, breeding, phenotyping (1 year)

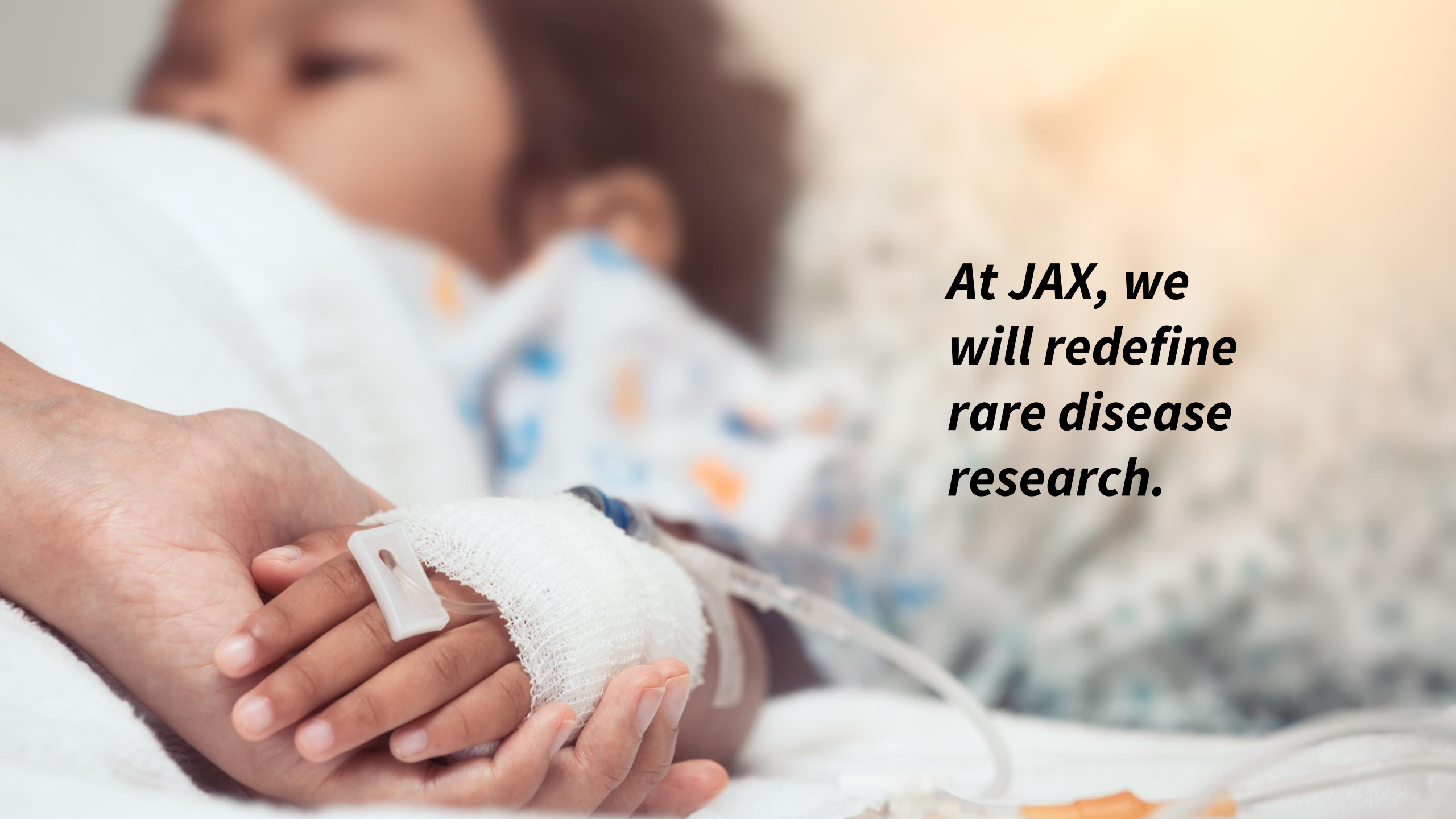
Drug efficacy, tolerability, cell modeling and proteomic studies typically need external funding

4

Share, Collaborate & Advance

All new models deposited in NIH-supported MMRRC for open access

Use strains to test new therapeutics, discover biomarkers and answer pharmacology questions


At JAX, we will redefine rare disease research.

Thank you

For new inquiries contact

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Clinical Research Project Manager
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