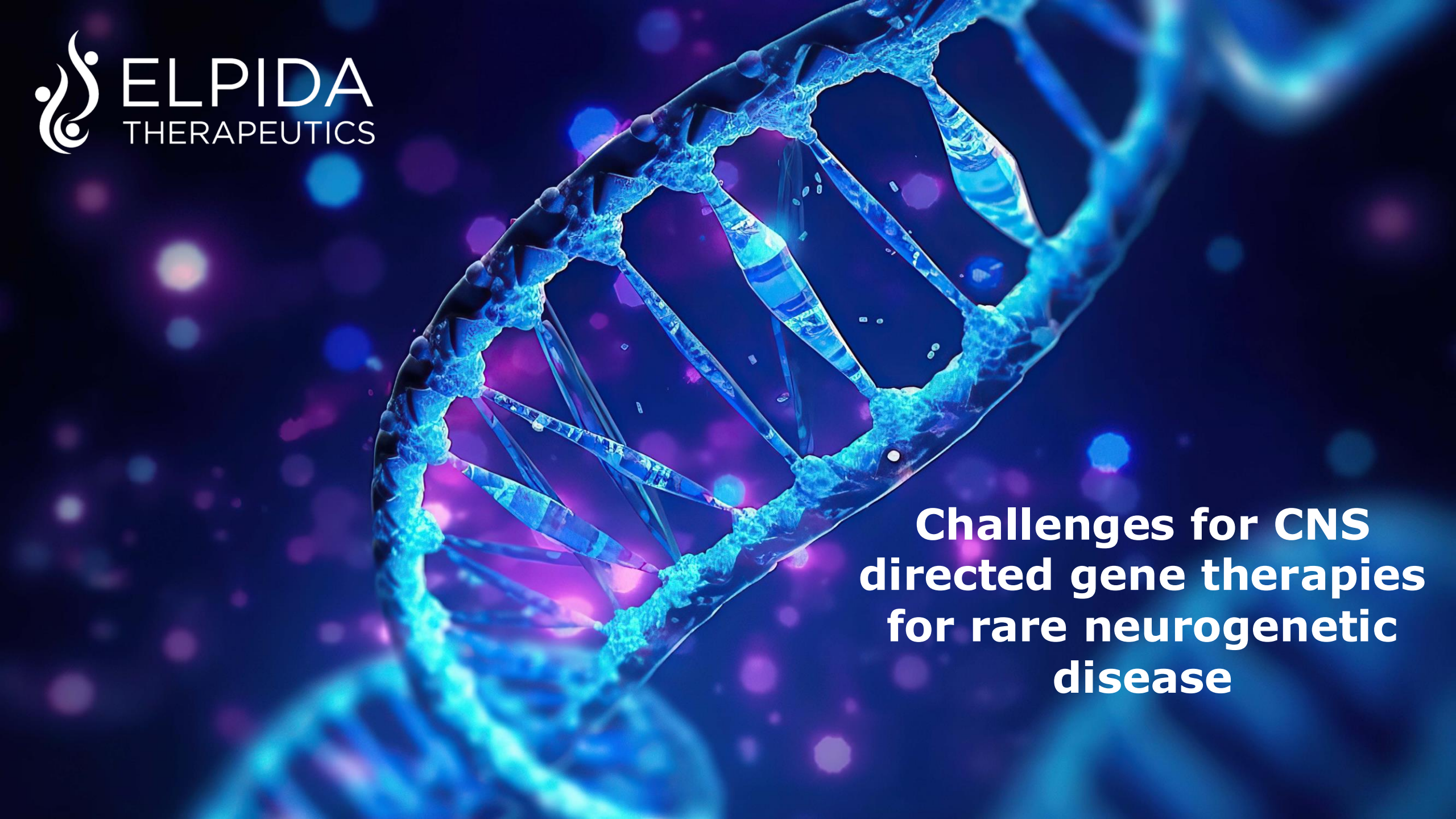

ELPIDA
THERAPEUTICS
Challenges for CNS directed gene therapies for rare neurogenetic disease

Agenda

ELPIDA THERAPEUTICS

A CLINICAL STAGE COMPANY

SPG50 –GENE THERAPY

CHALLENGES TO RARE DISEASE RESEARCH IN CHILDREN AND LESSONS LEARNT

Development of MELPIDA

Michael Pirovolakis

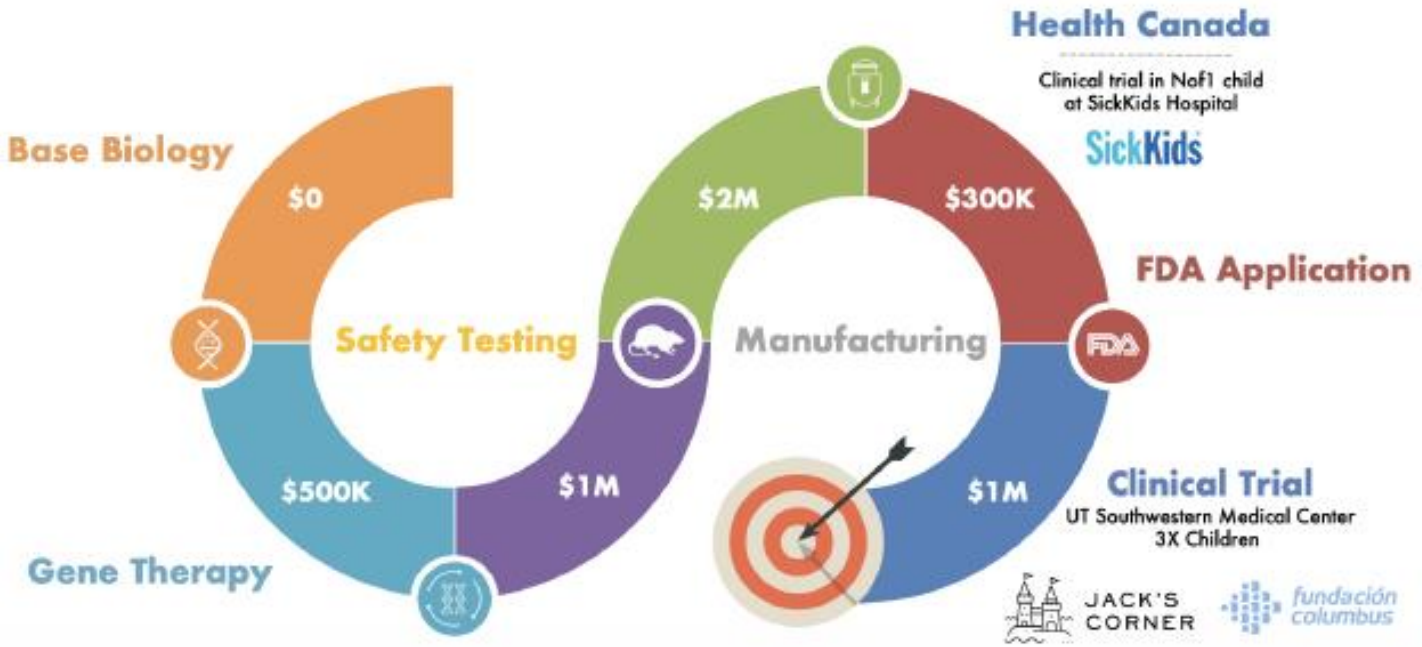
Spastic Paraplegia Type 50

CURE SPG50

www.cureSPG50.org

3 years

- **Gene Therapy AAV9/AP4M1**
- $4.5M
- Preclinical studies
- Health Canada approval
- FDA IND



Who we are…

- A Californian based nonprofit biotech
- Clinical Stage company
- Funded by grants and donations
- Bringing together the best of industry, academia and philanthropy

Our Team

Our core team is driven to bring meaningful treatments to children with rare diseases

Terry Pirovolakis
Founder & CEO

Souad Messahel, PhD
Head of Clinical Operations

Keith Gottlieb, PhD
Head of Program Management & Operations

Rachel Thomas, RN
Senior Program Manager

Caitlin Roll
Clinical Trial Project Manager

Meghan Eller
Preclinical Intern

Andrea Boitnott
Preclinical Intern

Emily Nettesheim
Clinical Intern

+ Consultants, Scientists and Doctors

What we do…

- Specialize in neurogenetic disorders affecting children
- Develop onetime gene therapies -AAV9 Gene replacement
- Open trials in different countries to allow patient access to drugs
- Our **goal** is to get drugs approved for children with rare disease

Our Process

ELPIDA THERAPEUTICS

SELECTION

PRE-IND FDA

TOXICOLOGY PLASMID

TOXICOLOGY MANUFACTURING

SAFETY STUDIES

CLINICAL PLASMID

CLINICAL MANUFACTURING

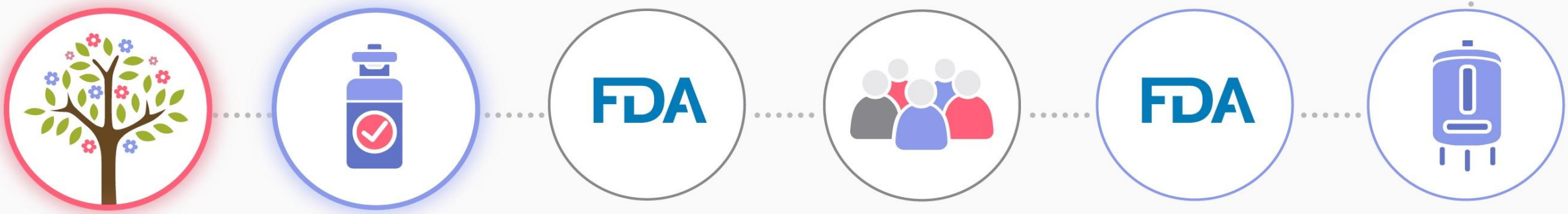
IND-FDA

CLINICAL TRIAL

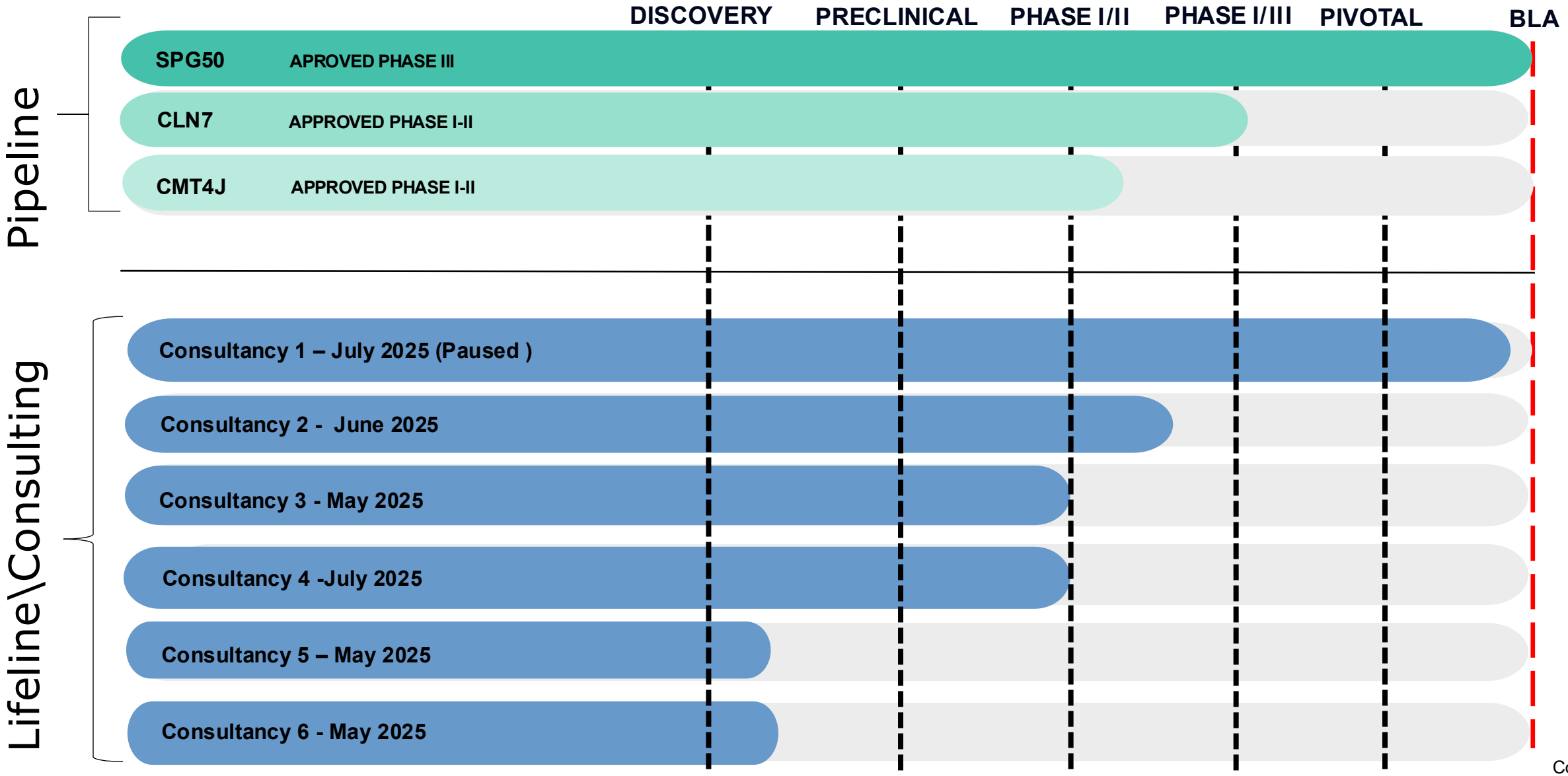
BLA-FDA

DRUG AVAILABLE

MORE PROGRAMS



Our Pipeline



Our Partners

ELPIDA THERAPEUTICS

Hospitals

UT Southwestern Medical Center

GREAT ORMOND STREET HOSPITAL CHARITY

NIH National Institute of Mental Health

Azienda Ospedaliera Papa Giovanni XXIII Bergamo

SJD Sant Joan de Déu Fundació de Recerca

University of Iowa Stead Family Children's Hospital

Children's Hospital of Philadelphia

Rigshospitalet

Stanford MEDICINE

St. Jude Children's Research Hospital
Finding cures. Saving children.

Boston Children's Hospital
Until every child is well

GREAT ORMOND STREET HOSPITAL CHARITY

Non-Profits

fundación Columbus.

CMTA Charcot-Marie-Tooth Association

CURE SPG50

TeleThon
COMBATTI LA DISTROFIA MUSCOLARE E LE ALTRE MALATTIE GENETICHE

ΙΣΝ / SNF
ΙΔΡΥΜΑ ΣΤΑΥΡΟΣ ΝΙΑΡΧΟΣ
STAVROS NIARCHOS FOUNDATION

GENETHON
CURE THROUGH INNOVATION

JACK'S CORNER

CURE CMT4J

CMT Research Foundation

Companies

LifeArc

VIRALGEN

Advanthera BIOPHARMA SOLUTIONS

CIRM
CALIFORNIA'S STEM CELL AGENCY

VENTURE PARTNERS

aldevron

citizen health

jsb

ultragenyx pharmaceutical

QUATRE LAB

Roche

Our key principles

Target Product Profile

- Defines development priorities aligned with regulatory expectations
- Enables early alignment on concepts and clinical endpoints

01

Trial design and execution

- Supports a streamlined Phase 1–3 clinical development pathway
- Drives early endpoint and biomarker alignment with regulators
-

02

CMC Manufacturing

- Establishes early manufacturing readiness to reduce regulatory risk
- Leverages platform-based CMC strategies to accelerated development

05

Registry efficiencies

- Minimizes participant burden while maximizing data quality
- Harmonizes data platforms across registries and FIH studies

03

Long term follow up

- Supports regulatory approval and post-marketing commitments
- Leverages remote monitoring, and centers of excellence

04

Three Key Challenges in Brain-Directed Research

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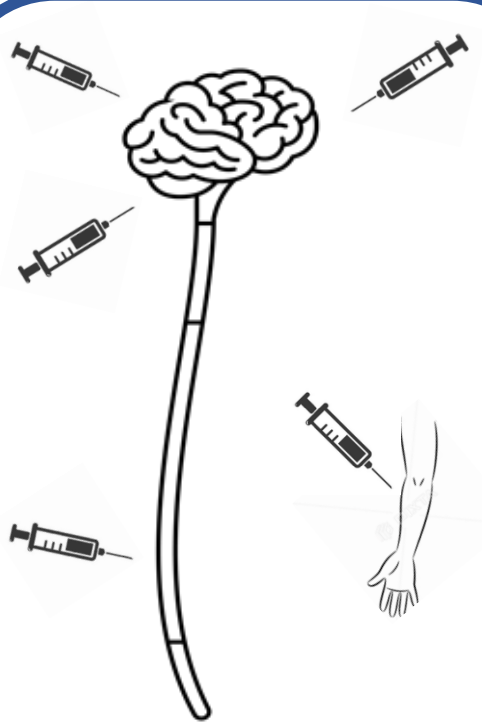
DOSE



DELIVERY

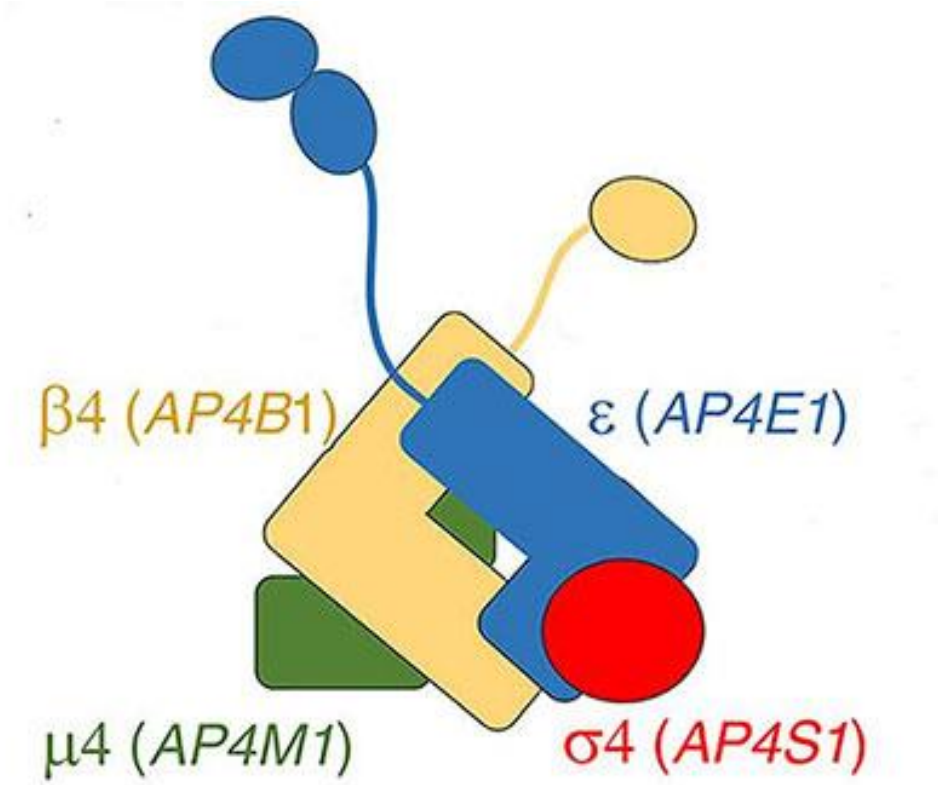
TIMING

SPG50 disease

Caused by biallelic pathogenic variants in the adaptor complex 4 subunit M1 (*AP4M1*) gene.

•Adaptor Protein Complex-4 (AP-4) is a vesicle trafficking complex
•Located at the trans-Golgi network (TGN)

- AP-4 is a Golgi adaptor complex that sorts specific proteins into vesicles leaving the trans-Golgi network (TGN).
- Mutations in AP4B1, AP4M1, AP4E1, or AP4S1 destabilize the complex → it can't export cargo properly.
- Key cargo like ATG9A gets trapped at the Golgi instead of reaching axons and autophagy sites.
- This causes impaired autophagy and defective membrane trafficking in neurons.
- Long motor neuron axons are especially vulnerable → progressive axonal degeneration.
- Result: AP-4–related HSP = a neuronal trafficking + autophagy disorder.



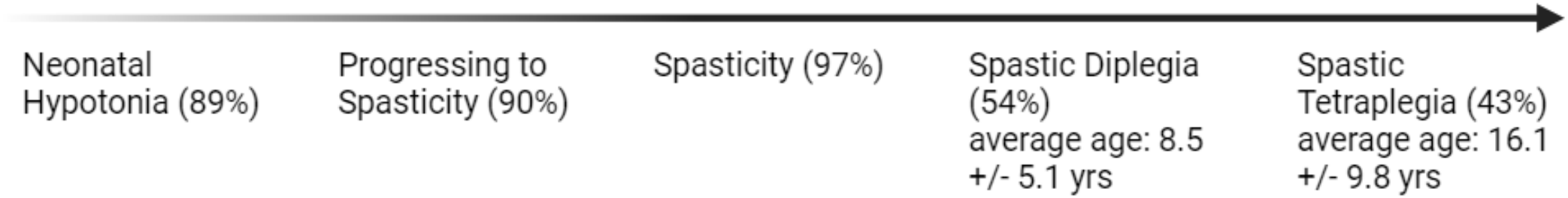
SPG50 disease

- **Prevalence:** <1 in 1,000,000
- **Incidence:** < ~0.01 per 100,000 live births
- **Total cases identified:** 120 cases globally
- **Age of symptom onset:** 6 months
- **Disease characteristics:**
  - Microcephaly
  - Hypotonia
  - Progressive Spasticity
  - Developmental regression
  - Epilepsy
  - Neurodevelopmental delay
  - Motor impairment and Wheelchair dependency

SPG50 Clinical Feature	Prevalence
DD/ID	100%
Developmental Regression	51%
Nonverbal	32%
Neonatal Hypotonia	90%
Spasticity	98%
Seizures	70%
Epilepsy	62%
Postnatal Microcephaly	85%

Mean age of symptom onset	0.9 +/- 0.8 yrs
Mean age of diagnosis	11.7 +/- 10 yrs

Adapted from Ebrahimi-Fakhari et al. (2020) *Brain*



Limited Patient Population

120 known SPG50 patients worldwide

Need for Well Established NHS

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Patient Registry

- Collection of patient characteristics
- Histories and surveys
- Conceptual models
- Pre and post treatment
- Used at every stage in regulatory process

Retrospective Cohort

- Review of medical records to summarize what has been passively discovered
- Review of case reports in the literature

Prospective Cohort

- Follow patients over time in a standardized way using specific assessments
- Gold standard for comparator/control arm of therapeutic intervention

Biomarker Study

- Explore objective measures of disease state and severity
- Used for accelerated approval pathway

Clinical Trial Readiness Programs

Preclinical/Clinical foundation

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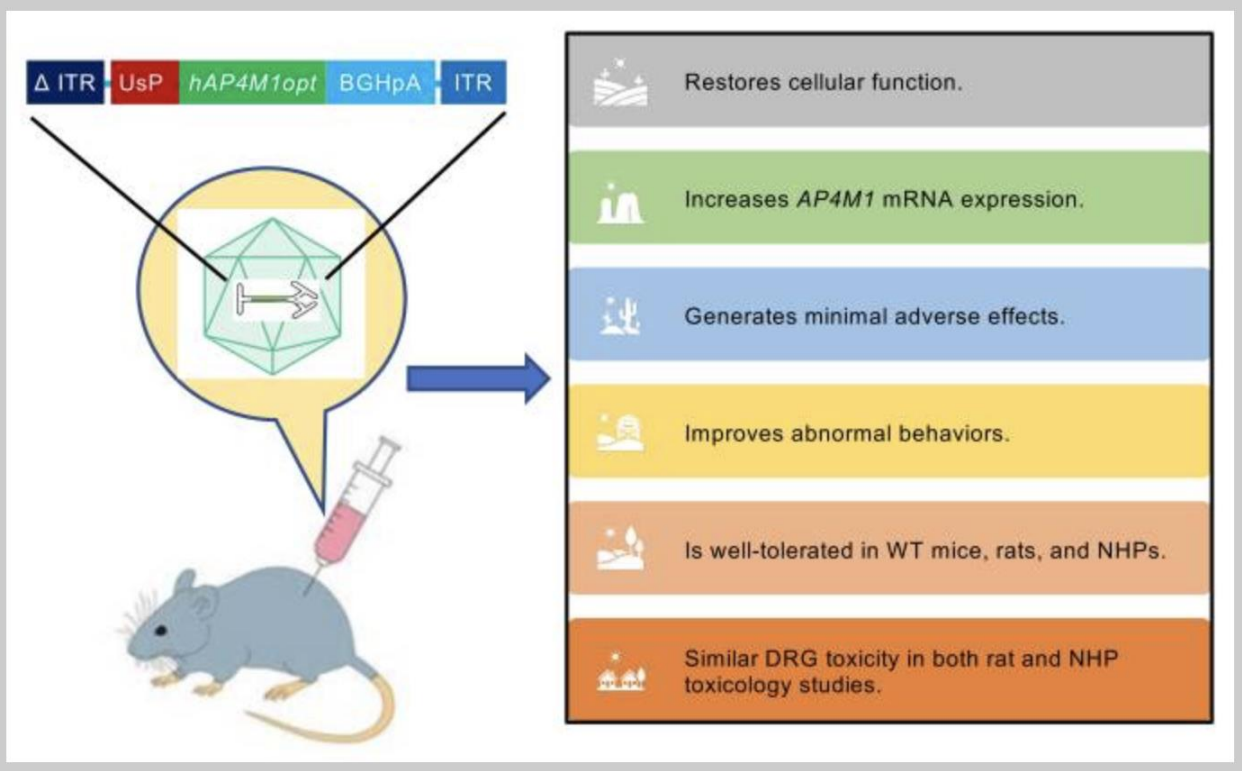
J Clin Invest. 2023 May 15;133(10):e164575. doi: 10.1172/JCI164575.

Intrathecal AAV9/AP4M1 gene therapy for hereditary spastic paraplegia 50 shows safety and efficacy in preclinical studies

Xin Chen [1], Thomas Dong [1], Yuhui Hu [1], Raffaella De Pace [2], Rafael Mattera [2], Kathrin Eberhardt [3], Marvin Ziegler [3], Terry Pirovolakis [4], Mustafa Sahin [3], Juan S Bonifacino [2], Darius Ebrahimi-Fakhari [3], Steven J Gray [1]



Clinical and genetic characterization of *AP4B1*-associated SPG47

Ebrahimi-Fakhari et al., Am J Med Genet A. 2018 Feb;176(2):311-318

Defining the clinical, molecular and imaging spectrum of adaptor protein complex 4-associated hereditary spastic paraplegia

Ebrahimi-Fakhari et al. Brain. 2020 Oct 1;143(10):2929-2944

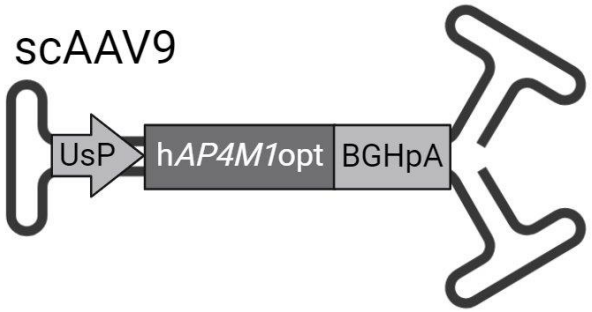
Systematic Analysis of Brain MRI Findings in Adaptor Protein Complex 4–Associated Hereditary Spastic Paraplegia

Ebrahimi-Fakhari et al. Neurology. 2021 Nov 9;97(19):e1942-e1954

Disease Severity and Motor Impairment Correlate With Health-Related Quality of Life in AP-4-Associated Hereditary Spastic Paraplegia

Jordan et al. Neurol Genet. 2021 Jul 20;7(4):e605

The Intervention



- GAN and CLN7 Trial
- Broad distribution
- Early disease
- Immune suppression regime

AAV9/AP4M1

scAAV9_UsP-h*AP4M1*opt-BGHpA

DOSE

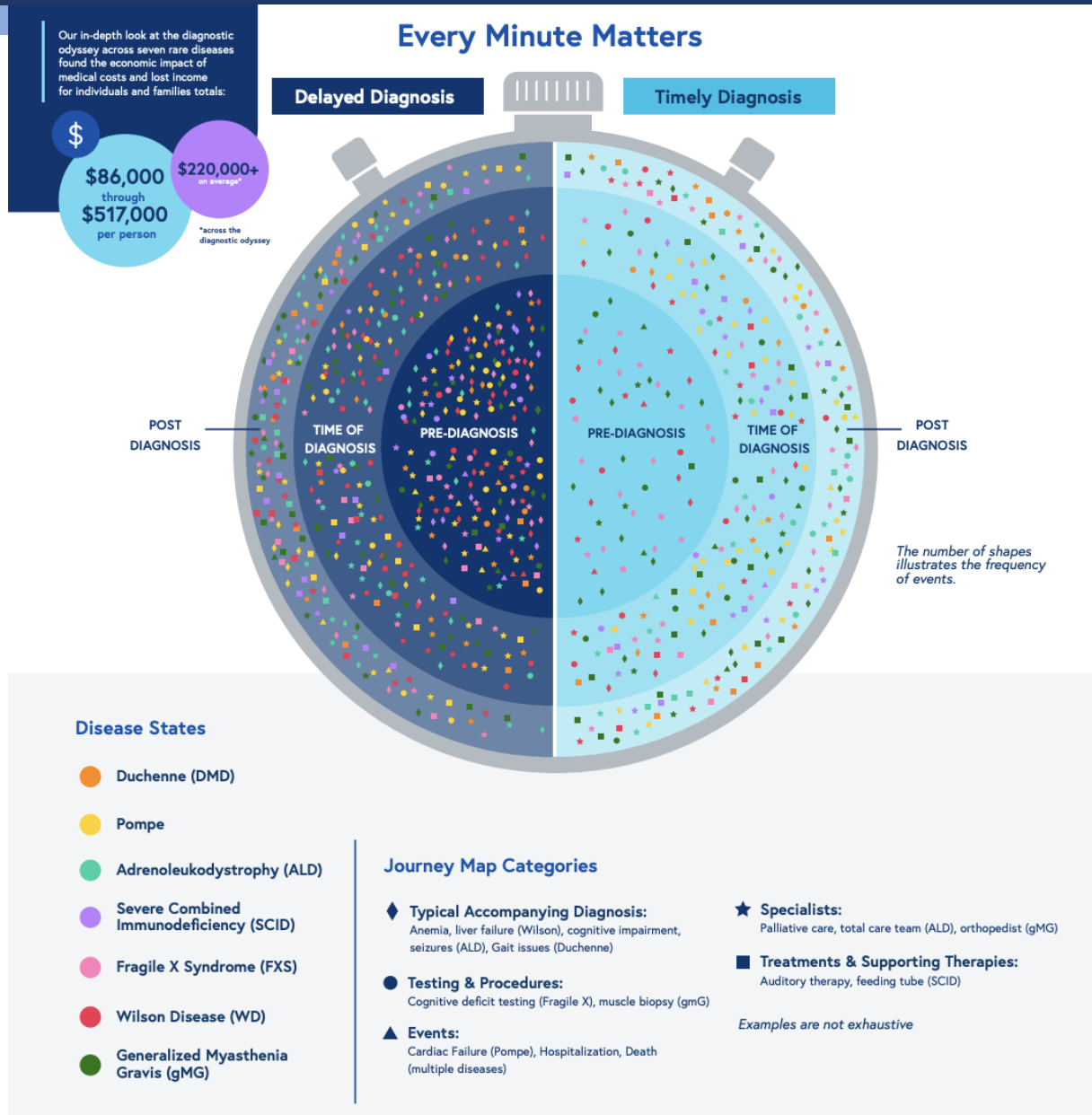
1E15 VG TOTAL

ROUTE OF ADMINISTRATION

INTRATHECAL LUMBAR

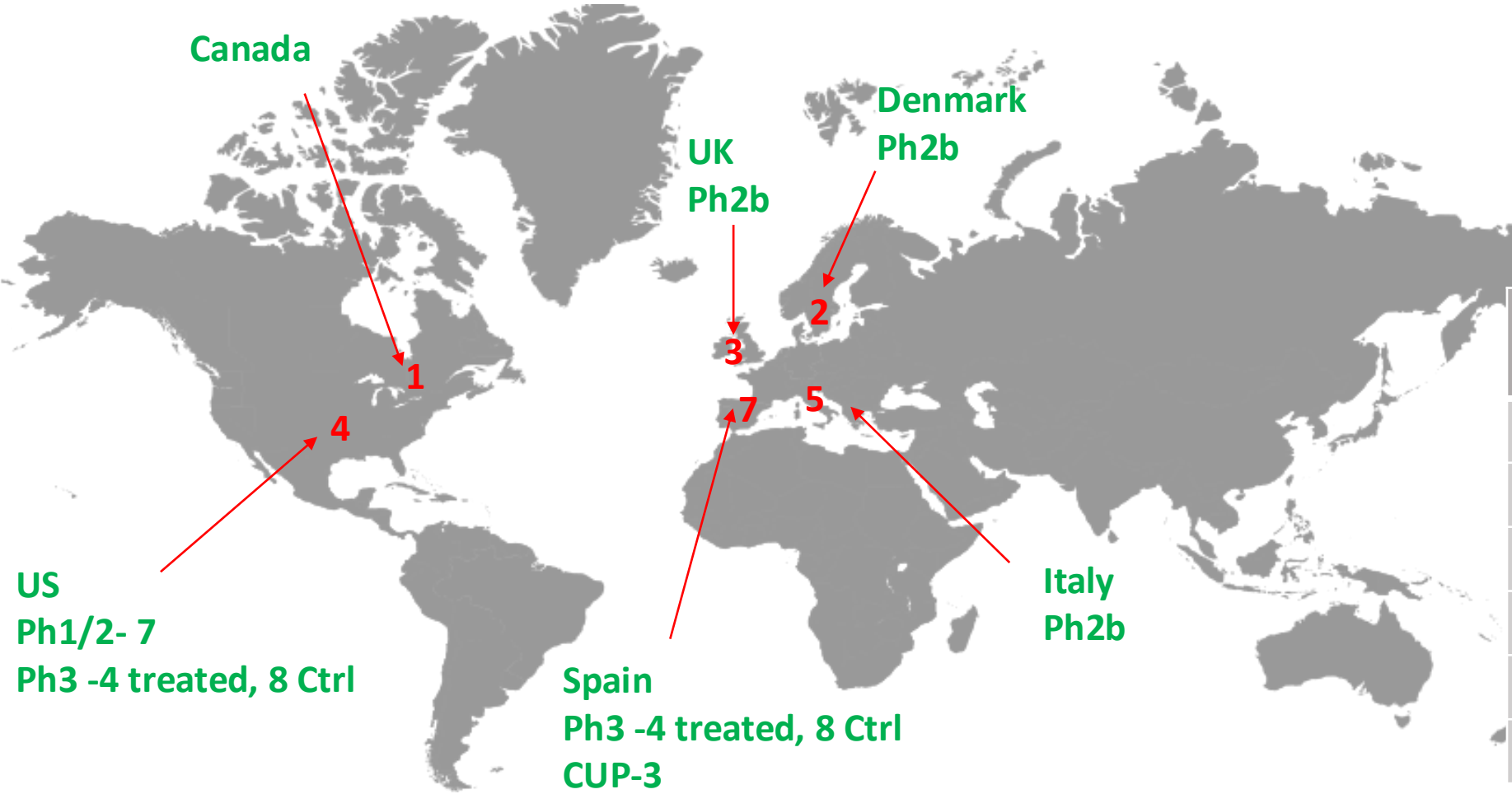
Impact of Delayed diagnosis

- Av. 6-year diagnostic odyssey
- $86-517,000 per patient/ year delayed
- Irreversible disease progression
- Worsened clinical outcomes
- Loss of opportunity for early intervention
- Impact on patient and family



EveryLife Foundation for Rare Diseases
In Partnership With: The Lewin Group, part of Optum Serve Expert Stakeholders The Rare Disease Community September 14, 2023

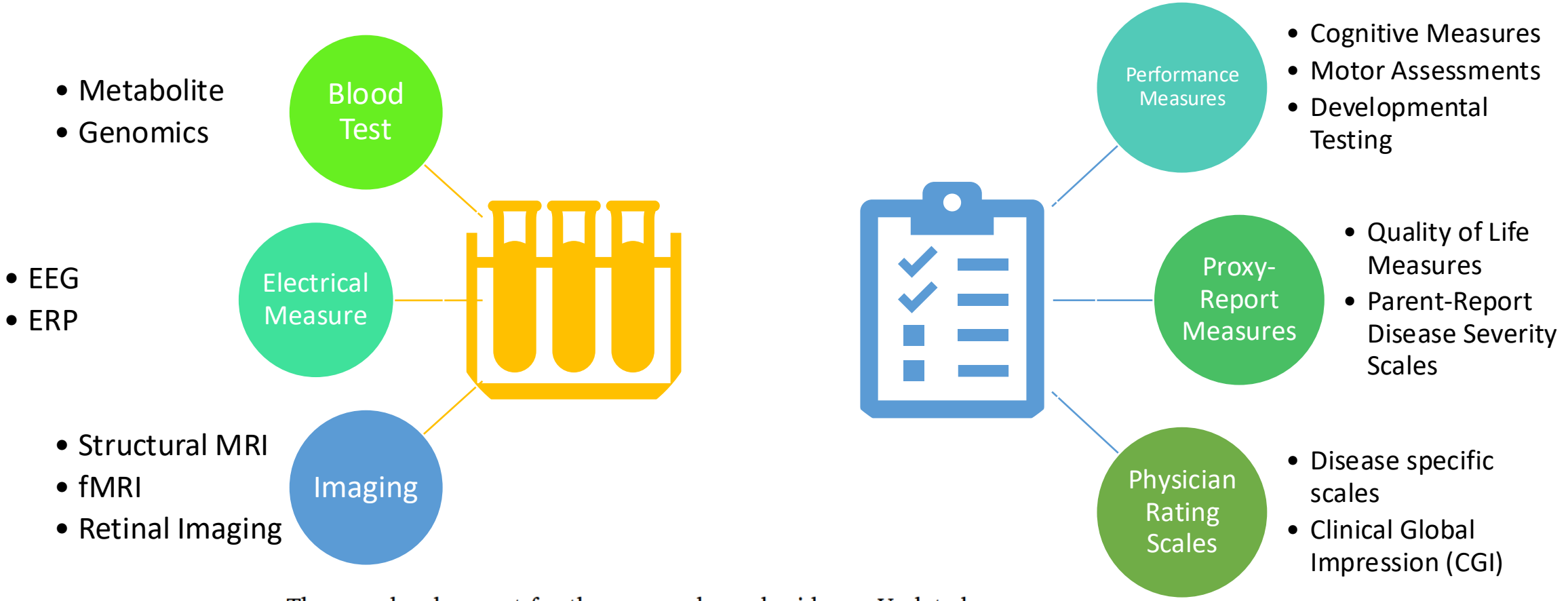
MELPIDA Patient Access



Subjects treated to date- 11
Subjects remaining - 18
Total 29 subjects

Country	Regulatory Agency	Ethics Board
Canada	HC	IRB
US	FDA	IRB
Italy	AIFA	CET
Spain	AEMPS	CEI
Denmark	DKMA	VK
UK	MHRA	REC

Challenges for Study designs



Therapy development for the mucopolysaccharidoses: Updated consensus recommendations for neuropsychological endpoints

Johanna H. van der Lee[a,b], Jonathan Morton[c], Heather R. Adams[d], Lorne Clarke[e], Julie B. Eisengart[f], Maria L. Escolar[g], Roberto Giugliani[h], Paul Harmatz[i], Melissa Hogan[j], Shauna Kearney[k], Joseph Muenzer[l], Nicole Muschol[m], Stewart Rust[n], Benjamin R. Saville[o,p], Margaret Semrud-Clikeman[e], Raymond Wang[q], Elsa Shapiro[g,r,*]

Selecting Endpoints

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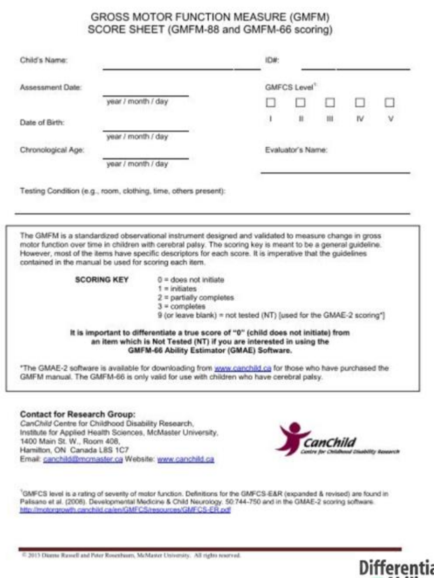
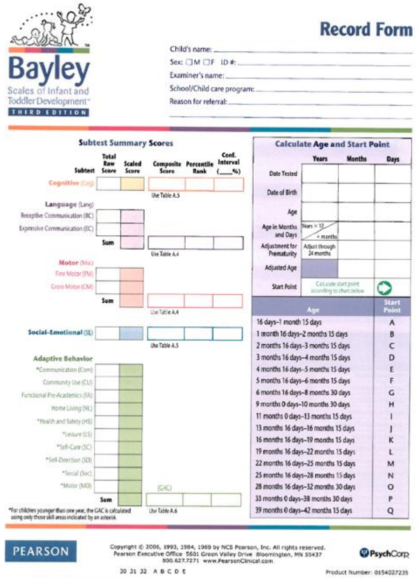
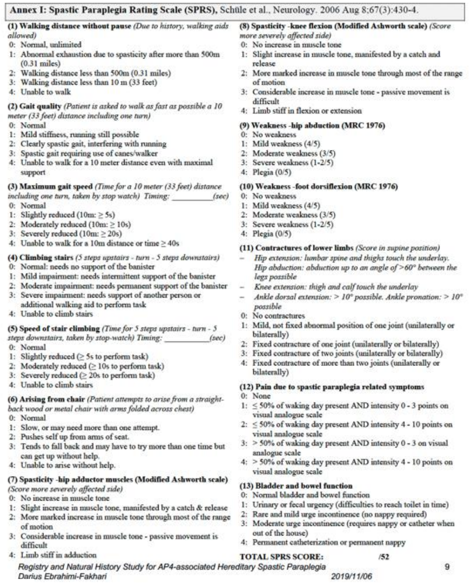
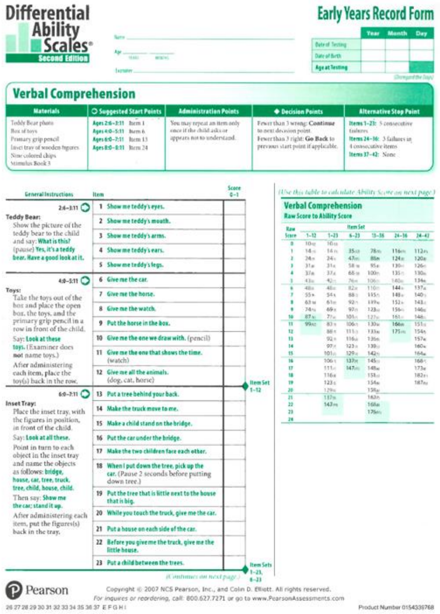
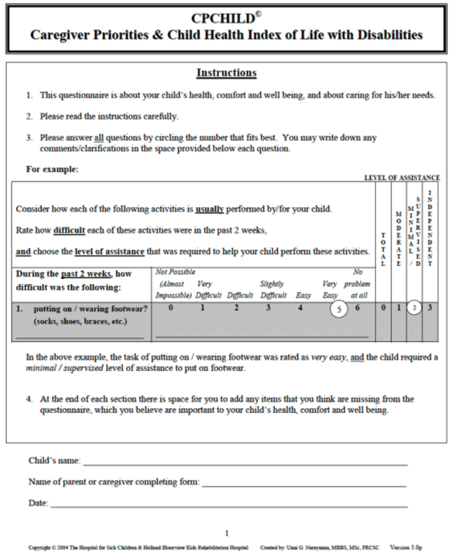
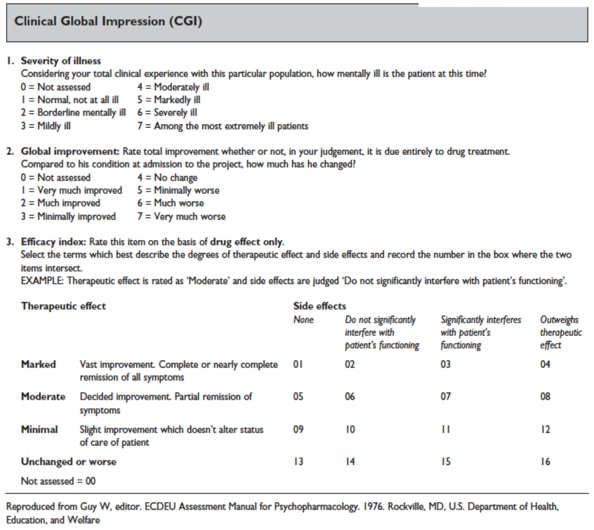




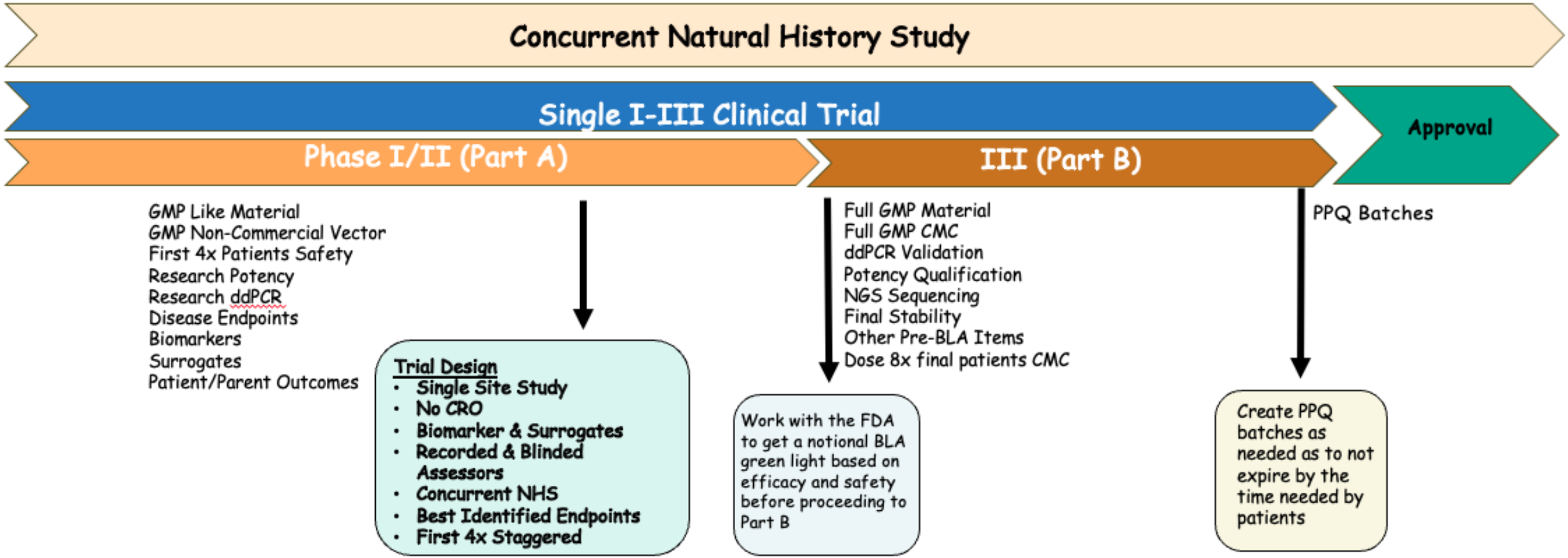






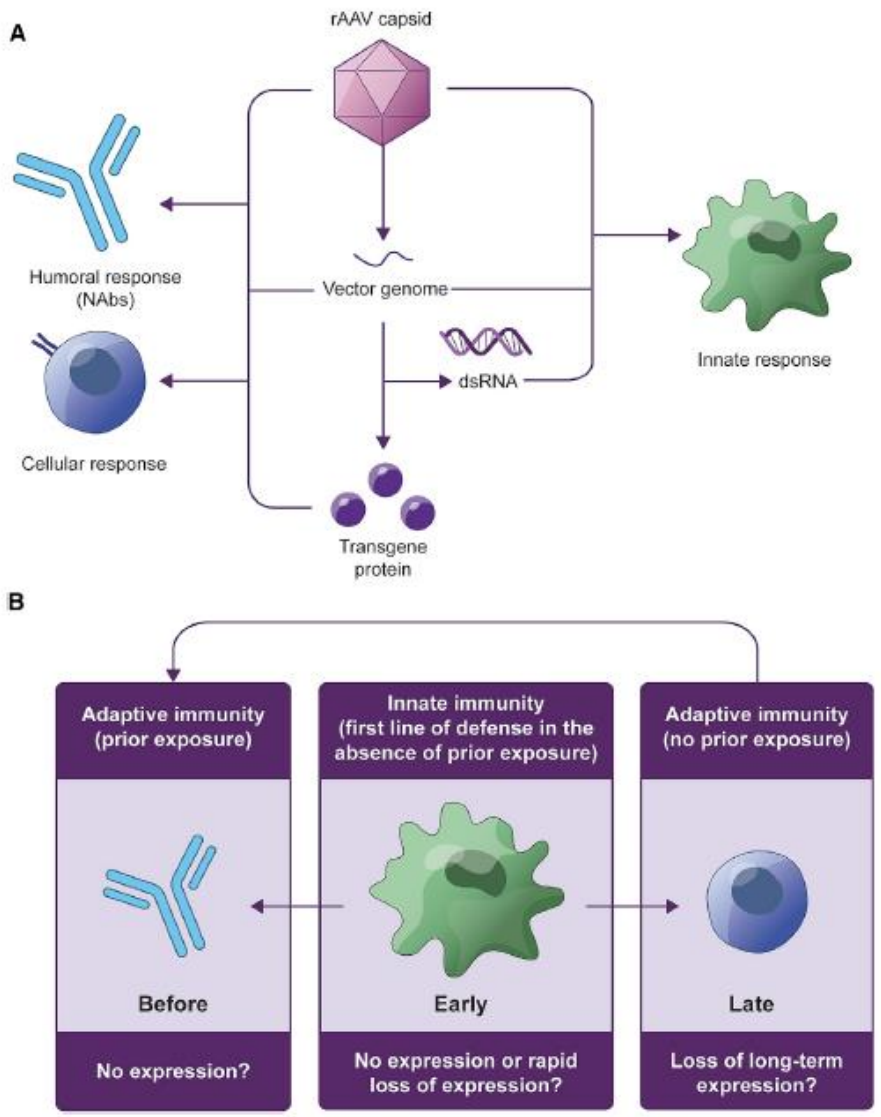


Adaptive trial designs



*Based on AAV platform serotypes

Mitigating Immune Responses

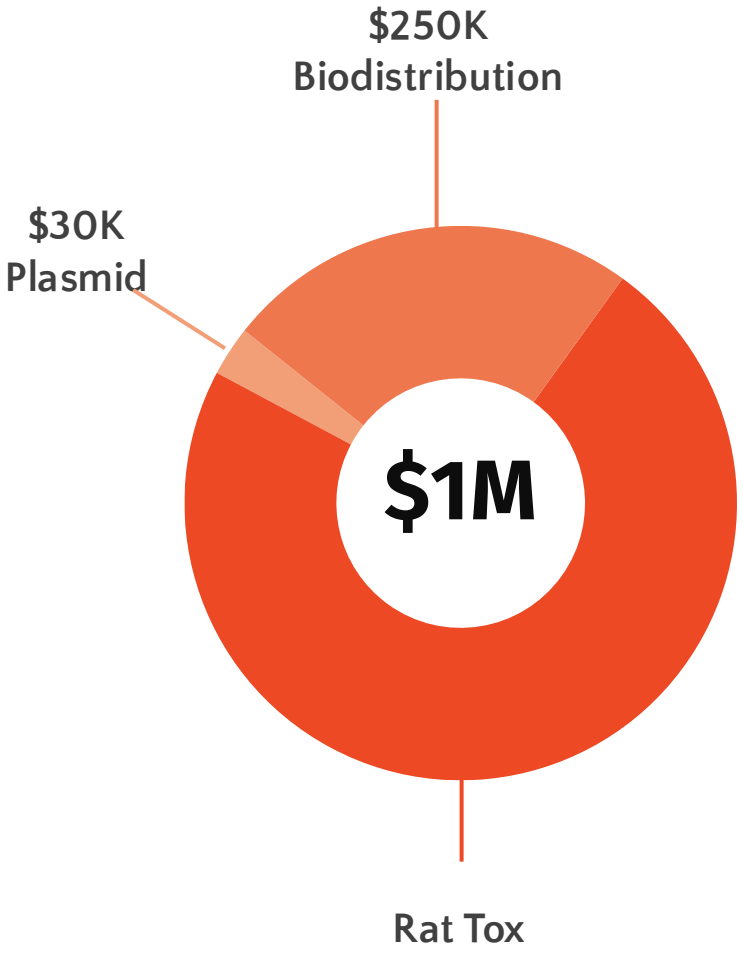


- Innate response can occur against capsid, transgene, or transgene protein (could cause no expression or rapid loss)
- Neutralizing Antibodies (pre-existing)
- Adaptive response may reduce or eliminate expression
- CRIM +ve/-ve
- Immune suppression
  - Prednisolone (reduce proinflammatory cytokines and chemokines)
  - Rapamycin (sirolimus) [T cell proliferation and differentiation]
  - Tacrolimus (T cell activation, inhibit T helper cell-dependent B cell response)

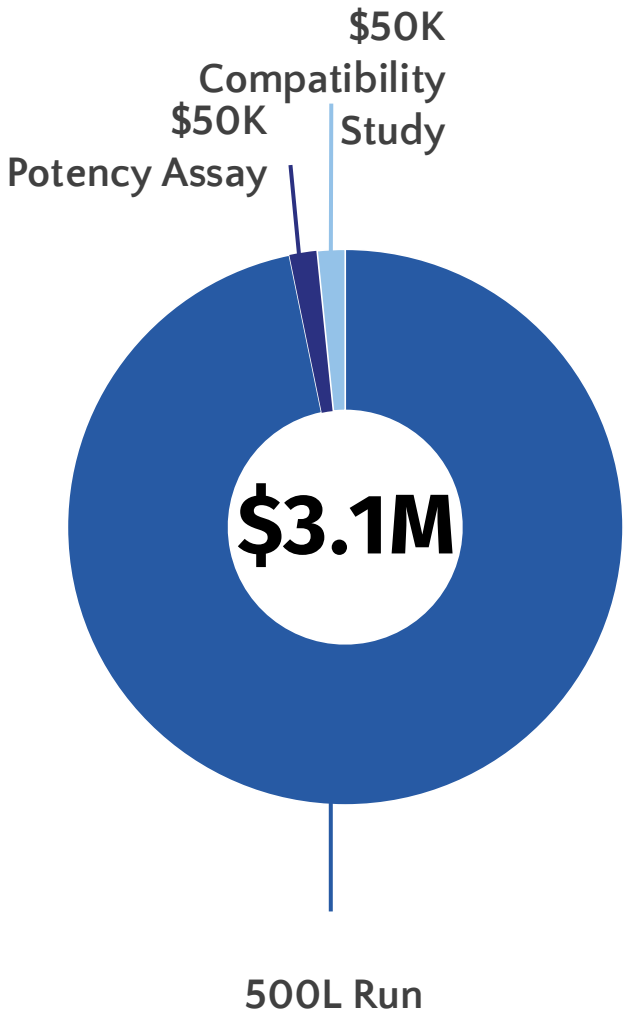
Managing Adverse Events

- Hematologic events -Neutropenia
- Neurophysiological- Reduced sensory amplitudes
- Hepatotoxicity
- Thrombotic microangiopathy
- Acute respiratory distress syndrome
- Capillary leak syndrome
- Cardiac toxicity
- Thrombocytopenia
- Newly diagnosed malignancy
- Immunogenicity
- Hemophagocytic lymphohistiocytosis
- Macrophage activation syndrome

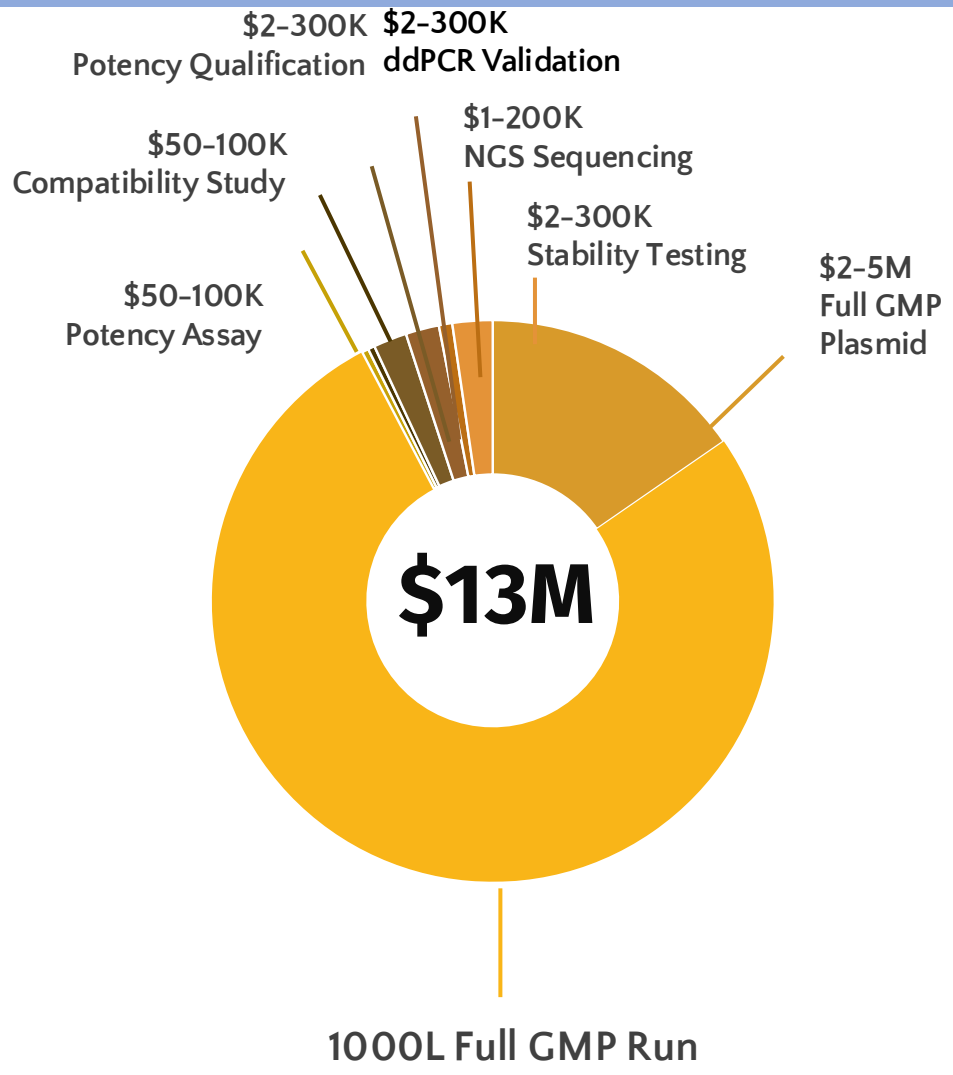
Financial barriers



GLP Rat Toxicology



GMP Non-commercial Vector Manufacturing



GMP Commercial Vector Manufacturing

Flexible CMC Requirements

- A single PPQ Batch is acceptable using historical data
- Drug Product validation is required
- E&L interim analysis is required along with a full study post BLA
- DP Filtration testing is required but a surrogate is acceptable
- Full GOI ddPCR validation is required on all lots
- Full potency validation on GOI is required

MELPIDA Development

Pre-Clinical Development
- POC Studies
- Pre-IND/Pre-CTA
- Toxicology Manufacturing
- Toxicology Studies
- IND Filing/CTA Filing
- CMC Manufacturing

Clinical Trials
- Phase I Canadian Trial Approved
  - First Patient Treated (SickKids Toronto)
- Phase I/II FDA Clinical Trial Approved
  - 5x Patients Dosed UTSW
  - Youngest Patient To Be Treated Via IT (5 Months Old)
- Compassionate Use Site In Spain
  - 2x Patients Treated In San Sebastien

Phase III/Pivotal Study
- Commercial Grade CMC completed
- Initiation Of Clinical Trial
- Beginning Of Phase III/Pivotal Study

BLA- Analysis and Validation
- Interim Analysis To Determine Efficacy
  - If Successful Apply For BLA
- If Interim Analysis Is Not Enough
  - Re-Evaluate At 5 Year Mark
- Successfully Receive BLA
  - Market/Commercialize MELPIDA

Thank you

Elpida Team
Terry Pirovolakis
Souad Messahel, PhD
Keith Gottlieb, PhD
Rachel Thomas RN
Caitlin Roll
Diane Balderson, PhD
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