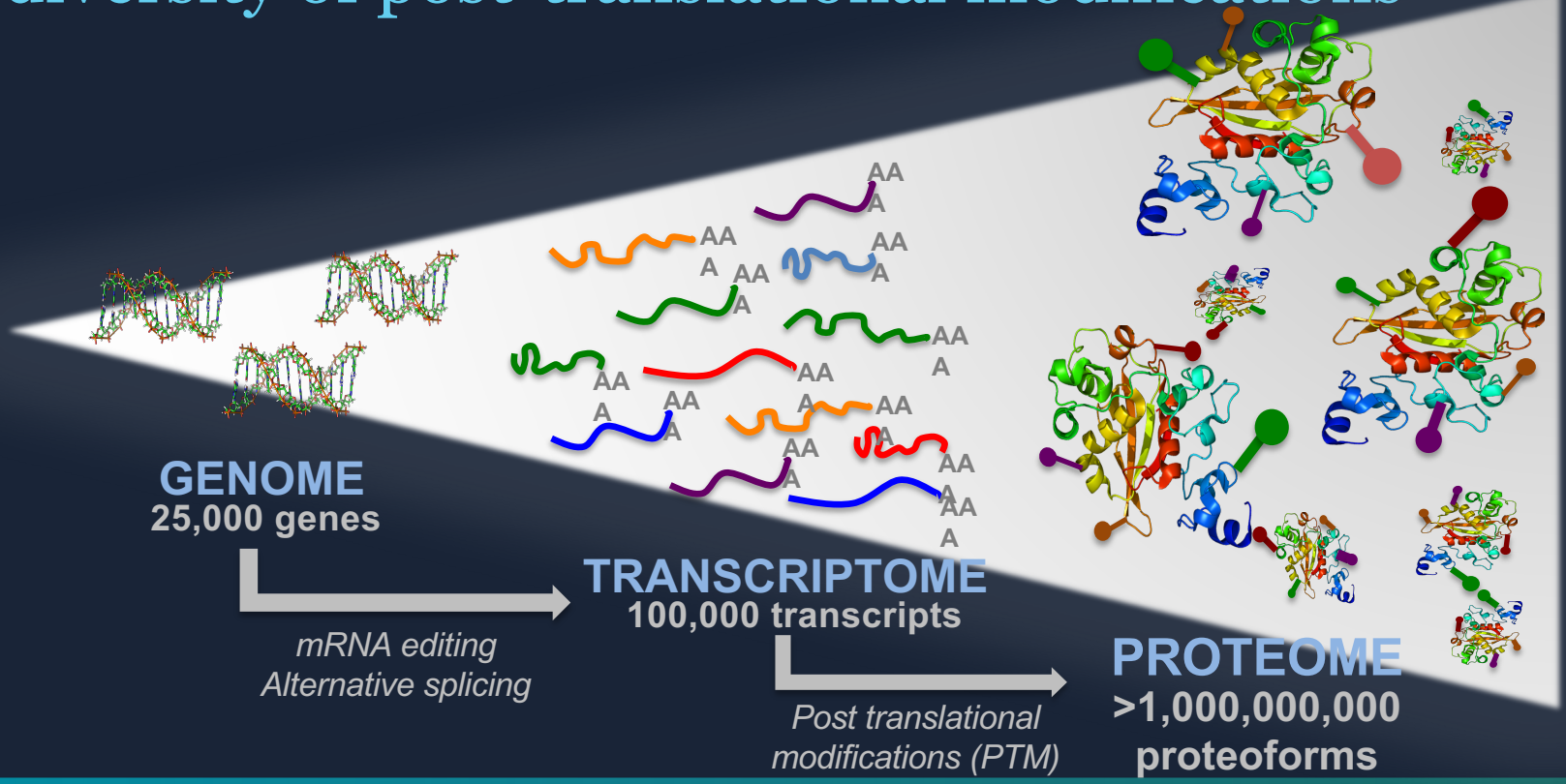
Nonconfidential Corporate Overview

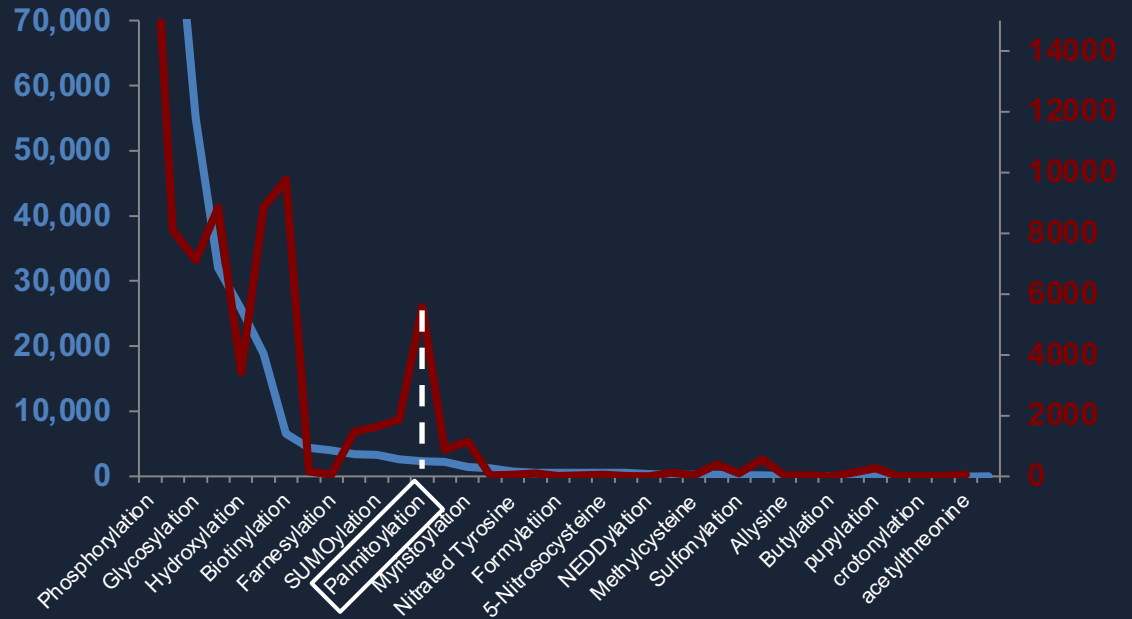
Envisioning a world where each individual retains full brain function and cognitive faculties throughout life

The PROTEOME world is huge due to the diversity of post-translational modifications



Palmitoylation–one of the most prevalent PTMs–has not been widely investigated

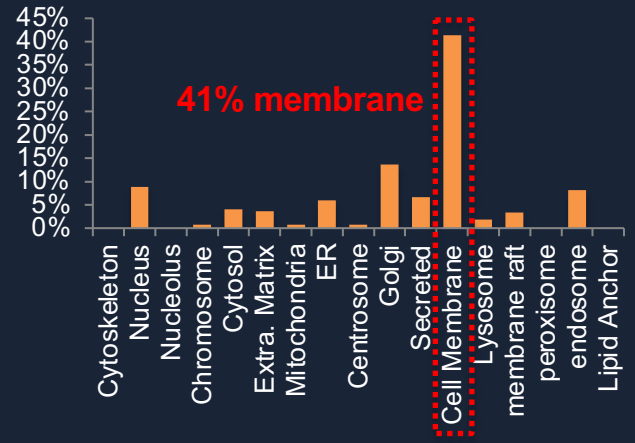
Prevalence in literature

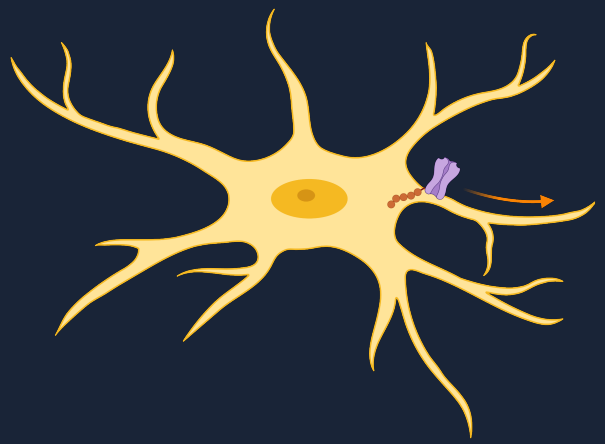


Number of identified sites

A functional relationship exists between palmitoylation and protein localization

Localization of palmitoyl-proteins





Half of all palmitoyl-proteins are found in synapses

Palmitoylation can rapidly and dynamically localize proteins to lipid membranes

Harnessing the biology of protein palmitoylation to treat serious neurological diseases

$4M in seed funding raised to date

Y DAYLI THE LONGEVITY FUND WTI Keystone Capital

Circumvent's Pipeline and Key Activities

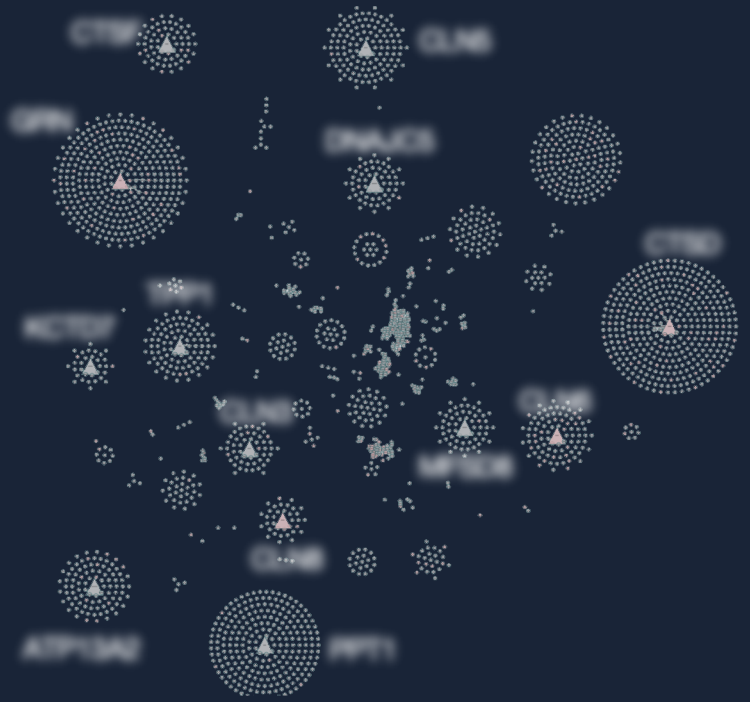
- **Palmitate erasers for Batten's Disease**
  Development Candidate in IND-enabling studies for CLN1 Disease
- **Targeting palmitoyl-proteins in other synaptopathies**
  Drug discovery and patient subtyping
- **Palmitoyl-proteomic profiling and target ID in other serious diseases**
  Discovery Research Platform

Mapping the palmitoylome and palmitoylation gene interactome yields putative disease targets

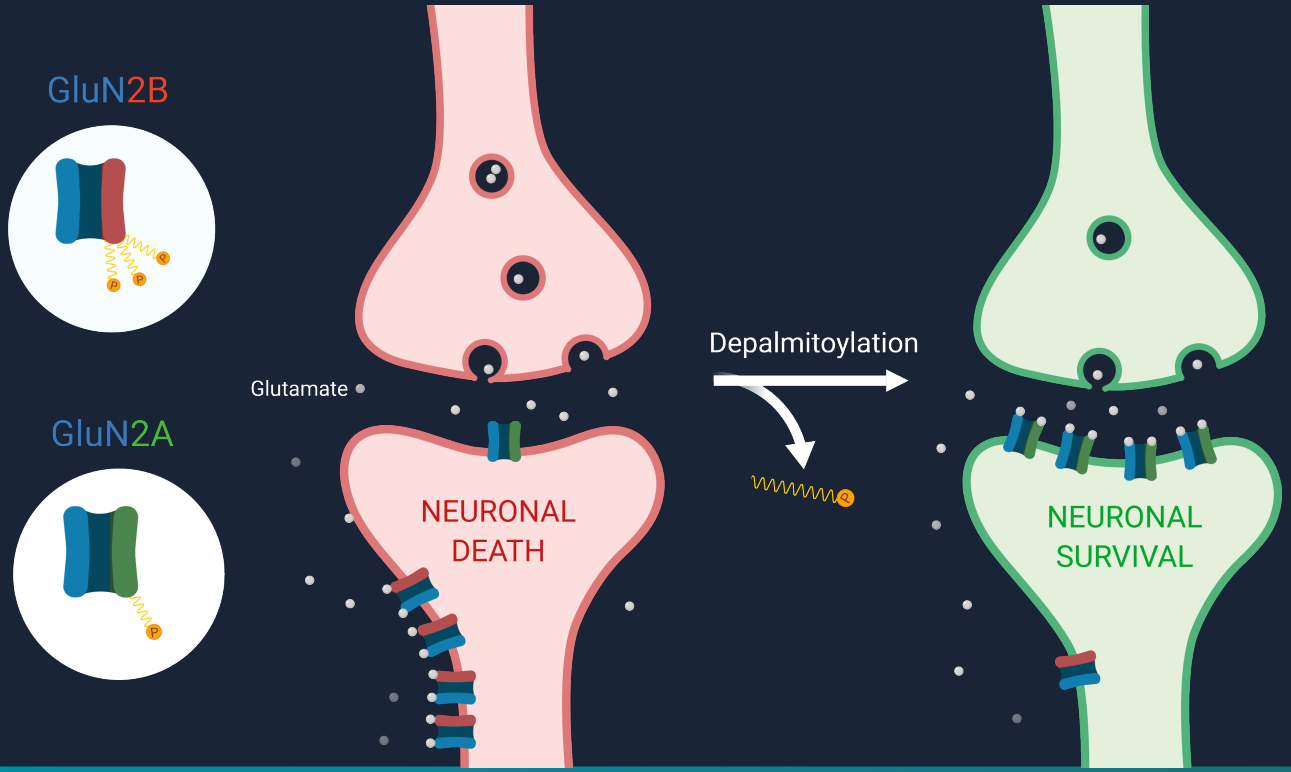
1. We mapped out the network of palmitoylation pathway genes, their interaction partners, and known substrates

2. We mine this network for any disease-associated proteins and score these targets based on disease relevance

3. We generate hypotheses of how dysregulation of palmitoylation and protein mislocalization drives disease



Localization of Glutamate Receptors Mediating Neuronal Excitotoxicity is Regulated by Palmitoylation

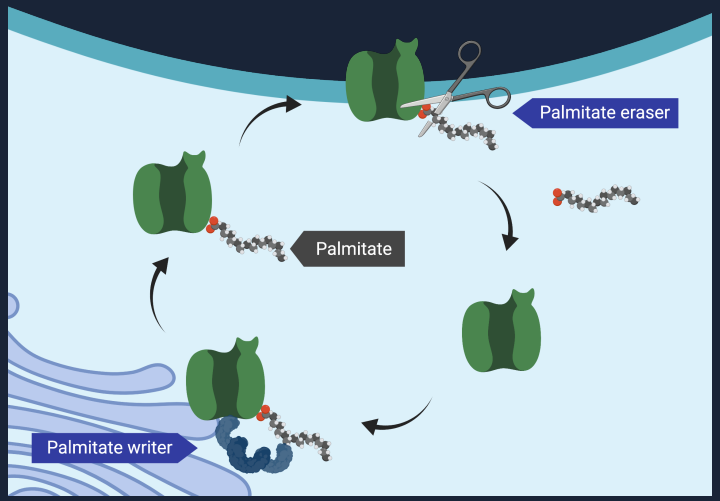


Higher extrasynaptic : synaptic NMDA receptor distribution makes neurons susceptible to glutamate excitotoxicity

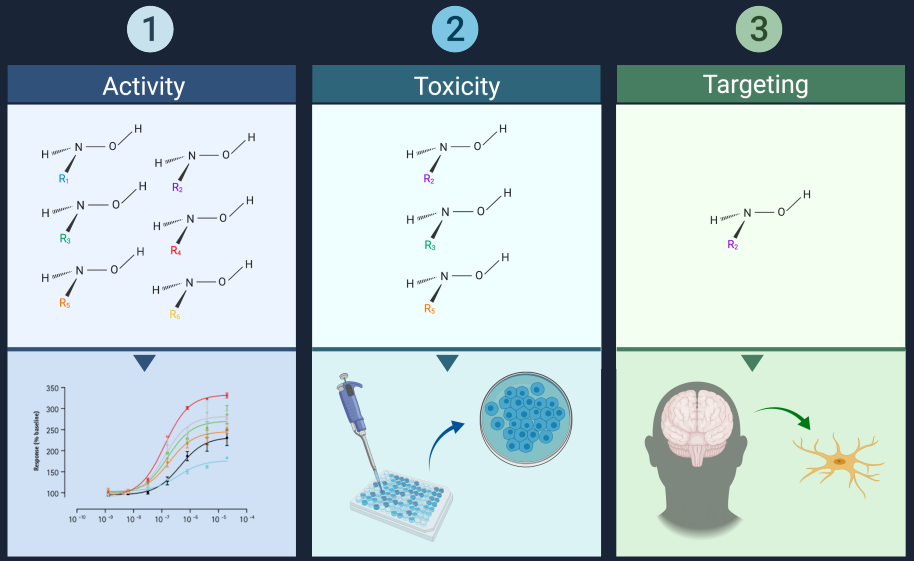
Palmitoylation regulates extrasynaptic : synaptic NMDA receptor distribution

Modulating palmitoylation can improve on the safety and efficacy of clinically validated anti-glutamatergic drugs that block NMDA receptors broadly

Circumvent's Medicinal Chemistry Platform for Small Molecule Palmitate Erasers

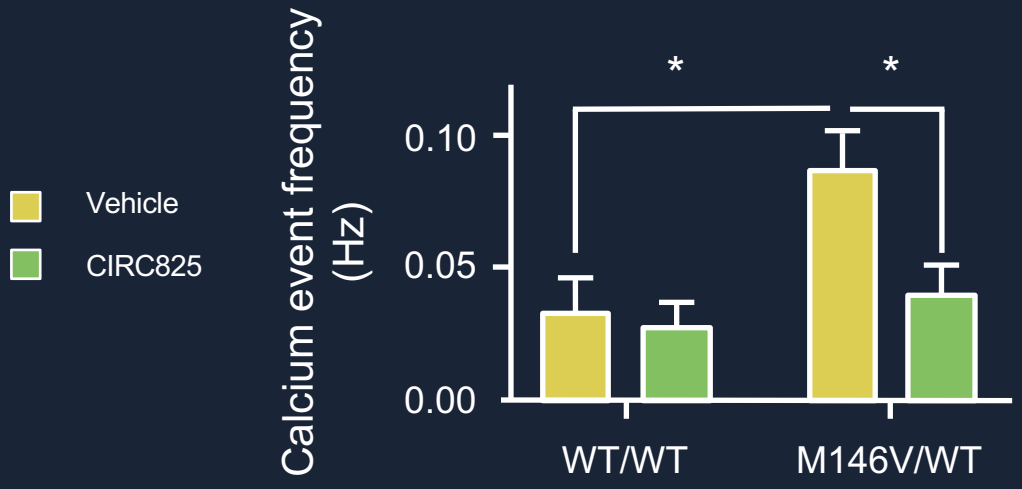


Palmitate is added to proteins by acetyltransferases (palmitate writers) and removed by thioesterases (palmitate erasers)



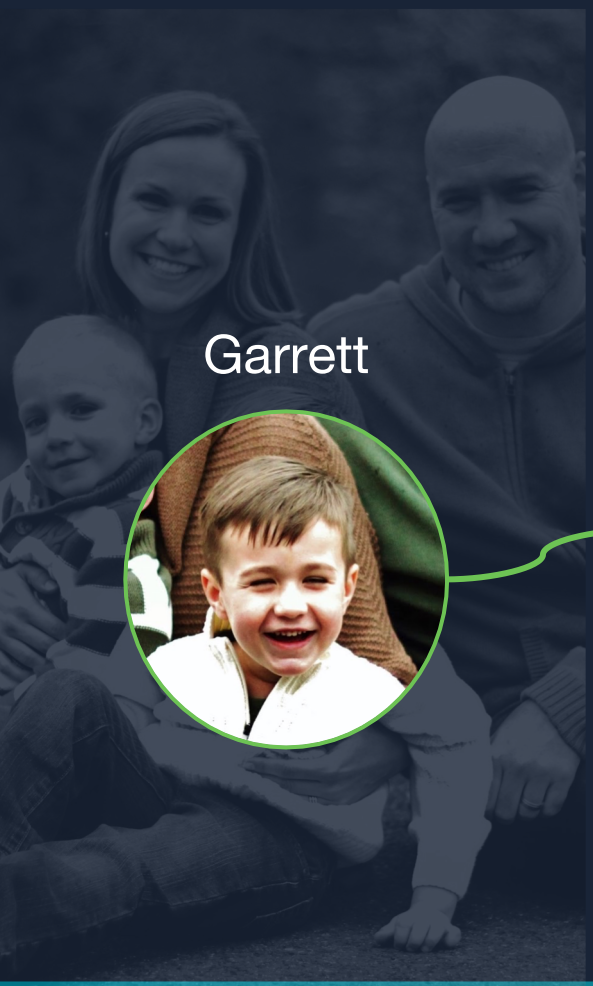
We've developed a platform of small molecule palmitate erasers that exploit a well-known chemical reaction to cleave palmitoyl-thioester bonds

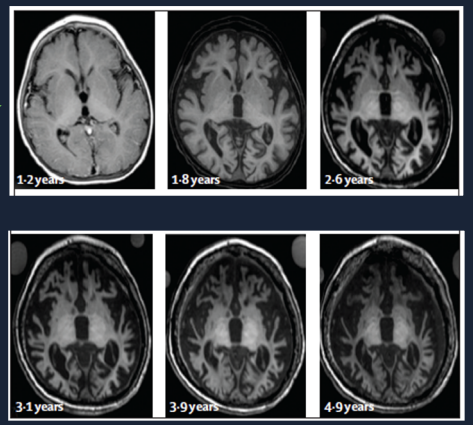
Small Molecule Palmitate Erasers Reduce Hyperexcitability in AD hiPSC-Derived Cerebrocortical Neurons



- AD neurons (containing familial PSEN1 mutation) manifest enhanced intracellular calcium levels and spontaneous transients compared with WT isogenic neurons
- Calcium event frequency is quantified before and after addition of compound
- Small molecule palmitate eraser inhibits spontaneous calcium activity

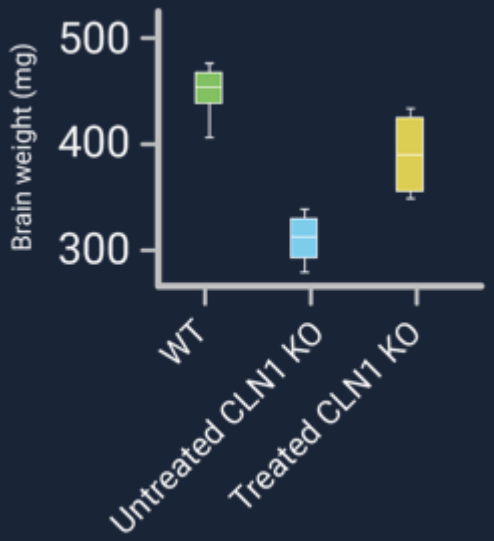
CLN1 Batten Disease is a Genetically Defined Synaptopathy Caused by Aberrant Palmitoyl Protein Processing

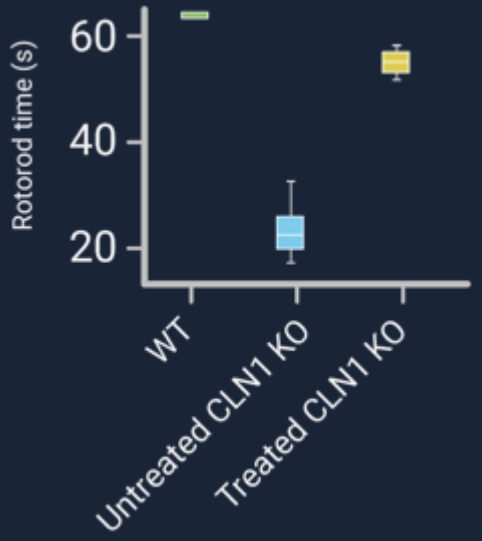




- Accelerated form of neurodegeneration that occurs in infants and children
- Caused by loss-of-function mutation in a palmitoyl-protein thioesterase (Ppt1)
- Causes over-palmitoylation of synaptic proteins, resulting in excitotoxic neuronal death

CIRC825 Drives Efficacy in Clinically Meaningful Endpoints of CLN1 Disease Animal Model





Conditions for CLN1 KO *in vivo* studies: 15 mg/kg oral dosing, initiated at 3 months of age, observation at 6 months of age

Highly Accomplished Leadership Team

Andrew Lim Chief Executive Officer	AVIDITY BIOSCIENCES	Calibr California Institute for Biomedical Research	
Samy Hamdouche PhD Chief Business Officer	AVIDITY BIOSCIENCES	KURA ONCOLOGY	wellspring biosciences
Devin Wiley MD PhD Chief Medical Officer	DANTARI	CERULEAN	intel Capital
Robert Steiner MD Head of Translational Medicine	Acer Therapeutics	OHSU Health	PREVENTION GENETICS
Robert DeVita PhD Head of Drug Discovery	MERCK	agios	
Steven Duddy PhD Head of Toxicology	Pfizer		

Supported by Leading Experts

Anil Mukherjee, MD, PhD
National Institutes of Health
CLN1 Disease Biology

Stuart Lipton, MD, PhD
Scripps Research
Alzheimer's Disease Biology
Inventor of Namenda®

Angela Schulz, MD, PhD
UKE Hamburg
Batten Disease Clinician
PI of Brineura® Trial

Rudy Tanzi, MD, PhD
Harvard MassGen
Alzheimer's Disease Biology
Discovered Familial AD Genes

Leonard Post, PhD
Former CSO of BioMarin
Batten Disease Biology
Led Brineura® Development

Dale Martin, PhD
University of Waterloo
ALS and Huntington's Biology
Palmitoyl proteomics innovator

Upcoming Milestones

Milestone	Timing
CIRC825: Advance palmitate eraser Development Candidate to IND	4Q 2021
Expand palmitoyl proteomics and biology platform across a range of ND conditions including AD, PD, HD and neuropsychiatric disorders	2021
Evaluate partnership opportunities	1H 2021
Designate a Development Candidate for additional palmitoylation driven synaptopathies	2Q 2021

Currently raising $1M in additional funds

Exit Scenarios – Significant Demand in Neuro

- Merck acquisition of TRPML1 agonist developer Calporta for up to $567M (preclinical) – Nov 2019
- Lilly acquisition of Disarm for $135M upfront (preclinical) – Oct 2020

Circumvent

Harnessing the biology of protein palmitoylation