

# Exolva Therapeutics



“Imagine a world in which protein therapeutics could be delivered efficiently to the cytosol and nucleus.”

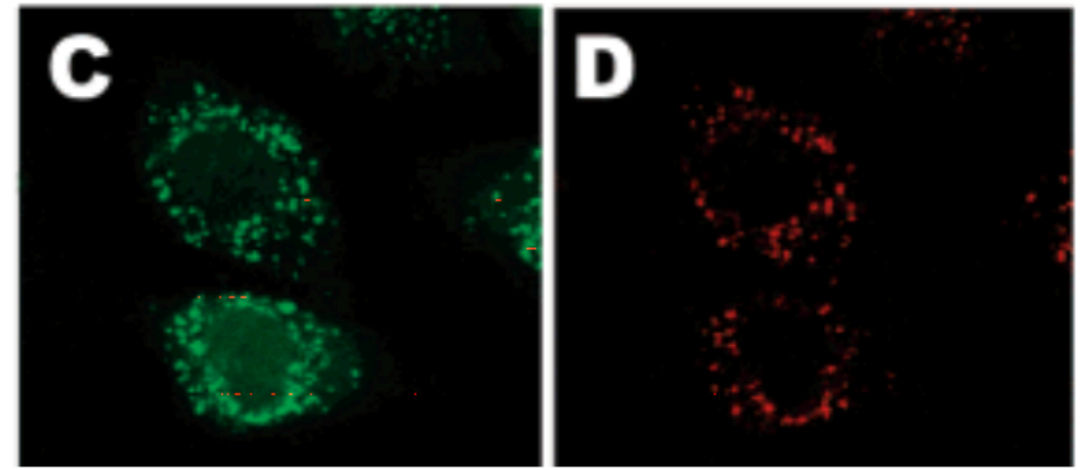
A **novel platform technology** applied (first) to **an illness with no disease-modifying therapy:** Type I Citrullinemia (CTLN I)



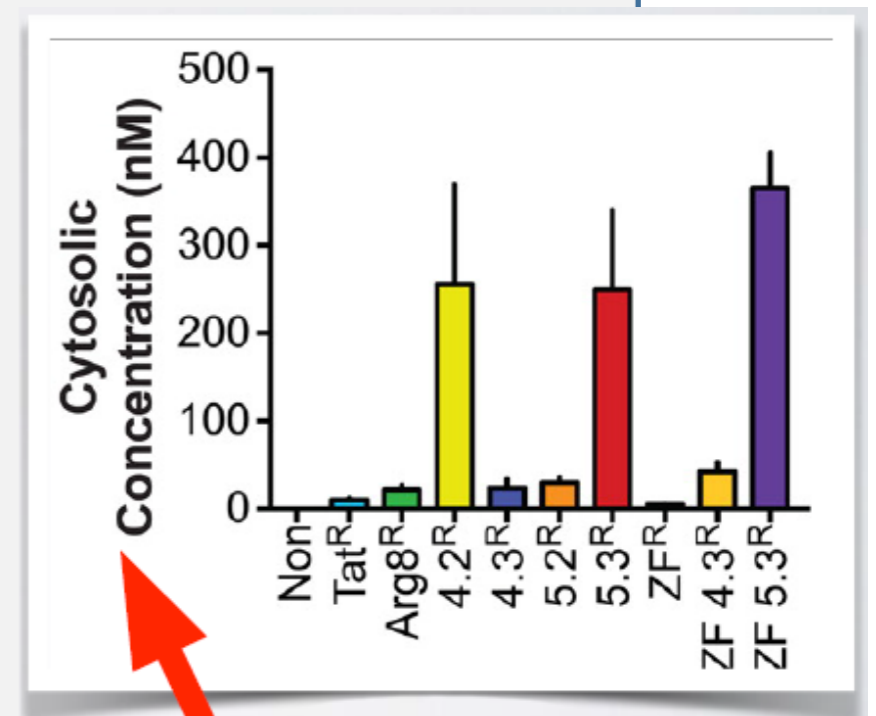
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# We discovered cell-permeable miniature proteins



- CPMPs reach cytosol and nucleus with **efficiencies as high as 75%**
- Efficiency **higher than all other ‘CPPs’ tested**
- Delivery efficiency quantified directly *via* FCS
- Deliver active **payloads 10 – 32 kD**
- **High and tunable serum stability**
- **Non-toxic; genetically encodable; easily manufactured**
- **Key difference:** CPMPs utilize well-defined, non-destructive mechanism
- **Fundamental patents and applications cover scaffold and delivery**

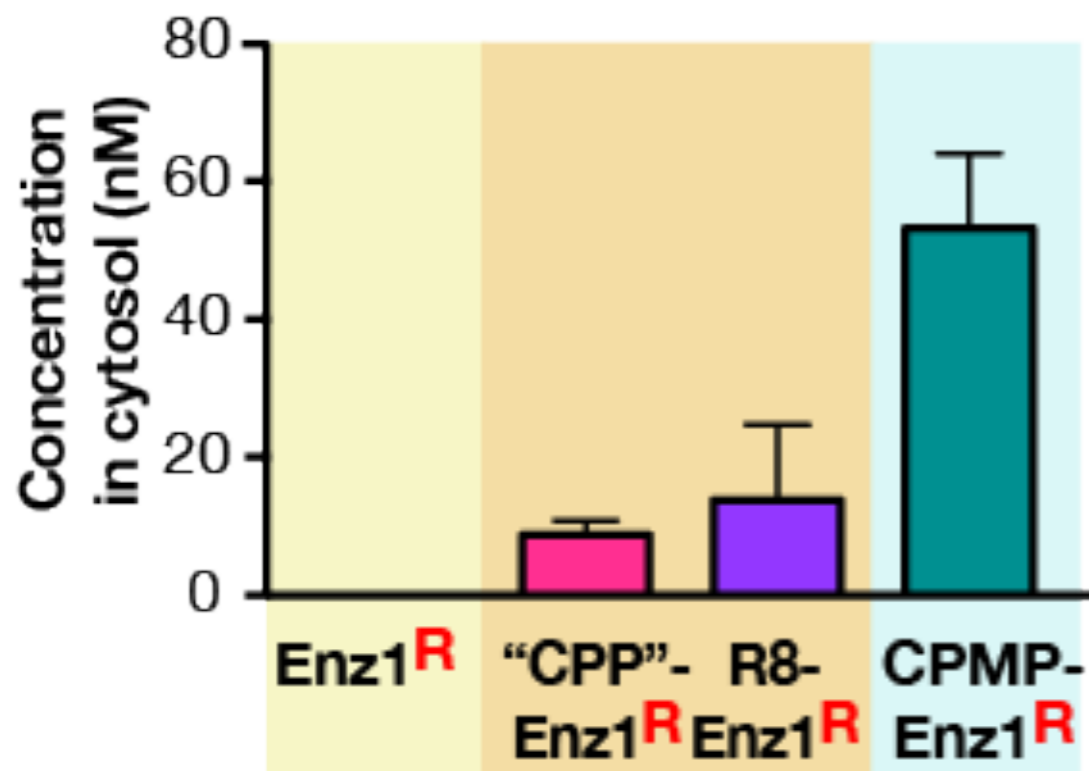


**endosomal escape**

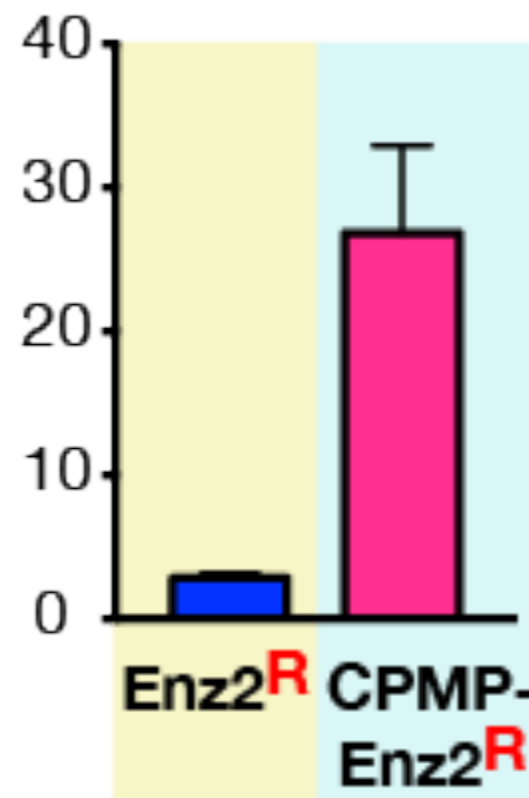


# CPMPs deliver multiple payload classes to the cytosol

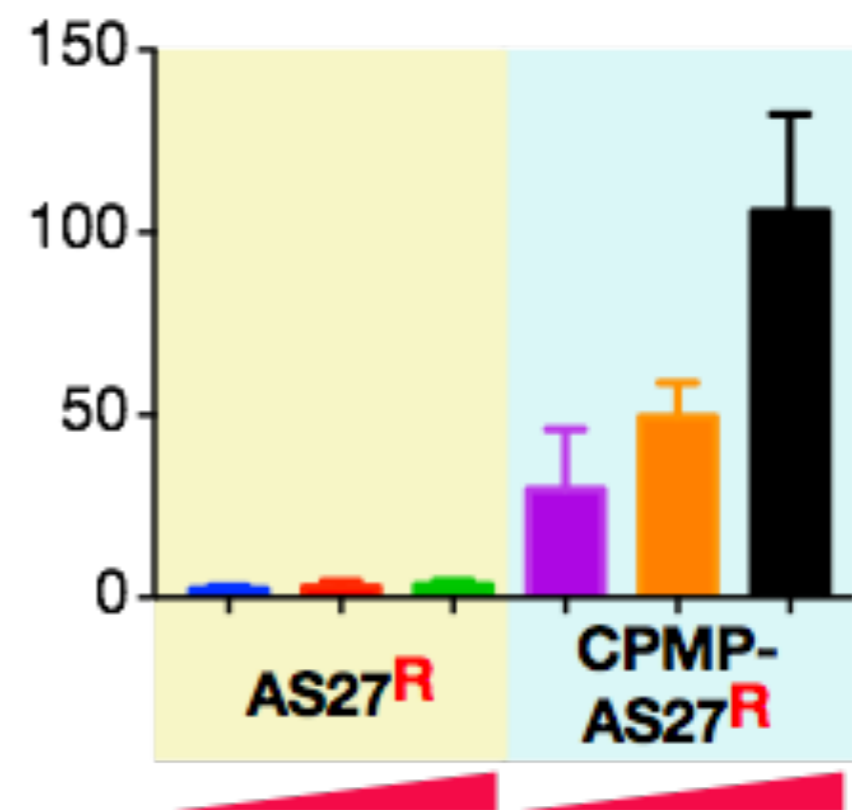
Enzyme #1  
(20 kD)



Enzyme #2  
(35 kD)



Ab mimetic  
(10 kD)



# Using a CPMP to deliver AS and correct 'inborn error of metabolism'

## The Problem

- Type I citrullinemia is an **incurable disease**
- Results from deficiency or absence of the urea cycle enzyme **argininosuccinate synthetase** (AS)
- Severe AS deficiency results in hyperammonemia and **irreversible neurological damage, coma, or death**

## The Market

- 1:57,000 affected worldwide; **19,000 patients in US/Europe**
- **No disease modifying therapy**
- Mutations suggests **activity >10%** is disease-modifying
- @ \$350K/patient/year, **15% treated = \$1B/year.**
- **Validates platform for therapeutic indications where delivery to cytosol is critical**



# Favorable competitive landscape

		Cure disease	Deliver enzyme	Broad scope	High stability	Non-toxic	High delivery efficiency
CTLNI treatments	Buphenyl® or Ravicti®	<b>X</b>	<b>X</b>	<b>X</b>	-	-	-
	Shire, PhaseRx	✓	<b>X</b>	<b>X</b>	<b>X</b>	-	<b>X</b>
	SynLogic	✓	✓	<b>X</b>	-	-	-
platforms	Aileron, Bicycle	<b>X</b>	<b>X</b>	<b>X</b>	✓	✓	✓
	Trojan Tech, Xigen, Portage, Cellivery	✓	✓	✓	<b>X</b>	<b>X</b>	<b>X</b>
	<b>Cell-permeable miniature proteins</b>	✓	✓	✓	✓	✓	✓



# Timeline and Milestones

## Objective 1

- Express CPMP-AS fusions/controls
- Evaluate uptake and trafficking efficiency in SK-HEP-1 cells
- Monitor reversal of AS deficiency
- **Milestone:** Successful overexpression/purification; **enhanced cytosolic trafficking**; AS deficiency reversal
- **Timeline:** **Q3-4 2017**

## Objective 2

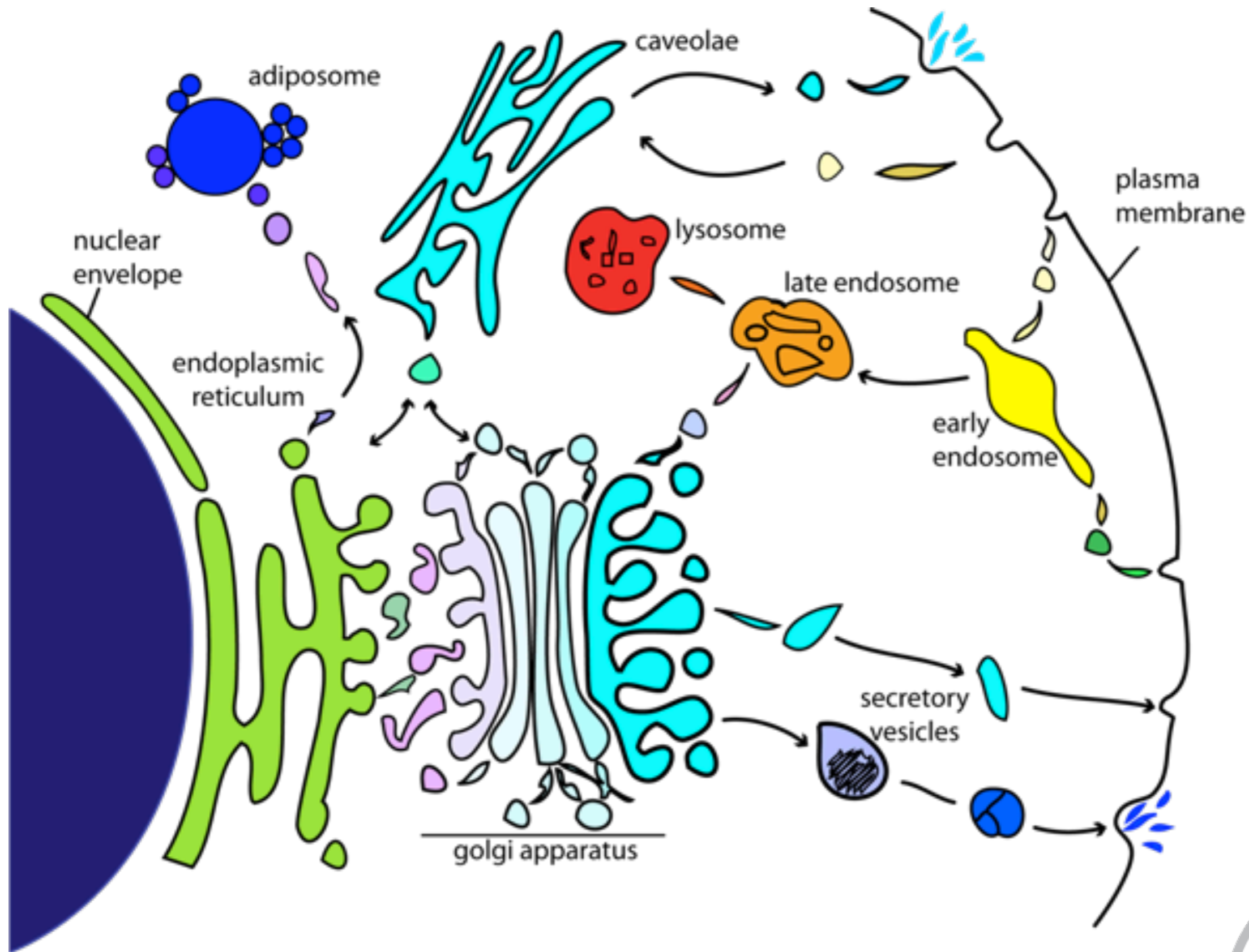
- Establish *in vitro* PK and metabolism of CPMP-AS fusions/controls
- Evaluate plasma stability, protein binding
- Compare results to those of FDA-approved biologics
- **Milestone:** **acceptable stability** ( $t_{1/2} > 30$  min); PPB comparable to Fabrazyme®; **establish fundamental PK**
- **Timeline:** **Q1 2018**

## Objective 3

- Establish *in vivo* PK and biodistribution CPMP-AS fusions/controls C57BL/6 mice
- **Milestone:** **presence in plasma; acceptable distribution to liver**
- **Timeline:** **Q3 2018**

## Objective 4

- Evaluate top CPMP-AS fusion in *fold* mouse model of human CTLN1 (iv)
- Assess lifespan, weight, length, and coat density, and plasma ammonia and citrulline.
- **Milestone:** **Inflection point— Demonstration that CPMPs can deliver an active enzyme to the cytosol of an animal to reverse the effects of a serious metabolic disease**



delivering better medicine

Exolva Therapeutics

