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

Exolva Therapeutics

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

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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 1 citrullenemia is an incurable disease
- Results from deficiency or absence of the urea cycle enzyme **argininosuccinate synthetase** (AS)
- Severe AS deficiency results in hyperammononemia 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

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## Favorable competitive landscape

<table>
<thead>
<tr>
<th>CTLNI treatments</th>
<th>Cure disease</th>
<th>Deliver enzyme</th>
<th>Broad scope</th>
<th>High stability</th>
<th>Non-toxic</th>
<th>High delivery efficiency</th>
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<tbody>
<tr>
<td>Buphenyl® or Ravicti®</td>
<td>X</td>
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<td>Shire, PhaseRx</td>
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<td>Cell-permeable miniature proteins</td>
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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

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