Developing the First Drug for Core Symptoms of Autism

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### Applying Yale Research to a Breakthrough Treatment for Autism

#### Market:
- No drugs are approved to treat core symptoms of autism
- Most costly pediatric/developmental disease in the US; annual burden ~ $250 billion*

#### Biology:
- Oxytocin: Most promising clinical data for autism; controlled trials on four continents
- Naloxone significantly amplifies oxytocin efficacy in monkeys; breakthrough potential

#### Product:
- Multiple layers of intellectual property; Yale patent being prosecuted by Saul Ewing
- Yale brings: Patent-pending addition of naloxone to improve oxytocin efficacy
- Pastorus brings: Efficacy/safety enhancement with patented formulation and delivery

#### Team:
- Yale researchers: Inventors on pending oxytocin/naloxone patent; recognized experts
- Pastorus: MD/PhD Neuroscientists (two from Yale); successful track record repurposing drugs

#### Economics:
- $300,000 for meaningful clinical study designed to demonstrate compelling treatment
- Favorable ROI: Successful trial plus current/pending patents → Valuation > $20 million

* [https://www.autismspeaks.org/autism-statistics](https://www.autismspeaks.org/autism-statistics)
Biology: Oxytocin, a human hormone, has the strongest clinical data set in autism - Success vs. core symptoms of autism in placebo-controlled trials on four continents

- NYC (2007): Early studies
- NYC (2003, 2007): Early studies
- Cambridge (2015)
- Tokyo (2014)
- Sydney (2010): Adolescents (12–17)
- France (2010)
- France (2016)
- Sydney (2016): Children (3–8)
- Stanford (2017): Children (6–12)
- Germany (2019)
- Tokyo (2015)

Studies in adults unless otherwise noted

Yale research: Naloxone amplifies oxytocin’s pro-social effects in monkeys; breakthrough potential
Monkeys:
Frequency of looking at the eyes of another monkey

Patent prosecuted by Saul Ewing Arnstein & Lehr; so far no specific objections to claims.

Adding naloxone amplifies oxytocin’s social effects ~ 5x

Source: Dal Monte, O, Piva M, ..., Chang, SWC. Oxytocin under opioid antagonism leads to supralinear enhancement of social attention. Proc Natl Acad Sci 2017 May 16;114(20):5247-5252.
Multiple layers of intellectual property:

1. Yale [oxytocin + naloxone] pending patent
2. Pastorus formulation patents
3. Pastorus delivery patents

Tests performed with radio-labeled Flonase® by independent UK laboratory

Pastorus’ patented, controlled, turbulent-flow delivery technology: Efficient delivery to preferred target

Existing spray-bottle technology: Loss to off-target areas

Problems with current technology

<table>
<thead>
<tr>
<th>Problems with current technology</th>
<th>Pastorus product solution</th>
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<tbody>
<tr>
<td>Dose consistency decreased by individual variability of nasal cavity and way device is held</td>
<td>Patented, precisely-controlled, turbulent-flow geometry increases dosing consistency, enhances delivery to brain</td>
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<tr>
<td>Concentration in anterior, lower, less-vascular areas of nose; less bloodstream absorption¹,²</td>
<td>Distribution to more-vascular areas; absorption increased; direct access to brain via olfactory area</td>
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Yale team: Extensive experience in basic and clinical science relevant to autism

Steve Chang, PhD
- Associate Professor of Psychology and Neuroscience, Kavli Neuroscience Institute, Child Study Center, Cognitive Science
- > 10 years studying oxytocin and fundamental social behaviors in non-human primate models

Research to be done at a Yale clinical center; details being finalized

Pastorus core team/board: Successful commercializing/repurposing track record; two Yale alumni

Glenn Cornett, MD, PhD: Chairman, CEO
- Founded Navitas Pharma, repurposing European cardiovascular drug; successful exit 3.5 years later
- McKinsey; Eli Lilly (strategy, marketing), Razorfish (VP, strategy practice)
- Structuring/valuation on deals driving > $1 billion in value
- MD (U Michigan, Distinction in Research), PhD (neuroscience, UCLA)

Jay Kranzler, MD, PhD: Chief Medical Officer
- 25 years as CEO of public companies
- Founder of McKinsey healthcare practice
- CEO, Cypress Bioscience (repurposed milnacipran for fibromyalgia)
- Pfizer VP External R&D Innovation
- Thought leader on emerging CNS treatments
- MD (Yale), PhD (neuroscience, Yale)

Srinivas Rao, MD, PhD: Senior Advisor
- Currently Chief Science Officer, ATAI (London-based investment firm)
- Chief Medical Officer at DepoMed, Axial Biotherapeutics
- While Chief Scientific Officer at Cypress Bioscience, identified and repurposed milnacipran for fibromyalgia
- MD (Yale), PhD (neuroscience, Yale)
Economics:
$300,000 for meaningful clinical study designed to demonstrate compelling efficacy

- Finalize trial / EEG methods
- Formulation
- **Milestones:**
  - Protocol ready
  - Team trained
  - Drugs obtained
  - Patient recruitment completed
- **Timeline:** Q3 2021

- Analyze data
- **Objective:** Oxytocin and naloxone together increase social function relative to placebo or oxytocin alone
- **Milestones:**
  - Demonstrate treatment efficacy in autism
  - Select optimal dose
- **Timeline:** Q2 2022 – Q3 2022

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**Study Site:**
Yale Child Study Center

- Collect data from 20 autistic patients
- **Milestones:** Data collected from all patients
- **Timeline:** Q4 2021 – Q1 2022

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Favorable ROI:
Successful trial plus current/pending patents → Valuation > $20 million
Possible exit if data are strong

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Longer term: Fast Phase II factorial with EEG; through Phase III in 4-6 years for ~$25-50 million with lean, focused program.
Good safety → Abbreviated tox: Oxytocin occurs naturally in the brain and naloxone interacts with it when administered.
A successful drug for core symptoms of autism should yield revenues > $1 billion / year.