pH-Dependent NMDA Receptor Antagonists

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NMDAR Antagonists – A Failed History

- Four generations of failure in the clinic
  - Selfotel - Ciba-Geigy Failed
  - Cerestat - Cambridge NeuroScience Failed
  - Remacemide - AstraZeneca Failed
  - Licostinel - CoCensys Failed
  - Gavestinone - Glaxo Wellcome Failed
  - Eliprodil – Sanofi-Synthelabo Failed

- So, is this the same old dog with the same fleas?
Opportunity

- Proprietary compounds with unique characteristics
- Unique clinical strategy
- Attractive initial indications:
  - Neurological impairment after vascular surgery
    - >1.5M patients WW, >$2B market
  - Vasospasm after SAH
    - 80K patients WW, potential orphan drug status
Role of NMDAR

Health

NMDAR are normally involved in:

- cognition
- movement
- learning & memory

Pathology

NMDAR activity contributes to:

- cell death (ischemia)
- pain (neuropathic pain)
- dyskinesia (Parkinson’s)
Novel pH-Dependent NMDAR Antagonists

- **The Key: pH Differential**
- Compounds do not block at normal pH. Healthy tissue pH is ~7.4
- Compounds are triggered by low pH. pH drops during ischemia. pH is ~6.5 at infarct core and rises to ~6.9 at rim of penumbra.
Development Stage
- Over 150 novel compounds synthesized
- Screened via in vitro bioassays
- Validation/POP in in vivo models
- 30 compounds have substantial pH dependent potency

Future Milestones
- Lead selection, GMP manufacturing, formal GLP preclinical development, filing IND
Proof of Principle In Vivo: Ischemia

Two structural isomers

A Digital threshold analysis

1. Measure stain intensity in contralateral cortex as standard
2. Threshold analysis of regions 30% lower intensity than standard

B Vehicle injected control

NP-B, 1-fold potency boost
NP-A, 20-fold potency boost

C NP93-B

D NP93-A

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Clinical Development Strategy

- First, demonstrate safe and effective neuroprotection in well controlled, in patient settings
- Drug is administered prior to the ischemic insult
- Potential Initial Indications:
  - Cognitive deficits following vascular surgery (CABG, CAE, aortic repair), >1.5M cases worldwide, $2B+ market
  - Delayed ischemic damage following subarachnoid hemorrhage (SAH burst aneurysm), ~80,000 cases worldwide, orphan status
- Next pursue more chronic treatment of those at high risk for stroke
“pH-Dependent NMDA Receptor Antagonists”
- Nationalized worldwide coverage
- Claims cover compositions and method of use

"Improved Selection of pH-Dependent Compounds for In Vivo Therapy“
- U.S. and PCT patent applications
- Broad protection for methods of discovery, methods of treatment, and compounds having a defined pH sensitivity and efficacy
Start-up: NeurOp, Inc.

- **Scientific founders:**
  - Raymond Dingledine, Ph.D. – Emory
  - Stephen Traynelis, Ph.D. – Emory
  - James MacNamara, M.D. – Duke

- **Management and consultants/advisors in place**

- **Funding history:** $1.9 million in non-dilutive funding from seed sources, SBIR Phase I and Phase II

- **Currently exploring PE funding opportunities**