NeuroTherapia

Developing novel biopharmaceuticals for the treatment of neuroinflammatory disorders

NOVEL STRATEGY FOR REDUCING NEUROINFLAMMATION

- NTRX-07 is a highly selective cannabinoid type 2 (CB2) receptor agonist with demonstrated central nervous system (CNS) activity.
- Targets CB2 receptors on microglia
- Reduces neuroinflammation resulting in neuronal survival and proliferation

SIGNIFICANT UNMET MEDICAL NEEDS

- Pre-clinical efficacy has been established in multiple neuropathic pain models and for prevention of memory-loss in Alzheimer’s model
- Despite its role in a host of neurodegenerative disorders, there are no FDA-approved therapeutics targeting neuroinflammation

CLINICAL STUDIES TARGETED FOR H1 2017

- Initial clinical indication will be treatment of chemotherapy induced peripheral neuropathy (CIPN)
- Conducted successful pre-IND meeting and on path to file IND in early 2017
- Funding from Cleveland Clinic and Alzheimer’s Drug Discover Foundation
Leadership

Joe Foss, M.D.
Co-Founder, Chief Medical Officer
- Practicing anesthesiologist and clinical pharmacologist
- Led development of Relistor & Entegreg - approved by FDA for treatment of opioid side effects

Mohamed Naguib, M.D.
Co-Founder, Chief Scientific Officer
- KOL in neuropathic pain with more than 130 peer reviewed published articles

Tom Steele, Ph.D.
Preclinical Development Consultant
- 20 years of experience in the design, synthesis, purification, and characterization of small molecules with direct expertise in CNS and pain

Rahul Aras, Ph.D.
Business Development Advisor
- Experienced entrepreneur with expertise in advancing early stage life science companies through key product development and financing milestones.

Funding

NeuroTherapia is currently being managed as a fully virtual company allowing us to employ all capital toward product development and permitting maximum funding flexibility as we evolve the organization.
Neuroinflammation and Disease

The role of microglia
Targeting Neuroinflammation

• **Neuroinflammation** is inflammation of the nervous tissue. It may be initiated in response to a variety of cues, including infection, traumatic brain injury, toxic metabolites, or autoimmunity.

• Activation of microglia in the CNS promotes the release of pro-inflammatory agents resulting in neuronal damage.

• Neuroinflammation is being studied as a therapeutic target for a host of neurologic disorders including neuropathic pain, Alzheimer’s, Parkinson’s, Huntington’s, multiple sclerosis, traumatic brain injury and stroke.

CNS toxin/injury → Activation of Microglia → Release of pro-inflammatory agents → Inflammation results in neuronal death.
Reducing neuroinflammation through targeting microglial activation

CNS toxin/injury → Activation of Microglia → Release of pro-inflammatory agents → Inflammation results in neuronal death

Long ignored, the nervous system’s glial cells may turn out to be key players in disease and prime targets for therapy.

The Dark Side of Glia
Microglia – Jekyll and Hyde

- Constitute 10-15% of cells in the brain
- First and main form of active immune defense in the CNS
- **Chronic activation of microglia causes neuronal damage** through the release of potentially cytotoxic molecules such as pro-inflammatory cytokines, reactive oxygen intermediates, proteinases and complement proteins.

Microglial activation with neuronal injury
NTRX-07

A potent CB2 receptor agonist
Cannabinoid receptors

- Cannabinoid receptors are part of the endocannabinoid system.
- The two known subtypes of cannabinoid receptors are termed CB1 and CB2. The CB1 receptor is expressed mainly in the CNS. The CB2 receptor is expressed mainly in the immune system, including microglia that reside in the brain.
- CB1 receptors are involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory and marijuana’s psychoactive effects.
- A highly-selective CB2 receptor agonist has the potential to produce an anti-inflammatory response without the psychotropic effects that accompany CB1 receptor-targeted drugs.
Cannabinoid Receptors

G-protein-coupled receptors

CB1

CB2

Immune System

T cells
B cells
Monocytes
Spleen
Tonsils

Microglia

Brain
Adipose Tissue
Muscle
Liver
GI Tract
Pancreas
CB2 receptors and microglial activation

NTRX-07* - a highly selective CB2 agonist

* Formerly known as MDA7
NTRX-07 Treats neuroinflammation

NORMAL MICROGLIA

ACTIVATED MICROGLIA

Neuroinflammation

CB2 agonist (NTRX-07)

Neuroinflammatory cytokines (IL-6) & T cell attracting chemokines (CCL4, CCL5, CCL17)

Neuronal loss And neurodegeneration
NTRX-07 down regulates inflammatory cytokines
NTRX-07 has no psychotrophic effects
Product Development Strategy

Initial focus on neuropathic pain
Neuropathic pain

- Neuroinflammation is a factor in all neuropathic pain, providing a novel therapeutic target for treatment.
- Neuropathic pain results from damage to or dysfunction of the peripheral or central nervous system, rather than stimulation of pain receptors.
- 16 million Americans suffer with neuropathic pain. The market is estimated to grow to $3.6 billion by 2020.
- Current treatments address symptoms but are not disease-modifying:
  - opioids, anti-depressants, anti-convulsants, topical painkillers, and antihistamines.
NTRX-07 prevents ischemic neuropathy

*Note: MDA7 is now identified as NTRX-07*
NTRX-07 inhibits ischemia-induced loss of epidermal innervation in the hind planter paw
Chemotherapy-induced peripheral neuropathy (CIPN)

- Nearly 4.5 million cancer sufferers suffer from CIPN with more than 300,000 new cases per year.

- No FDA-approved drugs for treatment of CIPN

- Current therapies work to alleviate symptoms.

- NTRX-07 is a potential disease-modifying drug that can prevent the neuronal damage that results in CIPN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of Cancer</th>
<th>Patients w/chemotherapy-induced neuropathy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraxane</td>
<td>Breast</td>
<td>71%</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Various</td>
<td>10-20%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Various</td>
<td>30-40%</td>
</tr>
<tr>
<td>Eloxatin</td>
<td>Colorectal</td>
<td>74%</td>
</tr>
<tr>
<td>Ixempra</td>
<td>Breast</td>
<td>63%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Breast, Lung, Ovarian</td>
<td>40-60%</td>
</tr>
<tr>
<td>Taxotere</td>
<td>Breast, Lung, Prostate</td>
<td>50%</td>
</tr>
<tr>
<td>Thalomid</td>
<td>Multiple Myeloma</td>
<td>20-40%</td>
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<tr>
<td>Velcade</td>
<td>Multiple Myeloma</td>
<td>47%</td>
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<tr>
<td>Vinblastine</td>
<td>Various</td>
<td>30-40%</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Various</td>
<td>30-40%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Various</td>
<td>30-40%</td>
</tr>
</tbody>
</table>

- Market size estimated at $500 million
NTRX-07 prevents neuronal damage associated with CIPN
NTRX-07 Decreases neuroinflammatory markers (IL-6 and IL10) in Paclitaxel CIPN
NTRX-07 Ameliorates Paclitaxel-induced Glial Activation

Control, Paclitaxel, Paclitaxel + MDA7 for 4 days, Paclitaxel + MDA7 for 14 days

NTRX-07: Pipeline Potential

A role in neurodegenerative disease
The role of inflammation in neurodegenerative disease

• Microglial overactivation linked to neurodegenerative diseases such as Alzheimer’s, Parkinson’s, multiple sclerosis, ALS, and Huntington’s

• Majority of therapies developed for neurodegenerative disease addresses symptoms.

• Pre-clinical data with NTRX-07 demonstrates potential to reduce neuroinflammation and improves memory loss in Alzheimer’s models

• The number of AD patients in the United States is estimated at 5.4 million with expenses related to health care, long-term care and hospice estimated to be greater than $200 million.
Neuroinflammatory response to amyloid plaques in Alzheimer’s models
NTRX-07 Increases clearance of Aβ
NTRX-07 restores synaptic plasticity

Wu, et al.. Neurobiol Aging 2013;34, 791-804
NTRX-07 restores memory

A

Time latency (sec)

Day 1  Day 2  Day 3  Day 4  Day 5

Session

- Aβ<sub>1-40</sub>
- Control
- MDA7
- Aβ<sub>1-40</sub> + MDA7

B

Swimming Speed (cm/s)

Day 1  Day 2  Day 3  Day 4  Day 5

Session

- Aβ<sub>1-40</sub>
- Control
- MDA7
- Aβ<sub>1-40</sub> + MDA7

Wu, et al.. Neurobiol Aging 2013;34, 791-804
NTRX-07 – a novel NCE for treatment of neuroinflammatory disorders

Neuroinflammatory disorders:

ACTIVATED

Result of Injury and Microglial Activation

Healthy microglia

NTRX-07 CB2 agonist

NTRX-07 reduces microglial inflammatory response

More than two decades of research has demonstrated that neuroinflammation is a causative factor in a broad range of disease. Through targeting this pathway we have the potential to treat a broad range of disorders ranging from neuropathic pain to Alzheimer’s disease.
Summary

• NTRX-07 is a highly selective and potent cannabinoid 2 agonist

• Through CB2 receptor binding on microglia in the CNS, NTRX-07 reduces inflammatory responses associated with a broad range of neurologic disorders

• Pre-clinical data demonstrates preliminary safety and efficacy for NTRX-07 treatment of neuropathic pain and Alzheimer’s Disease

• NeuroTherapia is looking for partners to advance our programs through multiple Phase 2 human proof of concept studies for NTRX-07
  – Milestone driven development plan with multiple value inflection points