Identification, Functional Characterization, and Potential Toxicity of a Neurotensin Derivative as a Potential First-In-Class Analgesic

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ABSTRACT

Neuropathic pain drugs with novel mechanisms of action are being sought as alternatives to opioids and non-opioids/NSAIDs. We are developing a mechanistically novel neurotensin (NT)-based compound **JT201** expected to have the potential for significant neuropathic pain relief in the absence of the side effects of current drugs. The preclinical properties of **JT201** are under evaluation as the requisite basis for supporting entry into clinical trials. **JT201** has been evaluated in various pain animal models, and key IND-enabling studies have been completed. **JT201** is active in the rat hotplate model (acute pain), the acetic acid-induced writhing model (chronic pain), and in the Chung mouse model (neuropathic pain). **JT201** has a similar potency and more prolonged analgesic effect versus morphine when administered IP in different models. Important toxicological screens have been completed. MTD studies in rats demonstrated a minimal ceiling for IV administration at 250 mg/kg; no abnormal changes in clinical chemistries or pathologies were noted in 28-day repeat dosing at 100 mg/kg per day. **JT201** also did not produce abnormalities in Cynos monkeys at the highest dose tested (100 mg/kg IV, three days). Since analgesic effects of **JT201** were observed in rodents and monkeys at ED_{50}s of 1.0 mg/kg and 2.5 mg/kg, this defines a *minimal* therapeutic window of 250/1 toxic/therapeutic dose (rats) and 40/1 (monkeys). **JT201** was inactive in brain and CYP receptor binding, and genetic and heart toxicity studies. IND-enabling studies are being completed so that **JT201** can enter clinical trials as a novel neuropathic pain drug.

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INTRODUCTION

- Pain is the most common symptom that leads people to seek medical intervention in the United States today.
- Neuropathic pain, pain originating from pathology of the nervous system, can result from a variety of diseases, conditions and treatments.
- Currently, there are two major types of pain medications used for neuropathic pain – opioids and non-opioids – both of which have inherent toxicities (nausea, vomiting, constipation, renal toxicity, depressed breathing, thromboembolytic risk, neurotoxicity, tolerance, addiction etc.).
- In this project, we seek to develop a neurotensin (NT)-based compound as a novel analgesic targeting neuropathic pain.
- **An NT-based analgesic would be a new type of pain medication**, working by a novel mechanism and having the potential for significant pain relief in the absence of the side effects associated with currently approved drugs.
- NT is a linear 13-mer peptide containing the active fragment NT(8-13).
- Development of a NT derivative as a neuropathic pain drug requires a compound that is physiologically stable and active in functional pain models.
- NT(8-13) is the obvious lead compound for development, but it is unstable and doesn't cross the blood brain barrier (much less the gut barrier) when administered systemically.
- The JT Pharmaceuticals peptide modification technology is ideally suited to be applied to convert NT(8-13) to a compound that has potential as a novel neuropathic pain drug (Figure 1).

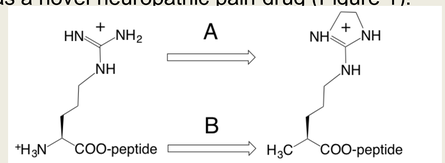

Fig.1. The JT Pharma Peptide Modification Strategy

MATERIALS AND METHODS

Subjects: Male Sprague-Dawley rats (Harlan) were singly housed in a 12 hr light/dark cycle. Food and water provided ad libitum.

Synthesis of Analogs: Application of the proprietary JT Pharmaceutical (JT Pharma) non-natural amino acid technology to the active fragment NT(8-13) in order in impart stability and to enable the fragment to cross biological barriers, while retaining its native activity.

Pain Assessments: Hot plate model; Acetic acid-induced rat writhing model; Chung model of neuropathic pain.

Toxicity Assessments: Maximum tolerated dose study; Dose escalating toxicity studies; hERG assay.

Statistical Analysis: For all pain assessments, a Student's t-test was used. All results were considered significantly different if $p<0.05$.

RESULTS FROM PAIN MODELS

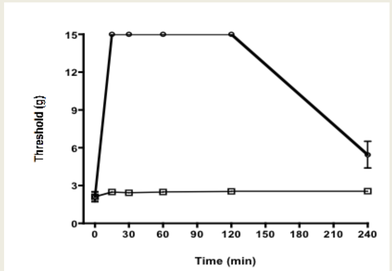

Fig. 2. Chung Model (Neuropathic Pain, mice). Relative activity of **JT201** (circles) vs. saline (squares) dosed IP (**JT201** 10 mg/kg, N = 6).

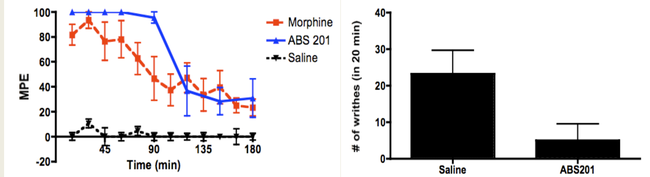

Fig. 3. a) Hotplate Model (Acute Pain, rats). Relative activity of morphine vs. saline dosed IP at equimolar concentrations (morphine 10 mg/kg, **JT201** (Previously named ABS201) 5 mg/kg, N = 6); b) Writhing model (Chronic Pain, mice) HPI201 dosed at 1 mg/kg IV versus saline (N = 6).

PRELIMINARY TOXICITY EVALUATIONS

- **JT201** did not produce any clinical chemistry abnormalities or pathology in Cynos at the highest dose tested, 100 mg/kg IV, QD for three days.
- The analgesic effect of **JT201** were observed in rodents and monkeys at ED_{50}s of 1.0 mg/kg and 2.5 mg/kg respectively.
  - This defines a *minimal* therapeutic window of 250/1 toxic/therapeutic dose (rats) and 40/1 (monkeys) using the animal species most likely to show toxicity.
- MTD studies in rats demonstrated a minimal ceiling for IV administration at 250 mg/kg; no abnormal changes in clinical chemistries or pathologies were noted in 28-day repeat dosing at 100 mg/kg per day.
- **JT201** was inactive in brain and CYP receptor binding, and genetic and heart toxicity studies.

SUMMARY

- **JT201** has a similar potency and more prolonged analgesic effect versus morphine when administered IP in different models.
- **JT201** does not display the inherent toxicities associated with conventional opioid and non-opioid pain medications.
- Toxicity results of **JT201** displayed that this class of compounds is inherently non-toxic at doses providing significant potency for development as a novel analgesic.
- **JT201** is is physiologically stable and active in functional pain models, making it a candidate for development as an analgesic for neuropathic pain.
- IND-enabling studies are being completed so that **JT201** can enter clinical trials as a novel neuropathic pain drug.

ACKNOWLEDGEMENTS

This work was supported by NIH grants MH-65099 and NS-073378 to TAD.