# NEURALSTEM INC.

## February 2017

## Corporate & Clinical Overview

# Safe Harbor Statement

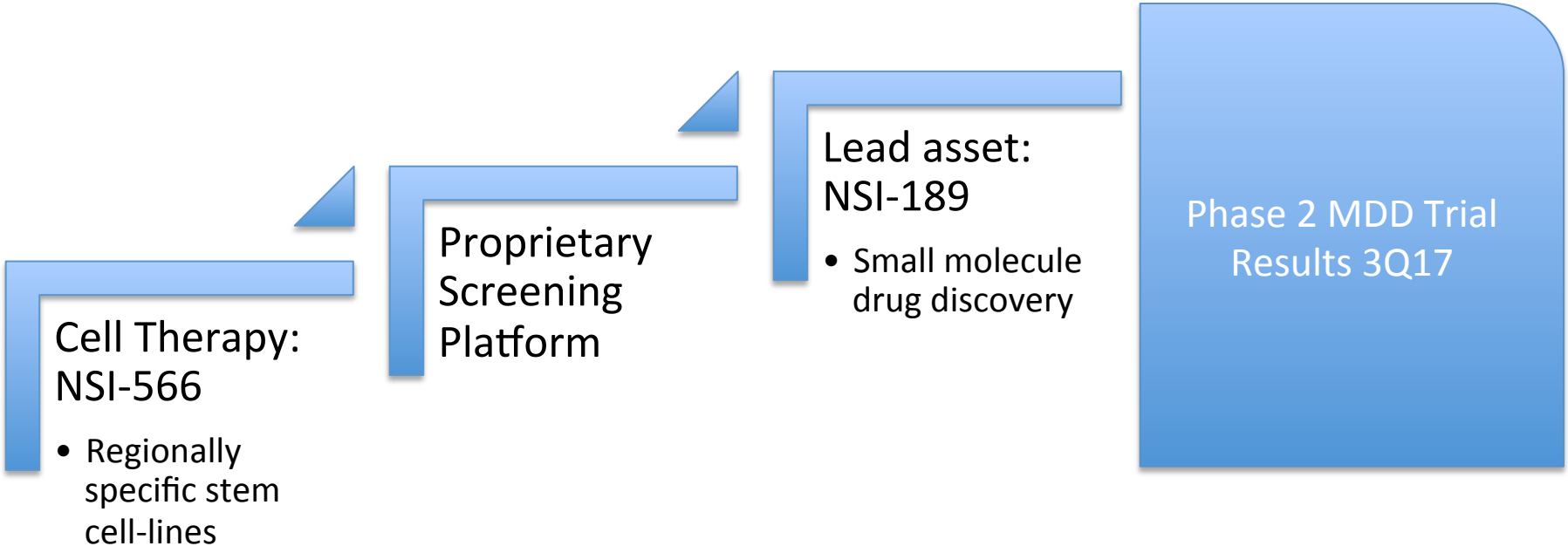
Safe Harbor statements under the Private Securities Litigation Reform Act of 1995: This presentation contains forward-looking statements as defined in Section 27A of the Securities Act of 1933 as amended, and section 21E of the Securities Exchange Act of 1934, as amended. Such forward-looking statements are based upon Neuralstem, Inc.'s management's current expectations, estimates, beliefs, assumptions, and projections about Neuralstem's business and industry. Words such as "anticipates," "expects," "intends," "plans," "predicts," "believes," "seeks," "estimates," "may," "will," "should," "would," "potential," "continue," and variations of these words (or negatives of these words) or similar expressions, are intended to identify forward-looking statements. In addition, any statements that refer to expectations, projections, or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. These forward-looking statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict. Therefore, our actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various risk factors. These risks and uncertainties include the risks associated with the effect of changing economic conditions, trends in the products markets, variations in Neuralstem's cash flow, market acceptance risks, technical development risks and other risk factors detailed in Neuralstem's Securities and Exchange Commission filings. For links to SEC documents please visit the company's Web site: neuralstem.com.

Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this presentation as a result of, among other factors, the factors referenced in the "Risk Factors" section of our Annual Report on Form 10-K for the year ended December 31, 2015 filed with the Securities and Exchange Commission on March 14, 2016, Form 10-Q for the period ended September 30, 2016, an in other reports filed with the SEC. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this presentation, they may not be predictive of results or developments in future periods. Any forward-looking statements that we make in this presentation speak only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this presentation, except as required by law.

# Overview

Human-derived stem cells platform technology

- Regionally specific for the development of CNS therapies
- Small molecule development capability & regenerative medicine



# Key Highlights

- Neuralstem Corporate Strategy
  - Business development initiatives
  - Tianjin Pharmaceuticals Group $20mn strategic investment
    - Cash runway into 2018

- Lead Program: Novel Neurogenic Small Molecule
  - NSI-189 Phase II MDD efficacy data expected in 3Q 2017
  - NSI-189 Phase II MDD long term durability data 1H 2018
    - Positive Phase 1b MDD randomized placebo control results

- Cell Therapy
  - Partner for continuing development

# Pipeline

***Neuralstem's proprietary technology uses regionally specific neural stem cells for the development of CNS therapies.***

| Compound / Indication | Preclinical | Phase I | Phase II | Phase III | Status* |
|---|---|---|---|---|---|
| **Small Molecule: Lead Asset** | | | | | |
| NSI-189 US<br>Major Depression Disorder | | | | | Results 2H17 |
| NSI-189<br>Preclinical Data | | | | | Ongoing |
| **Cell Therapy (outsourced funding)** | | | | | |
| NSI-566<br>ALS, cSCI, Stroke | cSCI, Stroke | | ALS | | BD initiatives |

# NSI-189 Major Depressive Disorder

# NSI-189 Overview

- New Chemical Entity (NCE)
  - Novel neurogenic MOA
  - Highly stable and well characterized

- MDD Market Opportunity
  - Unsatisfied patient population*
  - High patient turnover rate in MDD*
  - Strong IP position through 2024 – 2034

- Efficacy:
  - Compelling Phase Ib MDD randomized, double-blind data
  - Large effect size
  - Cognitive benefit profile
  - Potential disease modifying, durability profile
  - Excellent safety profile

- Preclinical Data
  - MOA insight: LTP biomarker data associated with cognitive enhancement
  - Orphan opportunity: Angelman Syndrome

- Gaynes BN, et al; A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR*D clinical trial. Gen Hosp Psychiatry. 2005 Mar-Apr;27(2):87-96 and Rush AJ, Fava M, et al; STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials. 2004 Feb;25(1):119-42.

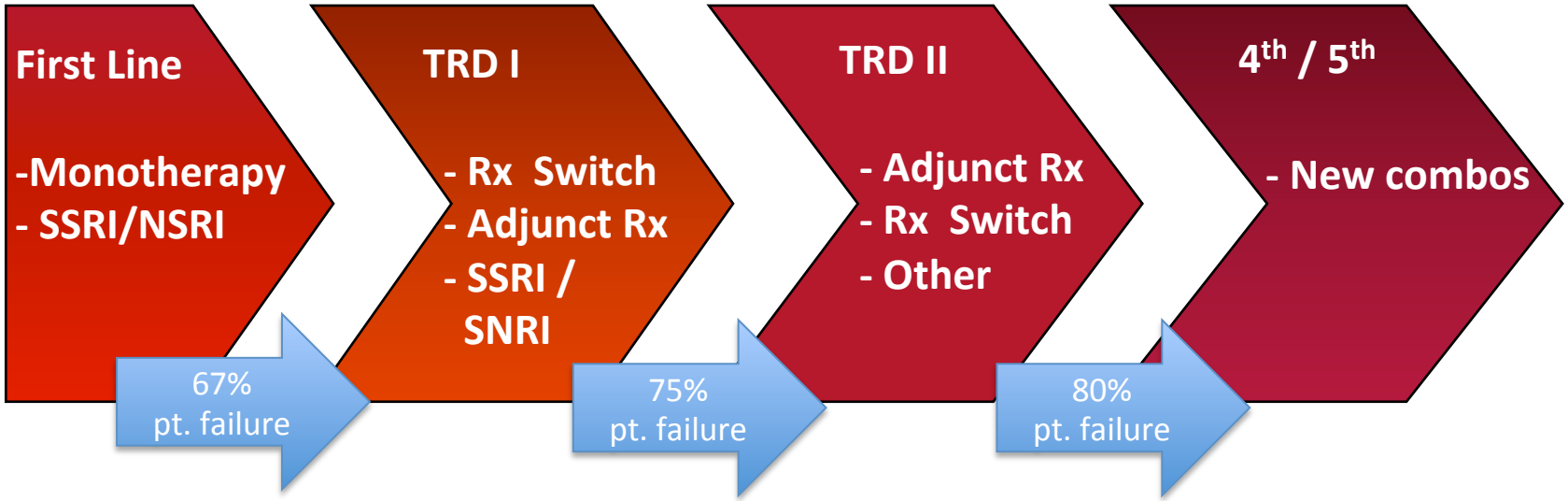
# NSI-189 Scientific Advisory Board

## World Class Psychiatric, Clinical and Regulatory Experts

| | |
|---|---|
| Dr. Maurizio Fava | Harvard, MGH, Executive Vice Chair, Dept. of Psychiatry<br>Principal Investigator: NSI-189 Phase 2 MDD clinical trial |
| Dr. Michael Thase | Univ. of Pennsylvania, Chief. Division of Mood and Anxiety Disorders Treatment and Research Program |
| Dr. Mark Frye | Mayo Clinic, Chair, Psychiatry and Psychology |
| Dr. John Greden | Univ. of Michigan, Founder and Executive Director, Healthy System Depression Center |
| Dr. Richard Keefe | Duke Institute for Brain Sciences, Director Schizophrenia Research Group |
| Dr. Thomas Laughren | Harvard, MGH, Director, Regulatory Affairs, Former Director of Psychiatric Division, CDER, FDA |

# MDD Market Opportunity

## Large Patient Rx Turnover, Low Barrier to Entry, Adjunct/Mono Market Opportunities




US Market: Estimated 14.8 mn patients

| Patients | First Line | TRD I | TRD II | 4th line + |
|---|---|---|---|---|
| % patients in given line of therapy | 33% | 17% | 10% | 40% |
| % patients that fail given line of therapy | 67% | 75% | 80% | N/A |


Source: 1. Gaynes BN, et al; A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR*D clinical trial. Gen Hosp Psychiatry. 2005 Mar-Apr;27(2):87-96.
2. Rush AJ, Fava M, et al; STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials. 2004 Feb;25(1):119-42.

# NSI-189 MDD Phase Ib trial design

**NSI-189 Phase Ib double-blind, randomized, placebo-controlled, dose-escalating study assessing safety and tolerability**

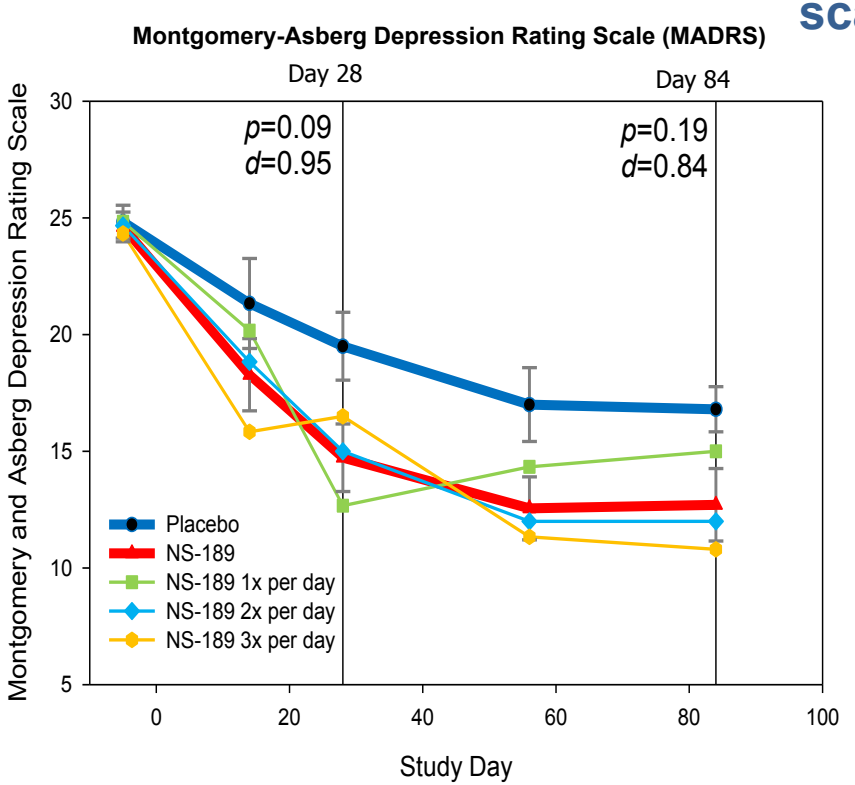
| | | |
|---|---|---|
| **Cohort 1** | N=8 (6 drug, 2 placebo) | 40 mg QD |
| **Cohort 2** | N=8 (6 drug, 2 placebo) | 40 mg BID |
| **Cohort 3** | N=8 (6 drug, 2 placebo) | 40 mg TID |

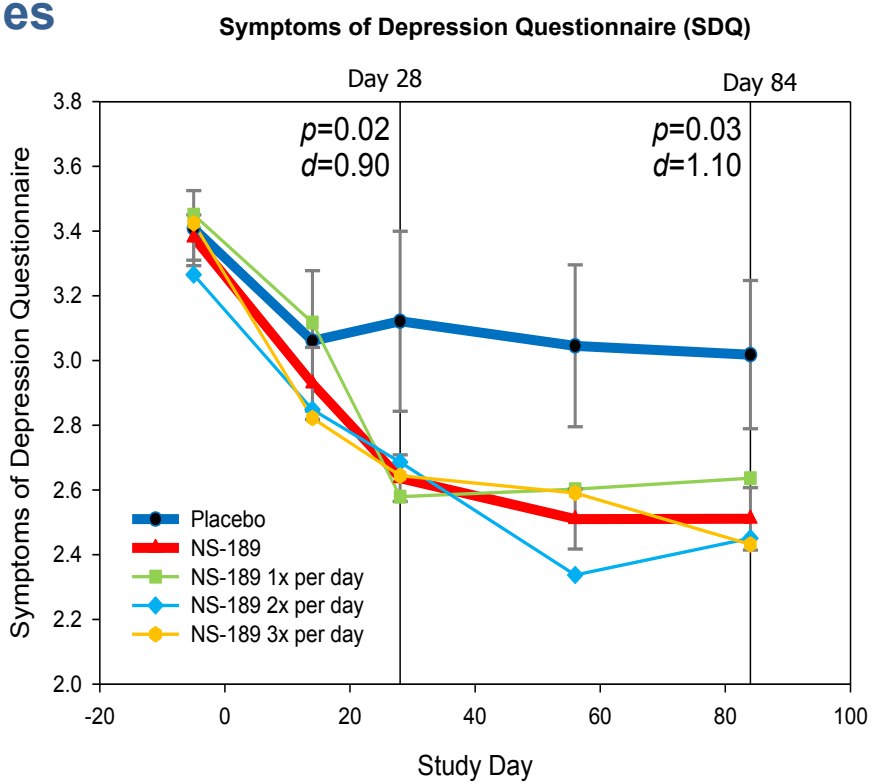
| | |
|---|---|
| **Acute treatment: 28 days** | **Drug free observational follow up: days 35, 42, 49, 56, 70, 84** |

- FDA NCE safety protocol for in-clinic dosing (28 days)
- Patient criteria: At least two prior depressive episodes and currently taking or history of antidepressant medication(s)
  - Five day washout period

# NSI-189 MDD Phase Ib results

## Encouraging durability effect across physician and patient depression scales



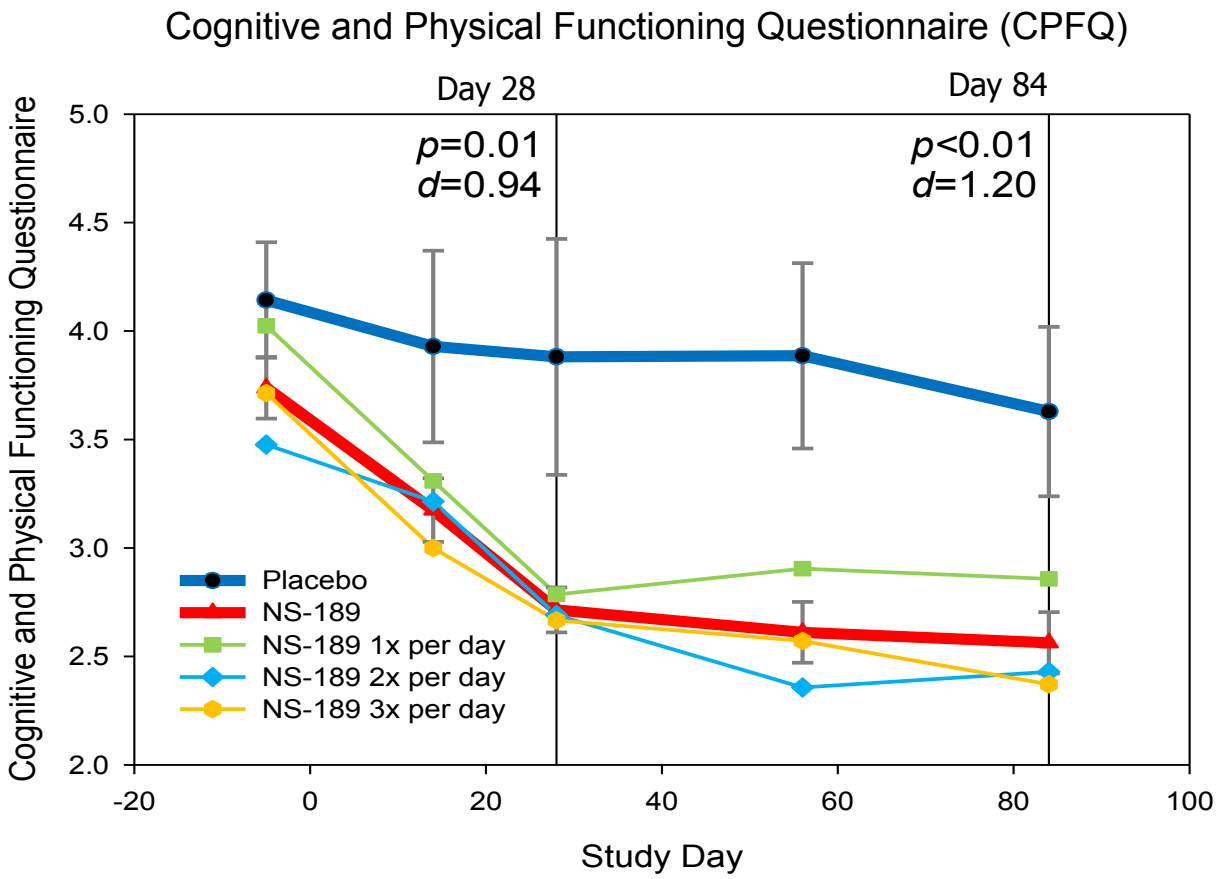

**Large MADRS effect size: d=0.95**

| MADRS outcome | # | Definition |
|---|---|---|
| 56% Responder | 10/18 | (≥ 50% reduction) |
| 50% Remission | 9/18 | (≤ 10 score) |
| 72% Partial + Responder | 13/18 | (<14 score) |

All: *A Phase 1B, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Escalation Study Evaluating the Effects of NSI-189 Phosphate, a Neurogenic Compound, in Patients with Major Depressive Disorder (MDD)*, presented June 2014, by Maurizio Fava, M.D., Karl Johe, Ph.D., Lev G. Gertsik, MD, Larry Ereshefsky, PharmD, Bettina Hoeppner, Ph.D., Martina Flynn, David Mischoulon, M.D., Ph.D., Gustavo Kinrys, M.D., and Marlene Freeman, M.D.

# NSI-189 MDD Phase Ib clinical results

## Persistent improvement over 8 week, drug-free, observational period in patient-reported CPFQ




**Large effect size (d=0.94)**

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# NSI-189 MDD Phase Ib: Adverse Events

| Side effect | Pooled placebo (n=6) N (%) | 40mg q.d. (n=6) N (%) | 40mg b.i.d. (n=6) N (%) | 40mg t.i.d. (n=6) N (%) | Pooled active (n=18) N (%) | Pooled placebo (n=6) N (%) |
|---|---|---|---|---|---|---|
| *Autonomic* | | | | | | |
| Dry mouth | 0 (0%) | 0 (0%) | 2 (33.3%) | 0 (0%) | 2 (11.1%) | – |
| Palpitation | 0 (0%) | 1 (16.7%) | 0 (0%) | 0 (0%) | 1 (5.6%) | – |
| | | | | | | |
| *CNS/psychiatric* | | | | | | |
| Headache | 3 (50.0%) | 3 (50.0%) | 3 (50.0%) | 3 (50.0%) | 9 (50%) | 3 (50%) |
| Dizziness | 1 (16.7%) | 0 (0%) | 1 (16.7%) | 4 (66.7%) | 5 (27.8%) | 1 (16.7%) |
| Somnolence | 1 (16.7%) | 3 (50.0%) | 1 (16.7%) | 1 (16.7%) | 5 (27.8%) | 1 (16.7%) |
| Fatigue | 0 (0%) | 1 (16.7%) | 0 (0%) | 0 (0%) | 1 (5.6%) | – |
| Restlessness | 0 (0%) | 0 (0%) | 0 (0%) | 1 (16.7%) | 1 (5.6%) | – |
| Poor quality of sleep | 0 (0%) | 1 (16.7%) | 0 (0%) | 0 (0%) | 1 (5.6%) | – |
| Nightmare/vivid dream | 0 (0%) | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) | 3 (16.7%) | – |
| Paresthesia | 0 (0%) | 1 (16.7%) | 0 (0%) | 1 (16.7%) | 2 (11.1%) | – |
| Insomnia | 0 (0%) | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) | 3 (16.7%) | – |
| Irritability | 0 (0%) | 1 (16.7%) | 0 (0%) | 0 (0%) | 1 (5.6%) | – |
| Difficulty concentrating | 1 (16.7%) | 0 (0%) | 0 (0%) | 0 (0%) | – | 1 (16.7%) |
| Hyperthymia | 1 (16.7%) | 0 (0%) | 0 (0%) | 0 (0%) | – | 1 (16.7%) |
| | | | | | | |
| *Gastrointestinal* | | | | | | |
| Dyspepsia | 1 (16.7%) | 0 (0%) | 0 (0%) | 0 (0%) | – | 1 (16.7%) |
| Abdominal pain | 1 (16.7%) | 0 (0%) | 0 (0%) | 0 (0%) | – | 1 (16.7%) |
| Nausea | 0 (0%) | 0 (0%) | 0 (0%) | 2 (33.3%) | 2 (11.1%) | – |
| | | | | | | |
| *Skin and subcutaneous tissue disorders* | | | | | | |
| Skin pain | 0 (0%) | 1 (16.7%) | 0 (0%) | 0 (0%) | 1 (5.6%) | - |
| Rash | 0 (0%) | 0 (0%) | 0 (0%) | 1 (16.7%) | 1 (5.6%) | - |

# Favorable NSI-189 DMPK Characteristics

Human PK supports QD dosing in clinic

- $t_{1/2}$ is 17-20 hours
- Total clearance is low (less than hepatic blood flow)
- No gender difference in exposure profiles
- No difference in AUC and $t_{1/2}$ between fasted and fed states

Attractive metabolic profile

- Few metabolites, multiple pathways, no unique human metabolites (hepatocytes)

Attractive pharmaceutical properties

- Good solubility and high permeability, single crystalline polymorph, optimized salt form

# NSI-189 Phase 2 MDD Trial

***Upcoming Phase II MDD Data Results 2017***

## Study Objectives

- Primary: Montgomery-Asberg Depression Rating Scale (MADRS)
- Secondary: SDQ, HAMD17, CGI-S, CPFQ, SFI, Cogscreen Battery, Cogstate Brief Battery

## Innovative Study Design

- Randomized, double blind, 3 cohorts (n=220): 40mg BID, 40mg QD, & placebo
- 12-week study, additional 6 month follow-up study
- Fewer, quality MDD trial sites (n=12)
- Placebo-reducing prescreen process
- Safety Interview: confirmatory, independent, remote MADRS diagnosis by MGH
- Potential registration study if successful in either active arm
  - Power: >80%, 2-sided p≤ 0.05; d=0.5

**Principal Investigator:** Maurizio Fava, M.D. Slater Family Professor of Psychiatry at Harvard Medical School, Massachusetts General Hospital

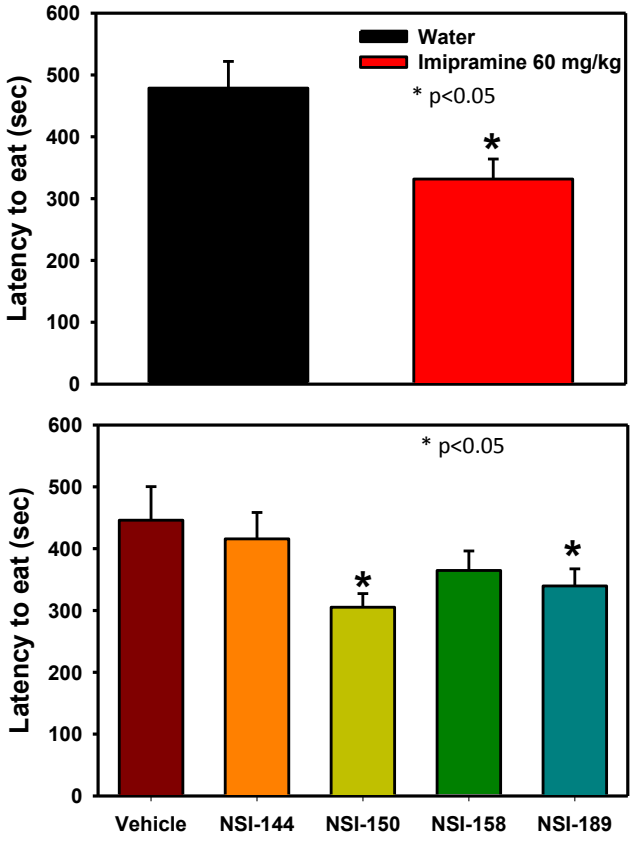
# NSI-189 Preclinical Data & MOA Insight

# NSI-189 Mouse Depression Models

## Chronic Novelty Suppressed Feeding (Mouse)

- Effects of 28-days of dosing of Neuralstem leads on latency to eat were evaluated during the 15-min test

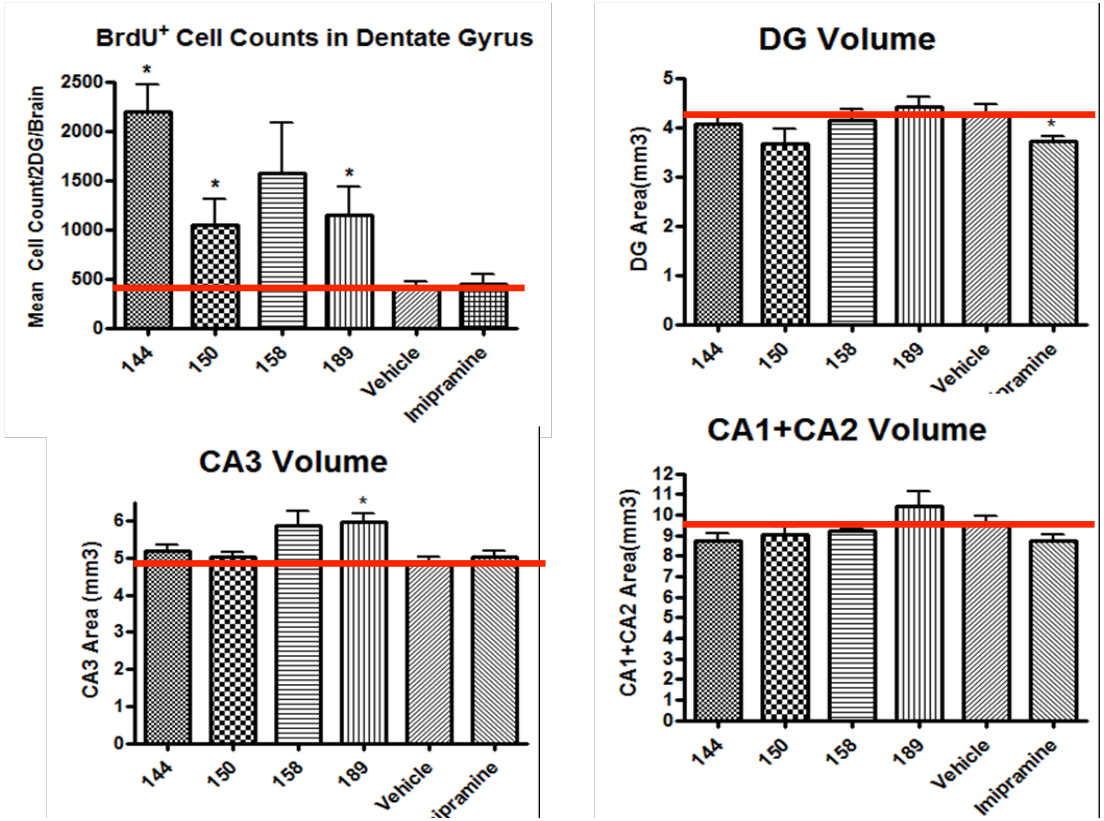
- NSI-189 and NSI 150 (30 mg/kg, oral gavage) significantly decreased the latency to eat compared to vehicle (water)
  - Effect size was similar to imipramine (60 mg/kg; oral gavage)




N=15-20/group; PsychoGenics, Inc.

# NSI-189 Mouse Depression Models

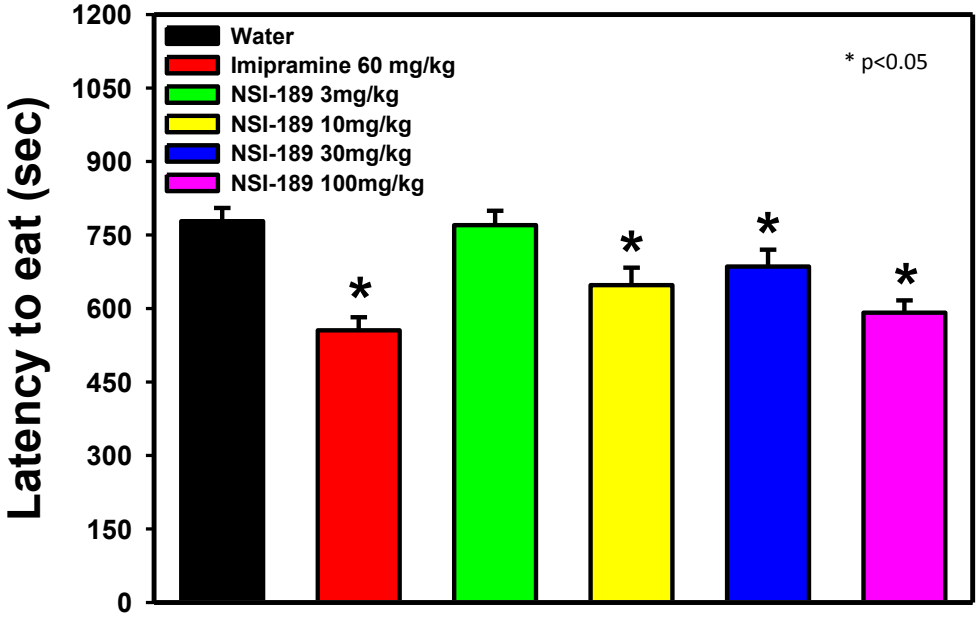
## Neurogenic Effects and HI Volume Changes in a Chronic Novelty Suppressed Feeding Model* (Mouse)




*Neuralstem leads were dosed at 30 mg/kg and imipramine at 60 mg/kg for 28 days by oral gavage (PsychoGenics, Inc.)

# NSI-189 Mouse Depression Models

## NSI-189 Doses of 10-100 mg/kg Activity
## Chronic Novelty Suppressed Feeding Model (Mouse)

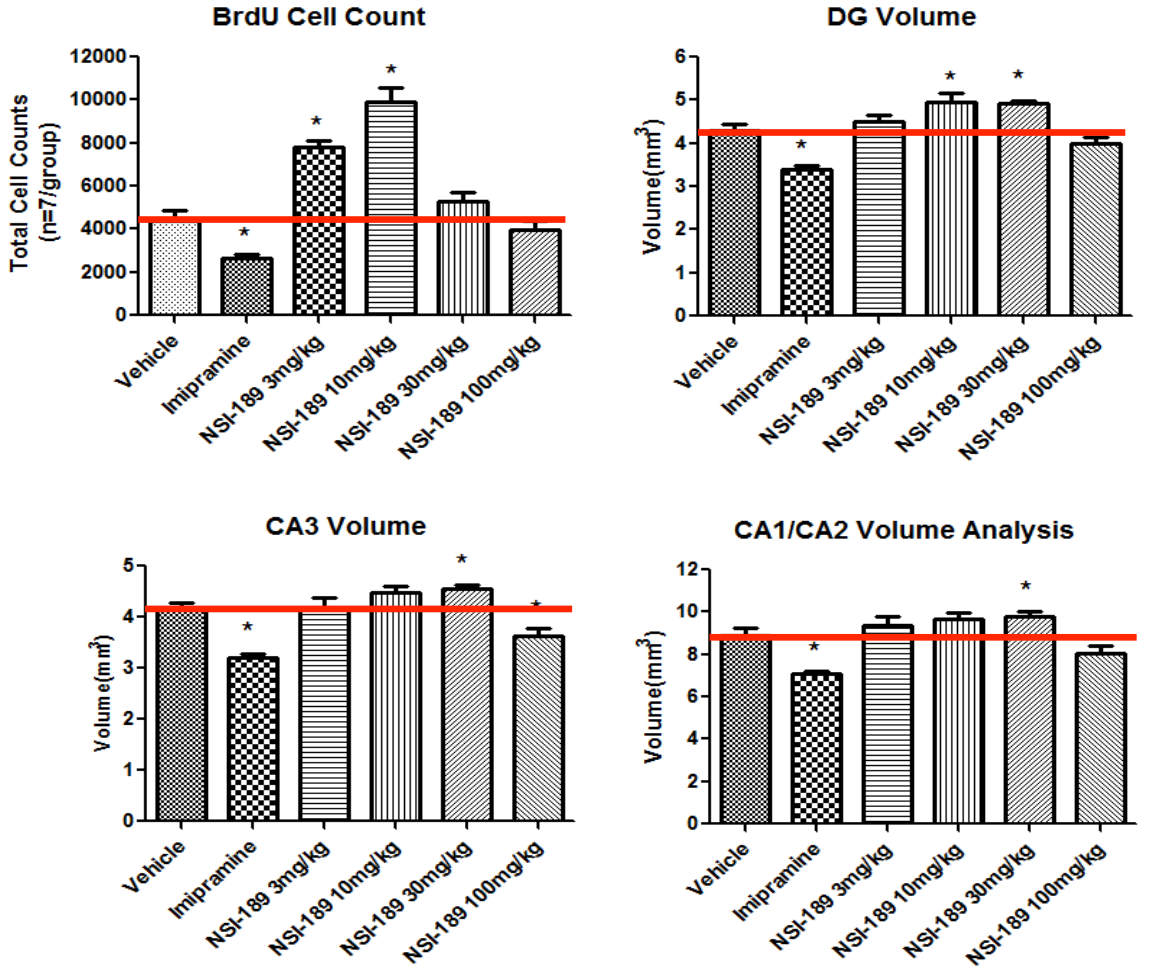



N=20/group; PsychoGenics, Inc.

- NSI-189 (10-100 mg/kg) and imipramine significantly decreased the latency to eat compared to vehicle (water) after 28 days of oral dosing
  - No significant treatment effects on either body weight or neurological observation seen

# NSI-189 Mouse Depression Models

## Neurogenic Effects and HI Volume Changes in a Chronic Novelty Suppressed Feeding Model* (Mouse)




*NSI=189 had been orally dosed for 28 days

**Depression (10-100mg/kg) ≠ Neurogenesis (10mg/kg) ≠ HI Volume Increase (30mg/kg)**

# Pipeline Update & MOA insight

| Compound / Indication |
| --- |
| **Small Molecule: Preclinical** |
| NSI-189<br>MCAO Stroke |
| NSI-189<br>Diabetes-related neuropathy |
| NSI-189<br>Irradiation-induced cognition |
| NSI-189<br>LTP Enhancement |
| NSI-189<br>Angelman Syndrome |

- Restores LTP in Angelman Syndrome mouse
- MOA: Enhances short-term and long-term potentiation in normal mice
- Reversal of cognitive deficit in irradiated mice
- Type 1 & 2 diabetic neuropathy reversal and prevention
- MCAO stroke in rats data provide a wider therapeutic window post-stroke in enhancing host neurogenesis

# NSI-189 Preclinical Stroke in Rat

- NSI-189 treatment from 6 hours post stroke for 12 weeks significantly ameliorated motor and neurologic deficits in a rat MCAO model of ischemic stroke.

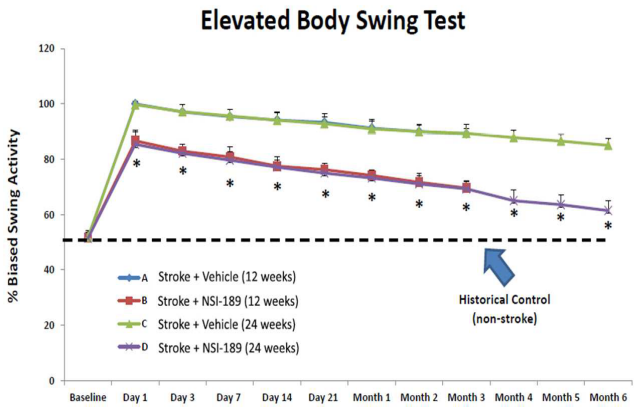
- This neuroprotective effect by NSI-189 was accompanied by increased cell proliferation in the peri-infarct area and increased dendritic branching in the cortex as well as in the hippocampus, suggesting structural remodeling by NSI-189.

- The dendritic remodeling in the hippocampus by NSI-189 was significant over the control even during the second 12-week period without any drug administration. This suggests NSI-189 may be beneficial during the first 6 months of post-stroke period by enabling recovery to a higher functioning level faster. Currently no treatment exists to help recovery from stroke.

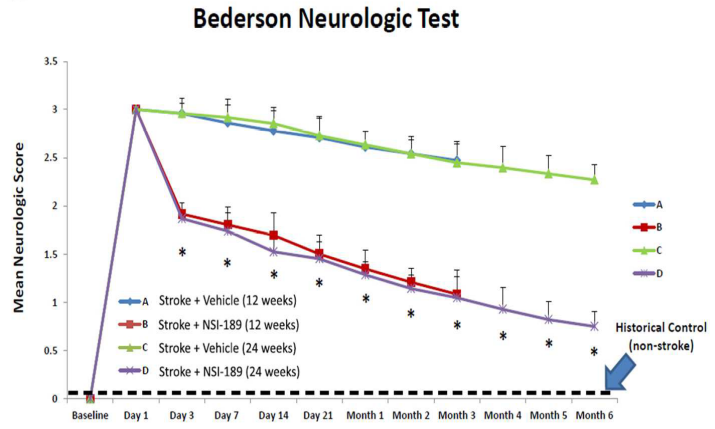
# NSI-189 Preclinical Stroke in Rat

| Group | Treatment |
|---|---|
| A | 12 Week-Control (Stroke + Vehicle) |
| B | 12 Week-Experimental (Stroke + NSI-189) |
| C | 24 Week-Control (Stroke + Vehicle)— No treatment |
| D | 24 Week-Experimental (Stroke + NSI-189)—No treatment |

A




B

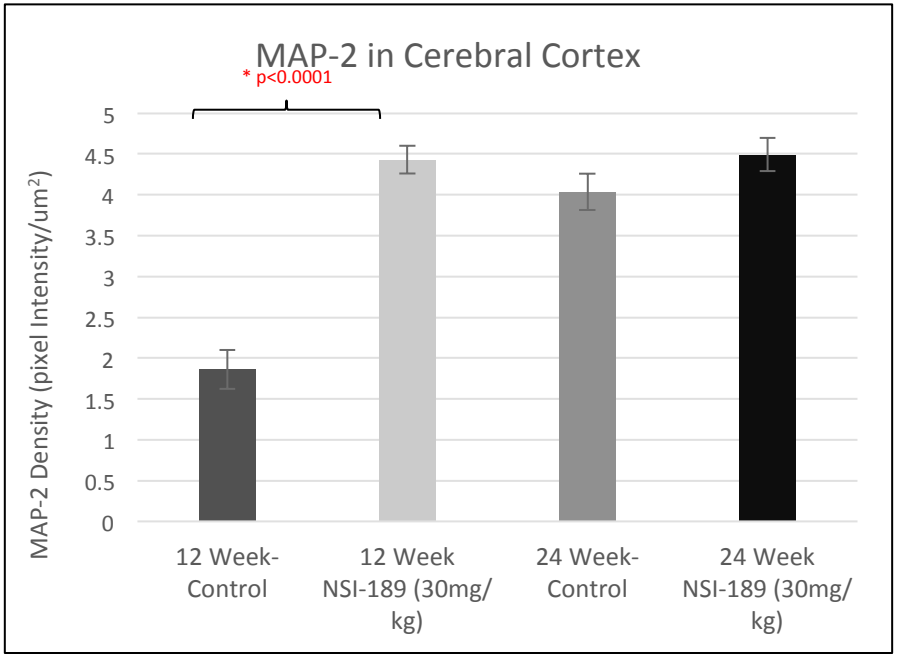



*p's < 0.05: B, D vs. A, C

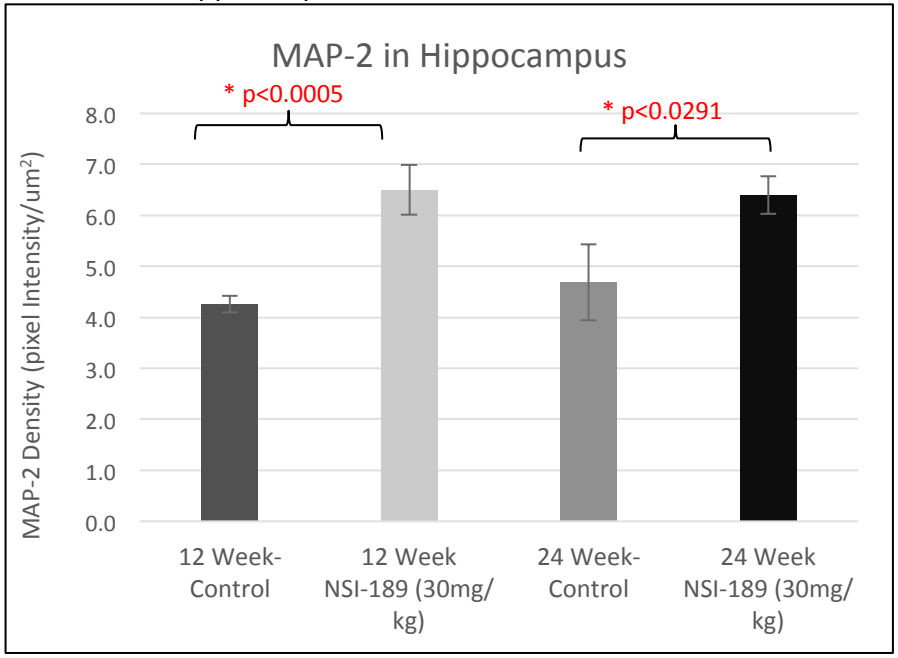
# NSI-189 Preclinical Stroke in Rat

## MAP-2 Density in the cerebral cortex and hippocampus after NSI-189 treatments:

A. MAP-2 in Cerebral cortex




B. MAP-2 in Hippocampus




Journ. Cell. Physiology, Tajiri et al

# NSI-189: Type 1 & 2 diabetic neuropathy

## NSI-189 prevention or reversal effects in Type 1 & 2 diabetic neuropathy indices

NSI-189 induced Type 1 diabetes prevention & invention results

- NSI-189 significantly protected nerve function and structure in mice when given at the beginning of disease
- NSI-189 improved the nerve function and structure given eight weeks after disease onset
- NSI-189 significantly improved all of these indices in comparison to vehicle-treated diabetic animals

NSI-189 type 2 diabetes (genetic db/db mouse) prevention results

- NSI-189 treatment showed significant reversal in all of the same indices of neuropathy

NSI-189 prevented or reversed effects on both large and small nerve functions in Type 1 & 2 diabetes

NSI-189 appears to have potential therapeutic utility outside of MDD

Poster: “Therapeutic Efficacy of NSI-189 in Diabetic Mice,” Calcutt, et al.

# NSI-189 Preclinical Type 1 & 2 neuropathy

**Summary of NSI-189 activities against Peripheral Neuropathy in Mouse Models of Diabetes**

*Prevention means test agent was given from the onset of diabetes. Intervention means test agent was given 7-8 weeks after the onset of diabetes.

ND = not determined
0 = no positive effect
\+ = partial positive effect
++ = complete positive effect
\- negative effect

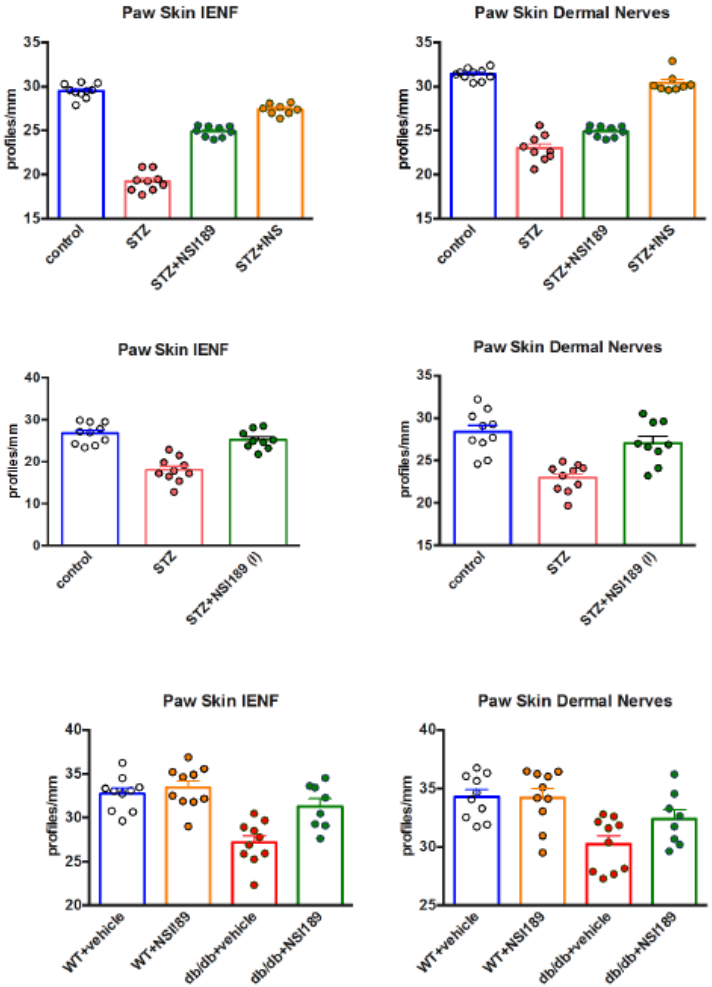
| | Vehicle | Insulin Prevention (positive control, Type 1 only) | NSI-189 Intervention in Type 1 Model (STZ) | NSI-189 Prevention in Type 1 Model (STZ) | NSI-189 Prevention in Type 2 Model (db/db) |
|---|---|---|---|---|---|
| Body wt. gain (g/month) | 0 | 0 | 0 | 0 | 0 |
| Change in blood glucose level | 0 | ++ | 0 | 0 | 0 |
| Change in blood HbA1c level | 0 | ++ | 0 | 0 | 0 |
| Rotorod Performance | 0 | + | 0 | 0 | ND |
| MNCV (m/sec) | 0 | ++ | + | + | ++ |
| Paw Tactile Allodynia | 0 | + | + | + | + |
| Paw Thermal Hypoalgesia | 0 | ++ | + | + | + |
| Paw Skin nerve density-IENF | 0 | ++ | ++ | + | ++ |
| Paw Skin nerve density-SNP | 0 | ++ | ++ | + | + |
| Corneal Nerve Density -SBNP | 0 | ++ | + | + | ND |
| Corneal Nerve Density-stroma | 0 | + | + | + | ND |

The mice were evaluated along several well-established indices of neuropathy, including: slowing of motor nerve conductance velocity, painful hypersensitivity of skin, insensitivity to heat, and reduction in dermal and epidermal nerve fiber density.

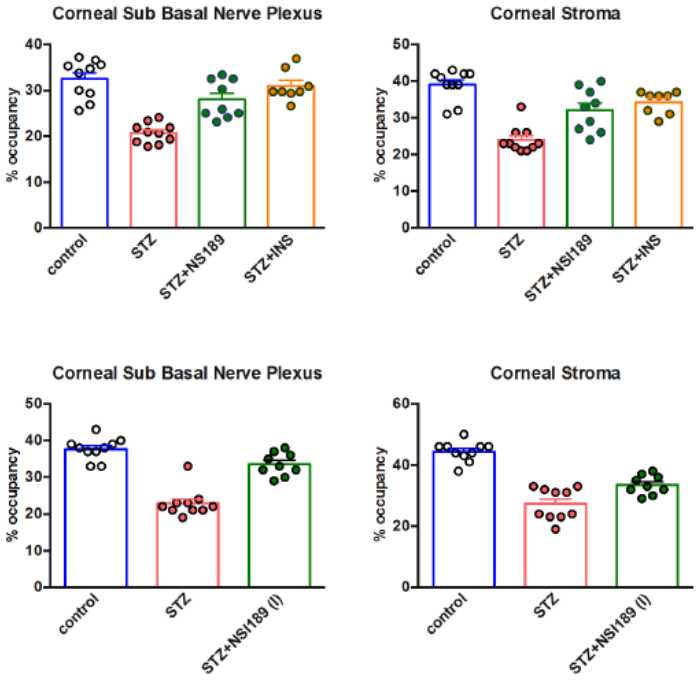
Poster: “Therapeutic Efficacy of NSI-189 in Diabetic Mice,” Calcutt, et al.

# NSI-189 Preclinical Type 1 & 2 neuropathy

Intra-Epidermal Nerve Fiber (IENF) Density &
Sub-Epidermal Nerve Plexus (SNP) Density




Sub-Basal Nerve Plexus (SBNP) Density &
Stromal Nerve Density in Cornea



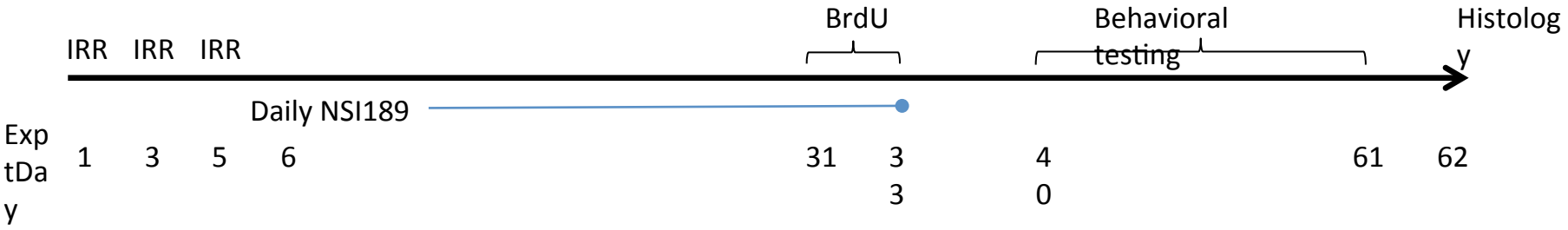

| For All Measures of Skin & Corneal Nerves | |
|---|---|
| STZ vs. control | p<0.05 |
| STZ vs. STZ+INS | p<0.05 |
| STZ vs. STZ+NSI189 | p<0.05 |

Poster: "Therapeutic Efficacy of NSI-189 in Diabetic Mice," Calcutt, et al.

# NSI-189 Irradiation-induced cognitive dysfunction

Three arms (Long-evans rats, n=16 per group):
- Sham irradiation (IRR) + vehicle
- Irradiation + vehicle
- Irradiation + NSI189

- NSI189 administered 30mg/kg/day PO
- Animal cohorts completed each behavior test on a single day
- Investigators were blinded at each level (animal group, treatment, testing, data analysis)

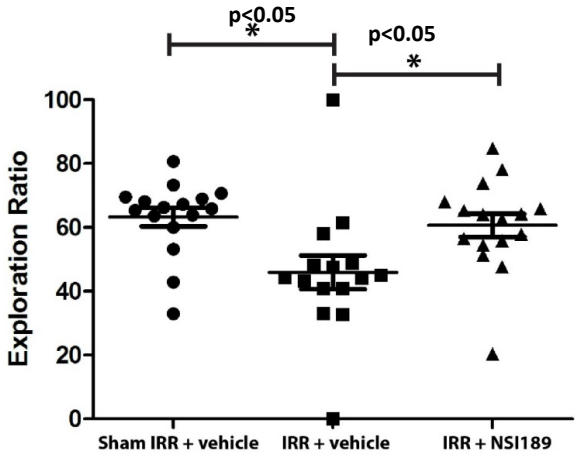



Brain Histology (blinded)
- Neurogenesis
- Hippocampal volume
- Synaptogenesis
- Dendritic morphometry

# NSI-189 Irradiation-induced cognitive dysfunction

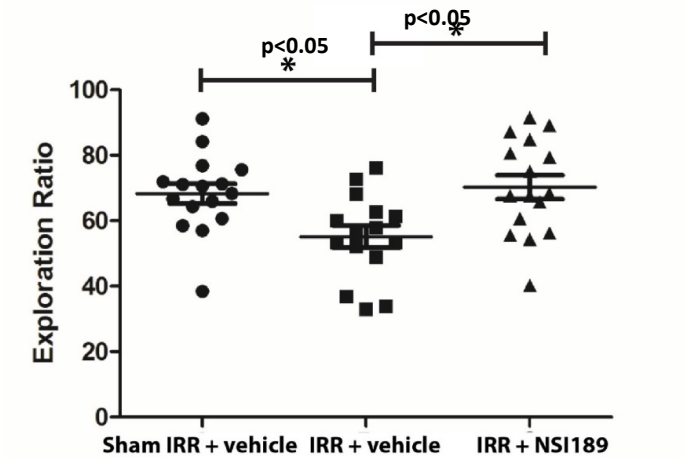
Spatial Cognitive Impairment

Novel Place Recognition Task



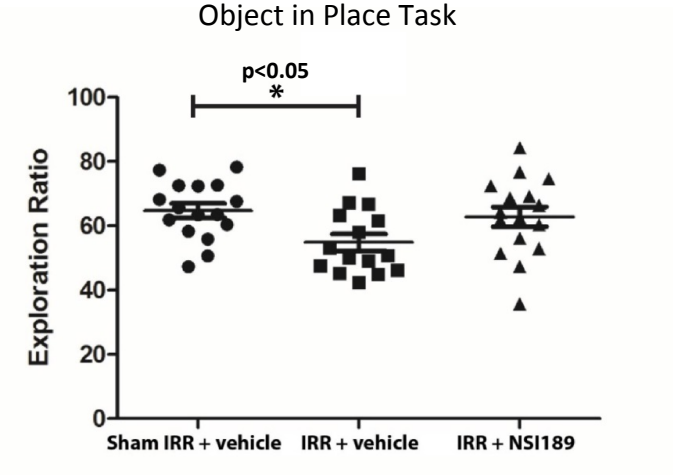

Episodic Memory Retention

Novel Object Recognition Task



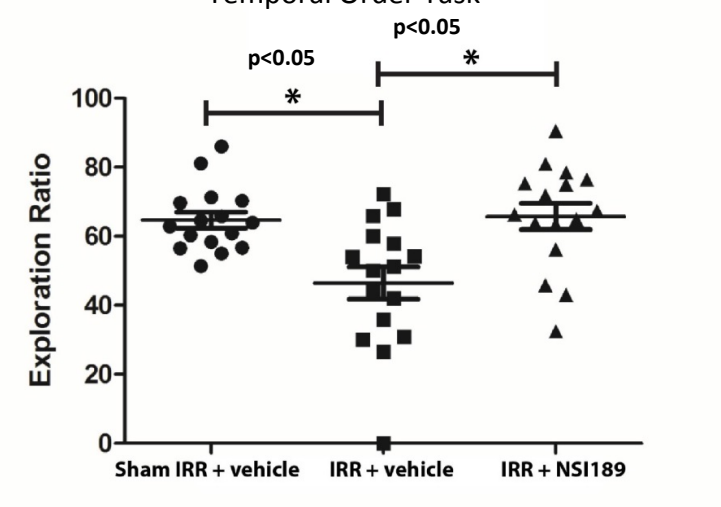

Spatial Memory Retention

Object in Place Task




Spatiotemporal Episodic Memory Retention

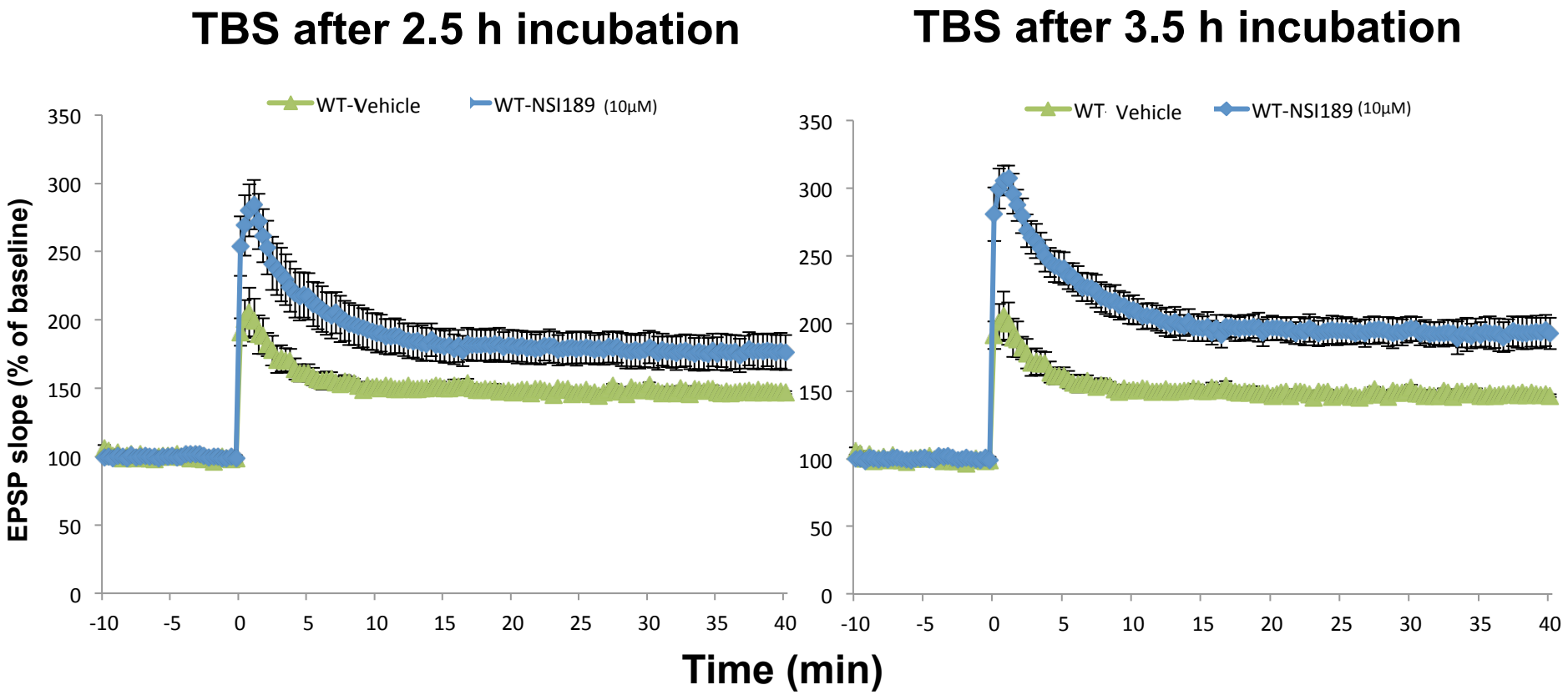
Temporal Order Task



# Understanding LTP and Memory

- For mechanistic studies: cognition = memory
- LTP is a cellular biomarker of memory
  - repetitive, high-frequency stimulus leads to long-lasting synaptic transmission
  - increased LTP means enhanced memory, decreased LTP means memory deficit.
- LTP occurs in hippocampus (memory), amygdala (emotion), cortex (attention), and striatum (motor)
- AMPA-receptor dependent Ca++ influx ultimately triggers the neuron firing.
  - Several different pathways can change responsiveness of this trigger - NMDAR, BDNF, Reelin, CaMKII, etc.

# NSI-189 enhances LTP magnitude

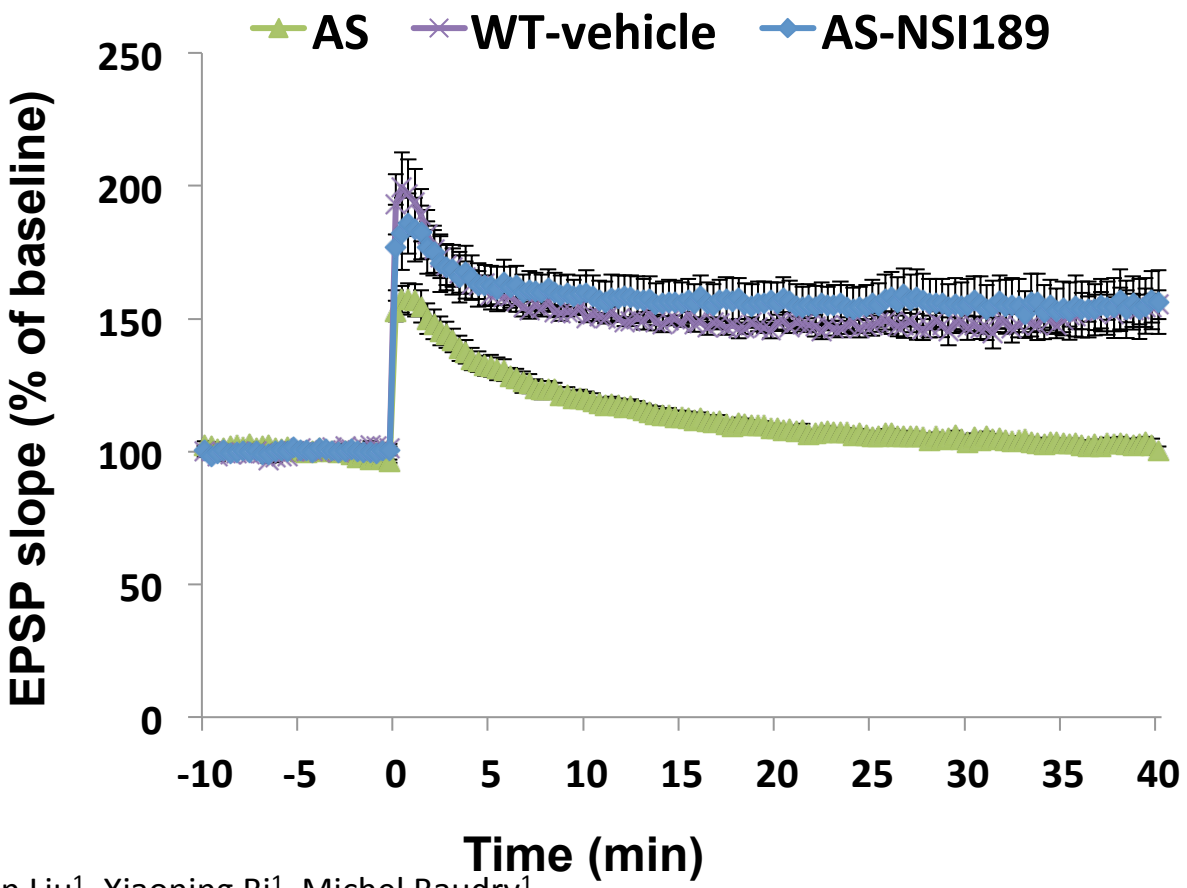



- **Enhances short-term and long-term potentiation in normal mice (n=8 slices)**
- **Increases with exposure time and concentration**
- **Reproducible**

By courtesy of Yan Liu[1], Xiaoning Bi[1], Michel Baudry[1]
Western University of Health Sciences, Pomona, CA 91766

# NSI-189: Angelman Syndrome

## NSI-189 restores STP & LTP in Angelman Syndrome Mice
## Confirmatory model in a genetic disease




By courtesy of Yan Liu[1], Xiaoning Bi[1], Michel Baudry[1]
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# LTP-based assay, NSI-189's molecular pathway

NSI-189 increases LTP magnitude in a time-dependent and concentration-dependent manner

- This effect is not from increased synaptic transmission or NMDA receptor properties
- This effect occurs within 1-3.5 hours of treatment (not before)
- The drug does not need to be present during LTP

NSI-189 restores LTP in a mouse model of Angelman syndrome, a genetic disease

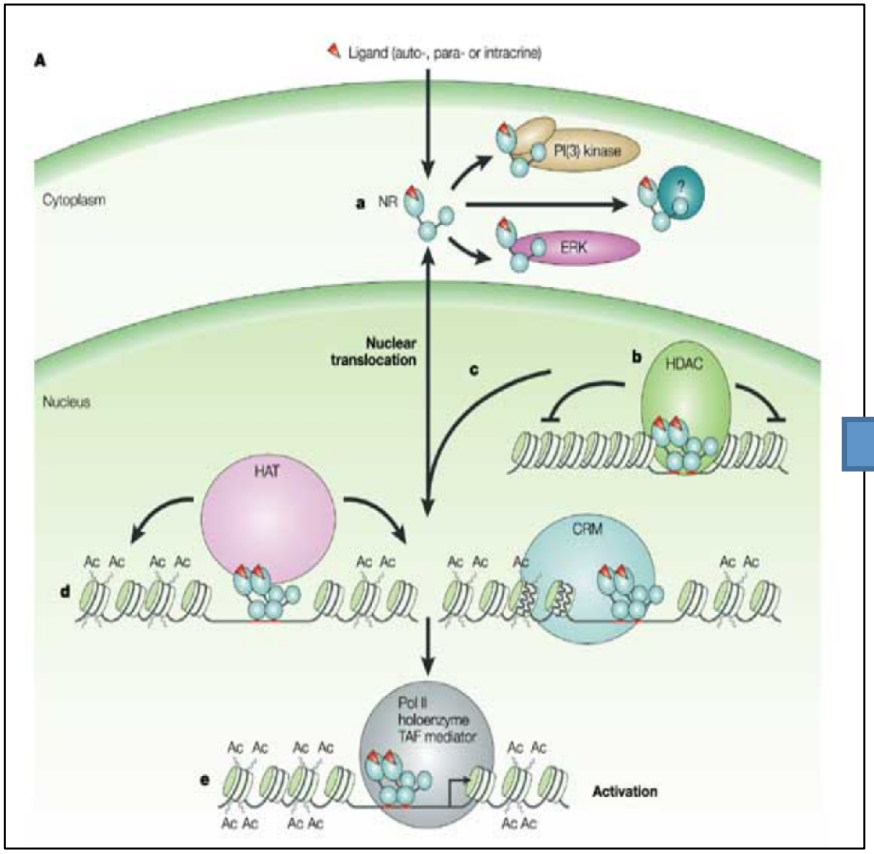
- By 3.5 hours of pre-treatment in vitro.

NSI-189 also increases neurogenesis, synaptic density, hippocampal volume in vivo

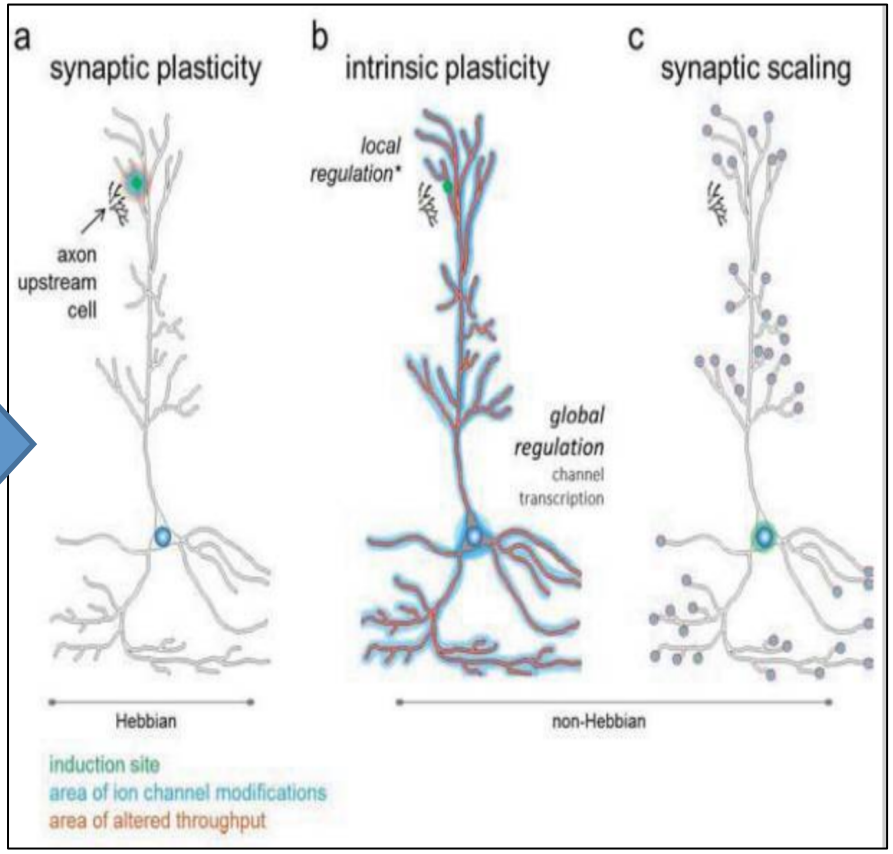
What is the common molecular pathway underlying all of these effects?

# NSI-189 Mechanism of Action: Dynamic transcriptional enhancer?

## Potential Molecular Pathways




## Potential Cellular Outcome





Gronemeyer H, Gustafsson JA, Laudet V. Principles for modulation of the nuclear receptor superfamily. Nat Rev Drug Discov. 2004 Nov;3(11):950-64. Review. PubMed PMID: 15520817.

Guzman-Karlsson MC, Meadows JP, Gavin CF, Hablitz JJ, Sweatt JD. Transcriptional and epigenetic regulation of Hebbian and non-Hebbian plasticity. Neuropharmacology. 2014 May;80:3-17. Epub 2014 Jan 10. Review. PubMed PMID: 24418102

# Limited epigenetic pathways

DNA methylation & histone acetylation/deacetylation of DNA are dynamically regulated

- leads to changes in protein synthesis and strength of neuronal connectivity

mRNA regulation at pre/post-synaptic ending modulates synaptic scaling

- changes neurotrophic factors, ion channels, neurotransmitter receptors, and synaptic structural proteins
- results in long-lasting structural and functional changes in neuronal connectivity

Necessary for learning and memory in vivo

# Stem cell Overview

# Cell Therapy Program Update

| Cell Therapy (outsourced funding) | |
|---|---|
| NSI-566 US<br>Amyotrophic Lateral Sclerosis | P2a Completed |
| NSI-566 US<br>Chronic Spinal Cord Injury | P1 follow-up |
| NSI-566 China<br>Ischemic Stroke | P1 follow-up |

- Phase I stroke completed dosing all 9 patients and currently evaluating safety
- cSCI is currently evaluating 4 Phase 1 thoracic patients; additional Phase 1 trial evaluating (Group B) 4 cervical patients
- ALS Phase 1 & 2 follow-up evaluation

# Stem cell Overview

Technology: committed human neural stem cells

- tissue restricted
- give rise to neurons, astrocytes, oligodendrocytes
- manufactured under GMP conditions for clinical applications
- over 500 lines isolated from diverse areas of fetal human CNS

Stem cell therapies: transplanted allogeneic neural stem cells integrate into host parenchyma and mitigate impact of disease/injury

- differentiated cells integrate into the host environment and replace cells lost to disease/injury
- differentiated cells produce trophic factors that nurture host cells
- differentiated cells form functional connections with host neurons

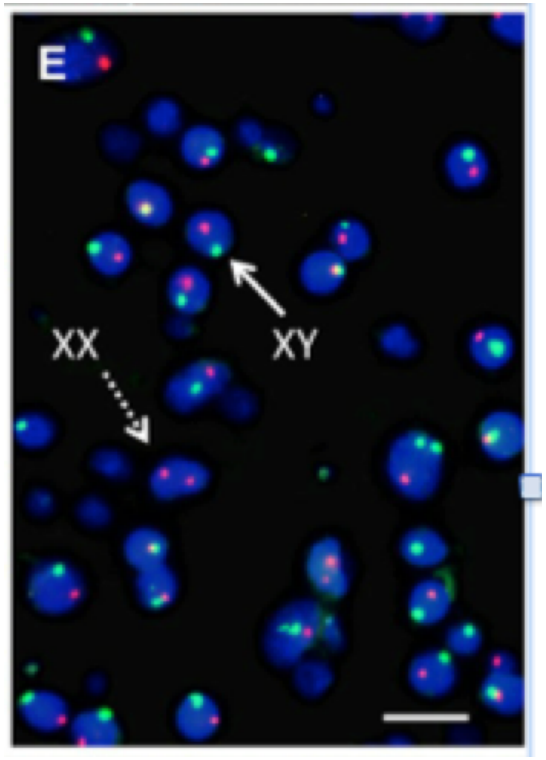
# NSI-566 POC of cell survival

Long term cell survival in 6 autopsy patients

- Survival of up to 2.5 yrs
- 4 cases of “nests” of round cells with cytoplasm
- Neural differentiation
- Maintenance of cell markers

| Patient number | Gender | # of days on FK506 | # of days on MMF | # of Days IM Meds Discontinued before death | Survival Days | % Donor DNA |
|---|---|---|---|---|---|---|
| **1** | M | 177 | 165 | 216 | 394 | 0.06 – 5.40 |
| **2** | M | 107 | 503 | 67 | 572 | 0.18 – 0.93 |
| **3** | M | 259 | 259 | 0 | 259 | 0.03 – 2.39 |
| **4** | M | 189 | 192 | 133 | 325 | 0.07 – 4.20 |
| **5** | M | 94 | 283 | 638 | 921 | 0.14 – 0.67 |
| **6** | F | 139 | 134 | 57 | 196 | 0.06 - 0.96 |

FK506 = tacrolimus, MMF=mycophenolate mofetil, IM=immunomodulatory




Annals of Clinical and Translational Neurology, 2014. Tadesse et. al

# Management

| | |
|---|---|
| Richard Daly, CEO | • President, AstraZeneca Diabetes, US; President, BMS Diabetes, US; EVP, Takeda Pharmaceuticals; VP, Commercial Strategy, TAP Pharmaceuticals<br>• Boards: Catalyst Pharmaceuticals; Synergy Pharmaceuticals<br>• Education: MBA, Kellogg Graduate School of Management; BS, Microbiology, University of Notre Dame |
| Karl Johe Ph.D., CSO | • Co-founder, Chairman of the Board of Neuralstem; NIH/NINDS Staff Scientist<br>• Education: Post-doctoral fellow, UCSF; Ph.D, Biochemistry, Albert Einstein College of Medicine; MA/BA, Biochemistry, University of Kansas |
| Jonathan Lloyd Jones, CFO | • Sr. Director, Corporate Development, Genzyme Corporation; V.P Finance, TransMolecular; CFO and V.P Corporate Development, TetraLogic; CFO, Columbia Laboratories, Inc..<br>• Education: MBA, University of Pennsylvania Wharton School of Business; BSc. Business Studies, University of Bradford |
| Thomas Hazel Ph.D.<br>Senior Vice President, Research | • Neuralstem's Stem Cell Discovery Program Director and Senior Scientist since 1998; Staff Scientist at the NIH Laboratory of Molecular Biology of the National Institute of Neurological Disorders and Stroke in Bethesda; and was a NIH IRTA fellow from 1993-1996.<br>• Education: PH.D, Genetics, University of Illinois College of Medicine; BA, Biology, Kalamazoo College |

# Key Highlights

- Near term milestones:
  - Phase II MDD clinical trial; results expect in 3Q 2017
  - Phase II MDD long term durability follow-up study 1H 2018
- Tianjin Pharmaceutical Group $20mn strategic investor
  - Cash runway into 2018
- Improved capital structure
- Business development initiatives
  - Cell therapy programs
  - Screening platform
- Lead Candidate: NSI-189 novel neurogenic small molecule
  - New Chemical Entity; Protected IP: 2024-2034
  - Novel MOA
  - Possible cognitive benefit with long-lasting effect
  - Safety profile applicable to multiple subsets of depression patients
  - Preclinical data suggest potential benefits in cognitive and neuropathy indications