Paradigm Shift in the Treatment of Alzheimer's

NEUROTROPE, INC. (OTCQB: NTRP)

October 2016

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Undervalued Asset by Clinical Stage and Therapeutic Area Potential

- Stock symbol: OTCQB: NRTP – market cap ~$30 million World-class science on memory, restoring synaptic networks
- Paradigm shifting approach to Alzheimer's Disease with the potential of reversing neurodegenerative diseases
- By date of Neurotrope funding, over $200 million invested in research & development by the NINDS of the NIH and Blanchette Rockefeller Neurosciences Institute (BRNI)
- > 300 publications in peer reviewed journals, Nature, Science
- Clinical trials in 1500 patients treated Bryostatin were well-tolerated
- Phase 2 ongoing, 150 patients, double-blind, placebo-control

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Major Valuation Inflection Ahead

- **Major Valuation Inflection Point (Six months)**

  Phase 2 clinical data readout – April 2017

- **Dynamic Clinical Program Development, next 12 – 18 months**

  Alzheimer's disease (AD) program – open label extension

  Fragile X Syndrome Program (FXS) – open label study

  Further development of other indications, including orphan diseases

- **Corporate Goals, six months**

  Up-listing to Major exchange: NASDAQ

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Two Main Competing Hypotheses of AD

Two main competing pathologic consequences resulting in AD:

Neurotrope Thesis

- ✓ Synaptic Loss - loss of synaptic networks and
- ✓ Neuronal Loss through amyloid plaque and tau tangles
  - ✓ Drug *should* treat underlying disease

Everyone Else

- ? Neuronal Loss through amyloid plaque and tau tangles
  - ? Current standard Hypothesis
  - ? 123 failures of AD drugs 1998 - 2014
  - ? No drugs to treat progression and underlying disease

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Synaptic (vs Neuronal) Loss Correlates with AD

Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

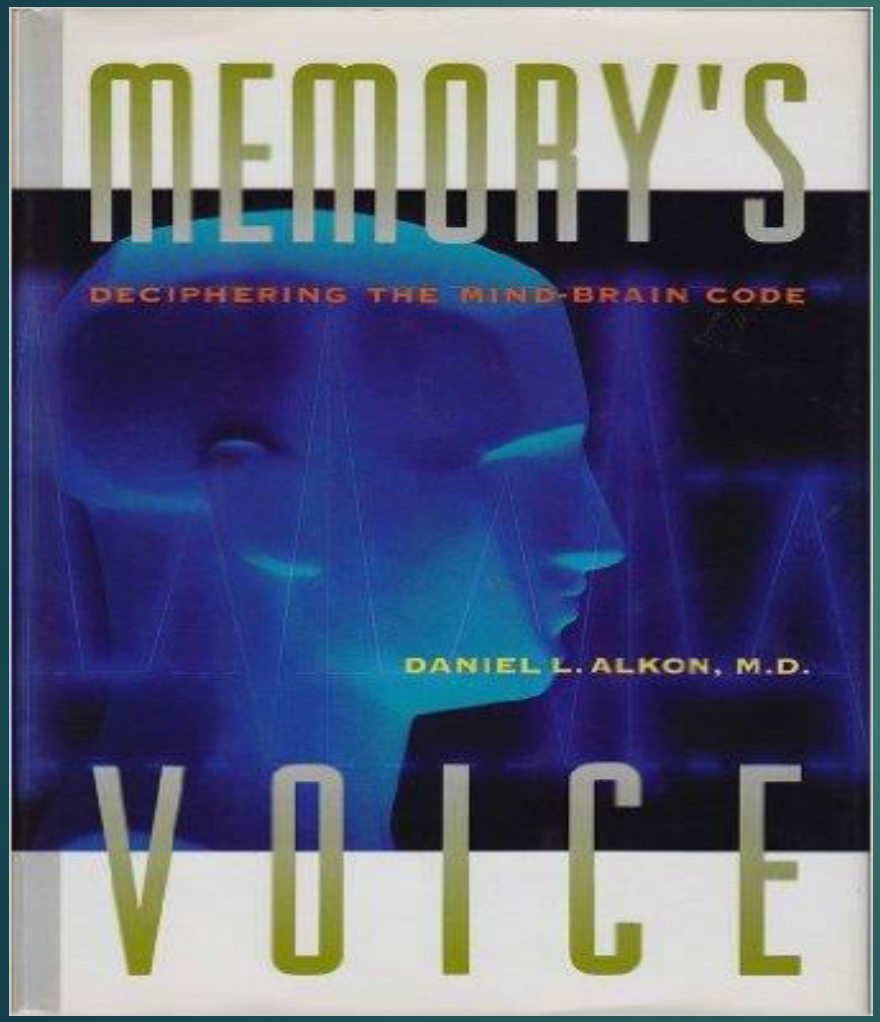
Robert D. Terry, MD,* Eliezer Masliah, MD,* David P. Salmon, PhD,* Nelson Butters, PhD,†
Richard DeTeresa, BS,* Robert Hill, PhD,* Lawrence A. Hansen, MD,* and Robert Katzman, MD*

We present here both linear regressions and multivariate analyses correlating three global neuropsychological tests with a number of structural and neurochemical measurements performed on a prospective series of 15 patients with Alzheimer's disease and 9 neuropathologically normal subjects. The statistical data show only weak correlations between psychometric indices and plaques and tangles, but the density of neocortical synapses measured by a new immunocytochemical/densitometric technique reveals very powerful correlations with all three psychological assays. Multivariate analysis by stepwise regression produced a model including midfrontal and inferior parietal synapse density, plus inferior parietal plaque counts with a correlation coefficient of 0.96 for Mattis's Dementia Rating Scale. Plaque density contributed only 26% of that strength.

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30:572–580

Ann Neurol 1991

World-Class Science – Dr. Dan Alkon



- 30 year quest to understand memory
- >300 peer- reviewed publications
- > $250MM Invested in NIH and BRNI funding etc.
- Synapses networks key to memory PKCe a master switch
- > 11 animal models for neurodegenerative diseases
- Extensive use of Electron Microscopy

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Potential Paradigm Shift in Alzheimer's

Alzheimer's Disease Modifying Treatment - Cognitive Effects

Symptomatic

- Memantine (Forest Labs)
- Aricept (Pfizer)

Symptomatic Market: $6 Billion - 2016

$30B spent
20 years
No drug yet

$>230MM spent
30 years
research
>300
publications

Synaptogenesis/ Synaptic Networks

Neuronal: Amyloid/ Tau tangles

- Biogen
- Eli Lilly
- Mild
- Single mechanism
- Modest overall effect

- Neurotrope
- Moderate to severe
- Multi-modal pathway
- Cognitive effects

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PKCe: Master Switch for Memory, Disease

Decreased PKCe activation leads to reduced synaptic density

- **Reduced Synaptic Growth Factors** – BDNF, IGF-1, NGF, others
- **nactivated amyloid-β degrading enzymes Increased neurotoxic amyloid-β**
- **Increasing pathological Tau**

Brain Health

- Memory and Learning
- Spatial Recognition

PKCε activation

Multi-modal effects

- **Activates Synaptic Growth Factors** – BDNF, IGF-1, NGF and others
- **Activates All amyloid-β Degrading Enzymes**
- **Increases in BDNF** via ApoE3 induced PKCϵ
- **Increases BDNF via loss of ApoE4** mitigated reduction of BDNF
- **Activates α-secretase** reducing neurotoxic amyloid-β
- **Bryostatin normalizes GSK3-β**, thereby inhibiting pathological Tau

Neurodegenerative Diseases:

- Alzheimer's
- Fragile X (FXS)
- Rett Syndrome
- Stroke

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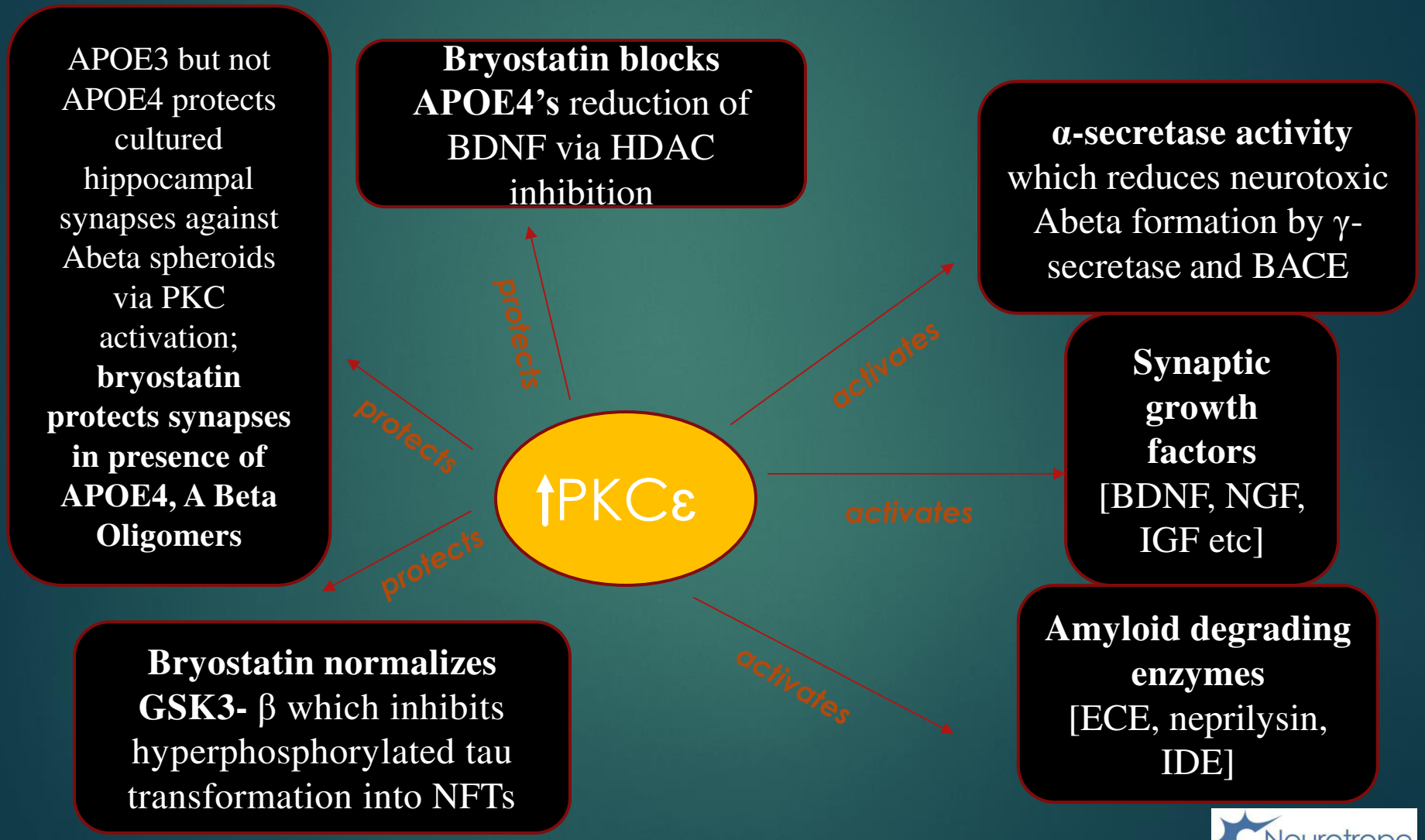
Activation of Protein Kinase C epsilon: Potent Downstream Effects



Multi-Modal Mechanism of Action

Activation of Protein Kinase C epsilon (PKCϵ)

- Activates Synaptic Growth Factors – BDNF, NGF, IGF, others
- Activates All amyloid-β Degrading Enzymes (ECE, Neprilysin, IDE)
- Activates α-secretase, which reduces formation of neurotoxic amyloid-β formed by γ-secretase and BACE
- ApoE3 induces PKCϵ; by activating PKCϵ, there is an increase in BDNF expression
- Bryostatin blocks ApoE4 reduction of BDNF via HDAC inhibition
- Bryostatin normalizes GSK3-β, thereby inhibiting pathological Tau protein transformation into neurofibrillary tangles (NFTs)

Other Alzheimer's drugs focus on single pathway; Bryostatin targets multiple pathways

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Snapshot of Bryostatin - Synaptogenesis

On The Cover: Integrative neurons in the hippocampus show large oval nuclei (*blue*) and presynaptic axonal boutons. *Yellow grains*, boutons with brain-derived neurotrophic factor (BDNF); *green grains*, boutons with no BDNF accumulation; *red grains*, postsynaptic dendritic spines with BDNF. BDNF is important for synaptic activity and neuron survival. The PKCε activator, bryostatin 1, enhanced the presence of the synaptogenic growth factor, BDNF, as indicated by the *yellow dots*. For details, see the JBC article by Sen *et al.*, pages 16462–16476.

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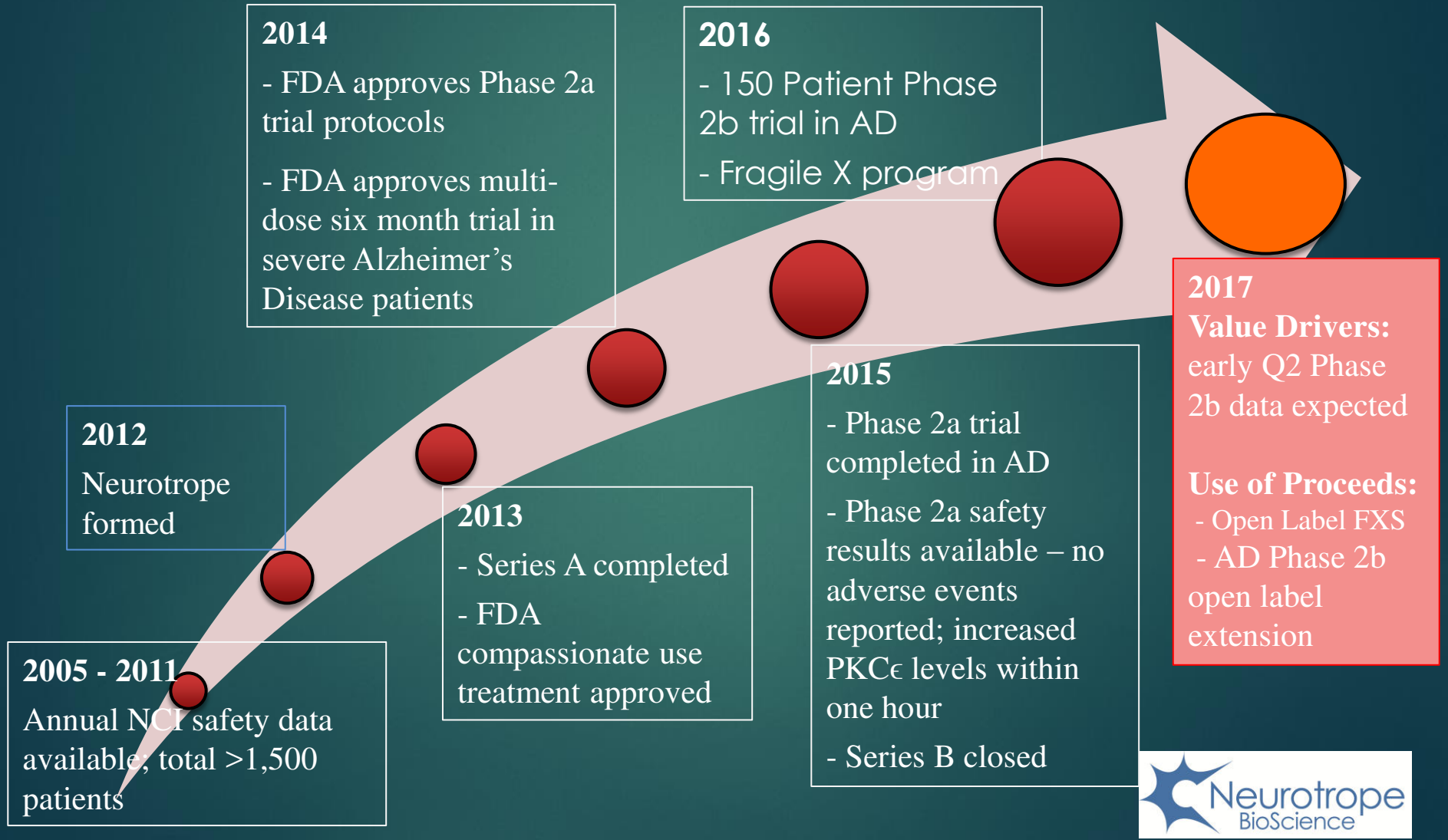
NTRP Milestones - Next Steps



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World Class AD Clinical Advisors

- **Dr. Jeffrey L. Cummings, MD, ScD, CCF - Chairman**
  - Director of Cleveland Clinic Lou Ruvo Center for Brain Health
  - Expert in clinical trial design & analysis, global trial implementation, outcome measures
  - Authored or edited 30 books and published 600 peer-reviewed papers
- **Dr. Martin R. Farlow, MD**
  - Professor and Vice Chairman of Research, Dept. of Neurology Indiana University
  - Associate Co-Director of the Indiana AD Center and member of gov't. AD task force
  - Published 200 peer-reviewed papers
- **Dr. Samuel E. Gandy, MD, PhD**
  - Mount Sinai Chair in AD Research, Professor of Neurology and Psychiatry at Mount Sinai
  - Discovered PKC regulation of amyloid precursor phosphorylation and processing
- **Dr. Michael Weiner, MD**
  - Professor UCSF School of Medicine in Radiology and Biomedical Imaging
  - Educated at Mount Sinai and Yale, Assistant Professor of Medicine at Stanford
  - Established MRI Unit at the San Francisco VA Medical Center

Bryostatin - Clinical Development

Clinical Development:

- Safety 1,500 patients in NCI – well tolerated
- Compassionate Use protocols in severe AD patients
  - ☑ Significant improvement in cognition and daily living
  - ☑ Possibility of disease reversal
  - ☑ Three patients treated, longest dosed patient ~ one year
- Phase 2a clinical trial completed

  Bryostatin achieved primary safety endpoint

  Demonstrated activation of PKCϵ target engagement

  Cognitive enhancement within 3 hours

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Phase 2b – Ongoing Clinical Trial

Double – Blind, Placebo – controlled, 150 moderately severe to severe AD patients, 12 weeks

- First patients dosed January 2016, robust enrollment, currently 119 enrolled
- Full data results expected beginning of Q2 2017

- **Primary efficacy endpoint**:
  - Severe Impairment Battery (SIB)
- **Secondary efficacy endpoints:**
  - Mini-Mental State Exam (MMSE)
  - Activities of Daily Living (ADL)
  - Neuropsychiatric Inventory (NPI)
- **Three (3) arms: two dosing levels of bryostatin vs. placebo**
- **30+ sites in the U.S.**

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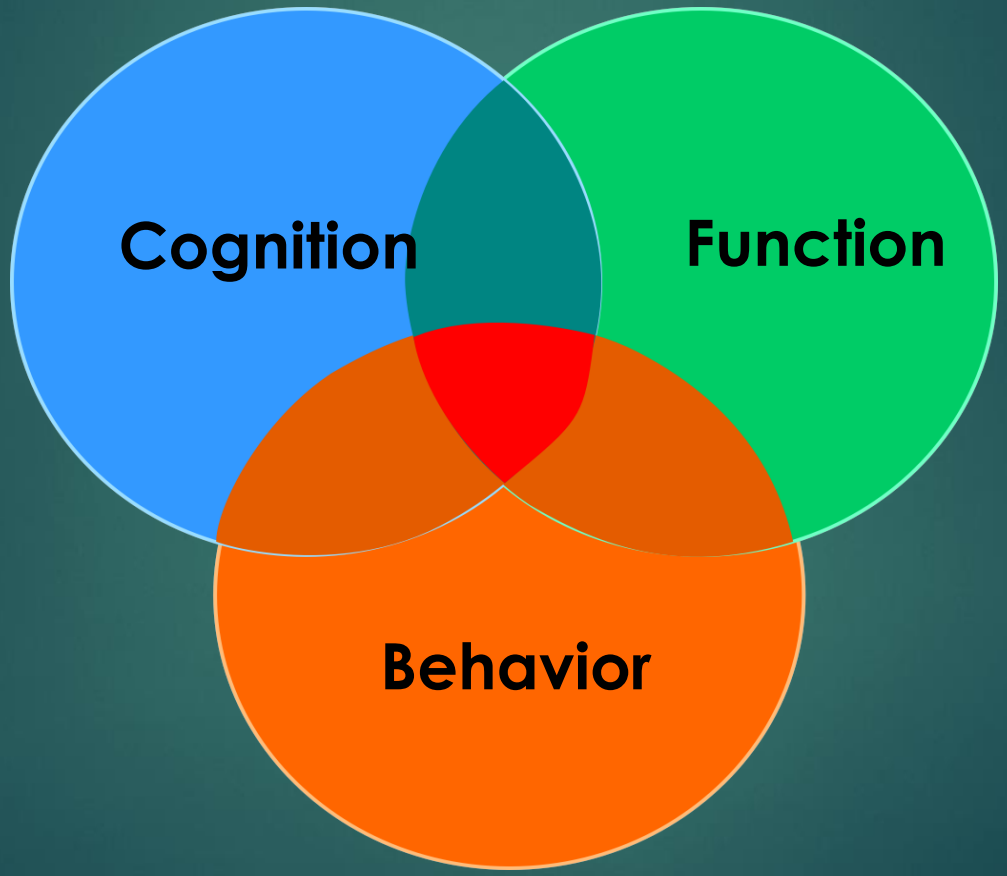
Phase 2b - Clinical Assessment Methods

Severe Impairment Battery **(SIB)**

Mini Mental State Examination **(MMSE)**



AD Cooperative Study – Activities of Daily Living, severe

(ADCS-ADL-SIV)

Neuropsychiatric Inventory **(NPI)**

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Fragile X Syndrome discussion

- Most common inherited cause of mental retardation, genetic cause of autism and single gene cause of intellectual disability
  - ~135,000 patients in U.S.
  - Affects 1 in 3000-4000 boys, 1 in 4000-8000 girls
- Subtle physical phenotype with striking neuropsychiatric phenotype
- 25-30% of full-mutation males meet criteria for a dx of autism, nearly all the rest have Autism Spectrum Disorder/Pervasive Developmental Disorder
- 20-25% of males have seizures
- Normal life expectancy
- True developmental disorder---not neurodegenerative
- Treatment is symptomatic only

Fragile X Syndrome - Orphan Drug

Strongest long-term, pre-clinical evidence for a disease modifying therapy yet, no tolerance:

- ✓ Bryostatin/ PKCe drives full rescue of adult and juvenile Fragile X Mice @13 weeks (*publications available*)
- ✓ Preclinical additional behavioral studies performed at University of Santiago de Chile (data *to be published*)
  - ▶ Funded by FRAXA (FXS advocacy group)
- ✓ Close Collaboration with world-class FXS Advisory Board
- ✓ Orphan Drug Designation granted Q1 2015

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World Class FXS Clinical Advisors

- Elizabeth Berry-Kravis MD, PhD, Rush Medical
  - Chairperson
- Randy Haberman, Mind Center, UCSD
- Craig Erickson, MD, Chief NIH Clinical Advisory Group
- Bryan King, MD, UCSF
- Sara Jane Webb, MD, U. Washington
- Mike Tranfaglia, MD, President of FRAXA

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World-Class Scientific Collaborations

Stanford
University

Leadership Team

- Dr. Susanne Wilke, Ph.D , MBA – Chief Executive Officer
  - Ph.D, University of Illinois – Chicago; MBA Tuck School of Business at Dartmouth
  - Kauffman Fellow in Venture Capital at Schroder Ventures Life Sciences (SVLS)
  - Hoffmann- La Roche, Amgen, Forest, NGN Capital
- Dr. Daniel Alkon, MD – President, Chief Scientific Officer
  - Specializing in memory disorders, >350 peer-reviewed publications
  - 30 year career as Medical Director at NIH
  - 15 years at the Blanchette Rockefeller Neurosciences Institute
  - Graduate of Cornell Medical School, Mt. Sinai
- Dr. Kenneth Gorelick, MD – Interim Chief Medical Officer
  - Managing Director of Zymo Consulting Group LLC
  - Graduate of Cornell Medical School, Mt. Sinai
- Robert Weinstein, CPA, MBA – Chief Financial Officer
  - Experienced CFO, healthcare private equity fund manager & investment banker
  - MBA from University of Chicago Graduate School of Business

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