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Applied Translational Medicine

Early Clinical Development: Case Study of Davunetide on Translation from the Bench to the Clinic

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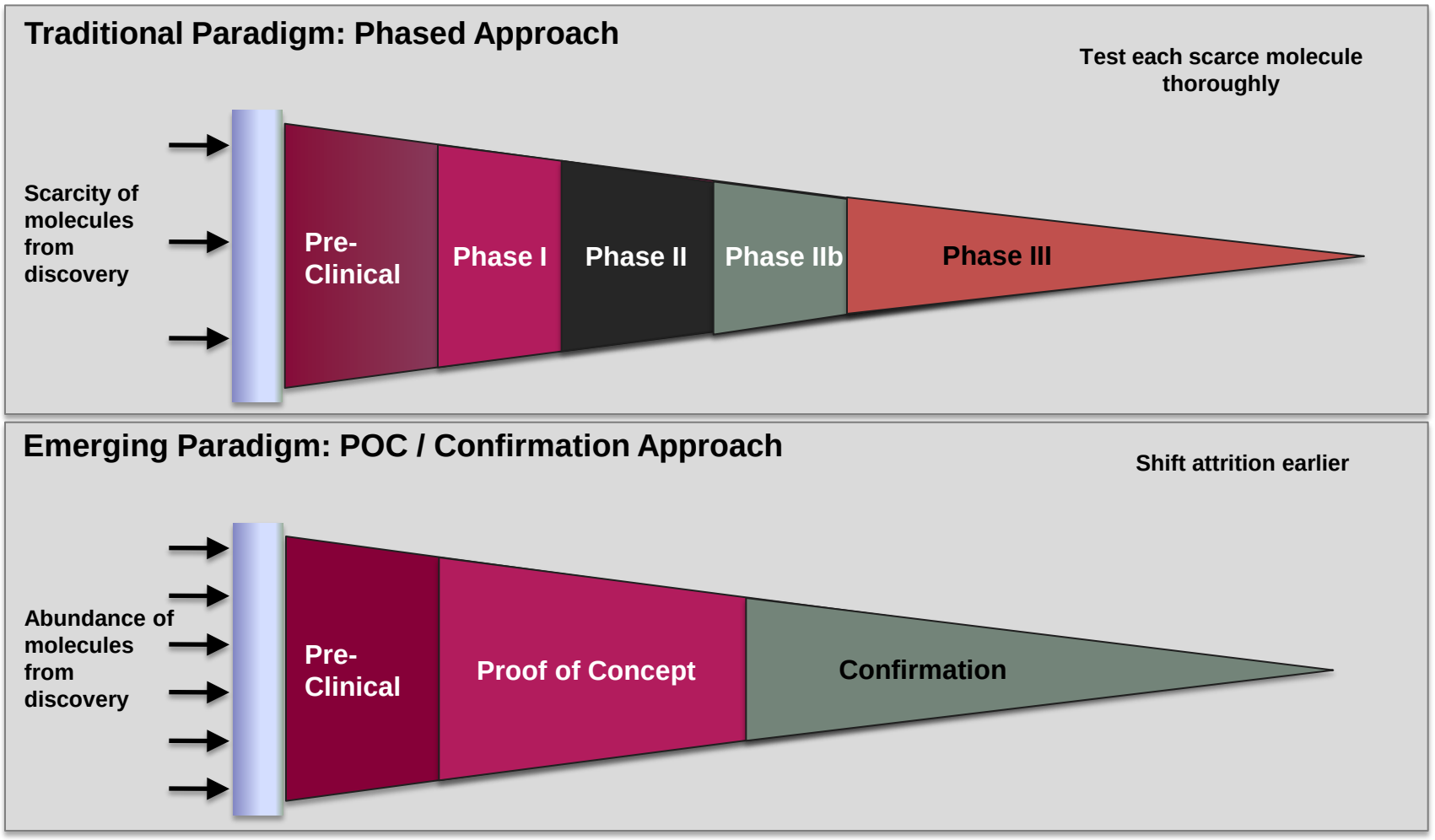
April 29, 2015

What are the Drivers in Early Clinical Research?

- Cost to get a drug to market
  - Estimated at $1.2 billion (!)
  - Cost of failure (less than 1 success for every 10 tries?)
- Time to get to market
  - 12 to 15 years (5 to 7 years in clinical development)
  - Patent clock ticking…
- Late-stage failures
  - Many high-profile drugs failing in Phase III up from 30% in 2011 to 35% in 2012
  - In 2012 alone, failure of a hepC drug was estimated to have cost $1.7 billion

Clinical Development is Evolving



Source: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010

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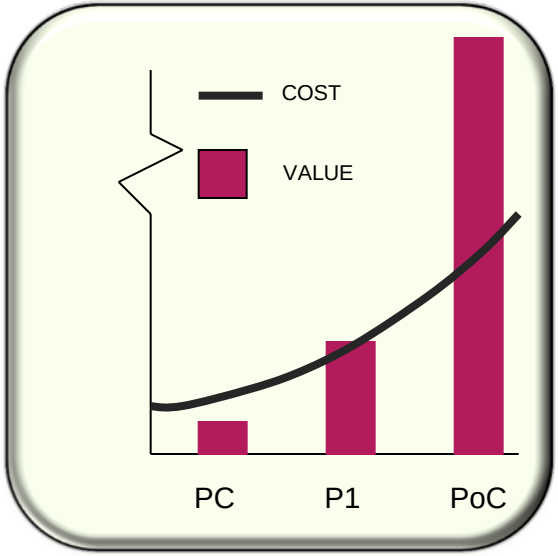
Importance of Proof-of-Concept Studies

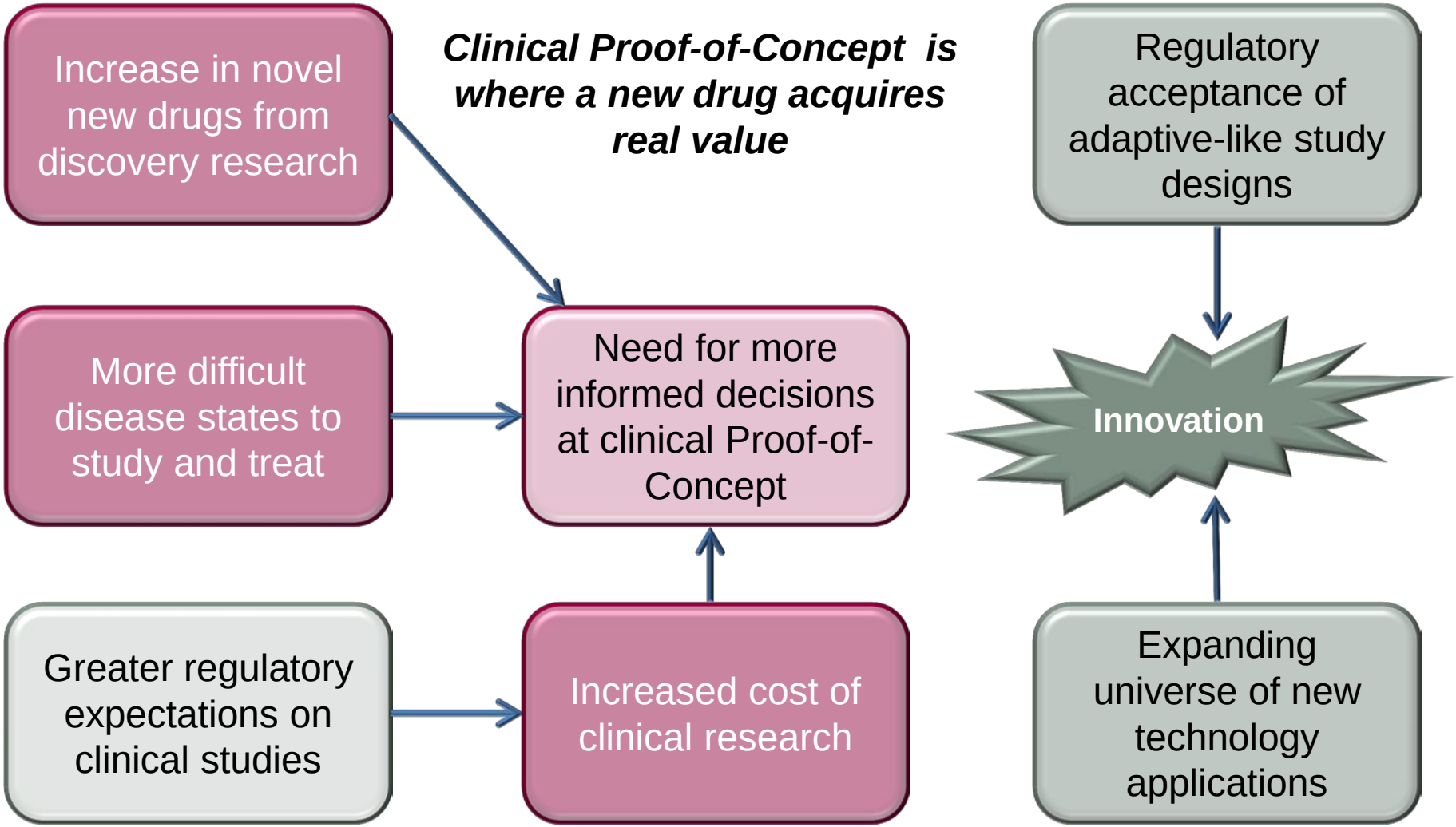
Defines Product Value For the First Time



% Chance of Reaching Market	
Preclinical	0.1-1
FIH study	5-10
POC study	10-30

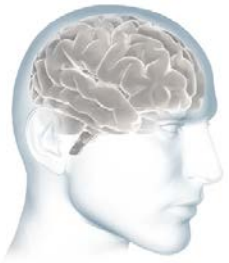
Typical Costs ($million)	
IND tox study	0.5 – 1.0
FIH study	0.7 – 1.4
POC study	2 - 20

What's Driving Evolution of New Paradigm?



Case Study: A Neuroprotective Peptide Davunetide

Discovery: Novel Growth factors

Disease →  ← Injury

↓

Glial-derived growth factors

Activity-Dependent Neuroprotective Protein 12 kilodaltons

Activity-Dependent Neurotrophic Factor 16-18 kilodaltons

J. Neurochem. 1999; 72, 1283-1293
J. Biol. Chem. 2001, 276, 708-714

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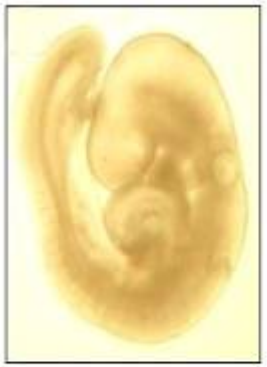
ADNP is a Critical for Neurodevelopment

Activity-Dependent Neuroprotective Protein (ADNP):

- Essential for brain development
- Homozygous (knock-out) animals: Embryonic lethal
- Synthesized in response to injury
- Neuronal expression (cerebellum, mesencephalon, pons, medullar oblongata)
- Cytoplasmic & axonal localization
- Heterozygous animals (ADNP +/-): Viable



Normal Embryo

ADNP Knockout has disrupted brain formation: Dies in utero

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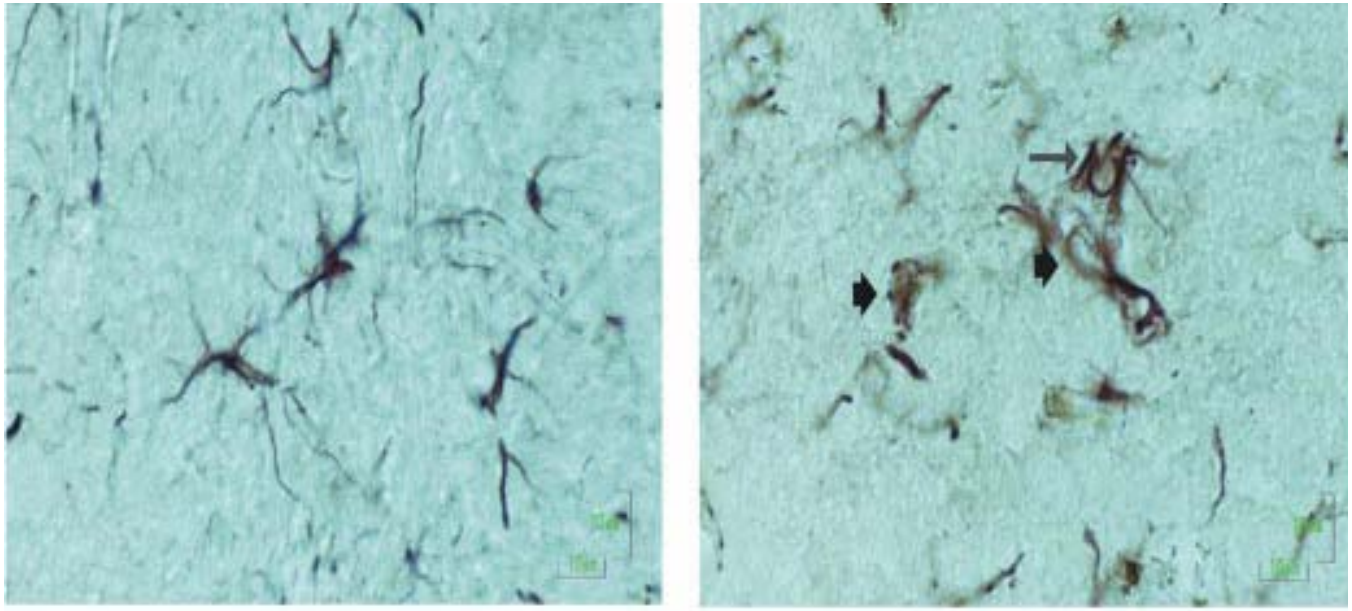
ADNP Deficiency Leads to Tauopathy

WT (+/+) mice

ADNP (+/-) mice



ADNP-deficiency is associated with neurofibrillary tangle-like pathology

J Pharmacol Exp Ther. 2007 Nov;323(2):438-4

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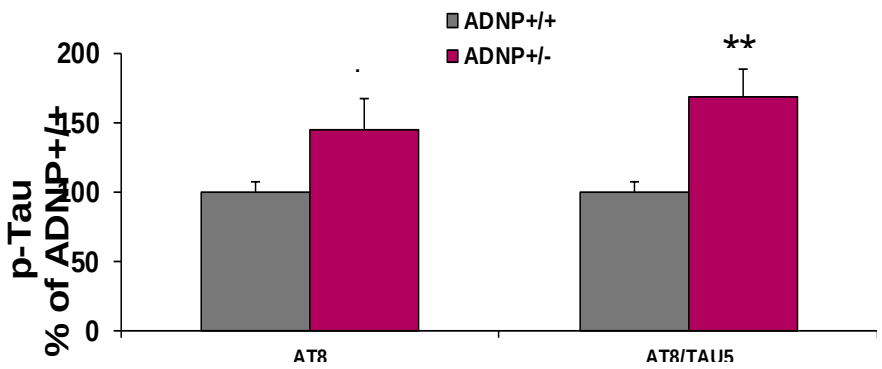
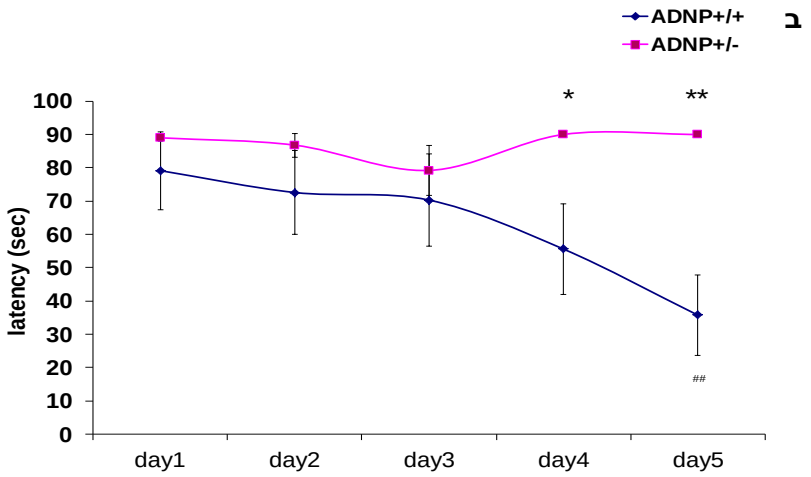
ADNP Deficiency Leads to Behavioral Deficits





- ADNP deficiency alters tau phosphorylation and results in cognitive deficits
- Biochemical and cognitive changes can be reversed by davunetide

J Pharmacol Exp Ther. 2007 Nov;323(2):438-4

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Davunetide Discovery

- Homology mapping and peptide scans identified an 8-amino acid region
- Smallest active fragment of ADNP which provides neuroprotection
- Designated: NAP peptide or AL-108. Davunetide: INN/USAN (generic) name

NAPVSIPQ (davunetide)

J. Neurochem. 1999; 72, 1283-1293
J. Mol. Neurosci. 2004; 24, 181-187
CNS Drug Rev. 2005;11(4):353-68.
Current Alzheimer's Res. 2005; 2(2): 149-153
Pharmacol Ther. 2007; 114(2): 146-154
J. Biol. Chem. 2007; 282: 34448-34456

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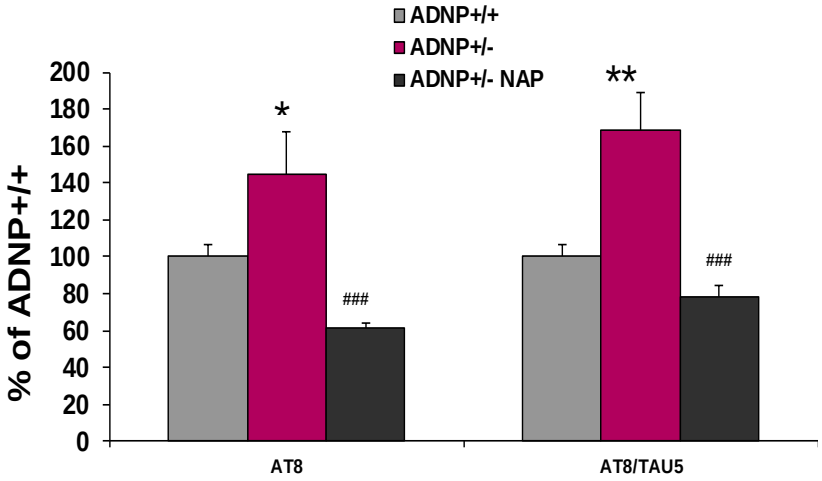
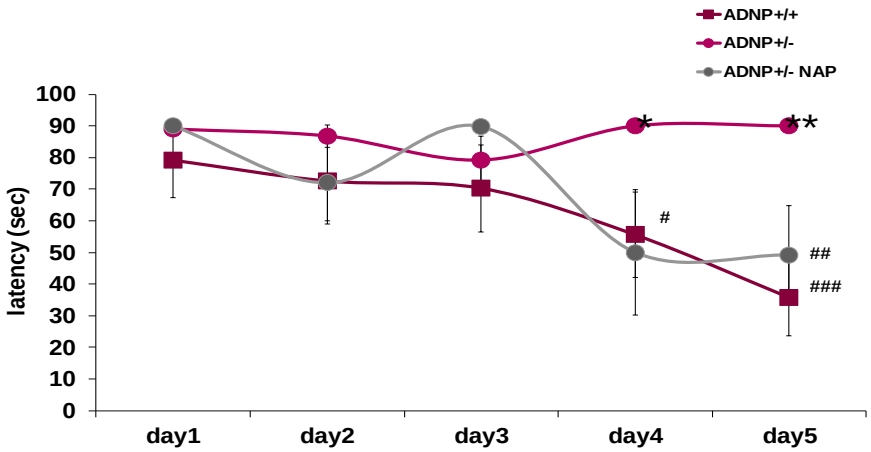
Davunetide: Tau Phosphorylation and Cognition





- ADNP deficiency alters tau phosphorylation and results in cognitive deficits
- Biochemical and cognitive changes can be reversed by davunetide

J Pharmacol Exp Ther. 2007 Nov;323(2):438-4

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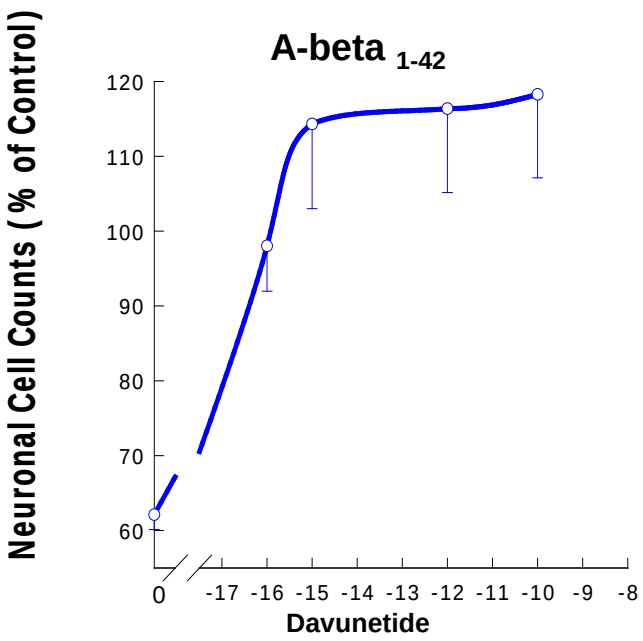
Potent Neuroprotectant In Vitro and In Vivo



- Davunetide promotes neuronal survival against a variety of insults including :
  - β Amyloid
  - Excitotoxicity
  - Glucose deprivation and oxidative stress
  - MPP+
  - Microtubule poisons

Gozes et al., unpublished

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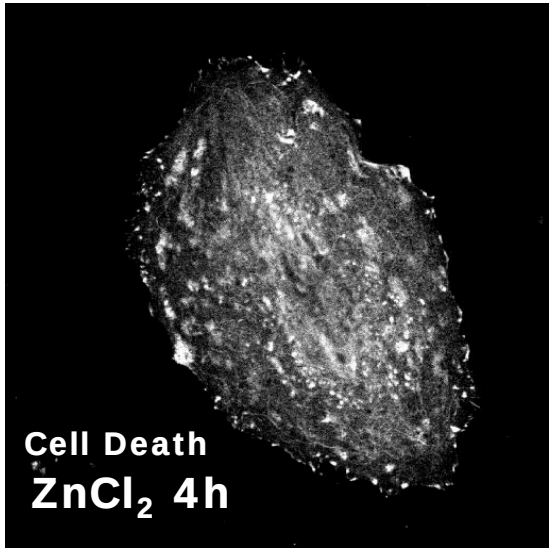
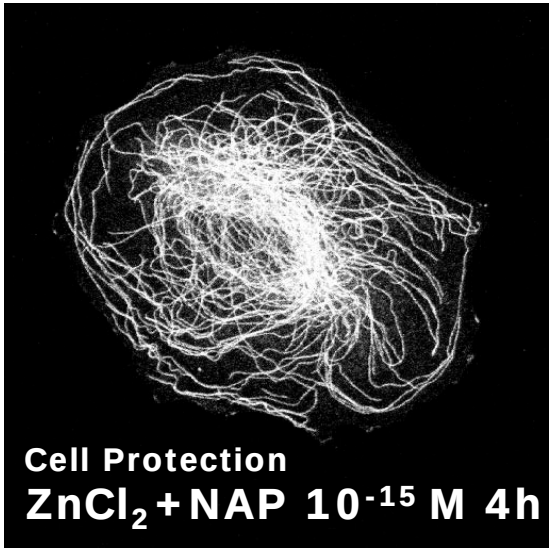
Cytoskeletal Protection

Davunetide protects astrocytes through interaction with microtubules promoting proper organization of the cellular skeleton





J Biol Chem. 2004 Jul 2;279(27):28531-8.

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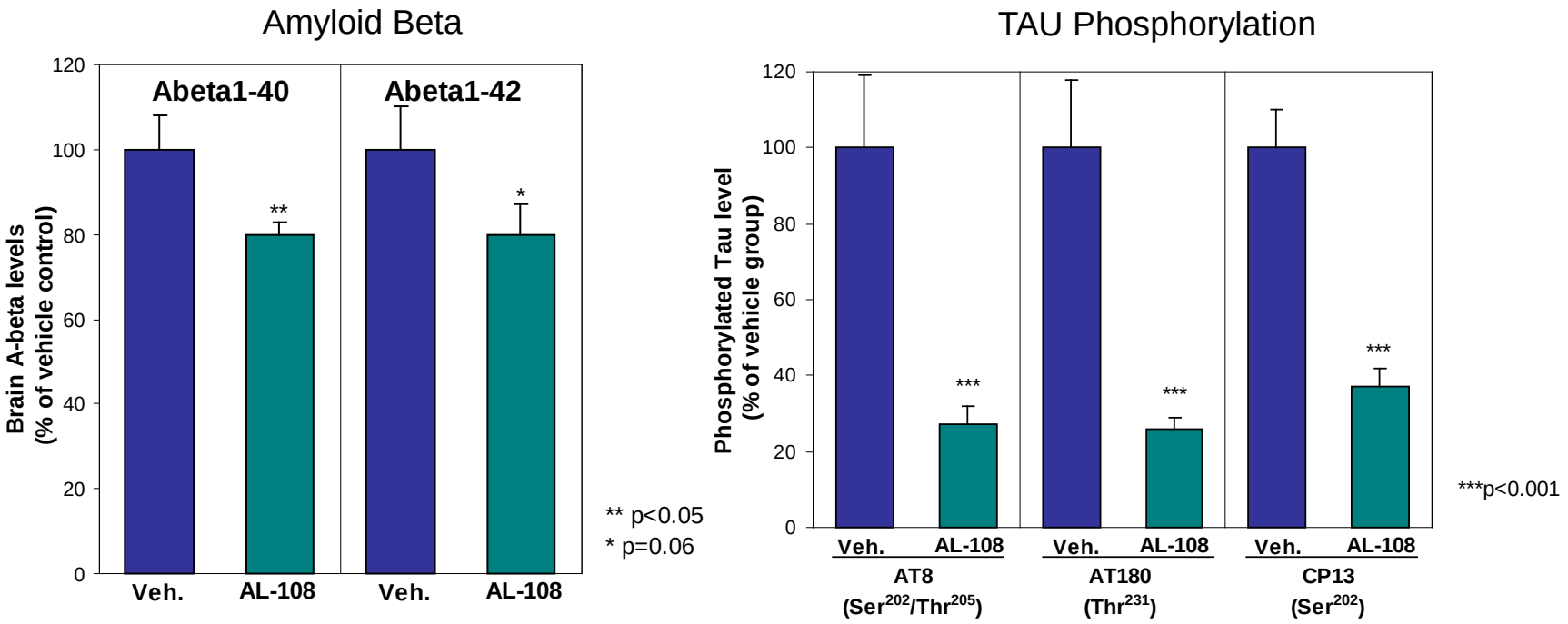
Triple Transgenic Model of Alzheimer's Disease

- Collaboration with Yasuji Matsuoka and Paul Aisen at Georgetown University Medical Center
- The triple transgenic model (3xTg)
  - First described in Oddo et al, Neuron, 39, 409-421, 2003
  - beta-amyloid precursor protein (Swedish)
  - presenilin-1(M146V)
  - Tau (P301L)
- Model progressively develops
  - neurofibrillary tangles
  - beta-amyloid plaques

Biochemical Markers in 3xTg Model



Reduction in levels of beta-amyloid and phosphorylated tau

J. Mol. Neuroscience, 2007, **31**, 165-170
JPET, 2008; **325**(1):146-53

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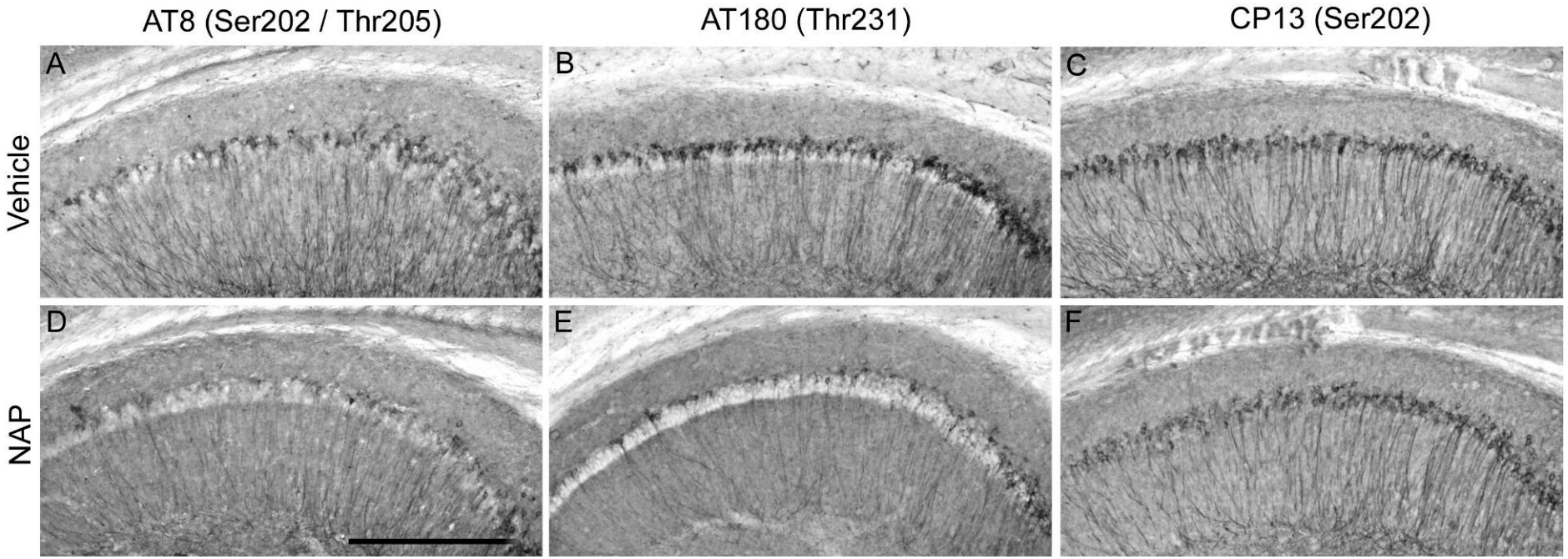
Histopathological Changes in 3xTg Model



- 12 month old, 3 month treatment
- Sections from treated animals were immunostained with phosphorylated tau-specific antibodies. No thioflavin S-positive mature neurofibrillary tangles were detected at this age.

J. Mol. Neuroscience, 2007, **31**, 165-170

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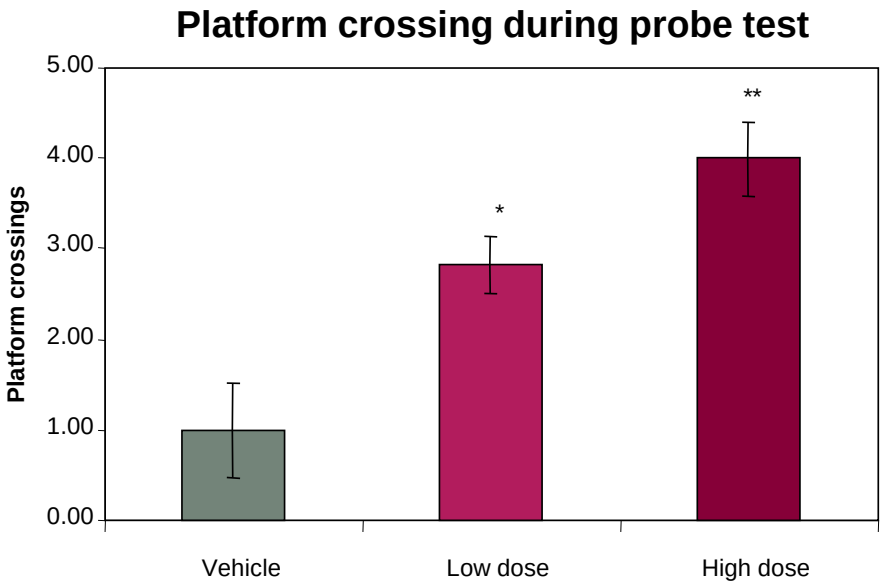
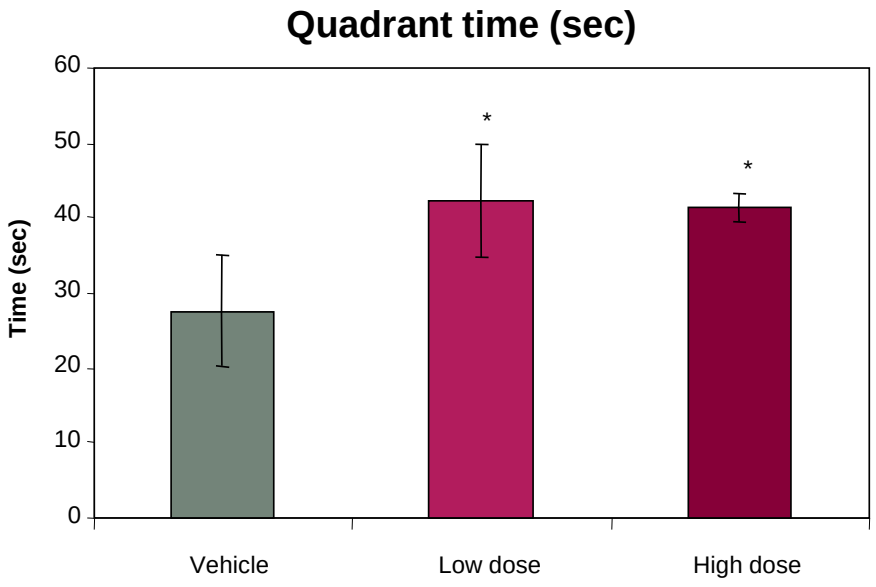
Morris Water Maze: Effect on Learning & Memory





Conclusion: AL-108 (davunetide) treatment improves indicators of learning and memory in the Morris water maze.

JPET, 2008; **325**(1):146-53

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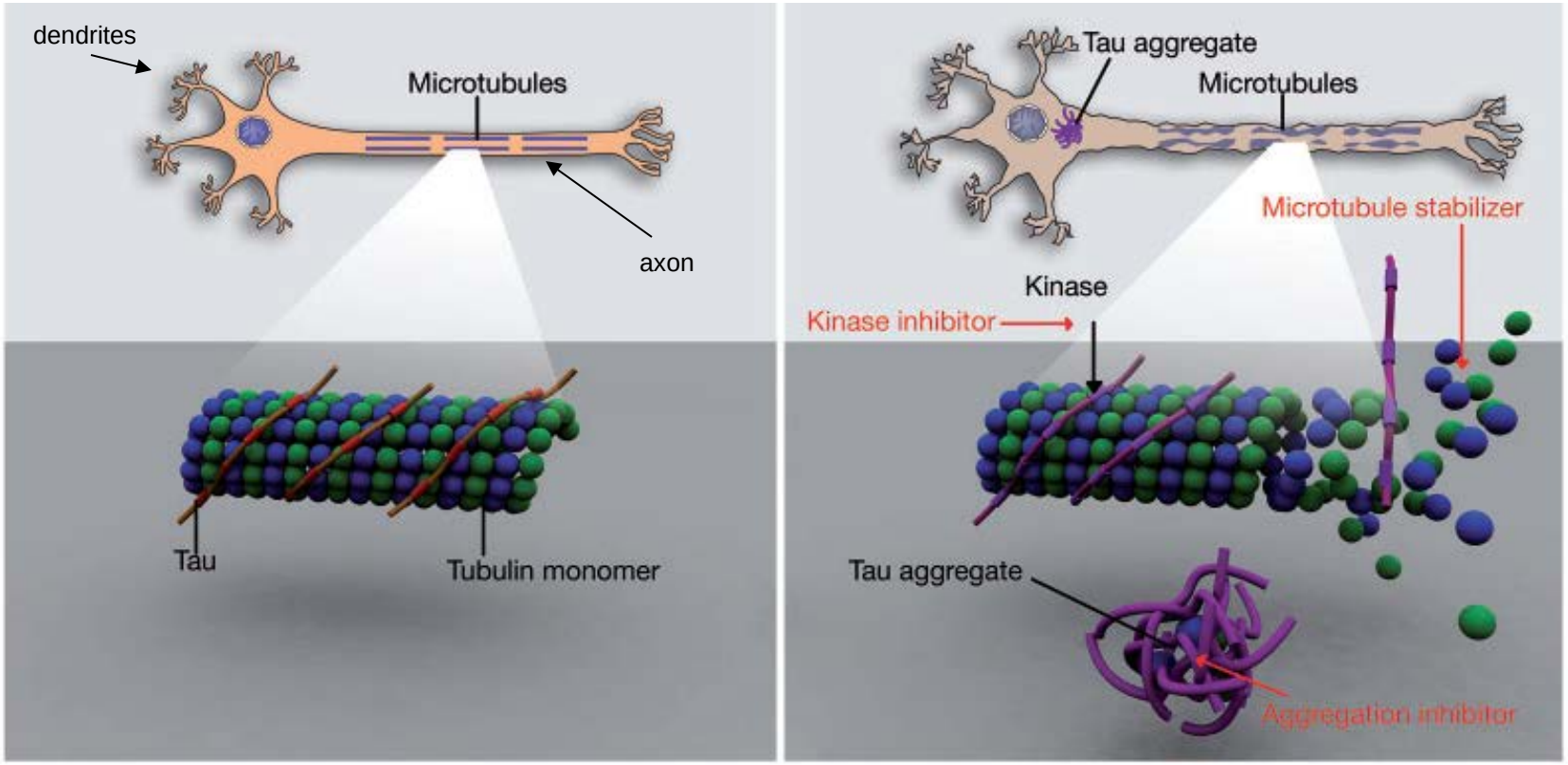
Preclinical Summary

- Davunetide (AL-108), active fragment of a larger glial-derived growth factor
- Neuroprotectant
- Cognitive protectant
- Reduces tau phosphorylation and improves cognitive function in transgenic animal model

Microtubules: Neuron Structure and Function

- Microtubules essential for neuronal structure & function
- Destabilization occurs in many neurodegenerative diseases

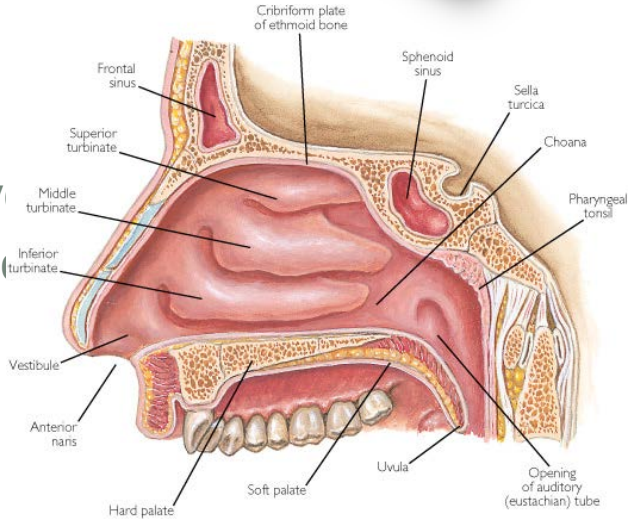


Stamelou, et al. *Brain* 2010: 133; 1578-1590

Key Questions Moving into Early Clinical

Route of Administration?

- Intranasal administration
  - Rapid, fast onset
    - Nasal Epithelium highly vascularized
    - Large absorption area
  - Non-invasive
    - Painless, no needles or injections
    - Easy administration by patient or caregiv
    - Amenable to peptides, oligos and biologi
  - Avoid gastric degradation
  - No hepatic first-pass metabolism



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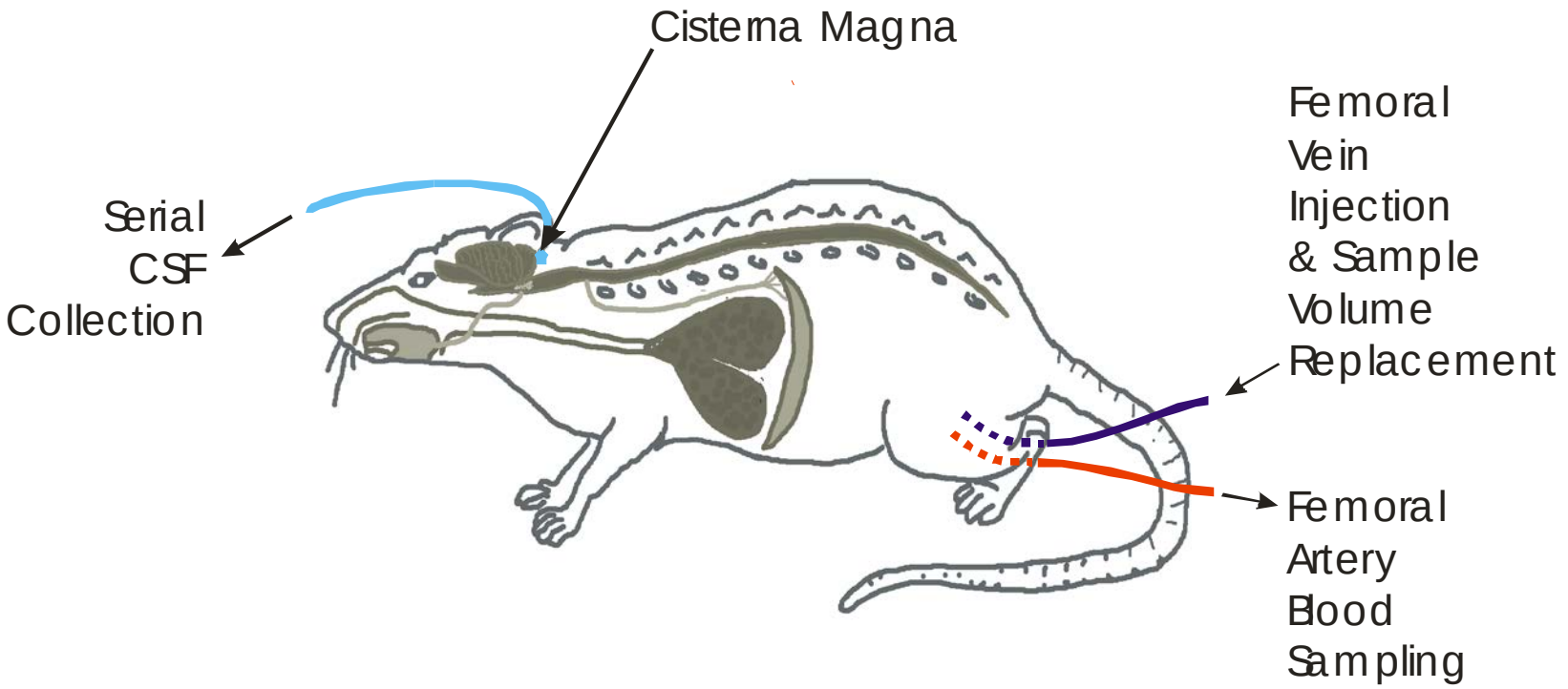
Additional Key Questions…

- Dose?
- Dose paradigm?

Pharmacokinetics

Serial Plasma-CSF Pharmacokinetic Model



Experimental Model

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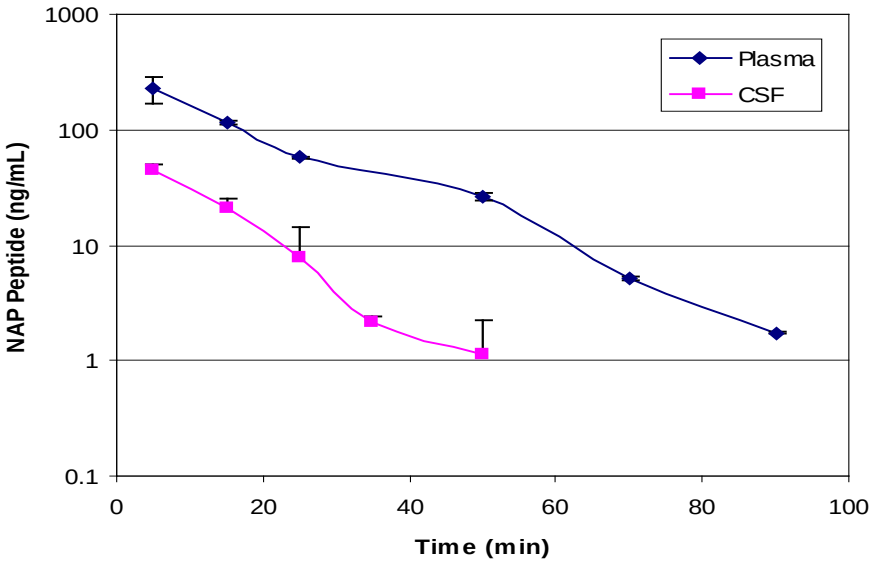
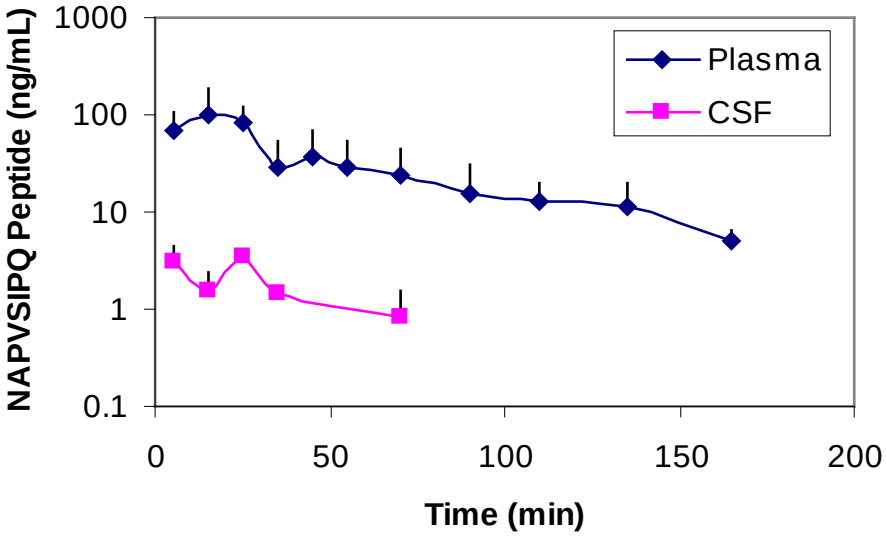
Plasma & CSF Pharmacokinetic Profile (Rat)

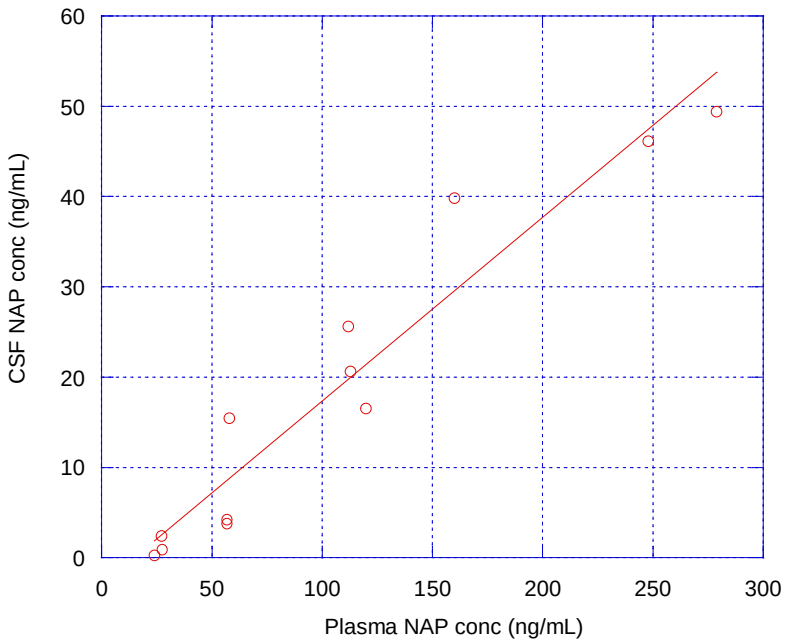
- Anesthetized rats
  - IV: 30 mg/kg (n=3)
  - IN: ~30 mg/kg, 10 mg per animal (n=5)
- Serial collection of plasma and CSF
- 14-20% CSF exposure





Davunetide Reaches the Brain via Plasma

- Anesthetized rats used to examine CSF concentrations of davunetide following intranasal and intravenous administration
- Data shows:
  - Drug is detectable in the brain through both routes of administration
  - Linear correlation between plasma and CSF levels indicates that drug accesses the brain through the plasma
  - Plasma concentrations can be used as a surrogate for CSF concentrations



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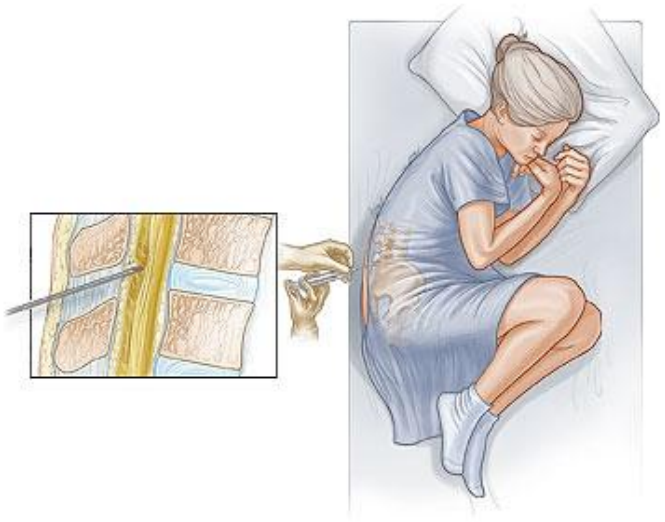
Translate Preclinical to Clinical PK

- Open-label, single dose, plasma & continuous CSF collection
  - Lumbar (L3-L4) catheterization
  - CSF collected at 0.2 mL/min for 4 hours, 1 mL fractions
  - 6 subjects per group
  - Measured drug levels as well as various AD biomarkers
- Healthy Adult (18-45 years)
  - 50 mg intravenous
  - 300 mg intravenous
  - 15 mg intranasal
- Mild-to-Moderate AD patients
  - 15 mg intranasal



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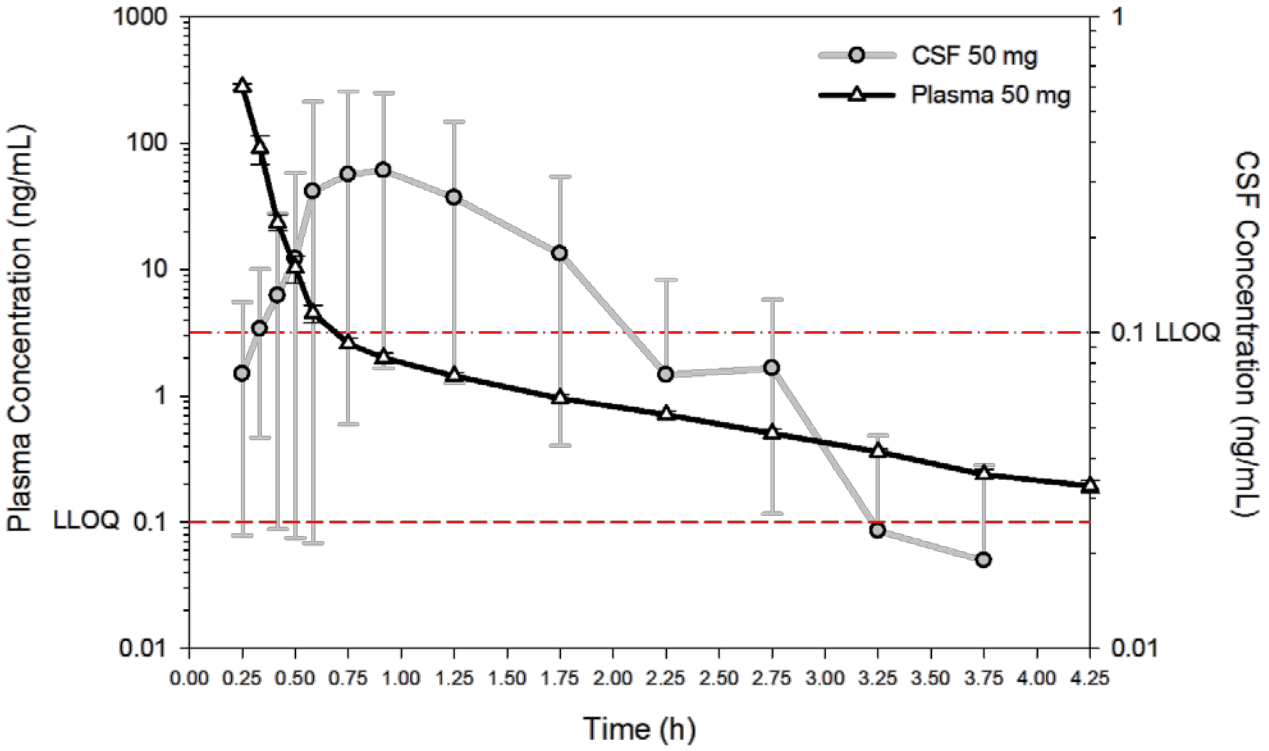
Plasma & CSF Profile: 50 mg IV

- Continuously collect CSF and plasma
- Healthy subjects (n=6)
- Measure drug levels with validated LC-MS/MS assay



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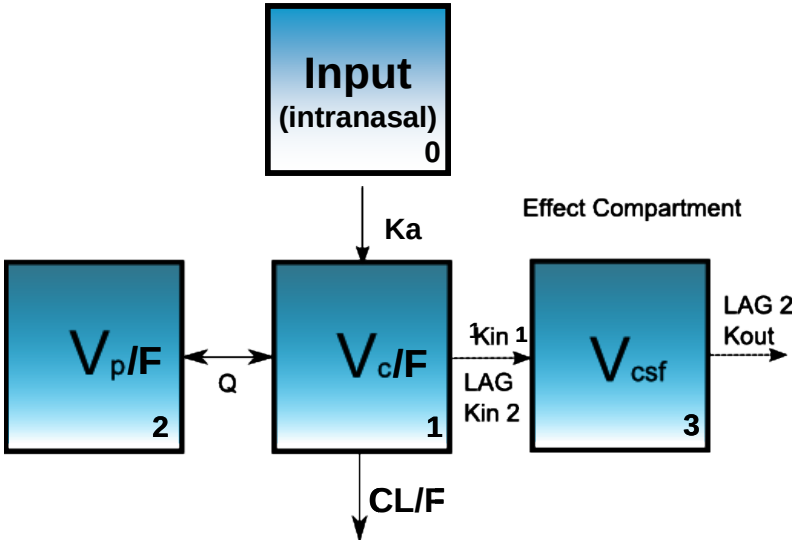
2-Compartment PK Model

- Explored various compartmental PK models
- Best fit: two-compartment model



The model was described by the following series of differential equations:

Plasma (Central Volume of Distribution):

For IN administration

$$\frac{dA_0}{dt} = \text{Dose} - Ka \times A_0$$

$$\frac{dA_1}{dt} = Ka \times A_0 + \frac{Q \times A_2}{V_p} - \frac{Q \times A_1}{V_c} - \frac{CL \times A_1}{V_c}$$

Peripheral Volume of Distribution (for IV and IN)

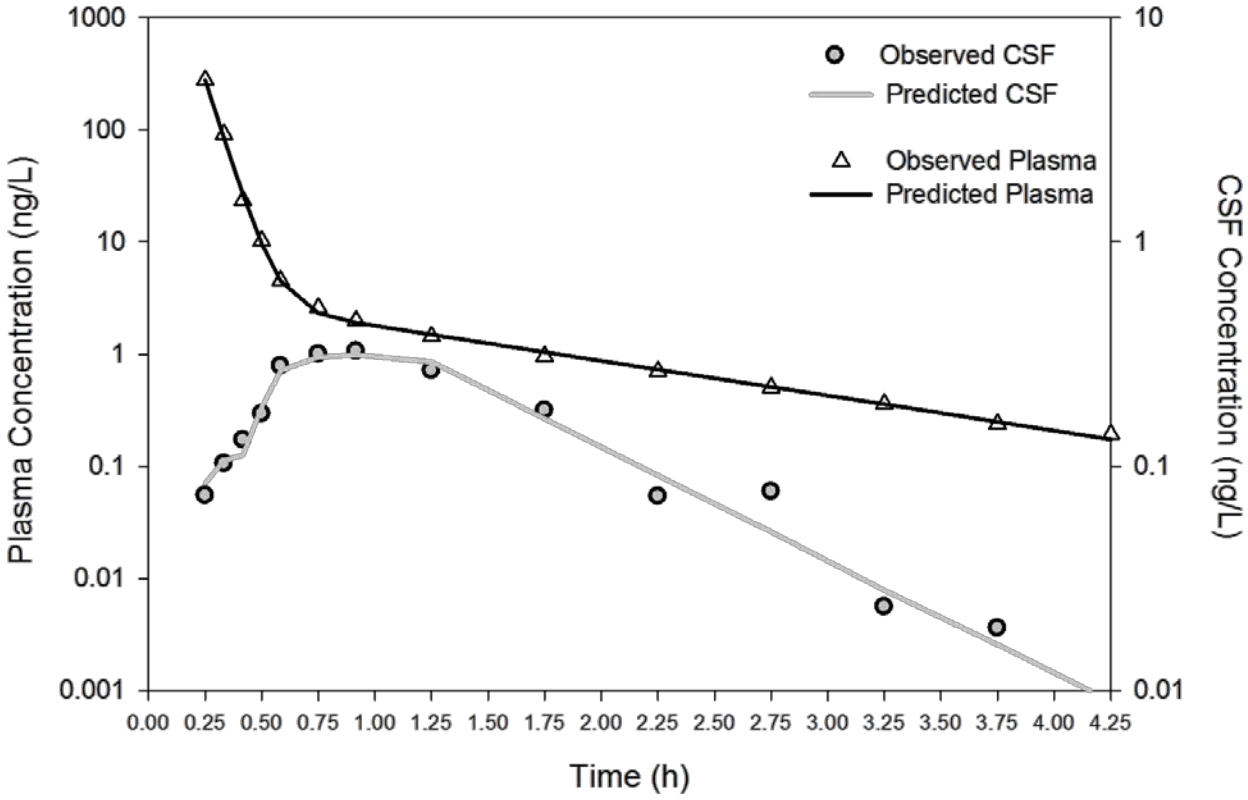
$$\frac{dA_2}{dt} = \frac{Q \times A_1}{V_c} - \frac{Q \times A_2}{V_p}$$

CSF:

$$\frac{dA_3}{dt} = +\left[\left(Kin1_{0 \text{ to } LAG1} + Kin2_{LAG1 \text{ to } LAG2}\right) \times A_1\right] - \left[Kout_{LAG2 \text{ to } \infty} \times A_3\right]$$

PK Model: Applied

- Computational model predicts experimental data



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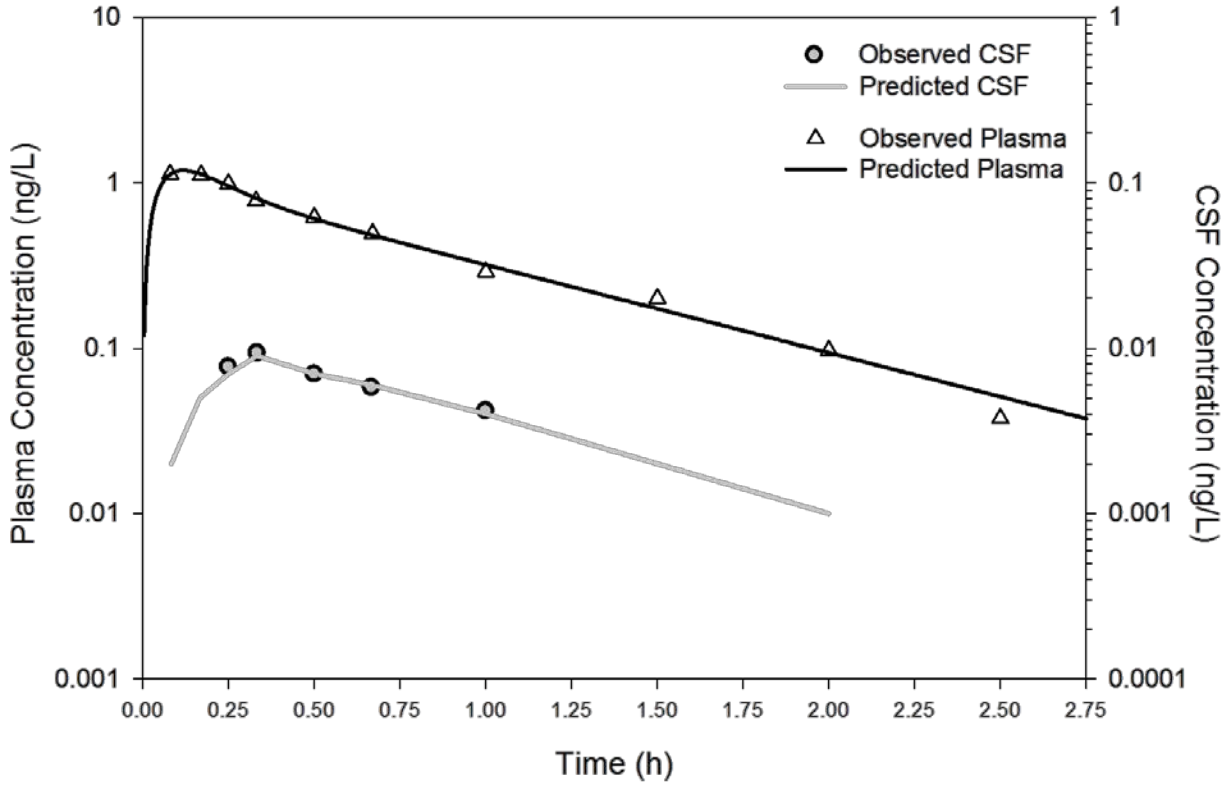
Intranasal Pharmacokinetics

- Model derived from intravenous data maps to intranasal experimental data



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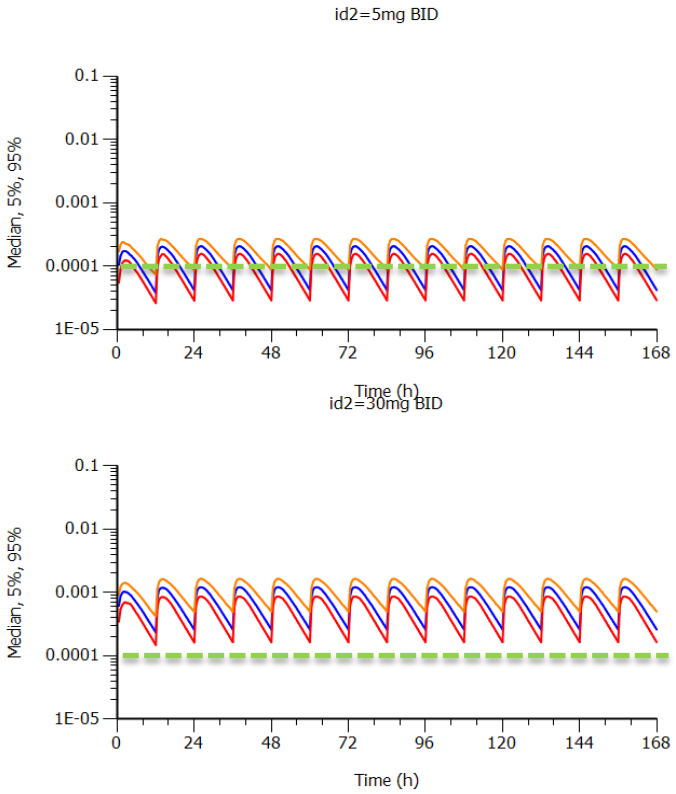
Translational Questions Answered

- Good translation from preclinical to clinical
- Intranasal drug administration results in systemic distribution (not direct nose-to-brain)
- PK model allowed for sparse blood sampling in Phase II/III
- Able to develop a robust PK model to conduct PK simulations for Phase II/III
  - Looked at dose and dose paradigms (QD, BID, TD)
  - Optimize for steady state CSF concentrations



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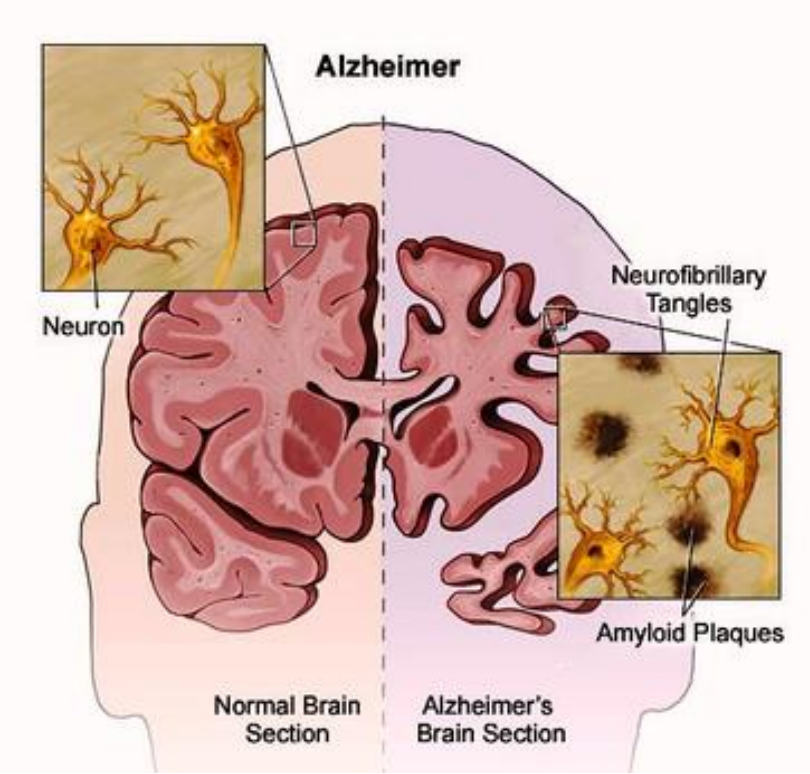
Target indication: Alzheimer's disease

- Two pathologies
  - Amyloid plaques
  - Neurofibrillary tangles
- Tangles composed of hyper-phosphorylated tau
- Phase 2a clinical trials in AD looking at changes in cognition are typically long
- Needed a biomarker or surrogate indication



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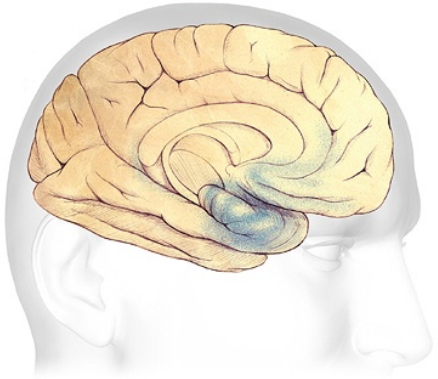
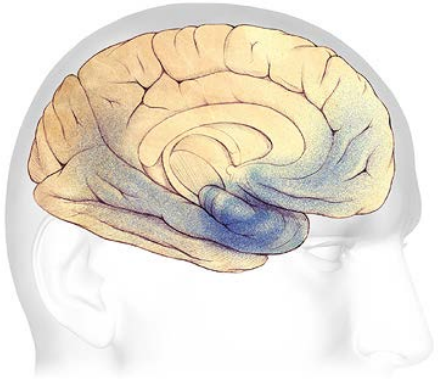
Amnestic MCI: Proof-of-Concept for AD

Amnestic MCI



- Prodromal AD
- Single domain cognitive impairment: short-term memory
- Tangles appear to be responsible for memory impairment
- High rate of conversion to AD

Mild to moderate AD



Alzheimer's Association

- Davunetide impacts tau/tangle pathology (preclinical)
- Hypothesis: reducing tangles should result in improved memory

Markesbery et al., 2006, Petersen et al., 2006, Jicha et al., 2006

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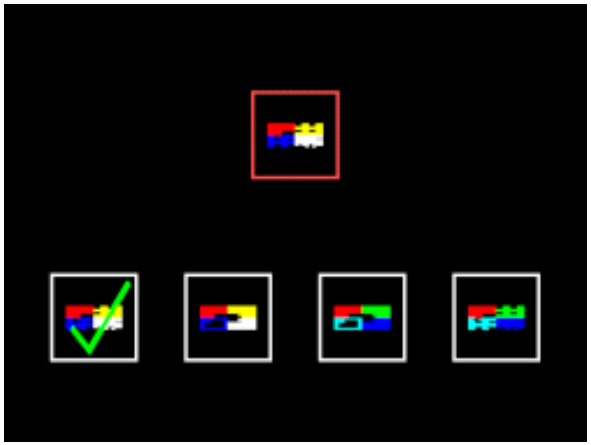
Davunetide Phase II aMCI Trial: Design

- Randomized, placebo-controlled, double blind trial
- 17 clinical sites in the U.S.
- 144 subjects amnestic MCI
  - Self-reported memory complaint confirmed by spouse or companion
  - MMSE ≥24; WMS-III; LM-II ≤5
- Davunetide: intranasal delivery
- Two doses plus placebo, 12 weeks of treatment
- Cognitive assessments at weeks -4, 0, 4, 8, 12, 16
- Combination of computerized (Cantab) and paper-and-pencil tests

Delayed Match-to-Sample (DMTS)

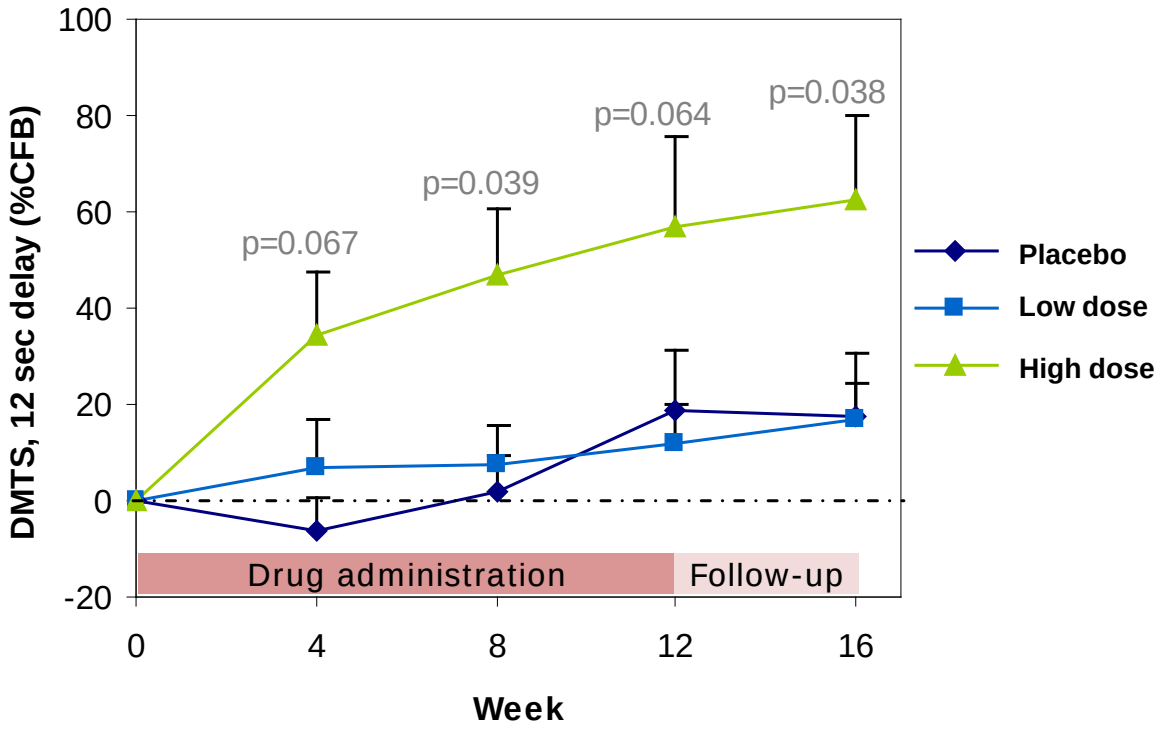
- Measures working memory, recognition memory and short term memory
- After a complex pattern is presented to the patient, four similar patterns are shown and the patient must identify the correct match
- Simultaneous, 0, 4 second delays only measure focus and attention not memory
- Conversely, the 12 second delay is a well validated test of memory function



Swainson et al, Dementia & Geriatric Cognitive Disorders, 2001

Delayed Match to Sample, 12 Second Delay

Activity on Visual Working Memory



- Treatment effect of high dose
- Rapid onset (4 weeks of treatment) and durable (week 16, 4 weeks post-last dose)

Summary

- Answered key questions in early clinical research
  - Route of administration
  - Plasma pharmacokinetics
  - CNS penetration
- De-risk clinical development program
- Move rapidly to clinical proof-of-concept

- Retrospective analysis:
  - Validate receptor engagement in Phase 1
  - Biomarker for proof-of-mechanism

Acknowledgements

Former colleagues at Allon Therapeutics Inc.

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- Matt Carlye
- Michael Gold
- Lesley Parker
- Daniela Nenciu
- Catherine Campbell
- Mina Virtusio
- Sue Anne Crocker

References

- Davunetide: Pharmacokinetics and distribution to brain after intravenous or intranasal administration to rat. *Chimica Oggi* **27**, 16-19, 2009
- The role of davunetide in neuroprotection and microtubule stabilization. *Chimica Oggi* **30 (2)**, 34-36, 2012
- A double-blind, placebo-controlled, ascending-dose, randomized study to evaluate the safety, tolerability and effects on cognition of AL-108 after 12 weeks of intranasal administration in subjects with mild-cognitive impairment. *Dement Geriatr Cogn Disord*. **35(5-6)**:325-36, 2013
- Davunetide: A review of safety and efficacy data with a focus on neurodegenerative diseases. *Expert Rev Clin Pharmacol.* **6(5)**, 483-502, 2013

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Questions?

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