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

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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

Traditional Paradigm: Phased Approach

- Scarcity of molecules from discovery
- Pre-Clinical
- Phase I
- Phase II
- Phase IIb
- Phase III
- Test each scarce molecule thoroughly

Emerging Paradigm: POC / Confirmation Approach

- Abundance of molecules from discovery
- Pre-Clinical
- Proof of Concept
- Confirmation
- Shift attrition earlier

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?

Clinical Proof-of-Concept is where a new drug acquires real value

- Increase in novel new drugs from discovery research
- More difficult disease states to study and treat
- Need for more informed decisions at clinical Proof-of-Concept
- Regulatory acceptance of adaptive-like study designs
- Greater regulatory expectations on clinical studies
- Increased cost of clinical research
- Expanding universe of new technology applications

Innovation
Case Study: A Neuroprotective Peptide Davunetide
Discovery: Novel Growth factors

Disease  Glial-derived growth factors  Injury

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
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
ADNP-deficiency is associated with neurofibrillary tangle-like pathology

ADNP Deficiency Leads to Tauopathy

WT (+/+) mice  ADNP (+/-) mice

ADNP-deficiency is associated with neurofibrillary tangle-like pathology
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
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)
- ADNP deficiency alters tau phosphorylation and results in cognitive deficits
- Biochemical and cognitive changes can be reversed by davunetide
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
Cytoskeletal Protection

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

![Cell Death](image1)

ZnCl$_2$ 4h

![Cell Protection](image2)

ZnCl$_2$+NAP $10^{-15}$ M 4h
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

**Abeta1-40**

**Abeta1-42**

**Brain A-beta levels (\% of vehicle control)**

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<th>Veh.</th>
<th>AL-108</th>
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<td>Abeta1-40</td>
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<td>85</td>
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<td>65</td>
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<td>Abeta1-42</td>
<td>100</td>
<td>90</td>
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**TAU Phosphorylation**

**Phosphorylated Tau level (\% of vehicle group)**

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<td>AT8 (Ser&lt;sup&gt;202&lt;/sup&gt;/Thr&lt;sup&gt;205&lt;/sup&gt;)</td>
<td>100</td>
<td>80</td>
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<td>AT180 (Thr&lt;sup&gt;231&lt;/sup&gt;)</td>
<td>100</td>
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<td>CP13 (Ser&lt;sup&gt;202&lt;/sup&gt;)</td>
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**p<0.05  p=0.06  *p<0.001**

Reduction in levels of beta-amyloid and phosphorylated tau

JPET, 2008; 325(1):146-53
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.
Conclusion: AL-108 (davunetide) treatment improves indicators of learning and memory in the Morris water maze.
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
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 caregiver
    - Amenable to peptides, oligos and biologics
  - Avoid gastric degradation
  - No hepatic first-pass metabolism
Additional Key Questions…

- Dose?
- Dose paradigm?

Pharmacokinetics
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
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.
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
Plasma & CSF Profile: 50 mg IV

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

\[
\frac{dA_3}{dt} = +\left[ (Kin_{0 \to LAG1} + Kin_{LAG1 \to LAG2}) \times A_1 \right] - \left[ Kout_{LAG2 \to \infty} \times A_3 \right]
\]
PK Model: Applied

- Computational model predicts experimental data
Intranasal Pharmacokinetics

- Model derived from intravenous data maps to intranasal experimental data
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
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
Amnestic MCI: Proof-of-Concept for AD

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

- 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
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
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References

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- 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

Questions?

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