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Applied Translational Medicine

Trials and Tribulations for an Intranasal Peptide: Davunetide, lessons learned

February 25, 2014

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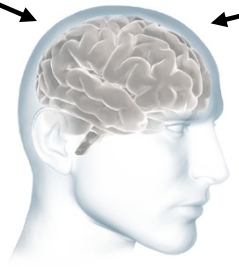
Davunetide Discovery

Disease **Injury**



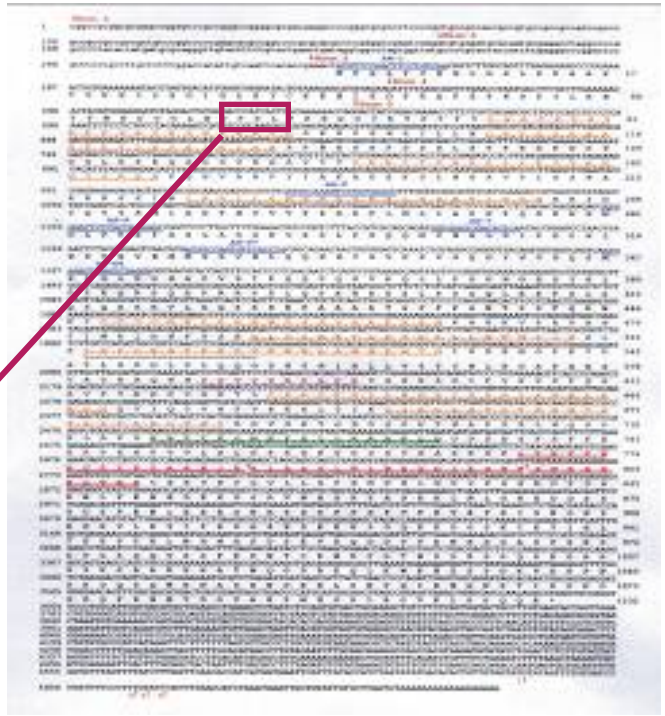
Glial-derived neuroprotectants

Activity Dependent Neuroprotective Protein (ADNP)

Davunetide

NAPVSIPQ peptide

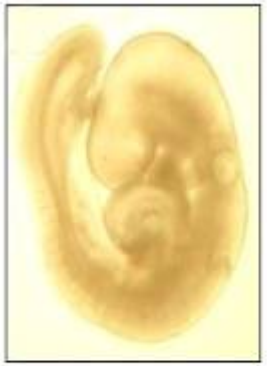
AL-108, AL-208



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

ADNP is a Natural Neuroprotectant

- Essential for brain development
- Synthesized in response to injury
- Important in learning and memory
- Neuronal expression (cerebellum, mesencephalon, pons, medullar oblongata)
- Cytoplasmic & axonal localization
- Heterozygous animals (ADNP +/-): memory impaired
- Davunetide ameliorates impairment



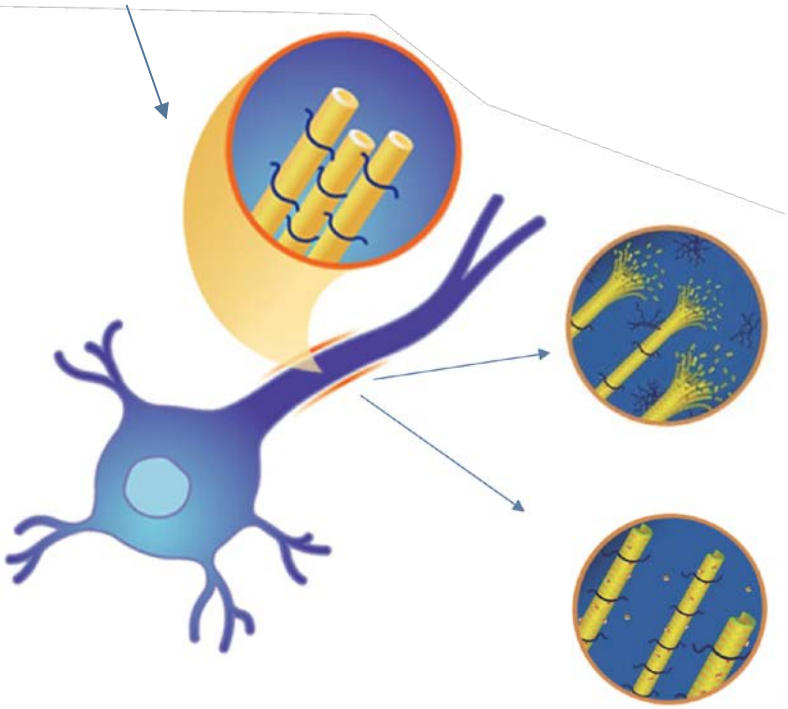
Normal Embryo

ADNP Knockout has disrupted brain formation: Dies in utero

Fundamental Mechanism of Action

Microtubules

Essential for neuronal structure and function



Neurodegeneration

- Destabilization and breakdown of microtubules
- Tau hyperphosphorylation
- Progressive loss of function
- Leads to cell death

Neuroprotection

- *Davunetide* crosses the human blood brain barrier
- Reduces Tau hyperphosphorylation
- Stabilize and repair microtubules
- Restore neuronal structure and function

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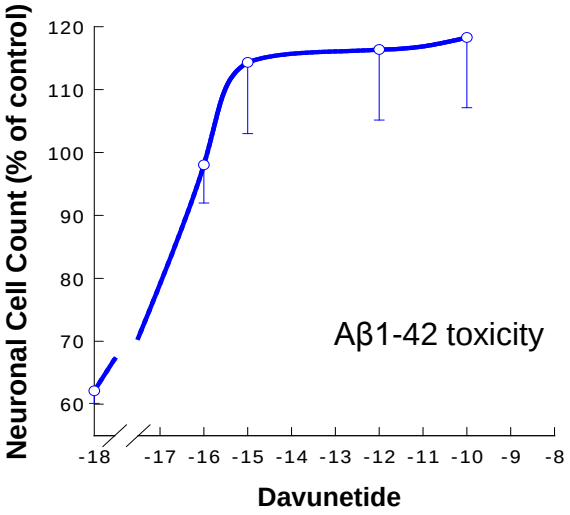
Summary of Davunetide Pharmacology

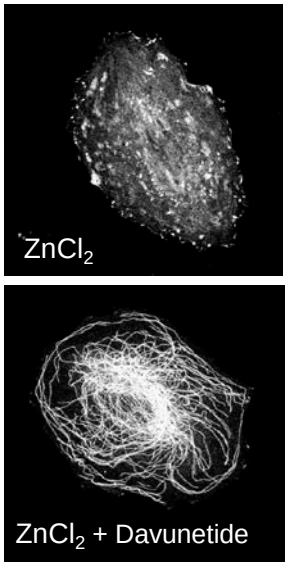
Neuroprotection



Davunetide promotes neuronal survival against a variety of insults including :

- Excitotoxicity
- Glucose deprivation
- Oxidative stress
- MPP+
- Microtubule poisons

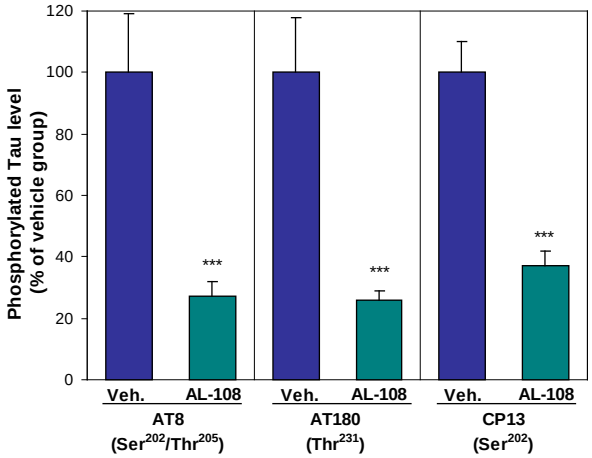
Microtubule stabilization



Davunetide stabilizes microtubules and protects the organization of the cytoskeleton

J Biol Chem. 2004; 279:28531-8

Reduction of tau Phosphorylation



Davunetide reduces tau phosphorylation in the triple transgenic AD model ($PS1_{M146V}$, APP_{SWE}, and tau_{P301L})

J. Mol. Neurosci. 2007; 31: 165-170
JPET, 2008; 325:146-53

Clinical Development

P/C & Phase I →
- Safety/PK Studies
- Safety to 60 mg/day
- CSF penetration
- Brain via systemic distribution
- Healthy/aged, AD, FTD
- 35 P/C studies in 17 models

PIIa – Mild Cognitive Impairment
- 144 participants
- 2 doses (5 mg QD, 15 mg BID)
- 12 weeks
- Randomized, placebo controlled, double blind
- 17 US sites

PIIa – Schizophrenia
- 63 participants
- 2 doses (5 mg QD, 15 mg BID)
- 12 weeks
- Randomized, placebo controlled double blind
- 7 US sites

PIIa – Schizophrenia Imaging Biomarker
- 18 participants
- 2 doses (5 mg QD, 15 mg BID)
- 12 weeks
- Randomized, placebo controlled double blind
- 3 US sites

→ **PII/III Pivotal Study**
- Progressive Supranuclear Palsy
- Tau pathology
- Rapid decline
- No effective treatment
- Validated rating scale
- Powered as a pivotal study

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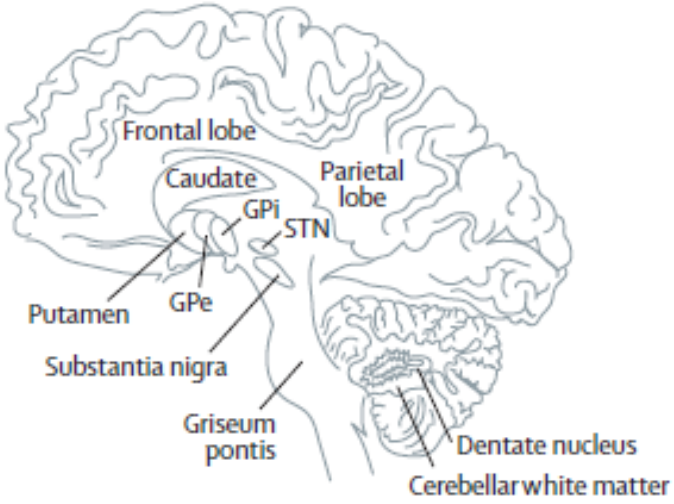
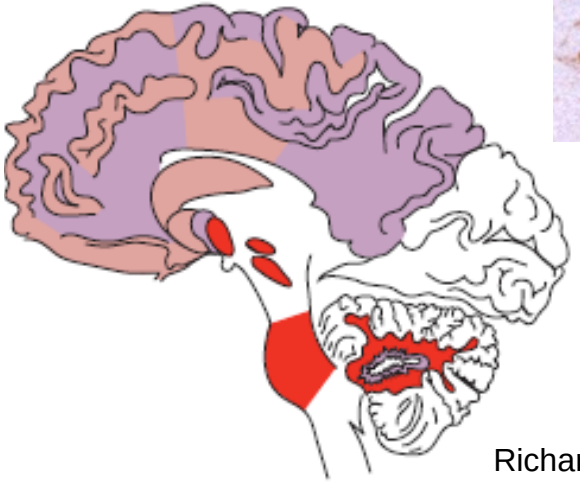
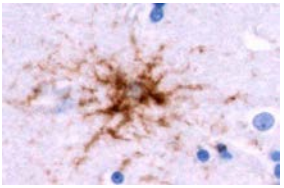
Progressive Supranuclear Palsy (PSP)

- A degenerative disease involving the brain stem, basal ganglia, cerebellum
- Clinical symptoms (movement problems, cognitive impairment) apparent result of the underlying tau pathology in the brain region controlling those functions

Steele JC, Richardson JC, Olszewski J. 1964 *Arch Neurol*;10: 333–59.







Richardson's Syndrome

Williams and Lees; *Lancet Neurol* 2009; 8: 270–79

Why PSP?

- Early-onset dementia characterized by tau pathology
- No available treatment
- Significant future potential in other sub-types of frontotemporal dementia and Alzheimer disease

- US Orphan granted (20,000 patients)
  EU Orphan granted (50,000 patients)
- Fast Track granted by FDA
- Appears to meet criteria for single study approval
- Phase II/III study powered as a pivotal study

PSP Study Design

- Phase II/III study in PSP
  - Recruited 313 patients
  - 1:1 active-to-placebo
  - Treated for 1 year
  - 47 clinical sites in US, Canada, Australia, Germany, UK and France
- Clinical Endpoints
  - Safety (adverse events, con meds)
  - Efficacy (disease severity, daily living, cognitive, mood)
  - Volumetric MRI
  - CSF biomarkers
  - DNA (tau genotype)
- Study unblinded in Dec 2012. Active, no different from placebo on any endpoint
- Valid study: PSP disease progression over 12 M as expected

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Why Negative Results?

- PSP patient pathology too advanced?
  - Patients have established pathology, not possible to intervene
  - Clinical instruments not sensitive to detect drug effect

- Right dose? Sufficient drug exposure?
  - Marker for target engagement
  - Ability to verify mechanism of action
  - PSP study used single strength (30 mg BID)

Retrospective Risk-Mitigation

- Run pilot PSP study (Phase II)
  - Multiple doses (dose-response)
  - Biomarker intensive
    - Note: post-hoc analysis of the Phase II/III data suggests correlation between MRI, CSF and sub-scales of PSP-RS
  - More intensive PK/PD

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General Lessons Learned

Manufacturing Scale-up

Cost-of-Goods

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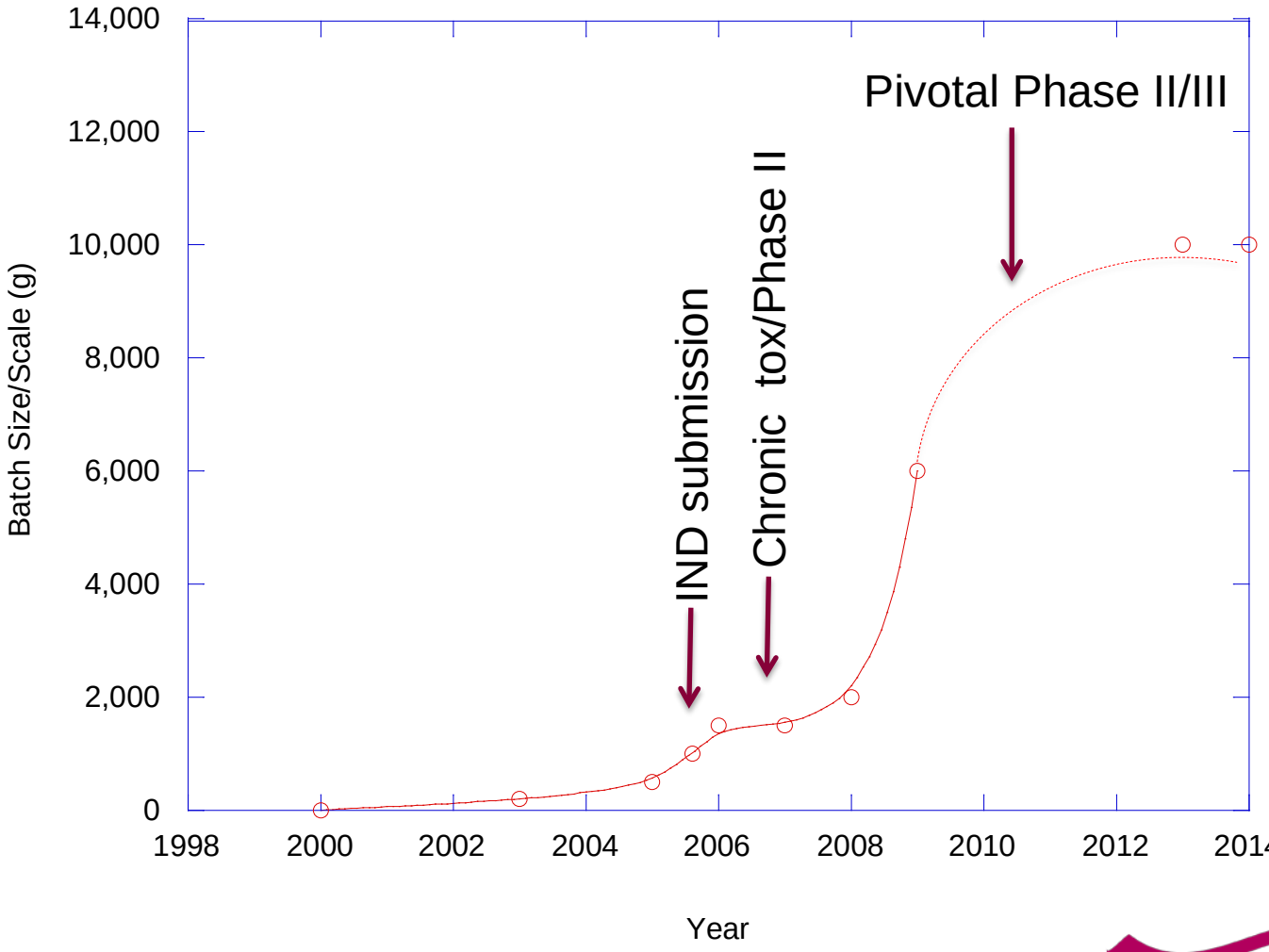
Solid-phase Scale-up



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Projections

- PSP market (US)
  - Orphan indication (prevalence ~6.5 per 100,000)
  - 60 mg daily dose
  - Need ~150 kilograms (at launch)
  - ~500 kilograms per annum (at peak sales)

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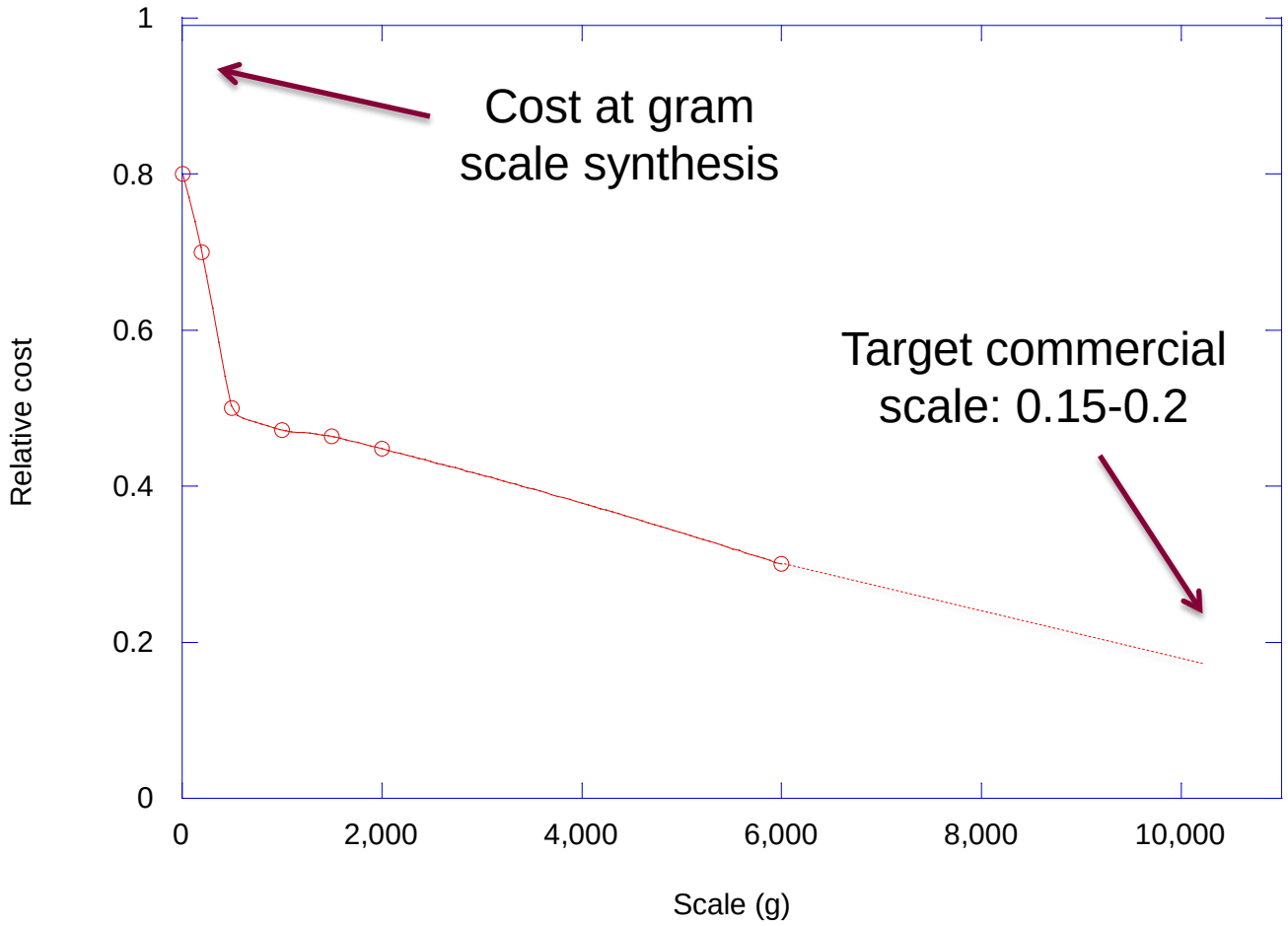
Solid-Phase Manufacturing

- Existing solid-phase synthesis (10 kg batch size):
  - 3 x 3.3 kg synthesis, pool crude peptide, HPLC purify, batch lyophilization
  - “Sufficient” for product launch for orphan indication
- Would require 10-15 batches per year
- Within existing capacity of CMO at single site
- Challenge: to get to 500 kg/annum to support peak sales (3-4 years post-approval) as well as follow-on product approval in other indications (like AD)

Need to rapidly bridge to additional solid-phase capacity (second supplier) or explore liquid-phase synthesis

Cost: Solid-Phase Synthesis

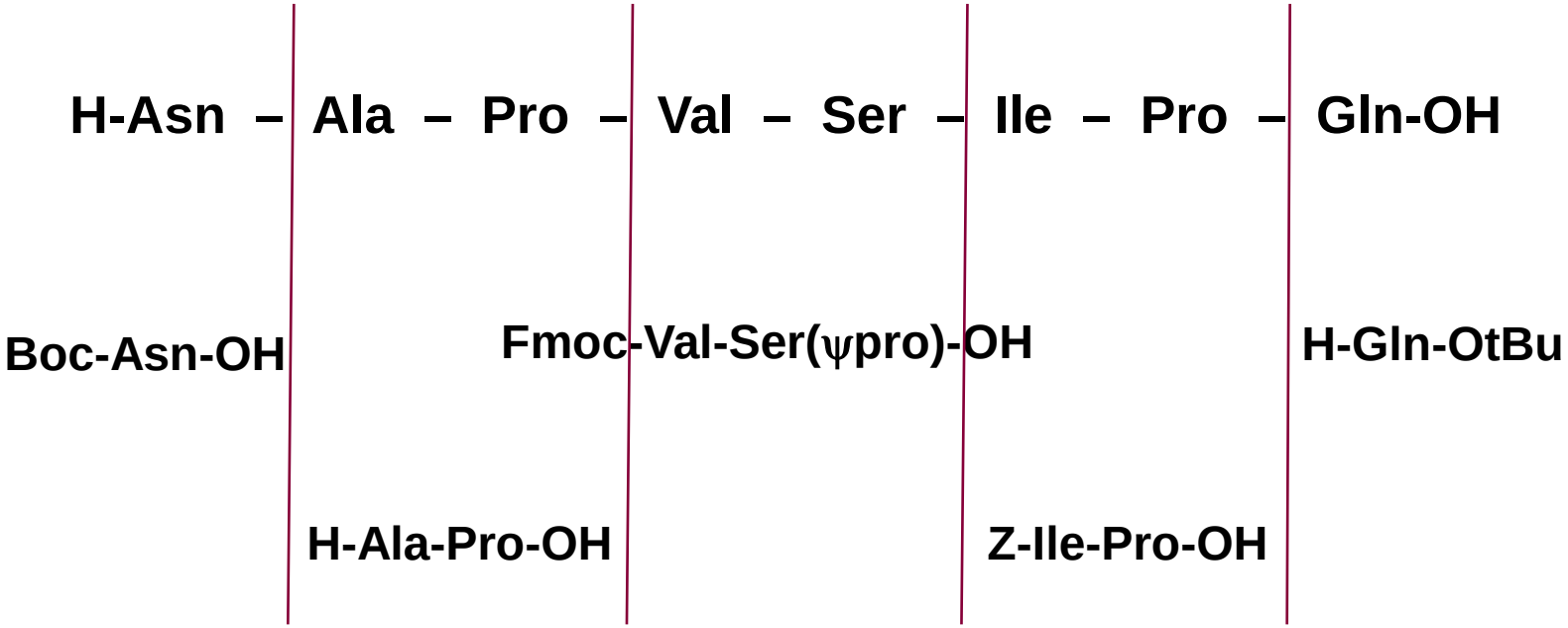


Cost-Scale Considerations

- Solid-Phase
  - 0.15-0.2 relative cost
- Solution-Phase
  - Cost of initial development
  - Impurity profile
  - 0.035-0.05 relative cost
  - Dramatic reduction in cost (3- to 6-fold)

Davunetide: Solution-Phase Strategy

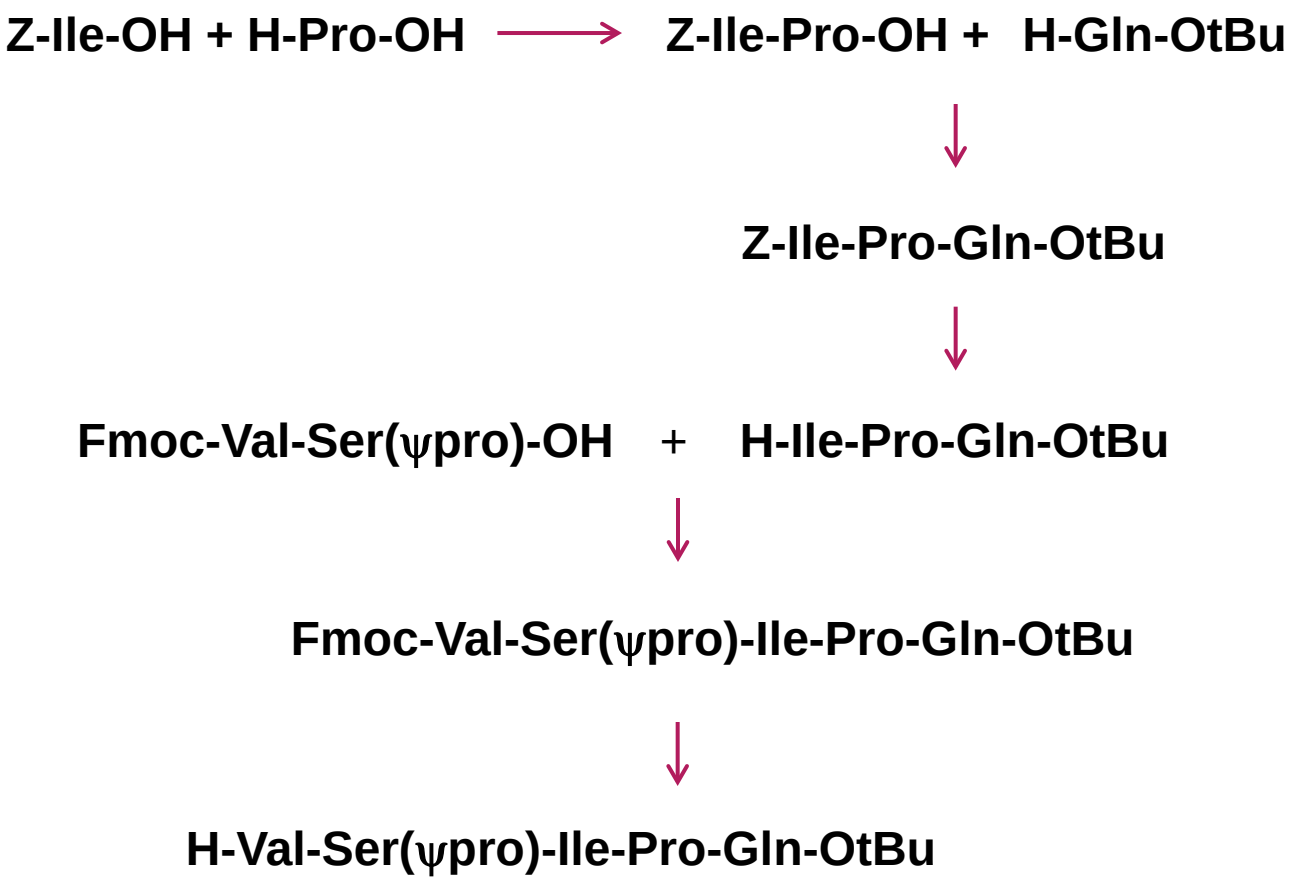
Condensation Segments and Building Blocks:



Solution-Phase Considerations

- Minimize Racemization/Epimerization Impurities by
  - Synthesize dipeptide building blocks from Boc-, Z- or Fmoc-protected single amino acids
  - Isolate and purify resulting condensation segments
  - Segment condensation only with di- and tripeptides containing proline or pseudoproline at the C-terminus

Synthetic Scheme I



Synthetic Scheme II

Z-Ala-Pro-OH + **H-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu** (From Scheme I)

↓

Z-Ala-Pro-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu

↓

Boc-Asn-OH + **H-Ala-Pro-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu**

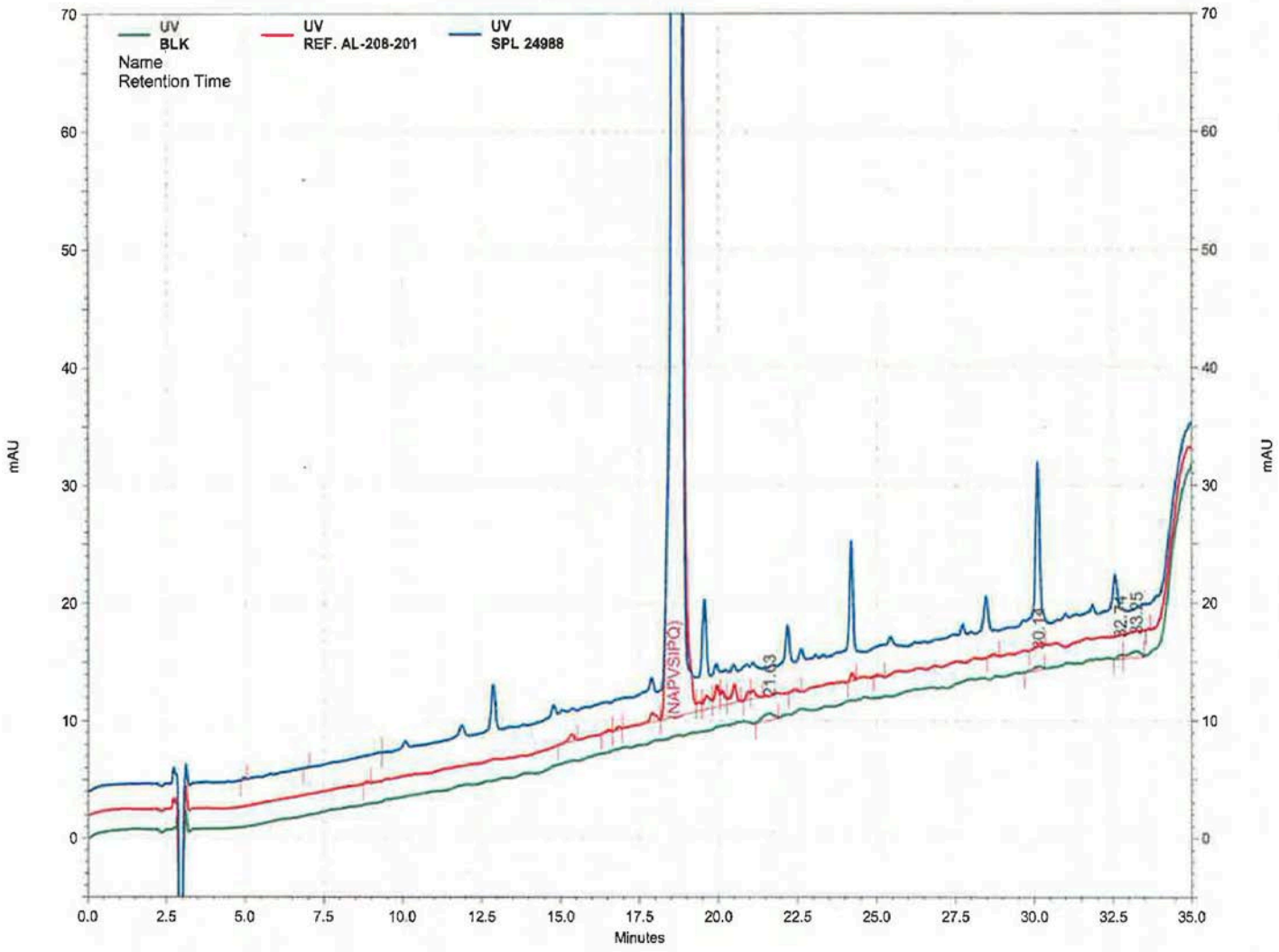
↓

Boc-Asn-Ala-Pro-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu

↓

H-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-OH

HPLC analysis: Purity profile



Solution-Phase Conclusions

- Yield better than anticipated
- Revised relative-cost: 0.01-0.02
- Process still needs optimization

Lessons Learned

- Important to integrate manufacturing plans into
  - Sales and marketing
    - Target population change from AD to PSP
    - 1.2 mil patients versus 70,000
  - Clinical Development
    - Dose change from 5 mg to 60 mg
    - Significant increase (12-fold)

Acknowledgements and Thanks

- Bachem (Torrance, CA USA)
- Corden Pharma Switzerland

- CMC advisors
  - William (Bill) Bennett
  - Randy Lane (Cato)

- Former colleagues at Allon Therapeutics
  - Daniela Nenciu
  - Catherine Campbell

Questions?

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