Microtubule (MT) Stabilizing Drugs For Abrogating and Preventing Alzheimer’s Disease And Related Tauopathies

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Disclosures:

May accrue revenue in the future as inventor on patents submitted by the University of Pennsylvania.

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No for profit relationships are related to the material discussed here on MT stabilizing agents as therapy for AD and related tauopathies.
Accumulating Data On Transmission Of Tau Pathology And Tau Mediated Neurodegeneration Indicate That Tau Is A Compelling Target For AD Drug Discovery.
However, Most Drugs In AD Clinical Trials Focus On Aβ

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial status</th>
<th>Mode of action</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bapineuzumab</td>
<td>Phase III, ongoing</td>
<td>Humanized monoclonal antibody to amyloid-β; targets the peptide’s N-terminus</td>
<td>Pfizer/Janssen</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Phase III, ongoing</td>
<td>Humanized monoclonal antibody to amyloid-β; targets the centre of the peptide</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IV Ig)</td>
<td>Phase III, ongoing</td>
<td>Isolated from pooled human blood, believed to have anti-amyloid-β and anti-inflammatory properties</td>
<td>Baxter</td>
</tr>
<tr>
<td>Latrepirdine (Dimebon)</td>
<td>Phase III, ongoing</td>
<td>Thought to stabilize mitochondria, thereby protecting neurons and preventing them from malfunctioning</td>
<td>Pfizer/Medivation</td>
</tr>
<tr>
<td>Scyllo-inositol / ELND 005</td>
<td>Phase II completed, Phase III in planning</td>
<td>Prevents or inhibits amyloid-β aggregation</td>
<td>Elan</td>
</tr>
<tr>
<td>Methylthioninium chloride (Rember)</td>
<td>Phase II completed, Phase III in planning</td>
<td>Unclear; thought to inhibit tau aggregation, but may be acting as an anti-amyloid-β disaggregator</td>
<td>TauRx Pharmaceuticals</td>
</tr>
<tr>
<td>CERE-110</td>
<td>Phase II, ongoing</td>
<td>Adenovirus-aided delivery of a nerve growth factor gene that helps protect neurons; delivered via surgery</td>
<td>Ceregene</td>
</tr>
<tr>
<td>PBT2</td>
<td>Phase IIb in planning</td>
<td>Metal chelator, small molecule that inhibits tau hyperphosphorylation and amyloid-β aggregation</td>
<td>Prana Biotechnology</td>
</tr>
<tr>
<td>Davenutide/AL-108</td>
<td>Phase II completed</td>
<td>Microtubule stabilizer, preventing tau hyperphosphorylation and tangle formation</td>
<td>Allon</td>
</tr>
<tr>
<td>BMS-708163</td>
<td>Phase II, ongoing</td>
<td>Inhibits formation of γ-secretase, thereby inhibiting formation of amyloid-β</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>PF-04494700/TTP488</td>
<td>Phase II, ongoing</td>
<td>RAGE inhibitor, modulates glial activity and reduces amyloid-β plaque formation</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Tideglusib/NP-12 (Nypta)</td>
<td>Phase II, ongoing</td>
<td>GSK-3 inhibitor, preventing tau hyperphosphorylation</td>
<td>Noscira</td>
</tr>
</tbody>
</table>

But Every AD Drug Targeting Aβ Has Failed

Alzheimer’s Drug Fails Its First Big Clinical Trial

By ANDREW POLLACK

The most closely watched experimental treatment for Alzheimer’s disease proved ineffective in its first large clinical trial, dealing a blow to the field, to a theory about the cause of the disease, and to the three companies behind the drug.

Pfizer, which is one of those companies, announced late Monday that the drug, bapineuzumab, did not improve either cognition or daily functioning of patients compared to a placebo in the Phase 3 trial.

The company did not provide detailed results, saying they would be presented at a medical meeting in September. But one of the principal investigators in the study, Dr. Reisa Sperling, said in an interview that there was no sign of any effect.

“There was absolutely no evidence at all of a clinical benefit of treatment on either of the primary measures, one cognitive and one functional,” said Dr. Sperling, director of the Center for Alzheimer Research and Treatment at Brigham and Women’s Hospital in Boston.
Drug Makers Push On With Alzheimer's Research After Setback
By Peter Loftus

This week's failure of an experimental drug for Alzheimer's disease underscores the limitations on scientific understanding of the brain disorder, but drug companies are plowing ahead in search of new treatments because of the high medical need and potential financial payoff.

Pfizer Inc. (PFE) and Johnson & Johnson (JNJ) announced Monday they would discontinue development of intravenously administered bapineuzumab after it failed to provide a benefit in a second late-stage clinical trial. It was the latest in a series of setbacks in the drug industry's attempt to find the first drug to halt or reverse Alzheimer's.

Another hypothesis for Alzheimer's is that so-called tau proteins in brain cells malfunction, leading to Alzheimer's symptoms. TauRx Pharmaceuticals Ltd. is running clinical trials of a drug that targets the tau proteins. Merck and other companies also are exploring compounds that target tau.

So while we await the outcome of the Aβ prevention trial in 2024, we need something for AD patient's now and it is time to try tau!
Because, if Aβ therapy eliminates plaques, it may not affect tau pathology or the clinical impairments of AD (Holmes et al., Lancet, 2008) with the following implications:

- Subtracting Aβ from disease brains with abundant tau, α-synuclein and Aβ pathologies in disorders such as
  - Lewy body variant of Alzheimer’s disease
  - Sporadic/Familial Alzheimer’s disease
  - Down’s syndrome

- Will convert these disorders into phenocopies of diseases characterized solely by abundant tau and/or α-synuclein lesions such as
  - Progressive supranuclear palsy (a pure tauopathy)
  - Dementia with Lewy bodies/Parkinson’s disease dementia
  - Guam Marianna Parkinson/Dementia Complex (a pure tauopathy)

Enter ADNI October 1st, 2004 To Help Target The Right Patients For AD Specific Therapy!

Funded by the National Institute on Aging


AND

The Industry Scientific Advisory Board (ISAB) and Site PIs, Study Coordinators, and 821 subjects enrolled in 58 sites in US and Canada
GOALS OF ADNI

• Optimize and standardize biomarkers for clinical trials
• Validate biomarkers as measures of change
• Validate biomarkers as diagnostics or predictors
• Establish world-wide network for clinical AD studies and treatment trials
ADNI: Naturalistic study of AD progression

All data in public database at ADNI
No embargo of data, 3,000,000 data uploads since 2004

• Goals of ADNI-2 are to continue to follow >400 controls and MCI from ADNI-1 for 5 more years and enroll:
  – 100 additional EMCI (supplements 200 from GO)
  – 150 new controls, LMCI, and AD
• MRI at 3,6, months and annually
• F18 amyloid (AV-45)/FDG baseline and Yr 2
• LP on 100% of subjects at enrollment
• Genetics
Although Biomarker Studies Show Aβ Biomarkers Become Abnormal Before Tau Biomarkers, Direct Examination Of The Brain Shows That Tau Pathology Appears Before Aβ Deposition
And Pathological Tau Amyloid Is Linked To Mechanisms Of Disease In Pure And Mixed Neurodegenerative Tauopathies

Pure Tauopathies
• Amyotrophic lateral sclerosis/parkinsonism-dementia complex
• Argyophilic grain disease
• Corticobasal degeneration
• Pick’s disease
• Progressive supranuclear palsy
• Subacute sclerosing panencephalitis

Mixed Tauopathies
• Tangle-predominant Alzheimer’s disease
• Alzheimer’s disease
• Dementia pugilistica
• Down syndrome
• Multiple system atrophy
• NBIA-1 (formerly Hallervorden-Spatz disease)
• Nieman-Pick disease type C
• Prion diseases
Features Of Normal Tau And Its Functions

- An abundant low Mr MT-associated protein predominantly in axons
- Promotes MT polymerization, binds to MTs and stabilizes MTs
- Phosphorylated at multiple serine and threonine residues which negatively regulates the binding of tau to MTs


Hyperphosphorylated tau accumulates as neurofibrillary tangles (NFTs) in AD and FTLD-Tau diseases.

Hyperphosphorylated tau fails to bind to MTs and NFTs sequester tau in tauopathies.

The loss of normal tau functions leads to MT instability which impairs axonal transport.

Accumulations of pathological tau in cell bodies and processes may disrupt normal neuronal functions and compromise the viability of affected neurons.

Normal Tau Stabilizes MTs To Maintain Neuronal Transport

While Tau Pathology Can Disrupt Neuronal Transport With Catastrophic Consequences Equivalent To A Train Wreck
Therapeutic Strategies to Reduce Tauopathy

- **HSP90 inhibitors** might increase proteasome-mediated clearance of misfolded and hyperphosphorylated tau.

- **Tau kinases or b-N-acetylglucosaminidase inhibitors** might inhibit tau hyperphosphorylation.

- **Tau assembly inhibitors** might decrease tau assembly and increase tau solubility.

- **Autophagy enhancers** might increase removal of tau aggregates.

The number of clinical trials of tau therapies for AD and related tauopathies is increasing

<table>
<thead>
<tr>
<th>Table 4. Tau-Targeted Therapies in Clinical Trialsª</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
</tr>
<tr>
<td>Tau phosphorylation by GSK3β</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Microtubule stabilization/tau phosphorylation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Tau aggregation</td>
</tr>
</tbody>
</table>

CBD, corticobasal degeneration; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PSP, progressive supranuclear palsy; p-tau, phosphorylated tau; RCT, randomized placebo-controlled trial.


ªªMay also reduce soluble tau levels.
In Addition To AD And Related Tauopathies, Several Other Neurodegenerative Diseases Are Linked Mechanistically To Impaired Axonal Transport

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutant Gene/Disease Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Spastic Paraplegia</td>
<td>Kinesin Heavy Chain (Kif 5a)</td>
</tr>
<tr>
<td>Familial Motor Neuron Disease</td>
<td>Dynactin p150 Subunit</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth Disease Type 2A</td>
<td>Kinesin Kif 1B Beta Subunit</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>Huntingtin</td>
</tr>
<tr>
<td>Familial Amyotrophic Lateral Sclerosis</td>
<td>Superoxide Dismutase 1</td>
</tr>
<tr>
<td>Parkinson’s Disease &amp; Synucleinopathies</td>
<td>Alpha-synuclein</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>Aβ, Tau, Presenilins</td>
</tr>
<tr>
<td>Pick’s Disease &amp; Related Tauopathies</td>
<td>Tau</td>
</tr>
</tbody>
</table>

Trojanowski JQ, Smith AB, Huryn D, Lee VM-Y. Exp Opin Pharm, 2005
AD PHFtau does not bind to and stabilize MTs, but these functions are critical for maintaining the network of MTs required for intraneuronal transport. Thus, the loss of function by PHFtau and sequestration of tau into NFTs could have deleterious consequences by depolymerizing MTs thereby disrupting axonal transport and compromising the function and viability of affected neurons in AD”. Hypothesis: MT stabilizing drugs have therapeutic benefits in mouse models of tauopathies.
A) The very acidic C-terminus of tubulin monomers is exposed on the outer surface (black projections). Tau is in blue. T = Taxol in beta-tubulin, * = GTP in beta-tubulin ‘cap’. B) Arrangement of domains of human 4-repeat tau, showing the distribution of basic and acidic residues. The acidic N-terminus of tau forms a projection (A) repelled by the negatively charged tubulin surface. The proline-rich region, with a net positive charge, is thought to interact with the MT surface. The repeat region has a net positive charge and to beta-tubulin partially overlapping with the Taxol binding site. (Amos, L. Org. Biomol. Chem., 2:2153-2160, 2004)
Paclitaxel Improves Motor Neuron Functions in Tau Tg Mice That Model Guam ALS Tauopathy

Microtubule-binding drugs offset tau sequestration by stabilizing microtubules and reversing fast axonal transport deficits in a tauopathy model


*Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, and Institute on Aging, and Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104; and Angiotech Pharmaceuticals, Inc., Vancouver, BC, Canada V6A 1B6

- 3 months i.p. injection of paclitaxel improves motor neuron structure and function including fast axonal transport and motor weakness in tau Tg mice that model Guam ALS.
Methods To Measure Rates Of Axonal Transport In Vivo And In Vitro

A. Ventral Horn Motor Neuron

- Inject radiolabeled amino-acids
- Dissect axon, cut into segments, resolve pulse-labeled proteins on gel, identify newly synthesized proteins

B. Cultured Neurons

- Axonal transport of GFP-labeled polymers
- Visualize GFP labeled proteins transported by live-cell imaging

35S-labeled methionine was microinjected into the L5 ventral horn using a stereotaxic apparatus (n = 3).
- Groups of animals were sacrificed 3 hours after microinjection for the analysis of fast axonal transport. The L5 ventral roots were removed and cut into consecutive 5 segments of 2 mm length from proximal to distal, following SDS PAGE processing.
FAT Is Improved In Ventral Roots Of Taxol Treated Tau T44 Tg Mice
(Zhang et al., PNAS, 102:227-231, 2005)

B: Ratio of proteins amount In each segment = Treated / Sham

C: Percentage of TP Proteins in each segments = (protein in 1 segment / total proteins in 5 segments) x 100/100
Summary

These data reveal a dose dependant improvement of FAT, MT numbers and motor impairments in PrpT44 Tau Tg mice following taxol treatment indicating that taxol ameliorates neurodegenerative tauopathies in Tg mouse models.

However, the blood brain barrier penetration of taxol could not be enhanced despite many side chain modifications by chemistry (Ballatore C, Zhang B, Trojanowski JQ, Lee VM-Y, Smith III AB. In situ blood-brain barrier permeability of a C-10 Paclitaxel carbamate. Bioorg Med Chem Lett, 18:6119-6121, 2008).

Molecular Structure Of Taxol
# MICROTUBULE STABILIZING AGENTS FROM NATURAL PRODUCTS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (Taxol)</td>
<td>Pacific Yew Bark</td>
</tr>
<tr>
<td>Dictostatins</td>
<td>Marine Sponges</td>
</tr>
<tr>
<td>Discodermolides</td>
<td>Marine Sponges</td>
</tr>
<tr>
<td>Epothilones A &amp; B</td>
<td>Myxobacteria</td>
</tr>
<tr>
<td>Sarcodictyins A &amp; B</td>
<td>Soft Ocean Coral</td>
</tr>
<tr>
<td>Taccalonolides</td>
<td>Tiger Whisker Plant</td>
</tr>
<tr>
<td>Tubercidin</td>
<td>Marine Sponges</td>
</tr>
<tr>
<td>Laulimalides</td>
<td>Marine Sponges</td>
</tr>
<tr>
<td>Eleuthererobin</td>
<td>Soft Ocean Coral</td>
</tr>
</tbody>
</table>

Trojanowski JQ, Smith AB, Huryn D, Lee VM-Y. Exp Opin Pharm, 2005
Since Taxol is poorly brain penetrant, Epothilone D was selected for study because of its more favorable pharmacokinetics/pharmacodynamics (PK/PD).

Naturally Occurring Epothilones (A), Selected Synthetic Epothilones (B).

**A**

- **R = H, X = H:** epothilone A (11)
- **R = CH₃, X = H:** epothilone B (12)
- **R = H, X = OH:** epothilone E (13)
- **R = CH₃, X = OH:** epothilone F (14)

**B**

- **R = CF₃, X = H:** fludelone (19)
- **R = CH₃, X = H:** (E)-9,10-dehydro-12,13-deoxy-EpoB (20)
- **R = CH₃, X = OH:** (E)-9,10-dehydro-12,13-deoxy-EpoF (21)

- **26-F₃-12,13-deoxyepothilone B (22)**
- **R = allyl, Sagopilone (24)** (ZK-EPO)

-Ixabepilone (23) (Ixempra®)
EpoD Improves CNS Neuron Function in Young PS19 Mice In A Prevention Trial

Epothilone D Improves Microtubule Density, Axonal Integrity, and Cognition in a Transgenic Mouse Model of Tauopathy

Kurt R. Brunden,^1 Bin Zhang,^1* Jenna Carroll,^1 Yueming Yao,^1 Justin S. Potuzak,^2 Anne-Marie L. Hogan,^2 Michiyo Iba,^1 Michael J. James,^1 Sharon X. Xie,^1,2 Carlo Ballatore,^1,2 Amos B. Smith III,^2 Virginia M.-Y. Lee,^1 and John Q. Trojanowski^1,3

Treatment from 3 to 6 months of age
Legend: Immunohistochemical (IHC) of total tau and phospho-tau in ON and retina from 6-mo old male WT and PS19 mice. IHC was with antibodies to total tau (17025) and phospho-tau (AT8). Low power images (left panel; bar = 500 μm) show eyes from WT and PS19 mice with the retina below in an inverted U through a plane in the eye that captures the attached ON in longitudinal section above. High power Images of the retina (right panel; bar = 100 μm) show phospho-tau deposits in retinal ganglion cells (GCL=ganglion cell layer; IPL=inner plexiform layer).
The Microtubule-Stabilizing Agent, Epothilone D, Reduces Axonal Dysfunction, Neurotoxicity, Cognitive Deficits, and Alzheimer-Like Pathology in an Interventional Study with Aged Tau Transgenic Mice

Bin Zhang,1 Jenna Carroll,1 John Q. Trojanowski,1 Yuemang Yao,1 Michiyo Iba,1 Justin S. Potuzak,2 Anne-Marie L. Hogan,2 Sharon X. Xie,3 Carlo Ballatore,1,2 Amos B. Smith III,2 Virginia M.-Y. Lee,1 and Kurt R. Brunden1

1Center for Neurodegenerative Disease Research, Institute on Aging and Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

The Journal of Neuroscience, March 14, 2012 • 32(11):3601–3611 • 3601
EpoD Efficacy Testing in Old PS19 Mice
An Intervention Study In 9 to 12-Month Old Diseased Mice

- **9M PS-19 (males)**
  - n=13
  - Vehicle Control (DMSO)
- **9M PS-19 (males)**
  - n=13
  - 0.3 mg/kg CNDR-66 (EpoD)
- **9M PS-19 (males)**
  - n=13
  - 1 mg/kg CNDR-66 (EpoD)
- **9M Non-Tg (males)**
  - n=13
  - Vehicle Control (DMSO)

**Efficacy Testing**
1. Fast Axonal Transport
2. ON Dystrophic Axon Analysis
3. MT Density Analysis
4. CNS IHC and Biochem
5. Behavioral Cognitive Testing

**Safety Testing**
1. Behavioral Observations
2. Motor Function
3. Body and Organ Weights
4. Examine of Peripheral Organs
5. Complete Blood Counts
6. High Dose of EpoD Safety Test in additional 15 WT mice (5 or 10mg/kg)
Dystrophic Axon Numbers in 12-Month Old PS19 Mice

One way ANOVA non-parametric statistic test
MT Numbers in 12-Month Old PS19 Mice

One way ANOVA non-parametric statistic test
Optic Nerve Fast Axonal Transport (FAT) in EpoD Treated 12-Month Old PS19 Mice

EXP design
- Treatment for 3 months, n=3/group
  - PS19 Vehicle
  - PS19 EpoD 0.3mg/kg
  - PS19 EpoD 1mg/kg
  - WT Vehicle

- ON FAT
  - Intravitreal injection of $^{35}$S-Methionie in both eyes, 0.5mci/eye

- 3 hours after injection
  - Dissect mouse ON and cut into 7 consecutive 1 mm segments from individual mouse (without pooling ON together)

- CPM counts for $^{35}$S in each ON segment.

- SDS gels for individual mouse optic nerve segments.
$^{35}$S-CPM Counts:
Mixed Model Parametric Test

ON Segments
Distance to Retina (mm)
Barnes Maze Test for Spatial Memory in 12-Month Old EpoD Treated PS19 Mice

The part of memory responsible for recording information about the environment and its spatial orientation.
The Lowest Levels Of Tau Tangle Pathology Are Seen In EpoD- Treated Mice At 12-Months Of Age

A. AT8

B. MC1

C.

D. *

E. *
Correlation of Insoluble Tau and MC-1 and AT8 IHC Scores in EpoD- or Vehicle-Treated Mice at 12-Months of Age
Synaptophysin and NFL IHC in Hippocampus of EpoD- or Vehicle-Treated Mice at 12-Months of Age
NeuN IHC in Hippocampus of EpoD- or Vehicle-Treated Mice at 12-Months of Age
Safety Analysis for EpoD-Treated PS19 Mice at 12-Months of Age

No Significant Difference in Body and Organ Weights between Vehicle- and EpoD-Treated Mice at 12-months of age.
Summary

EpoD

- Attenuates dystrophic axons in mouse model of tauopathy at 12 months
- Recovers MT density in PS19 Tau Tg mice
- Improves FAT in PS19 Tau Tg mice
- Reduces tau pathology in PS19 Mice at 12m of Age
- Improves working and spatial learning and memory in aged tau Tg mice
- No detectable toxicities observed in the Tau or WT mice treated with EpoD

EpoD might be a therapeutic drug candidate for the treatment of tauopathies such as AD or FTLD-Tau
Hyperdynamic Microtubules, Cognitive Deficits, and Pathology Are Improved in Tau Transgenic Mice with Low Doses of the Microtubule-Stabilizing Agent BMS-241027


1Neuroscience Drug Discovery, Bristol-Myers Squibb, Wallingford, Connecticut 06492, 2KineMed, Inc., Emeryville, California 94608, 3Mayo Clinic College of Medicine, Jacksonville, Florida 32224, and 4Oncology Drug Discovery, Bristol-Myers Squibb, Princeton, New Jersey 08543

Tau is a microtubule (MT)-stabilizing protein that is altered in Alzheimer’s disease (AD) and other tauopathies. It is hypothesized that the hyperphosphorylated, conformationally altered, and multimeric forms of tau lead to a disruption of MT stability; however, direct evidence is lacking in vivo. In this study, an in vivo stable isotope-mass spectrometric technique was used to measure the turnover, or dynamicity, of MTs in brains of living animals. We demonstrated an age-dependent increase in MT dynamics in two different tau transgenic mouse models, 3xTg and rTg4510. MT hyperdynamicity was dependent on tau expression, since a reduction of transgene expression with doxycycline reversed the MT changes. Treatment of rTg4510 mice with the epothilone, BMS-241027, also restored MT dynamics to baseline levels. In addition, MT stabilization with BMS-241027 had beneficial effects on Morris water maze deficits, tau pathology, and neurodegeneration. Interestingly, pathological and functional benefits of BMS-241027 were observed at doses that only partially reversed MT hyperdynamicity. Together, these data suggest that tau-mediated loss of MT stability may contribute to disease progression and that very low doses of BMS-241027 may be useful in the treatment of AD and other tauopathies.

The Journal of Neuroscience, May 23, 2012 • 32(21):7137–7145 • 7137

Phase I clinical trials of EpoD have been launched by BMS (http://clinicaltrials.gov/ct2/show/NCT01492374).
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EpoD Trials

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CNDR Drug Discovery (Biology)
Edward Hyde, Ph. D, Kelvin Luk, Ph. D, Alex Crowe, MS, Magdalena Krysiak, MS

CNDR Drug Discovery (Chemistry)
Amos Smith Ph. D, Carlo Ballatore Ph. D
Ann-Marie Hogan Ph. D, Francesco Piscitelli Ph. D, Justin Potuzak Ph. D.

Virginia M.-Y. Lee, MBA, PhD