Treatments for Alzheimer's Disease: Challenges in Early Clinical Research

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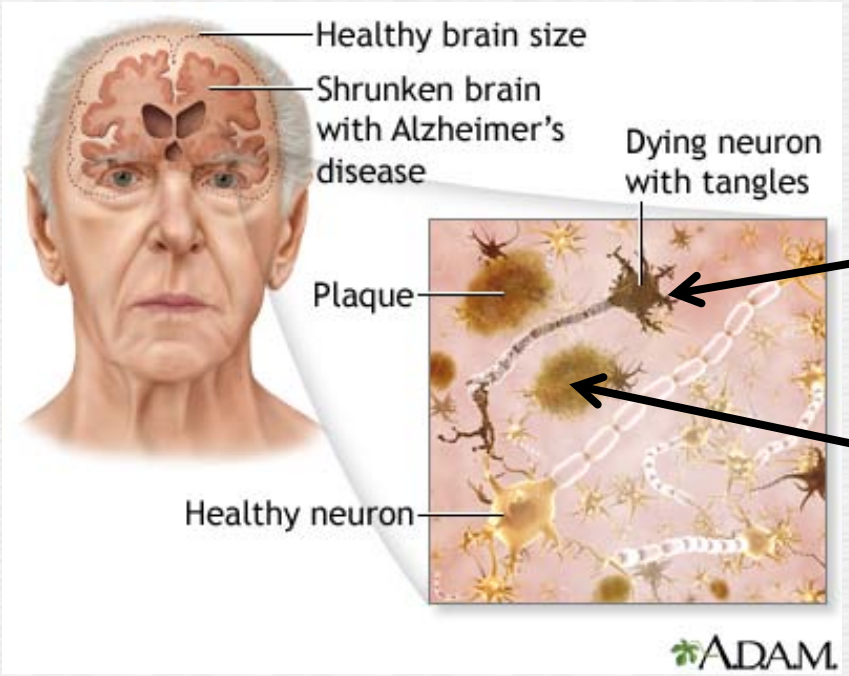
Questions

- What is the pathogenesis of Alzheimer's Disease?
- What are the targets for treatment?
- If the disease is so apparent, why is it so difficult to study the effectiveness of treatments?
- What does Clinical Proof-of-Concept and Clinical Proof-of-Mechanism mean for this disease?
- What are some considerations for planning studies in an early clinical research plan for a treatment of Alzheimer's disease?

Pathogenesis of Alzheimer's Disease



Phosphorylation

Tau monomers

Neurofibrilatory tangles (NFTs)

MTBR

healthy

microtubules

Aβ

Aβ

Amyloid-β_{1-40} and $A\beta_{1-42}$ peptide aggregates

α–secretase

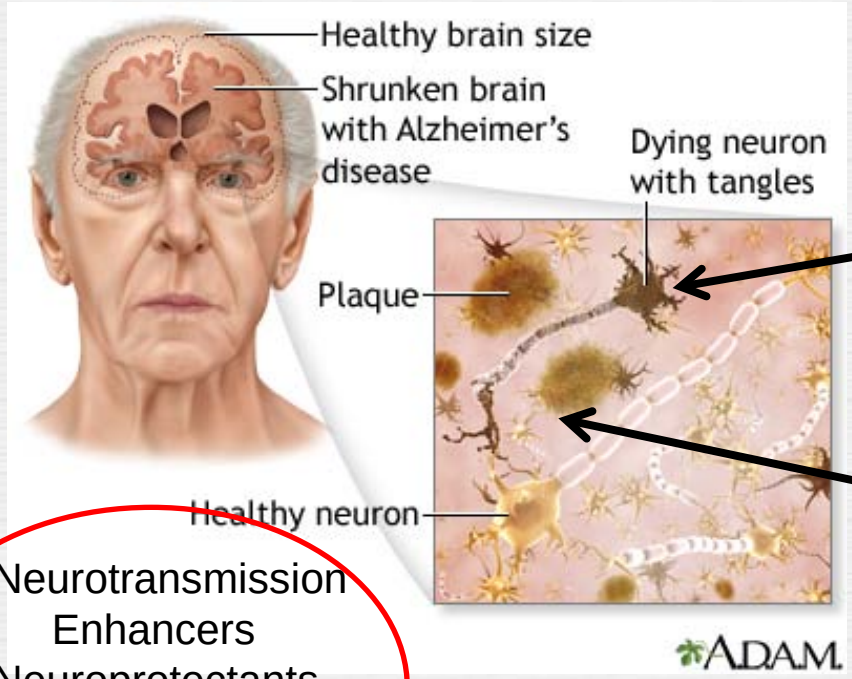
Amyloid protein

β–secretase (BACE1)

Cell Membrane

γ–secretase

Pathogenesis of Alzheimer's Disease



Specific Kinase Inhibitors

Phosphorylation

Tau monomers

Neurofibrilatory tangles (NFTs)

MTBR

healthy microtubules

Aβ clearing antibodies

Aβ

Aβ

Neurotransmission Enhancers
Neuroprotectants
Neurotropic Agents
Cellular Energy Enhancers

Inhibitors of amyloid peptide aggregation

α–secretase

Amyloid protein

β–secretase

Cell Membrane

γ–secretase Inhibitors/antibodies

Anti-inflammatory Agents

BACE1 Inhibitors

γ–secretase

Current Treatments

- Approved treatments enhance neurotransmission in healthy neurons
  - Cholinesterase inhibitors: donepezil (Aricept), rivastigmine (Excelon), galantamine (Razadyne), tacrine (Cognex)
    - enhance cholinergic neuronal transmission
  - NMDA agonist: memantine (Namenda)
    - Regulates activity of glutamate – stimulate dopinergic pathways
- Approved treatments only result in a temporary effect (e.g. 6 months) and then neurodegeneration resumes

Lots of Targets But So Far Nothing Works

- 70 to 80 drugs candidates/therapies in clinical trials
- Studies with Aβ clearing antibody, γ-secretase inhibitor showed proof-of-mechanism but no impact on progression of neurodegeneration
- Long-term studies with Vitamin E, cholesterol lowering agents, anti-diabetic drugs and antihistamines showed no reproducible effects.
- Exercise and diet do appear to affect time of onset of disease and rates of neurodegeneration
  - Maintaining good CNS oxygenation and energy metabolism is an important element in maintaining brain health

Animal Models For Alzheimer's Disease

Types of Animal Models

- Spontaneous models in animal species – senescence accelerated mice,
- Surgical or chemical denervation in rodents
- Direct injection of Aβ peptides, CNS pro-inflammatory agents
- Transgenic animals – mice, flies, fish, worms – uncover pathogenesis

Several models show histological evidence of pathogenesis and physiological loss of learning functions in trained rodents

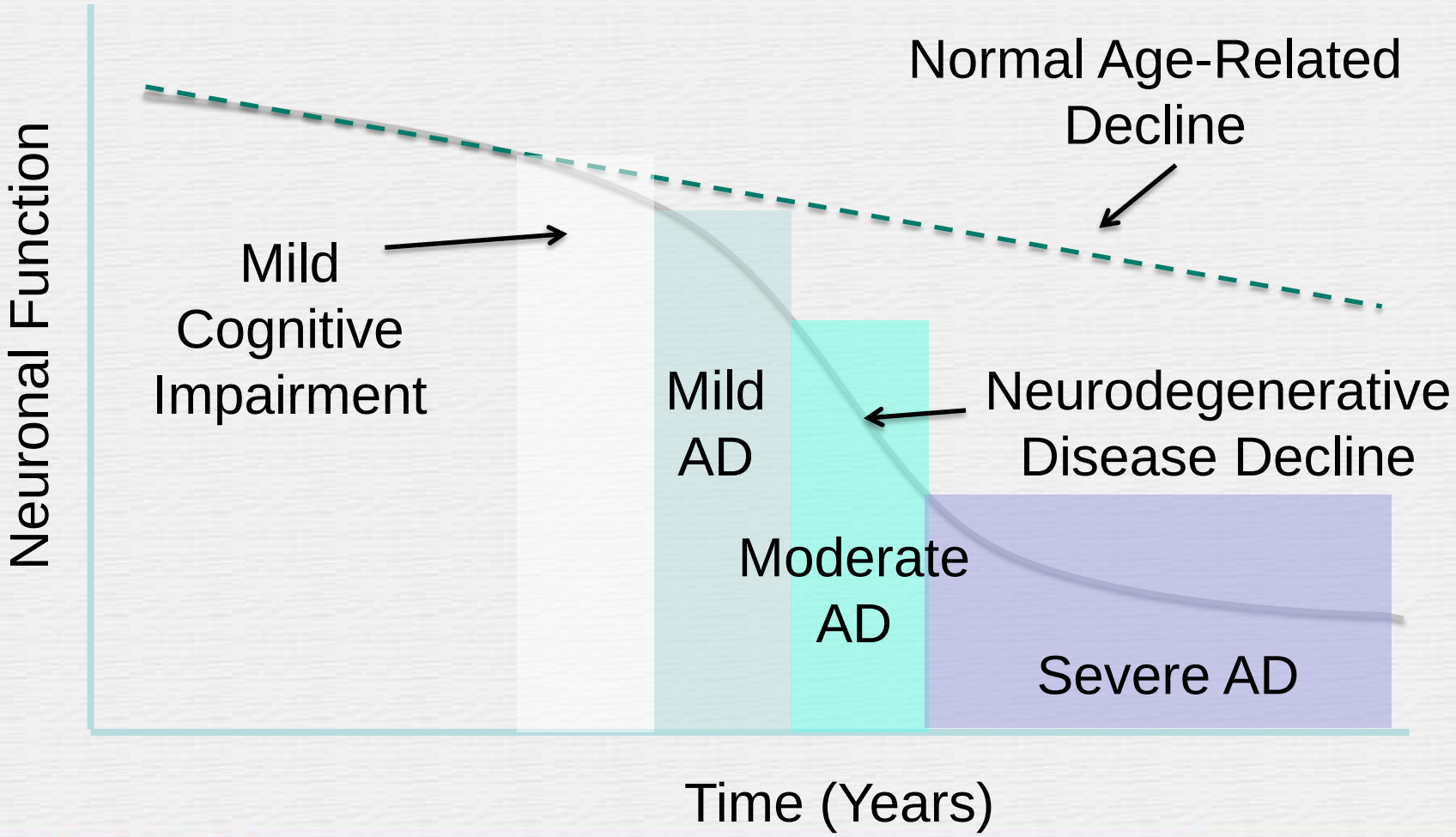
Challenge # 1: Many Animal Models – No Translational Validity

No model truly replicates all the pathological elements of human AD

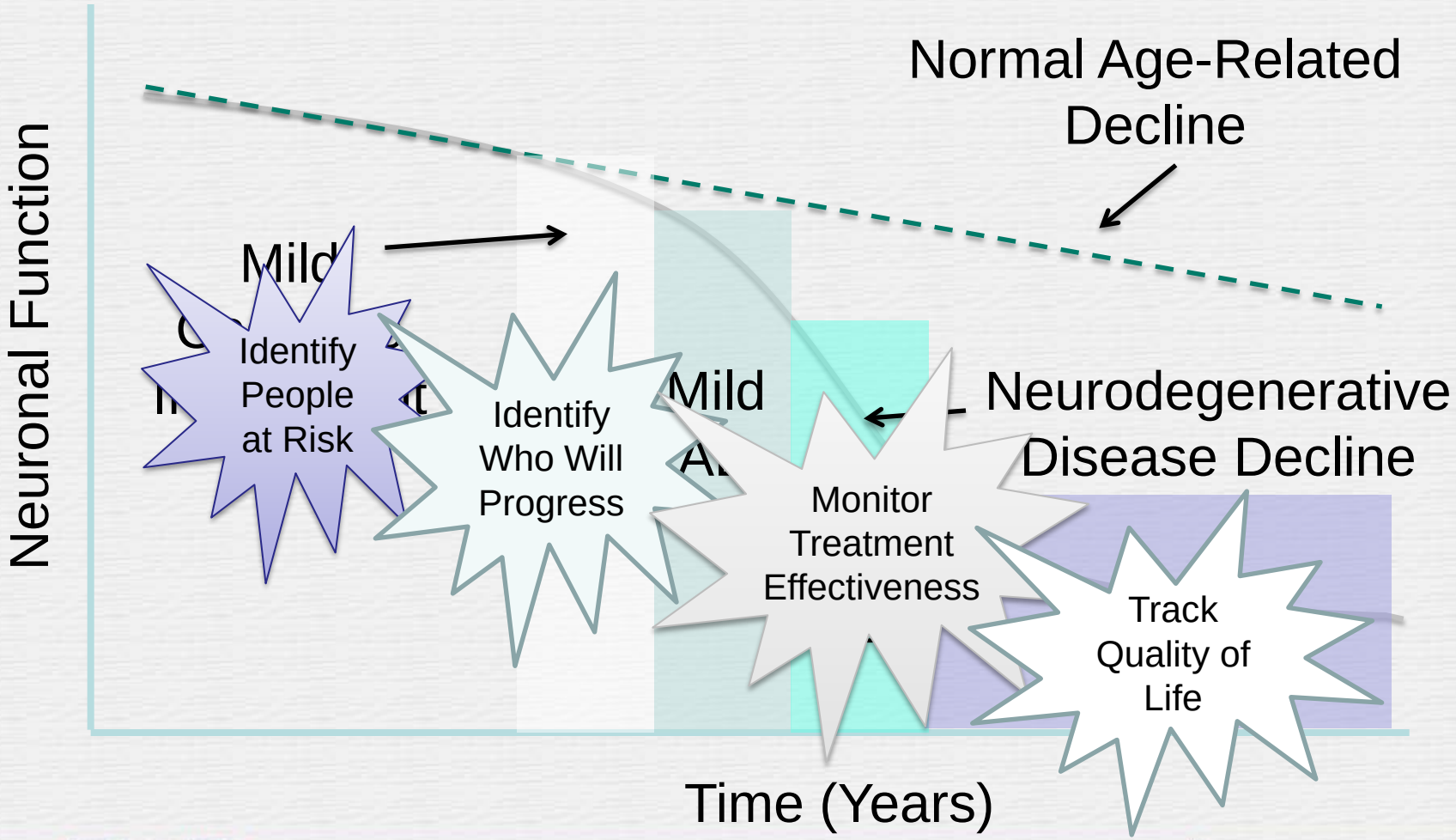
Asking too much of animal models that don't have the higher cortical functions of humans?

With no treatment that can arrest the disease progression, there is no positive treatment standard to compare models against – therefore no translational validity possible.

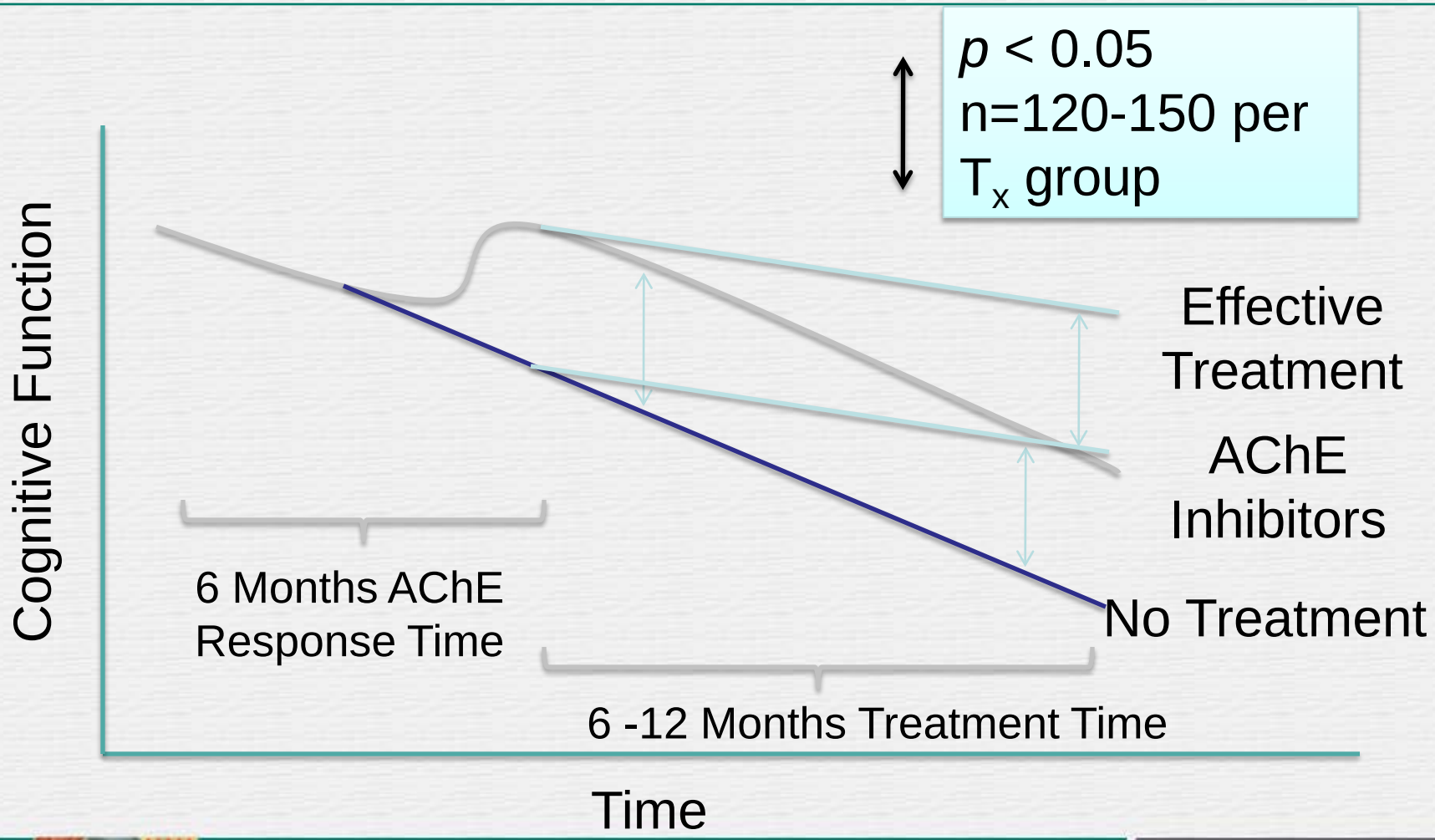
Phases of Alzheimer's Disease



Challenge # 2: Who to Target for Therapy?



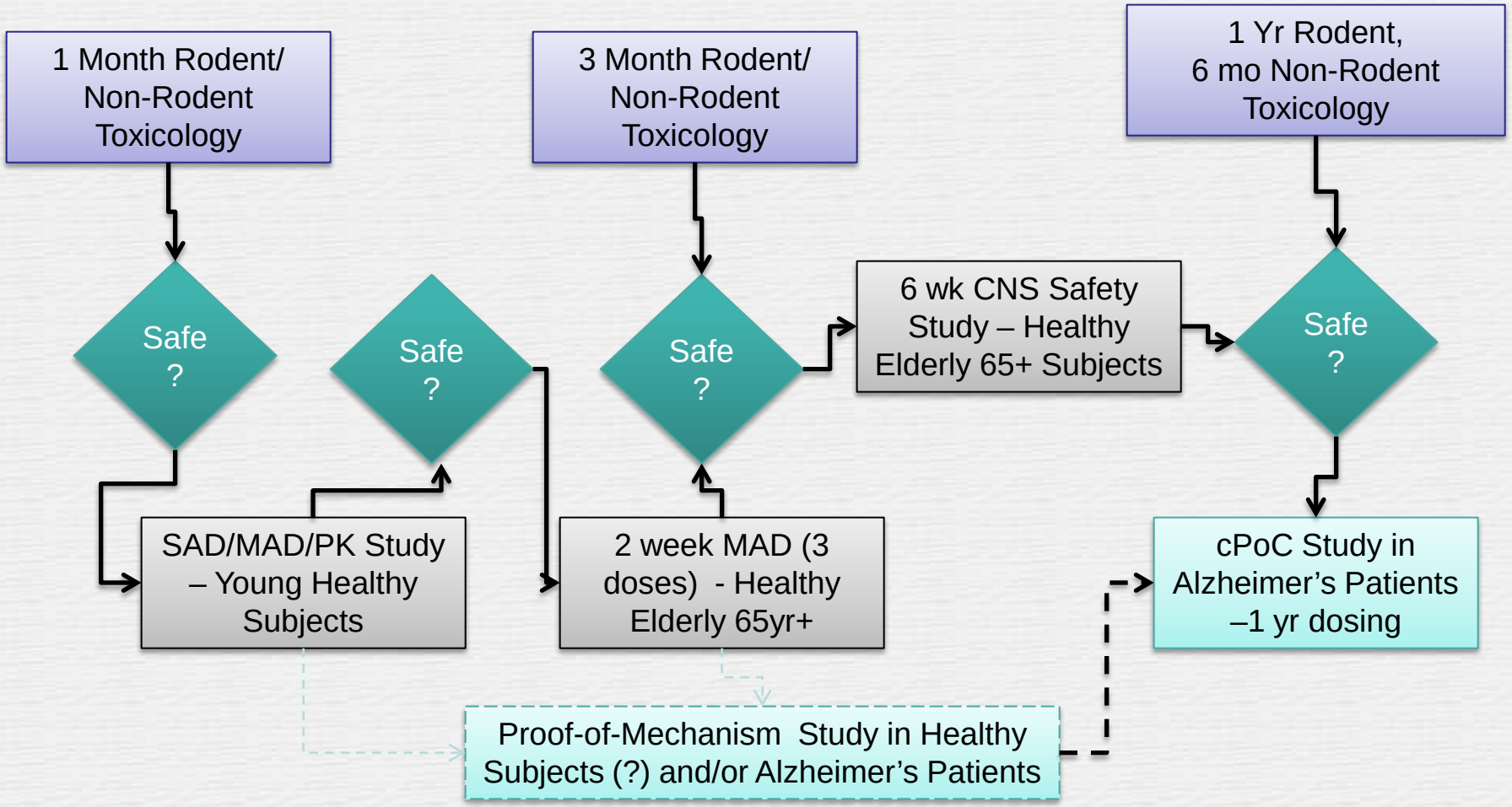
Clinical Study Design Elements



Challenge # 3: Clinical Proof-of-Concept Studies are Long and Large

- Most cPoC require demonstration of change in rate of loss of cognitive function as measured by semi-subjective testing models (e.g. ADAScog, CIBC+)
- Mild/moderate AD patients naïve to treatment are rare in US, Canada, Western Europe – add-on treatment is practical
- Control of variability in response measures is important
  - Standardized testing of evaluators
  - Limiting number of clinical sites
- Need 120-150 patients completing 6 mo – 1 yr of treatment per treatment arm – limits number of doses that are practical to test – dose selection is critical

Challenge # 4: Need to Move to Long Term Dosing in Patient Quickly



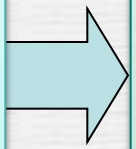
6 Week Elderly Study Design

- Primary endpoints: safety/tolerability Secondary: PK
- 24 male and female subjects (65-82 years)
- Randomized, double blind, placebo controlled, 6 weeks treatment, one dose daily before breakfast
- 9 low dose, 9 high dose, 6 placebo controls
- Confined to site Day 1-7, 13-15, 20-22, 27-29, 34-36 and 41-43.
- PK Day 1, 21 and 42.
- CDR cognitive testing protocol done at: screening (practice), Day 1 (0, 2, 6 h), Day 21 (0, 2, 6 h) and Day 42 (0, 2, 6 h).

Cognitive Drug Research
Basic Cognitive Assessment Package

Tests (45 minutes to conduct)

- Immediate word recall
- Picture task
- Simple reaction time
- Digit vigilance
- Choice reaction time
- Spatial working memory
- Numeric working memory
- Delayed word recall
- Word recognition
- Picture recognition
- Bond-Lader visual analogue scale of mood and alertness



Composite Outcomes

- Power of attention
- Continuity of attention
- Quality of working memory
- Quality of episodic secondary memory
- Speed of memory

Challenge # 5: Proof-of-Mechanism: Deployment of Novel Biomarkers

- Most reliable biomarkers of Aβ and tau protein pathways require CSF sampling
  - Measurements of $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, sAPPβ, tau protein fragments
- PET Ab Imaging agents
  - Florbetapir (Lilly) – pre-approval
    - Concerns over consistency of reading images
  - Flutametamol (GE Healthcare) – Phase III
    - Pittsburgh Compound b - PiB
  - Florbetaben (Bayer) – Phase III
- Radioactive amino acid IV infusions with continuous sampling from CSF from indwelling catheter
  - Follow Amyloidβ pathways – inhibition of BACE1 or γ-secretase

Challenge # 6: Proving Drug Gets to the Brain

- Drug must penetrate blood brain barrier from systemic circulation
  - Intranasal delivery – higher concentrations through olfactory capillaries
- Imaging – if can label drug molecule
- CSF sampled via lumbar spinal tapping
  - Sample volume small – need very sensitive methods to measure drug (HPLC tied to LC/MS/MS)
  - Accelerator Mass Spectrometry using small doses of radiolabeled drug (<500 nCi requires no animal tissue distribution and dosimetry in Nebraska)

Challenge # 7: Predicting Drug-Drug Interactions

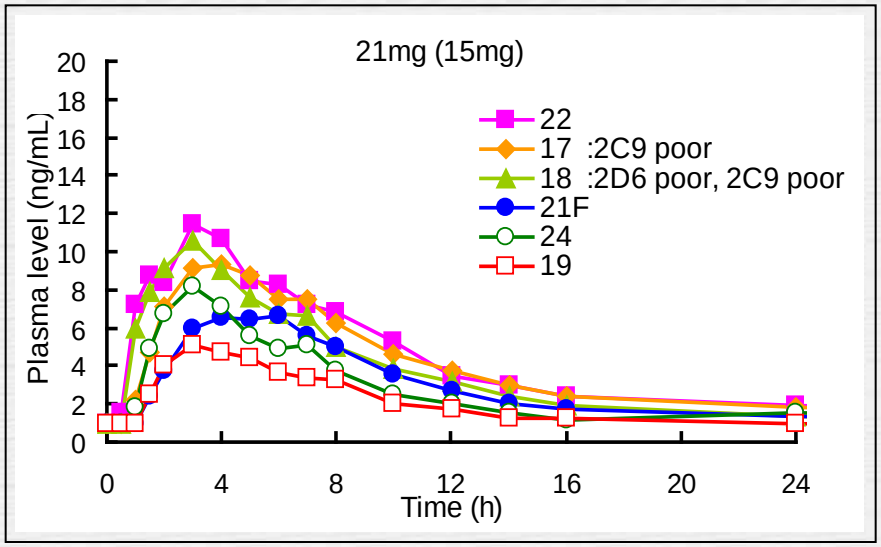
- Rare in North America or Western Europe to find healthy elderly subjects who are not on any medications or nutraceutical preparations
- What medicines to allow on study?

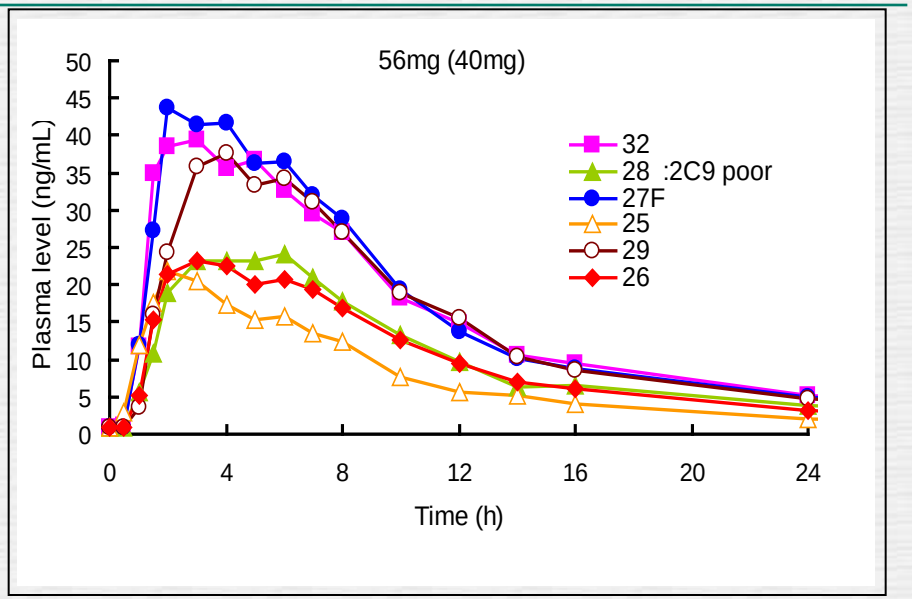
  - those that are unlikly to compete with each other for receptors or clearance enzymes.
- Preclinical studies
  - Which human enzymes or transporters are involved in new drug clearance?
  - Does new drug inhibit or induce activity of human metabolic enzymes or transporters involved in drug clearance?

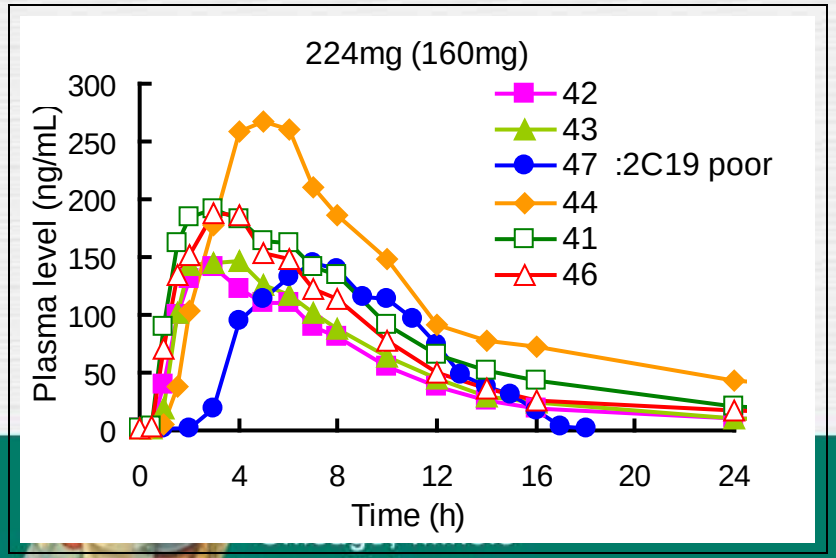
Leveraging Genetic Polymorphisms

- People with genetic polymorphisms of certain drug metabolizing enzymes are most often “slow metabolizers” of substrates (drugs) utilizing that enzyme
  - Similar to having another drug inhibit that enzyme
  - Do people with “poor metabolizer” genotypes clear the new drug more slowly than others?

Enriching Phase I Studies with CYP Genotyping







6 PK Studies in Young and Elderly Volunteers = 118 Subjects
Received Drug:
poor metabolizer genotypes:
9 CYP2D6
16 CYP2C9
5 CYP2C19

Where Are We Going?

- Incidence (and cost) of Alzheimer's Disease and other dementias is increasing as the population ages
- Awaiting the first truly effective treatment of the disease, not just the symptoms
  - Will help establish translational validity of animal models
- Detecting people at risk before the appearance of symptoms is best hope for effective treatments
  - Imaging agents of Aβ plaques?
  - Reliable diagnosis of mild cognitive impairment (MCI)?

Additional Final Thoughts

- Successful treatment will likely involve a combination of therapies working by different mechanisms
  - How do you do the clinical research to show additive/synergistic effects in a timely way?
- Routine vigorous exercise and preventing Type 2 diabetes are currently best way to slow onset of disease