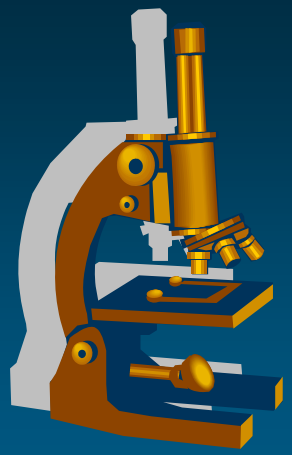

Translational Science to improve the Treatment of AD

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Translational Science

- Scientists are increasingly aware that this bench-to-bedside approach to translational research is really a two-way street. Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations.

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Why do we need a focus on translation?

- Although many kinds of basic research are important, not all are important to human disease
- Interspecies differences mean that experiments in animals may not predict results in humans

Examples of translational issues in AD treatment research

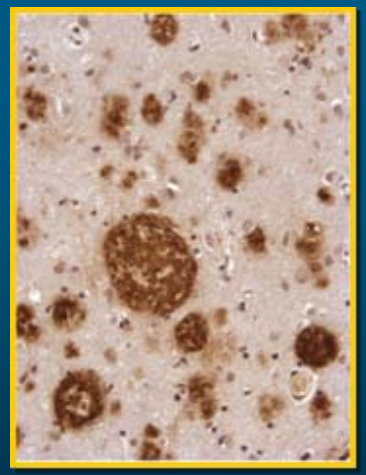
- Isoform specific binding of Apo E to amyloid
- Human AD mutations do not cause AD in mice
- Small molecules that reverse amyloid accumulation in mice do not improve human AD

Examples of translational issues in AD treatment research

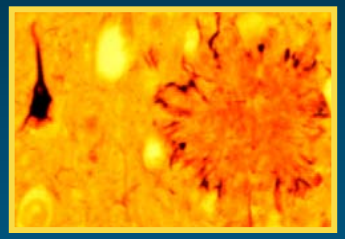
- Health factors that reduce risk of AD in humans impact some transgenics
- AD onset in humans may begin focally
- Drugs that reduce risk of AD in humans impact some transgenics

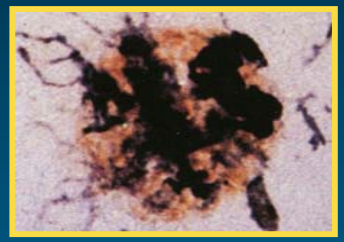
What causes AD?

- Plaques and tangles?
- Loss of reserve?
- Biochemistry of aging?
- "Weak" genetic background?
- Chronic inflammation?
- All of the above?



AD Begins Long Before the Onset of Dementia: Evidence from the temporal course of neuropathological changes in Down's





Age

10
20
30
40
50
60
70

Amyloid Deposition

Microglial Changes

Neurofibrillary Tangles

Neuronal Loss/ Neurochemical Changes

Dementia

No cognitive impairment **Mild cognitive impairment** **Dementia**

(based on DMA Mann, 1991 Courtesy Steve Salloway MD Dementia Congress)

Is the only effective therapy prevention?

- Experiments with transgenic mice suggest that once extracellular amyloid deposits, certain aspects are irreversible
- Task Force on Early (Predementia) AD Trials suggesting approaches to early drug development

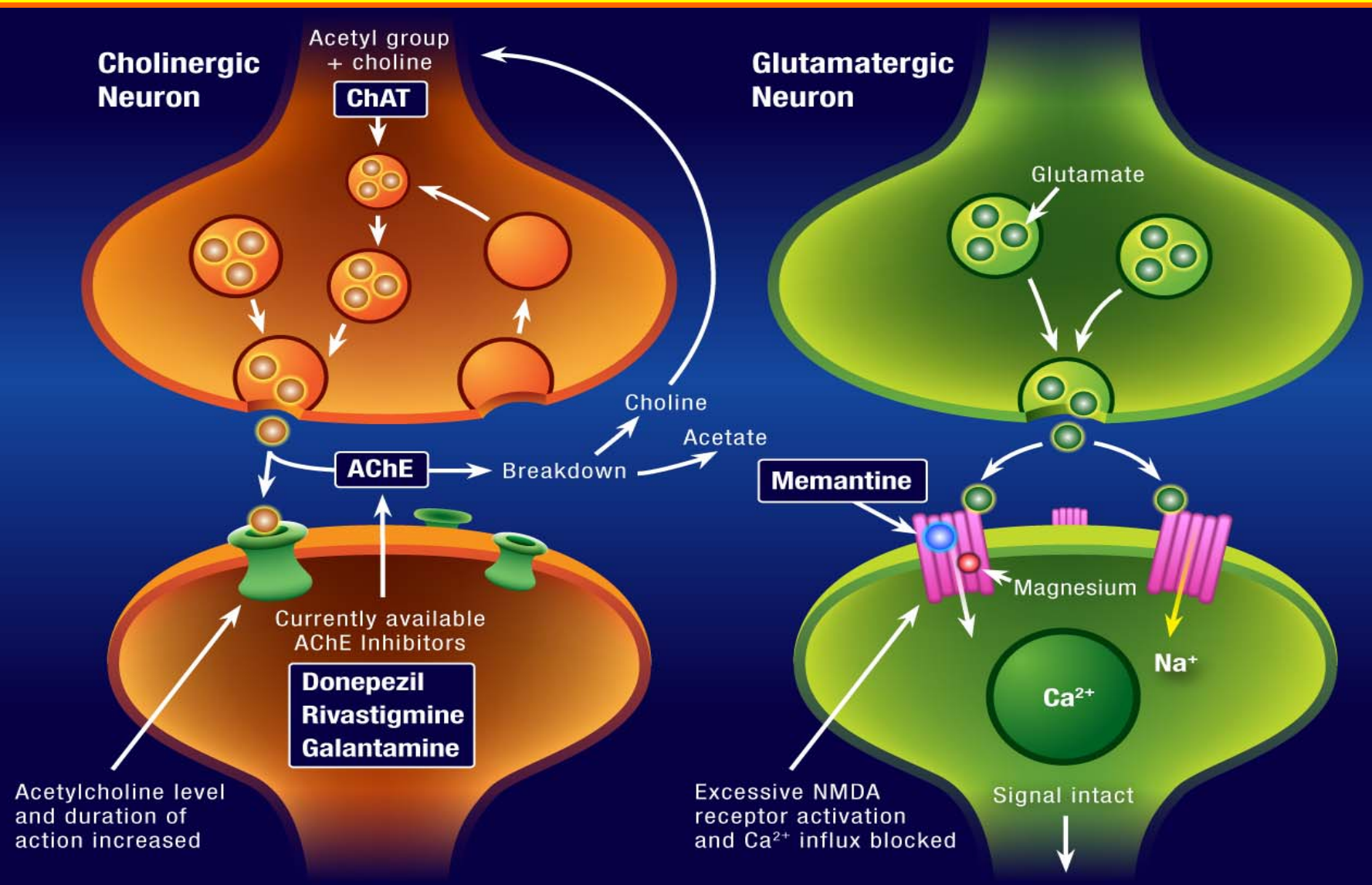
Strategies for Antidementia Drug Development

- Drugs/nutraceuticals based upon epidemiologic observations
- Neurotransmitter-based therapies
- Glial modulating drugs
- Neuroprotective drugs
- Tau modulating drugs
- Amyloid modulating drugs

AD Trials Based on Risk Factors

- Nonsteroidal anti-inflammatory drugs do not slow progression
- Estrogen may increase the risk after age 65 and does not slow progression
- Lowering blood homocysteine does not slow progression (B6, B12 and folate)
- Lowering cholesterol (statins) does not slow progression
- DHA does not slow progression

Molecular Targets for Current AD Therapies



Current Therapies

- Cholinesterase Inhibitors (donepezil/Aricept; rivastigmine/Exelon; galantamine/Reminyl)
- NMDA Receptor Antagonist (memantine/Namenda)
- Anti-oxidant Vitamins? (Vitamin E 2000 IU; Vitamin C 1000 mg)
- Medications for Behavioral and Psychological Symptoms of Dementia

Variations on Current Therapies

- Huperzine? ZT 1?
- ST 101
- Muscarinic agonists (AF267B?)
- Nicotinic agonists
  - Alpha4 Beta2 (Chantix, AZD 3480?)
  - Alpha 7, (GTS 21, Mem 3454, EVP 6124)

Variations on Current Therapies

- NMDA R antagonists (ASP 0777, EVT 101)
- AMPA receptor agonists/Ampakines
  - LY 451395?
  - CX 717

Behavioral and Psychological Symptoms of Dementia

- Apathy
- Depression
- Anxiety
- Agitation
- Psychosis
- Sleep Disturbance
- Disinhibition/Perseveration

Principles of management BPSD

- Anti-dementia drugs reduce BPSD
- An analysis must be done to look for avoidable triggers
- Some behaviors may need medications eg antidepressants, antipsychotics
- The risk/benefit ratio of antipsychotic meds is controversial
- Sleep disturbance and anxiety should usually not be treated with medications

Holmes etal Neurology 2004:63:214-219;

Doody etal Neurology 2001; Schneider etal NEJM 2006;355(15):1525-1538; Ballard etal Lancet 2009;8:151-157

Neurotransmitter-based therapies under development for AD

- Serotonin: 5 HT_4 partial agonists (PRX 03140), 5 HT_{1A} agonists/antagonists, 5HT_6 antagonists (SB 742457, SUVN 502)
- Norepinephrine/Dopamine: MAO A and MAO B inhibitors, re-uptake inhibitors
- GABA: $GABA_B$ antagonists
- Glycine: partial agonists
- H3 Antagonists

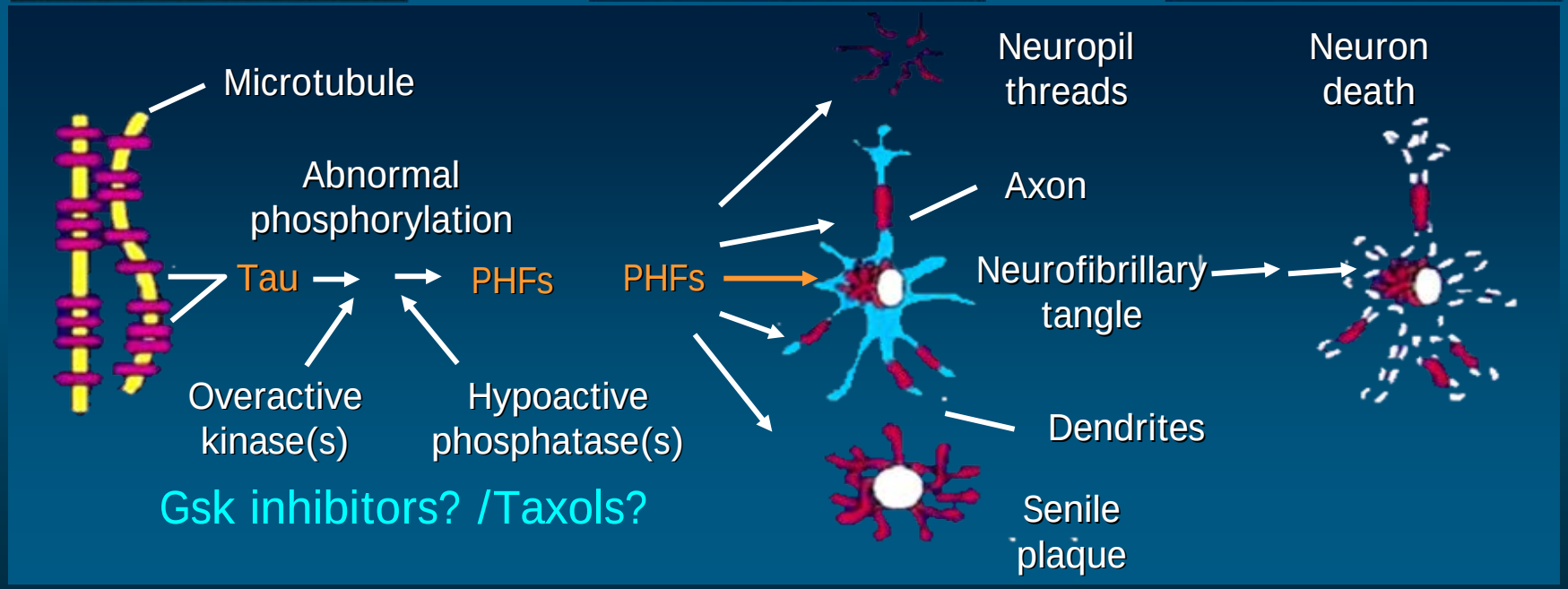
Metabolic/Mitochondrial/Neurotrophic Targets for Alzheimer's Disease

- **Antioxidants** (Vit E, Vit C, alpha lipoic acid, CoQ10,)
- Methylene Blue
- PPARγ Agonists
- Sir1 activators
- Dimebon/latrepirdine

Neuroprotective Treatments

- Neurotrophic drugs
  - PDE4 inhibitors (MEM 1414, AVE 8112, MK 0952) to increase cAMP levels
  - NAP=AL 108 and 208=Davunetide

Neurofibrillary Tangle Formation

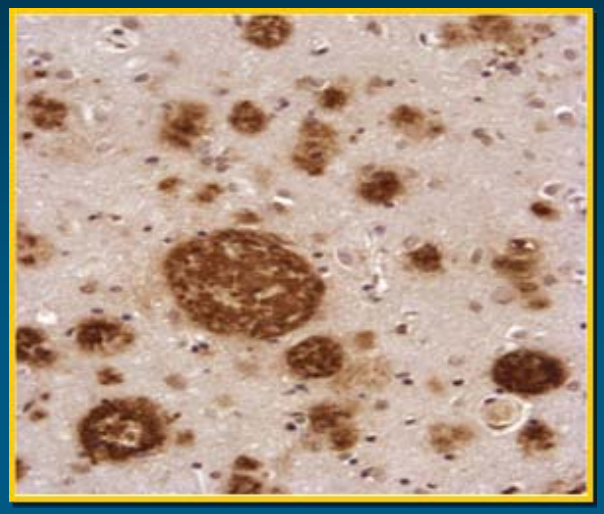


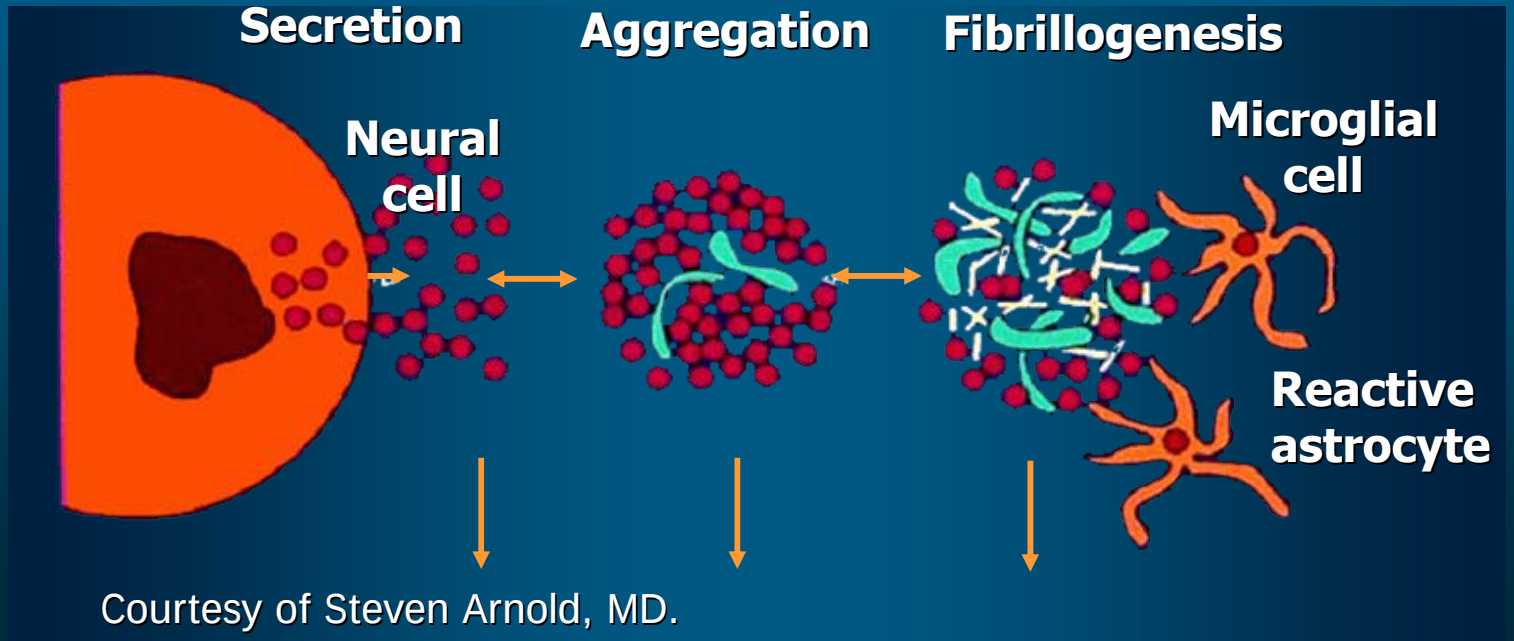
Courtesy of Steven Arnold, MD. W/modifications

Anti-tangle approaches

- Micro-tubule stabilizers, eg NAP (AL-108) or Methylene blue (Rember)
- Kinase inhibitors (GSK3α, GSK3β, CDK 5) eg AZD-1080, NP 13, Li
- Phosphodiesterase-4 Inhibitors
- Minocycline?
- Taxols?

Senile Plaque Formation





Courtesy of Steven Arnold, MD.

Anti-amyloid drugs

Anti-inflammatories

Anti-plaque immunotherapies

- **Passive immunization** (AAB-001, GSK933776A, LY2062430, R4909832, PF 04360365)
- **IVIG**
- **Monoclonal vaccines** (ADD001, CAD106, Merck V950, Affitope ADO1 & 2, ACI24)

Glial Modulating Drugs

- Affect glial cells directly (Nitro-flurbiprofen?, ONO-2506?, Tacrolimus)
- RAGE receptor antagonist (TTP 488)
- TNF alpha antagonists (Enbrel)

Anti-amyloid strategies

- **Anti-fibril, anti-aggregation (Curcumin?, scyllo-inositol, PBT2)**
- **Beta secretase inhibitors (CTS 21166?)**
- **Gamma (LY 450139, GSI 935, BMS 708163, MK 0752, PF 3084014)**

What can a translational core do for TARC?

- Ensure that basic experiments are informed by clinical observations
- Help to focus the development of biological markers
- Help to define relevant phenotypes
- Help to test drugs with new mechanisms supported by basic data