Translational Science to improve the Treatment of AD

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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

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

Cholinergic Neuron

- Acetyl group + choline
- ChAT
- Currently available AChE inhibitors
- Donepezil
- Rivastigmine
- Galantamine
- Acetylcholine level and duration of action increased

Glutamatergic Neuron

- Glutamate
- Memantine
- Magnesium
- Excessive NMDA receptor activation and Ca²⁺ influx blocked
- Signal intact
- Calcium (Ca²⁺)
- Sodium (Na⁺)
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

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\(_{A}\) 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

Microtubule

Abnormal phosphorylation

Tau

PHFs

Overactive kinase(s)

Hypoactive phosphatase(s)

PHFs

Neurofibrillary tangle

Axon

Dendrites

Senile plaque

Neuropil threads

Neuron death

Gsk inhibitors? / Taxols?

 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, CDK5) eg AZD-1080, NP 13, Li
- Phosphodiesterase-4 Inhibitors
- Minocycline?
- Taxols?
Senile Plaque Formation

Secretion → Aggregation → Fibrillogenesis

Microglial cell
Reactive astrocyte

Anti-amyloid drugs
Anti-inflammatories

Courtesy of Steven Arnold, MD.
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 (Nitroflurbiprofen?, ONO-2506?, Tacrolimus)
- RAGE receptor antagonist (TTP 488)
- TNF alpha antagonists (Enbrel)
Anti-amyloidoid 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