Systems Therapeutics: Effective Treatment for Alzheimer’s Disease and MCI

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“The goal of education is to turn an empty mind into an open mind.”

--Malcolm Forbes
30,000,000

patients in 2012

NAPA summit
160,000,000 patients in 2050
0

Cures

X Prize
Alzheimer’s Disease (AD) Therapeutic Landscape

**APPROVED**
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)
- Tacrine (Cognex)
- Memantine (Namenda)

**PHASE 3**
- Solanezumab
- Bapineuzmab
- Alzemed *
- Semagacestat*
- Flurizan*
- Rosiglitazone*
- Phenserine*
- ELND005
- Valproate*
- Antioxidant
- Statins
- Dimebon
- EGCg

**PHASE 2**
- PBT2*
- NIC5-15
- Bryostatin-1
- EHT-0202*
- BMS708163
- ABT089*
- AZD3480*
- Huperzine-A*
- EVP6124
- MEM3454
- PF04447943
- AL-108*
- PF04360365
- Nicotinamide
- NP12
- ACC001
- NGF
- SB742457
- PRX03140*
- PUFA*
- TTP448

**PHASE 1**
- GSK933776*
- MABT5102A
- UB311
- R1450
- V950
- E2012*
- MK0752
- AF102B*
- Talsaclidine
- Begacestat
- PF3084014
- CTS21166
- CHF5074

* Clinical Trial in AD terminated

- ↓ Ab production
- ↓ Aβ aggregation
- ↑ Aβ clearance
- ↓ Tau aggregation/phosphor
- Cholinergic drugs
- Others
Recent Clinical Trial Failures

- Dimebon x2
- Semagacestat
- Rosiglitazone
- AN-1792
- Alzhemed
- Flurizan
- Rember
- Bapineuzumab
The big problem with neurodegenerative disease

Healthy Brain

Advanced Alzheimer’s

PET Scans:

Normal

Alzheimer’s

Alzheimer’s Disease Histopathology

Crump Institute for Biological Imaging
The Status Quo: Alzheimer’s is a disease of toxicity

- Focus is on the chemical & physical effects of Aβ peptide:
  - Lysosomotropic detergent
  - Metal-binding peptide
  - Reactive oxygen species
  - Many other theories
- Approach reinforced by 50,000+ papers...all of which fail to answer key questions
- Why do healthy brains produce Aβ peptide?
- Recent results from transgenic mice
A New View of Alzheimer’s Disease

Proliferation

Migration

Integration
Cancer: imbalance in proliferation/survival vs. turnover

**Proliferation**

- Oncogenes

**Migration**

- Tumor Suppressor Genes

**Integration**

- Cancer
Alzheimer’s disease: imbalance in plasticity

Proliferation  Migration  Integration

Synaptic Reorganization  Synaptic Maintenance

ALZHEIMER’S

Alzheimer’s Disease
• It has been generally assumed that trophic factor withdrawal is associated with the loss of a positive survival signal, such as that associated with the phosphorylation of Akt.

• However, data accumulated over the past 20 years argue that there is a complementary cell death signal mediated by specific receptors, dubbed dependence receptors, activated by trophic ligand withdrawal but blocked by ligand binding (Rabizadeh et al., Science 1993; Mehlen et al., Nature 1998).

• Rita Levi-Montalcini, the 1986 Nobel Prize, and the trophic factor hypothesis.
Levi-Montalcini and the classic view

Trophic factor
The old view: passive death

No trophic ligand
The Dependence Receptor Concept

- **Trophic ligand**
- **No ligand (or anti-trophic ligand)**

Dependence Receptor

Programmed Cell death
An engineer’s view of the neuron
An engineer’s view of the neuron

Integration
Analog $\rightarrow$ digital
Electrical (chemical) input
Via membrane conductance
$\Sigma =$ Electrical input $\rightarrow$ electrical output
Integration over anatomical vs. biochemical space

- **Reelin**
- **Vitamin D**
  - (Thyroid, Estrogen, Progesterone)
- **Hormones**
- **Trophic Factors**
  - (NGF, BDNF, N1, etc.)
- **Cholesterol Metabolism**
  - (ApoE, ABCA1, etc.)
- **Neurotransmitters**
  - (Ach, glutamate, GABA, etc.)
- **ECM**
  - (collagen, laminin, netrin, heparin, etc.)
Integration over anatomical vs. biochemical space

- **Cholesterol Metabolism**: (ApoE, ABCA1, etc.)
- **Neurotransmitters**: (ACh, glutamate, GABA, etc.)
- **Vitamin D**
- **Hormones**, (Thyroid, Estrogen, Progesterone, etc.)
- **Trophic Factors**, (NGF, BDNF, N1, etc.)
- **ECM** (collagen, laminin, netrin, heparin, etc.)

Integration
Analog → digital (slow) output
Receptor signaling input
Via nuclei and cytoplasm
Σ = Chemical milieu input → morphogenetic output
Synaptic element interdependence

\[
\begin{align*}
\text{APP + Trophic Factor} & \quad \downarrow C_{31}, \beta\text{CTF}, s\text{APP}_\beta, A_\beta \\
\text{APP + A}_\beta & \quad \uparrow \text{AICD, KAI1} \\
& \quad \uparrow \text{APP-Fe65} \\
& \quad \uparrow \text{APP-Dab} \\
& \quad \downarrow \text{Thr668 phos} \\
\end{align*}
\]
The readout: plasticity ratio (cf. HDL:LDL)
ApoE4 and plasticity ratio

![Diagram showing the relationship between sAPPα, sAPPβ, CTFα, Aβ, Jcasp, and APP in trophic and anti-trophic conditions.](image)

<table>
<thead>
<tr>
<th>Condition</th>
<th>sAPPα/ sAPPβ</th>
<th>sAPPα/ Aβ1–40</th>
</tr>
</thead>
<tbody>
<tr>
<td>App</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>App+ApoE4</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>App+ApoE3</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>App+ApoE4Δ</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* indicates statistical significance.
The Mouse That Remembered to Roar: Alzheimer’s Electrophysiology Normalized by Blocking C31

Galvan et al., PNAS 2006
Control mice in Morris water maze
“Mouzheimer’s”
Mouzheimer’s blocked
Is APP involved in physiological plasticity?
Normal mouse (trial #8)
“Sheldon Cooper mouse”
Alzflymer’s
Left: Off   Right: On
Activity Assay

Total Activity: 24 hours

- **DR-**
- **DR+** (*)
- **AL-**
- **AL+**

**APP, BACE/GS**
Response to treatment with d-amphetamine

Before D-amphetamine treatment

On D-amphetamine (1.0 mg/ml)

24hr off D-amphetamine

Total Activity: 24 hours

DR-               DR+                             DR-               DR+                            DR-              DR+

Before D-amphetamine treatment

On D-amphetamine (1.0 mg/ml)

24hr off D-amphetamine

APP,BACE/GS
A Drosophila Hyperactivity Disorder (ADHD)

• Males >> Females.
• Exacerbated markedly by high CHO:protein diet.
• Reduced with aging.
• Associated with sleep/nocturnal dysrhythmic pattern.
• Reversibly responsive to d-amphetamine.
• “Paradoxical response” to d-amphetamine.
Screening for Novel Therapeutics
APP forms homodimers
F03: Multiple Mechanisms Against Alzheimer’s

- Reduces $A\beta$
- Increases $sAPP\alpha$
- Blocks ApoE4 effect
- Improves LTP
- Blocks neuronal programmed cell death
- Excellent blood-brain barrier penetration
- High therapeutic index
- Markedly outperforms memantine and donepezil in Tg Mo
F03 restores novel object recognition completely.
A roof with 36 holes...
The first systems therapeutics clinical trial

- Systems Therapeutics (and U.S. case)
- F03
- Synaptik (multiple network-specific components)
- Computer-based assessment and memory training
- Sleep enhancement
- Exercise-induced BDNF increase
- AD-specific diet

First clinical trial is set for 2014.
Summary

• Our model suggests that AD is fundamentally related to a plasticity balance, analogous to oncogene:tumor suppressor gene balance.

• In this model, AD results from a synaptoblastic:synaptoclastic imbalance that is metabolically induced, mediated by dependence receptors (including APP), and amplified by prionic loops.

• Therefore, one translational approach involves correcting this imbalance by targeting APP signaling directly.

• However, an optimal approach would include impacting multiple network components, as physiologically and as far upstream as possible.

• We have had initial success both pre-clinically and clinically with this approach, but much more proof is needed, as well as optimization of each network component therapeutic.
Is Alzheimer’s disease incurable?

“Never doubt the ability of a small group of committed individuals to change the world. Indeed, it is the only thing that ever has.”

--- Margaret Mead