Vaccination Therapy for Alzheimer Disease

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Alzheimer’s Disease

Onset with Memory Impairment

Slowly Progressive Dementia

Neurofibrillary Tangles

Senile Plaques

Neuronal Loss

Brain Atrophy
Amyloid Precursor Protein

Secreted Form

Normal

Alzheimer’s Disease

Membrane

Senile Plaque

β amyloid

β protein

A β 40: 40 amino acids, water soluble
A β 42: 42 amino acids, easy to aggregate, highly toxic
Possible Vaccination Therapy in Alzheimer’s Disease


Start 6 wk

Start 12 mo

13 mo

12 15 18 mo
Immune-mediated clearance of β amyloid (=vaccination)

• Mechanism
  1) Fc receptor-mediated phagocytosis
  2) Phagocytosis by T cell-activated microglia
  3) Antibody-mediated fibrillolysis and prevention of Aβ aggregation
  4) Peripheral sink

• Clinical trial: AN-1792 (Aβ1-42 + QS21)
  halted due to side effect “meningoencephalitis”
Aβ vaccine-related meningoencephalitis is probably autoimmune-mediated.

- Similarity to postvaccinal or post-infectious encephalomyelitis (ADEM).
- Infiltrated cells: CD4⁺ T cells.
- Aβ-reactive T cells: present in PBL, the frequency is higher in the aged and AD.
- Aβ-immunization induces similar meningoencephalitis in mice crossed with IFN-γ tgm

Thus, it is highly possible that this is a Th1-mediated autoimmune disease.
Neuropathology of human Alzheimer disease after immunization with Amyloid-β peptide: a case report

THE GUT IMMUNE SYSTEM

• The mucosa of the small intestine is estimated to be 300 m² in humans.
• The gut mucosa is characterized by abundance of the lymphoid tissue, i.e. $10^{12}$ lymphoid cells/m in humans.
• The most food antigens are degraded when absorbed, but some undegraded or partially degraded antigens are absorbed.
• Systemic immune responses to food antigens are suppressed.
• Gut immune response is shifted to Th2.
Oral vaccine with Aβ rAAV

AAV/ Aβ vaccine

Signal Peptide Aβ1-43 or 1-21

Antibodies

Immune System
Method

Treatment of APP transgenic mouse (Tg2576)
Peroral administration of Aβ1–43 or 1-21 rAAV
5 x 10^{11} viral genome per mouse
i) Group A : 15 weeks of age
ii) Group B : 30 weeks of age
iii) Group C : 45 weeks of age

Control APP-Tg mouse received PBS only.
All mice were analyzed at 56 weeks (13 months) of age.
Serum IgG antibody against Aβ42 in the treated APP-Tg mouse

Ab subtypes: IgG1, IgG2b

ELISA

Mouse serum

TAPIR

Thioflavin S
Hippocampus; 4G8

control

Group D

Group E

Group F
Reduction of Aβ burden in mice treated with AAV/Aβ vaccine

Vaccine was given at 15 wks (A, D), 30 wks (B, E) and 45 wks (C, F) of age and Aβ burden was examined at 56 wks of age.
### Summary of Immunohistochemistry

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<thead>
<tr>
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<th>Control</th>
<th>Treated</th>
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<tbody>
<tr>
<td>CD4</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>CD86</td>
<td>(-)</td>
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<tr>
<td>CD19</td>
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<tr>
<td>CD11b</td>
<td>(-)</td>
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<tr>
<td>GFAP</td>
<td>(++~++++)</td>
<td>(+)</td>
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<tr>
<td>Iba-1(microglia)</td>
<td>(+)</td>
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</table>
Effect of oral vaccine treatment on cognitive function of APP transgenic mice. Conditioned-fear learning task. Retention session was carried out 24hr after the training. Context-dependent test (A) and Cue-dependent test (B) were measured on 13months after birth. Values indicate means ± s.e.mean (wild con: n=7 wild vac: n=8 APPtg con: n=7  APPtg vac: n=8). *P<0.05 vs trained wild type control mice. #P<0.05 vs trained APP transgenic control mice.
Effect of oral vaccine treatment on cognitive function of APP transgenic mice. Novel object recognition task.

Retention session was carried out 24hr after the training. Exploratory preference (A) and total approach time (B) during an 10-min session in the novel object recognition task were measured on 13months after birth. Values indicate means ± s.e.mean (wild con: n=7 wild vac: n=8 APPtg con: n=7  APPtg vac: n=8). *P<0.05 vs trained wild type control mice. #P<0.05 vs trained APP transgenic control mice.
African Green Monkey ♂ 6 months after treatment

Frontal

Control

Vaccine

Occipital

Control

Vaccine
Sendai Virus (SeV) Vector

NP  P  M  F  HN  L

Deletion Form

- Gene integration in host DNA does not occur, because it is cytoplasmic RNA virus.
- Recombination does not occur among viruses.
- Non-pathogenic in humans.

DNAVEC
Serum antibodies to Aβ42 in SeV/Aβ-IL-10-immunized mice

24 months old tg2576 mice were given with SeV/Aβ vaccine per nasally or intramuscularly, and the mice were examined 4 and 8 weeks after.
Aβ staining of the frontal lobe 8 weeks after vaccination

Nasal

Intramuscular
Changes of Aβ burden after treatment with SeV-Aβ1-43/mIL-10

Nasal

Intramuscular
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