Relieving one of the symptoms of Alzheimer’s Disease in a mouse model

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ONE IN EIGHT OLDER AMERICANS HAS ALZHEIMER’S DISEASE. ALZHEIMER’S DISEASE IS THE SIXTH-LEADING CAUSE OF DEATH IN THE UNITED STATES. OVER 15 MILLION AMERICANS PROVIDE UNPAID CARE FOR A PERSON WITH ALZHEIMER’S OR OTHER DEMENTIAS. PAYMENTS FOR CARE ARE ESTIMATED TO BE $200 BILLION IN 2012.
Hallmarks of Alzheimer’s Disease

- Incurable
- Current drug treatments only attempt to alleviate symptoms
- Cholinesterase inhibitors - prevent breakdown of acetylcholine
- Memantine - regulates the activity of glutamate
A closer look at Tau pathology
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1. microtubule
2. Tau
3. Kinases
4. Hyperphosphorylated Tau

Diagram: Microtubule, Tau, Kinases, Hyperphosphorylated Tau
A closer look at Tau pathology

- Tau microtubule
- Kinases
- Hyperphosphorylated Tau
- Neurofibrillary Tangles
A closer look at Tau pathology

- Microtubule
- Tau
- Kinases
- Hyperphosphorylated Tau
- Cell Death
- Neurofibrillary Tangles
A closer look at Tau pathology

- Tau
- Hyperphosphorylated Tau
- Cell Death
- Neurofibrillary Tangles
A closer look at Tau pathology.

- Microtubule
- Tau
- Hyperphosphorylated Tau
- Kinases
- Neurofibrillary Tangles
A closer look at Tau pathology

Tau microtubule

Hyperphosphorylated Tau

Neurofibrillary Tangles
A closer look at Tau pathology

microtubule

Tau

X

Kinases

Dementia

Time
Given 3 mutations

Alzheimer’s Disease
Given 3 mutations

Alzheimer’s Disease
... I don’t remember

Given 3 mutations

Alzheimer’s Disease
Inject mice
extract brain
cut brain in half
CORONAL SLICING OF HALF BRAIN
choose slices
Neurofibrillary Tangles
Neurofibrillary Tangles
Neurofibrillary Tangles
Neurofibrillary Tangles

CA1 of hippocampus
Treatment reduces hyperphosphorylated tau

- Nuclei
- Hyperphosphorylated tau

- Untreated
- Compound 1, low dose
- Compound 1, high dose
Treatment reduces hyperphosphorylated tau

untreated

Compound 1
low dose

Compound 1
high dose

Compound 2
low dose

Compound 2
high dose
1. area of CA1
2. # of blue nuclei
1. area of CA1
2. # of blue nuclei

neurons are not undergoing cell death
1. area of CA1
2. # of blue nuclei

1. # of blue nuclei
2. # of PHF-1+ cells (hyperphos. Tau)

Neurons are not undergoing cell death
neurons are not undergoing cell death

Compound 1
- low
- high

Compound 2
- low
- high

treatment reduced the level of hyperphosphorylated tau

Nuclei density in treated 3xTg-AD mice

<table>
<thead>
<tr>
<th>dose admin. treatment</th>
<th>v</th>
<th>low</th>
<th>high</th>
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<tbody>
<tr>
<td>Compound 1</td>
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<tr>
<td>Compound 2</td>
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density of PHF-1 + cells in treated 3xTg-AD mice

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1. # of blue nuclei
2. # of PHF-1+ cells (hyperphos. Tau)
Histological Analysis
Histological Analysis

1. dissect and homogenize hippocampus from other half of brain
SDS PAGE gel electrophoresis
1 Histological Analysis

SDS PAGE gel electrophoresis
Verification of Histology

- 40% PEG400
- Compound 1 - highest
- high
- low

68 KDa

PHF-1 Tau
MC-1 Tau
pSer²³⁵ Tau
Tau-5
β-actin
Verification of Histology

PHF-1
Verification of Histology

![Image of a gel with different bands labeled with different proteins and molecular weights.]

- **PHF-1**
- **β-actin**

The gel shows bands for PHF-1 Tau, MC-1 Tau, pSer^{235} Tau, Tau-5, and β-actin with molecular weights of 68 KDa and 50 kDa.
Verification of Histology

PHF-1 densitometry in treated 3xTg-AD mice

![Western Blot Image]

- Compound 1 - highest
- high
- low

- Compound 2 - highest
- low
- high

68 KDa
50

MC-1 Tau
pSer^{235} Tau
Tau-5
β-actin
Ensure reproducibility
FDA approval

Dementia

Time
Acknowledgements

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Dr. Kenneth Kosik
The compounds reach the brain and are not significantly toxic

Compounds 1 (shown) and Compound 2 can be found in the blood plasma and in the brain 20–220 minutes after injection.

Administration of either of the two inhibitors does not cause significant weight loss over the course of treatment.