Therapeutic Approaches to Neurodegeneration
Recent Advances in Neurology
University of California
San Francisco, CA

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February 16, 2011

Some features of the tauopathies at an interface between psychiatry and neurology

- The tauopathies are the great imitators of CNS disorders and in that sense, they resemble syphilis.
- Changes in personality, behavior and language appear to be caused by pathologic accumulation of tau in frontotemporal dementia (FTD).
- FTD is often misdiagnosed as a psychiatric problem or as Alzheimer's disease.
- Behavioral symptoms range from lethargy to disinhibition. Impulsive or inappropriate behavior, such as frequent swearing, outbursts of frustration, petty theft, and lack of social tact.
- Apathetic patients may become socially withdrawn.
- Repetitive compulsive behaviors including overeating and a decline in personal hygiene.
- Mood swings from euphoria to marked depression can precede suicide.
- Addictive behaviors and alcoholism are sometimes seen.

The Neurodegenerative Diseases

- There is not a single medicine that halts or even slows one of the neurodegenerative diseases.
- Millions of people worldwide suffer from progressive degeneration of the nervous system.
- These illnesses include Alzheimer's, Parkinson's, Huntington's and Creutzfeldt-Jakob disease (CJD) as well as the frontotemporal dementias (FTDs) and some forms of traumatic brain injury (TBI) and chronic traumatic encephalopathy (CTE).

Neurofibrillary tangles form in response to CNS injury from many causes including trauma

- Diseases with Neurofibrillary Tangles
  - Tauopathies (FTDs, PSP, CBD, Pick's disease)
  - Alzheimer's disease
  - SSPE
  - Rabies
  - Dementia pugilistica
  - Chronic Traumatic Encephalopathy
  - Niemann-Pick Type C disease
  - Postencephalic Parkinson's disease (PD)
  - Guam ALS-PD with dementia
  - Argyrophilic grain disease
  - Myotonic dystrophy
  - Familial prion disease - GSS(F198S)
Dementia pugilistica and chronic traumatic encephalopathy are tauopathies

Owen Thomas played defensive end for the University of Pennsylvania

- In his junior year, he was selected to the 2nd team All-Ivy League and was named co-captain of the team.
- He had played football since he was 9 years old but never had a documented concussion.
- In April, 2010, at age 21 he committed suicide (by hanging), an act that all who knew him considered to be unexplained and completely out of character. There was no history of psychiatric disturbance, evidence of prior depressive episodes or suicidal tendencies.

Neurofibrillary tangles are composed of hyperphosphorylated tau

Tau proteins are normally associated with microtubules but undergo hyperphosphorylation after CNS injury. Phosphorylated tau polymerizes into fibrils that coalesce into tangles.
Each neurodegenerative disease is caused by a different protein

- The distinct neurodegenerative illnesses are each caused by the misprocessing of a specific protein.
- For CJD and mad cow disease, it is PrP\textsubscript{Sc} that accumulates and causes CNS dysfunction. For AD, it is Aβ and for PD, it is α-synuclein. For the FTDs, some TBIs and CTE, the problematic protein is tau.
- Each of the proteins specifies a molecular target and thus, each neurodegenerative disease requires a highly focused approach to develop drugs that work.
- Each drug has to match the particular protein target.

### Spectrum of Neurodegenerative Diseases

#### Self-propagating protein conformation

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Prion Diseases</th>
<th>Alzheimer’s Disease</th>
<th>FTDs</th>
<th>Parkinson’s Disease</th>
<th>Huntington’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic (85 – 90%)</td>
<td>sCJD sFI</td>
<td>AD</td>
<td>TBI, CTE, FTD, CBD, PSP, Picks</td>
<td>PD, LBD</td>
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<tr>
<td>Inherited (10 – 15%)</td>
<td>fCJD GSS FFI</td>
<td>fAD</td>
<td>FTDP17, CBD, PSP, Picks</td>
<td>IPD</td>
<td>All HD</td>
</tr>
<tr>
<td>Infectious (&lt;1%)</td>
<td>iCJD vCJD Kuru</td>
<td>Experimental AD</td>
<td>Experimental tauopathy</td>
<td>Lewy bodies in striatum of PD patients</td>
<td>Cytoplasmic polyglutamine aggregation</td>
</tr>
<tr>
<td>Self-propagating proteins</td>
<td>PrP</td>
<td>Aβ</td>
<td>Tau</td>
<td>α-Synuclein</td>
<td>Huntingtin</td>
</tr>
</tbody>
</table>

### Discovering prions form amyloid suggested plaques and tangles in other neurodegenerative diseases might also be etiologic....

**NEURODEGENERATION**

**Could They All Be Prion Diseases?**

Recent studies renew interest in the idea that many neurodegenerative diseases may involve prionlike mechanisms.

**OCCASIONAL NOTES**

Some Speculations about Prions, Amyloid, and Alzheimer’s Disease

The finding that prions aggregate into amyloid-like rods suggests the possibility that amyloid deposition in the brains of patients with Alzheimer’s disease represents something more than a pathologic byproduct of the disease process. For nearly half a century, amyloid plaques have generally been thought to represent waste collections of pathologic macromolecules. We must now ask whether, or not the amyloid deposits in Alzheimer’s disease may represent accumulations of the etiologic agents, as they appear in Creutzfeldt-Jakob disease, kuru, and the Gerstmann-Sträussler syndrome. However, if prions exist in Alzheimer’s disease, then they must be different from the agents causing Creutzfeldt-Jakob disease. Differences in trans...
Pharmacotherapeutic strategies for clearing self-propagating proteins causing CNS disease

- Prion proteins adopt at least two conformational states, one of which is self-perpetuating. Some prions are toxic to cells.
- Strategies for decreasing prions: (1) decrease the precursor, (2) inhibit conversion into the prion state and (3) enhance prion clearance.
- Once the level of the prion form is sufficiently low, cells will clear the remaining pathological conformers.
- Administration of multiple anti-prion drugs for limited periods of time will likely prove the best therapeutic strategy.

CJD and Mad Cow Disease

- For many years, people thought Creutzfeldt-Jakob disease (CJD) was caused by a slow acting virus.
- The discovery that some proteins, now called prions, are infectious and cause CJD, mad cow disease and chronic wasting disease (CWD) of deer was unexpected.
- The most advanced cell and animal models exist for the prion diseases, so therapeutics for these disorders may be the first to be devised for any neurodegenerative disease.

From Targets to Clinical Candidates

Modern drug discovery has become a highly developed science

- Drug discovery is no longer “lots of good luck and a pinch of serendipity.” It has become a science.
- Once protein targets are identified and rapid assays developed, thousands of chemicals can be screened to identify hits. The hits can be classified according to structure and many analogs tested.
- From such studies, leads emerge and after structure-activity-relationship (SAR) investigations, efficacy studies in transgenic mice are performed.
**PrP<sup>sc</sup> Drug Pipeline – Diverse Chemicals**

<table>
<thead>
<tr>
<th>Library</th>
<th>HTS</th>
<th>SPC</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>PK</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChemBridge-1</td>
<td>Screened: 24,000 CB-1</td>
<td>2033 compounds found 14 scaffolds</td>
<td>EC&lt;sub&gt;50&lt;/sub&gt; on 467 initial SPC</td>
<td>Over 60 compounds from 9 scaffolds</td>
<td>4 compounds from 2 scaffolds</td>
</tr>
<tr>
<td>SPECS ChemBridge-2 (CNS focused)</td>
<td>28,000 SPECS</td>
<td></td>
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</tbody>
</table>

**Scaffold Analysis by Spotfire (PrP<sup>sc</sup> - dividing cells)**

**Comparison of EC<sub>50</sub> values determined by ELISA and Western blotting**

**PrP<sup>sc</sup> Drug Pipeline – Diverse Chemicals**

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<td></td>
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</tbody>
</table>

**Non-dividing ScN2a Cells**

- No brain exposure

**PK Efficacy**

- PK on 3 leads
- Pending on PK results

**PrP<sup>sc</sup> Efficacy**

- PK on 3 leads
- Pending on PK results
Firefly luciferase (luc) + ATP, O\(_2\), Mg\(^{2+}\) \rightarrow \text{Luciferase} \rightarrow \text{Oxylucifirenin} + \text{CO}_2 + \text{LIGHT} \rightarrow \text{Gfap-luc}

BLI in models of neurodegeneration

Tg(\text{Gfap-luc})

Tg(\text{\Delta APP:Gfap-luc})

Tg(\text{Gfap-luc})

Diagnosis by clinical signs

Diagnosis by bioluminescence

Rx of RML-infected mice with phenylhydrazone and aminothiazole

Compd B

AMT 163

AMT 082

A

PrP\(^{Sc}\)

GFAP

Actin

B

Time from inoculation (days)

Bioluminescence (x10\(^6\) photons/s)

Rx of RML-infected mice with phenylhydrazone and aminothiazole

B

PrP\(^{Sc}\)

GFAP

Actin

A

Time from inoculation (days)

Bioluminescence (x10\(^6\) photons/s)
AMT 082 extends survival in Tg(Gfap-luc) mice treated with 3 different doses beginning 50 days after inoculation

- 210 mg/kg/day (n=3)
- 100 mg/kg/day (n=4)
- 50 mg/kg/day (n=4)

Delayed treatment of prion-infected Tg(Gfap-luc) mice with AMT 082

- Start dosing at day: 0 34 46 60 77 90 (210 mg/kg/day)

Delayed treatment of prion-infected Tg(Gfap-luc) mice with AMT 163

- Start dosing at day: 0 65 (210 mg/kg/day)

Treatment of prion-infected wt FVB mice with AMTs 082 and 163

- AMTs 082 and 163 extended the lives of mice ~100 days.
- 50 mg/kg/day of AMT 082 was effective.
- Treatment could be started as late as 77 days after intracerebral inoculation of RML prions.
- 100 days in a mouse corresponds roughly to 5,000 days or ~14 years in a human.
- When should we begin treating CJD patients, who typically live 3-6 months after diagnosis?
The increasing size of annual polio epidemics each summer demanded action!

- Polio vaccine development was funded by the National Foundation headed by Basil O’Connor who had been FDR’s law partner.
- January 1953, the members of Committee on Immunization chaired by Tom Rivers “could agree on almost nothing beyond the need to proceed slowly. O’Connor respected its members as scientists but reviled them as a deliberative group.”
- In May 1954 clinical trial, 250,000 children were vaccinated with the Salk vaccine.
- During the winter of 1955, the results were analyzed; 34 years after FDR had been stricken with polio, the Salk vaccine was declared effective on April 12, 1955.

Rivers, Salk, O’Connor, Francis

Lowering precursor proteins as an approach to therapeutics for neurodegeneration

- Decreasing the normal, precursor protein of the disease-causing protein will slow and/or prevent the neurodegenerative disease.
- Lowering PrPC slows the development of prion disease in Tg mice.
- Mice with genetic ablation of their PrP, APP or tau genes exhibit normal lifespans, behavior and reproduction, making these proteins superb drug targets.
- Conversely, overexpression of PrP or mutant APP shortens the time to onset of prion or experimental Alzheimer’s disease as well as the tauopathies.

**PrP** Drug Pipeline – Diverse Chemicals

<table>
<thead>
<tr>
<th>Library</th>
<th>HTS</th>
<th>SPC</th>
<th>EC_{50}</th>
<th>PK</th>
<th>Efficacy</th>
</tr>
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<tr>
<td>ChemBridge-1</td>
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<tr>
<td>ChemBridge-2</td>
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<td>Screened:</td>
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<tr>
<td>9.7k CB-1</td>
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<tr>
<td>15.5k of 40k CB-2 in IMR32 cells</td>
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<tr>
<td>15.5k of 40k CB-2 in T98G cells</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>SPC on 173 compounds from CB-2 in IMR32 cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Found 38 potential hits</td>
<td></td>
<td></td>
<td>EC_{50} to be performed on selected hits</td>
<td></td>
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<tr>
<td>SPC on 109 compounds from CB-2 in T98G cells</td>
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<td></td>
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<tr>
<td>Found 60 potential hits</td>
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<td></td>
<td>Pending EC_{50} results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T98G SPC hits</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Phosphatase inhibitors</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sulphinpyrazole</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>IMR32 SPC hits</td>
<td></td>
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</tr>
</tbody>
</table>

**Alzheimer’s Disease**

- Currently 36 million people are demented worldwide, and 66 million by 2030 and 120 million by 2050.
- The majority of demented people suffer from Alzheimer’s disease for which there is no effective treatment.
- In 2010, the cost of caring for demented patients was $600 billion worldwide and about $200 billion in the U.S.
- The greatest risk factor for Alzheimer’s is age: by 85, one in every three people will develop the disease.
Aβ42 peptide causes Alzheimer’s disease

- AD is the most common neurodegenerative disease. It is age dependent: ~35% over 85 develop AD.
- AD appears to be caused by the accumulation of Aβ42 peptide, which is neurotoxic.
- Oligomers consisting of a few Aβ peptides correlate with loss of synapses and dementia as well as aggregation of tau into neurofibrillary tangles (NFTs).
- Both Aβ oligomers and NFTs correlate with the level of dementia in AD patients at autopsy; Aβ plaques do not.
- Aβ deposition begins in entorhinal cortex, spreads like a prion to the hippocampus and then to the neocortex.

Tangles (NFTs) and soluble Aβ correlate with the degree of dementia but Aβ plaques do not in Alzheimer’s disease

[Graph showing the correlation between Aβ deposition and dementia severity.]

[Graph showing the distribution and burden of amyloid pathology in AD.]

[Blessed Dementia Scale (BDS) showing correlation between Aβ deposition and dementia severity.]

[Images of PET scans demonstrating different stages of Aβ deposition.]
**Genetics of Alzheimer’s disease**

- Familial AD is caused by mutations in the APP gene or γ-secretase genes (presenilins) that increase Aβ levels.
- Duplication of the APP gene in Down’s produces AD.
- Mutations in tau gene produce familial forms of FTDs, CBD, PSP and Pick’s, but not AD.
- ApoEε4 increases the risk and lowers the age of AD onset.
- Swedish (KM670/671NL) and Indiana (V717F) mutations used in Tg mouse models.

**Bioluminescence imaging in a bigenic mouse model for familial Alzheimer’s disease**

- التواصل بين الجينات المسببة للذبحة في الدماغ والتأكسد في الدماغ.
- في عام 1970s، نُقلت الأرواح في الأناضwruti مع الجمجمات المُناعية من 52 مريضاً مصاباً بـ AD إلى القرود، حيث نجت 0/33 من الحالات المزمنة بـ AD ولكن 2/18 من الحالات المزمنة بـ fAD بعد ~50 شهر، مما يظهر التغيرات السوسية مثل تلك في CJD (Goudsmit et al. 1980).
- في ثلاثينيات القرن الحادي والعشرين، 18/20 من القرود الأصغر من 10 سنوات كانت Aβ إيجابية بالعنوان بعد نقل الإغاثات من حالات الـ AD المزمنة، familial AD، و Down’s. 0/11 من القرود المريضة غير المريضة <10 سنة كانت Aβ إيجابية (Ridley et al. 2006).

**Transmission of Alzheimer’s to monkeys**

- In 1970s, monkeys inoculated with brain homogenates prepared from 52 AD patients; 0/33 sporadic AD cases transmitted to monkeys but 2/18 cases of fAD transmitted after ~50 months showing spongiform changes like those in CJD (Goudsmit et al. 1980).
- In the 1990s, 18/20 marmosets <10 y.o. were Aβ positive by immunostaining after inoculation with sporadic AD, familial AD or Down’s brain homogenates. 0/11 uninjected marmoset controls <10 y.o. were Aβ positive (Ridley et al. 2006).

**Bioassay for Alzheimer’s disease in Tg mice**

- Brain from AD patient
- Homogenize and inject into mice
- Tg(HuAPP23)
- Wait for about one year
- Stain for Aβ aggregates
- Post-mortem analysis
**Widespread Aβ deposition throughout the brain in AD-inoculated Tg(APP23) mice**

AD-inoculated

Control-Inoculated

11-12 months post-inoculation  Stain: Aβ-40

**Bioluminescence imaging in bigenic AD mice**

**APP Drug Pipeline - FDA Drugs**

<table>
<thead>
<tr>
<th>LibraryHTS</th>
<th>SPC</th>
<th>EC₅₀</th>
<th>PK</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA drugs</td>
<td>Screened 1700 FDA drugs in T98G and IMR32 cells</td>
<td>Screened 57 HTS hits in SPC</td>
<td>Selected 23 SPC hits for EC₅₀ confirmation</td>
<td>5 confirmed leads in PK studies</td>
</tr>
</tbody>
</table>

Anti-tau drugs that prevent tau from aggregating into NFTs will find wide application in AD, FTDs, TBIs and CTEs.

- Such drugs are likely to be used in prophylaxis prior to possible head injury in both athletics and combat.
- Creating cellular tauopathy models will be critical for developing complimentary therapeutics.
- Identifying tau reporters for PET imaging is crucial for confirming diagnoses, detecting NFTs in asymptomatic people and measuring responses to therapeutics.
- Assessing therapeutic efficacy for neuropsychiatric disease can be notoriously difficult.
Numerous CNS insults stimulate NFT formation

- In familial FTDs, mutations in tau provoke NFT formation.
- Rabies and SSPE viruses as well as sphingomyelin accumulation in Niemann-Pick disease stimulate NFT formation.
- In Alzheimer’s disease, Aβ peptides form oligomers that stimulate phosphorylation of tau which polymerizes into PHFs that coalesce into NFTs.
- Traumatic brain injuries stimulate tau deposition into NFTs.

Prion-like tau aggregation in cells and Tg mice

- After fibrillization with arachidonic acid, recombinant wtHuTau(243-375) from E. coli was internalized by C17.2 neuronal cells in culture. The fibrils induced truncated or wt HuTau-YFP to aggregate inside cells; aggregated tau could be transferred to other cells.
- Tau aggregates from Tg(HuTau,P310S) mice were injected into Tg(wtHuTau) mice where they induced hyperphosphorylated tau aggregates after 6 months.
- Tg mice expressing mutant (∆∆K280) repeat domain (244-372) under control of the Tet-off system initiated the persistent aggregation of wt mouse tau.

Therapeutic strategies for clearing self-propagating pathologic forms of tau

- Much evidence argues that tau adopts at least two conformational states, one of which is self-perpetuating and toxic to neurons.
- Strategies for decreasing tau: (1) decrease the precursor, (2) inhibit conversion into the prion-like state and (3) enhance tau clearance.
- Tau null mice are normal. Once the level of the prion-like tau is sufficiently low, cells will clear the remaining pathological conformers.
- Administration of multiple anti-tau drugs for limited periods of time will likely prove the best therapeutic strategy.

Steps in anti-tau drug discovery

- Libraries
- HTS/HCS
- SAR for brain delivery
- Lower tau in brain
- Increase survival/lower BLI signal in brain

- FDA drugs/chemicals
- Hits lower tau in cells
- SAR of leads to optimize for drug-like properties
- Efficacy lowering brain tau in mice
- Efficacy in mouse taupathy models
Some strategies for developing anti-tau drugs

- Therapeutics for tauopathies: (1) diminishing the substrate, (2) inhibiting formation of nascent prions, and (3) increasing clearance.
- Cultured human neuronal cells offer a good system for identifying hits that lower tau levels using HTS.
- No cellular models of the tauopathies exist: in cells from patients with tauopathies may prove to be superb; alternatively, prion-like models of tau aggregation and/or phosphorylation may be useful.
- Cocktails of drugs aimed at different targets are likely to be needed but can probably be administered for only a few weeks.
- BLI will be useful in assessing efficacy of anti-tau leads in mice.
- PET imaging in humans will be needed to establish correct diagnoses and assess quantitatively responses to therapeutics.

Anti-tau pipeline — Diverse Chemicals

<table>
<thead>
<tr>
<th>Library</th>
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<th>EC_{50}</th>
<th>PK</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChemBridge-1</td>
<td>Screened:</td>
<td>SPC on 1764</td>
<td>14 Piperazine</td>
<td>Pending on</td>
<td></td>
</tr>
<tr>
<td>SPECS</td>
<td>24 K CB-1</td>
<td>compounds (from CB-1 &amp; SPECS)</td>
<td>Aminothiazole</td>
<td>PK results</td>
<td></td>
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<tr>
<td>ChemBridge-2 (CNS focused)</td>
<td>28K SPECS</td>
<td>found: 4 scaffolds IMR32: 42 hits T98G: 174 hits</td>
<td>Aminothiazole</td>
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<tr>
<td></td>
<td>12K of 40K CB-2</td>
<td>12 Piperazine</td>
<td>Aminothiazole</td>
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<td></td>
<td>In IMR32 cells</td>
<td>17 Aminothiazole</td>
<td>Aminothiazole</td>
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<tr>
<td></td>
<td></td>
<td>21 Sulfonamide</td>
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<tr>
<td></td>
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<td>23 Amide</td>
<td>Aminothiazole</td>
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<td>58 miscellaneous</td>
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<td></td>
<td></td>
<td>1 Piperazine</td>
<td>Aminothiazole</td>
<td></td>
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</tr>
</tbody>
</table>

Adapting BLI to tauopathy Tg mouse models since GFAP is upregulated

Upregulation of GFAP should be detectable in vivo using BLI

PS19 mice expressing mutant (P301S) human tau have extensive GFAP upregulation by 6 months. Astrocytic gliosis precedes tangle formation

Breeding underway
Increased GFAP and phosphorylated tau in brains of older Tg(HuTau,P301S) mice

<table>
<thead>
<tr>
<th>Line</th>
<th>Experimental plans</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg(Gfap-luc:PAC-MAPT)8Dav</td>
<td>Inoculate with human tauopathy and aged Tg(Tau) brain homogenate to monitor induced tau deposition by BLI</td>
<td>Breeding underway</td>
</tr>
<tr>
<td>Tg(Gfap-luc:Prnp-MAPT,P301S)19Vle</td>
<td>Bioluminescence imaging of the kinetics of spontaneous tau deposition (P301S mutation)</td>
<td>Breeding underway</td>
</tr>
<tr>
<td>Tg(Gfap-luc:Prnp-MAPT,P301L)JNPL3</td>
<td>Bioluminescence imaging of the kinetics of spontaneous tau deposition (P301L mutation)</td>
<td>Breeding underway</td>
</tr>
<tr>
<td>Tg(Gfap-luc:Tg(Tau,P301S))Goe</td>
<td>Inoculate with human tauopathy and aged Tg(Tau) brain homogenate to monitor induced tau deposition by BLI</td>
<td>Breeding underway</td>
</tr>
<tr>
<td>Tg(Gfap-luc:Tg(Tau,P301S))Goe</td>
<td>Inoculate with human tauopathy and aged Tg(Tau) brain homogenate to monitor accelerated tau deposition by BLI</td>
<td>Breeding underway</td>
</tr>
</tbody>
</table>

Evaluating new therapeutics for treatment of AD, FTDs, TBI and CTE

- In Tg mice, determine the effects of anti-tau drugs in reducing GFAP expression using BLI and levels of brain tau.
- In humans, assess quantitatively the effects of drugs designed to lower tau.
- Measuring the effectiveness of a therapeutic intervention in a neuropsychiatric disorder is challenging unless changes in patients are dramatic.
- Monitoring the severity of symptoms is insufficient in making an accurate diagnosis and in assessing the incremental increases is therapeutic efficacy.
- With [18F] reporters, measure tau levels or reactive gliosis using PET.

Expanding spectrum of prion diseases and novel strategies for developing therapeutics

- Prions are infectious proteins. They have been found in mammals and fungi but are surely present in all eukaryotes.
- All prions aggregate to form amyloid. Some prions cause disease while others function in normal metabolism.
- Besides the neurodegenerative diseases (ND) caused by PrPSc, there is increasing evidence that other illnesses including AD, PD, FTDs, CTE, and some TBIs have prion-like etiologies.
- Strategies for treating prion diseases include (1) diminishing the substrate, (2) inhibiting formation of nascent prions, and (3) increasing clearance.
- Cocktails of drugs aimed at different targets will be needed, but administering these for short periods will probably be adequate.
- PET imaging will be needed to establish correct diagnoses and assess responses to therapeutics.
Creating the first effective therapeutics for neurodegeneration

- Producing the first drug that slows neurodegeneration is a great challenge but will represent a landmark in medical science.
- Expansion of the IND at Mission Bay provides the space required for a nucleus of the most imaginative and talented investigators in neurodegeneration, pharmacology, brain imaging and medicinal chemistry to gather and develop such urgently needed therapies.
First floor will have neurology research clinics, and MRI and PET scanners. There will also be a 180 seat auditorium.
IND will occupy the entire third floor

IND medicinal-synthetic-radio chemistry unit will occupy about one-third of the fourth floor