Developing New Molecular and Clinical Targets for Nervous System Disorders

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Accelerating Therapeutic Development for Nervous System Disorders towards First-in-Human Trials

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APP/Aβ_{42} : Pathogenic and Protective Mutations with Known MOA

- Genetic forms ~homogeneous, but etiology of sporadic AD more pleiotropic
- Aβ_{42}/oAβ accumulation begins 15-25 yrs before symptoms
- Aβ_{42}/oAβ toxicity resistance factors poorly understood
- Aβ_{42}/oAβ-reducing agent (antibodies, vaccines, protease modulators) safety profile must be extremely favorable and should be less expensive than custodial care (~$500K-$1MM per patient)
What makes a good drug target?

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\textbf{BOX 1}

\textbf{Properties of an ideal drug target:}

- Target is disease-modifying and/or has a proven function in the pathophysiology of a disease.
- Modulation of the target is less important under physiological conditions or in other diseases.
- If the druggability is not obvious (e.g. as for kinases) a 3D-structure for the target protein or a close homolog should be available for a druggability assessment.
- Target has a favorable ‘assayability’ enabling high throughput screening.
- Target expression is not uniformly distributed throughout the body.
- A target/disease-specific biomarker exists to monitor therapeutic efficacy.
- Favorable prediction of potential side effects according to phenotype data (e.g. in k.o. mice or genetic mutation databases).
- Target has a favorable IP situation (no competitors on target, freedom to operate).
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Novelties for consideration

- **Novel timing** of intervention in high risk subjects
- **Novel system** for screening for $\text{A}\beta_{42}/\text{oA}\beta$ reducing drugs
- **Novel approach** to secretase modulation (conventional target)
- **Novel biological antagonism** to $\text{A}\beta_{42}/\text{oA}\beta$ toxicity (unconventional target process)
Initiation of pathogenesis can be accurately identified in traumatic encephalopathy: Might existing Aβ42/oAβ reducing drugs improve outcome if given acutely post-TBI?
### A-beta regulation by signal transduction

#### First messengers
- ACh
- Glutamate
- IL-1
- 5-HT₄
- Estrogen
- Testosterone

#### Second messengers
- cAMP
- Ca²⁺
- DAG

#### Protein kinases
- PKC
- PKA
- ERK
- ROCK1,2
- src
- JAK

#### Isoprenoid- and Rho-GTPase related signals
- FTI
- GGTI
- Rho
- Rac
- Rap

#### Protein phosphatases
- PP1
- PP2A

#### Electrical depolarization
Nerve terminals are likely to be one source of synaptic $\alpha\beta_{42}$.
Which neurotransmitter signaling pathways most closely mimic depolarization-induced Aβ42 metabolism at the synapse?
Synaptic Group II Metabotropic GluRs Modulate $\gamma$-Secretase Speciation of A$\beta$

DCG-IV stimulated generation of A$\beta$42 but not A$\beta$40

Pretreatment with mGluR2/3 antagonist LY341495 blocked DCG-IV stimulated generation of A$\beta$42
The mGluR2/3 antagonist BCI-838 reduced oAβ accumulation and improved learning and anxiety behaviors in APP transgenic mice.
APP transgenic mice showed exaggerated neurogenesis when treated with BCI-838:

Can neurogenesis act as an unconventional biological antagonist of \( \text{A}\beta \) toxicity?

Can neurogenesis act as an unconventional biological antagonist of tau toxicity?

Could such a drug be both acutely symptomatic and disease-modifying when administered chronically?
Novelties for consideration

- **Novel timing** of intervention in high risk subjects (e.g., acute post TBI)
- **Novel system** to screen for synaptic Aβ₄₂/oAβ reducing drugs
- **Novel approach** to secretase modulation (conventional target)
- **Novel biological antagonism** to Aβ₄₂/oAβ toxicity (unconventional target process, might not be Aβ₄₂/oAβ, so could be relevant to tauopathy as well)
- **Novel two-hit benefit**: Could a drug (e.g., BCI-838) offer both acute symptomatic and chronic disease-modifying benefits?
Past and Planned Future Development of BCI-838

Single- and multiple-ascending-dose first-in-man Phase I well-tolerated in young healthy controls x 2-3 wk by BCI for TRD indication

“First-in-geriatric-humans” RCT with prodromal/mild AD (w Mary Sano)

Fundraising for AD RCT in progress: Federal, private, philanthropic sources

Preclinical assessment in tauopathy models including TBI/CTE/PTSD ongoing

VA MERIT awarded to support preclinical development in TBI/CTE/PTSD

Fundraising for FTD (preclinical and RCT) in progress”: Federal, private, philanthropic sources