



## A Unique Approach to Protein Misfolding Diseases

### A Platform Technology Company

Treventis Corporation ([www.Treventis.com](http://www.Treventis.com)) is a pre-clinical platform company focused on the development of innovative therapeutics and diagnostics for conditions in which pathogenic protein misfolding causes the formation of toxic protein aggregates (oligomers) leading to brain cell death. This process is the underlying pathological feature of Alzheimer's disease (AD; beta-amyloid and tau), Progressive Supranuclear Palsy (PSP; tau), Frontotemporal Dementia (FTD; tau), Parkinson's disease (alphasynuclein), Huntington's disease (huntintin protein) and Type II diabetes (amylin/IAPP). There are at least 34 disease indications in which protein misfolding and amyloid aggregation are implicated.

### Efficient Discovery via New Drug Target and *In Silico* Model

We have discovered a new drug target. Using state of the art computer modeling techniques, we have identified the abnormal shape that enables a protein to misfold and become toxic. This computer based model enables us to achieve *in silico* drug discovery by both high throughput screening and rational drug design approaches. Using this model as a high throughput screen, we evaluated 11.8 million compounds followed by initial hit-to-lead optimization that furnished several proof of concept compounds which bind to this target. These compounds show robust evidence of blocking beta-amyloid and tau aggregation. We have also collected *ex vivo* long term potentiation (LTP) and chronic *in vivo* measures, including the prevention of cognitive decline in APP/PS1 transgenic models of AD, data that are supportive of efficacy.

### TREVENTIS Drugs Prevent Aggregation of Both A-beta and Tau Proteins

In terms of preventing oligomerization, we have data on beta-amyloid 40/42 and tau 441 (4N2R). The range of experiments includes functional biochemical readouts of fibril formation (Thioflavin T/S), electron microscopy, and other *in vitro* measures of fibril and oligomer formation. We have also collected other measures of target engagement including two-dimensional NMR and surface plasmon resonance.

We are working to further enhance our base of tau data to be as comprehensive as that of beta-amyloid, including an improved molecular-level conceptualization regarding the amount and type of oligomer reduction. We are currently working with leading experts to design and implement cell-based and acute *in vivo* mechanism of action assays to demonstrate an effect of our compounds on oligomer levels, and potentially cell-to-cell transmission and neurotoxicity. These assays may also provide an early readout on pharmacodynamics in advance of selecting doses for proof of concept in transgenic mice. The *in vivo* transgenic models we are considering for our lead compound(s) are APP/PS1 for beta-amyloid and Tg4510 or P301S for tau.

### Most Recent Financing - \$4.7 Million by Wellcome Trust

In 2013, we received \$4.7 million (USD) in funding over three years from the Wellcome Trust to progress the discovery and optimization of compounds that are unique in their ability to inhibit the misfolding of both beta-amyloid and tau. The criteria for and selection of the lead compound is adjudicated by an external steering group of drug development experts commissioned by the Wellcome Trust. Our most advanced leads are orally available, permeable to the blood-brain barrier, and, in preliminary studies, show no observed adverse effects at 30mg/kg exposure for 90+ days.

Over the next 18 months, as funded by the Wellcome Trust, we will have a candidate compound by Q3 2015 and commence IND enabling work by Q2 2016. At that point, we will then require approximately \$15 million in a Series A financing to move forward into the IND enabling studies, complete Phase 1 and, establish a Phase 2a proof

of clinical concept. Such a milestone will de-risk our lead compound and also provide an efficacy proof of concept for our entire platform of rationally designed anti-aggregants.

### **Big Pharma Interest – Most Recent Deals**

The emerging understanding of the role of tau, and its interaction with beta-amyloid, represents an exciting new frontier in neurodegenerative disease. Recent transactions validating industry's interest include:

- JNJ's January 2015 licensing of AC Immune's phase 1b tau vaccine for \$509 million
- BMS's April 2014 acquisition of Iperian Inc., including its preclinical assets targeting tau dysfunction \$175million upfront and \$550 million in milestones
- Roche's June 2012 licensing of AC Immune's pre-clinical tau antibody for \$400 million

### **Diagnostic Program for Alzheimer's Also in Development**

Treventis also has a significant program underway for the development of Alzheimer's disease diagnostic agents to be employed in SPECT and PET imaging. Currently available diagnostics target the presence of beta-amyloid in plaques. However, because up to 30 percent of cognitively normal older adults have beta-amyloid plaques in the brain, this fact greatly diminishes the clinical utility of imaging beta-amyloid. The Treventis technology targets another protein called butyrylcholinesterase that is characteristically associated with plaques in Alzheimer's disease but not with those present in cognitively normal older adults and will provide more definitive diagnosis of Alzheimer's disease. Currently, Treventis is engaged in pre-clinical evaluation of <sup>123</sup>I and <sup>18</sup>F reagents for SPECT and PET scanning as diagnostics for Alzheimer's disease. Assuming a well-funded program, it is anticipated that within a year or two, Treventis Diagnostics will be in a position to file for eIND for human clinical trials.

At Treventis, we would welcome your interest and be most pleased to provide you with a non-confidential presentation of our work and planned milestones as we move forward. I look forward to hearing from you.

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