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**ORAL SESSIONS**

**04-05**

**PRECLINICAL (NONHUMAN): THERAPEUTIC STRATEGIES FOR FRONTOTEMPORAL DEMENTIA**

### 04-05-01

**PROGRANULIN GENE THERAPY IMPROVES PATHOLOGY AND REVERSES SOCIAL DEFICITS IN MOUSE MODELS OF FRONTOTEMPORAL DEMENTIA AND NEURONAL CEROID LIPOFUSCINOSIS DUE TO PROGRANULIN MUTATIONS**

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**Background:** Loss-of-function mutations in progranulin (GRN) are a major autosomal dominant cause of frontotemporal dementia (FTD). GRN mutations exhibit a gene-dose effect, with homozygous GRN mutations causing the lysosomal storage disorder neuronal ceroid lipofuscinosis (NCL). GRN polymorphisms are also associated with Alzheimer’s disease. All known disease-causing GRN mutations are loss-of-function mutations, most of which cause progranulin haploinsufficiency. Therefore, boosting progranulin levels is a rational approach to treatment. **Methods:** We generated an AAV2/1-progranulin vector (AAV-Grn) to test whether restoration of progranulin could correct lipofuscinosis and microgliosis in Grn<sup>-/-</sup> mice, and social behavior deficits in Grn<sup>+/--</sup> mice. AAV-Grn or an AAV-GFP control vector were infused into the medial prefrontal cortex (mPFC) of 10–12 month-old wild-type, Grn<sup>-/-</sup>, and Grn<sup>+/--</sup> mice. Grn<sup>-/-</sup> mice were euthanized for assessment of pathology 8–10 weeks later, and Grn<sup>+/--</sup> mice were assessed for social behavior 4–6 weeks later. **Results:** AAV-Grn reduced lipofuscinosis and normalized catechol D activity in Grn<sup>-/-</sup> mice. AAV-Grn also reduced microgliosis in Grn<sup>-/-</sup> mice in several brain regions. At the AAV injection site, AAV-Grn induced an apparent non-self reaction to progranulin that was not observed in wild-type or Grn<sup>+/--</sup> mice and is unlikely to occur in FTD-GRN patients. AAV-Grn reversed social deficits and normalized markers of lysosomal dysfunction in Grn<sup>+/--</sup> mice. **Conclusions:** These data show that restoration of progranulin to progranulin-insufficient mice reduces FTD/NCL-like pathology, normalizes markers of lysosomal dysfunction, and reverses deficits in social behavior. Our AAV-Grn vector expressed progranulin with a C-terminal tag that disrupted binding of progranulin to sortilin, showing that sortilin is not required for these beneficial effects of progranulin. These data provide support for the use of progranulin-boosting therapies in GRN mutation carriers.

### 04-05-02

**THE INVESTIGATIONAL STEREOPURE ANTISENSE OLIGONUCLEOTIDE WVE-3972-01 PREFERENTIALLY REDUCES G<sub>4</sub>C<sub>2</sub> REPEAT-CONTAINING C9ORF72 TRANSCRIPTS: A POTENTIAL THERAPEUTIC APPROACH FOR THE TREATMENT OF FRONTOTEMPORAL DEMENTIA**

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**Background:** A large hexanucleotide GGGGCC (G<sub>4</sub>C<sub>2</sub>) repeat expansion in the first intronic region of the C9ORF72 gene is the most common genetic cause of frontotemporal dementia (FTD). The G<sub>4</sub>C<sub>2</sub> repeat expansion reduces the normal expression of the C9ORF72 gene, causing the production of mutant repeat-containing transcripts that form pathogenic nuclear RNA foci and dipeptide repeat (DPR) proteins. **Methods:** Using a luciferase reporter assay and patient-derived induced pluripotent stem cell (iPSC) neurons, antisense oligonucleotide (ASO) sequences that preferentially reduced repeat-containing transcripts compared to the total transcripts were identified. In vitro activity of the lead candidate, WVE-3972-01, was then confirmed under transfection conditions in patient-derived fibroblasts and under gynotic conditions in neuronal cultures. **Results:** Optimisation of ASO chemistry and the chirality of the phosphorothioate backbone resulted in potent stereopure ASOs, with sub-nanomolar activity in the reporter assay, and nanomolar activity in C9-ALS patient-derived fibroblasts and neurons, as well as in primary neurons from C9BAC mice. Intracerebroventricular injection of WVE-3972-01 into C9BAC mice resulted in substantial and sustained reduction of repeat-containing C9orf72 transcripts, RNA foci, and DPR proteins, without altering total C9orf72 protein levels. **Conclusions:** WVE-3972-01 specifically targets transcripts that contain the G<sub>4</sub>C<sub>2</sub> repeat expansion in the first intronic region of the C9ORF72 gene, thereby preventing production of toxic RNA foci and DPR proteins with minimal alteration of total C9orf72 protein levels. Results suggest that preferential targeting of repeat-containing transcripts using stereopure ASOs may be a viable therapeutic approach for the treatment of FTD.

### 04-05-03

**TAU PATHOLOGY REDUCTION WITH SM07883, A NOVEL, POTENT, AND SELECTIVE ORAL DYRK1A INHIBITOR: A POTENTIAL THERAPEUTIC APPROACH FOR ALZHEIMER’S DISEASE**

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**Background:** Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1a) overexpression in Alzheimer’s Disease (AD) is correlated to Tau hyperphosphorylation, formation of oligomers, and neurofibrillary tangle (NFT) formation. This study assessed the potential of SM07883, an oral DYRK1a inhibitor, to inhibit Tau hyperphosphorylation, aggregation, NFT formation, and associated functional phenotypes, in mouse models. Glial activation was also analyzed to assess potential impact on neuroinflammation. **Methods:** SM07883 selectivity and potency was evaluated in kinase panels and Tau phosphorylation (pTau) was measured in cell-based assays. SM07883 pharmacodynamics were measured in wild type (WT) mice. To assess long-term efficacy, pTau, oligomeric and aggregated Tau were biochemically quantified in brain stems and spinal cords from ten-month-old JNPL3 mice (P301L human Tau overexpression mutation) treated with SM07883 or vehicle (3mg/kg, QD, 3 months). NFT-containing cells were detected and quantified by immunostaining. Astrocyte activation was assessed using glial fibrillary associated protein (GFAP) staining with Western Blot quantification. Motor coordination was evaluated biweekly using a wire hanging test. **Results:** SM07883 selectively...
and potently inhibited DYRK1a kinase activity (IC_{50} = 2nM). In cells, SM07883 reduced pTau at the Threonine 212 site (EC_{50} = 16nM). In pharmacokinetic studies, SM07883 demonstrated good exposure across multiple species (mouse brain : plasma ratio > 3). Compared to vehicle, WT mice showed a dose dependent reduction of transiently induced brain pTau in a pharmacodynamic model starting with a single, 1.25mg/kg SM07883 dose (47%, p<0.0002). JNPL3 mice treated with SM07883 demonstrated significant (p<0.05) reductions in Tau hyperphosphorylation, oligomeric and aggregated Tau, and significantly lower NFT staining compared to vehicle. Reduced GFAP immunoreactivity was confirmed by Western Blotting (37%, p<0.0010). SM07883 was well tolerated with weight gain over the 3 month treatment period and reduced morbidity and mortality in treated animals compared to vehicle. Motor function in the wire hanging test was significantly improved in SM07883-treated JNPL3 mice compared to vehicle (p=0.034) starting 5 weeks after treatment initiation. **Conclusions:** SM07883, a selective and potent, oral, brain-penetrant, DYRK1a inhibitor significantly reduced Tau phosphorylation, the effects of pathological Tau overexpression, and neuroinflammation, and improved functional endpoints compared to vehicle. SM07883 has potential as a treatment for chronic tauopathies such as AD.

**O4-05-04** **TAU IMMUNOTHERAPY FOR ALPHA-SYNUCLEINOPTHY**

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**Background:** The pathological hallmark of synucleinopathies, including Parkinson’s disease, is the deposition of insoluble aggregates of misfolded α-synuclein. However, it is now accepted that soluble aggregates, termed oligomers, are a key causal agent in synucleinopathies. An emerging concept in neurodegenerative disease research and diagnosis is that disease pathologies overlap or even form a continuum. For example, α-synuclein and tau pathology often coexist in Parkinson’s disease and dementia with Lewy bodies. We posit that while α-synuclein is the primary trigger for synucleinopathies, tau likely contributes to secondary symptoms and clinical heterogeneity in these dementia disorders. We further hypothesize that α-synuclein and tau interaction is essential for the development of full neurotoxicity. **Methods:** To test our hypothesis, we used either a preventative (immunotherapy initiated at 4-months of age) or a treatment (immunotherapy initiated at 9 months of age) experimental design using A53T α-synuclein transgenic mice. Monotherapy with either F8H7 anti-α-synuclein oligomers antibody or TOMA anti-tau oligomers antibody as well as combination therapies were performed. Immunotherapy effectiveness was tested with neurobehavioral testing and post mortem analysis of α-synuclein and tau pathology. Neurobehavioral testing included elevated plus maze, SHIRPA, open field, rotarod, grip strength, tail suspension, gait analysis, novel object recognition, fear conditioning, acoustic startle, and pre-pulse inhibition. Immunohistochemical and biochemical assays for α-synuclein and tau pathology were performed on fixed and fresh tissue samples, respectively. **Results:** Preliminary studies indicate that monotherapy and combination therapy alleviated motor deficits in A53T α-synuclein transgenic mice as measured with rotarod, grip strength, and gait analysis. We revealed a depression-like phenotype in A53T mice with tail suspension that was not affected by immunotherapy. **Conclusions:** The effectiveness of monotherapy targeting α-synuclein versus tau with a prevention versus treatment design reveals novel disease mechanisms. Combination therapy in a treatment design appears to be as effective, and possibly more effective, than F8H7 monotherapy targeting α-synuclein oligomers. The effectiveness of tau monotherapy supports the notion that targeting a component of secondary clinical pathology may have translational value.

**O4-05-05** **PREVENTION OF TAU SEEDING AND SPREADING IN TRANSGENIC MOUSE MODELS BASED ON INTRACRANIAL-INJECTION OF P301L-K18 FIBRILS OR ALZHEIMER’S DISEASE LYSATE BY PASSIVE IMMUNOTHERAPY**

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**Background:** In tauopathies such as Alzheimer’s disease (AD), Tau protein becomes pathologically hyperphosphorylated leading to its intracellular accumulation and aggregation which will progressively cause neuronal loss and cognitive decline. Anti-Tau immunotherapy is increasingly considered as a potential treatment to block progression of tauopathies. We report that anti-Tau antibody treatment reduces Tau seeding & spreading in two mouse models of tauopathy. **Methods:** Previously, we showed that an anti-Tau antibody (Ab) produced by UCB Pharma, is able to block Tau aggregation induced by AD patient-derived materials in vitro. Here, we used two in vivo transgenic mouse (tg) models of tauopathies: First, a seed model, based on the unilateral injection of AD brain lysate into the hippocampus of THY Tau30 transgenic mice before the appearance of basal pathology due to transgene expression. Second, a model of Tau spreading, by injecting P301L-K18 tau preformed fibrils in P301L tg mice. Tau pathology induced by seed injection was quantified in the ipsi and contralateral hippocampus after weekly intraperitoneal injections of the anti-Tau Ab or negative control. Hyperphosphorylated abnormal Tau species were detected in brain sections using AT8 (pSer202, pThr205 Tau) or AT100 (pThr212, pSer214) Abs. Tau pathology was then quantitatively analyzed using Mercator (Explora Nova, La Rochelle, France). **Results:** In the seed model, the anti-Tau Ab reduced the AT8 (p<0.001) and AT100 (p<0.01) immunoreactivity by 80% compared to negative control antibody. Significant reduction of Tau pathology was observed in both the ipsi and contralateral hippocampus. In the P301L-K18 injection-based model, the anti-Tau Ab significantly reduced secreted Tau spreading in the contralateral hippocampus compared with the negative control (p<0.05). **Conclusions:** Our data show that the anti-Tau Ab reduces not only Tau pathology induced by intracranial injection of human seeds but also the transsynaptic spreading of Tau pathology. Investigations are now under way to determine the mechanisms by which the anti-Tau Ab reduces Tau pathology mediated by extracellular pathological Tau species.