AevisBio
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AevisBio Pipeline: AEV103

Anti-Neurodegenerative Disease Therapeutics

Company: **Aevis Bio, Inc.** (Daejeon, Korea), **Aevisbio, INC.** (Gaithersburg, MD, USA)

Target indications: **Parkinson's diseases (POC), Alzheimer's Disease, Brain Injuries**

Preclinical POC DATA

- Chronic neuroinflammation drives the progression of neurodegeneration in neurodegenerative disorders including Parkinson's disease (PD). Based on the pivotal role of neuroinflammation in neurodegeneration, immunomodulatory imide drugs (IMiDs) with anti-inflammatory actions have been considered and have shown potential to alleviate symptoms of PD and alter the course of disease progression. AEV103, a novel IMiD, potently mitigates neuroinflammation and provides efficacy in animal models of Alzheimer's disease (AD), traumatic brain injury (TBI), stroke, and potentially PD and levodopa-induced dyskinesia.

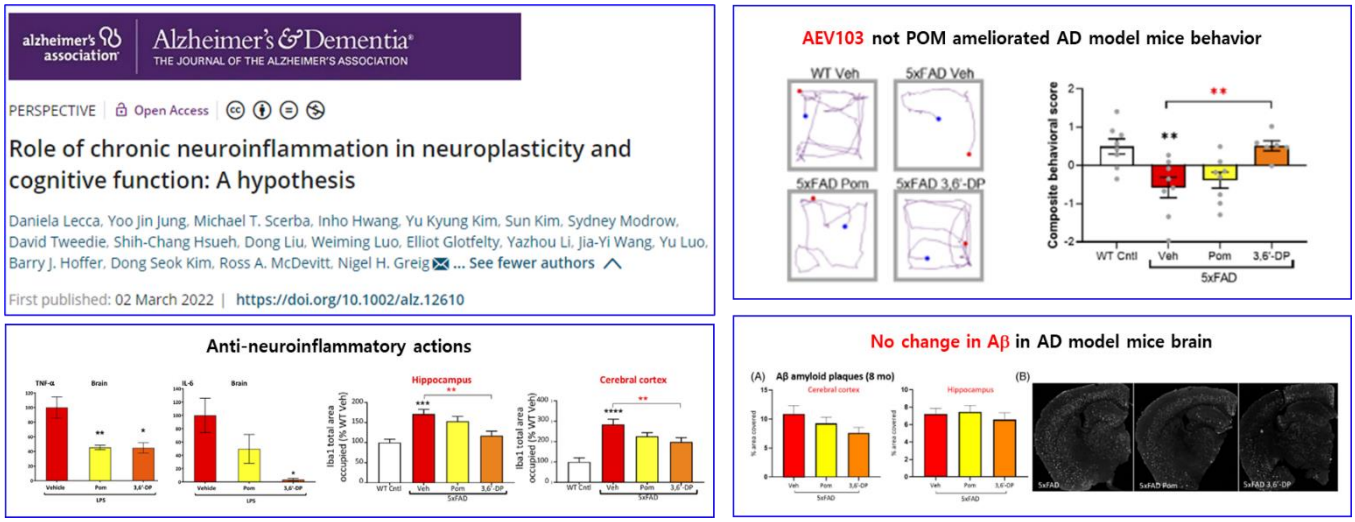

Figure 1. AEV103 (Orange) but not Pomalidomide (Yellow) mitigated behavioral defects of 5X AD mice without affecting Aβ plaques

- Anti-neuroinflammatory, antioxidant and neuroprotective actions of AEV103 may rely on binding to cereblon (CRBN). Moreover, a CRBN-independent pathway regulating TNF-α expression potentiates the anti-inflammatory action of AEV103, as TNF-α provides a master switch that orchestrates the inflammatory response.

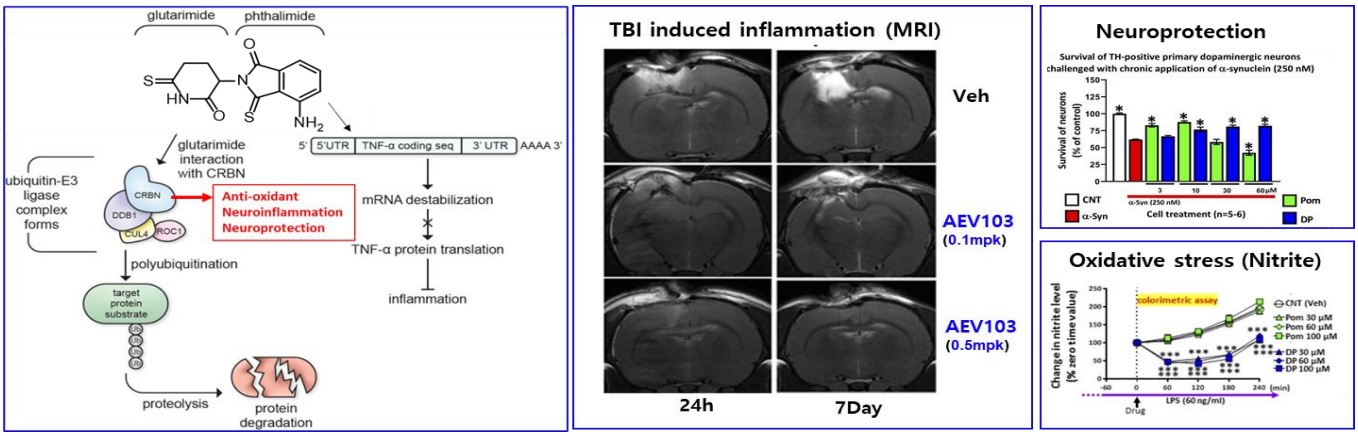

Figure 2. Proposed mechanism of AEV103. AEV103 reduces TBI-induced secondary inflammation (MRI). AEV103 (blue, DP) but not pomalidomide (green, Pom) protects neuronal cell death and reduces oxidative stress

- AEV103 is in the lead optimization process to maximize bioavailability for efficacy studies with oral administration. Non-GLP mammalian chromosome aberration/AMES fluctuation/hERG channel assays have been performed. CRBN-mediated biological actions are under investigation using a proteomics approach as the roles of CRBN are related to the stability of binding partners, and several IMiDs are known to regulate key neo-substrates of CRBN that impact measures of efficacy and potential adverse actions.

CRBN-mediated biological actions

- IMiDs can inhibit TNF-α generation independent of CRBN; however, growing evidence indicates that multiple biological actions of IMiDs are mediated via CRBN (Jung et al., 2020). AEV103 binds CRBN with greater affinity than FDA-approved IMiDs. Therefore, their mode of actions in mitigating pathogenesis of PD/AD/TBI/Stroke are hypothesized to be mainly via CRBN binding; however, they do not impact classical IMiD-CRBN downstream proteins associated with classical IMiD actions on cancer/teratogenicity (Lecca et al., 2022).

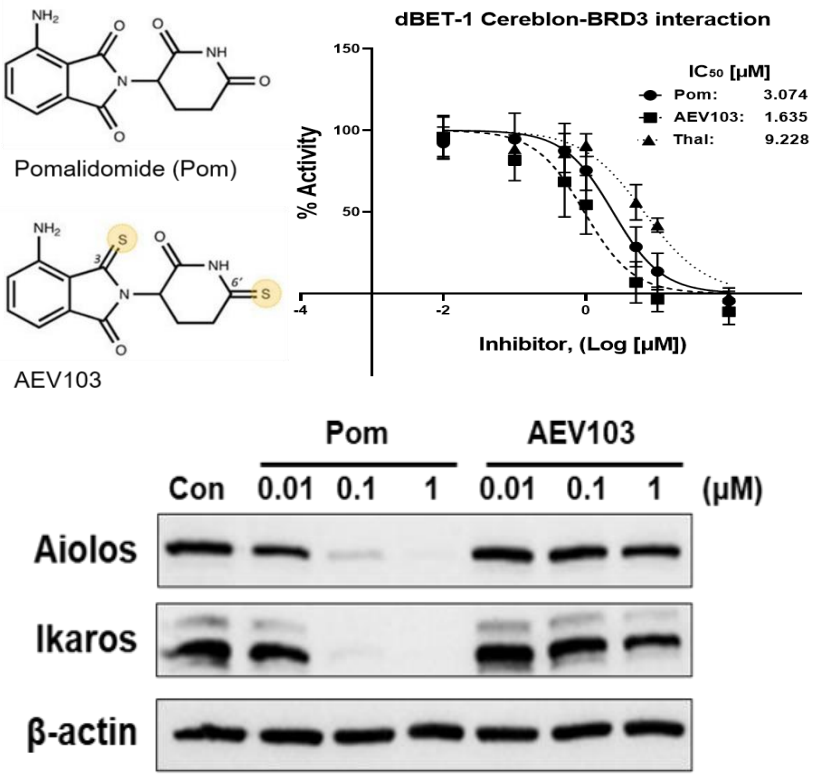

Figure 3. Structure of AEV103 and pomalidomide. AEV103 binds to CRBN but the mode of binding and the resulting biological actions are different from pomalidomide (and other FDA-approved IMiDs)

IP/PATENT Landscape

- AEV103 is protected under US Patent 8,927,725 that is in-licensed to Aevisbio from NIH to support its clinical development for treatment of neurodegenerative disorders.

- CRBN was originally identified as a gene causing human intellectual disability when mutated. It has a proposed role in cerebral tissue development, is expressed in hippocampus among other areas, and is associated with memory and learning processes (Choi et al., 2018). It is a well-known target protein of IMiDs underpinning their therapeutic anti-cancer effects. However, endogenous CRBN roles relate to inflammation, mitochondrial dysfunction and oxidative stress – all critical in pathogenesis of neurological disorders. CRBN mitigates TLR4 signaling (a target of LPS and α-Syn) by binding to TRAF6, TAK1, and c-jun (Min et al., 2016). CRBN regulates p62-mediated α-Syn aggregation. It also interacts with AMPK, GS, ClC-2, BK_{Ca} and p53, thereby regulating neuron excitability and survival (Moon et al., 2020). CRBN degrades CK-1 α to regulate Wnt signaling - a key player in dopaminergic neuron survival and protection (Shen et al., 2021).