An Effective and Safe Drug Against Progression in Alzheimer’s and Parkinson’s Disease

**Background / Unmet Need**
AD affects 5.5M US people, yet no disease-modifying treatment is available. Many of the 0.8M US patients with PD develop dyskinesias and the effects of L-dopa or dopamine agonists “wear off”. GBA-associated PD often manifests at younger age and causes more significant cognitive impairment.

**Description of the Invention**
The etiology of cancers and PD are known to overlap. A common component in the etiology of cancers and AD/PD is “derailed” or “deranged” endocytosis, one of the few biologic processes that do not slow down with age. The invention relates to the down-regulation of serum phospholipids (PL) by αCDs (Figure 1) to prevent endocytosis from overloading aging cells with APP in AD (Figure 3) and α-synuclein in PD (Figure 4).

**Proof of Concept**
βCDs have been effective in vivo against cancers, AD, PD. αCD is more effective against BC than βCD.

**Applications**
Oral/intrathecal ASD-003/004 is effective against AD and (GBA-)PD.

**Competitive advantages**
- Many PD patients inevitably become refractory to L-dopa.
- Treatment options for AD are limited.
- HPβCD is in Phase 2 for the treatment of Niemann-Pick C disease, but was abandoned in AD/PD because of the risk of permanent hearing loss (not applicable to αCDs).
- αCD is generally recognized as safe (GRAS) and approved for injection as an expedient in Caverject®.
Figure 2: EEC underlying mesenchymal tumor cell migration and invasion in carcinomas. Cell migration starts with internalization of β1 integrin. In the early endosome (EE), integrins may be sorted for degradation in lysosomes, recycled to the plasma membrane (RAB4), or transported to the recycling endosome. (adopted from Messei et al. 2008) (De Franceschi 2017).

Figure 3: EEC in Parkinson’s (PD) disease. Following endocytic entry, α-synuclein is transported to early endosomes. From there, it can recycle back to the plasma membrane, either directly or via recycling endosomes. Alternatively, it can be retained in the EEs, which will form LEs/MVBs, and fuse with lysosomes for degradation. Alterations in these processes lead to dysfunctional lysosomes and accumulation of undegraded macromolecules (adopted from Schreij 2015).

Figure 4: EEC in Alzheimer’s (AD) disease. Cell-surface APP can be internalized to endosomes from which it can either be recycled back to the cell surface or delivered to lysosomes for degradation. Within the EE, the acidic environment favors production of Aβ, which can be degraded in lysosomes, accumulated in EEs, or released to extracellular spaces via exocytosis. (adopted from Chen 2014).

Figure 5: Common EEC variations in BC and AD/PD. EEC stages: Formation of clathrin-coated vesicles, E3 ubiquitination, separation of inactive integrin (fast recycling) from active integrins (slow recycling), sorting between secretory, lysosomal, and (slow) recycling pathway, and lysosomal degradation (see Figure 1 for color-matched phosphoisitides).

Pink: most of the genes identified in three BC GWAS had been identified previously in functional studies of BC, PD, and AD. Red and green genes are known breast cancer promoters and suppressors, respectively.

From Figure 5, reducing endocytosis by scavenging PLs in serum restores the balance between robust endocytic control and aging lysosomal function (GBA, ...), prevents lysosomal degradation from becoming overloaded and, thus, intracellular tau tangles (PD) and extracellular Aβ plaques (AD) from being formed.

Contact
ASDERA, LLC
Dr. Knut M. Wittkowski
220 East 70th Street
New York, NY, 10021
U.S.A.

knut@asdera.com
http://www.asdera.com/

References