Summary
ASDERA is proposing exclusive / non-exclusive licenses or collaborations on a family of new interventions to treat or prevent cancers (incl. triple-neg breast cancer, TNBC), Alzheimer’s/ Parkinson’s disease (AD/PD), coronary artery disease (CAD), and other age-related disorders.

Field
This invention relates to a pharmaceutical intervention comprising novel derivatives of α-cyclo-dextrin (αCD) for the prevention and treatment of disorders involving PI-cycle hyperactivity.

US Market (@ $20,000/yr/pp)
10% of HR pos. (HR+) BC × 10 yr = $6B/yr
50% of triple neg (TN) BC × 4 yr = $10B/yr

US Market (prevention @ $3/d/pp)
10% of 77M >50 yr = $10B/yr

Patent status
International patent application PCT/IB2017/000373; Priority date: March 20, 2016.
Knut M. Wittkowski, PhD ScD (Inventor/Assignee)

Development status
505(b)(2): Ready for phase 2b/3 after single mouse bridging study per condition at $500K each to pre-IND meeting.
Prevention: 6 months to approval as a medical food (option).

Relevant Publication
https://doi.org/10.1101/152405. (Wittkowski 2017)

Cyclodextrins in Age-Related Diseases (Senescence) and Disorders Involving Phospholipid Dysregulation

Background / Unmet Need
Breast cancer is the most common cancer in women worldwide, with 250,000 new US cases in 2016. Most breast and prostate cancer deaths are caused by metastases for which treatment options beyond radiation and chemotherapy are urgently needed. AD affects 5.5M US people, yet no disease-modifying treatment is available. Many PD patients develop dyskinesias and the effects of dopamine agonists “wear off”. Atherosclerosis, type-2 diabetes (T2DM), and non-alcoholic fatty liver diseases (NAFLD/NASH) become more prevalent with age.

Description of the Invention
“Derailed” or “deranged” endocytosis (Figure 1) is a common component in the etiology of cancer (β1 integrin Figure 2) and AD (APP Figure 3)/PD (α-synuclein Figure 4), respectively, and also of atherosclerosis and metabolic diseases. The invention relates to down-regulating the PI-cycle by controlling serum phospholipids to match endocytosis to the age-dependent functional decline of downstream intracellular processes.

Proof of Concept
Genetics results (Wittkowski 2017) point to phospholipids (Px) as a drug target against senescence and, thus, to αCDs, which are more effective and safer (too small to fit cholesterol).

Applications
Intrathecal ASD-003 is applicable as a treatment of AD and PD. Oral forms are applicable as an adjuvant e.g. for cancers (targeted) and for prevention / control for many age-related diseases (non-targeted).

Competitive advantages
• Many MC (incl. HR+ BC) and PD patients inevitably become refractory to (hormonal) treatments and L-dopa, respectively.
• βCD carries the risk of permanent hearing loss, but αCD is generally recognized as safe (GRAS) and approved for injection (Caverject®).

Figure 1: Efficacy of βCD in vivo and in vitro and clinical Px upregulation.
Studies have shown βCDs to be effective against many age-related diseases, but scavenging cholesterol can cause permanent hearing loss. CF/IPF: fibrooses; SLE: syst. lupus.
can be degraded in lysosomes, accumulation favors production of Aβ or delivered to lysosomes for degradation. Alterations in these processes lead to dysfunctional lysosomes and accumulation of undegraded macromolecules (adopted from Mosesson 2008) (De Franceschi 2015)

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).

From Figure 5, reducing endocytosis by scavenging serum PLs prevents lysosomal degradation from becoming overloaded and, thus, intraneuronal tau tangles (PD) extraneuronal Aβ plaques (AD) from being formed or macrophages from forming atherosclerotic plaques consisting of dying foam cells (CAD). (Agola 2011; Balla 2013)

References


