20230808 Ambroxol – cleaning inside neurons where mAbs can't reach

Recent clinical trial results from monoclonal antibody (mAb) therapies directed against toxic amyloid beta have ushered in a hopeful era for the treatment of Alzheimer's disease. mAbs including aducanumab (Budd Haeberlein et al., 2022), lecanemab (van Dyck et al., 2023), and donanemab (Sims et al., 2023) have all shown efficacy in clearing amyloid beta from cerebrospinal fluid and serum of patients enrolled in these trials. Clearing amyloid beta in turn has proven effective in reducing levels of biomarkers associated with disease progression such as phosphorylated tau species and markers of neuroinflammation including glial acidic fibrillary protein.

Despite these encouraging results, mAb therapies do not appear to be the final answer to the problem of Alzheimer's disease. Even in successful mAb clinical trials, the effects on rates of cognitive decline in patients receiving treatment have been described by clinicians as modest. This small clinical effect is mirrored by biomarker tests of the neuronal protein neurofilament light chain (NfL). NfL levels in cerebral spinal fluid and serum become elevated when neurons die (Giacomucci et al., 2022). In all mAb clinical trials to date where NfL was tested as a secondary outcome (van Dyck et al., 2023), levels remained similar in samples derived from patients in the placebo and treatment arms of the studies. These results suggest that although mAb therapies are effective at removing the extracellular drivers of pathophysiology of Alzheimer's disease, they are less capable of preventing neuronal death.

Indeed, the pathophysiology of Alzheimer's Disease (AD) begins with disruptions to neuronal proteostasis. Early in the disease process, degradation of proteins such as beta amyloid and tau made in neurons become dysregulated, driving the formation of cytotoxic protein aggregates (Nixon, 2013). Although the pathology begins inside neurons, mAb therapies are directed primarily at the removal of extracellular aggregates of beta amyloid and tau. Therapies that work outside of neurons leaves the intracellular drivers of neurotoxicity intact, indicating a probable mechanism for the continued evidence of neuronal loss suggested by persistently high NfL levels. Thus, it is likely that a complete arrest to the Alzheimer's disease process will require removing both extracellular and intraneuronal drivers of pathology.

Multiple lines of evidence suggest that ambroxol, a drug patented for use in the United States by Zywie, aids neurons in clearing intracellular waste. Originally developed as a mucolytic for treatment of respiratory disease (Malerba and Ragnoli, 2008), more recent evidence has shown that ambroxol enhances the autophagic cellular waste disposal system in multiple beneficial ways (Maegawa et al., 2009; McNeill et al., 2014; Magalhaes et al., 2018; Mullin et al., 2020). Early realizations of its potential included successful treatment of patients of the lysosomal storage disorder, Gaucher's disease (Zimran et al., 2013; Narita et al., 2016; Istaiti et al., 2021) and promising results in the treatment of Parkinson's disease (Mullin et al., 2020).

Ambroxol exerts a direct effect on autophagy by increasing Transcription Factor EB activity. Ambroxol is known to accumulate in lysosomes, the primary degradative organelle of the cell (Fois et al., 2015). There, ambroxol mobilizes intraorganellar calcium stores which results in the activation of lysomome-associated transcription factor EB (TFEB). Activated TFEB relocalizes to the nucleus where it initializes transcription of a gene network with master regulatory control over lysosomal and mitochondrial biogenesis (Medina et al., 2015). Upregulation of this gene network results in increased expression of lysosomal enzymes such as cathepsin D (Sardiello et al., 2009) known to degrade lysosomal substrates including alpha synuclein,

beta amyloid, and hyperphosphorylated tau (Martini-Stoica et al., 2018; Suire and Leissring, 2021). Ambroxol-driven TFEB activity has been shown to enhance expression of these degradative enzymes in the lysosomes of multiple model systems (McNeill et al., 2014; Choi et al., 2018; Magalhaes et al., 2018) as well as markers of mitochondrial turnover (Magalhaes et al., 2018). In terms of AD pathology, ambroxol has been shown to enhance tau clearance in several cell lines (Chauhan et al., 2015; Yang et al., 2022), and reduced serum levels of tau in humans enrolled in a Parkinson's disease clinical trial (Mullin et al., 2020). Zywie has further engineered ambroxol derivatives which more effectively engage cellular autophagy. These compounds are currently pending patent approval.

Over the history of its clinical use, Ambroxol has proven to be an exceptionally safe drug with no known severe drug interactions, highlighting its potential for inclusion in drug cocktails for the treatment of Alzheimer's disease. Ambroxol has been shown to be well-tolerated at high doses even by medically fragile patients (Kantar et al., 2020) or complex (Mullin et al., 2020; Istaiti et al., 2021) patients. Ambroxol also has exceptionally high brain penetrance when taken orally (Mullin et al., 2020), simplifying administration of clinical trials.

Thus, Ambroxol serves a complimentary and potentially synergistic function to therapeutic approaches like those exemplified by lecanemab, a monoclonal antibody that attaches to and removes aggregated amyloid beta from the brain parenchyma (van Dyck et al., 2023). Ambroxol has an excellent safety profile with gram-level dosage well-tolerated by patients and can be taken with many standard-of-care drugs with minimal risk of adverse interactions. It has been approved for decades for use in the treatment of bronchopulmonary disease, further mitigating the risk of unexpected long-term side effects arising in chronic use cases. Ambroxol is therefore a strong candidate compound for use in drug cocktails designed to treat Alzheimer's disease.

References:

Budd Haeberlein S et al. (2022) Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis 9:197–210.

Chauhan S, Ahmed Z, Bradfute SB, Arko-Mensah J, Mandell MA, Won Choi S, Kimura T, Blanchet F, Waller A, Mudd MH, Jiang S, Sklar L, Timmins GS, Maphis N, Bhaskar K, Piguet V, Deretic V (2015) Pharmaceutical screen identifies novel target processes for activation of autophagy with a broad translational potential. Nature Communications 6:8620.

Choi SW, Gu Y, Peters RS, Salgame P, Ellner JJ, Timmins GS, Deretic V (2018) Ambroxol Induces Autophagy and Potentiates Rifampin Antimycobacterial Activity. Antimicrobial Agents and Chemotherapy 62.

Fois G, Hobi N, Felder E, Ziegler A, Miklavc P, Walther P, Radermacher P, Haller T, Dietl P (2015) A new role for an old drug: Ambroxol triggers lysosomal exocytosis via pH-dependent Ca^{2+} release from acidic Ca^{2+} stores. Cell Calcium 58:628–637.

Giacomucci G, Mazzeo S, Bagnoli S, Ingannato A, Leccese D, Berti V, Padiglioni S, Galdo G, Ferrari C, Sorbi S, Bessi V, Nacmias B (2022) Plasma neurofilament light chain as a biomarker of Alzheimer's disease in Subjective Cognitive Decline and Mild Cognitive Impairment. J Neurol 269:4270–4280.

Istaiti M, Revel-Vilk S, Becker-Cohen M, Dinur T, Ramaswami U, Castillo-Garcia D, Ceron-Rodriguez M, Chan A, Rodic P, Tincheva RS, Al-Hertani W, Lee BH, Yang C-F, Kiec-Wilk B, Fiumara A, Rubio B, Zimran A (2021) Upgrading the evidence for the use of ambroxol in Gaucher disease and GBA related Parkinson: Investigator initiated registry based on real life data. Am J Hematol 96:545–551.

Kantar A, Klimek L, Cazan D, Sperl A, Sent U, Mesquita M (2020) An overview of efficacy and safety of ambroxol for the treatment of acute and chronic respiratory diseases with a special regard to children. Multidiscip Respir Med 15:511.

Maegawa GHB, Tropak MB, Buttner JD, Rigat BA, Fuller M, Pandit D, Tang L, Kornhaber GJ, Hamuro Y, Clarke JTR, Mahuran DJ (2009) Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease. J Biol Chem 284:23502–23516.

Magalhaes J, Gegg ME, Migdalska-Richards A, Schapira AH (2018) Effects of ambroxol on the autophagy-lysosome pathway and mitochondria in primary cortical neurons. Scientific Reports 8:1385.

Malerba M, Ragnoli B (2008) Ambroxol in the 21st century: pharmacological and clinical update. Expert Opinion on Drug Metabolism & Toxicology 4:1119–1129.

Martini-Stoica H, Cole AL, Swartzlander DB, Chen F, Wan Y-W, Bajaj L, Bader DA, Lee VMY, Trojanowski JQ, Liu Z, Sardiello M, Zheng H (2018) TFEB enhances astroglial uptake of extracellular tau species and reduces tau spreading. J Exp Med 215:2355–2377.

McNeill A, Magalhaes J, Shen C, Chau K-Y, Hughes D, Mehta A, Foltynie T, Cooper JM, Abramov AY, Gegg M, Schapira AHV (2014) Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain 137:1481–1495.

Medina DL, Di Paola S, Peluso I, Armani A, De Stefani D, Venditti R, Montefusco S, Scotto-Rosato A, Prezioso C, Forrester A, Settembre C, Wang W, Gao Q, Xu H, Sandri M, Rizzuto R, De Matteis MA, Ballabio A (2015) Lysosomal calcium signalling regulates autophagy through calcineurin and TFEB. Nat Cell Biol 17:288–299.

Mullin S et al. (2020) Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucocerebrosidase Gene Mutations: A Nonrandomized, Noncontrolled Trial. JAMA Neurol 77:427–434.

Narita A et al. (2016) Ambroxol chaperone therapy for neuronopathic Gaucher disease: A pilot study. Ann Clin Transl Neurol 3:200–215.

Nixon RA (2013) The role of autophagy in neurodegenerative disease. Nat Med 19:983–997.

Sardiello M, Palmieri M, Ronza A di, Medina DL, Valenza M, Gennarino VA, Malta CD, Donaudy F, Embrione V, Polishchuk RS, Banfi S, Parenti G, Cattaneo E, Ballabio A (2009) A Gene Network Regulating Lysosomal Biogenesis and Function. Science 325:473–477.

Sims JR et al. (2023) Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 330:512–527.

Suire CN, Leissring MA (2021) Cathepsin D: A Candidate Link between Amyloid β-protein and Tauopathy in Alzheimer Disease. J Exp Neurol 2:10–15.

van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T (2023) Lecanemab in Early Alzheimer's Disease. New England Journal of Medicine 388:9–21.

Yang SY, Taanman J-W, Gegg M, Schapira AHV (2022) Ambroxol reverses tau and α-synuclein accumulation in a cholinergic N370S GBA1 mutation model. Human Molecular Genetics 31:2396–2405.

Zimran A, Altarescu G, Elstein D (2013) Pilot study using ambroxol as a pharmacological chaperone in type 1 Gaucher disease. Blood Cells Mol Dis 50:134–137.