Alzheimer’s Disease Therapeutics: Alternatives to Amyloid 2021

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1. The Role of Physiological Functions of TDP-43 in FTLD and ALS Based on hTDP-43 and Transgenic Mouse Models

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Recapitulating certain pathological phenotypes in FTLD and ALS, TDP-43 transgenic models can express hTDP-43 wild types or ALS-like mutants. Previous studies defined that homogeneous toxicity to ALS associated disease mutants can be caused by wild type TDP-43 if navigated at high enough level. Considering nuclear toxicity theory states that either alternation or loss of TDP-43 nuclear function (transcription, splicing, miRNA processing etc.) and cytoplasmic toxicity theory suggests some other separated toxic gain of function (i.e., promotion of stress granule formation). We've stated two methods by showing some physiological functions of TDP-43 (Immunoprecipitation techniques(combined CLIP-sequencing-revealed RNA footprints of Nova in multiple mouse brains), UG-rich sequence of RNAs-binds to 3’ UTRs of mRNA, nuclear depletion of TDP-43-performed by dysregulating of the splicing processes in motor neurons, overabundance of TDP-43, Q331K and M337V mutations can be used to change mRNA splicing processes in rodent models) and by adjusting levels of TIA-1 and G3BP1. Immunoprecipitation shows low background noise and high resolution in advantages. Overabundance of TDP-43 forms dysfunctional complexes in disadvantages. By preventing cytoplasmic toxicity SG formation can be retard when regulating levels of TIA-1 and G3BP1. But it remains unclear whether our solution can confirm some advantages or not for the more toxic ALS-associated disease mutants.

2. Lateral Entorhinal Cortex Recruits Specific Inhibitory Neurons in Hippocampal Area CA1

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Episodic memory formation relies on the functional interactions between two brain regions found in the medial temporal lobe: the entorhinal cortex and hippocampus. The lateral entorhinal cortex (LEC) is one of the first brain regions affected by early-stage Alzheimer’s Disease (AD). Both plaque and tangle pathophysiology have been shown to spread from LEC to the CA1 subdivision of the hippocampus. However, the circuit interactions between these two brain regions is underexplored. Our study examined how long-range excitatory LEC inputs modulate the excitation-inhibition balance in area CA1. In a non-pathological mouse animal model, we used acute slice electrophysiology and optogenetics to characterize the connectivity of LEC inputs onto various neuronal populations in area CA1. We demonstrated that these inputs specifically recruit the vasoactive intestinal peptide (VIP)- and cholecystokinin (CCK)-expressing inhibitory neuron populations. Our findings identify key interneuron types that may be recruited by LEC inputs during non-pathological memory formation. The disruption of the LEC-to-CA1 neural circuit likely contributes to the memory impairment seen in AD patients, but previous studies investigating hippocampal interneuron dysfunction in AD mouse models have not focused on VIP- or CCK-expressing interneurons. Thus, our results suggest two inhibitory neuron populations that future studies should investigate as potential cellular targets for Alzheimer’s Disease therapies.
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We examine the effect of XPro1595, a next generation tumor necrosis factor (TNF) inhibitor that selectively neutralizes soluble TNF, on white matter metrics of neuroinflammation, axonal density and myelin and compared these to traditional CSF biomarkers in a Phase1b trial in 16 AD patients with biomarkers of inflammation (ADi). MRI was assessed every three months using 3T structural and diffusion MRI. Quantitative tractometry was done using indices of free-water (a proxy of neuroinflammation), apparent fiber density (AFD – a proxy of axon integrity) and tissue radial diffusivity (RDt – a proxy to myelin content) in the AD bundles as composite biomarkers of neuroinflammation, axon regeneration and remyelination respectively. MRI metrics showed a progressive improvement over 12 months in all white matter metrics; including: i) a 46% reduction in free-water (neuroinflammation), ii) 17% increase in AFD, iii) a 17% reduction in RDt, iv) and an increase in total WM volume and left temporal lobe volume increased. These measures correlated with multiple protein CSF biomarkers of neuroinflammation and neurodegeneration. In this Phase 1b trial, we showed that XPro1595 improves white matter structure within bundles that are specifically affected in AD. High correlation with gold standard CSF protein neuroinflammatory and neurodegenerative biomarkers validate the use of non-invasive MRI tools to measure WM pathology.

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Regional abdominal adiposity can be used to reveal new potential mechanistic pathways underlying the adipose-brain link. The Israel Registry for Alzheimer’s Prevention(N=500) was capitalized. Regional abdominal adiposity(abdominal(AAT) visceral(VAT), pancreatic, and hepatic) was assessed by MRI(N=92). Adiposity-related factors of VAT(TNF-α, Leptin), pancreas (PP, PYY), and liver(PAI-1)(N=26) were quantified by MILLIPLEX. Pancreatic fat negatively associated with hippocampal and IFG volumes, and executive
memory. Hepatic fat negatively associated with hippocampal volume and executive memory. VAT percentage negatively associated with amygdalar and hippocampal volumes, while VAT volume negatively associated with executive and working memory, language, and global cognition. PAI-1 and PP negatively associated with hippocampal and IFG volumes. Levels of PYY, PAI-1, and TNF-α negatively associated with executive memory. This comprehensive large-scale study will identify key neuropathological indices linking regional abdominal adiposity with cognition, and ascertain adiposity-related factors as modifiable potential mechanisms to prevent or delay AD.

5. Total Brain Health Intervention in Independent Living Communities

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Aging adults often experience some loss in cognition and health. Decades of research shows that cognitive function and long-term brain vitality are best supported by ongoing and robust engagement across physical, intellectual, and socio-economic wellbeing. The Total Brain Health Intervention® was designed based on three evidence-backed methods: training across the wellness spectrum, social-based brain training, and experiential learning. Here, we report the results from this intervention. Adults aged 65 and older (N=549) were recruited from 23 Acts Retirement-Life Communities. Groups met weekly across 8 sessions over 2 months. The Brain Workout Group learned about behaviors promoting cognitive (how to focus attention), physical (how to eat healthy), and socio-emotional (how to stay socially engaged) wellbeing. The Memory Group learned how memory works, what environmental factors impact memory, and how to use memory strategies. The Book Club discussed brain health knowledge from a new book chapter each week. Participants were given surveys to assess their wellbeing and brain knowledge at pretest, posttest, and 2 months later. Compared to controls, the three active groups showed greater gains in brain knowledge, memory self-efficacy, and memory strategy use at posttest and follow-up. Daily health habits increased most in the Brain Workout and Book Club Groups compared to controls at post-test only. These results provide strong support for this community-based intervention.


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After aging itself, female sex is the major risk factor for late-onset Alzheimer’s disease (AD), the most common cause of dementia, with postmenopausal women accounting for over 60% of all those affected.
Emerging data indicate sex differences in AD pathophysiology, onset, and progression, which may help account for the higher prevalence in women. Notably, AD-related brain changes develop during a 10-20 year prodromal phase originating in midlife, thus proximate with the hormonal transitions of endocrine aging characteristic of the menopause transition. Preclinical evidence for neuroprotective effects of gonadal sex steroid hormones, especially 17beta-estradiol, strongly argue for associations between female fertility, reproductive history, and AD risk. Epidemiological studies have yielded contrasting results of both protective and harmful effects of estrogen exposure on dementia risk. However, brain imaging studies provide more consistent evidence for negative consequences of estrogen deprivation on brain structure, function, and biochemistry, and for positive associations between greater cumulative lifetime estrogen exposure and lower AD risk in women. Herein, we review the existing literature of observed associations between female-specific reproductive health factors and AD risk in women, with a focus on the role of endogenous and exogenous estrogen exposures as a key underlying mechanism to inform preventative efforts and therapeutic development.


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The clinical diagnosis of Alzheimer’s Disease (AD) is frequently not well correlated to imaging findings with existing Positron Emission Tomography (PET) tracers. Therefore, identifying novel biomarkers for neurodegeneration through PET imaging is a top priority in biomedical research. Loss of microtubules (MTs), a major component of cytoskeleton, have been identified as a validated biomarker for neurodegenerative disorders including AD. [11C]MPC-6827 developed by our team is the specific and validated blood brain barrier-penetrating PET tracer, currently available for in vivo imaging of MTs in brain. Herein, we present the in vivo comparison [11C]MPC-6827 with gold standard amyloid tracer [11C]PiB, and tau tracer [18F]MK6320 in transgenic mice models of J20 (amyloid line), hTau and PS19 (tau line) and corresponding age matched controls. PET image analyses show reduced brain uptake of [11C]MPC-6827 in all transgenic mice group compared to control. Whereas, [11C]PiB and [18F]MK6320 tracers exhibited only modest higher binding in amyloid and tau groups respectively than corresponding controls. Our preliminary findings show that in J20, hTau and PS30 transgenic mice, binding of the MT PET ligand [11C]MPC-6827 exhibit higher effect size and standardized uptake value than the amyloid and tau PET tracers. Therefore, [11C]MPC-6827 can be used as a potential PET tracer for human brain imaging of AD and related neurodegenerative diseases.
8. Detecting Alzheimer’s Associated MicroRNAs Using a DNA-Based Smart Reagent

Arun Richard Chandrasekaran, PhD, Ken Halvorsen, PhD; The RNA Institute, University of Albany, State University of New York

Alzheimer's disease (AD) is the most common neurodegenerative disorder, with significant research efforts devoted to identifying new biomarkers for clinical diagnosis and treatment. MicroRNAs have emerged as likely disease regulators and biomarkers for AD, now implicated as having roles in several biological processes related to progression of the disease. In this work, we use the miRacles assay (microRNA activated conditional looping of engineered switches) for single-step detection of AD-related microRNAs. The technology is based on conformationally responsive DNA nanoswitches that loop upon recognition of a target microRNA and report their on/off status through an electrophoretic readout. Unlike many methods, our approach directly detects native microRNAs without amplification or labeling, eliminating the need for expensive enzymes, reagents, and equipment. For known AD-related microRNA miR-107, we demonstrated sensitivity of ~8 fM, specificity among four similar microRNAs of the same family, and simultaneous multiplexed detection of those four microRNA targets. Toward clinical use, we screened 56 AD-related microRNAs and found four that showed detectable differences between total RNA extracts derived from human healthy and AD brain samples. In the context of AD, this "smart reagent" could facilitate biomarker discovery, accelerate efforts to understand the role of microRNAs in AD, and have clinical potential as a diagnostic or monitoring tool for validated biomarkers.

9. Neurogenesis Hypothesis: a Case Study- Phase 2A Clinical Trials of NA-831 for the Treatment of Alzheimer’s disease

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The hippocampus is a brain area critical for learning and memory and one of the first brain regions to be affected in Alzheimer’s disease (AD). Hippocampal neurogenesis is persistent through the tenth decade of life and is detectable in patients with Alzheimer’s disease. NA-831 is a small drug molecule and a positive modulator of AMPA receptors. The main neuropsychotropic effects of NA-831 are the results of accumulation of Brain Derived Neurotropic Factor (BDNF) upon the activation of AMPA receptors. NA-831 serves as a catalyst to restore neurogenesis in Alzheimer’s patients, increasing DCX+PCNA+ cells. A randomized clinical trial of NA-831 was performed in 32 patients with MCI, and 24 patients with mild and moderate Alzheimer’s disease. The patients with MCI received 10 mg of NA-831 or placebo orally per day. The patients with mild and moderate Alzheimer’s disease received 30 mg of NA-831 or placebo orally per day. NA-831 showed a significant improvement for MCI patients, with ADAS-Cog-13 score of an average of 3.4 as compared to the placebo after 24 weeks of treatment (p = 0.01; ITT). NA-831 showed a significant improvement for patients with mild and moderate AD with the ADAS-Cog-13 score change of an average of 4.1 as compared to the placebo after 24 weeks of treatment (p = 0.001; ITT). CIBIC-Plus showed 78 % patients improved (p = 0.01; ITT). Details of the Phase 2A clinical trials and the neurogenesis hypothesis will be presented and discussed.
10. KYNA-1 Analog Exert an Immunomodulatory and Neuroprotective Role in the Transgenic Model for Tauopathy

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Tauopathies are a heterogeneous group of neurodegenerative disorders, pathologically characterized by intracellular inclusions of the microtubule-binding protein, tau. The pathogenesis of tauopathies has been associated with systemic inflammation and disruption of the serotonergic signaling system. A common link between neuroinflammation and disruption of the serotonergic signaling system is the catabolism of L-tryptophan (L-TRP). Kynurenines exert immunomodulatory and neuroactive properties and can influence the central nervous system. Several preclinical studies have led to the hypothesis that microglial-derived quinolinic acid harbor neurotoxic functions while astrocyte-derived kynurenic acid neuroprotective functions. In neurodegenerative conditions, the TRP metabolism is shifted in the direction of neurotoxic agents and the significant reduction of neuroprotectant products. The shift of the TRP metabolism in the neuroprotectant direction may serve as a new and effective potential therapeutic approach. In the present study, we used synthesized neuroprotective derivate of kynurenic acid N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamid (KYNA-1). The analog was intraperitoneally administrated into a transgenic rat model for tauopathies. At low concentration KYNA-1 treatment induced a marked decrease in glial fibrillary acid protein (GFAP) levels and reduction in sarkozyl-insoluble tau. Acknowledgment: CRP/19/016 (ICGEB), APVV-18-0302, VEGA 2/0129/21

11. Alignment of Alzheimer’s Disease Amyloid-β Peptide and Herpes Simplex Virus-1 pUL15 C-Terminal Nuclease Domain

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Background: The cause of Alzheimer's disease (AD) is poorly understood. Neurotropic microbes, particularly herpesviruses, might set off chronic neuroinflammation. Amyloid-β (Aβ) has antimicrobial properties and could represent a brain defense against infection. Objective: We searched for protein sequence alignment between herpes simplex virus type I (HSV-1) HSV-2, and Aβ. Methods: Protein data bank (pdb) structures for Aβ, HSV-1, and HSV-2 were searched on the RCSB Protein Data Bank. The protein structures were superimposed and aligned on PYMOL v 2.3.4. Results: For HSV-1 and Aβ, amino acid residues ser549 - his569 of HSV-1 aligned closely with residues asp7 - asn27 of Aβ. For HSV-2 and Aβ, amino acid residues of HSV-2 aligned less closely than those of HSV-1 with residues of Aβ. Conclusion: Conjugating and binding to the same alpha helix in the HSV-1 protease, Aβ could be marking HSV-1 for attack by the immune system, providing a rapid inherited immune response to a destructive neurotropic virus that would otherwise require the more time-consuming involvement of T-cells, B-cells, and the adaptive immune system. But older people do not respond to viral infections as well as younger individuals. When HSV-1 infection advances in an old person, more and more amyloid is produced, forming an adhesive web. As the brain tries to hold the pathologic process in check, neuroinflammation increases and spreads. Progressive neurodegeneration and cognitive decline are the outcome.
**12. Induction of a Novel AIF Isoform Causes Mitochondrial Dysfunction and Neurodegeneration**

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Introduction: Apoptosis-inducing factor (AIF) plays a fundamental role in mitochondrial bioenergetics and also mediates caspase-independent cell death. It remains unknown which AIF splicing isoform will be induced under pathological conditions and how it impacts neurodegeneration. Methods: AIF splicing induction and its roles were determined by its biochemical properties, cell death analysis, morphological and functional alterations and animal behavior. Three animal models were applied to explore underlying mechanisms of AIF splicing-induced neurodegeneration. Results: A novel splicing AIF isoform was identified and named AIF3. AIF3 splicing in mouse brain caused severe neurodegeneration similar to AD. AIF3 splicing is associated with both mitochondrial dysfunction and AIF3 nuclear translocation, leading to neuronal cell death. Meanwhile, AIF3 inhibited NADH oxidase activity, ATP production, oxygen consumption, and mitochondrial biogenesis. Conclusions: We identified AIF3 as a disease-inducible isoform and established AIF3 splicing as a good mouse model for neurodegenerative diseases including AD. The molecular mechanism underlying neurodegeneration involves mitochondrial dysfunction and AIF3 nuclear translocation, resulting from the synergistic effect of loss-of-AIF and gain-of-AIF3. Our study provides a valuable tool to understand the role of AIF3 splicing in brain and a potential therapeutic target to prevent/delay the progress of neurodegenerative diseases.

**13. Epichaperomes: An Emerging Target for Precision Medicine in Alzheimer’s Disease**

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Alzheimer’s disease (AD) is a disease of complex etiology in which genetic, epigenetic and environmental factors, alone or combined, lead to patient-specific alterations in brain circuitry and ultimately, in the cognitive decline associated with AD. Such complexity has limited our ability to identify therapeutic target(s) to account for the multiple pathological pathways that contribute to AD progression. Our recent findings that stressors and vulnerabilities associated with AD rewire proteome-wide connectivity, and thus cellular function through epichaperomes, maladaptive disease-associated pathologic scaffolds composed of tightly bound chaperones, co-chaperone and other factors, provide such a core unifying AD mechanism. In AD, epichaperomes negatively impact assembly of proteins important for synaptic...
plasticity, cell-to-cell communication, protein translation, cell cycle re-entry, axon guidance, and metabolic processes and inflammation, all biological functions known to decline in AD. This disrupts and remodels brain networks ranging from intercellular to brain connectome levels. Therefore, epichaperomes are an emerging target that provides unique precision medicine opportunities for detection and reversal of functional imbalances associated with AD. Ultimately, this approach may aid the transition from a limited single-alteration perspective in AD treatment to a comprehensive network-based mindset.

14. An Oral Disease-Modifying Drug to Improve Autophagy and Reduce Inflammation in Neurodegenerative Diseases (NDs) and lysosomal storage diseases (LSDs) by Modulating the Endocytosis-Lysosome-Autophagy (ELA) Axis

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Introduction: There are few disease-modifying drugs (DMTs) for NDs, incl. Alzheimer’s disease (AD). HP-beta-cyclodextrin (HPbCD) improved some behavior in a model of AD (Yao 2012), but causes cholesterol-related ototoxicity (Hastings 2021). After recent phase 1 and 2 trials of intravenous (iv) HPbCD given over >8 h every 14 d showed a reduction of brain tau protein after 84 d, the FDA accepted HPbCD as a brain-active drug against Neyman-Pick type C (NPC) and AD (Hastings 2021).

Methods and Results: A reanalysis of genetics data using a novel computational biostatistics approach (Wittkowski 2008) pointed to phospholipid (PL)-related ELA dysregulation. Intraperitoneal PL-specific HP-aCD (HPaCD, 6 sugars) is not ototoxic (Davidson 2016) and more effective in vitro against LSDs (McKew 2014). It was also more effective than HPbCD (7 sugars) in models of breast cancer (related to NDs, Ancidoni 2021) and effective in models of Huntington’s disease (HD) and ALS (Wittkowski 2018). Oral aCDs, however, are not absorbed from the intestine unless the diet contains milkfat. With the milk compound capric acid (C10) added, some HPaCD and increases in PLs were seen in urine, but twice as much with a clathrate complexing them (Wittkowski 2019).

Conclusion: Several barriers against convenient, safe, and effective DMTs for NDs and LSDs have recently been overcome:

• HPbCD was shown to act by “depleting” PLs, not cholesterol,
• A PL-specific HPaCD/C10 clathrate is intestinally absorbed, effective, and safe,
• The FDA (in 02-2021) has accepted HP-CDs as brain-active drugs,

Hence, modulation of the ELA axis with oral aCD compounds (to mimic the known benefit intermittent fasting) emerges as an alternative to targeting A-beta or tau.