Chronically Elevated Cortisol and Cognitive Impairment: The Therapeutic Potential of Xanamem™, a Potent Inhibitor of the 11β-HSD1 Enzyme

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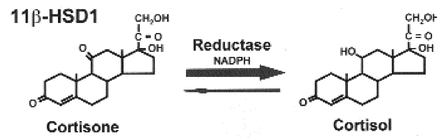
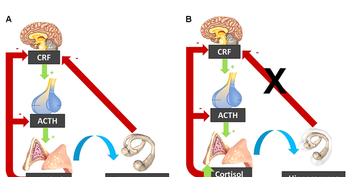
Introduction

- Xanamem™ is a potent and selective 11β-HSD1 inhibitor.
- 11β-HSD1 amplifies cortisol in brain regions, including the hippocampus.
- There is abundant evidence from animal and clinical studies linking elevated cortisol with hippocampal dysfunction, leading to poor learning, recall, and objective memory impairment.
- Thus, interventions that reduce cortisol levels may improve cognition and have long-term benefits in reducing the risk of glucocorticoid toxicity and thereby reducing the risk of development and/or progression of dementia.
- Xanamem™ has potential to treat additional indications beyond AD.



Background Research

A. Elevated cortisol may lead to HPA-axis dysregulation and hippocampal atrophy[1]



(A) In normal circumstances, the CRF released by the hypothalamus activates ACTH release by the pituitary gland, which stimulates the adrenal glands to secrete cortisol. Cortisol inhibits its own secretion via a negative feedback loop. The hippocampus inhibits the hypothalamo-pituitary-adrenal axis. **(B)** When cortisol is elevated, it can induce hippocampal atrophy, which "lifts the brake" on the hypothalamo-pituitary-adrenal axis. The resulting cortisol increase induces further hippocampal atrophy, resulting in a vicious circle. CRF, corticotropin-releasing factor; ACTH, Adrenocorticotropic hormone

B. How elevated cortisol levels may contribute to known AD pathogenesis

Direct:

[1] Increased levels of amyloid precursor protein (APP) and BACE leading to increased Ab42 formation[2,3,4]
[2] Reduced Ab42 degradation via attenuation of insulin degrading enzyme[5]

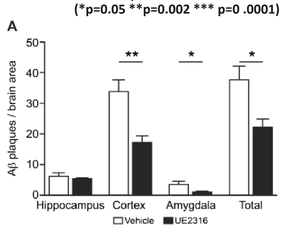
Indirect:

[1] Insulin resistance
[2] Angiopathic and antiangiogenic actions
[3] Increased excitatory (N-methyl-D-aspartate) neurotransmission[2,3]
[4] Increased postsynaptic calcium signaling promoting neurotoxicity, metabolic endangerment of neurons, and deleterious alterations in neuroimmune function[6]
[5] Facilitation of β-adrenergic signaling inhibiting the medial prefrontal cortex thus leading to an impairment in frontal functions, in particular in working memory[7]
[6] Alteration of long-term potentiation (LTP), potentially worsening long-term memory consolidation[8]
[7] Broadly: positive or negative early life experiences may play a key role in cortisol dysregulation[9]

Results to Date

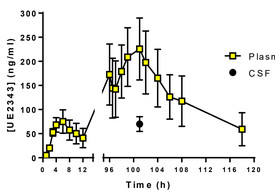
A. Pre-Clinical Efficacy Studies[10]

Total plaque area of short-term (29 days) treated mice was decreased in UE2316 (Xanamem analog) in comparison with vehicle (*p=0.05 **p=0.002 *** p=0 .0001)



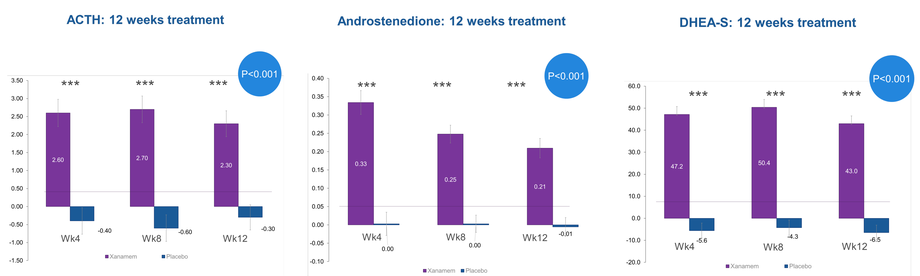
B. ACW0001 MAD CSF Study[11]

Measured CSF Concentration: Confirming Brain Penetration (UE2343 = Xanamem)



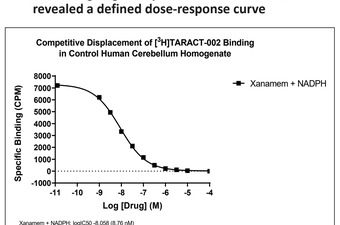
C. ACW0002 XanADu Study

PD biomarkers of ACTH, androstenedione, DHEAS, and cortisone (not shown), all showed statistically significant results indicating successful target engagement of 10mgQD Xanamem™



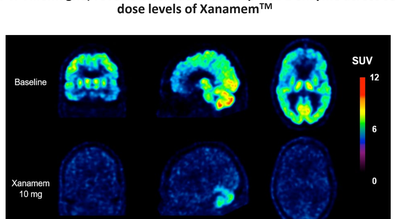
D. Receptor Binding Studies

Homogenate binding studies with Xanamem at Gifford Biosciences are ongoing. Competition studies have to date revealed a defined dose-response curve



E. Phase I PET Target Occupancy Study

Ongoing Investigator-Initiated Trial (IIT) at Austin Health (Prof C. Rowe and A/Prof V. Villemagne) reveals blockade of the 11β-HSD1 enzyme across several dose levels of Xanamem™



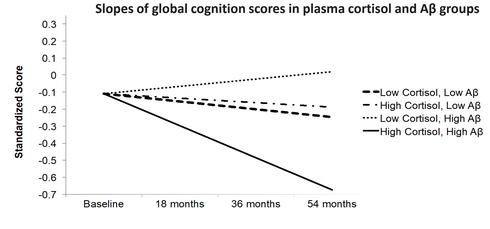
Independent Supportive Research

Many independent studies, including the Australian Imaging Biomarkers and Lifestyle Study of Ageing[12] and the Framingham Study[13] have concluded that higher plasma cortisol is significantly related to lower hippocampal and gray matter volume, and that chronic elevated cortisol could exacerbate pathological processes associated with the onset and progression of Alzheimer's disease.

A. Association between cortisol levels and the risk of developing dementia[12]

"Plasma cortisol, brain amyloid-b, and cognitive decline in preclinical Alzheimer's disease: a 6-year prospective cohort study"[12] revealed that high baseline plasma cortisol levels are associated with 2.2 times the risk of Aβ+ and are associated with greater decline in: global cognition (Cohen's d=0.42), episodic memory, and attention (Cohen's d=0.31).

Slopes of global cognition scores in plasma cortisol and Aβ groups



Future Directions

Numerous independent studies have highlighted the potential complexities of attempting to directly modify the HPA-axis to reduce chronically elevated cortisol levels; these studies do though strongly recommend therapies targeted toward lowering plasma cortisol should be pursued.

Xanamem™ provides a mode of action wherein it inhibits intracellular cortisol production through inhibition of the 11β-HSD1 enzyme; this remains an elegant and scientifically robust target for both symptomatic treatment and potential disease course modification in Alzheimer's disease, non-Alzheimer's dementias, and other neurodegenerative disorders.

Further studies are needed to confirm the therapeutic potential of Xanamem™ for the treatment, prevention, and/or management of cognitive impairment.

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