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UNMET NEED

Clinical responses to amyloid- and tau-directed therapies in AD remain highly variable, particularly among individuals with metabolic dysfunction. Brain energy failure and peripheral metabolic stress (insulin resistance, obesity, prediabetes and type-2 diabetes) are tightly correlated, substantially increase AD risk and accelerate cognitive decline, yet metabolic status is rarely incorporated into therapeutic strategies or trial design. This gap represents both a biological blind spot and a missed opportunity for patient stratification and combination therapy.

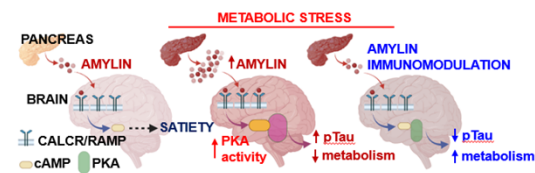
INNOVATION & DIFFERENTIATION

Circulating amylin, a pancreatic hormone dysregulated early in insulin resistance, is a **modifiable upstream driver of tau pathology and neuronal metabolic dysfunction**. Unlike CNS-penetrant agents, we target a **peripheral factor that engages CNS signaling indirectly**, offering a differentiated safety and regulatory profile.

Key differentiators:

- Targets an **upstream metabolic trigger** rather than downstream tau aggregates
- Operates through **cAMP-PKA and convergent tau kinase pathways**, addressing redundancy in tau phosphorylation
- Enables **precision medicine** by identifying a metabolically defined patient subset
- Compatible with, and potentially synergistic with, existing anti-tau and anti-amyloid therapies

BIOLOGICAL RATIONALE



THERAPEUTIC STRATEGY

Titrate immunomodulation of circulating, pathologic amylin using a selective anti-human amylin antibody is designed to:

- Neutralize aggregated/ excess amylin without disrupting amylin physiologic/ metabolic signaling
- Normalize upstream kinase “tone” rather than fully suppressing tau phosphorylation
- Preserve neuronal metabolism and vascular function under metabolic stress

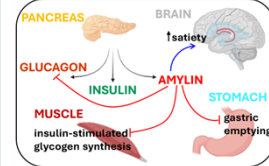
This peripheral-first approach minimizes CNS exposure while achieving CNS benefit, attractive for safety and combination use.

CLINICAL & COMMERCIAL OPPORTUNITY

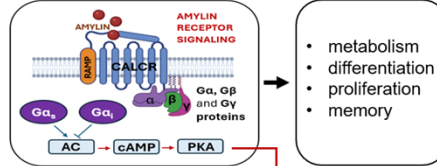
- **New therapeutic category** at the intersection of metabolic disease and neurodegeneration
- Focus on early-stage, metabolically compromised individuals
- A large, identifiable patient population
- Potential for combination strategies to improve response rates
- Opportunities for companion diagnostics and trial enrichment
- Amylin modulation has potential as both a **standalone disease-modifying therapy** and **sensitizer** of existing AD drugs.

Peripheral Immunomodulation of Amylin to Prevent Tau Pathology and Restore Cerebral Glycolysis

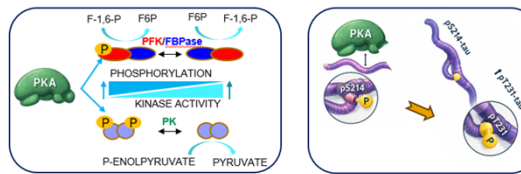
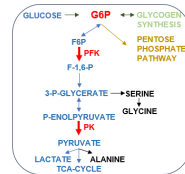
Amylin Regulation & Functions



Amylin Dysregulation, Metabolic Failure & Tau Pathology



Glycolysis – metabolic pathways



Neutralization of Excess Circulating Amylin in AD-Model Mice



Improves Brain Function

APP/PS1/hA
N=8 males
APP/PS1/hA
N=8 males

Age (months) 5 6 1/2

P2 ↓ anti-amylin ab
IgG ↑

Recognition Index (%)

P = 0.0100

IgG P2 ab

Plasma Amylin (ng/ug of total protein)

P = 0.0203

IgG P2 ab

Brain Amylin (ng/mg of total protein)

P = 0.0040

IgG P2 ab

Plasma P2 ab (ug/mg of total protein)

P < 0.0001

IgG P2 ab

Brain P2 ab (ug/mg of total protein)

P = 0.5875

IgG P2 ab

Brain P2 ab (ug/mg of total protein)

P = 0.0096

IgG P2 ab

Brain P2 ab (ug/mg of total protein)

P = 0.0378

IgG P2 ab

Brain P2 ab (ug/mg of total protein)

Preserves Metabolic Capacity & Amylin Signaling

cAMP (nM normalized with total protein)

P = 0.0378

IgG P2 ab

PKA (O.D.20ug of Total Protein)

P = 0.0324

IgG P2 ab

Brain P2 ab (ug/mg of total protein)

Reduces Tau Phosphorylation

pS214Tau (O.D.ug of Total Protein)

P = 0.0096

IgG P2 ab

Brain P2 ab (ug/mg of total protein)

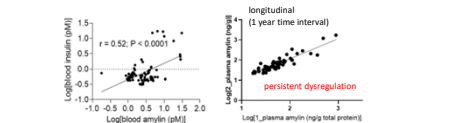
P = 0.0378

IgG P2 ab

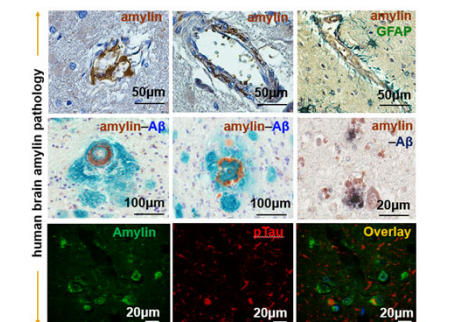
Brain P2 ab (ug/mg of total protein)

HUMAN DATA SUPPORTING THE PROJECT

Metabolic Stress Drives Amylin Hypersecretion

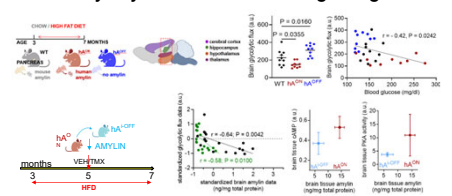


Amylin Accumulates in Human AD Brain

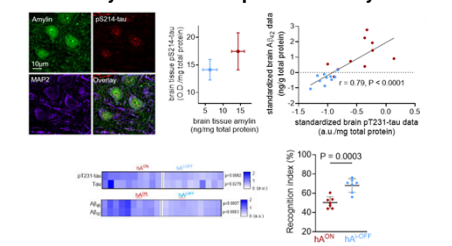


MODEL DATA SUPPORTING THE PROJECT

Peripheral Amylin Modulation Rebalances Brain Glycolysis via cAMP-PKA Signaling



Reducing Excess Amylin Slows AD Biomarker Dynamics and Improves Memory



WHY NOW

Advances in plasma tau biomarkers, growing recognition of AD heterogeneity and renewed interest in precision neurology create a timely opportunity to translate this work. Targeting the peripheral-CNS amylin axis aligns with current priorities in disease modification, patient stratification, and risk reduction.

REFERENCES

PMID: 41858884; PMID: 33521236;
PMID: 28696548; PMID: 36596993;
PMID: 37030503; PMID: 24077098;
PMID: 23794448

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