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PHASE II DRUG DEVELOPMENT FOR ALZHEIMER'S DISEASE – SYSTEMS BIOLOGY

Title: "Drug Development Approach and Mechanism of Action of T3D-959"

Presenter: John, Didsbury, Ph.D., Founder and CEO of T3D Therapeutics, Inc.

Lead Product / Mechanism of Action: T3D-959; small molecule nuclear receptor agonist of PPAR delta (primary) and PPAR gamma (secondary)

Stage of Development: Phase 2 PIONEER study ongoing in mild to moderate AD subjects with topline results in early 2Q2023

AD Drug Development Approach: Correcting dysfunctional glucose and lipid metabolism

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POLICIES



The information included in this presentation may be shared on other platforms.

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DISCLOSURES

- John Didsbury is a shareholder in T3D Therapeutics, Inc.
- PIONEER is supported in part by grant AG-061122 from the National Institutes of Health (NIA/NIH)
- PIONEER is supported in part by a grant from the Alzheimer's Association – Part the Cloud-Gates Foundation Program

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METABOLIC HYPOTHESIS OF AD – 4 TENETS

1. **Metabolism function alterations (glucose and lipid) antedate structural change in AD brain**
   The brain is the most metabolically active organ in the body. An organ of 2% body weight uses:
   - 25% of total glucose
   - 25% of total body free cholesterol pool
   - 20% of whole body oxygen consumption

2. **Decreased glucose metabolism is a cause not a consequence of neurodegeneration**
   - Decreased Glucose > decreased ATP> decreased ER/Golgi/Trans Golgi function (ER stress) > misfolded proteins (tangles and plaques)

3. **Aberrant lipid metabolism a 3rd pathological hallmark of AD, impacts structure and function**.
   The brain is half lipid.
   - Alois Alzheimer (1906) noted a high occurrence of "adipose inclusions" (fat deposits identified as triglycerides in 2015)
   - ApoE4 – strongest genetic risk factor

4. **AD involves a massive positive feedback loop** of altered glucose/lipid metabolism alterations and pathological sequelae - It is not a simple pyramid of cascading events.

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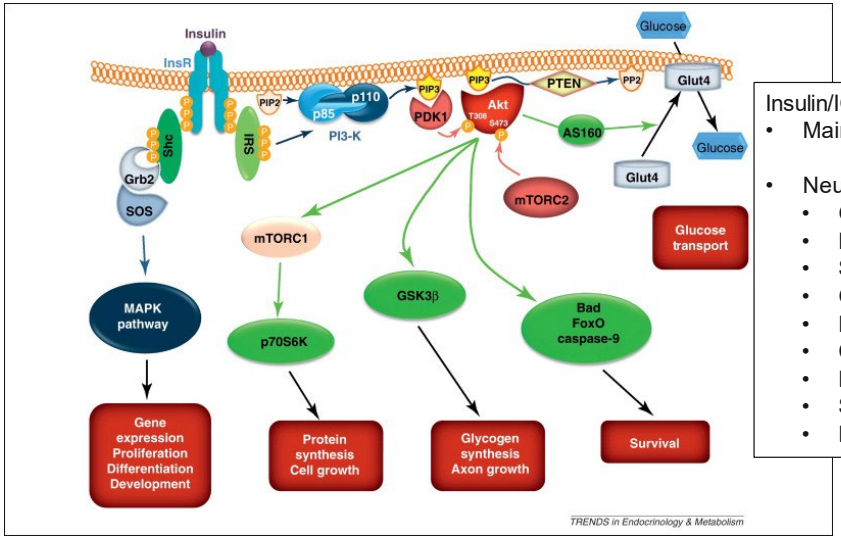
METABOLIC APPROACH TO AD THERAPY DEVELOPMENT

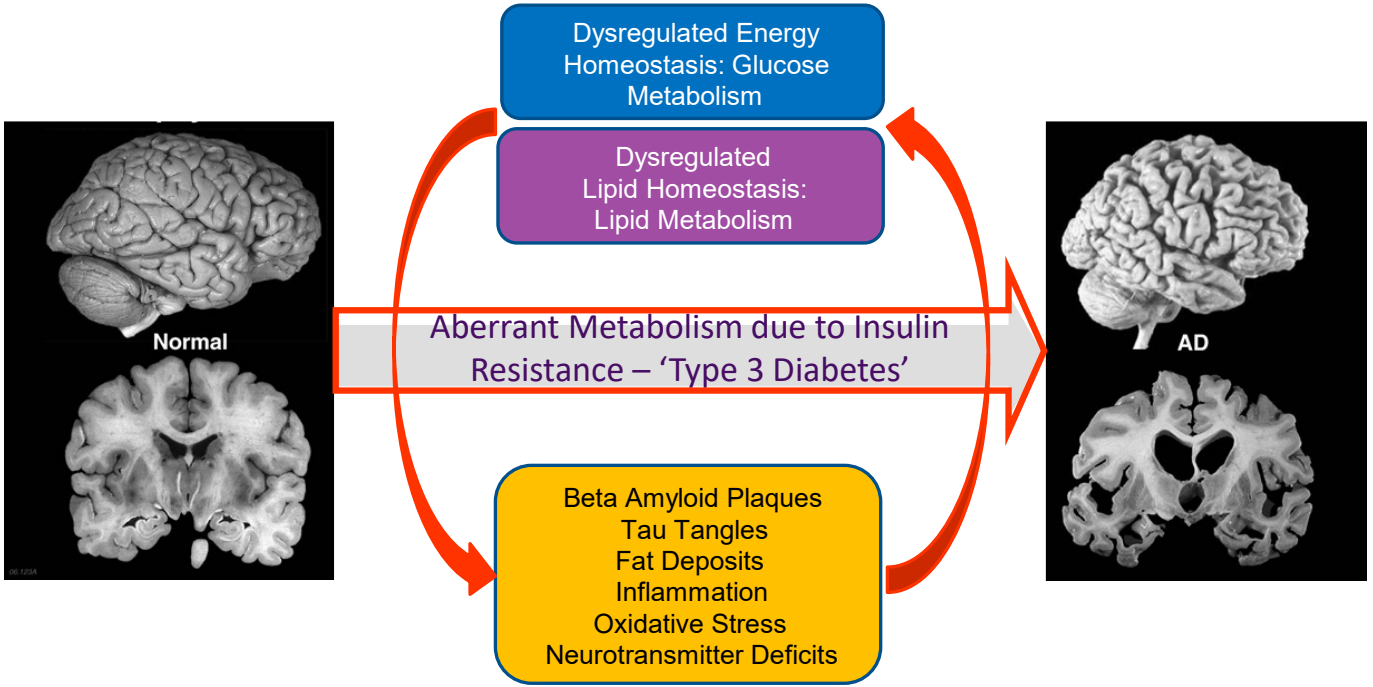
1. Focus on the single most important regulator of brain functions – Insulin
2. Correct resistance to this regulator which is inherent in AD and precedes AD symptoms
3. Systems Biology – Use a pluripotential drug target that can bypass multiple dysfunctional insulin signaling pathways



Insulin/IGF-1 Signaling
- Maintaining cognitive functioning
- Neuronal and glial functions
  - Growth
  - Metabolism
  - Survival
  - Gene expression
  - Protein Synthesis
  - Cytoskeletal Assembly
  - Neurotransmitter Function
  - Synapse Formation
  - Plasticity

References: de la Monte SM (b). Brain Insulin Resistence and Deficiency as Therapeutic Targets in Alzheimer's Disease. Curr Alzheimer Res 2012;9:35-66. 39. D'Ercole AJ, Ye P. Expanding the mind: insulin-like growth factor I and brain development. Endocrinology 2008;149:5958-5962.

METABOLIC HYPOTHESIS OF AD – 'TYPE 3 DIABETES' CAUSING BRAIN 'STARVATION'



Massive Positive Feedback Loop Driving Neurodegeneration

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METABOLIC HYPOTHESIS OF AD IS CONGRUENT WITH THE PLAQUE HYPOTHESIS

Insulin Resistance → **Amyloid Plaque Formation**

Dysregulated Glucose Metabolism

- → Decreased IDE-1 Activity → Increase in Aβ
- → Decreased Insulin Signaling → Increased secretion of $A\beta_{1-42}$
- → Decreased Insulin Signaling → Decreased removal of Aβ oligomers

Dysregulated Lipid Metabolism

- → Increased Ceramide → Increased BACE > Increase in Aβ
- → Increased Cholesterol Esters → Increased secretion of $A\beta_{1-42}$
- → ApoE4 with Aβ → Cause formation of toxic oligomers
- → ApoE4 and Aβ → Compete for LRP1 > decreased Aβ removal
- → Decreased HDL → Increased Aβ oligomerization

METABOLIC HYPOTHESIS OF AD IS CONGRUENT WITH THE PLAQUE HYPOTHESIS

Insulin Resistance ← **Amyloid Plaque Formation**

Dysregulated Glucose Metabolism

- Insulin Resistance < Hyperinsulinemia ← Aβ binds to and blocks IDE-1
- Insulin Resistance < Hyperinsulinemia ← Increased BACE increases insulin & Aβ biogenesis
- Decreased Insulin Signaling ← Aβ binds to insulin
- Decreased Insulin Signaling ← Aβ binds to insulin receptor

Dysregulated Lipid Metabolism

- Increased Ceramide ← $A\beta_{42}$ increases SMase
- Imbalance of Cholesterol & Cholesterol Esters ← $A\beta_{40}$ inhibition of HMG-CoA reductase
- Imbalance of Cholesterol & Cholesterol Esters ← APP regulation of cholesterol metabolism

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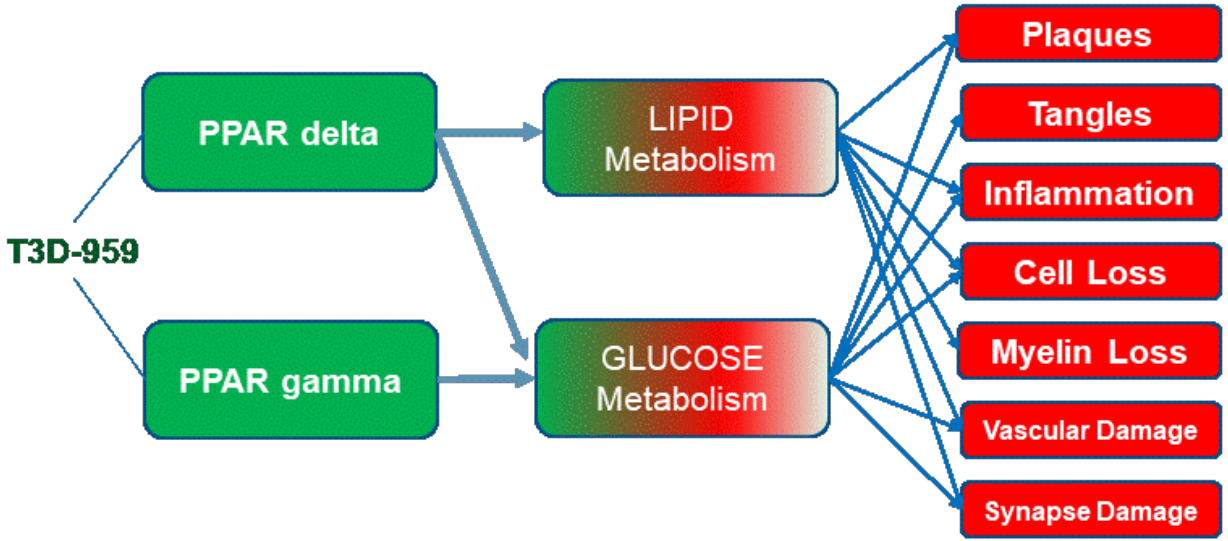
METABOLIC HYPOTHESIS TESTING WITH T3D-959 – MECHANISM OF ACTION

T3D-959: Dual Nuclear Receptor Agonist

Primary Target is PPARδ (delta), Secondary Target is PPARγ (gamma); regulating expression of multiple genes involved in glucose and lipid metabolism. PPARδ (energy expenditure) and PPARγ (energy storage) are master regulators of metabolic homeostasis



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T3D-959 – MECHANISM OF ACTION IN AD - PPAR DELTA & GAMMA

Impaired Glucose Metabolism > Insulin resistance –

PPAR delta/gamma > ↑ Insulin receptors, ↑ IRS-1, ↑ GLP-1, ↑ AMPK, activates AKT pathway, ↑ GLUT4

A. **Energy blockade (mitochondrial dysfunction)** –

PPAR delta/gamma > ↑ PGC1-a for mitochondrial biogenesis & oxidative capacity ↑ catalase, SOD1 & glutathione

B. **Altered posttranslational modifications (glycosylation, phosphorylation, ubiquitination, methylation) > ER stress > misfolded proteins that lead to:**

B1. Inflammation > JNK pathway activation, NFκB activation –

PPAR delta/gamma > ↓ JNK pathway & NFκB activation, ↓ AGEs, ↑ Adiponectin

B2. Structure/Function deficiencies >Lipid Metabolism > Cholesterol forms imbalance, toxic ceramides, altered sphingolipids, decreased myelin –

PPAR delta/gamma > ↑ reverse cholesterol transport, fatty acid oxidation & HDL, ↓ ceramides ↓ triglycerides, ↑ myelination

B3. Amyloid Plaques >

PPAR delta/gamma > ↓ BACE1, ↑ Neprilysin & IDE-1, ↑ ABCA1, Microglia shift to M2

B4. Tau Tangles >

PPAR delta/gamma > ↓ tau hyperphosphorylation

TRANSLATION OF SYSTEMS BIOLOGY TO THE CLINIC – ADAS-COG11 BLINDED PIONEER DATA

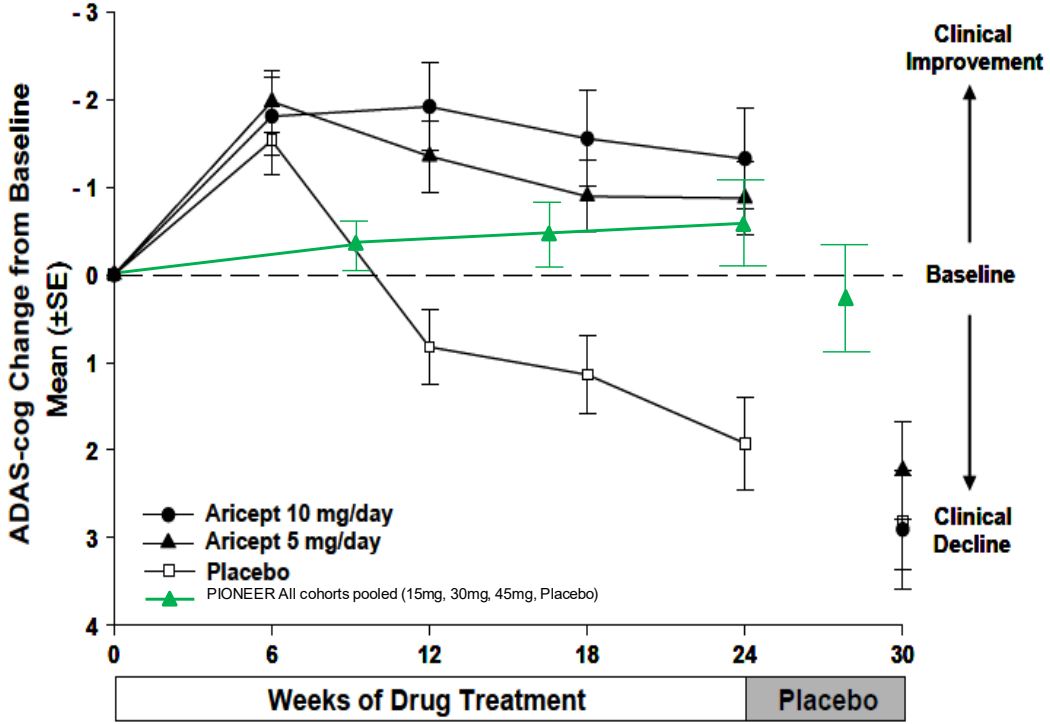

Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

PIONEER Interim Results

Blinded, grouped single average of:

- 15mg T3D-959
- 30mg T3D-959
- 45mg T3D-959
- PLACEBO

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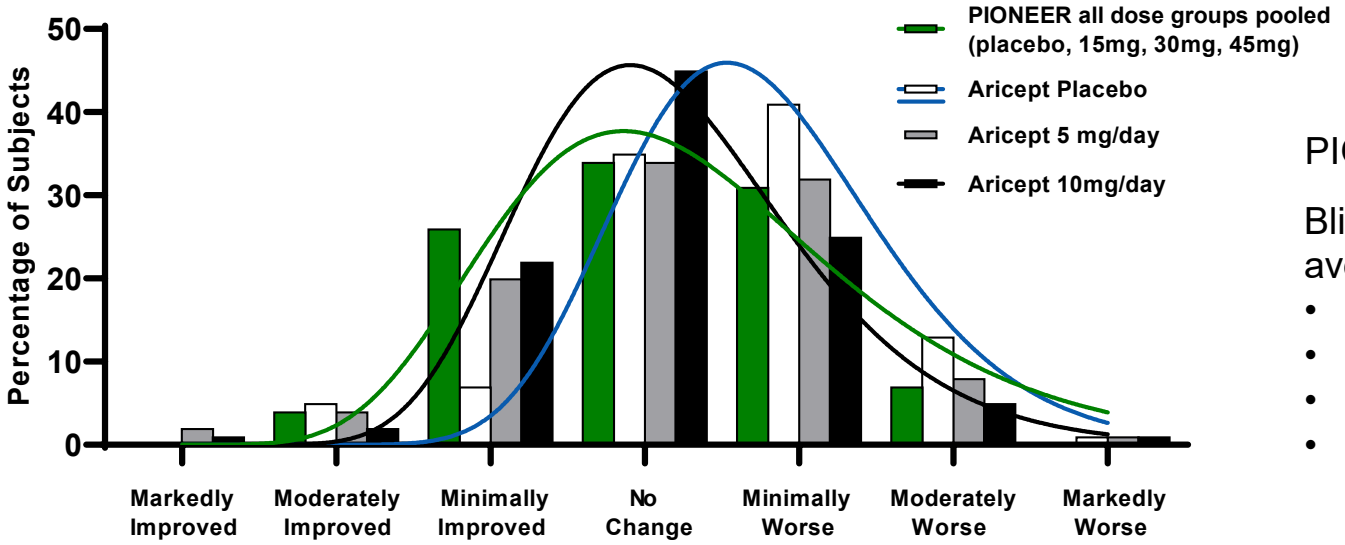
TRANSLATION OF SYSTEMS BIOLOGY TO THE CLINIC – ADCS-CGIC BLINDED PIONEER DATA

PIONEER CGIC vs. Aricept CIBIC+



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SUMMARY

- Complex Organ
- Complex Disease
- Will require a complex systems biology approach for discovering efficacious new therapies
- AD is too complex for one-off single pathology-specific targets