ISTAART
alzheimer's association

alzheimer's association
Business Consortium

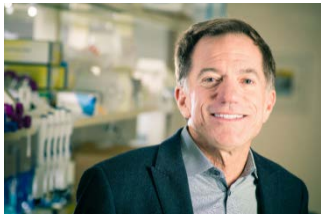
AABC/ISTAART Joint Webinar:
Biotech Innovation in New Therapeutic Approaches to Alzheimer's Disease
October 19, 2017

Judy Walker, MD, FRCPC
Chief Medical Officer

Accera, Inc.

John Didsbury, PhD
President & CEO,
Chairman of the Board

T3D Therapeutics



Mark Gurney, PhD
Chairman & CEO

Tetra Discovery Partners, Inc.

Judy Walker MD FRCPC – mini bio

- Neurologist trained in Canada
- Medical monitor at Quintiles (New Jersey) and led a project management group. 1999-2001
- Head of Neurology for ROW at Serono, Geneva. 2001-2004
- Head of Medical Affairs for Teva Neuroscience (Kansas City, MO). 2004-2008
- VP Quintiles Strategic Drug Development group, UK.
- Chief Medical Officer, Accera since April 2017
- Extensive experience in Alzheimer's Drug Development throughout her career.

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Alzheimer's as a metabolic disease

ACCERA'S APPROACH TO AD

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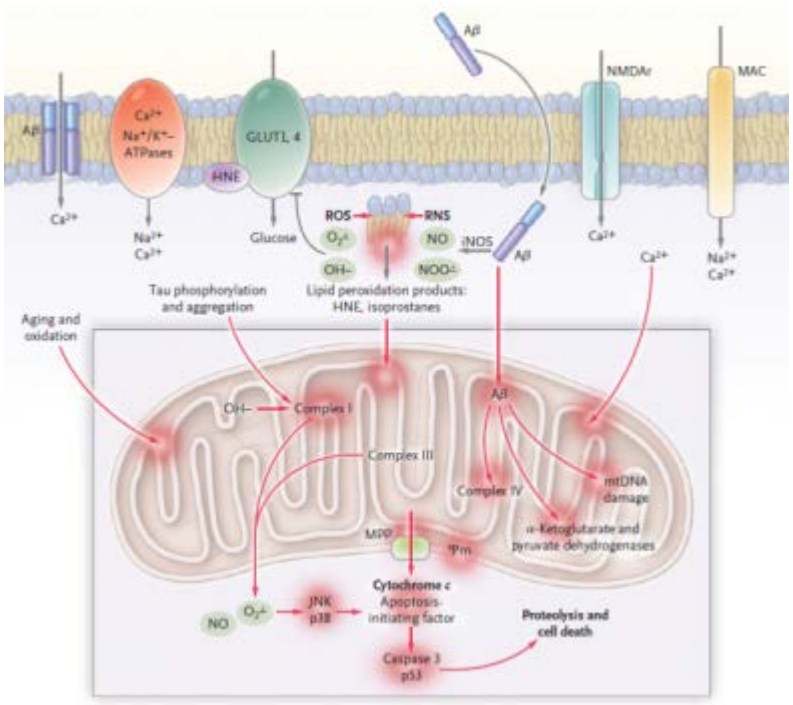
Mitochondrial Cascade Hypothesis of AD: Mitochondrial Dysfunction due to APOE4, Aβ, ROS, aging, diet etc. contribute to disease progression



In Alzheimer's damaged mitochondria cannot utilize glucose(1)

- Amyloid and other factors inhibit mitochondrial function resulting in early and progressive glucose hypometabolism in cerebral neurons.

1. Querfurth, H. W. and F. M. LaFerla (2010). N Engl J Med **362(4): 329-44.**

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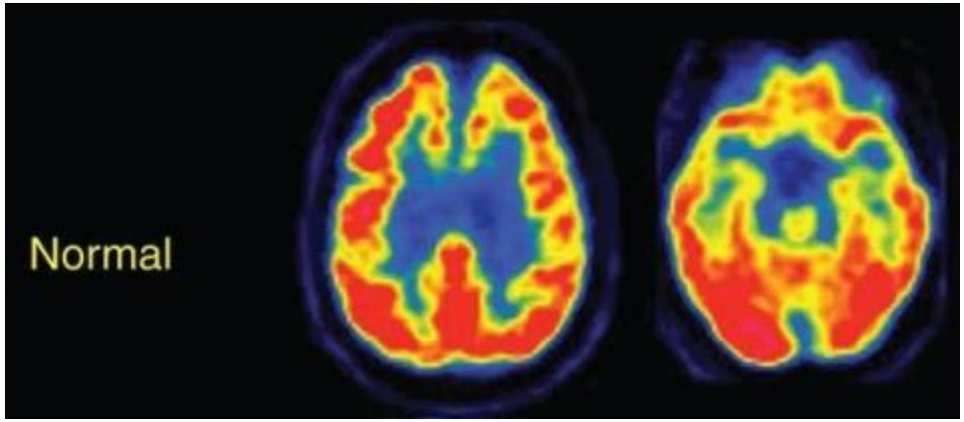
Brain Metabolism: The Brain Relies Almost Exclusively on Glucose as an Energy Substrate

Brain Metabolism

- 2% of body weight
- 120-130 g glucose/day
- Uses 25% of total body glucose
- Receives 15% of cardiac output
- Uses 20% of total body oxygen

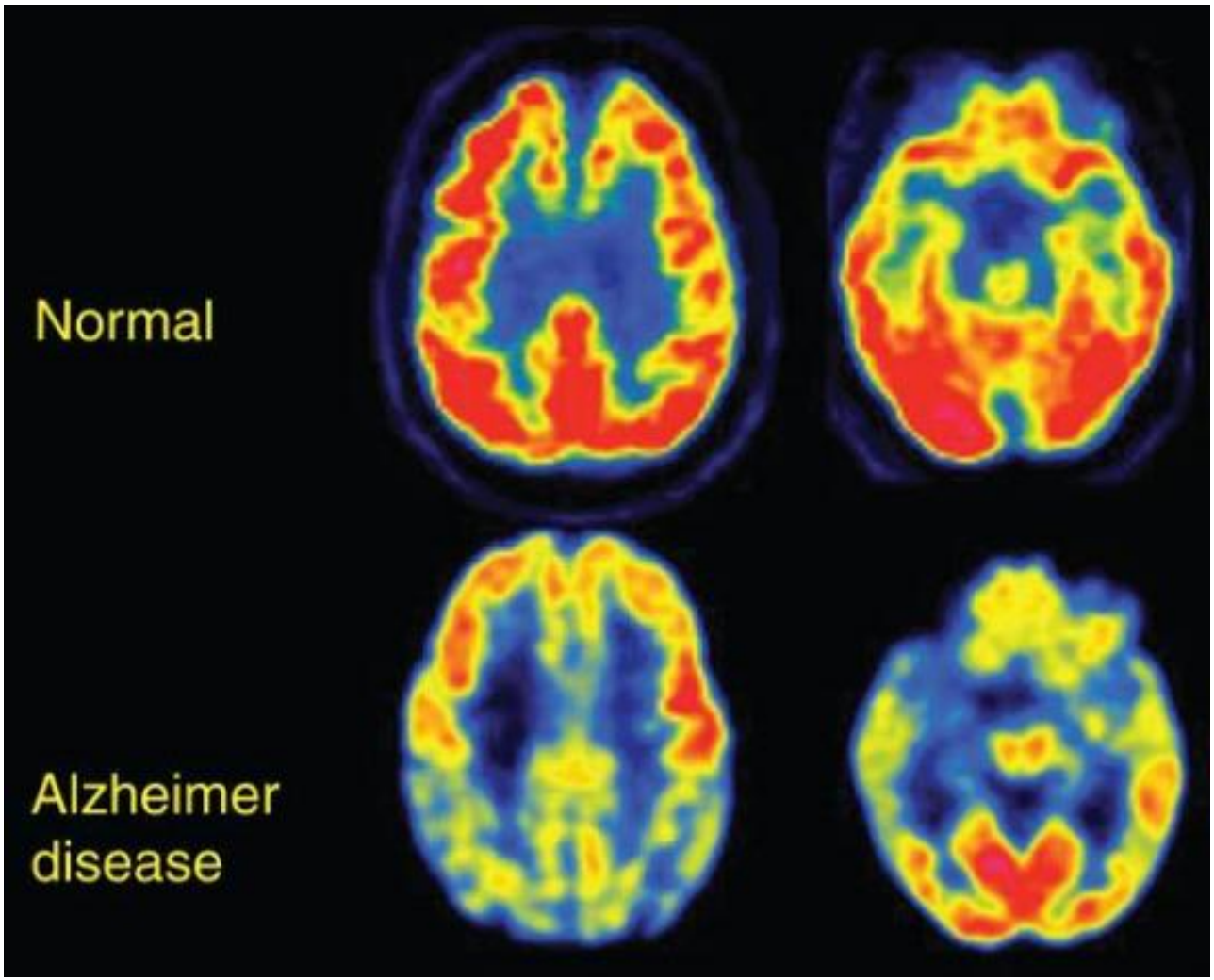
FDG PET



Johnson, K. A., N. C. Fox, et al. (**2012**). "Brain imaging in Alzheimer disease." Cold Spring Harb Perspect Med **2(4): a006213.**

Clarke, D. D. and L. Sokoloff (**1994**). Circulation and Energy Metabolism of the Brain. Basic Neurochemistry. G. J. Siegel, B. W. Agranoff, R. W. Albers and P. B. Molinoff. New York, Raven Press**: 645-680.**

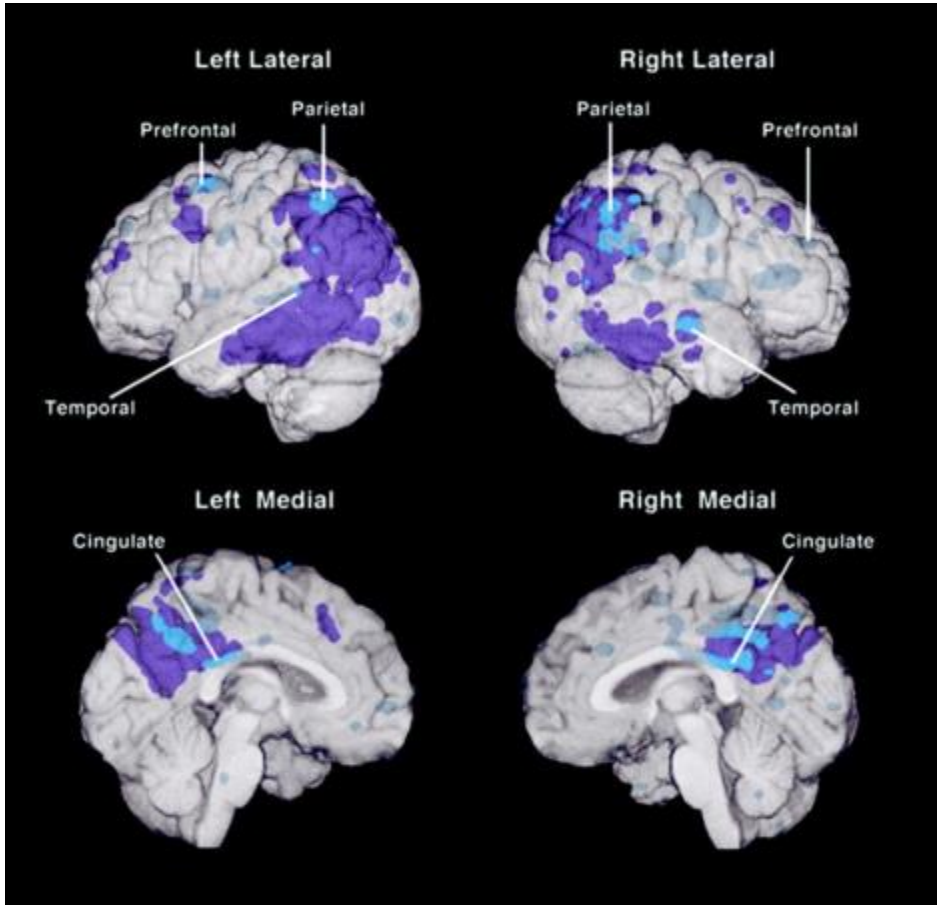
AD is characterized by declines in the cerebral metabolic rate of glucose (CMRglc)



Johnson, K. A., N. C. Fox, et al. (**2012**). "Brain imaging in Alzheimer disease." Cold Spring Harb Perspect Med **2(4): a006213.**

Regional declines in CMRglc Occur Early in AD

- Hypometabolism is most notable in the posterior cingulate, parietal, temporal, and prefrontal cortices
- Regional low CMRglc can be detected decades before clinical signs of dementia
- Found in APOE4(+) subjects at risk for AD
- Mean age of subjects: **30.7**



Reiman, E. M., et al. (**2004**). "Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia." Proc Natl Acad Sci U S A **101(1): 284-9.**

Studies have Demonstrated that the Metabolic Defect in AD is Specific to Glucose and the Alzheimer' Brain is now Oxidizing Substrates other than Glucose to Meet its High Energy Demands

	Young	Middle Age	Normal Elderly	Early Onset AD	Late Onset AD
O_2	1.58 ±0.18*	1.54 ±0.11*	1.49 ±0.04*	1.45 ±0.10*	1.27±0.12*
Gluc	0.26 ±0.04*	0.26 ±01*	0.26 ±0.01*	0.12 ±0.01*	0.14 ±0.03*
Glucose Ox Ratio	0.99 ±0.02	1.01 ±0.02	0.97 ±0.02	0.50 ±0.02	0.66 ±0.03

Adapted from {Hoyer, 1992 #31} , Glucose Ox Ratio = (Gluc x 6)/O_2
*Cerebral metabolic rate (µmol/g x min

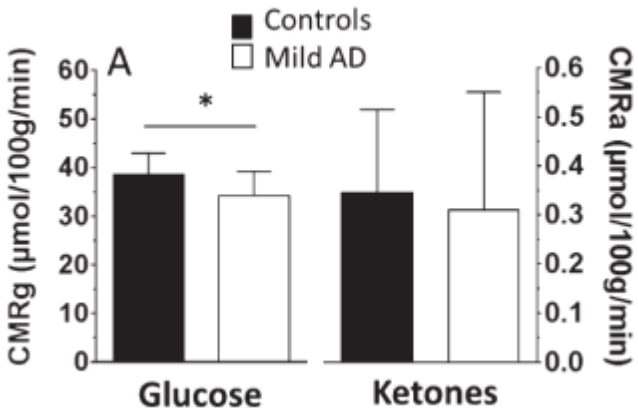
40-50% Decrease in glucose oxidation

The authors conclude:
*"This abnormal metabolic pattern may bring the cerebral glucose metabolism into focus as the point of primary metabolic damage in DAT and raises the questions as to which substrates other than glucose is (are) utilized from the remaining oxygen for energy generation" **

Accera

Hoyer, S., *Oxidative energy metabolism in Alzheimer brain. Studies in early-onset and late-onset cases. Mol Chem Neuropathol, 1992.* ***16(3): p. 207-24.***

Ketone metabolism is preserved in AD, even when glucose metabolism is defective

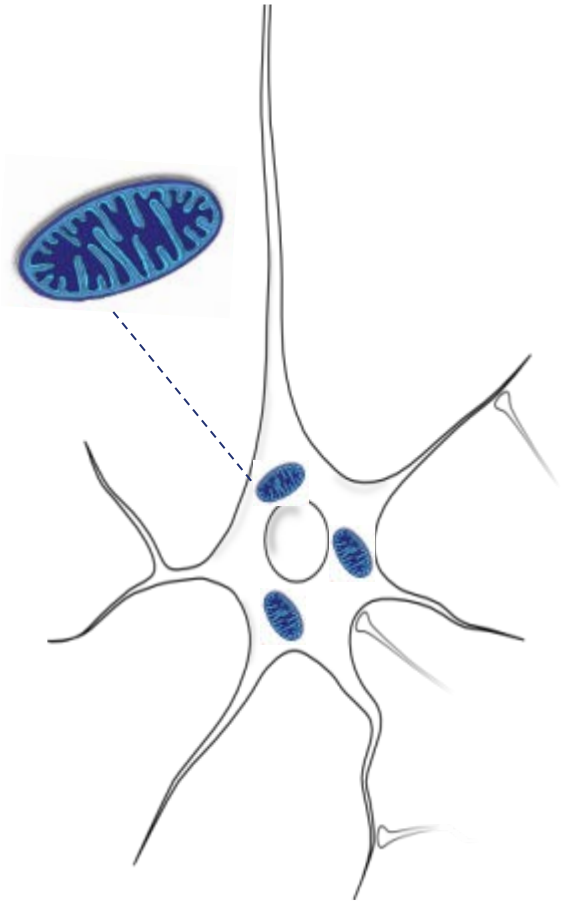


Defect specific to glucose

"…. these results suggest that increasing energy availability to glucose-deficient brain regions by increasing glucose (18F-FDG) uptake or by providing alternative energy substrates such as ketones is a potential complementary strategy for the treatment of early AD."

1. Castellano, C.A., Nugent, S., Paquet, N., Tremblay, S., Bocti, C., Lacombe, G., Imbeault, H., Turcotte, E., Fulop, T., and Cunnane, S.C. (**2014**). Lower Brain 18F-Fluorodeoxyglucose Uptake But Normal 11C-Acetoacetate Metabolism in Mild Alzheimer's Disease Dementia. J Alzheimers Dis.

Treatment Hypothesis: Can addressing Glucose Hypometabolism improve Cognitive Function in Patients with Alzheimer's disease



THE PROBLEM IN ALZHEIMER'S DISEASE

In Alzheimer's damaged mitochondria cannot utilize glucose
A series of genetic and environmental factors inhibit glycolysis and mitochondrial function resulting in early and progressive glucose hypometabolism in the neurons and brain.

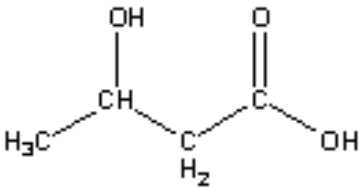
TREATMENT HYPOTHESIS

If the AD brain is having difficulty metabolizing glucose, can we provide the brain with another substrate that it can metabolism in place of glucose and will this improve symptoms of the disease?

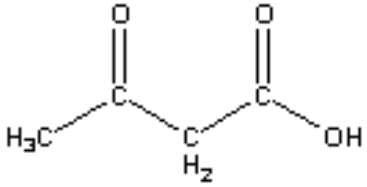
Update on ketosis in Alzheimer’s disease

KETOSIS

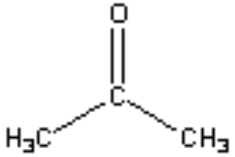
Ketone Bodies are the Brain's Natural Backup Fuel



B-hydroxybutyrate

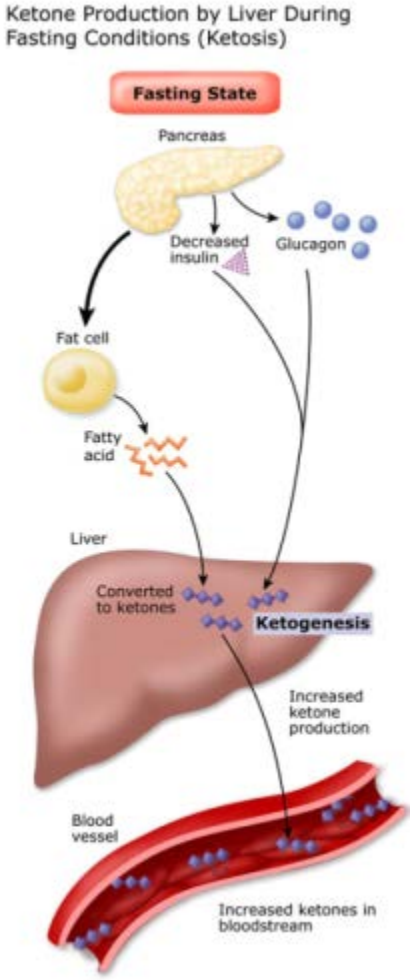


Acetoacetate



Acetone

- Normally produced under conditions of low glucose availability, such as ketogenic diets or fasting
- Can provide up to 60 percent of your brains energy needs
- Production of ketone bodies is suppressed by carbohydrate in the diet



Owen, O. E. et al. (**1967**). Brain metabolism during fasting. J Clin Invest 46, 1589-1595.

KETONE BODIES ARE MORE THAN A FUEL SOURCE

Neuroprotection by Ketogenic Diets

Injury	Lesion	Species	Outcome	Ref
Alzheimer's disease	Transgenic APP expression	Mice	Reduced Aβ levels	1
Amyotrophic lateral sclerosis	Transgenic SOD1 mouse	Mice	Increased motor neuron counts	2
Traumatic brain injury	Controlled cortical impact	Rats	Reduced contusion volume	3
Parkinson's disease	Human PD patients	Human	Improved motor function	4
KA-induced seizures	Kainic acid	Mice	Increased cell survival	5
GLUT1 haploinsufficiency	Glucose deprivation	Human	Decrease seizure frequency	6
Ischemia	Cardiac arrest induced ischemia	Rats	Protection from neurodegeneration	7
Alzheimer's disease	Human AD patients	Human	Improve cognitive performance	8

1. Van der Auwera, I., et al. (**2005**). "A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease." Nutr Metab (Lond) **2: 28.**
2. Zhao, Z., et al. (**2006**). "A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis." BMC Neurosci **7: 29.**
3. Prins, M. L., et al. (**2005**). "Age-dependent reduction of cortical contusion volume by ketones after traumatic brain injury." J Neurosci Res **82(3): 413-20.**
4. Vanitallie, T. B., et al. (**2005**). "Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study." Neurology **64(4): 728-30.**
5. Noh, H. S., et al. (**2003**). "The protective effect of a ketogenic diet on kainic acid-induced hippocampal cell death in the male ICR mice." Epilepsy Res **53(1-2): 119-28.**
6. Klepper, J. and B. Leiendecker (**2007**). "GLUT1 deficiency syndrome--2007 update." Dev Med Child Neurol **49(9): 707-16.**
7. Tai, K. K., et al. (**2008**). "Ketogenic diet prevents cardiac arrest-induced cerebral ischemic neurodegeneration." J Neural Transm **115(7): 1011-7.**
8. Krikorian, R., et al. (2012). "Dietary ketosis enhances memory in mild cognitive impairment." Neurobiol Aging **33(2): 425 e19-27.**

Neuroprotection by Ketone Bodies Alone

Intervention	Injury	Lesion	Species	Outcome
Injection of acetoacetate	Glutamate toxicity	Inhibition of glycolysis by iodoacetate	Rat, cell culture	Neuroprotection
Infusion of 4mM BHB, 5mM ACA	Glutamate toxicity	Incubation with 5mM glutamate	Cell culture	Increased cell survival
Infusion of BHB	Glutamate toxicity	Glutamate and iodoaceate treatment	Rats	Neuroprotection and reduced lipid peroxidation
1mM BHB 1mM ACA	Glutamate toxicity	Glutamate treatment	Cell culture	Increased mitochondrial efficiency
4mM BHB	Hypoxia	2hr exposure to hypoxia	Cell culture	Increased cell survival
Infusion BHB	Hypoxia	Carotid artery ligation	Mice	Maintained ATP and low lactate
Infusion BHB	Ischemia	Occulsion of middle cerebral artery	Mice	Reduced cerebral infarct area
Infusion BHB	Traumatic brain injury	Controlled cortical impact	Rats	Restored ATP levels after CCI
Ketogenic agent	Alzheimer's disease	Memory problems in Alzheimer's disease	Human	Improved cognitive performance
BHB treatment	Alzheimer's disease	Aβ in cell culture model of AD	Cell culture	Increased cell survival
BHB infusion	Parkinson's disease	MPTP lesioning	Mice	Improved neuronal survival, improved mitochondrial efficiency
BHB treatment	Parkinson's disease	Rotenone treatment of cells	Cell culture	Increased cell survival
Ketogenic agent	Aging	Cognitive decline with age	Dog	Improved cognitive performance

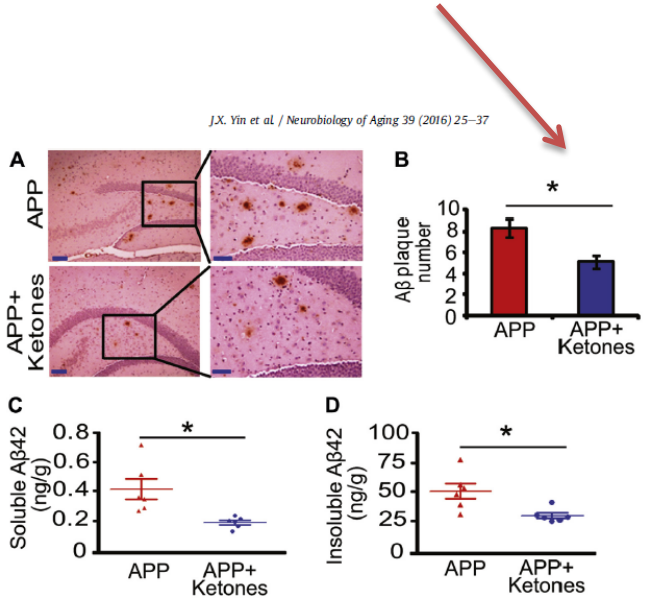
For review see: Henderson, S. T. (**2008**). "Ketone bodies as a therapeutic for Alzheimer's disease." Neurotherapeutics **5(3): 470-80.**

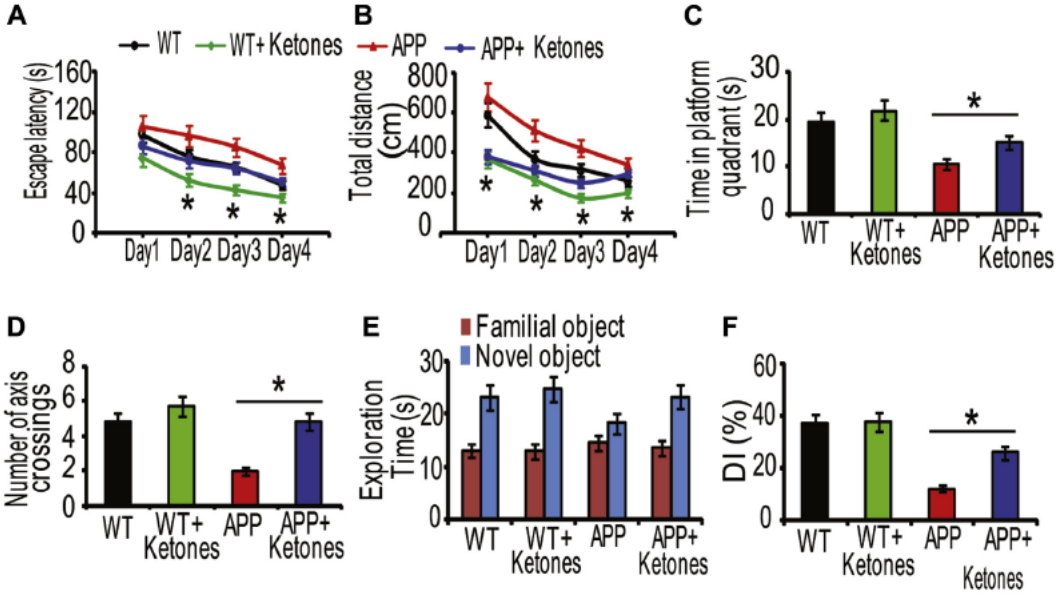
KETOSIS AS A TREATMENT FOR AD

Support for Mechanism of Action: Recent studies continue to support ketosis as a treatment for Alzheimer's disease

Yin et al (2016)[1] demonstrated that Ketone bodies:

- Blocked amyloid-beta 42 entry into neurons
- Rescued mitochondrial complex I activity, reduced oxidative stress, and improved synaptic plasticity
- When administered peripherally significantly reduced amyloid burden and greatly improved learning and memory ability in a symptomatic mouse model of AD





1. Yin, J.X., et al., *Ketones block amyloid entry and improve cognition in an Alzheimer's model. Neurobiol Aging, 2016.* ***39: p. 25-37.***

Ketogenic Diets Require Strict Compliance

Very low carbohydrate and protein intake

- No bread
- No pasta
- No pizza
- No rice

Compliance in AD

- AD patients have change in food selection toward sweet, carbohydrate-rich foods making compliance difficult[1,2,3]

Table 1
Typical day of food for a child on a 4:1 ratio, 1500 calorie ketogenic diet

Breakfast:	Egg with Bacon Egg 28g Bacon 11g 36% heavy whipping cream 37g Butter 23g Apple 9g
Snack:	Peanut Butter Ball Peanut Butter 6g Butter 9g
Lunch:	Tuna Salad Tuna fish 28g Mayonnaise 30g Celery 10g 36% heavy whipping cream 36g Lettuce 15g
Snack:	Keto Yogurt 36% heavy whipping cream 18g Sour Cream 17g Strawberries 4g Artificial sweetener (e.g. Splenda™)
Dinner:	Cheeseburger Ground beef 22g American cheese 10g Butter 26g Cream 38g Lettuce 10g Green beans 11g
Snack:	Keto Custard 36% heavy whipping cream 25g Egg 9g Pure vanilla flavoring

1. Wolf-Klein, G. P., F. A. Silverstone, et al. (**1991**). "Sweet cravings and Alzheimer's disease." J Am Geriatr Soc **39(5): 535-6.**
2. Greenwood, C. E., C. Tam, et al. (**2005**). "Behavioral disturbances, not cognitive deterioration, are associated with altered food selection in seniors with Alzheimer's disease." J Gerontol A Biol Sci Med Sci **60(4): 499-505.**
3. Mungas, D., J. K. Cooper, et al. (**1990**). "Dietary preference for sweet foods in patients with dementia." J Am Geriatr Soc **38(9): 999-1007.**

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Accera's tricaprilin is an 8-carbon medium chain triglyceride

Medium Chain Triglycerides (MCTs) are specialized lipids

- MCTs are fatty acids consisting of 5-12 carbons that do not occur in the normal diet
- Undergo obligate oxidation to **generate ketone bodies**
- MCTs are self-affirmed GRAS and have undergone extensive its toxicology studies

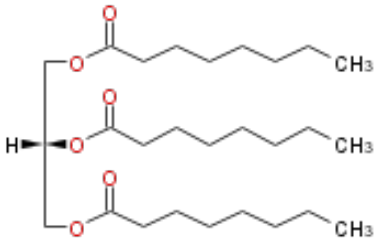
Accera's tricaprilin is an 8 carbon MCT

- A structured lipid in which the fatty acids are all C8
- C8 fatty acids are not subject to esterification and are transported to the liver via the portal vein
- These provide an energy rich substrate for the production of ketone bodies
- Human dose is several folds lower than NOAEL levels in rat and dog studies.

Tricaprilin (Caprylic triglyceride)

- Molecular formula: $C_{27}H_{50}O_6$
- Molecular weight: 470.68

Structural formula



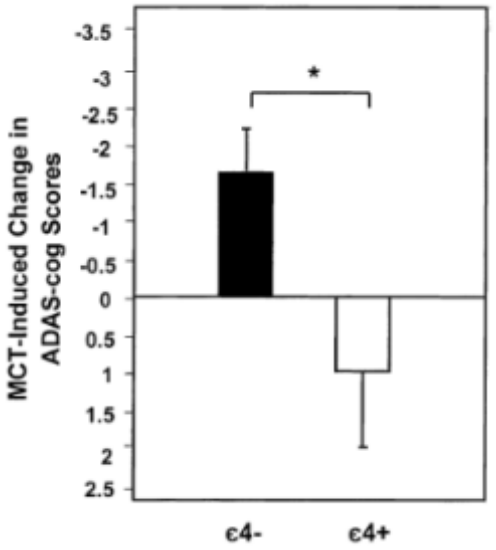
Accera's Phase 2a Study: Tricaprilin administration results in rapid improvement in metabolism & cognition

Design

- 20 mild to moderate AD patients
- Mean age 74.7 years
- Single dose crossover design

Results

- AC-1202 significantly elevated serum ketone bodies
- AC-1202 significantly improved ADAS-cog in ApoE4(-) patients after single dose ($p < 0.05$)
- BHB serum levels correlated with improved memory ($p < 0.05$)



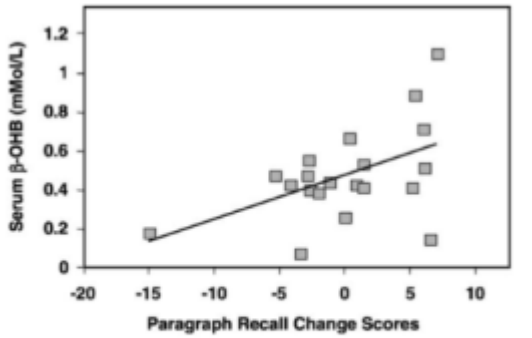


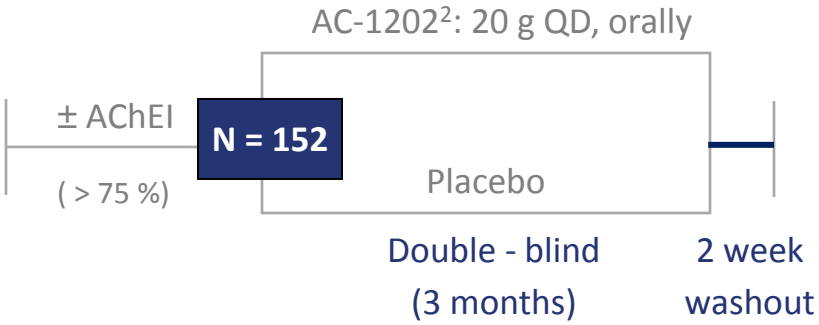
Fig. 2. Relationship between β-OHB levels at the time of cognitive testing and the change in paragraph recall following MCT treatment; $r = 0.50$, $P = 0.02$.

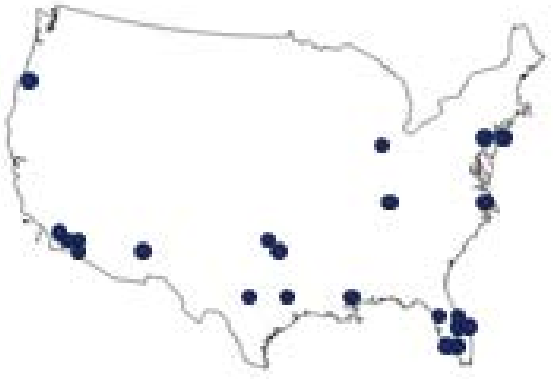
- APOE4 non carriers ADAS-Cog scores improve in 90 minutes
- Rapid improvement is likely due to switch in neuronal metabolism to utilize the available ketone bodies

1. Reger et al (2004) ***Effects of β-hydroxybutyrate on cognition in memory-impaired adults*** *Neurobiology of Aging. 25 (2004) 311.*

Accera's Phase 2b Study : Multi-center, double-blind placebo-controlled study in subjects with mild-to-moderate Alzheimer's disease

Design: n= 152, 90 Day intervention, Primary endpoint ADAS-Cog[1]



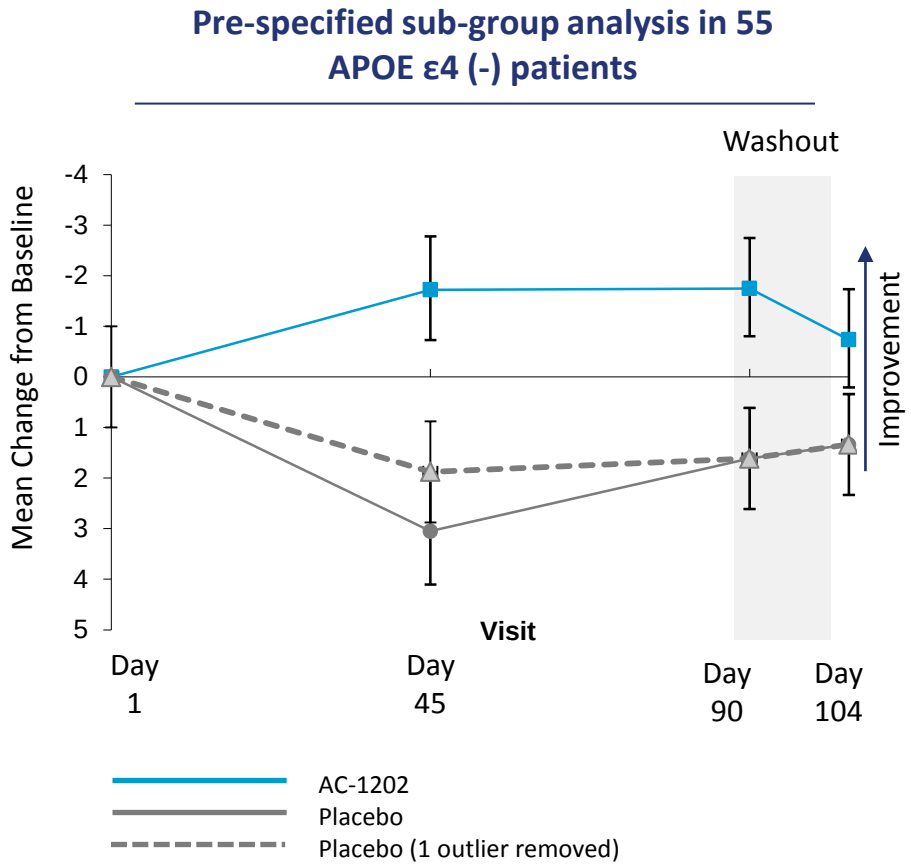


Conducted at top clinical trial sites in the US

- Performed at 23 clinical trial sites
- Single pre-specified analysis of APOE ε4 non-carriers (as seen in P2a study)
- Full service CRO : CRC (Cognitive Research Corporation)
- Published in peer-reviewed journal[1]

1. Henderson, S.T. et al. (2009). Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond) 6, 31.*
2. Phase 2b study used a slightly different formulation (AC-1202) but the API and dose were the same

Phase 2b Study: Change from baseline in ADAS-Cog scores in APOE ε4 non-carriers (a pre-specified analysis)

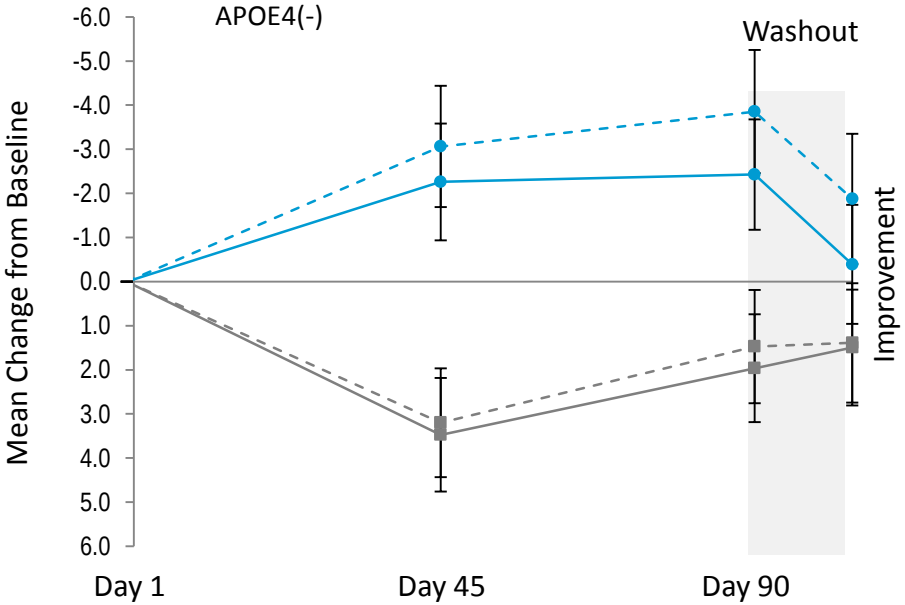


- Effect size of 3.4 pts in ADAS-Cog seen at 90 days
- Persistence of effect after washout

Time point	Score Difference	P-value
Day 45	4.77	0.0005
Day 90	3.36	0.015
Day 104 Washout	2.08	0.154

N=29 ApoE4(-) AC-1202; N=26 ApoE4(-) Placebo

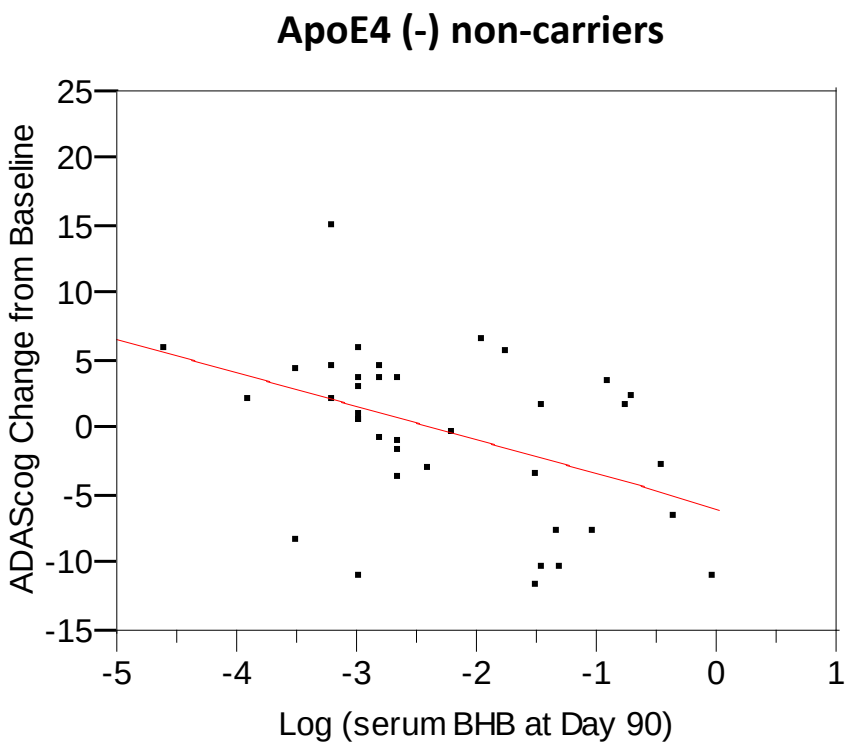
Phase 2b Study: Strongest effect observed in dosage compliant APOE4 non-carrier patients



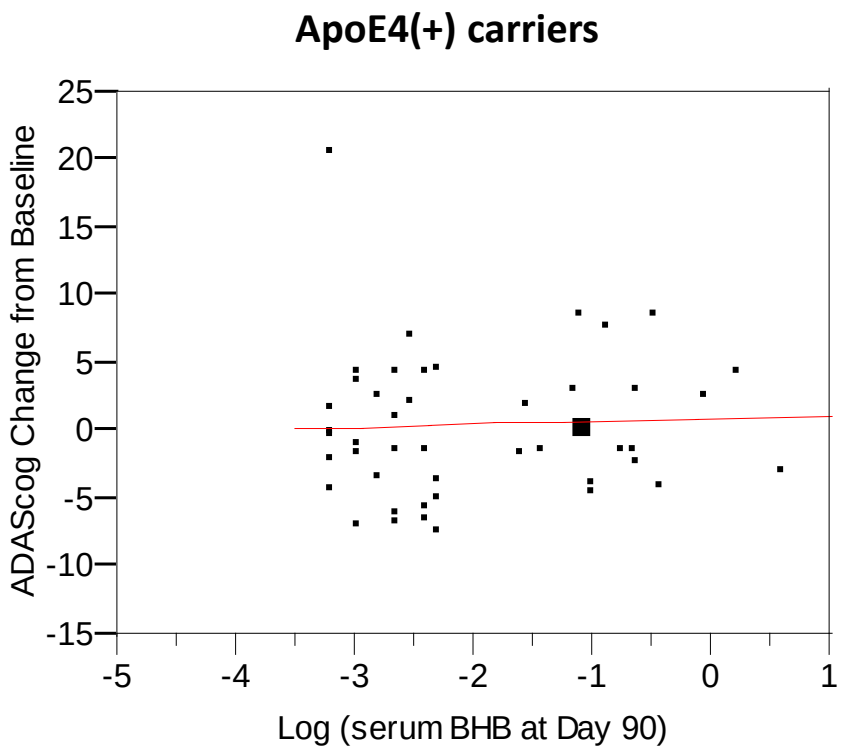
Dosage compliant APOE4 non-carriers

Time point	Score Difference	P-value
Day 45	6.26	0.0011
Day 90	5.33	0.0063
Day 104 Washout	3.26	0.1070

Phase 2b Study: Serum βHB levels correlated with improvement in ADAS-Cog scores among APOE4 non-carriers



Correlation -0.448
***p < 0.01**



Correlation 0.0461
p = 0.7610

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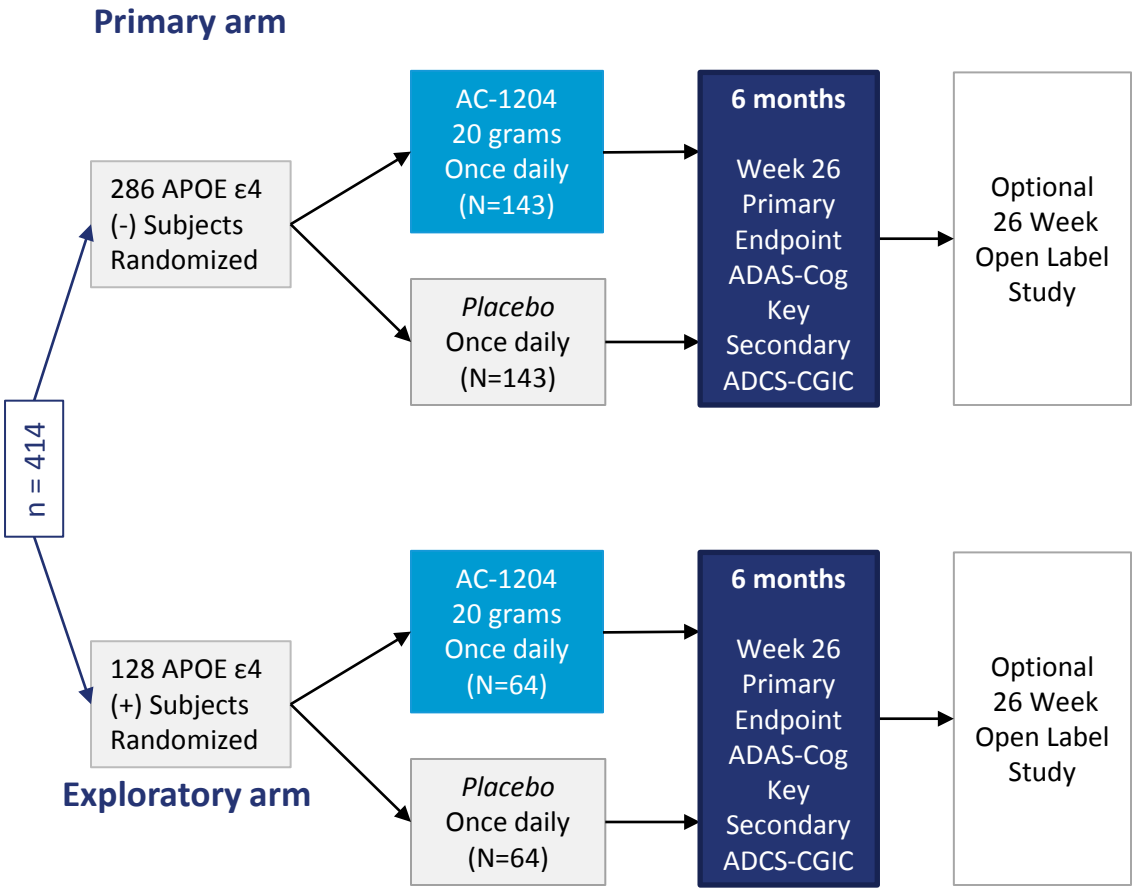
Accera's Phase 2/3 Study (NOURISH AD):



Run by Accera's clinical operations team with a leading CRO: INC Research

- Conducted at 80 US sites
- Secondary endpoints include:
  - Alzheimer's Disease Co-operative Study – Activities of Daily Living
  - Quality of Life – Alzheimer's Disease
  - Resource Utilization in Dementia.
  - Clock Draw Interpretive Scale
  - Mini-Mental State Exam (MMSE)

Exploratory arm included at the request of the FDA to:

- Ensure no efficacy in APOE ε4 carriers after a longer duration
- Ensure no safety concerns

Full Results to be presented at CTAD 2017

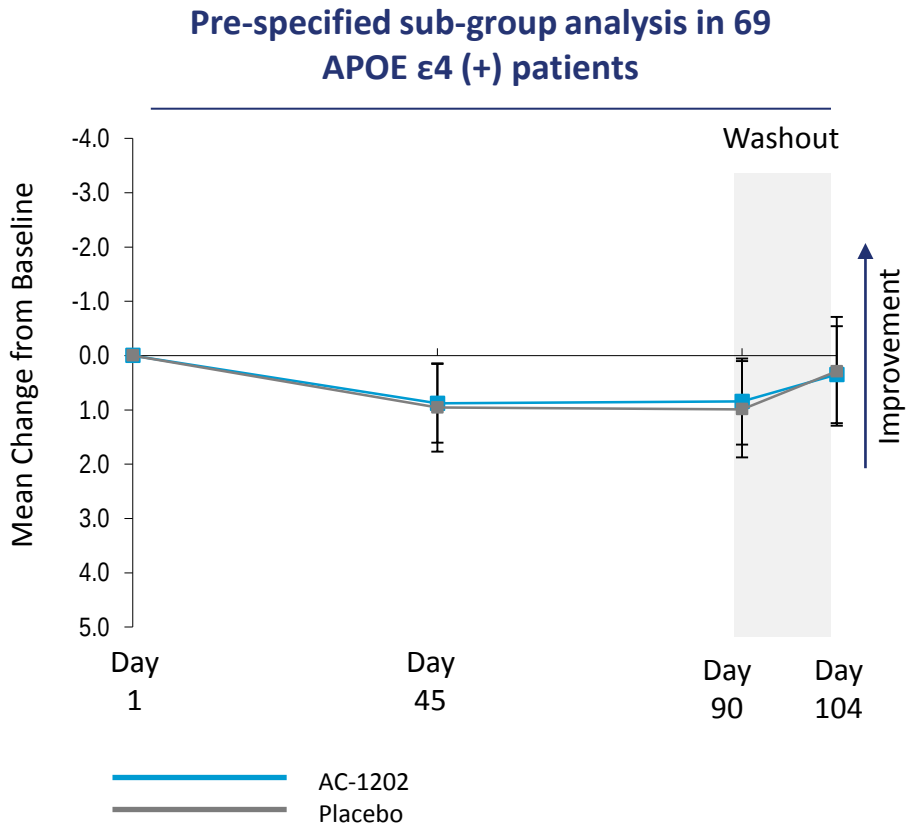
Summary

- Accera is developing novel approaches to Alzheimer’s disease based on metabolic defects present in the disease
- Under “normal” conditions the brain runs almost exclusively on glucose
- In mild AD, CMRglc decreases yet metabolism of ketone bodies remains intact
- Ketone bodies act as signaling metabolites with protective properties
- Defective metabolism is an attractive target in Alzheimer's drug development

Acknowledgements –Thanks to the Accera staff!

BACK UP SLIDES

Phase 2b Study: No change from baseline in ADAS-Cog scores in APOE4 carriers



- APOE ε4 carriers showed no statistical difference between placebo and active at any time point

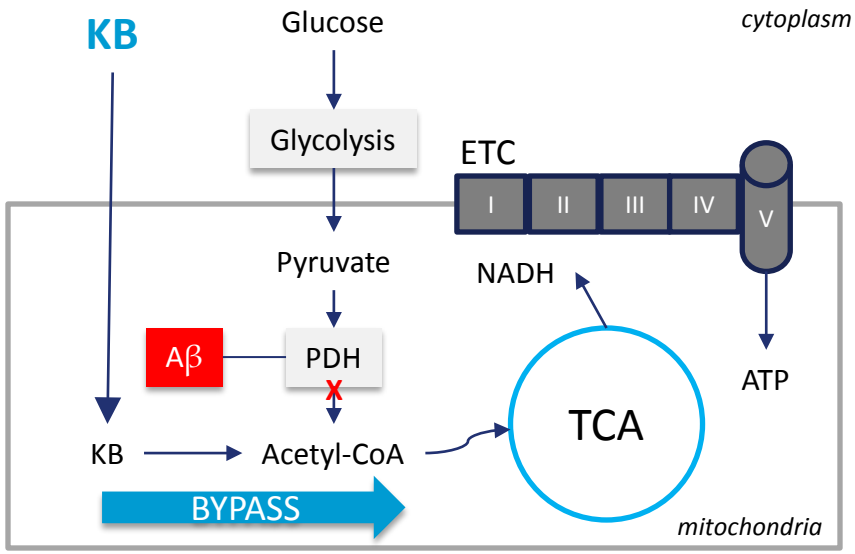
Time point	Score Difference	P-value
Day 45	0.05	0.964
Day 90	0.12	0.921
Day 104 Washout	-0.25	0.845

N=38 ApoE4(+) AC-1202; N=31 ApoE4(+) Placebo

Ketone bodies can bypass some defects in mitochondrial function in AD

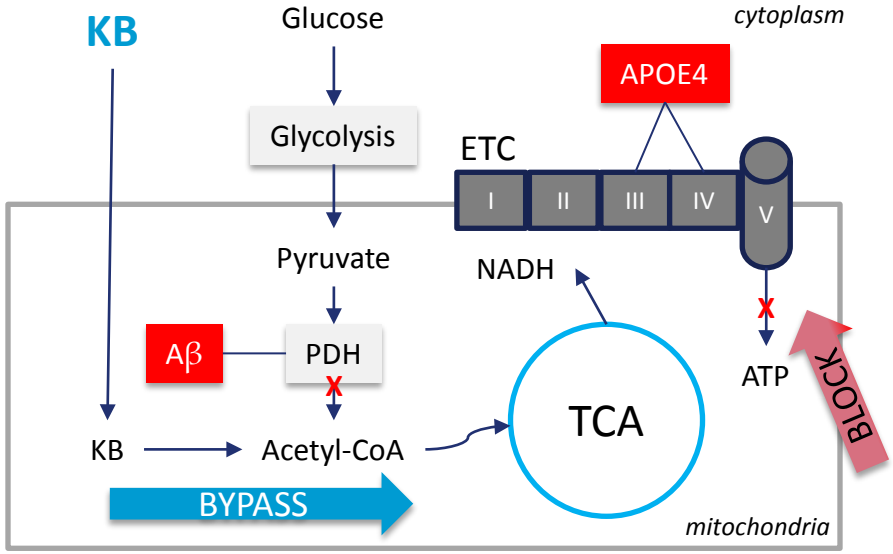
APOE4 non-carriers

- Primary block in mitochondrial function by Aβ occurs pyruvate dehydrogenase (PDH) preventing the utilization of glucose(1)
- Ketone bodies provide acetyl-CoA independent of PDH



APOE4 carriers

- Block in mitochondrial function by Aβ occurs pyruvate dehydrogenase (PDH) preventing the utilization of glucose
- Further block at Complex III and IV by APOE4 (2)
- Ketone bodies can't bypass block in ETC



1. Kashiwaya, Y., T. Takeshima, et al. (2000) Proc Natl Acad Sci U S A **97(10): 5440-4.**
2. Nakamura, T., A. Watanabe, et al. (2009) Mol Neurodegener **4: 35.**

Alzheimer's disease: What causes Glucose Hypometabolism?

1. Neuronal damage - cellular/synaptic loss
2. Low expression of energy generation genes in AD [1]
3. Activities of Aβ [2-4]
4. Activities of ApoE4 protein inhibiting mitochondrial function [5]
5. Defects in mitochondrial transport [6]
6. Brain Insulin Resistance [7]
7. **Deleterious effects of glucose on the brain leading to mitochondrial dysfunction [8]**

1. Liang, W. S., E. M. Reiman, et al. (**2008**). "Alzheimer's disease is associated with reduced expression of energy metabolism genes in posterior cingulate neurons." Proc Natl Acad Sci U S A 105(11): 4441-6.
2. Atamna, H. and W. H. Frey, 2nd (**2007**). "Mechanisms of mitochondrial dysfunction and energy deficiency in Alzheimer's disease." Mitochondrion 7(5): 297-310.
3. Veech, R. L., B. Chance, et al. (**2001**). "Ketone bodies, potential therapeutic uses." IUBMB Life 51(4): 241-7.
4. Devi, L., B. M. Prabhu, et al. (**2006**). "Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction." J Neurosci 26(35): 9057-68.
5. Mahley, R. W., K. H. Weisgraber, et al. (**2006**). "Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease." Proc Natl Acad Sci U S A 103(15): 5644-51.
6. Trushina, E., E. Nemutlu, et al. (**2012**). "Defects in mitochondrial dynamics and metabolomic signatures of evolving energetic stress in mouse models of familial Alzheimer's disease." PLoS One 7(2): e32737.
7. De La Monte, S.M. (**2012**). Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. Curr Alzheimer Res 9, 35-66.
8. Henderson, S.T. (**2004**). High carbohydrate diets and Alzheimer's disease. Med Hypotheses 62, 689-700.

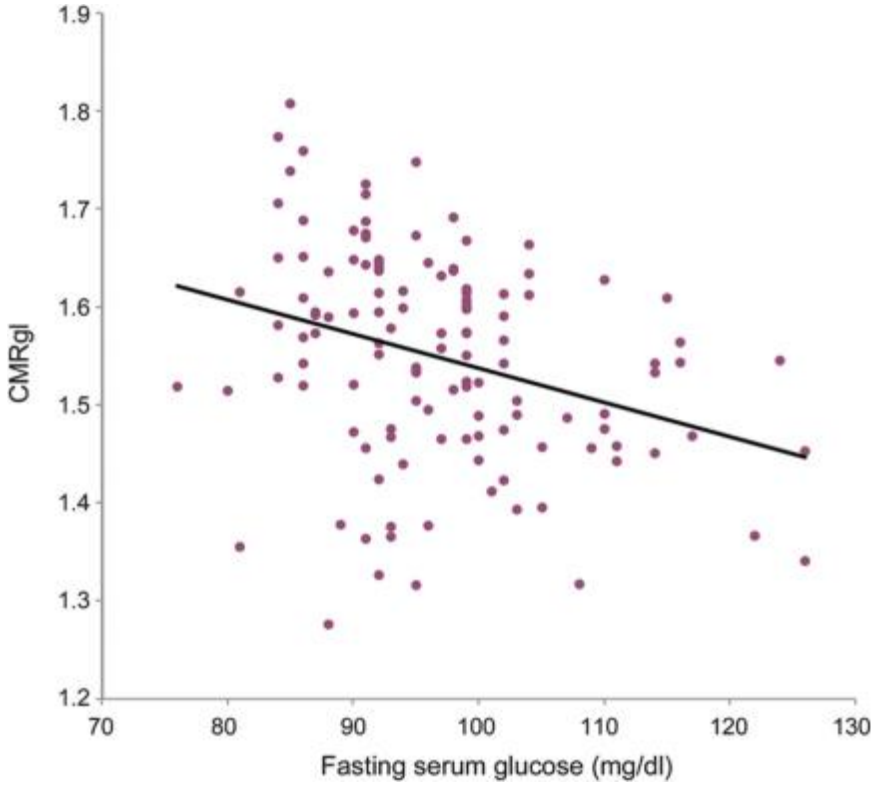
High “Normal" Blood Glucose is Associated with Lower CMRglc

Design

- 124 cognitively normal subjects
- Mean age 64 years
- 61 APOE4(-)
- 63 APOE4(+)

Results

- Both groups showed lower CMRglc correlated with higher fasting glucose
- Pattern of reduced CMRglc was confined to areas associated with AD



Accera

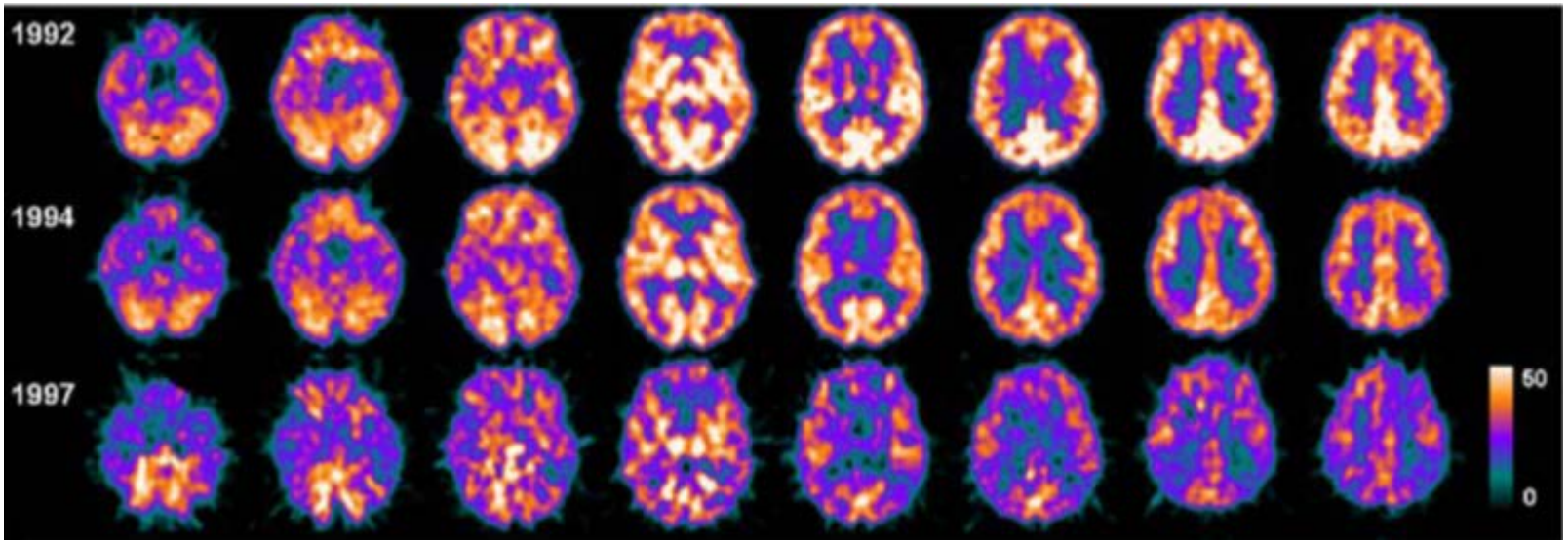
Burns, C.M., et al., Higher serum glucose levels are associated with cerebral hypometabolism in Alzheimer regions. Neurology, **2013**. 80(17): p. 1557-1564.

Glucose Hypometabolism is Progressive in AD and Correlates with Cognitive Decline

Age 69
MMSE 29

Age 71
MMSE 24

Age 74
MMSE 23

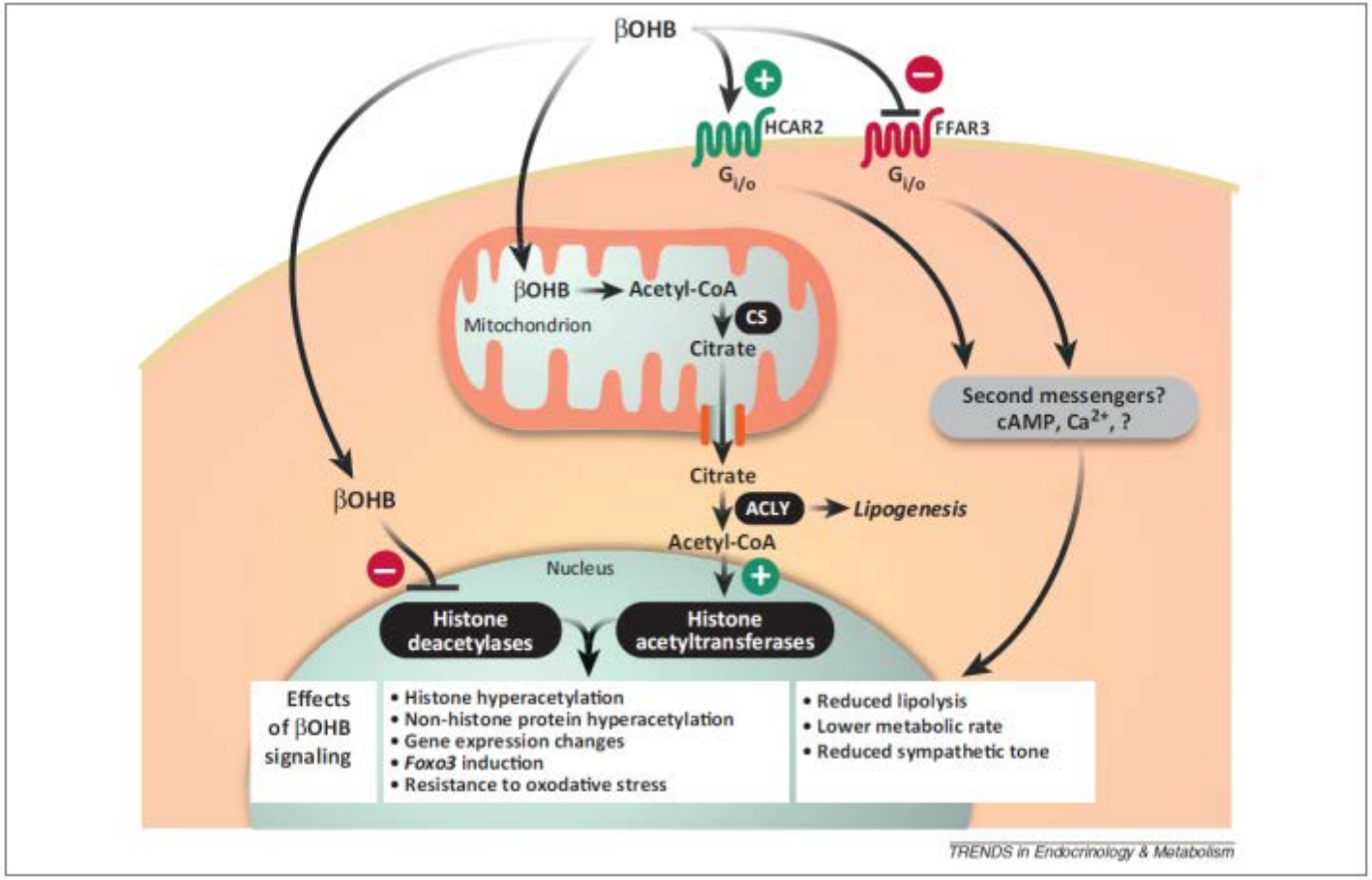


- Decline in CMRglc ranges from 17-24% across the brain
- Represents a serious problem for the brain which relies on glucose.

Accera

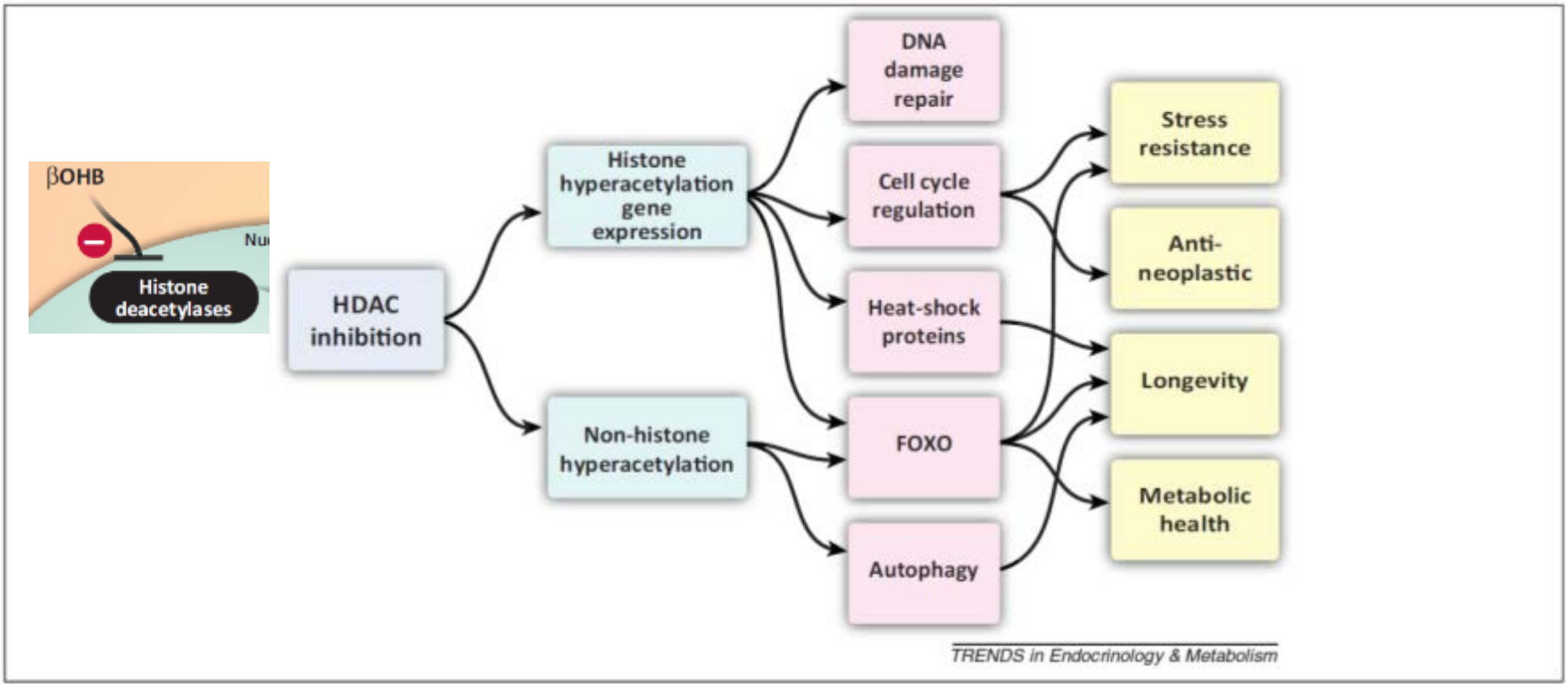
Mosconi, L., M., et al. (**2007**). "Early detection of Alzheimer's disease using neuroimaging." Exp Gerontol 42(1-2): 129-38.

Ketone Bodies as Signaling Metabolites



Newman, J.C., and Verdin, E. (**2014**). Ketone bodies as signaling metabolites. *Trends Endocrinol Metab 25, **42-52.***

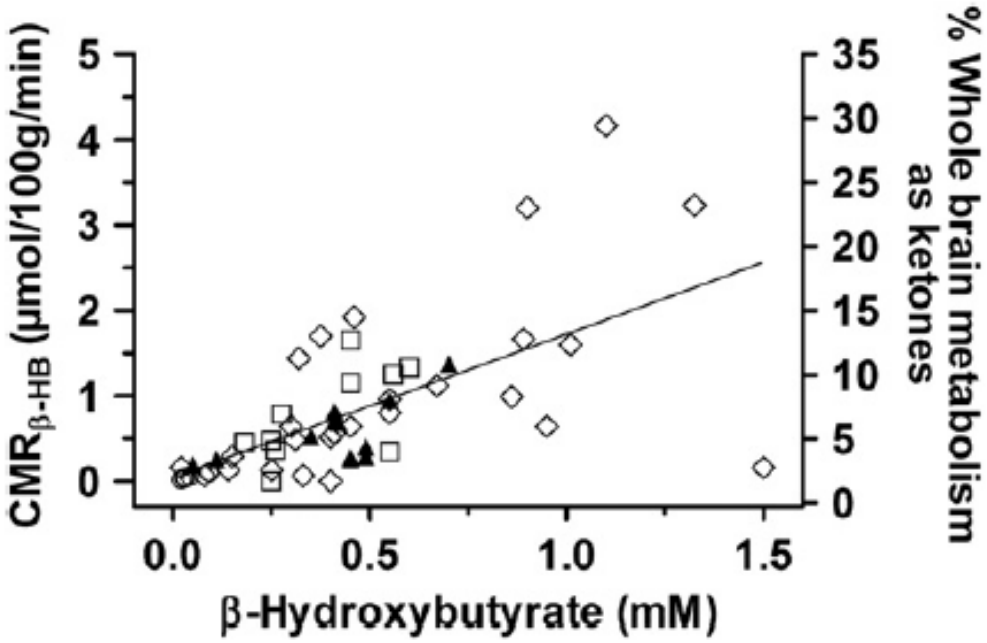
Ketone Bodies act as Histone De-acetylase (HDAC) Inhibitors and Activate HCAR2



Newman, J.C., and Verdin, E. (**2014**). Ketone bodies as signaling metabolites. *Trends Endocrinol Metab 25, **42-52.***

The Brain's Utilization of Ketone Bodies Varies Directly with Blood Concentrations

Blood BHB (mM)	CMR (% of total)
0.3-0.5	3-5%
1.5	18%
6	60%



Cunnane, S. et al. (2011). "Brain fuel metabolism, aging, and Alzheimer's disease." Nutrition 27(1): 3-20.

Support for Mechanism of Action: Independent studies continue to support ketosis as a treatment for Alzheimer's disease

- **Krikorian et al. (2012) demonstrated improved memory performance that correlated with urine ketone levels**
- Randomly assigned 23 older adults with Mild Cognitive Impairment to either a high carbohydrate or very low carbohydrate diet for six weeks.
- For the low carbohydrate subjects:
  - Verbal memory performance improved (p = 0.01)
  - Weight reduced (p < 0.0001)
  - Waist circumference reduce (p < 0.0001)
  - Fasting glucose reduced (p =0.009)
  - Fasting insulin (p = 0.005)
  - Ketone levels were positively correlated with improved memory performance (p = 0.04)

Post-intervention dietary parameters by group

	High carb	Low carb	*t*(21)	*p*
Total energy, kcal	1592 (395)	1042 (347)	3.55	0.001
Carb, g	197 (53)	34 (18)	9.94	< 0.0001
Protein, g	58 (12)	67 (19)	1.32	0.20
Fat, g	61 (24)	69 (27)	0.74	0.49
Urinary ketone, mg/dl	0	5.4 (3.3)	4.54	< 0.001

Note: High carb = high carbohydrate group. Low carb = low carbohydrate group.

Urinary ketone = acetoacetic acid. Data represent unadjusted, mean (SD) daily values.

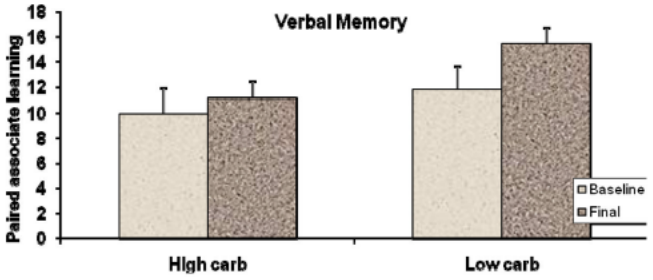


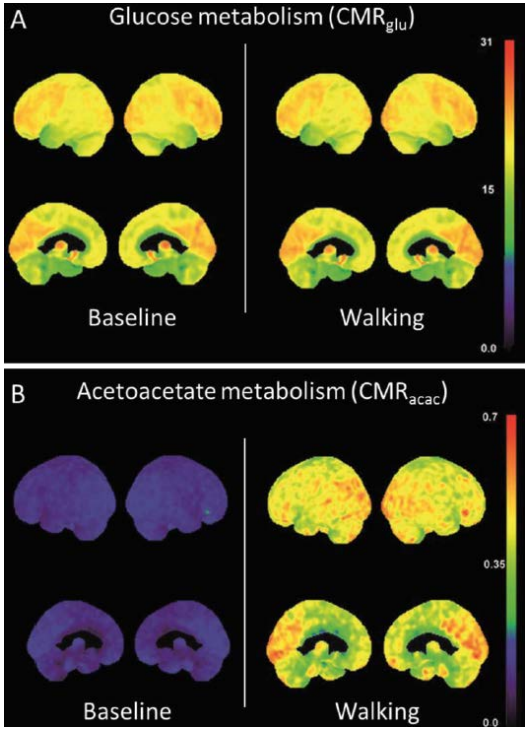
Figure 1.
Pre- and post-intervention memory performances for the low and high carbohydrate groups as measured by the Verbal Paired Associate Learning Test (Krikorian, 1996). Values are unadjusted means of the cumulative number of correct immediate recall responses summed across four learning trials. Vertical bars represent standard error. The ANCOVA analysis indicated improved learning for the low carbohydrate subjects, $F(1,20) = 6.45$, $p = 0.01$, Cohen's $f = 0.26$.

1. Krikorian, R., M. D. Shidler, et al. (2012). "Dietary ketosis enhances memory in mild cognitive impairment." Neurobiol Aging 33(2): 425 e19-27.

Support for Mechanism of Action: Recent studies continue to support ketosis as a treatment for Alzheimer's disease

Castellano et al (2017)[1] demonstrated that moderate exercise increases ketone body uptake in the brain:

- Exercise has been proposed to reduce risk of developing AD[2]
- 10 Patients diagnosed as having probable or possible AD dementia were trained to walk on a motorized treadmill 3 days/week for 12 weeks
- Measurement of Glucose uptake was measured with FDG-PET
- Measurement of Ketone uptake was measured with Ketone-PET
- Compared to the Baseline, after Walking, CMRacac was three-fold higher (0.6±0.4 versus 0.2±0.1mol/100 g/min; $p = 0.01$).
- CMRglu was unchanged after Walking (28.0±0.1mol/100 g/min; $p = 0.96$).
- Plasma acetoacetate concentration and the blood-to-brain acetoacetate influx rate constant were also increased by 2–3-fold (all $p \leq 0.03$)
- There was a trend toward improvement in the Stroop–color naming test (–10% completion time, $p = 0.06$) and performance on the Trail Making A&B tests($p \leq 0.01$)

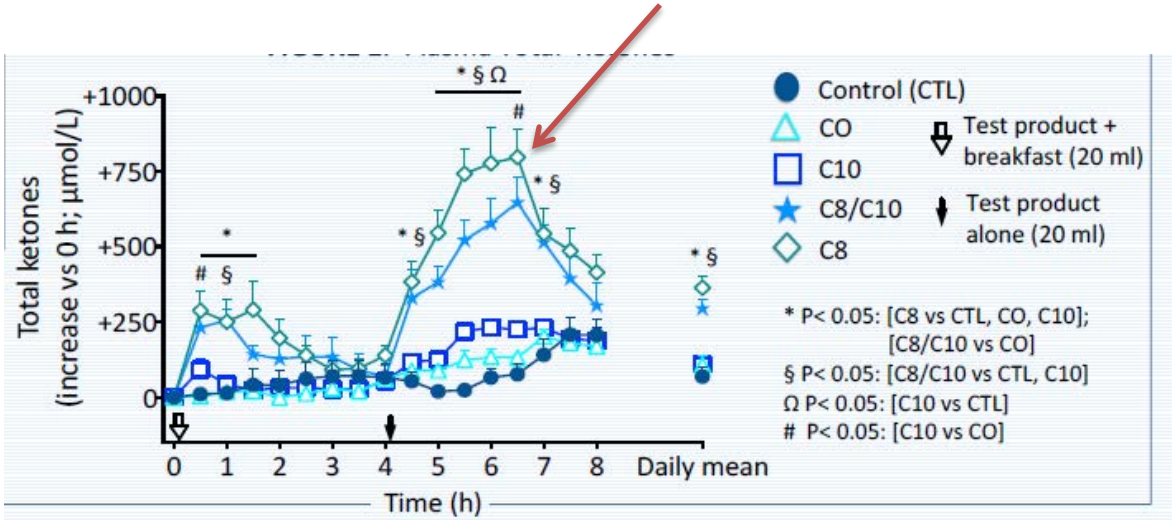


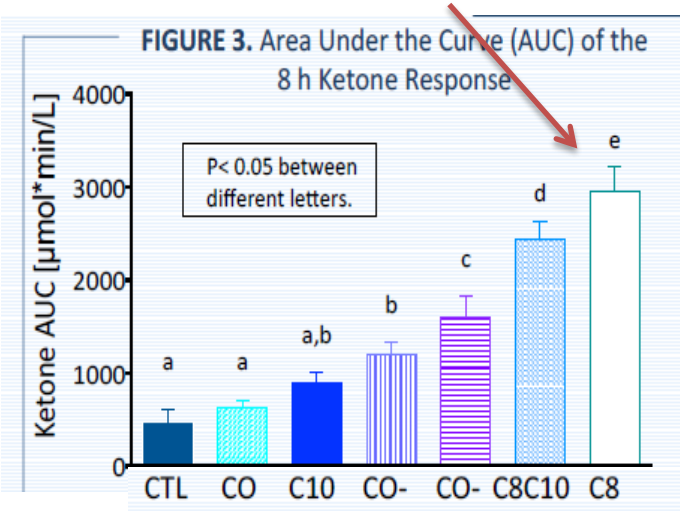
1. Castellano, C.A., et al., *A 3-Month Aerobic Training Program Improves Brain Energy Metabolism in Mild Alzheimer's Disease: Preliminary Results from a Neuroimaging Study. J Alzheimers Dis, 2017.* ***56(4): p. 1459-1468.***
2. Weuve J, Kang JH, Manson JE, Breteler MMB, Ware JH, Grodstein F (2004) *Physical activity, includingwalking, and cognitive function in older women*. *JAMA* **292, 1454-1461**.

Support for Mechanism of Action: Recent studies continue to support ketosis as a treatment for Alzheimer's disease

Vandenberghe et al (2016)[1] demonstrated that caprylic triglyceride is more ketogenic than other MCTs:

- Caprylic triglyceride was more ketogenic than C8/C10 blends for both Cmax and AUC
- Capric triglycerides are weakly ketogenic
- Coconut oil is weakly ketogenic





Vandenberghe C et al 2016. ACUTE PLASMA KETONE RESPONSE TO COCONUT OIL ALONE OR IN COMBINATION WITH DIFFERENT MEDIUM CHAIN TRIGLYCERIDES

Animal Model: Administration of MCTs improved mitochondrial function and cognition in aged beagles

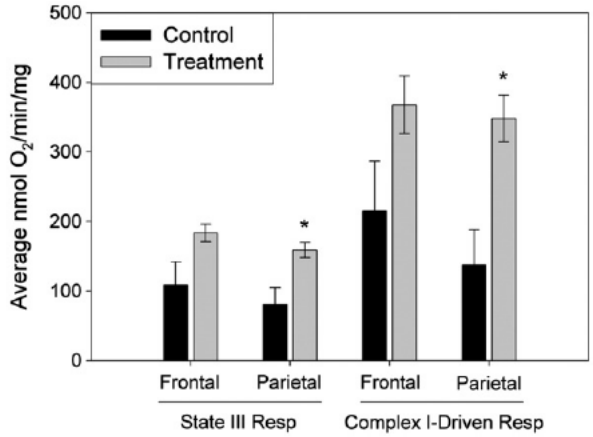


Fig. 2 – Mitochondrial respiration. The treatment animals had larger rates of state III respiration in the parietal lobes, as compared to controls (t-test, P=0.025). The treatment animals also had an increased ability to drive electrons through Complex I in the parietal lobes, as compared to controls (t-test; P=0.013). Although the trend was in the same direction in the frontal lobes, the differences were not statistically significant (t-tests, P=0.080 and P=0.115, respectively). Statistically significant differences, as compared to the control group, are indicated by an asterisk (*).

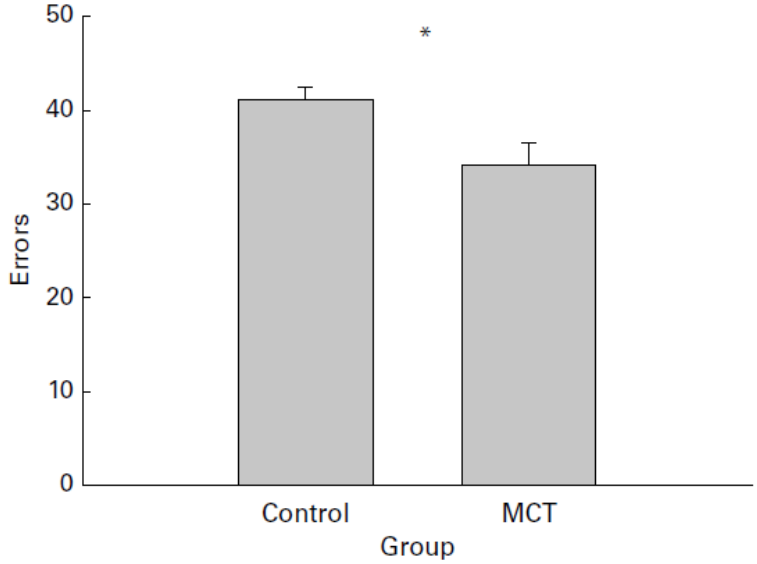


Fig. 3. Effects of dietary medium-chain TAG (MCT) supplementation on dogs' performance in complex landmark discrimination task (land-2). The data are means with their standard errors, *n* 11. The performance was expressed as total number of errors over ten sessions. * Mean values were significantly different ($P<0{\cdot}05$).

1. Studzinski, C. M., W. A. Mackay, et al. (2008). "Induction of ketosis may improve mitochondrial function and decrease steady-state amyloid-beta precursor protein (APP) levels in the aged dog." Brain Res **1226: 209-17.**
2. Pan, Y., B. Larson, et al. (2010). "Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs." Br J Nutr: 1-9.

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Phase 2b Study: Enrolled patients were typical mild to moderate AD patients

Safety population		Treated, N = 86	Placebo, N = 66
Age	Mean (± SD)	76.9 (± 8.9)	76.8 (± 7.4)
	Median	78.0	78.0
	Range	52 -93	51 -89
AD medications n (%)*	Aricept	43 (50)	28 (42.4)
	Exelon	11 (12.8)	11 (16.7)
	Namenda	32 (37.2)	31 (47)
	Reminyl/Razadyne	3 (3.5)	9 (13.6)
Genotyped population		Treated, N = 67	Placebo, N = 57
APOE Genotype n (%)	Total E4 (+)	38 (56.7)	31 (54.4)
	Total E4 (-)	29 (43.3)	26 (45.6)
ITT population		Treated, N = 77	Placebo, N = 63
Baseline MMSE	Mean (± SD)	19.68 (± 4.48)	19.48 (± 4.37)
	Median	20.00	20.00
	Range	10 - 28	8 -29
Baseline ADAS-Cog	Mean (± SD)	23.88 (± 9.17)	23.35 (± 8.7)
	Median	23.67	23.00
	Range	7 – 54.33	11.33 – 62.00

* Some patients were on multiple medications

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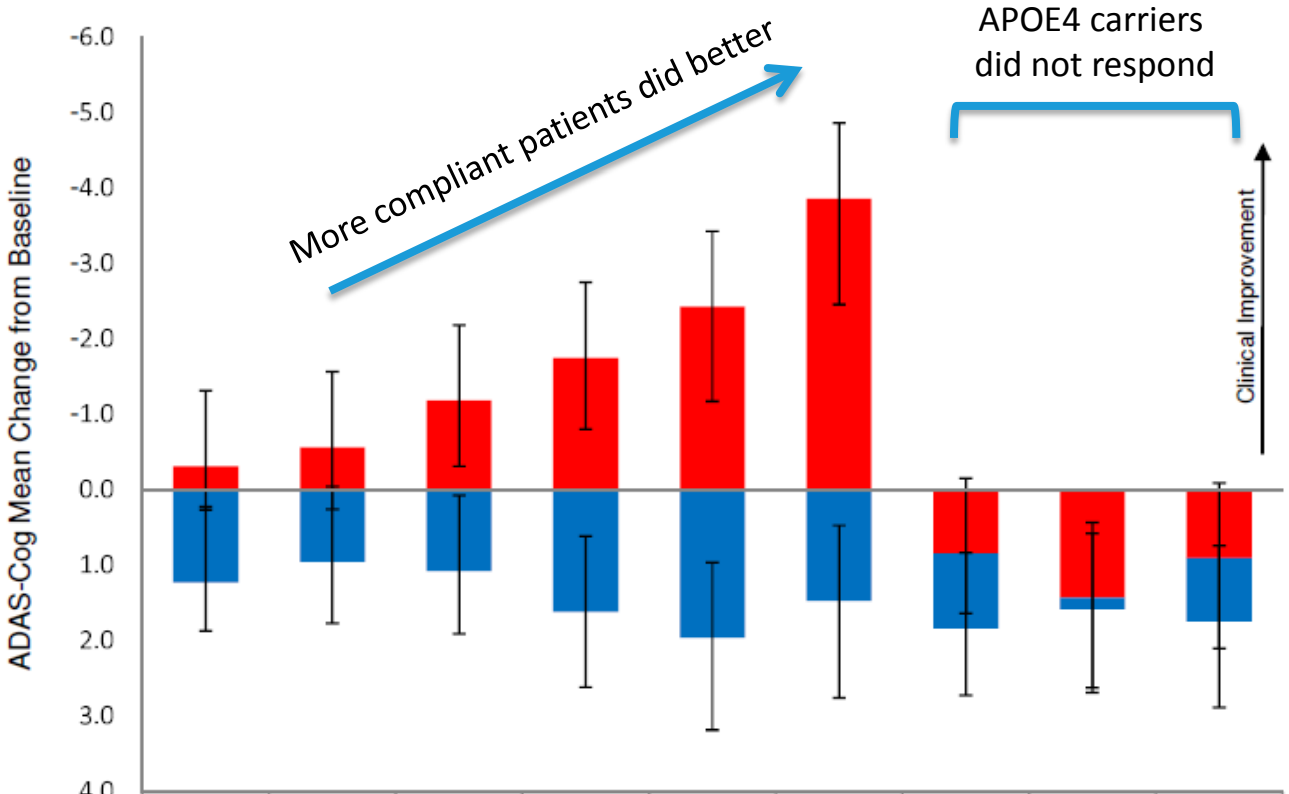
Modified from Henderson, et al. 2009.

Summary of efficacy results



	ITT w/LOCF	Per Protocol	Dosage Compliant	E4(-) ITT w/LOCF	E4(-) Per Protocol	E4(-) Dosage Compliant	E4(+) ITT w/LOCF	E4(+) Per Protocol	E4(+) Dosage Compliant
Placebo	1.227	0.956	1.076	1.614	1.963	1.472	0.989	0.145	0.833
AC-1202	-0.312	-0.563	-1.182	-1.747	-2.426	-3.854	0.846	1.433	0.909

Dr. John Didsbury

President & CEO, Chairman of the Board
T3D Therapeutics

- Dr. Didsbury is a seasoned Executive Manager with over 27 years of experience within the pharmaceutical and biotechnology industries in both small and large public and private companies.
- Former roles:
  - President of DARA BioSciences, Inc. (NASDAQ:CM – DARA). He played a key role in taking the company public in 2008 through a reverse merger.
  - Head of Strategy and Operations for one of GlaxoSmithKline's six worldwide drug discovery centers.
  - Assistant Professor of Medicine at Duke University Medical Center and a scientist at Genentech, Inc.

A Transformational Approach to Treating Alzheimer's Disease

AABC/ISTAART Webinar
19 October 2017

Forward-Looking Statements

Statements contained in this presentation that are not statements of historical fact may be deemed to be forward looking statements. Without limiting the generality of the foregoing, words such as “may,” “will,” “expect,” “believe,” “anticipate,” “intend,” “could,” “estimate” or “continue” are intended to identify forward-looking statements. Readers are cautioned that certain important factors may affect the Company’s actual results and could cause such results to differ materially from any forward looking statements which may be made in this presentation or which are otherwise made by or on behalf of the Company. Factors which may affect the Company’s results include, but are not limited to, product demand, market acceptance, impact of competitive products and prices, product development, commercialization or technological difficulties, the success or failure of negotiations and trade, legal, social and economic risks.

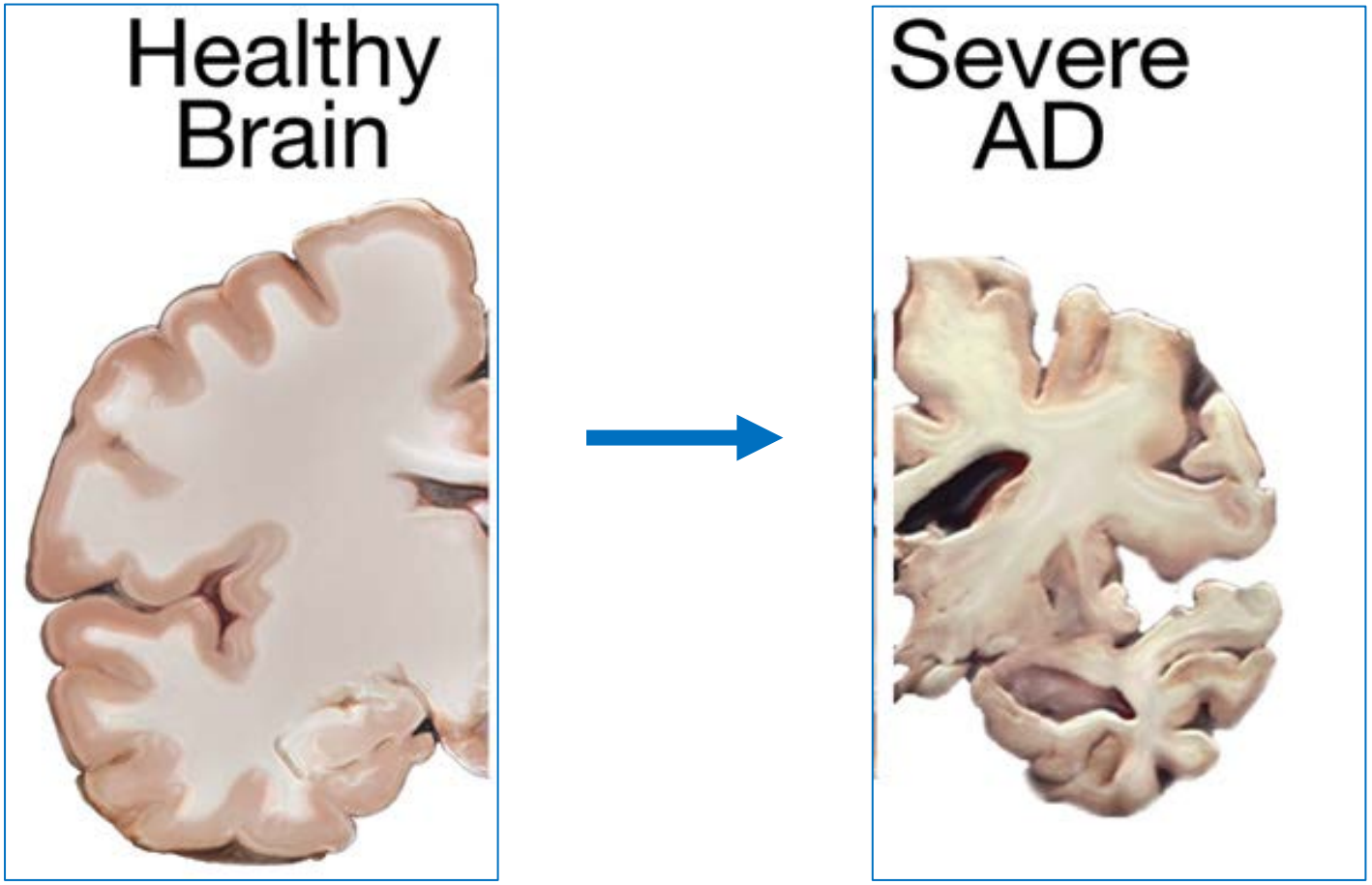
Highlights

1. **Innovative Approach - Challenging Current Paradigms to Treat the Disease**

2. **Possibility of the First Truly Effective Treatment for Alzheimer's Disease (AD) – Phase 2a Evidence**

3. **Lower Risk – Investigational New Drug T3D-959 Has All Three Key Facets of a Successful Pharmaceutical Drug**

Key Tenet: The Alzheimer's Brain is Being Starved



Three Major Changes in the Alzheimer's Brain

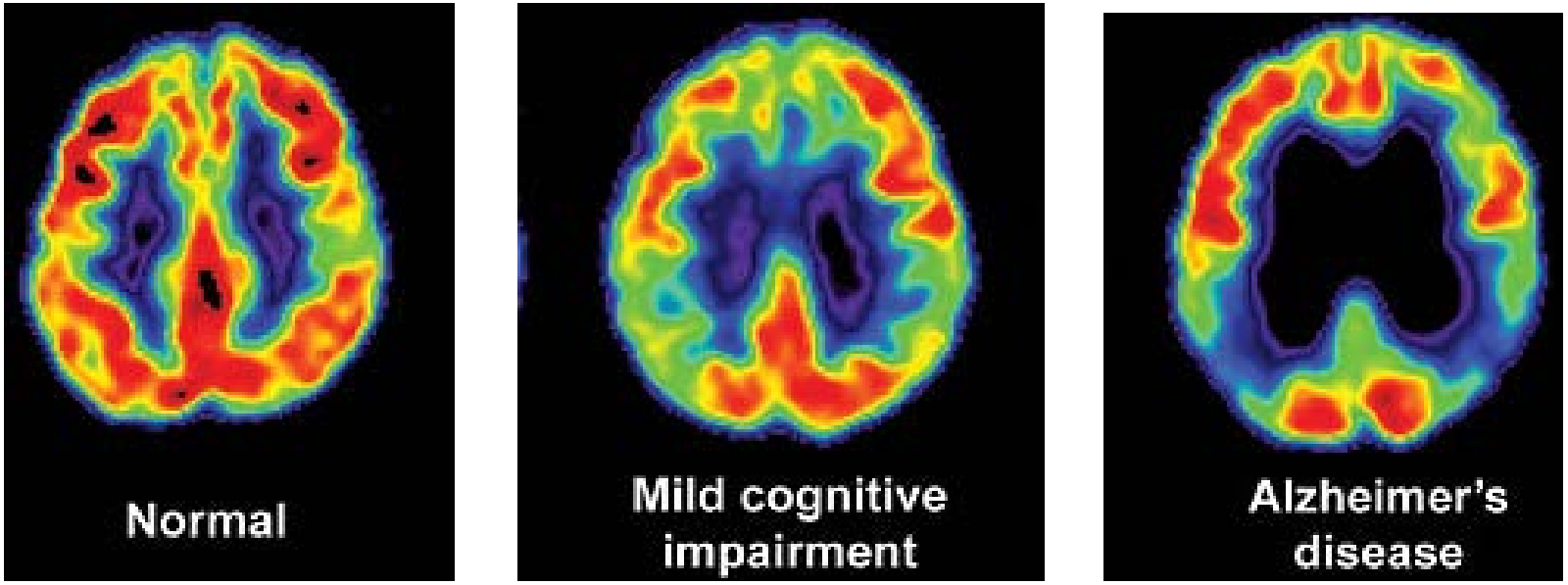
1. **Metabolism Changes – Glucose + Lipids**

2. **Structural Changes – Amyloid Plaques + Tau Tangles**

3. **Stress Changes – Inflammation + ROIs**

Metabolism Changes May Be the Initiating Event

Metabolism Changes Precede Cognitive Decline



Progressive Dysfunctional Glucose Energy Metabolism

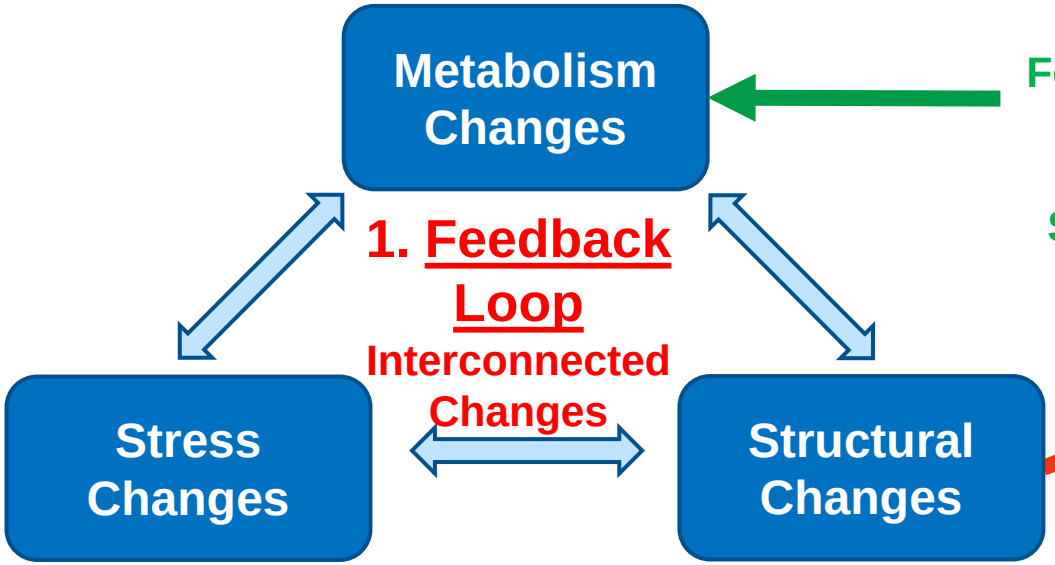
Low glucose metabolism > energy deficiency > brain starvation > cognitive decline

FDG-PET Imaging – Measuring Brain Glucose Metabolism. Warm colored areas indicate regions of higher glucose metabolism.

Glucose Metabolism Link With Cognitive Function

- **Diabetics Have 2-Fold Increased Risk of Getting AD**
- **37% of AD Patients are Diabetic (vs. 9.4% General Population)**
- **Multiple Similarities of AD & Type 2 Diabetes: The Common Theme is Insulin Resistance**
  - **Cognitive Decline**
  - **Neurodegeneration**
  - **Amyloid Aggregation and Deposition**
  - **Inflammation**
- **Clinical Symptoms of AD Do Not Occur Without Decreases in Brain Glucose Metabolism**
- **Association – Elevated Blood Sugar > Memory Problems & Lower Brain Volume**

Innovative Approach



1. Feedback Loop
Interconnected Changes

T3D-959
Correct Metabolism Dysfunctions
↓
Feed the Starving Brain, Intervene Here
↓
Slow, Stop or Reverse Disease Course

2. Focus Today
Multiple Drug Failures
↓
High Perceived Risk
↓
Investor Recalcitrance
↓
Innovation Stifled
↓
Wrong Intervention Point

Innovative Approach

Unique Molecule T3D-959

- Central Regulator of Glucose and Lipid Metabolism
- Acting to Restore Normal Metabolism – Overcoming Insulin Resistance
- Accesses the Brain – Penetrating the Blood Brain Barrier
- T3D-959 Target is Highly Expressed in Brain Tissue
- Clear Pre-Clinical and Clinical Evidence of a Strong Brain Pharmacological Effect
- Good API and Drug Product Properties
  - Reliable GMP API Manufacture in Hand
  - Facile Drug Product Preparation
  - Excellent API and Drug Product Stability
  - Orally Delivered as a Once-A-Day Capsule

T3D-959 Mechanism of Action

- **Regulating genes to correct dysfunctional glucose and lipid metabolism**
- **Drug Target:** **Primary – PPAR delta**
  Secondary – PPAR gamma

Central Regulators of Glucose and Lipid Homeostasis

Actions:
- Insulin sensitivity/signaling
- Fatty acid oxidation/catabolism
- Cholesterol transport
- ↑ HDL
- Reduction in adiposity, ↓ TGs
- ↓ Inflammatory signaling
- Macrophage differentiation

Actions:
- Insulin sensitivity/signaling
- Glycogen synthesis
- Adipogenesis
- Anti-oxidation
- ↓ Inflammatory signaling
- ↑ BDNF, NGF, Klotho

Other Metabolic Approaches

- **Rosiglitazone (PPAR gamma agonist)**
- **Pioglitazone (PPAR gamma agonist) – TOMORROW Trial Ongoing**
- **Inhaled Insulin – SNIFF Trial Ongoing**

[Rosiglitazone – Success in Phase 2, Failure in Phase 3]

- **Restricted target expression in the brain (PPAR gamma)**
- **Poor brain penetration of Rosiglitazone (pgp substrate)**
- **Improper dose selection**
- **ApoE genotype-specific differential response**

T3D-959 is Distinctly Different

- **Flawed comparisons to "failed" PPAR γ-selective agent (Rosiglitazone/Avandia)**
- **The Primary Target of T3D-959 is PPAR δ (delta)**
- **All 'PPARs' are <u>not</u> the same**:
  - PPAR δ is ubiquitously found in the brain, PPAR γ is not
  - PPAR δ regulates energy expenditure, PPAR γ regulates energy storage
  - PPAR δ activates the key memory and learning wnt pathway, gamma does not
  - PPAR δ restores memory and spatial learning in animal models, gamma does not
  - PPAR δ plays helps maintain cholesterol homeostasis, gamma does not
- **T3D-959 has better pre-clinical brain exposure than Rosiglitazone** (or Pioglitazone)
  - 30 to 35% of rat plasma concentration of T3D-959 is found in rat brains
- Initial safety data indicates we should be able to use higher doses than Rosiglitazone
- T3D-959 has a different chemical structure. It is an indane acetic acid derivative not a thazolidinedione. Rosiglitazone and Pioglitazone are racemic mixtures.

T3D-959 Target Rationale

- **PPAR delta null mice are AD-like:**
  a) cognitive impairment,
  b) impaired canonical wnt signaling pathway,
  c) tau hyper-phosphorylation,
  d) increased inflammation in cerebral cortex,
  e) altered myelination,
  f) altered brain phospholipid composition,
  g) increased oxidative stress,
  h) brain atrophy
- .
- **PPAR delta activation Effective in AD animal models**
  a) Complete rescue of cognitive impairment,
  b) Reduced amyloid burden,
  c) Reduced brain inflammation,
  d) Inhibited production of BACE1,
  e) Increased expression of plaque degrading enzymes,
  f) Inhibition of tau phosphorylation of tau,
  g) Increased gene expression of anti-oxidants catalase and SOD
  h) Inhibition of astrocyte and microglia activation,
  i) Stimulation of the production of acetylcholine.

Pre-Clinical and Phase I Data Supporting Phase 2a Clinical Study

- **Pre-Clinical**
  - **Efficacy in i.c. STZ Model of Sporadic AD**
  - **Rat Brain Penetration Study**
  - **Rat and Monkey Tox data**
  - **Safety Pharmacology Studies**

- **Phase 1**
  - **Single Escalating Dose**
  - **Multiple Escalating Dose**
  - **Good PK supporting oral qd dose**
  - **Good exposures over a broad range of doses**
  - **Excellent Safety Profile, no adverse effects, no MTD**

Exploratory / Feasibility Phase 2a Study of T3D-959 in Mild to Moderate Alzheimer's Disease Patients

- **High Safety Profile – 2-week and 22-week dosing**
- **Multiple Efficacy Signals – Cognition and Brain Glucose Metabolism**
- **Successful Dose Range Finding for Subsequent Trials**

Translate to Lower Risk

Phase 2a High Safety Profile

- One drug-related AE(1)
- No changes in clinical labs
- No changes in physical and neurological exams
- No changes in ECGs
- No respiratory rate or orthostatic blood pressure and heart rate changes
- No potential bone marrow effects as monitored with hematology testing
- No potential increases in plasma volume as assessed by the presence or absence of edema
- No weight gain
- No tolerability issues

(1) First patient enrolled, subject 1001 (30mg) – Self-limited, resolved within 1-day

Multiple Efficacy Signals

1. Cognitive Improvement (ADAS-cog11) in Both Alzheimer's Patient Subgroups (ApoE4 positive & ApoE4 negative)

ApoE4 Negative Patients	Improvement from Baseline at Follow-up	ApoE4 Positive Patients	Improvement from Baseline at Follow-up
3mg	Yes 5.25 pt. avg..	3mg	No
10mg	Yes 6.17 pt. avg.	10mg	No
30mg	Yes 4.60 pt. avg	30mg	Yes 3.52 pt. avg.
90mg	No	90mg	Yes 1.00 pt. avg

- **Effective in Both Patient Sub-Groups**
- **Dosing Trend - Low Dose for One Group (ApoE4 negative), High Dose for the Other Group (ApoE4 positive)**
- **Highly Competitive Versus Marketed Drugs – e.g. Aricept 1.82 pts. at 6-weeks**

Multiple Efficacy Signals

2. Cognitive Improvement (DSST)

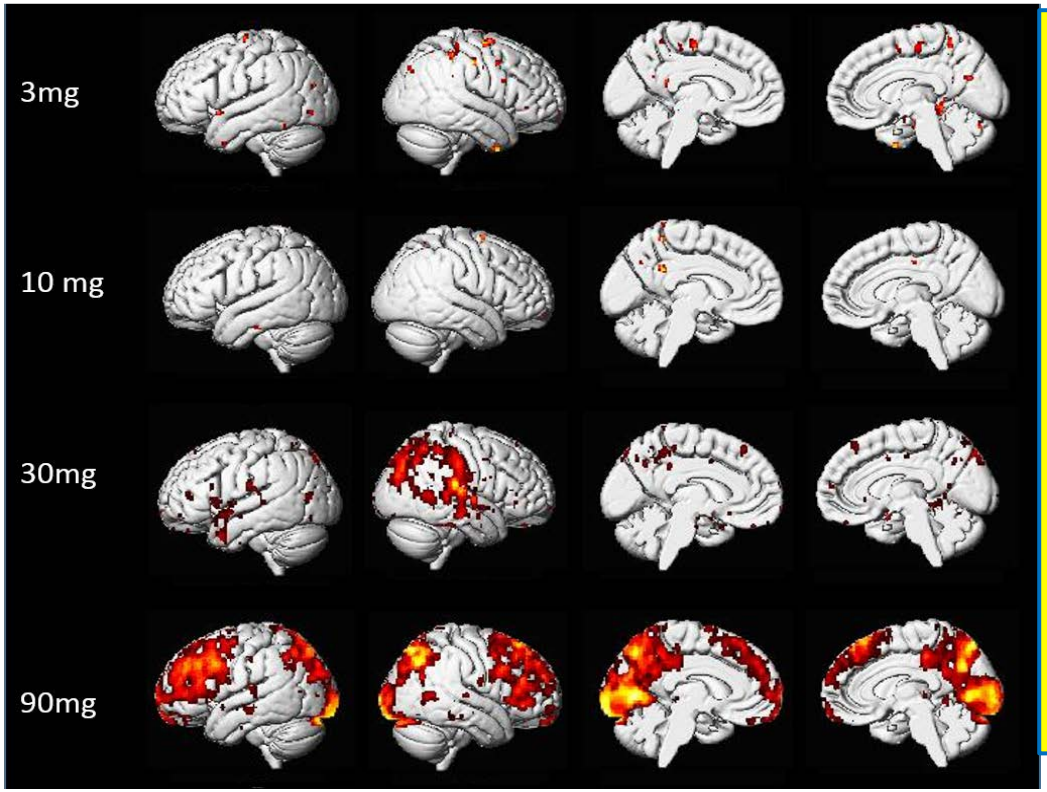
Improvement (regardless of dose or ApoE genotype) is sustained at 21 days (7 days post discontinuation of dosing). Less improvement in moderate patients. as expected

Average Improvement at D21 (all doses)		
	Moderate Patients	Mild Patients
All	2.4	7.0
ApoE4-	1.7	8.0
ApoE4+	4.4	6.5

Multiple Efficacy Signals

3. FDG-PET Neuroimaging Data Supports Brain Exposure & Activity

Dose Dependent Increase in the Spatial Extent of Regions of Statistically Significant Change in Relative CMRgl (EOT-BL)



Composite of Trial Subjects by dose group (n=8-9)

- **Statistically Significant Change Even at Lowest Dose (3mg)**
- **Dose Dependent Change**
- **Regional Specificity - Affecting Alzheimer's Regions.**

Multiple Efficacy Signals

4. Unsolicited Caregiver Feedback – Example – Improved Activities of Daily Living

Subject 3014: MMSE=25, 3mg dose,

Caregiver=Spouse, stated in letter received 7-days after dosing cessation:

1. *"**Much more alert & aware** of surroundings*
2. ***Much more engaged in conversation** at home & in public*
3. *Critical of my driving…aware of every changing light and tried to direct me as to when to stop & go…critical of other drivers…commented on other driver's traffic violations, etc.*
4. *Without prompting, went outside to repair polaris that had disconnected from pool wall…got the necessary tools without asking where they were located*
5. *Started dispensing vitamins at breakfast. He did this on a daily basis for a number of years but quit 6-8 months ago. Now, **routine has resumed**.*
6. *At my daughter's house in Charlotte, he asked if anyone would like a glass of wine. He got the wine that he had chilled earlier, got the wine opener and opened the wine & then served it. For the last year or more he has not remembered where he has chilled the wine nor where the wine opener was kept. **He also has not remembered how to operate my daughter's wine opener for the last year or more. He asked for no assistance when using it after the trial***
7. *He has been choosing his clothes to wear without asking for advice.*
8. *He packed his suitcase (twice) without assistance. He has needed assistance with this task for at least 1 ½ to 2 years."*

Multiple Efficacy Signals

5. Clinical Investigator Impressions

"Our trial site has received **consistently positive reports from patients and their caregivers** in this Phase 2a clinical trial. I would like to congratulate T3D on this successful study. We eagerly anticipate a longer [and larger] trial,"

- *Marc Agronin, MD*, Principal Investigator - Miami Jewish Health Systems, Miami, FL

"Since the launch of the T3D-959 study, we have unexpectedly received unsolicited, spontaneous **caregiver submissions of feedback, noting significant improvements** in some of the trial participants. We are excited about these preliminary results and look forward to furthering our understanding of the safety and efficacy of T3D-959 in patients with mild to moderate Alzheimer's disease."

- *Santosh Gopalakrishnan MD*, Principal Investigator – New Hope Clinical Research, Charlotte, NC

"I am familiar with T3D959 and actually had several patients on it for a Phase 2 clinical trial. This was through New Hope Clinical Research here in Charlotte. I am interested in putting many more people on the trial. **We had several of our patients improve, some dramatically, on the drug. I am the world's leading skeptic and even I was impressed**."

- *Charles Edwards MD*, Physician – Memory Center, Charlotte, NC

Phase 2a – 22-week Expanded Access Extension: Early indicator of potential long term safety

4 Subjects

- **All were ApoE4 positive patients (genotype was determined after dose selection & extension study start),**
- **Selected dose not optimal for ApoE4 positive patients**

Monthly cognitive and safety assessments

At **22-weeks** dosing (15mg q.d.):

- No Adverse Events
- No Safety Signals
- No tolerability issues
- CIBIC+ improvement in all subjects Group avg. = 2.75

T3D-959 – All 3 Facets For a Successful Pharmaceutical Drug

Top Tier Drug Properties

EFFICACY

- Phase 2a Cognitive Improvement – Sustained After Dosing Discontinuation
- Phase 2a Increase in Brain Glucose Metabolism
- Evidence of Disease Reversal in Animal Model
- Caregiver-Driven Extension Study

SAFETY

- No MTD, No SAEs, No Drug-Related AEs, No Tolerability Issues in Phase 1
- No Safety Signals, No Tolerability Issues in Phase 2a
- No Safety Signals, No Tolerability Issues in 4 patients dosed for 22-weeks
- No prototypical PPARγ – related side effects

PRODUCT PROPERTIES

- Orally Delivered
- Once-Day-Dosing PK
- Brain Penetration
- High Drug Stability
- High Solubility
- Simple Formulation
- Scalable Synthesis
- Low Cost of Goods

Translate to Lower Risk

Summary

I. New Approach - Correcting AD Metabolic Dysfunctions - Supported by Early Human Clinical Data

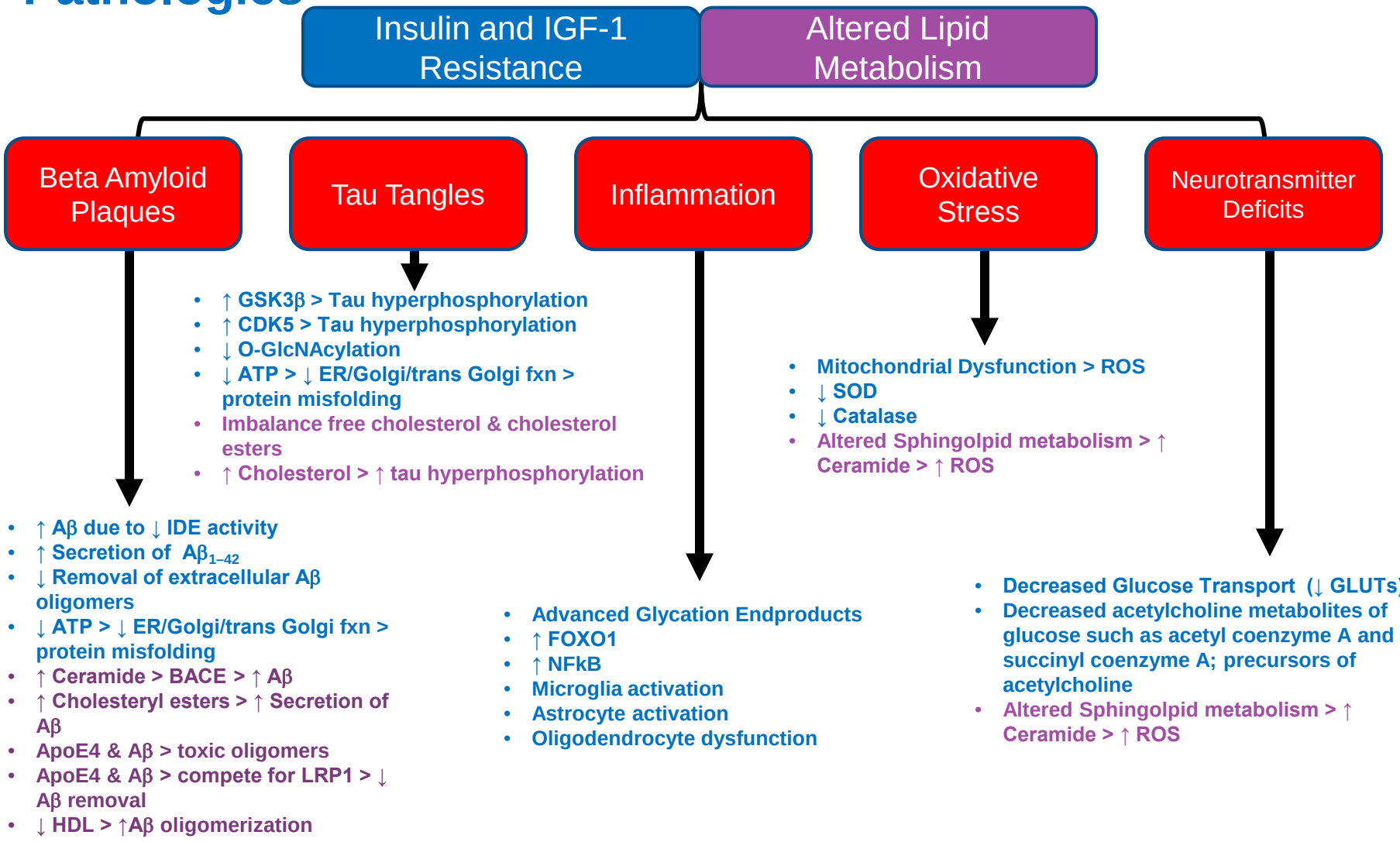
II. T3D-959 MOA >
   a. Potential to Treat Multiple Dementia Forms
   b. Potential Disease-Modification
   c. Potential Monotherapy or Combination agent

III. Therapeutic Utility for Different Severities and ApoE Sub-Groups

IV. Results Support Future Phase 2b Clinical Testing
   - ✓ High Safety/Tolerability (incl. 4 patients dosed 22-weeks w/ no safety signals)
   - ✓ Cognitive Tests
   - ✓ FDG-PET
   - ✓ Metabolomics
   - ✓ Unsolicited Caregiver Feedback
   - ✓ Clinical Investigator Impressions

Appendix – Additional Information

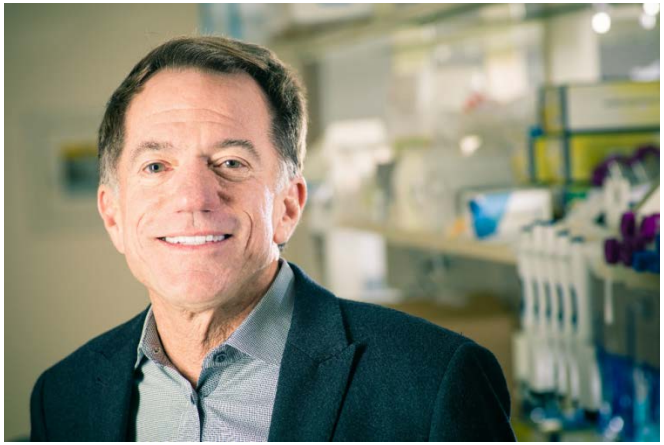
Interrelationship of Metabolic Defects and AD Pathologies



PPAR Delta Null Mouse Phenotype (AD-like)

- Cognitive impairment
- Impaired canonical wnt signaling pathway – key memory pathway
- Tau phosphorylation
- Increased inflammation in cerebral cortex
- Altered myelination
- Altered brain phospholipid composition
- Inactivation of peroxisomal β oxidation
- Increased oxidative stress (↑malondialdehyde,↓Mn-SOD,↓glutathione)
- Brain atrophy
- Significant increase vs. wt mice in cerebral infarct size in a focal cerebral ischemia model

References:
Hall, et.al.,, Peroxisome Proliferator-Activated Receptor *β/δ* in the Brain: Facts and Hypothesis. PPAR Research (2008) Article ID 780452, 10 pages doi:10.1155/2008/780452.



Dr. Mark Gurney

Chairman & CEO of Tetra Discovery Partners, Inc.

- Tetra is a clinical stage biotech developing BPN14770, a negative allosteric modulator of phosphodiesterase-4D, for the treatment of Alzheimer's disease and other dementias, psychiatric disease, and neurodevelopmental disorders including Fragile-X.
- Work in drug discovery and development as Senior Vice President at deCODE genetics, Inc.; Director Genomics, Pharmacia Corporation; Associate Professor, Northwestern University Feinberg School of Medicine; and Assistant Professor, University of Chicago Medical School.
- Developed the SOD1-G93A transgenic mouse model of ALS.
- Authored 117 peer reviewed scientific articles that have been cited over 21,000 times and holds 36 issued patents.
- PhD in neuroscience from the California Institute of Technology and an MBA from the Kellogg Graduate School of Management at Northwestern University.

ISTAART-AABC Webinar

BPN14770 For Early Alzheimer's Disease

Mark Gurney, PhD
Chairman & CEO
Tetra Discovery Partners Inc.

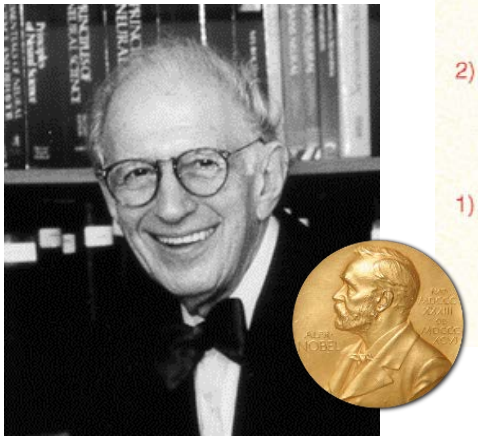
October 19, 2017

tetra

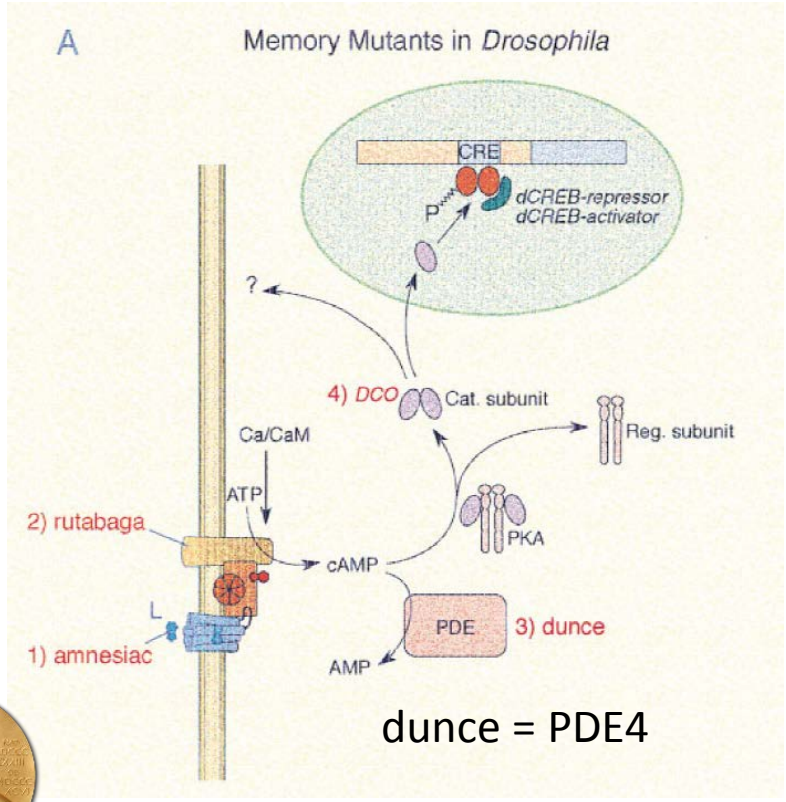
RESTORING CLARITY OF THOUGHT

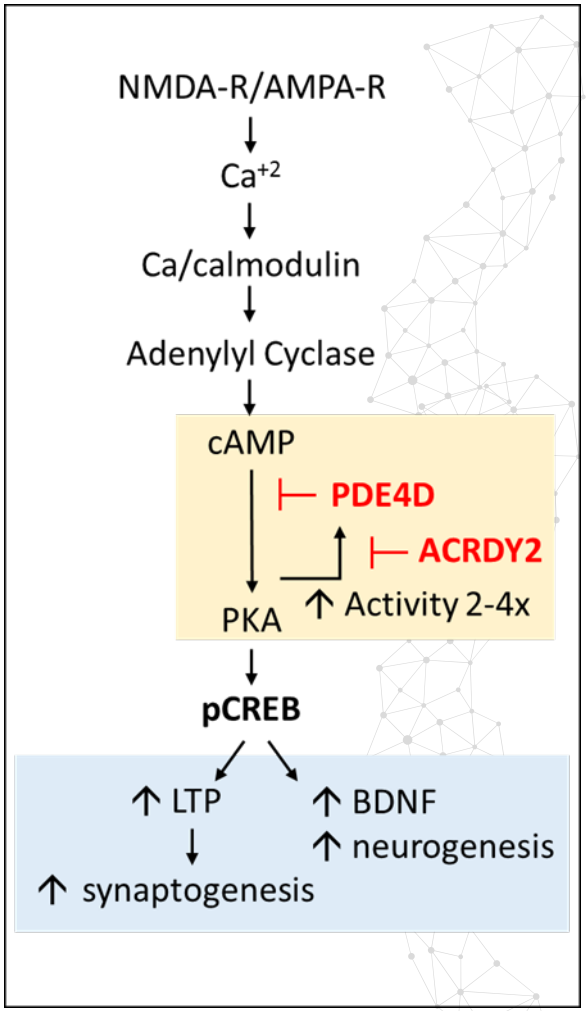
ROLE OF PDE4D IN MEMORY

Prof Seymour Benzer, Caltech



Prof Eric Kandel, Columbia



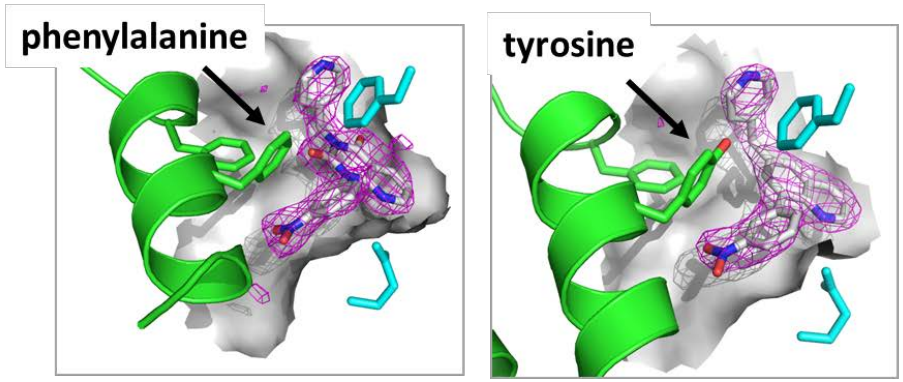


- The PDE4 *dunce* mutation in *Drosophila* impairs learning and memory
- **PDE4D** missense mutations in **humans** cause mental retardation associated with brachydactyly (acrodysostosis type 2; **ACRDY2**)

BPN14770 ALLOSTERIC INHIBITOR BINDING POSE HUMANIZED PDE4D MICE

The Phenylalanine UCR2 Selectivity Residue Is Present Only In Primate PDE4D

UCR2 Selectivity Residue



PDE4D phenylalanine

PDE4A,B & C tyrosine

Primate UCR2

PDE4A	GNQVSEYISNTFLD
PDE4B	GNQVSEYISNTFLD
PDE4C	GNQVSEYISNTFLD
PDE4D	GNQVSEFISNTFLD

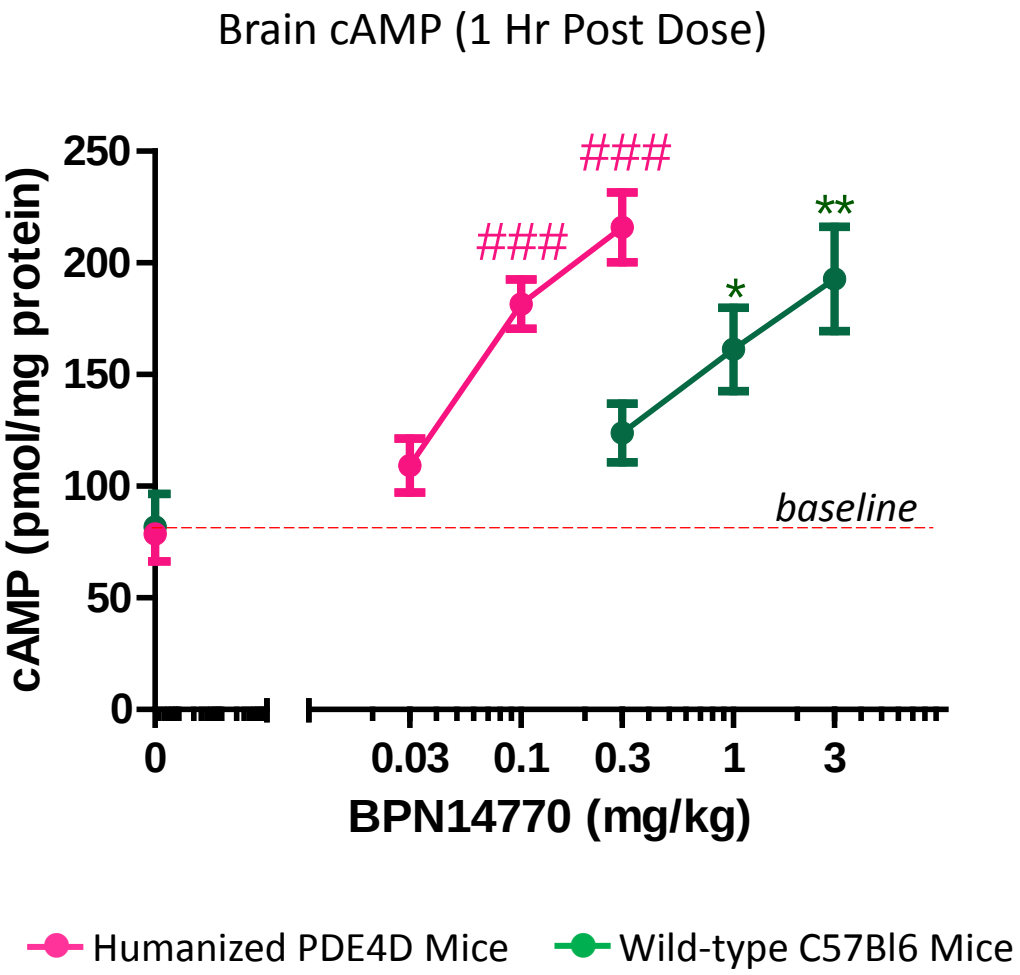
Non-primate UCR2

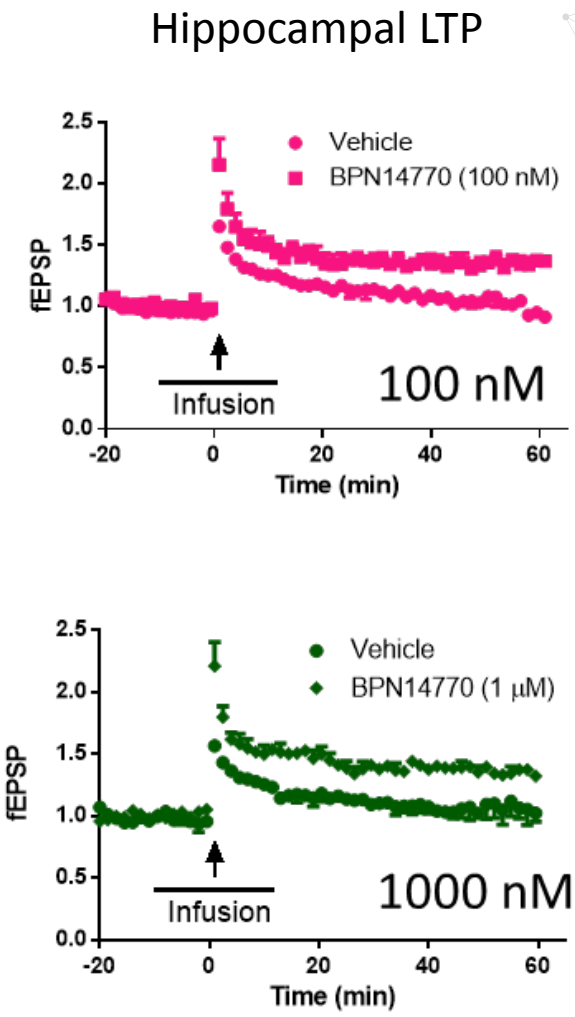
PDE4A	GNQVSEYISNTFLD
PDE4B	GNQVSEYISNTFLD
PDE4C	GNQVSEYISNTFLD
PDE4D	GNQVSEYISNTFLD

	Mouse PDE4D IC_{50} (nM)	Mouse PDE4D Y271F IC_{50} (nM)	Human PDE4D IC_{50} (nM)	Human PDE4B IC_{50} (nM)
BPN14770	133 ± 18	3 ± 0.3	7.7 ± 1.8	2,013 ± 256
rolipram	12 ± 1.5	36 ± 1.5	47 ± 6	171 ± 50

Humanizing mouse PDE4D by mutating UCR2 tyrosine271 → phenylalanine (Y271F) improves potency of BPN14770 to the level observed with the human enzyme

BPN14770 EFFECTS ON cAMP AND HIPPOCAMPAL LTP

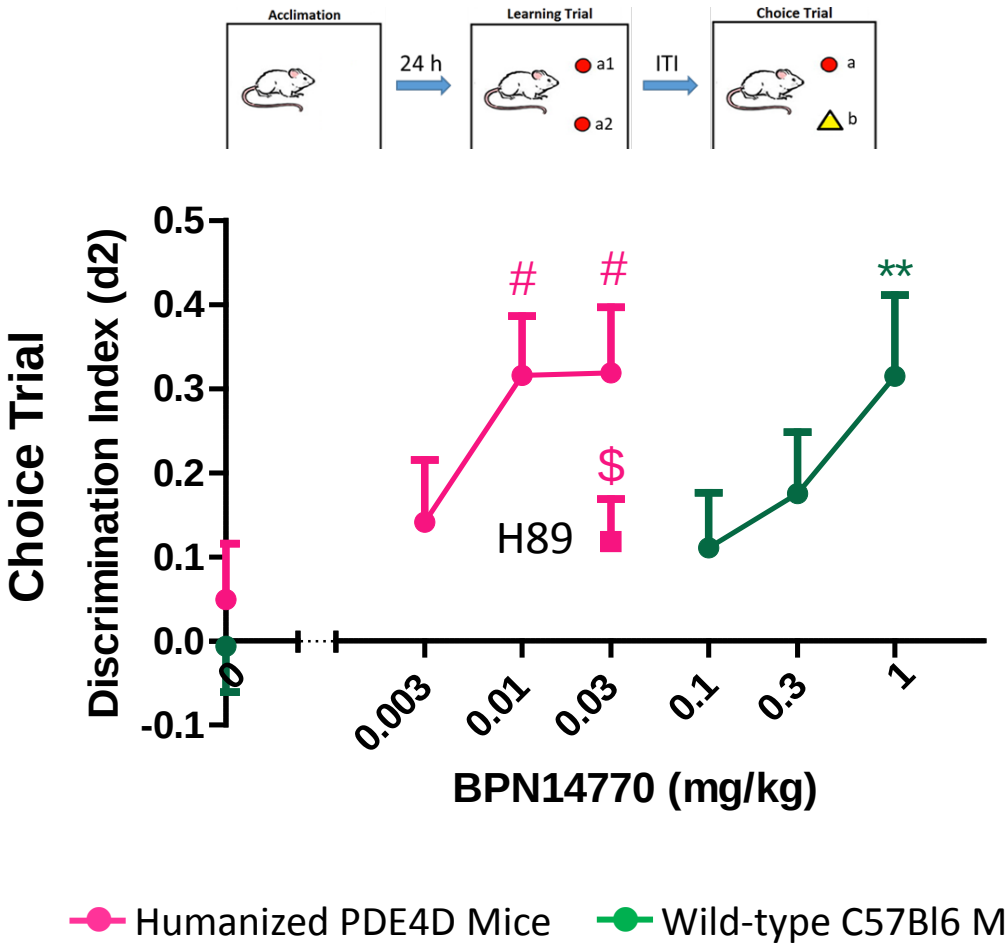




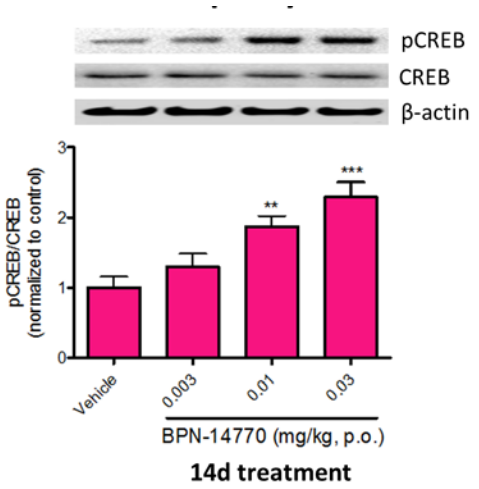
Prof James O'Donnell, Prof Ying Xu, Chong Zhang, University at Buffalo

BPN14770 IMPROVES LONG TERM MEMORY

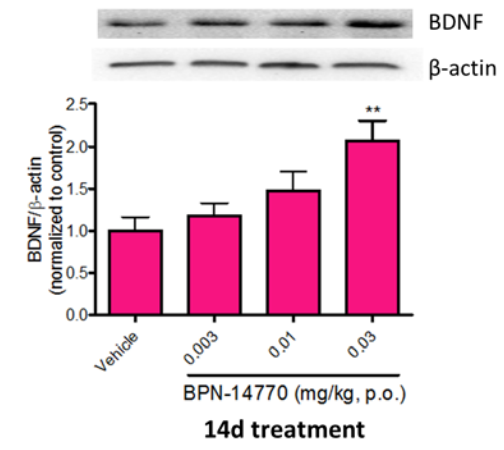
Novel Object Recognition (24 Hr Recall)



Hippocampal pCREB

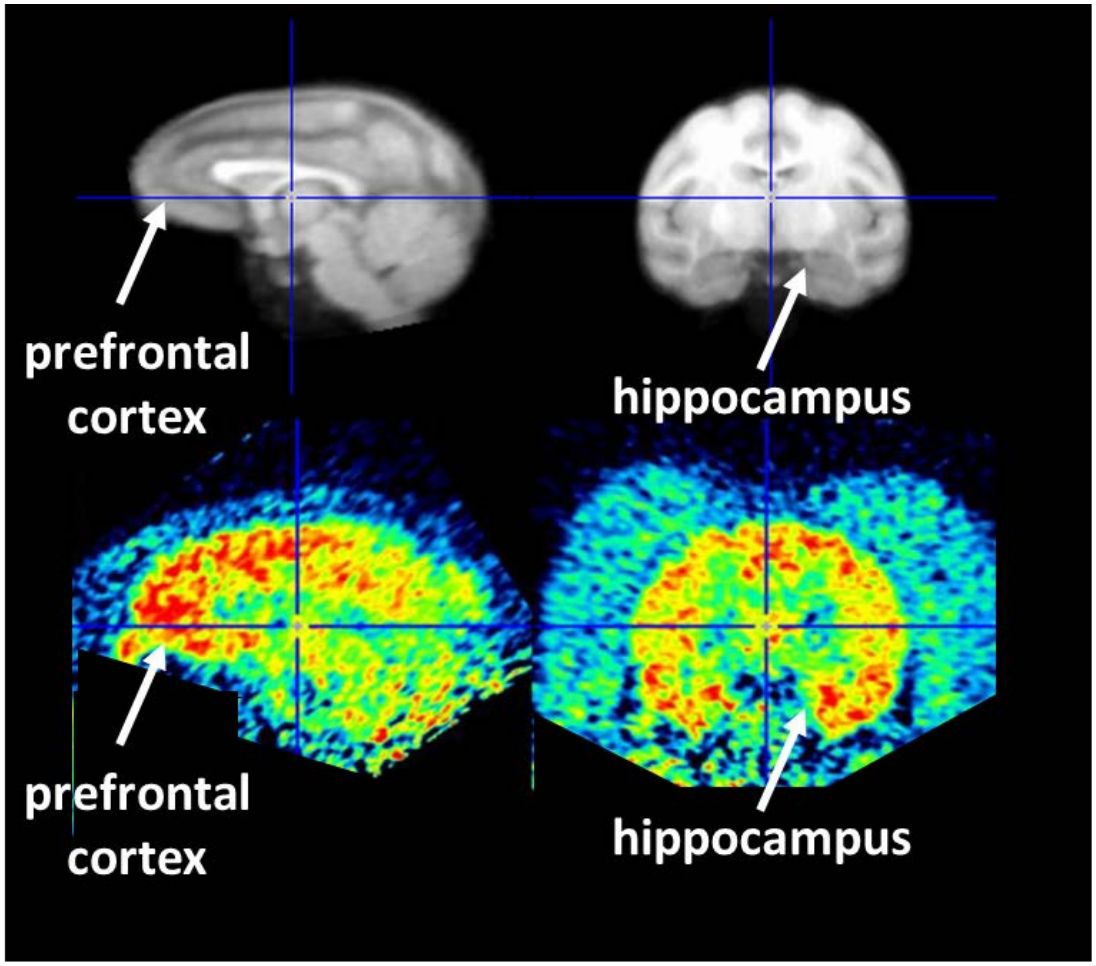


Hippocampal BDNF



Prof James O'Donnell, Prof Ying Xu, Chong Zhang, University at Buffalo

PDE4D TARGET IS PRESENT IN BRAIN REGIONS IMPORTANT FOR MEMORY



PET scan of rhesus monkey brain showing ^{11}C-T1650 tracer bound to PDE4D target

Hippocampus

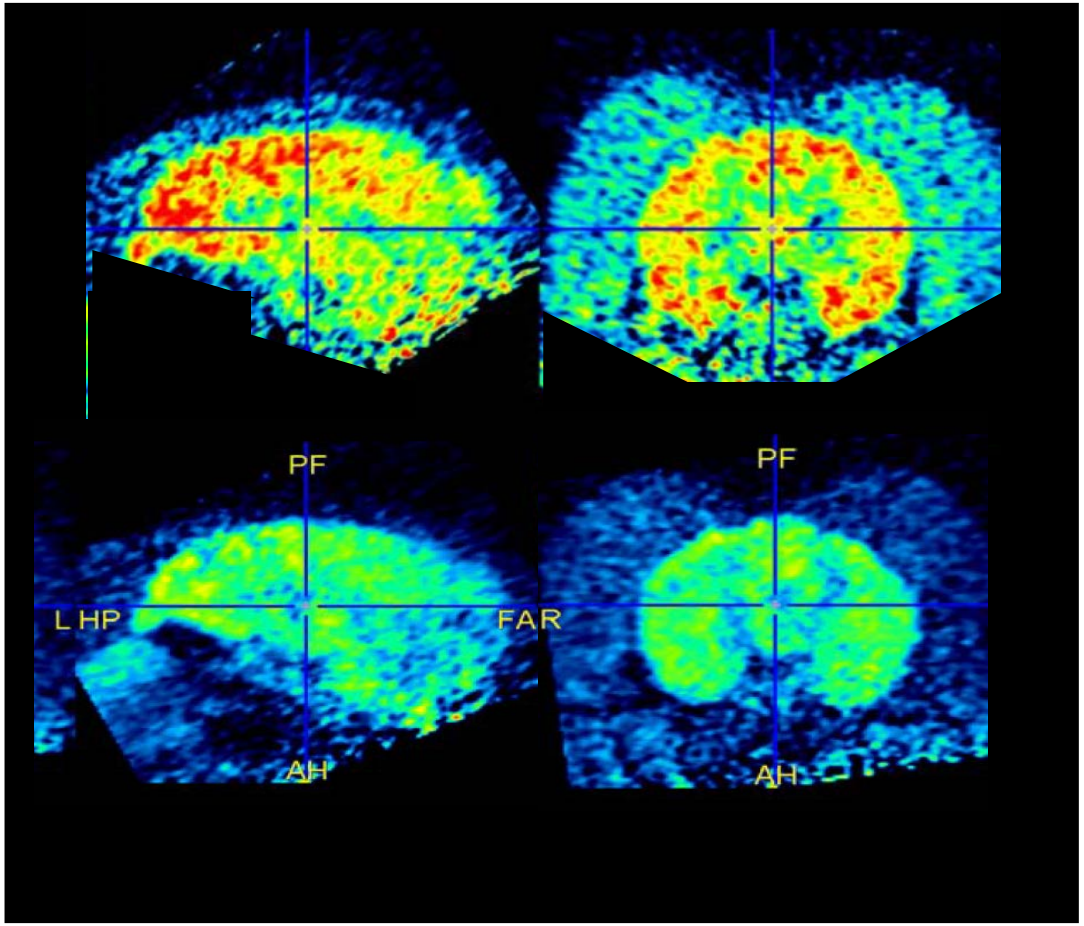
- Important for working memory
- Target of Alzheimer's disease pathology
- Volume correlates with BDNF levels

Prefrontal Cortex

- Important for planning & executive function
- Long term memory

Robert Innis, Victor Pike, Masahiro Fujita, Sanjay Telu, NIMH

PET TRACER DEMONSTRATES BPN14770 ENGAGES PDE4D TARGET IN BRAIN



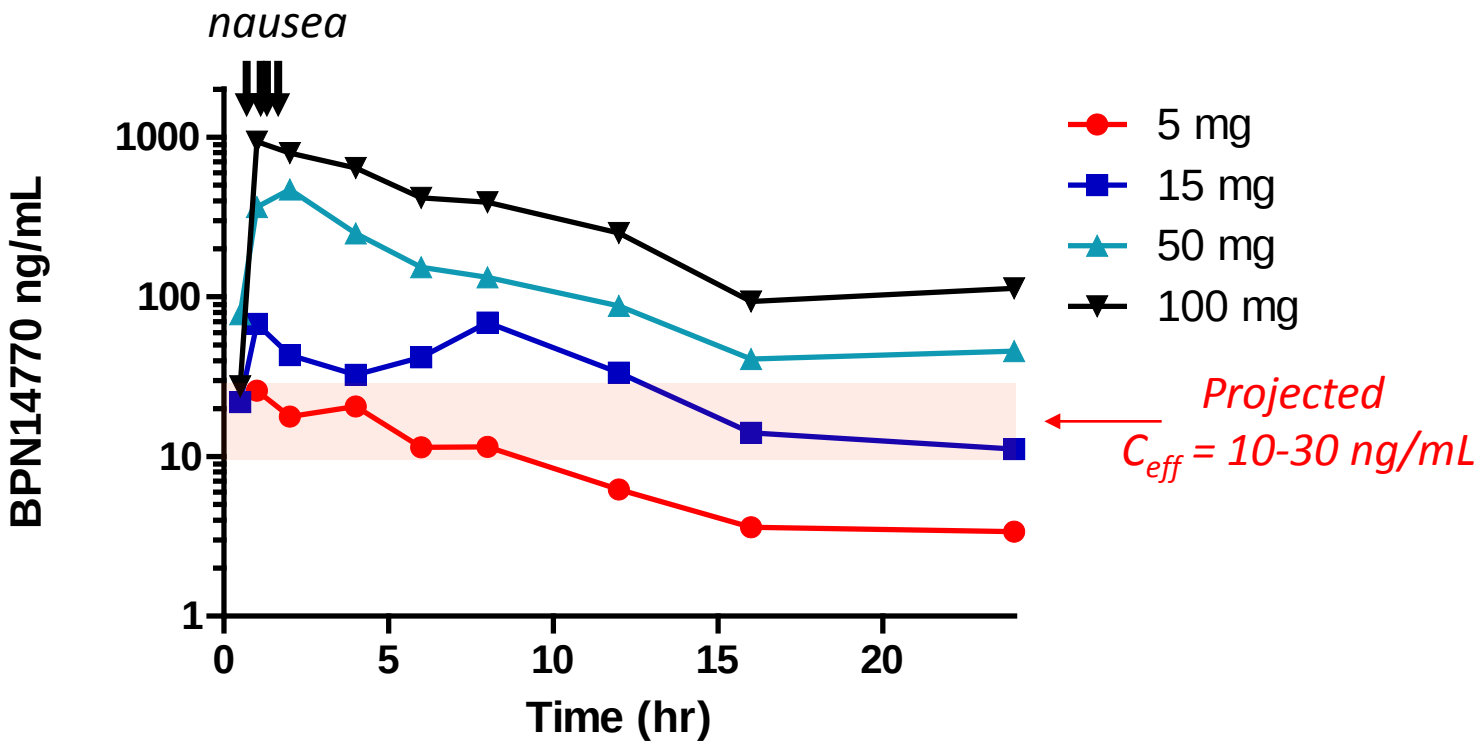
Strength of PET tracer binding is scaled from blue (lowest) to red (highest)

PET scan showing ^{11}C-T1650 tracer bound to PDE4D in rhesus monkey brain

PET scan showing displacement of ^{11}C-T1650 tracer by BPN14770

Robert Innis, Victor Pike, Masahiro Fujita, Sanjay Telu, NIMH

BPN14770 HUMAN PHASE 1 SINGLE DOSE PK



- BPN14770 was dosed as the crystalline material in an HPMC capsule
- The 5 and 15 mg doses achieved projected exposure for efficacy based on humanized PDE4D mice (C_{eff} = 10-30 ng/mL)
- Nausea at the 100 mg dose (arrows) was transient and associated with C_{max} (1,337 ng/mL)

BPN14770 DEMONSTRATED A FAVORABLE TOLERABILITY PROFILE

Elderly Subjects > 60 Years of Age

			BPN14770 Doses	
Organ System	**Adverse Events**	**Placebo**	**10mg BID**	**20mg BID**
		n=15	n=10	n=10
GI	**Overall # subjects in SOC with events**	**2 (13%)**	**2 20%**	**1 (10%)**
	Abdominal Discomfort		1 (10%)	
	Diarrhea	1 (7%)	1 (10%)	
	Flatulence	1 (7%)	1 (10%)	
	Nausea		1 (10%)	1 (10%)
	Vomiting		1 (10%)	
CNS	**Overall # subjects in SOC with events**	**2 (13%)**	**1 (10%)**	**2 (20%)**
	Headache	2 (13%)		1 (10%)
	Sinus headache			1 (10%)
	Bad Taste			
	Dizziness		1 (10%)	
	Paresthesia			1 (10%)

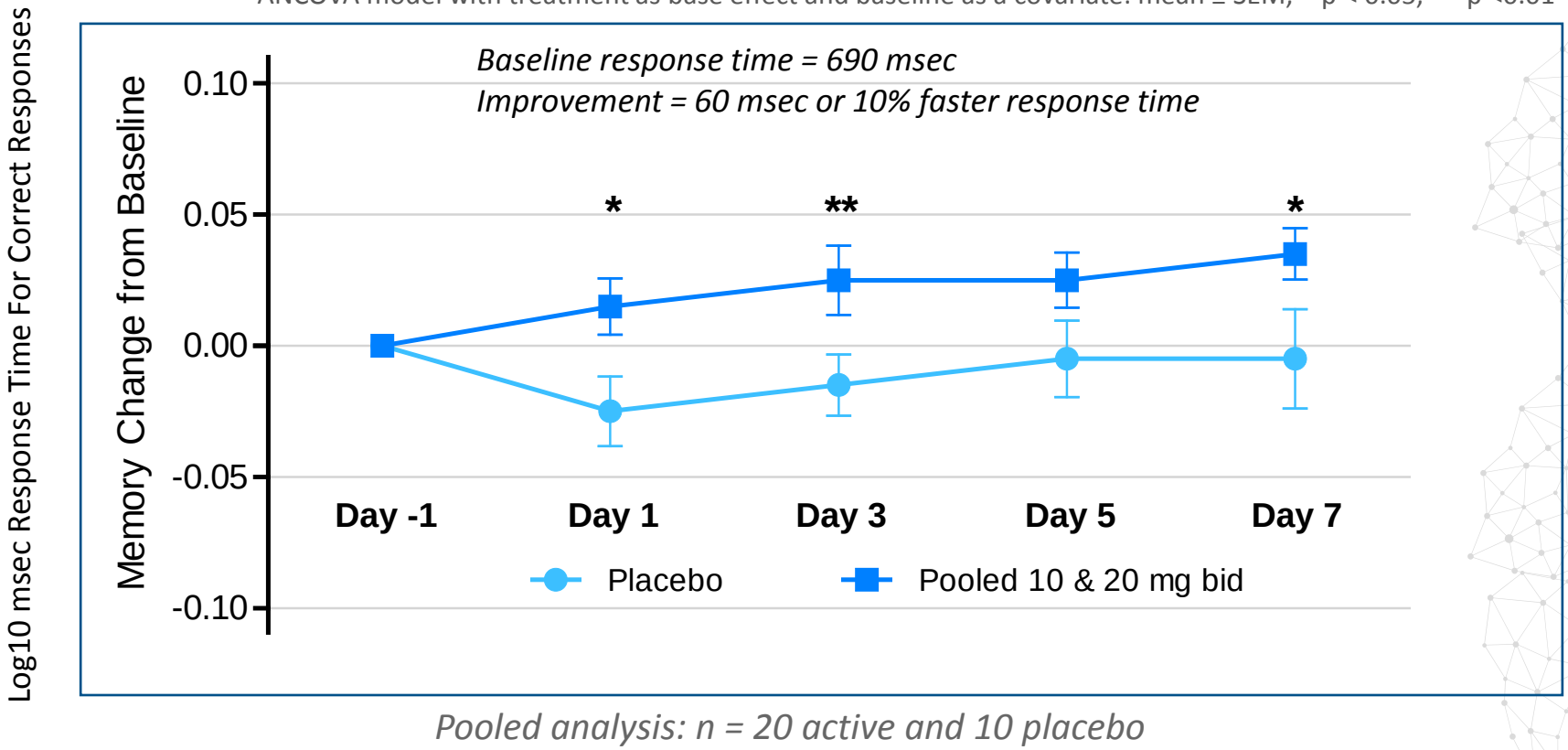
Does not cause diarrhea unlike marketed PDE4 inhibitors such as Otezla™

Nausea and vomiting occur with BPN14770 at single doses of 75 mg or 100 mg in young subjects, well above the projected cognitive dose

BPN14770 IMPROVED MEMORY IN ELDERLY ADULTS

BPN14770 Improved Memory In Elderly Adults After Single Or Multiple Doses

ANCOVA model with treatment as base effect and baseline as a covariate: mean ± SEM, * p < 0.05, ** p <0.01



Pooled analysis: n = 20 active and 10 placebo

BPN14770 Significantly Improved Working Memory (One Card Back Task)

BPN14770 IMPROVES FUNDAMENTAL MECHANISMS OF MEMORY

Supports Potential Utility in Early Alzheimer's Disease

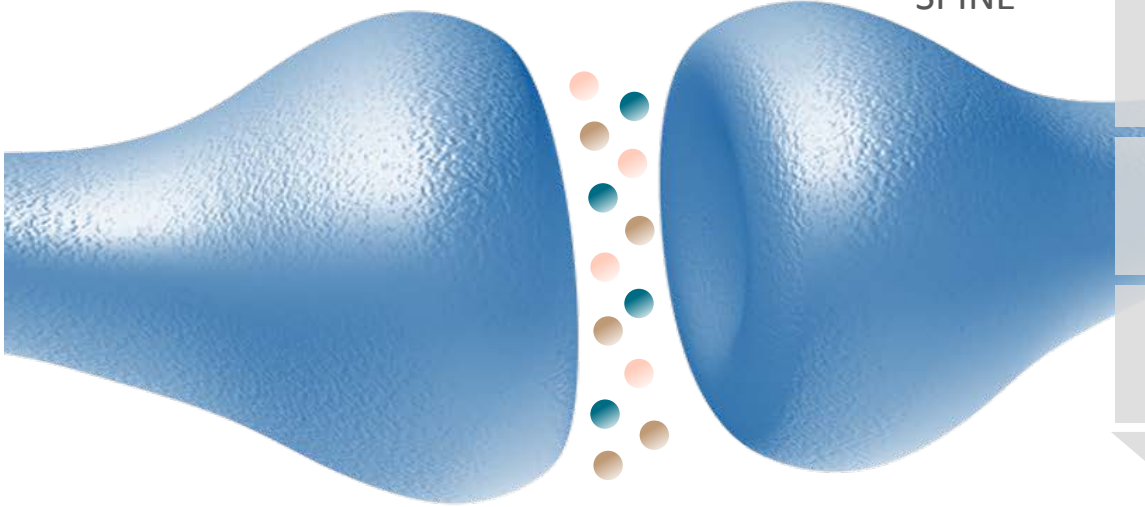
Donepezil increases acetylcholine

Cholinesterase

BPN14770 increases cAMP by inhibiting phosphodiesterase-4D (PDE4D)

AXON

DENDRITIC SPINE



cAMP

PKA

CREB

BPN14770 augments hippocampal long term potentiation (LTP)

BPN14770 stabilizes synapses

Acetylcholine

Other Neurotransmitters

Glutamate

BPN14770 increases brain derived neurotrophic factor (BDNF)

Reduced BDNF correlates with age-related memory decline, rapid progression of AD