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**Memtin™ – our patented hormone replacement  
therapy for slowing cognitive decline in  
Alzheimer’s disease and other dementias**  
**“Our flagship”**

**Nikolaos Tezapsidis, President & CEO**  
August 5, 2019

## the problem

## ALZHEIMER'S DISEASE

\$10 million  
Financing Sought

Starting at \$500,000

### Alzheimer's disease

- is the most common form of dementia of the elderly
- gets progressively worse and there is no remission
- is the 6th leading cause of death in the USA
- affecting more than 5 million Americans / 30 million worldwide
- is the only cause of death among the top 10 in America that cannot be prevented, cured or even slowed.

## 2019 ALZHEIMER'S DISEASE FACTS AND FIGURES

ALZHEIMER'S  
DISEASE IS THE

6<sup>TH</sup>

leading cause of death  
in the United States

5.8  
MILLION Americans  
are living  
with  
Alzheimer's

BY 2050, this  
number is  
projected to  
rise to nearly

14  
MILLION



82% of seniors say it's important  
to have their thinking or  
memory checked

BUT  
ONLY

16% say they receive  
regular cognitive  
assessments

MORE THAN  
16 MILLION  
AMERICANS

provide unpaid care  
for people with  
Alzheimer's or  
other dementias

These caregivers provided an estimated  
18.5 BILLION HOURS  
valued at nearly  
\$234 BILLION

IN 2019, Alzheimer's and other  
dementias will cost the nation  
\$290 BILLION

BY 2050, these costs  
could rise as high as  
\$1.1 TRILLION



EVERY 65  
SECONDS

someone in the  
United States  
develops the disease

Between 2000 and  
2017 deaths from heart  
disease have decreased

9% ↓



while deaths from  
Alzheimer's disease  
have increased

↑ 145%



1 IN 3  
seniors dies with  
Alzheimer's or  
another dementia

It kills more than  
breast cancer and  
prostate cancer  
COMBINED

alzheimer's association®

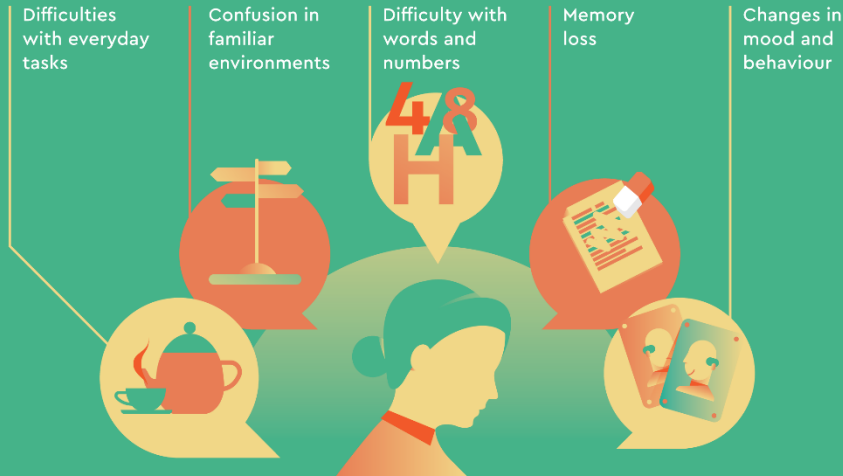


# DEMENTIA

## A public health priority



### What are the symptoms?



### Who is affected?



### What is the cause?

Conditions that affect the brain, such as Alzheimer's disease, stroke or head injury

### What does it cost?



## The Global Action Plan on the Public Health Response to Dementia 2017 - 2025

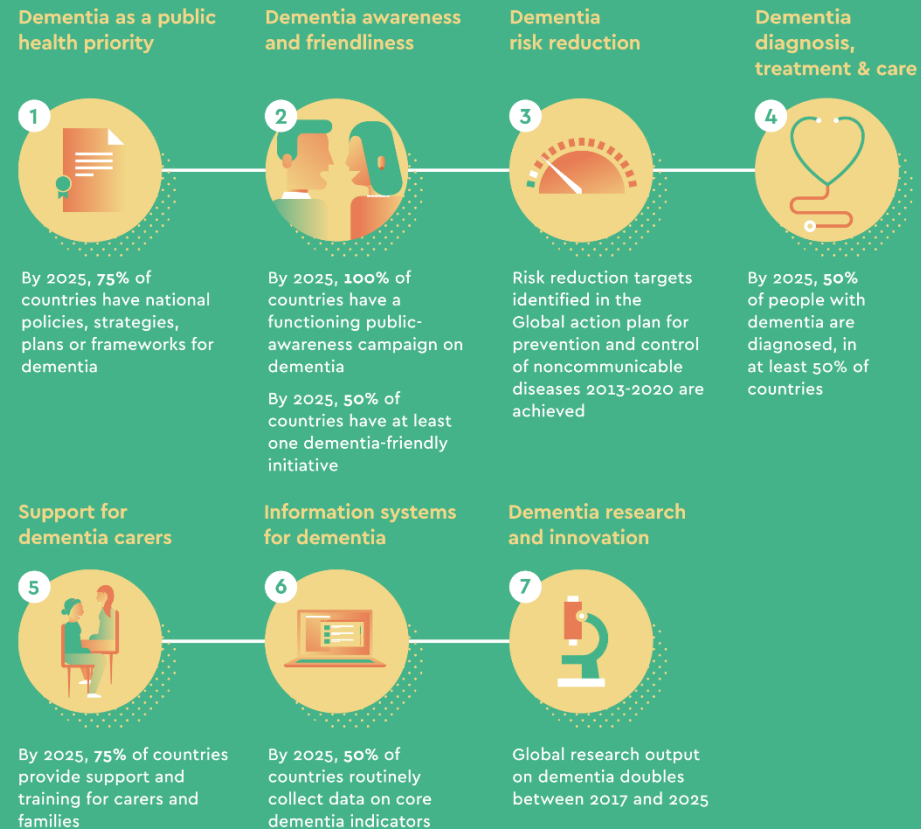
### Vision

A world in which dementia is prevented and people with dementia and their carers live well and receive the care and support they need to fulfil their potential with dignity, respect, autonomy and equality.

### Goal

To improve the lives of people with dementia, their carers and families, while decreasing the impact of dementia on them as well as on communities and countries.

### The seven action areas and targets



**Alzheimer's disease accounts for 60 percent to 80 percent of dementia cases.**

## The Alzheimer's Disease challenge requires a combination of Diagnostics and Therapeutics

	Pre-clinical stage	Mild Cognitive Impairment due to Alzheimer's	Dementia due to Alzheimer's
Diagnostics	<p>No clinical symptoms</p> <p>Can begin 20 years in advance of clinical symptoms</p> <p>Emerging imaging and molecular diagnostics</p>	<p>Cognitive decline greater than expected.</p> <p>Affects 15 percent to 20 percent; age 65 or</p> <p>Emerging imaging and molecular diagnostics</p>	<p>Significant impairment of a daily function.</p> <p>30% of MCI Pts progress to dementia w/in 5 yrs.</p> <p>Emerging imaging and molecular diagnostics</p>
Therapeutics	<p>Very few drugs in the pipeline.</p> <p>Need for screening diagnostics.</p> <p>Requires long-term trials</p>	<p>Current approved drugs only treat and slow symptoms.</p> <p>No approved treatments to stop or reverse progression.</p> <p>Current aim of next gen therapies</p>	

# A VERY PROMISING SOLUTION

## MEMTIN™ (Leptin) for Cognitive Decline

- ❑ Ten years of *in vitro* and *in vivo* pre-clinical studies (Neurotez)
- ❑ Retrospective (including one by Neurotez) and prospective human studies and a few anecdotal interventional human studies

### Support a role of Leptin in

- ❑ Neuroprotection, Cognitive enhancement, Decreasing levels of phospho-tau/tau, Decreasing beta amyloid (A $\beta$ )
- ❑ **and** is associated with lower risk for dementia in elderly

### Leptin as Replacement Therapy

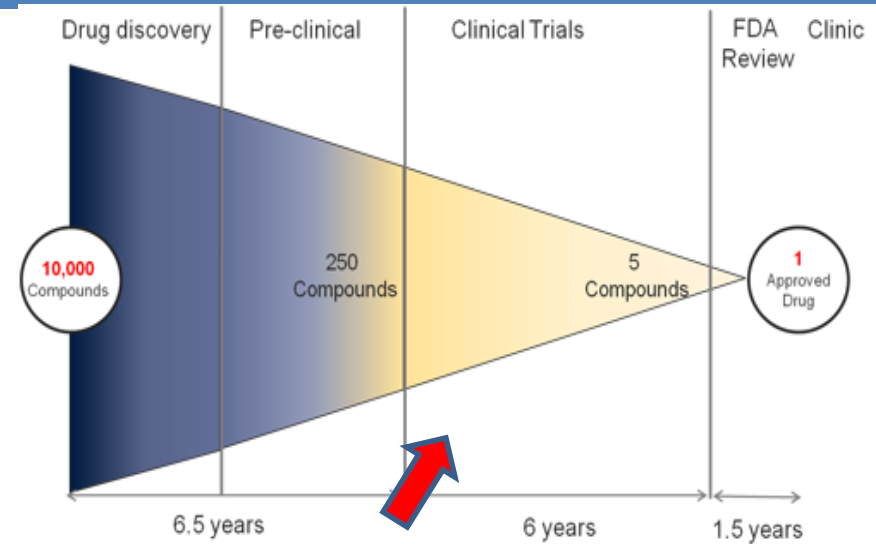
A relatively de-risked multi-functional preventative and therapeutic approach for cognitive decline due to Alzheimer's and optimally for early stage (prodromal AD) hypoleptinimics.

# Linking Leptin to Alzheimer's Disease



Leptin regulates feeding behavior, metabolic activity and cognition

# DRUGS SUCCESFULLY REPOSITIONED



## DRUG

Amphotericin B  
**Aspirin**  
Bromocriptine  
Finasteride  
Gemcitabine  
Methotrexate  
**Minoxidil**  
Raloxifene  
**Thalidomide**  
**Sildenafil**

## ORIGINAL INDICATION

Fungal infections  
Inflammation, pain  
Parkinson's disease  
Prostate hyperplasia  
Viral infections  
Cancer  
Hypertension  
Cancer  
Morning Sickness  
Angina

## NEW INDICATION

Leishmaniasis  
Antiplatelet  
Diabetes mellitus  
Hair loss  
Cancer  
Psoriasis, rheumatoid arthritis  
Hair loss  
Osteoporosis  
Leprosy, multiple myeloma  
Erectile dysfunction



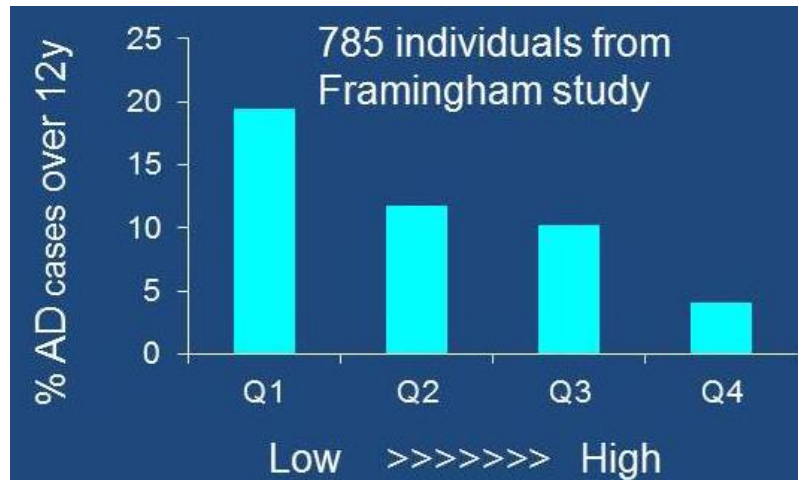
# REPOSITIONING LEPTIN CLEAR PATH

Route and frequency of administration	Subcutaneous, once a day
Recommended starting dose for generalized lipodystrophy	0.06 mg/kg/day (if body weight $\leq 40$ kg)
	2.5 mg/day (males $>40$ kg)
	5 mg/day (females $>40$ kg)
Maximum dose	0.13 mg/kg (if body weight $\leq 40$ kg)
	10 mg/day (if body weight $>40$ kg)
C <sub>max</sub>	4.0–4.3 hours
T <sub>max</sub>	4 hours (range 2–8 hours)
Half-life	3.8–4.7 hours
Most common adverse reactions ( $\geq 10\%$ )	Headache, hypoglycemia, decreased weight, and abdominal pain
Use in geriatric patients $>65$ years-old	Unclear; dose selection should be cautious, and start at the low end of the dosing range
Drug interactions	Potential to alter the formation of CYP450 enzymes

# STUDIES: SERUM LEPTIN LEVELS IN ELDERLY AND PROGNOSIS

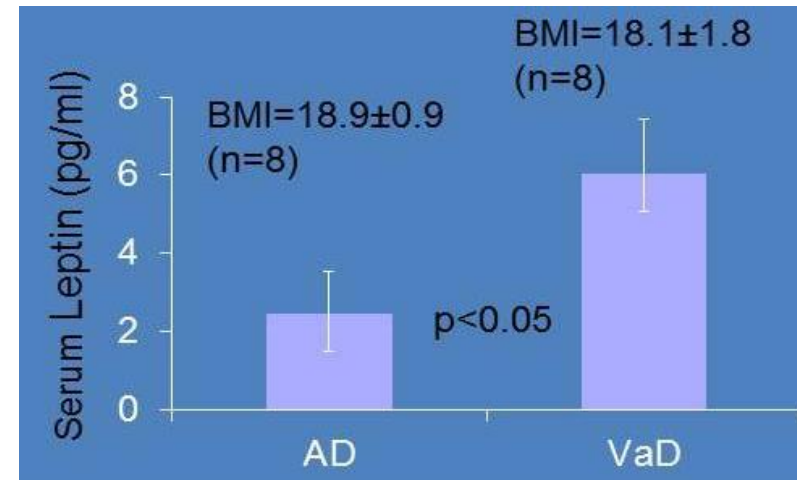
**In elderly, higher serum Leptin is associated with a lower risk for Alzheimer's disease and dementia**

*Lieb et al, JAMA, 2009*



**For BMI<25, patients with AD have lower serum Leptin levels compared to patients with Vascular Dementia (VaD)**

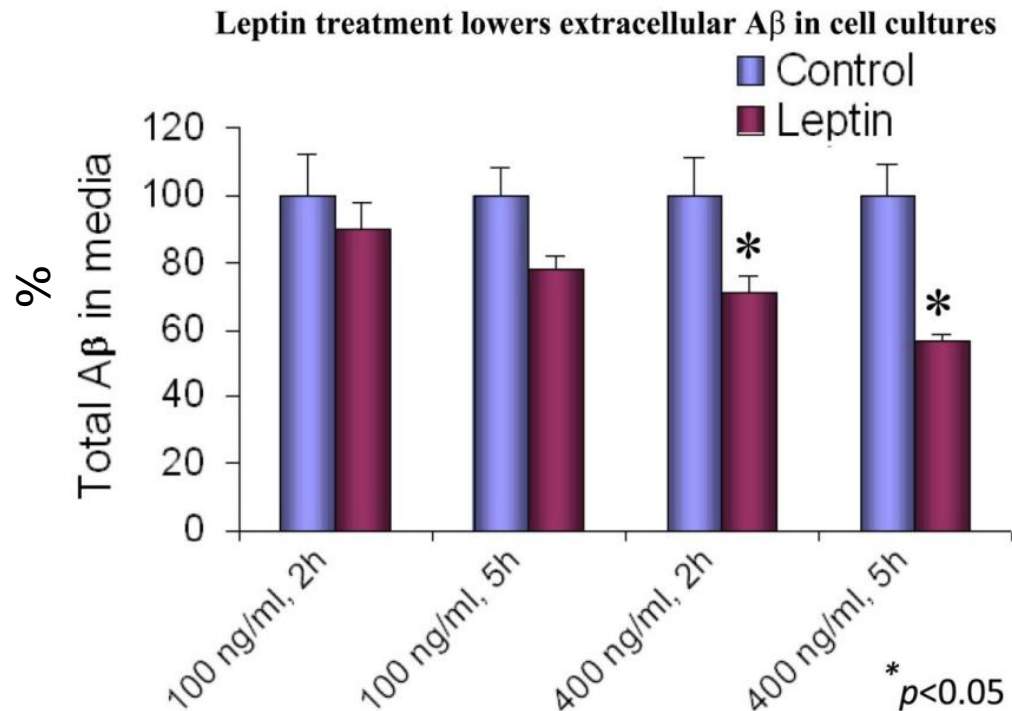
*Power et al, Dementia, 2001*



# STUDIES: LEPTIN TARGETS AMYLOID BETA AND TAU PROTEIN

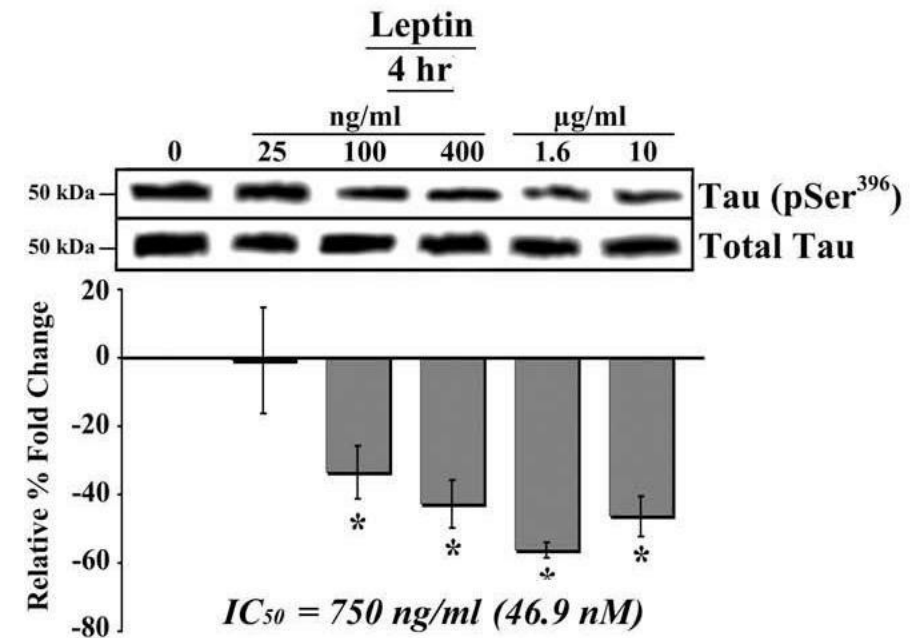
## Amyloid Plaques

- Inhibition of amyloid beta (A $\beta$ )
- Up-regulation of A $\beta$  uptake
- Reduction of brain levels of A $\beta$
- Reduction of plaque density



## Neurofibrillary Tangles

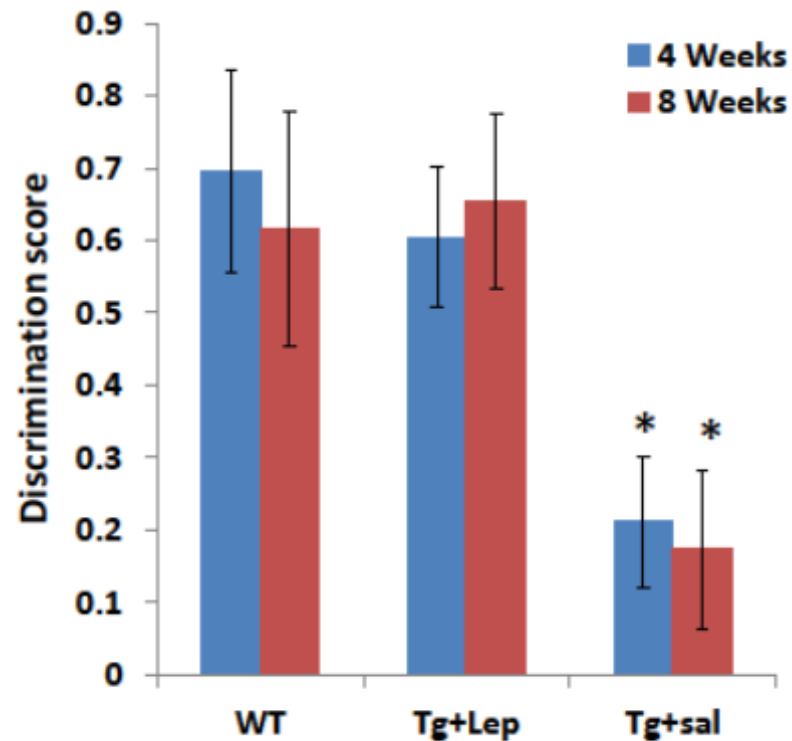
- Reduction of phosphorylation of tau protein in vitro and in vivo
- Phosphorylation of tau protein precedes the formation of neurofibrillary tangles



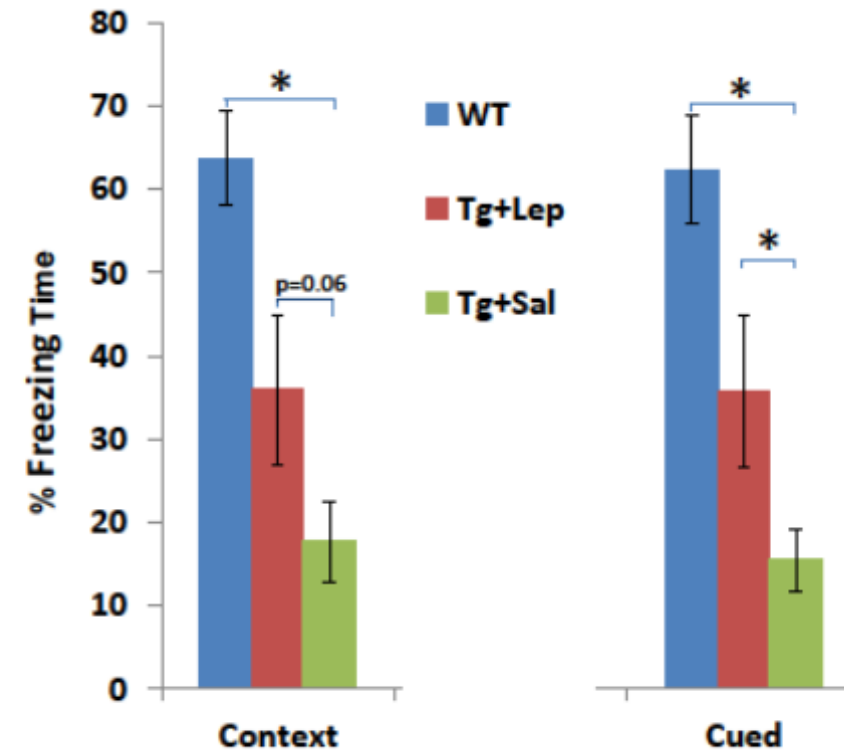
# STUDIES: LEPTIN IMPROVES MEMORY IN AD ANIMAL MODELS

Animal studies: Behavioral (CRND8)

Novel Object Recognition, 4 & 8 wks



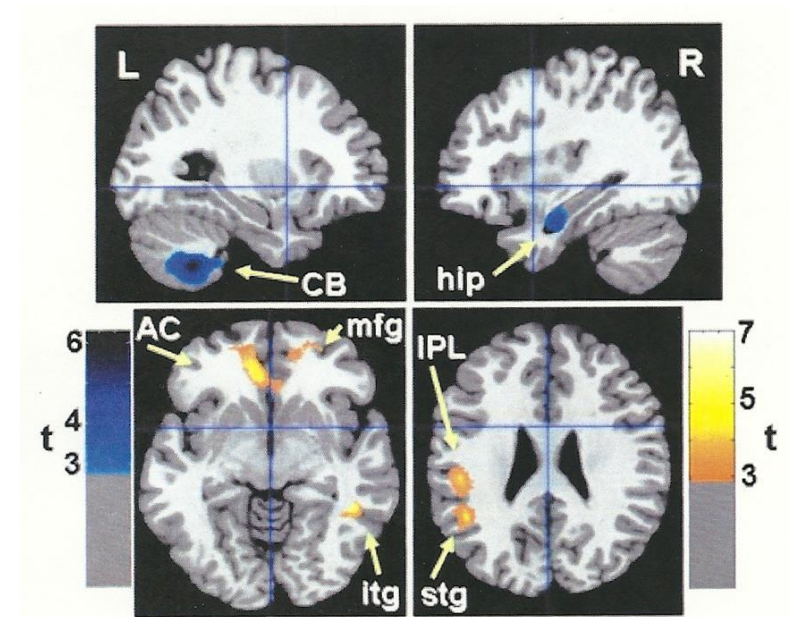
Fear Conditioning, 8 wks



# STUDIES: DIRECT EVIDENCE FOR A CAUSATION

## Cognitive benefits in humans: treating leptin deficiency in adults and young”

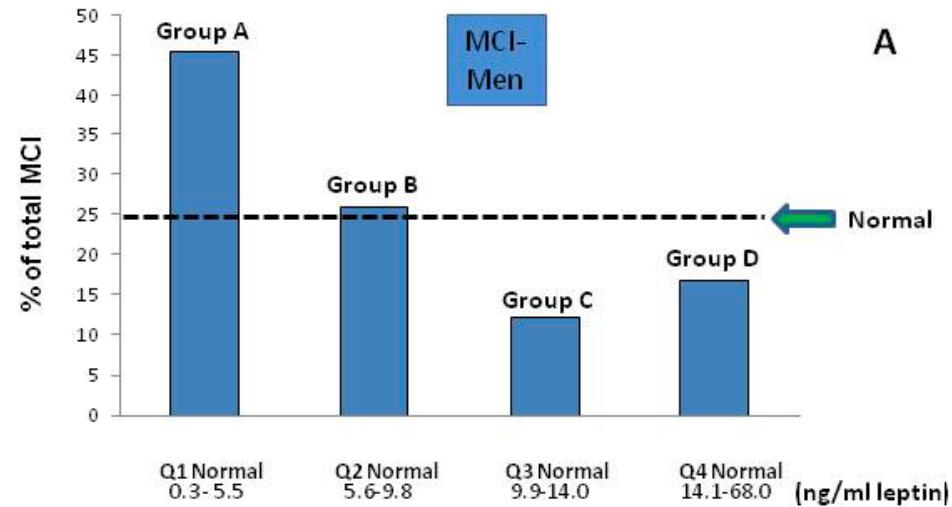
- Behavioral changes after 2 wks Licinio et al (2004)
- Leptin Replacement increases Gray matter concentration in Leptin (-) adults Matochik et al (2005)
- Plasticity of Gray Matter changes following Leptin discontinuation / reinitiation in Leptin (-) adults London et al (2011)
- Leptin Replacement improves Cognitive Development in Leptin (-) young Paz-Filho et al (2008)



**(Licinio's interventional clinical studies)**

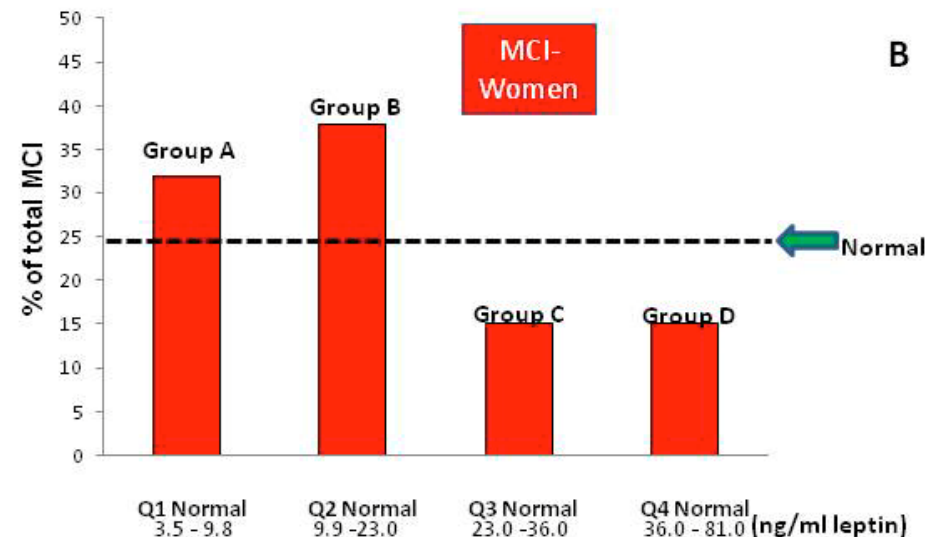


# STUDIES: SERUM LEPTIN LEVELS IN MCI

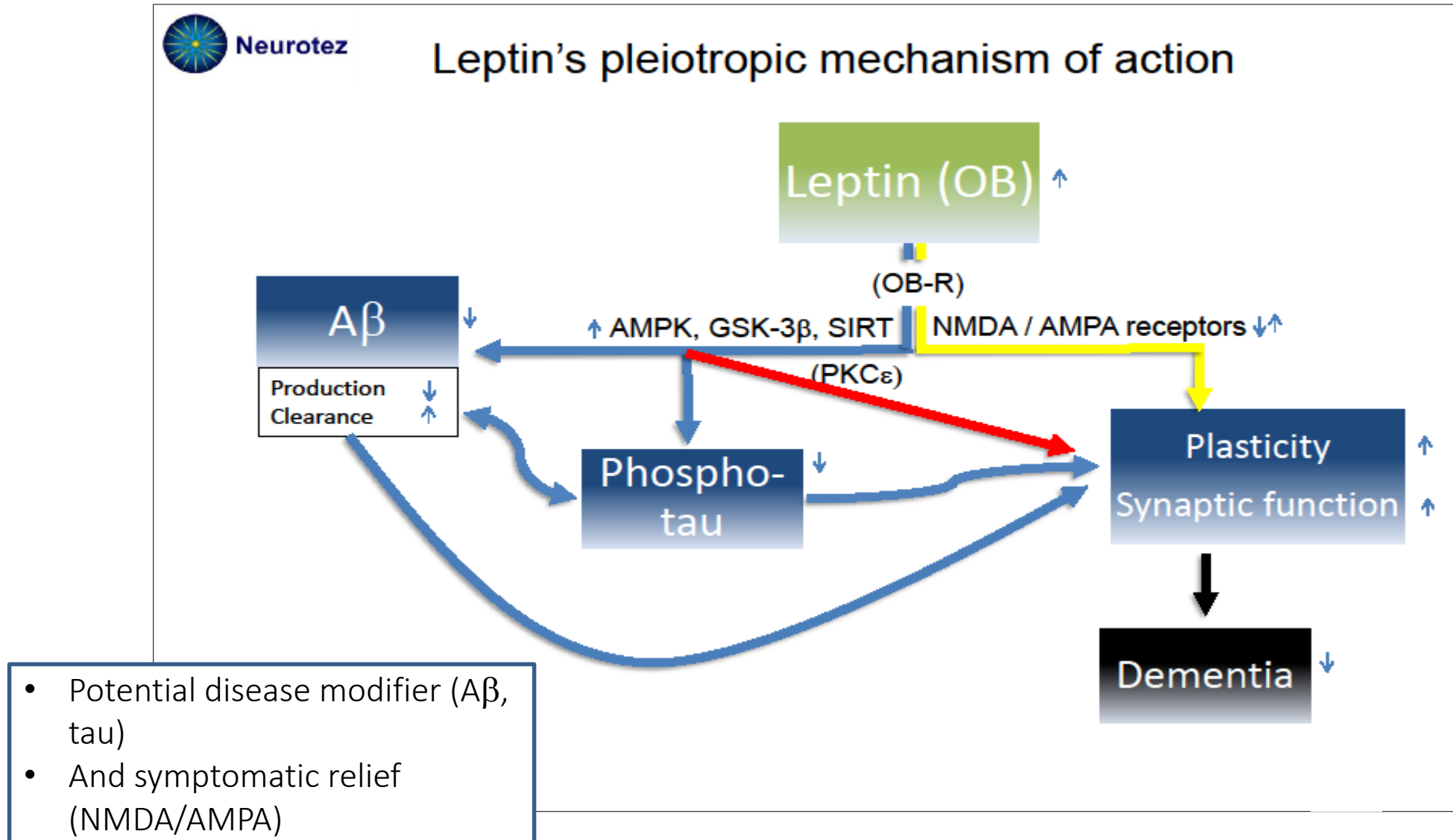


**Approximately 70% of MCI Subjects Have Plasma Leptin Values Lower than the Median Leptin Value of Normal Elderly.**

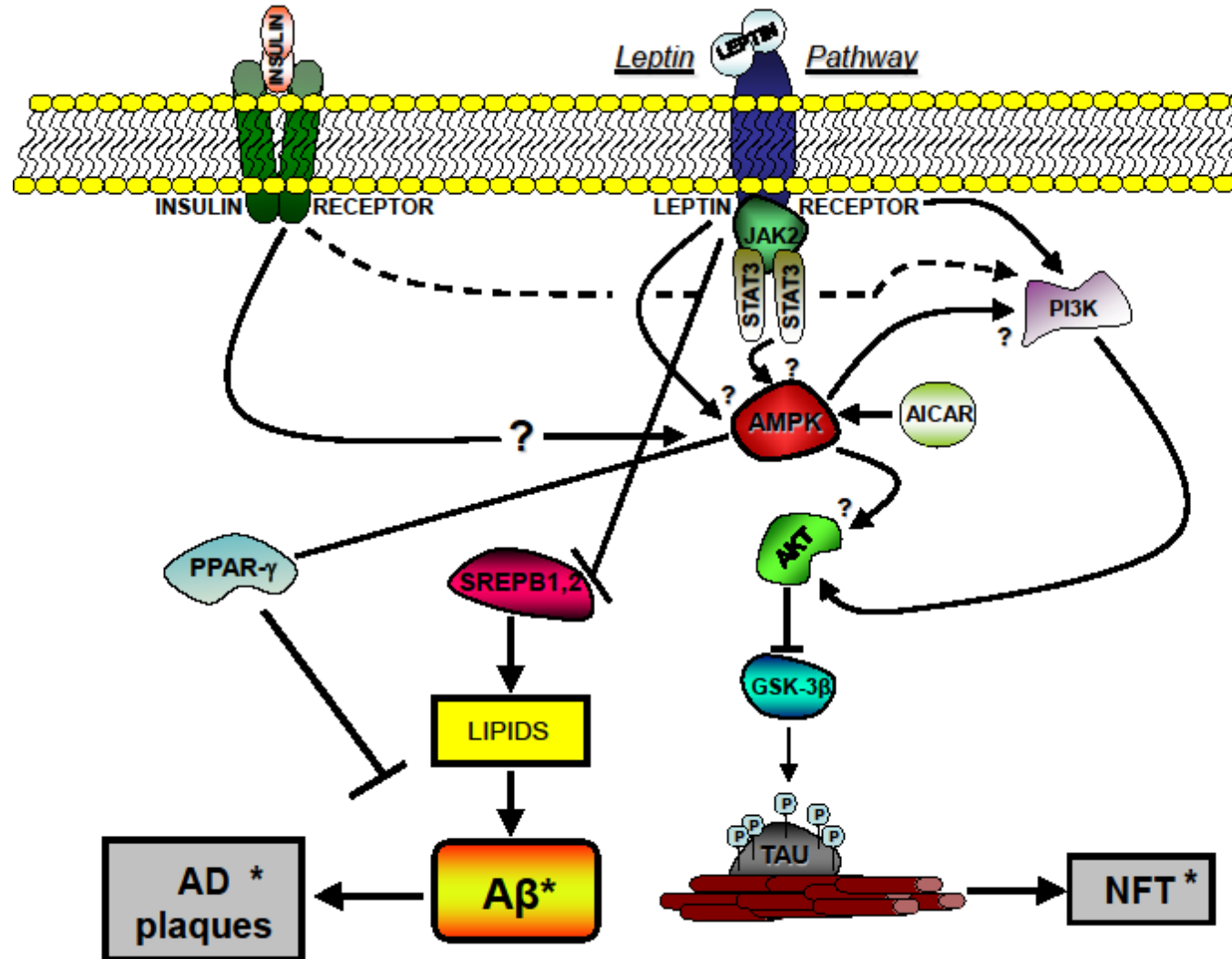
*(Neurotez)*



# MECHANISM OF ACTION



# Leptin shares pathways with insulin in neurons



# NOVEL, DIFFERENTIATING

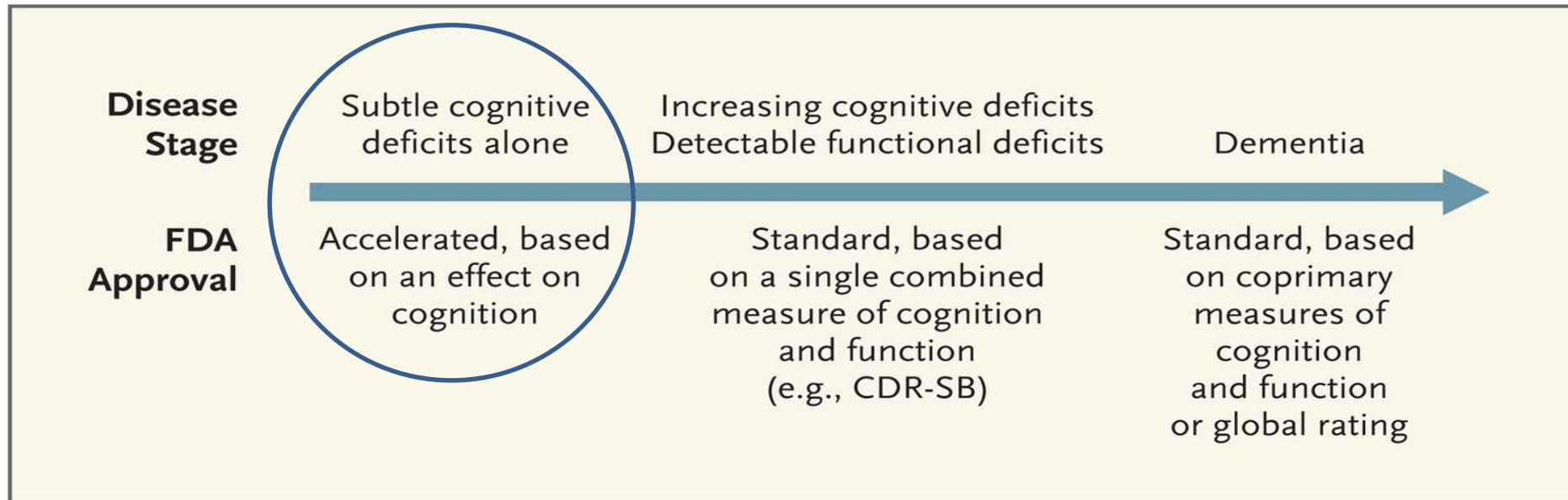
## **MEMTIN™ –**

- Alzheimer's disease as diabetes of the brain or Type III diabetes
- A natural protein with procognitive properties at Low levels in Alzheimer's (AD) with known Safety Profile (Effectively Phase II ready)
- Ameliorates both Abeta and tau pathologies, upstream molecular target related to metabolism
- Clinical Strategy involving enrichment of patients, targeting patient group most likely to respond

## **PREVIOUS FAILURES-**

- Antibodies directed against Abeta or tau are difficult to penetrate into the brain and are toxic at the high doses needed for efficacy
- Heterogeneity in patient groups and targeting late stage AD patients
- Wrong targets (Abeta and/or tau may be biomarkers, not culprits)

# POTENTIAL REGULATORY PATHWAYS



Kozauer N, Katz R. N Engl J Med 2013;368:1169-1171.

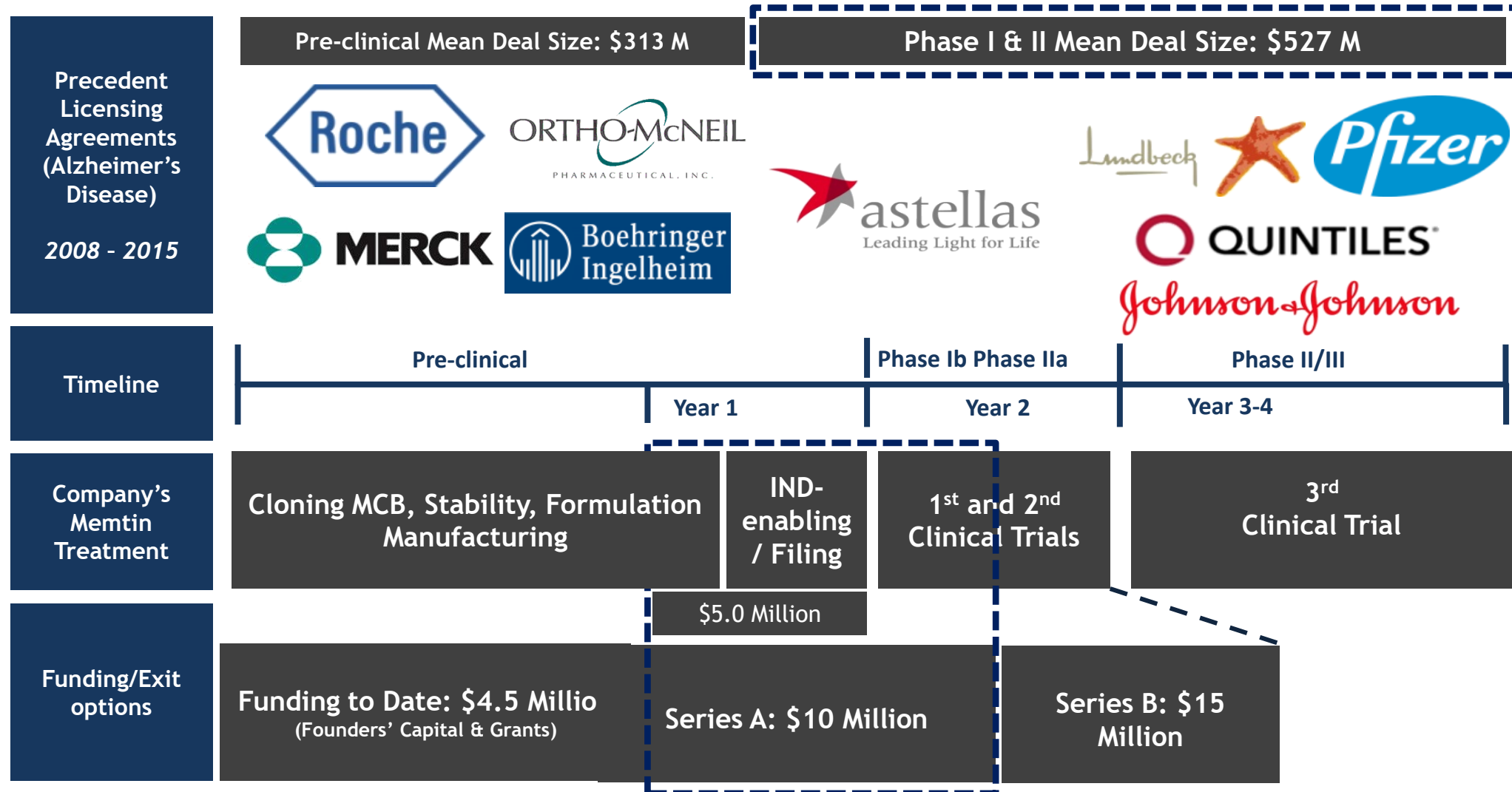


The NEW ENGLAND  
JOURNAL of MEDICINE

- Surrogate biomarkers, accelerated approval (FDA preliminary interactions about our approach)
- 12y Market Exclusivity from BLA approval



# DRUG DEVELOPMENT PATH FOR MEMTIN: KEY MILESTONES



# CLINICAL TRIALS:

## PHASE 1 & 2

### PHASE 1B

#### Participants

Enriched MCI/Early AD (MMSE>23)  
with high probability to convert to AD

#### Outcome Measures

- Leptin in CSF/plasma
- Markers in CSF/plasma: A $\beta$ 40/42, tau/p-tau
- FDG-PET and Amyvid-PET
- Metabolic markers
- Safety & tolerance
- Open-label 1-yr extension: preliminary efficacy data

### PHASE 2

**Biomarkers of exposure and cognitive enhancement (26-52 wks)**

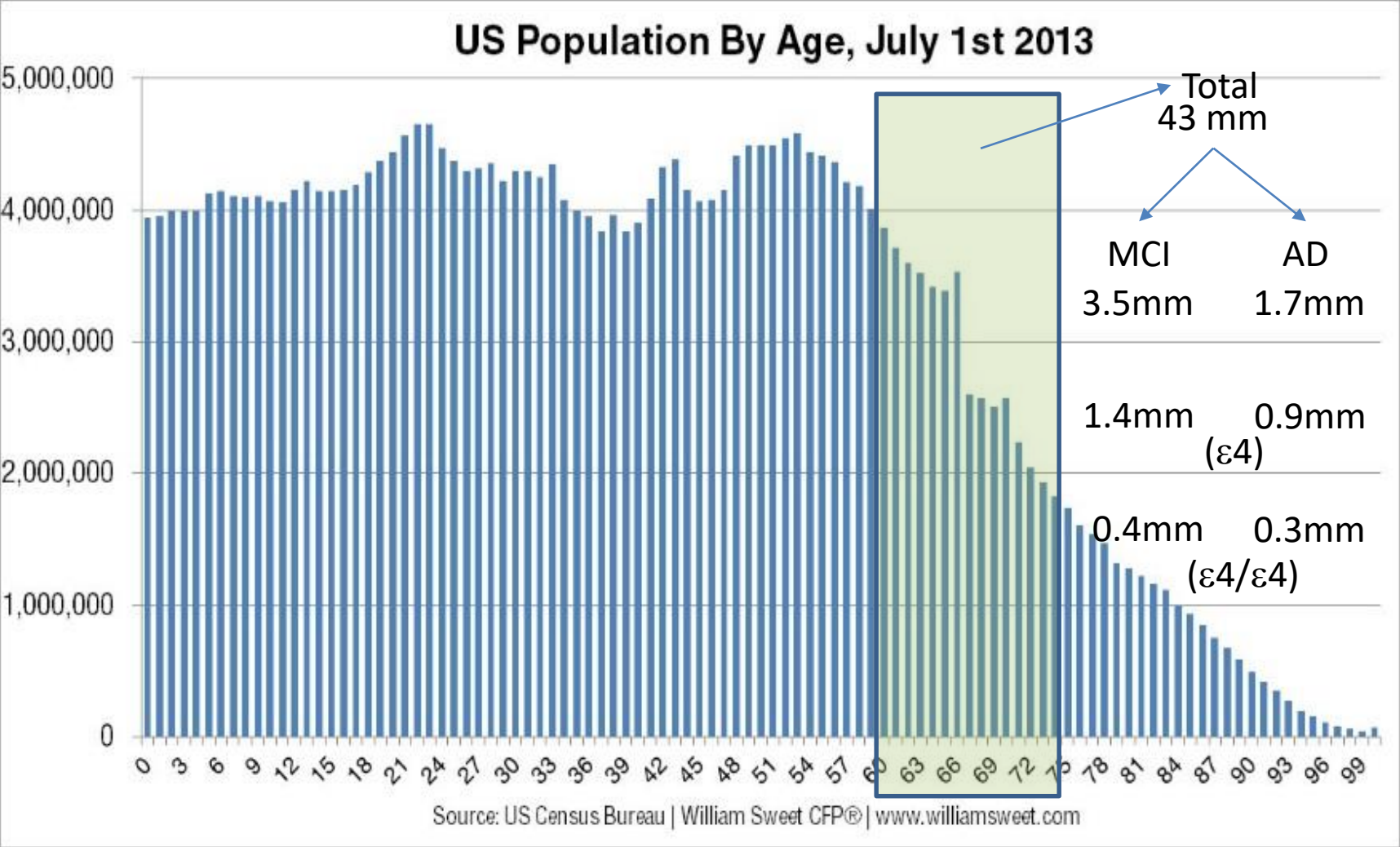
#### Participants

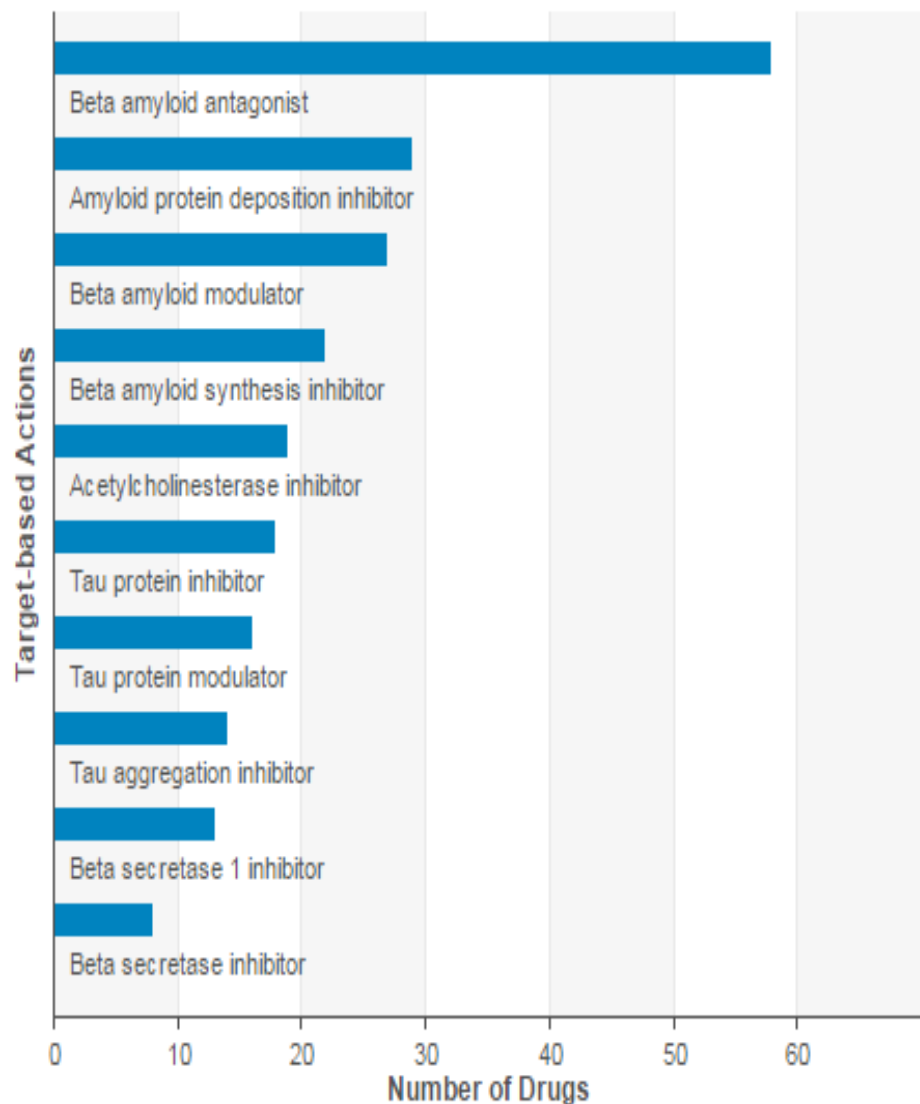
aMCIs or mild AD (MMSE>15)

#### Outcome Measures

- Surrogate markers in CSF/plasma: A $\beta$ 40/42, tau/p-tau
  - MRI
  - Metabolic markers
  - Cognition & function
- Potentially accelerated approval mechanism under 21 CFR 601.41 for biologics**

# DEFINING A SUBSET OF MCI/AD FOR LEPTIN TREATMENT





Source: Clarivate Analytics Cortellis

## A $\beta$ on the fast-track

- **Lanabecestat** (AstraZeneca/Lilly): BACE1 inhibitor; Phase III
- **AMG-520** (Amgen/Novartis): BACE1 inhibitor; Phase II
- **Aducanumab** (Biogen): anti-A $\beta$ ; Phase III
- **Elenbecestat** (Eisai/Biogen): BACE1 inhib; Phase III
- **ELND-005** (Transition): A $\beta$  aggregation inhib; Phase II/III

## A $\beta$ Disappointments

- **Verubecestat** (Merck): Phase II/III terminated in Feb 2017
- **Solanizumab** (Lilly): Failed Phase III in mild AD in 2016.
- **Bapinezumab** (Pfizer): Discontinued in Phase III
- **LY-2599666** (Lilly): Discontinued in Phase I
- **AN-1792** (Elan/Wyeth): Discontinued in 2002.
- **Affitope** (Affiris/GSK): A $\beta$ vaccine ; Phase I terminated in 2013.

**Major pharma: notable deals since 2005 have focused on A $\beta$  and Tau**

**Source: Clarivate Analytics Cortellis**

	Total Size (\$M)	Buyer	Seller	Year	Drug	Stage @ Sign/Today
A-BETA	\$530/\$130 upfront	Lilly	AZ via Astex	2014	Lanabecestat	PI/PIII
	\$340/\$25 upfront	Genentech	AC Immune	2006	Crenezumab	Discovery/PIII
	Not-specified	JnJ	Shionogi	2012	BACE inhibitor	Discovery/PIII
	\$825	Otsuka	Lundbeck	2013	Lu-AF20513 vaccine plus others	Clinical
	Not-specified	JnJ	Cellzome	2008	Gamma-secretase mods.	Discovery
TAU	\$638	Roche	reMYND	2010	ReS3-T and others	Discovery
	Not-specified	Mitsubishi	Sanofi	2005	SAR-502250	Discovery
	\$509/\$26 upfront	JnJ	AC Immune	2014	ACI-35; Tau vaccine	Phase I
	Not specified	Abbvie	C2N	2015	Anti-Tau mAb	Discovery/PII
OTHER	\$31	JnJ	Orion	2013	A2C-adrenoreceptor	Phase II
	\$289	Merck	Alectos	2010	MK-8719; N-acetyl glucose amidase mod.	Discovery/ PI Orphan



# EXPERIENCED MANAGEMENT TEAM

- **Nikolaos Tezapsidis, PhD**, *Chairman, Chief Executive Officer & President* 18+ years experience in biomedical research; Two awards from the Alzheimer's Association Fellow of the Science and Engineering Council and the Wellcome Trust
- **Hamish McArthur, PhD**, *Manufacturing Chief Officer*, Executive with 33 years biologics experience within Pfizer, directly involved in numerous approved products .
- **J. Wesson Ashford, MD, PhD**, *Chief Medical Officer* Clinical Professor (affiliated), Department of Psychiatry & Behavioral Sciences, Stanford University, Scientific Advisory Board Member and Chair of the Memory Screening Advisory Committee of the Alzheimer's Foundation of America
- **George Perry, PhD**, *Chief Scientific Officer* Holder of the Semmes Foundation Endowed Chair in Neurobiology at the Univ of Texas at San Antonio Distinguished as one of the top Alzheimer's disease researchers with over 1,000 publications
- **Jukka Karjalainen, MD, PhD**, *Chief Operating Officer*. Experience in pharmaceuticals and medical devices and clinical drug development from Phase I to Phase IV
- **James Harris, MBA**, *Chief Financial Officer* 20+ years experience in startups, licensing and biosimilars.
- **Michael J. Hoy, MS**, *Consultant of Regulatory Affairs* 15+ years in the pharmaceutical industry; Served as a consultant with pharmaceutical companies of all sizes
- **Jane Johnston, PhD**, *VP of Operations* 18+ years of research in cellular neuroscience

# BOARD OF DIRECTORS & ADVISORS

## Directors

<b>Nikolaos Tezapsidis, PhD (Chair)</b>	Neurotez
<b>J Wes Ashford, MD, PhD</b>	Stanford U/ Neurotez
<b>James Harris III, MBA</b>	Healthcare Economics
<b>Tom Humphries, MD</b>	Bayer, retired
<b>Bob Oliver, MBA</b>	Recent CEO, Otsuka (US)
<b>George Perry, PhD</b>	Dean, U Texas, S. Antonio

## Advisors

<b>Julio Licinio, MD, FRANZCP</b>	SVP and Dean at SUNY
<b>Arthur Klausner, MBA</b>	Director at Monopar Therapeutics
<b>Steven Jacobsen, PhD</b>	CEO at ALSP Inc
<b>Daniel P. van Kammen, MD, PhD</b>	CNS Pharma
<b>Gil Block, MD</b>	CMO at Neuraltus, Inc
<b>Robert Winkler, MD</b>	SVP at Taiho Oncology
<b>Kent Iverson, BS</b>	Pharmaceutical Advisors
<b>Lex Van der Ploeg, PhD</b>	CSO at Rhythm Pharma
<b>Izabela Ochocka</b>	BIMA Capital

# FINANCING

- **RAISED: \$4.5million**
  - National Institutes of Health
  - New Jersey Commission of Science and Technology
  - Internal Revenue Service
  - Founders, Small private investments

- This round: \$10,000,000, starting with \$500,000
- **MILESTONES (12-18months):**
  - Drug Manufacturing
  - IND-enabling studies
  - IND application
- **MILESTONES (next 12-18months):**
  - Phase I (Safety and biomarkers)
  - Phase II (Efficacy and biomarkers)

# ALZHEIMER'S DISEASE MARKET FORECAST.

- *Goldman Sachs projects Alzheimer's disease modification drugs could top **\$30 billion**, (**\$12 billion** at peak)*

# SUMMARY

- Repurposing MYALEPT, an approved drug, as **Memtin™**
- Drug is an endogenous protein naturally transported into the brain with receptors in the hippocampus (area affected by disease)
- Data from thousands of patients supporting an association of the drug to protection against Alzheimer's
- Data from preclinical studies demonstrating efficacy as a disease modification entity
- Perfectly positioned to allow early intervention and prevention therapy for those at risk (because of its safety profile)
- Novel use patents issued in US, Japan, China, Australia, S Africa and have pending in Europe, Canada and India, protection until 2029
- Drug as a biologic, will get 12 y of market exclusivity from approval in the US (similar provisions ex-US)
- Drug can be produced cost-effectively and in large batches in Ecoli
- Treatment will be combined with diagnostic tests (plasma leptin)/apoE4)
- **Can be subject to accelerated approval, using protein as a surrogate marker as an endpoint, can cut clinical development costs by 10s of \$millions and time by 3-4 years.**



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