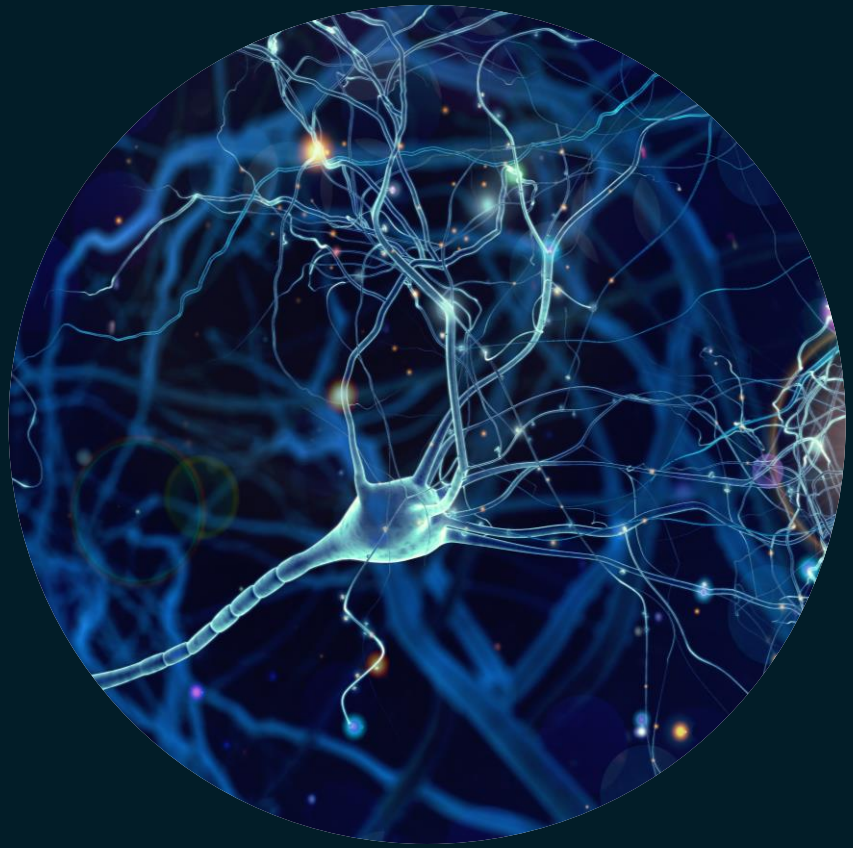


Brainstorm
Cell Therapeutics

July 8, 2020

KOL Webinar
Phase 2 trial with NurOwn for
Alzheimer’s Disease

Agenda – KOL Webinar to Discuss NurOwn for Alzheimer's

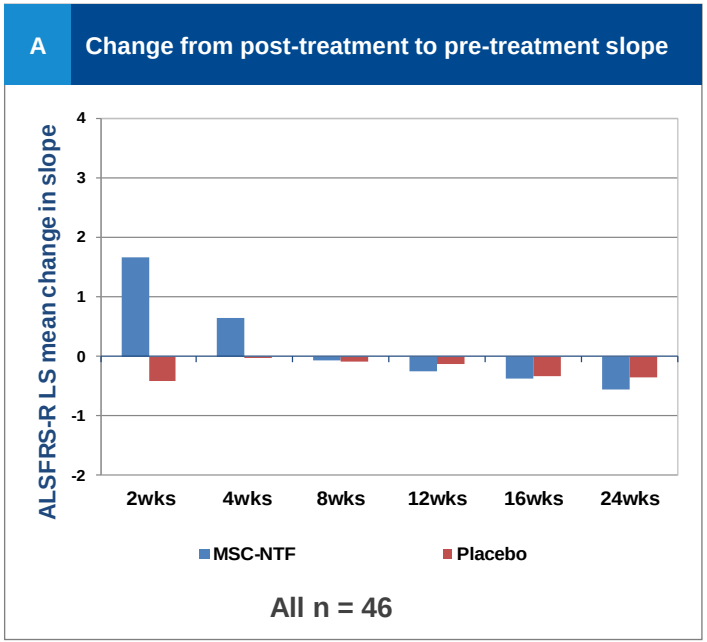
8:15-8:25	Chaim Lebovits, CEO Brainstorm Ralph Kern, M.D., MHSc, President & CMO Brainstorm ○ Introduction and overview
8:25-8:40	Pr. Dubois, Salpétrière University Hospital ○ High prevalence of the disease worldwide ○ Great progress in diagnostic procedures ○ Disappointment with current treatment
8:40-9:00	Pr. Scheltens, Amsterdam UMC ○ New emerging therapies ○ Biomarkers progress ○ What's attractive about Brainstorm approach
9:00-9:10	Stacy Lindborg, Ph.D. EVP & Head of Global Clinical Research Brainstorm ○ Study Protocol
9:10-9:30	Participants ○ Q&A

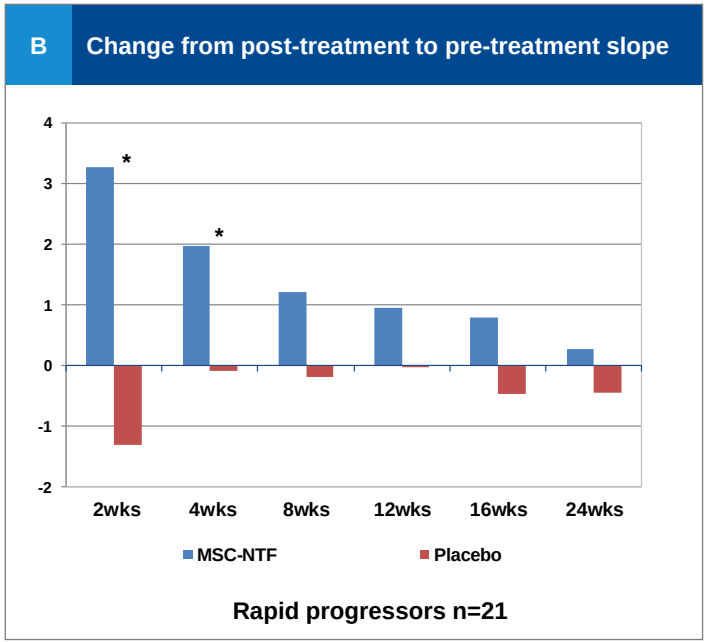
Brainstorm’s Pipeline

Indication	Preclinical	IND Enabling	Phase 1	Phase 2	Phase 3	Next Milestones
NurOwn® MSC-NTF Technology Platform						
ALS						Q4’20E Top-line data
Progressive MS						Q4’20E Top-line data
Alzheimer’s Disease						IND: Q2’20E Phase 2: 2H’20E
Parkinson’s Disease						
Huntington’s Disease						
Autism Spectrum Disorder						
Peripheral Nerve Injury						

ALS Phase 2 Clinical Trial: Functional Outcomes

Single dose NurOwn® slowed the rate of disease progression by improving the ALSFRS-R LS mean change in slope vs. pre-treatment slope





MSC-NTF Placebo

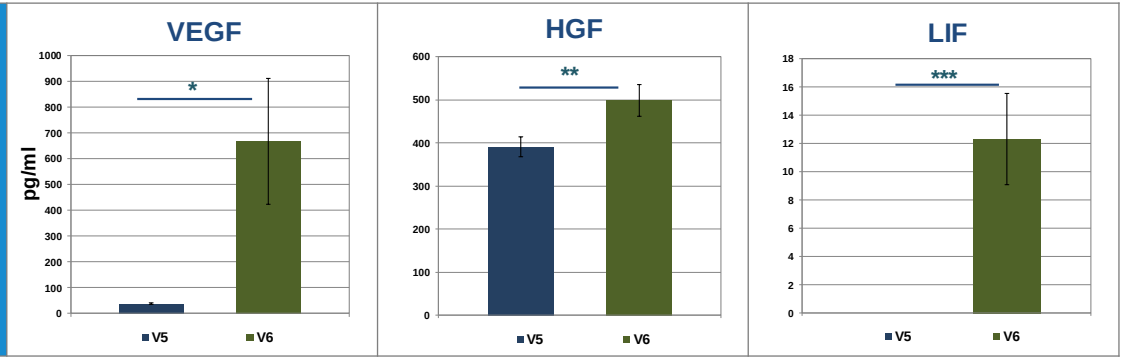
- Primary safety endpoint met
- Efficacy demonstrated in ALSFRS-R, a measure of ALS function

Berry et al Neurology 2019, * for $p < 0.05$

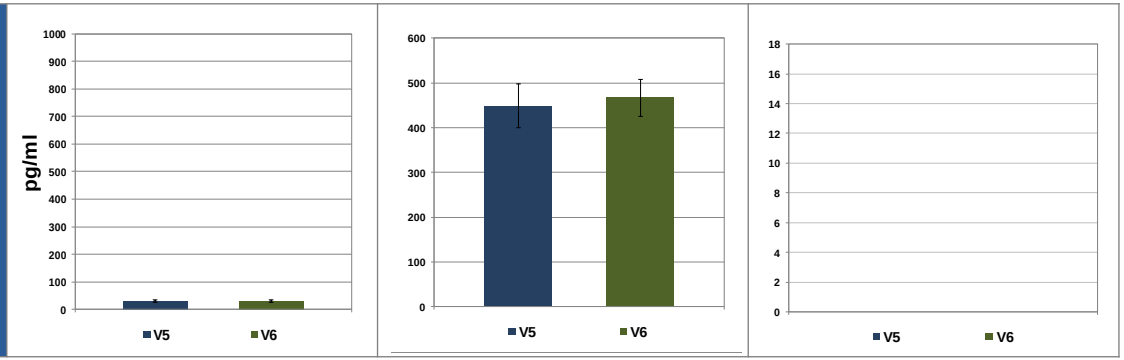
ALS Phase 2: CSF Delivery of NTFs Confirmed

CSF Profile 2 Weeks Post Treatment Demonstrates Delivery of NTFs

NurOwn®
(n = 26)



Placebo
(n = 9)



V5 -Pre transplantation

V6 - Post transplantation

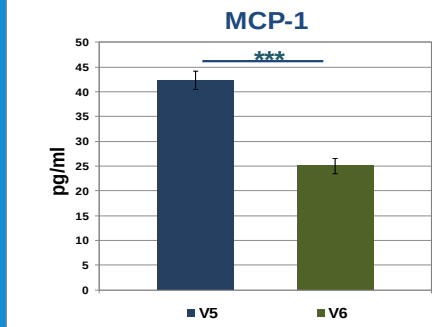
Berry et al Neurology 2019

***p<0.05, **p<0.01, ***p<0.001**

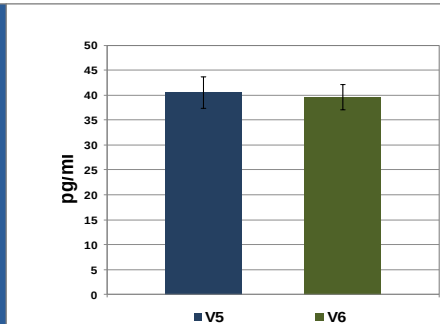
ALS Phase 2: CSF MCP-1 Reduction

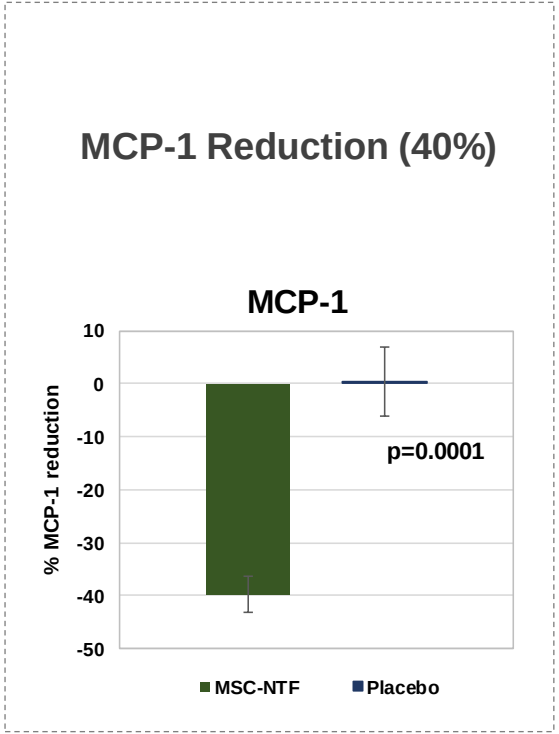
MCP-1 (an inflammatory mediator) is Significantly Reduced 2 Weeks Post-Treatment

NurOwn®
(n = 26)



Placebo
(n = 9)





*p<0.05, **p<0.01, ***p<0.001

Berry et al Neurology 2019

NurOwn's MOA Demonstrated in ALS- Relevant to Alzheimer's Disease

Underlying pathologies of ALS, MS, and AD	NurOwn® MSC-NTF MOA
Neuronal Degeneration	**Neuroprotection** ↑CSF miR-132, ↓CSF Caspase-3
Astrocyte Dysfunction and Loss of Neurotrophic Support (NTFs)	**Enhanced delivery of NTFs** ↑CSF VEGF, HGF, LIF, BDNF, GDNF
Neuroinflammation and Microglial Activation	**Immunomodulation** ↑CSF miR-146, ↓CSF MCP-1, SDF-1, CHIT-1

ALS: Amyotrophic lateral sclerosis; pMS: Progressive multiple sclerosis; AD: Alzheimer's Disease; MOAs: Mechanisms of action; Sources: Prion. 2013 Jan 1; 7(1): 47–54. Front Immunol. 2018; 9: 217. J Neurosci Res 2017 Dec 95(12):2430-2447. Brain. 2018 Sep 1;141(9):2561-2575. Curr Neuropharmacol. 2011 Dec; 9(4): 559–573. Front Neurosci. 2010; 4: 32. Int J Mol Sci. 2012; 13(10): 13713–13725. Lancet Neurol. 2015 Apr; 14(4): 388–405. Curr Pharm Des. 2017 23(5):693-730. Front Immunol. 2017; 8: 1005. J Neuroinflammation. 2019 Feb 21 16(1):46.

Introducing Today's KOLs

French National Coordinator of AD Trial	Principal Investigator of AD Trial
Bruno Dubois, M.D., Ph.D.	**Philip Scheltens, M.D., Ph.D.**
Professor of Neurology: Salpétrière University Hospital	Professor of Cognitive Neurology: Amsterdam UMC
President: Scientific Committee of France-Alzheimer	Director of the Alzheimer Centre: Amsterdam UMC
President: International Fund Raising for Alzheimer's Disease	Extensive experience as PI of international AD trials
Hôpital Pitié-Salpêtrière AP-HP	Amsterdam UMC

AD: Alzheimer's disease **PI:** Principal investigator

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Alzheimer’s Landscape

1) High prevalence of the disease worldwide
2) Great Progress in diagnostic procedures
3) Disappointment with current treatment

A High Prevalence

- >7.5M in EU
- >5M patients in the US

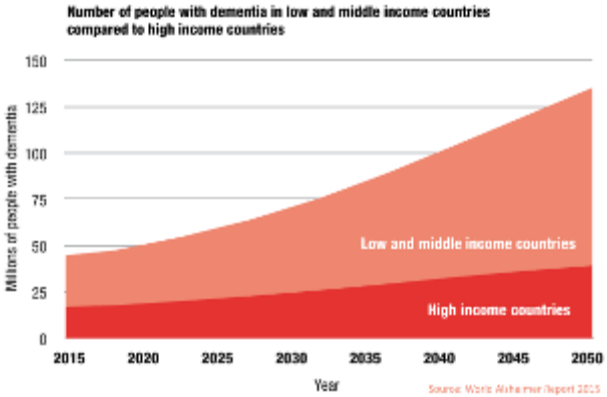
Every 65 seconds someone in U.S. develops Alzheimer‘s disease

35% of Americans age ≥60 are most afraid of developing AD or dementia (cancer 23%)

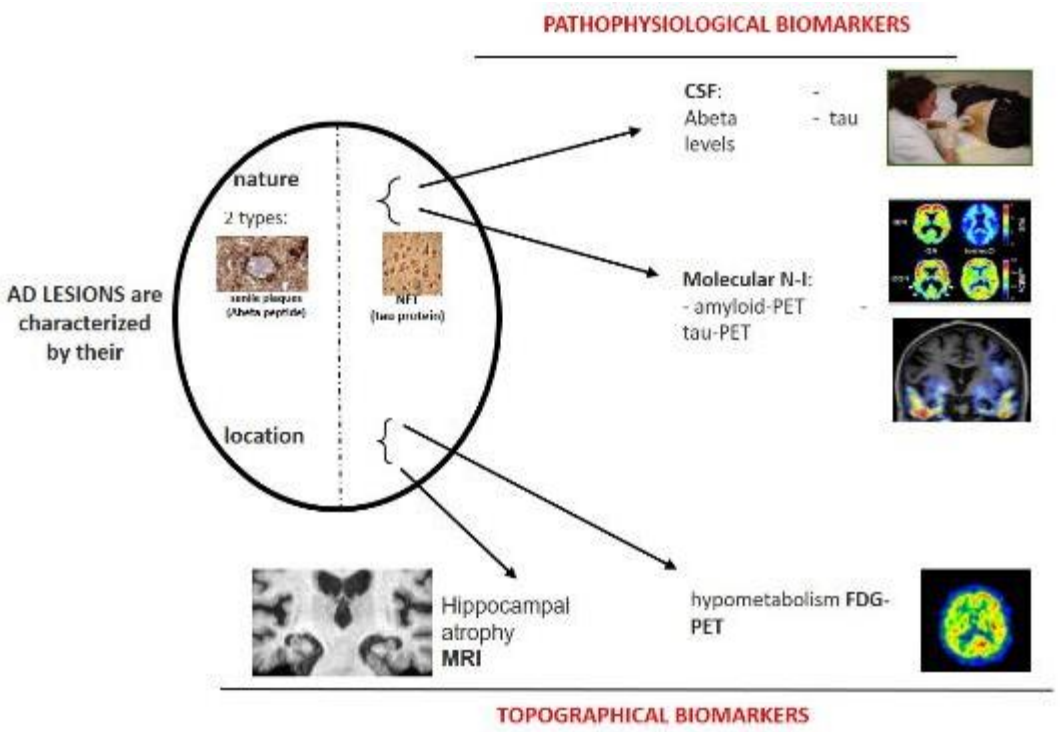
$7.9 trillion is the potential cost saving from early AD diagnosis only for current population in U.S.

Projection

- EU: Projected to grow to 13.1M by 2040
- US: Projected to grow to 13.8M by 2050



Significant Progress in Diagnostic Procedures



The 2 types of biomarkers

Pathophysiological markers = Diagnostic markers

- **Reflect in-vivo pathology (amyloid and tau changes)**
- **Are present at all stages of the disease**
- **Observable even in the asymptomatic state**
- **Might not be correlated with clinical severity**
- **Indicated for inclusion in protocols of clinical trials**

Topographical markers = Progression markers

- **Lesser disease specificity**
- **Indicate clinical severity (staging marker)**
- **Might not be present in early stages**
- **Quantify time to disease milestones**
- **Indicated for disease progression**

Dubois et al, *Lancet Neurol*. 2014

AD Diagnosis Framework

Clinical-biological entity

Clinical + Biological

Clinical phenotype

Typical AD:

- aMCI
- Amnestic syndrome of hippocampal type

Atypical AD:

- Posterior cortical
- Logopenic variant
- Frontal variant

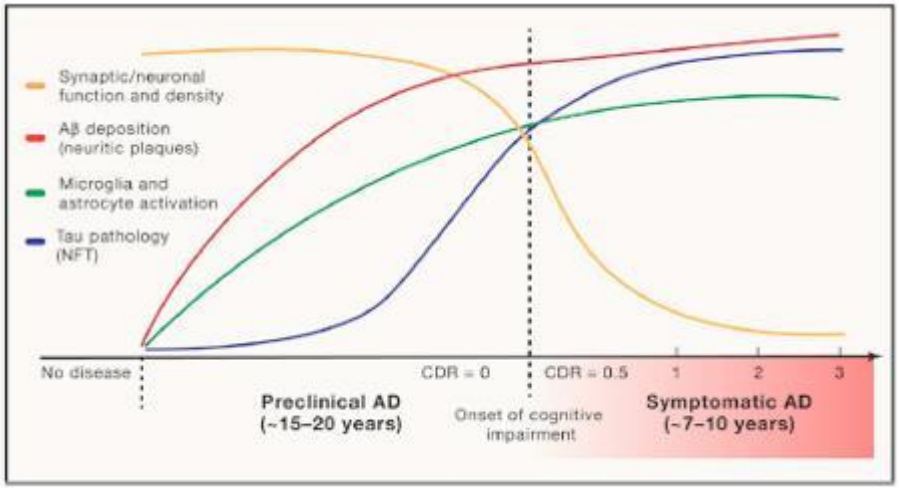
Biomarker positivity

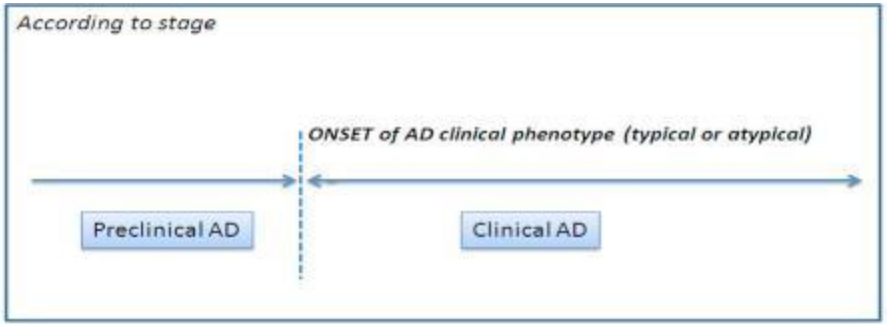
- CSF abeta
- CSF tau
- CSF phosho tau
- amyloid PET
- tau PET

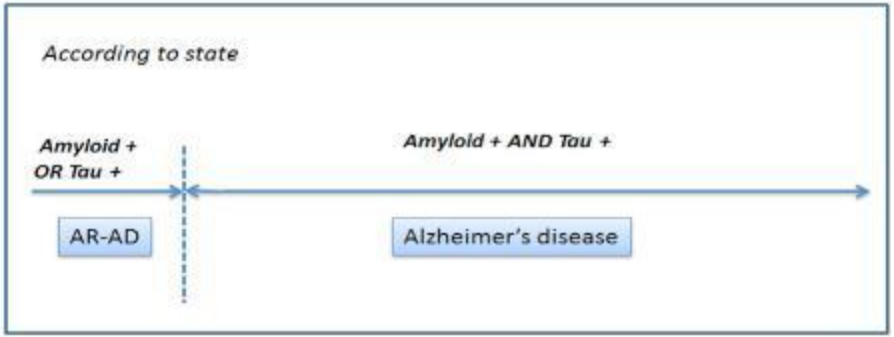
Alzheimer's Disease: "Turning to the left"

Alzheimer Disease:
An Update on Pathobiology and Treatment Strategies

Justin M. Long[1] and David M. Holtzman[1,*]
[1]Department of Neurology, Hope Center for Neurological Disorders, Charles F. and Joanne Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO 63110, USA
*Correspondence: holtzman@wustl.edu
https://doi.org/10.1016/j.cell.2019.09.001



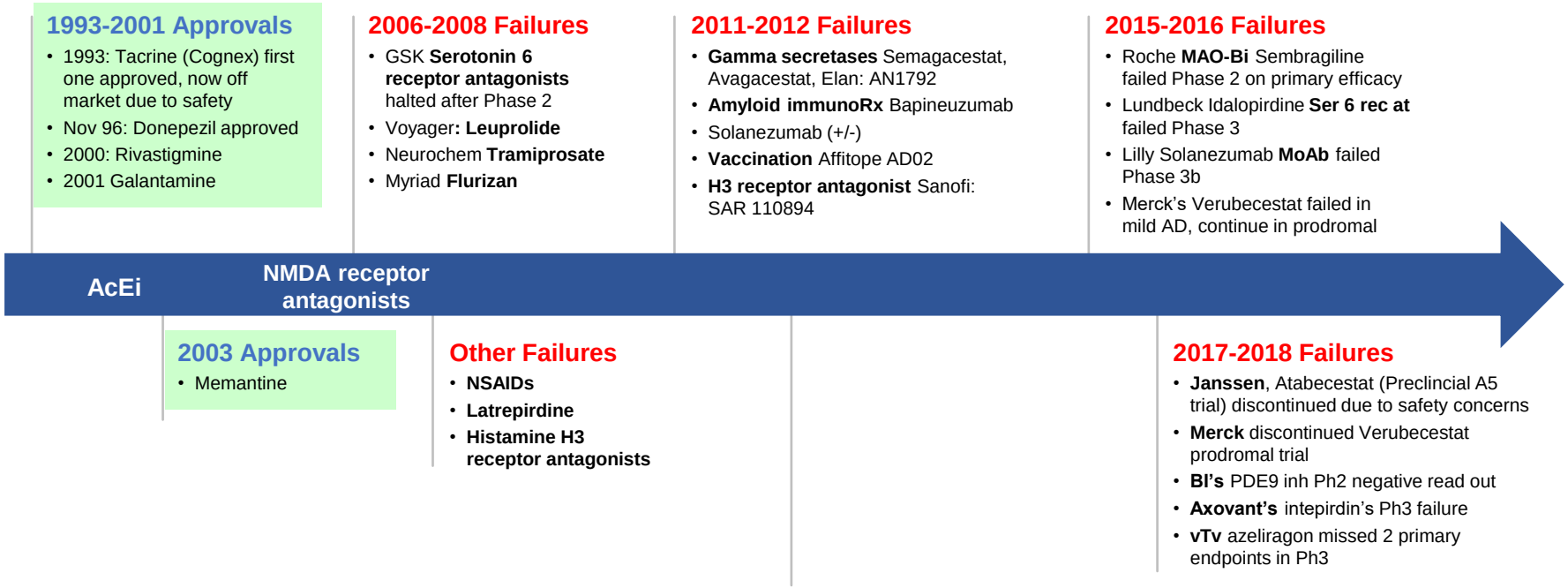




Dubois B et al. Alz Dement 2016

Disappointment with Current Treatment Research

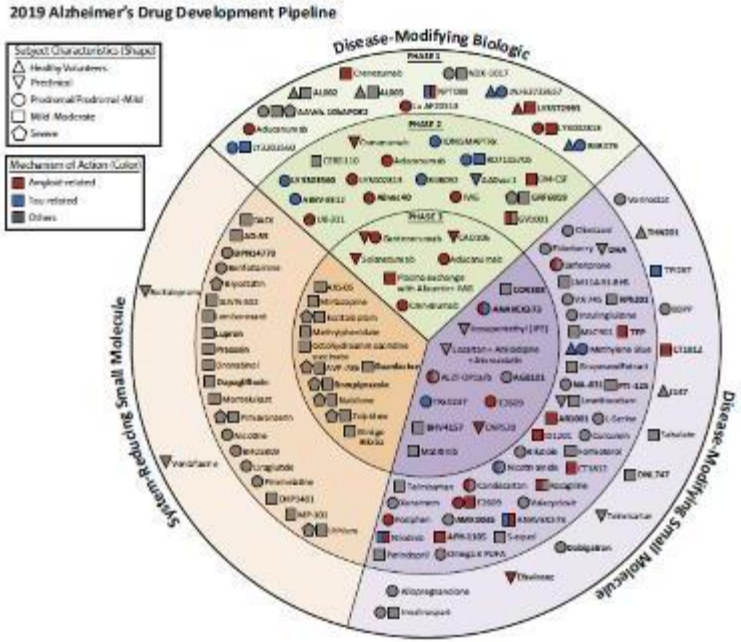
Last 20 years, more than 100 negative trials



2018: BAN2401 and Aducanumab showed promise in slowing of cognitive decline in addition to target engagement

Alzheimer's Disease:

Current Phase 2 and Phase 3 trials



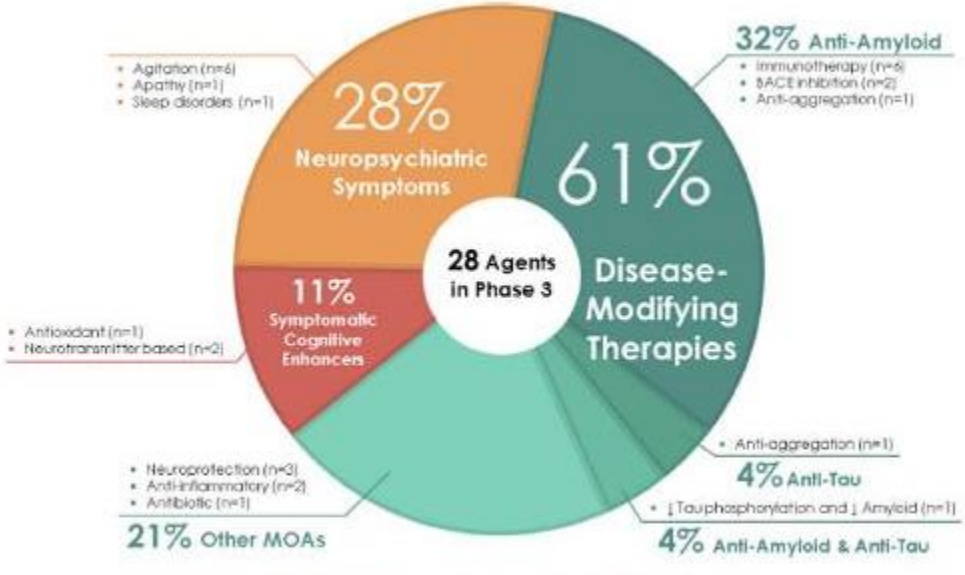


Fig. 2. Mechanisms of action of agents in phase 3.

Cummings et al. / Alzheimer's & Dementia: Translational Research & Clinical Interventions 5 (2019) 272-293

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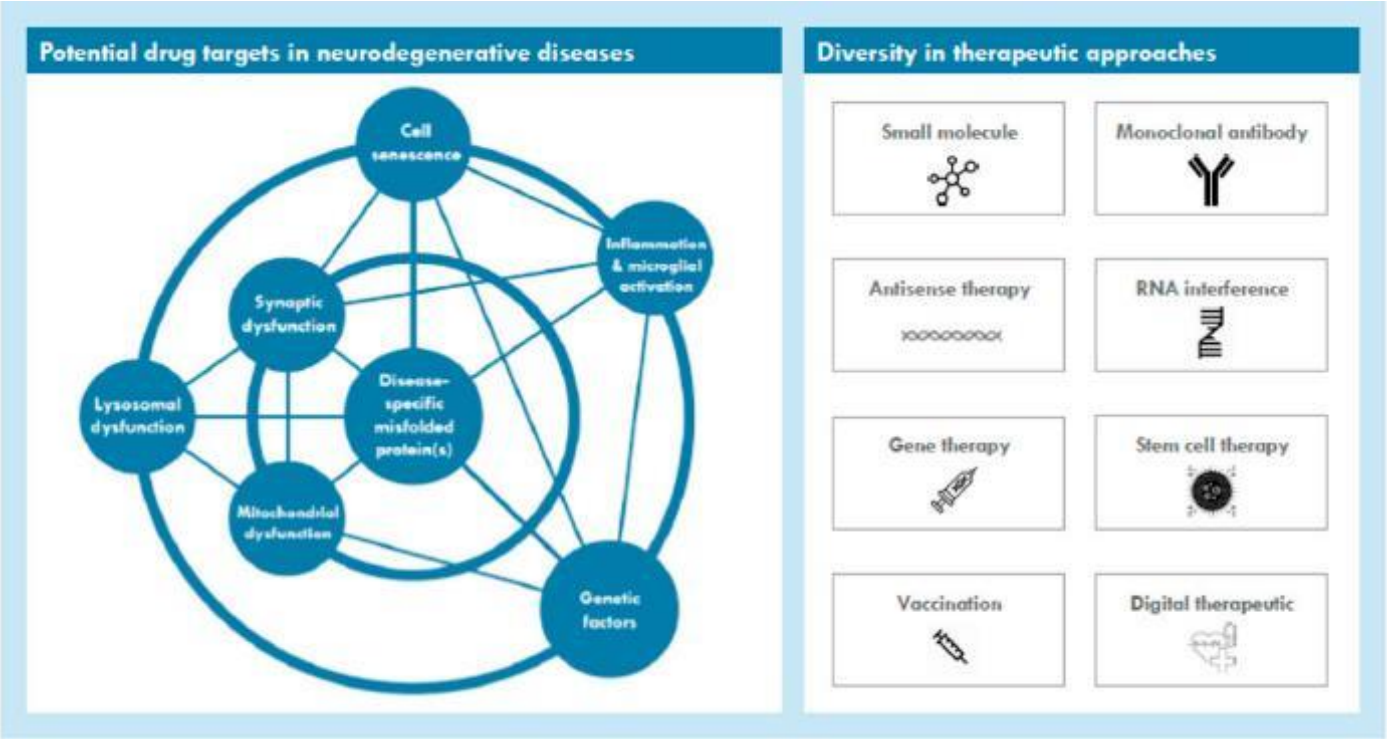
The Use of Biomarkers to Advance NurOwn® in Alzheimer's Clinical Trials

Prof. dr Philip Scheltens, FAAN, FEAN
Amsterdam UMC
Alzheimer Center Amsterdam

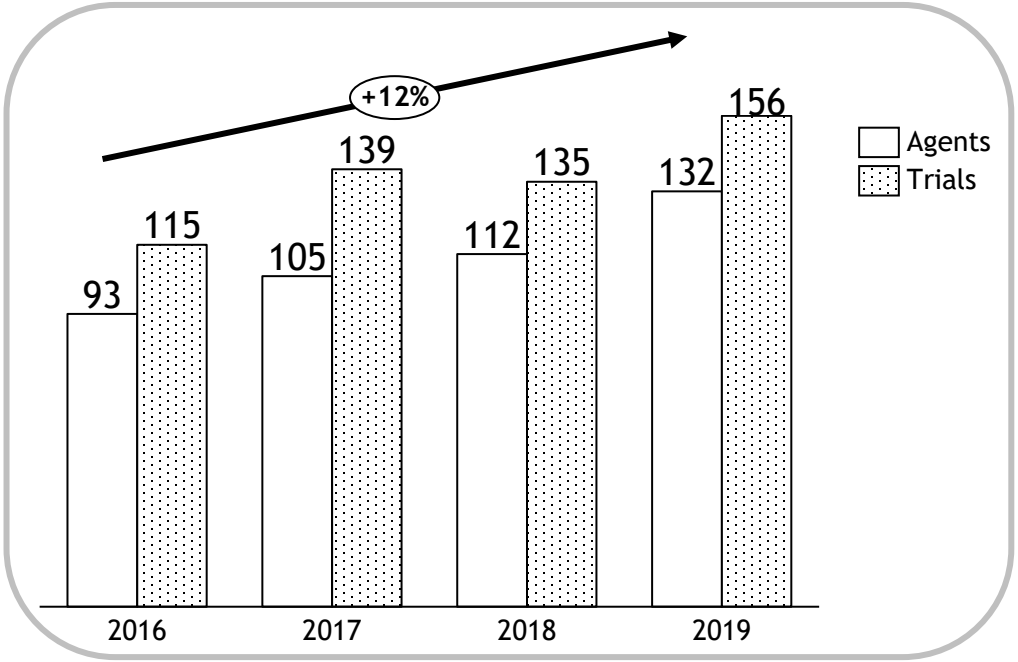
Contents

- New emerging therapies
- Biomarker progress
- Brainstorm approach

Beyond amyloid-β targets and approaches



Yearly increase in number of Alzheimer's disease clinical trials and agents between 2016-2019



Cummings et al., *Alzheimer's & Dementia: TRCI* (2016, 2017, 2018, 2019)

Issues in drug development

REVIEW Open Access

The "rights" of precision drug development for Alzheimer's disease

Jeffrey Cummings[1*], Howard H. Feldman[2] and Philip Scheltens[3]

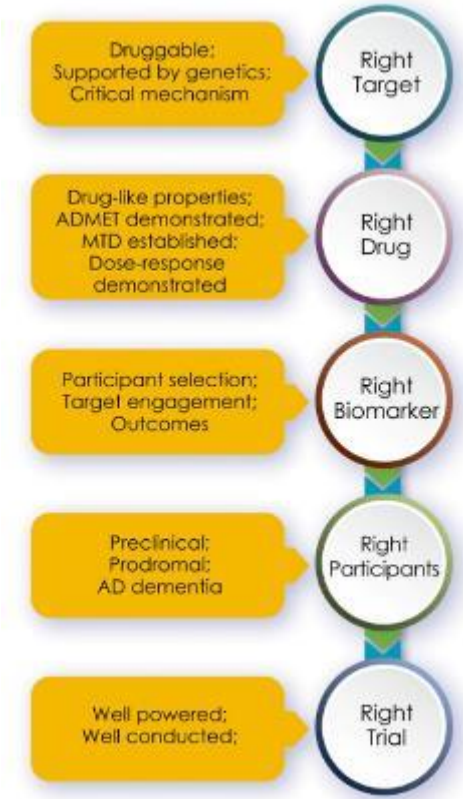


Fig. 1 The rights of AD drug development

The right patients

ATN profiles	Biomarker category	
A-T-N-	Normal AD biomarkers	
A+T-N-	Alzheimers pathophysiology	Alzheimer's pathophysiological continuum*
A+T-N+	Alzheimers pathophysiology	
A+T+N-	Alzheimers disease	
A+T+N+	Alzheimers disease	
A-T+N-	Non- AD pathophysiology	
A-T-N+	Non- AD pathophysiology	
A-T+N+	Non- AD pathophysiology	

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]
Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

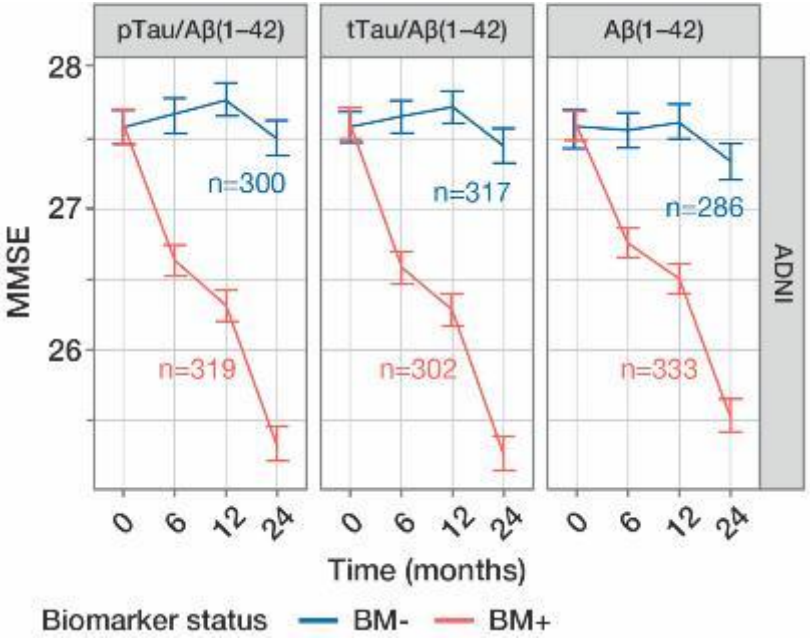
CSF amyloid and tau are linked to cognitive decline in AD

SCIENTIFIC REPORTS
nature research

OPEN

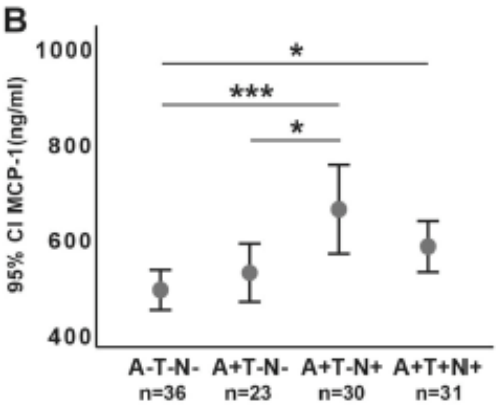
Predicting clinical decline and conversion to Alzheimer's disease or dementia using novel Elecsys Aβ(1–42), pTau and tTau CSF immunoassays

Kaj Blennow[1,2,10], Leslie M. Shaw[3,10], Erik Stomrud[4,5], Niklas Mattsson[4,6], Jon B. Toledo[3,7], Katharina Buck[8], Simone Wahl[8], Udo Eichenlaub[8], Valeria Lifke[8], Maryline Simon[9], John Q. Trojanowski[3] & Oskar Hansson[4,5*]



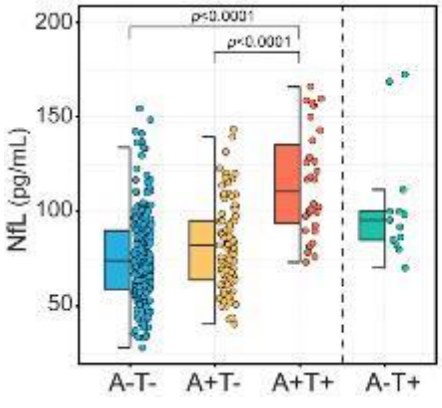
CSF Amyloid/Tau are linked to neuroinflammation and neurodegeneration

Amyloid+/Tau+ linked to neuroinflammation

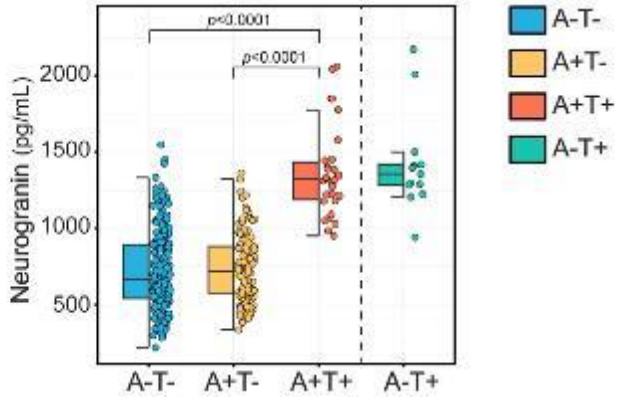


MCP-1

Amyloid+/Tau+ linked to neurodegeneration (NfL and Neurogranin)



NfL

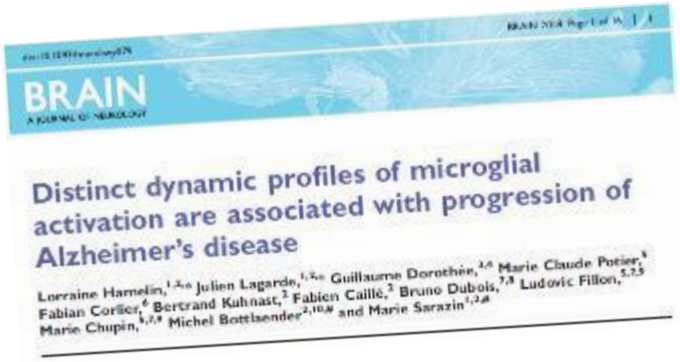


Neurogranin

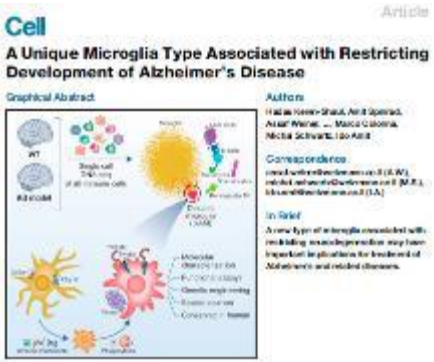
Nordengen et al. Journal of Neuroinflammation (2019)

Mila-Aloma Alzheimer's & Dementia (2020)

Neuroinflammation plays a key role in AD….


BRAIN

Distinct dynamic profiles of microglial activation are associated with progression of Alzheimer's disease


Cell

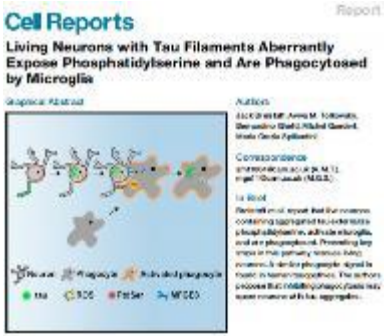
A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease


Article

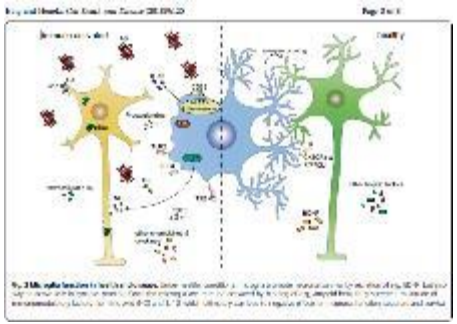
Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease


ARTICLE

Sustained microglial depletion with CSF1R inhibitor impairs parenchymal plaque development in an Alzheimer's disease model


Cell Reports

Living Neurons with Tau Filaments Aberrantly Expose Phosphatidylserine and Are Phagocytosed by Microglia




RESEARCH

Glial activation and inflammation along the Alzheimer's disease continuum

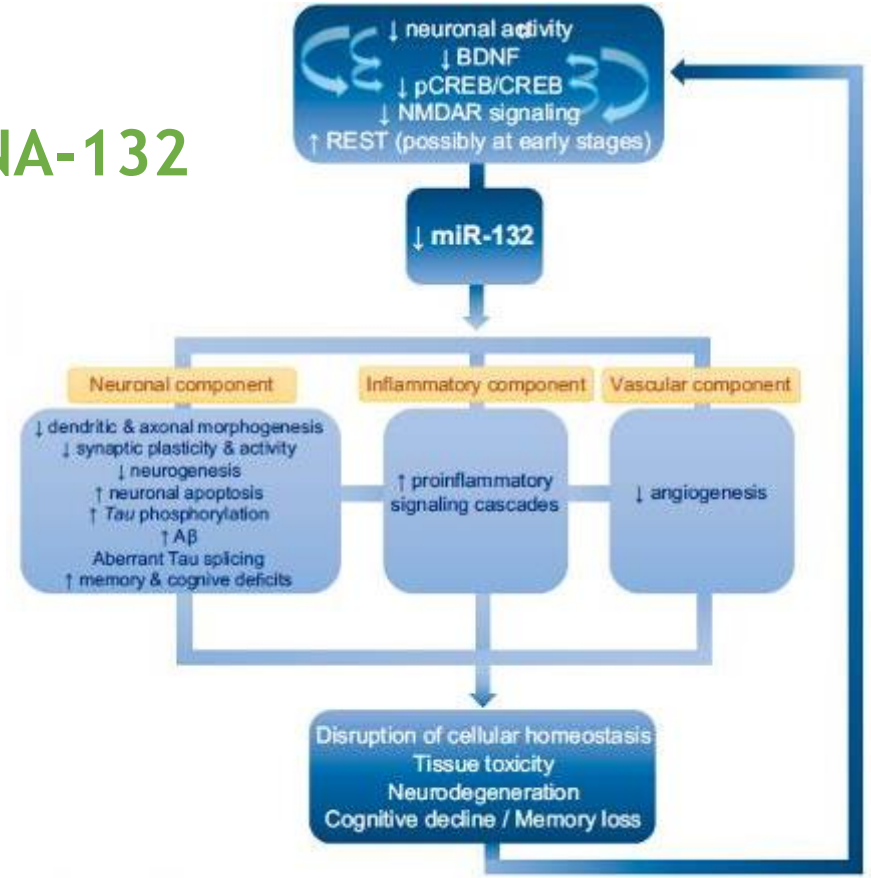
Journal of Neuroinflam

Ising and Heneka Cell Death and Disease (2018) 9:120
Nature | Vol577 | 16January2020 | 399

…which is mediated by microRNA-132

microRNA-132: a key noncoding RNA operating in the cellular phase of Alzheimer's disease

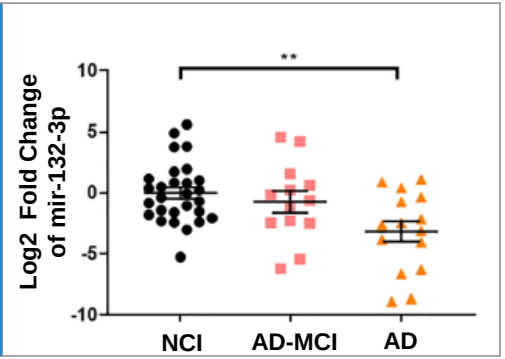
Evgenia Salta[a,†,1] and Bart De Strooper[a,†,2,2]



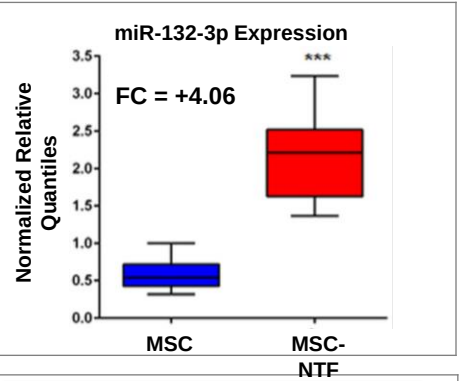
NurOwn® delivery of miR-132 addresses AD Pathology

NurOwn® MSC-NTF cells express and deliver miR-132, which is downregulated in AD

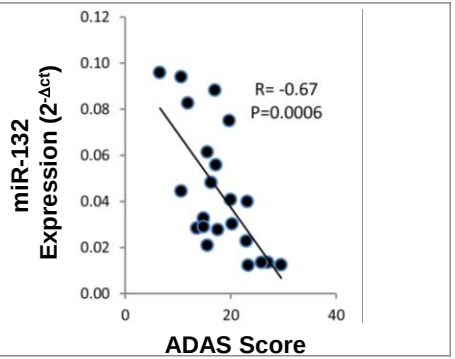
miR-132 is downregulated in AD[1]



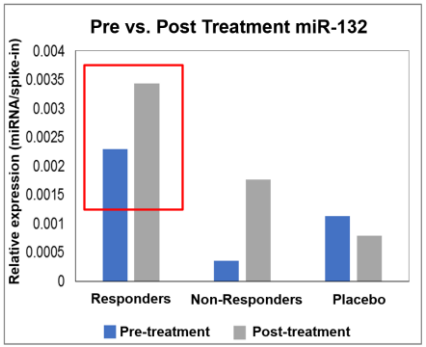
miR-132 is upregulated in MSC-NTF cells[3]



Decreased miR-132 correlates with AD Severity[2]



Phase 2 ALS: Single NurOwn® treatment increased CSF miR-132 in responders



AD: Alzheimer's disease; NCI: No cognitive impairment;
AD-MCI: Mild cognitive impairment due to Alzheimer's disease; FC: Fold change

1. Front Neurosci. 2019; 13: 1208;
2. Sci Rep. 2018; 8: 8465.
3. Stem Cell Res Ther. 2017 Nov 7; 8(1):249.

In conclusion

NurOwn®

- Has shown promising results in ALS by increasing NTFs and micro-RNA 132
- Which is downregulated in AD and is considered the right target in AD
- Which mediates a large array of pathologies in AD

- The upcoming trial includes the right patients, uses the right biomarker and is the right trial to provide important safety information and efficacy signals needed to build the next phase of the development

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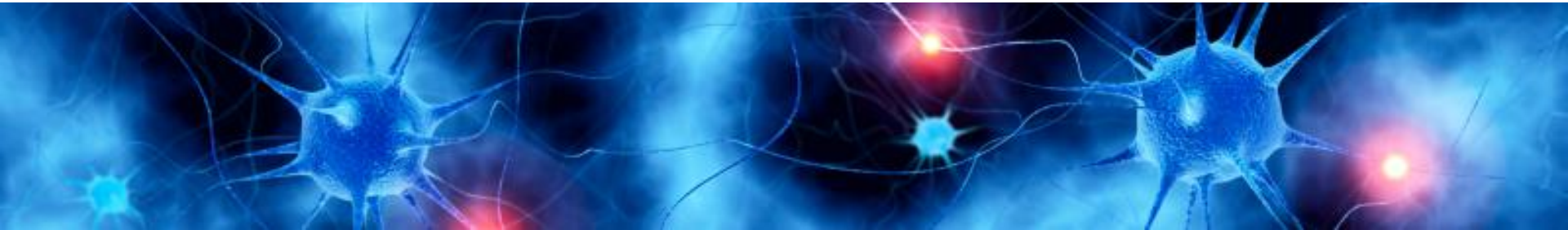
BCT-201-EU Study Overview

Prodromal to Mild Alzheimer's Disease Study

Stacy Lindborg, Ph.D.



BCT-201-EU, AD Phase 2a Study

Patient Selection:

40 participants with Prodromal to Mild AD at Medical Centers in France and the Netherlands

- Clinical diagnosis of prodromal to mild dementia* at least 6 months prior to enrollment
- MMSE 20-30, CDR global score 0.5-1.0
- CSF profile consistent with AD**

Rationale for Patient Selection Criteria:

Stage of disease where measures important to Alzheimer's disease exhibit the largest dynamic range

- Clinical measures
- AD biomarkers
- Neuroinflammatory markers linked to Alzheimer's disease progression

Objective:

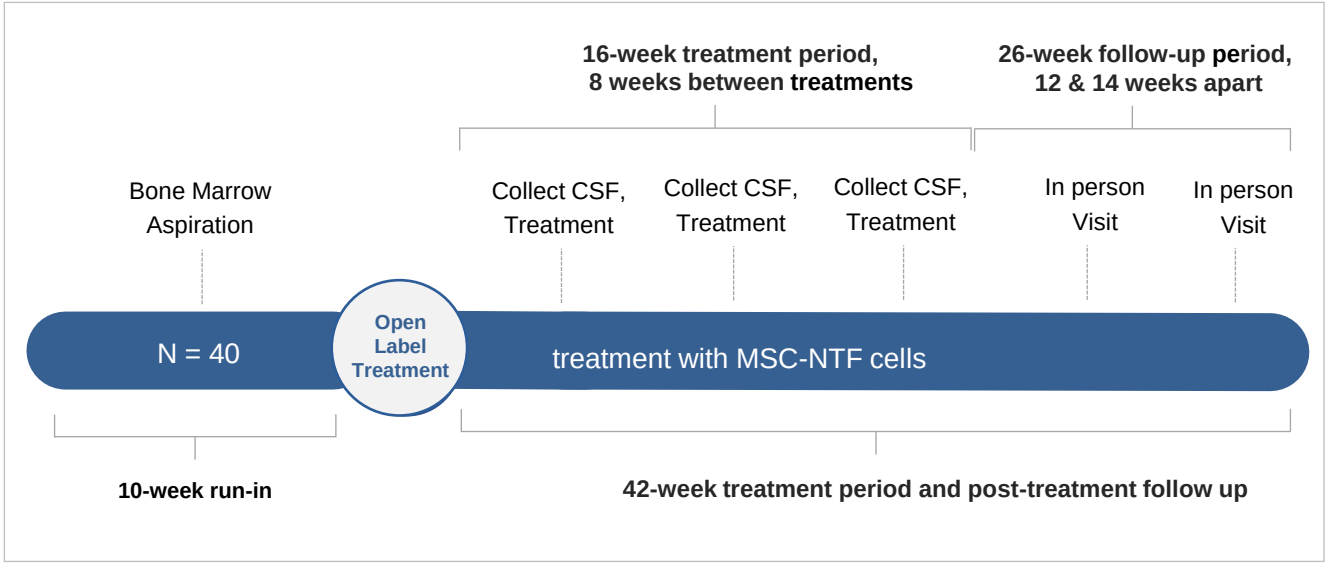
Safety and Efficacy of NurOwn® (Mesenchymal stem cells differentiated into neurotrophic factor secreting cells, MSC-NTF cells)

*IWG-2 (Second International Working Group) and NIA-AA (National Institute on Aging and Alzheimer's Association)

** aβ42<1000 pm/ml and P-tau>19 pm/ml or ratio >0.024 (Elecsys assay)

BCT-201-EU, AD Phase 2a Trial Design

52 Week clinical trial



- Follow up visits on Week 28 and 42
- CSF collection: pre-treatment, Week 0, 8, 16,
- Serum sample collection: pre-treatment, Weeks 0, 8, 16 and follow-up visits week 28, 42
- Patient phone calls after treatment visits at Weeks 0, 8, 16
- Total Study length 52 weeks, Final visit at Week 42

Primary Objective

To evaluate safety and tolerability of 3 Intrathecal administrations of MSC-NTF cells

Secondary Objectives

To evaluate the modulation of CSF and blood biomarkers

To evaluate clinical outcomes measures to assess efficacy (cognition and function)

BCT-201-EU, Phase 2a Study Measurements

Biomarkers: paired serum and CSF samples

Interested in biomarker levels over time to explore:

- Neurotropic, neurodegenerative and inflammatory factors (e.g., VEGF, HGF, NfL, NfH, MCP-1, IL-6)
- Markers associated with amyloid deposition (e.g., aβ40, aβ42)
- Markers of tau protein levels (e.g., p-tau, t-tau)

Clinical outcome measures: cognition* and activities of daily living

Interested in changes from baseline over time in the following tests:

- Clinical Dementia Rating Scaled – Sum of Boxes (CDR-SB)
- Free and Cued Selective Reminding Test (FCSRT)
- Neuropsychological Test Battery (NTB)
- Delis-Kaplan Executive Function System (D-KEFS) subtests
- Mini Mental State Examination (MMSE)
- Amsterdam Instrumental Activities of Daily Living Questionnaire - Short Version (A-IADL-Q-SV)

* Including memory, executive function, and attention

Question & Answer