RICERCA
DEMENZE
FONDAZIONE SYNAPSIS SVIZZERA

Meet the Researchers Lugano

-

18 aprile 2024

Presentazione 1

Biomarcatori precoci e non invasivi per la malattia di Parkinson e altre malattie neurodegenerative: novità della ricerca in Ticino

Prof Dr.med Giorgia Melli

Laboratorio Malattie Neurodegenerative (LRT-EOC)

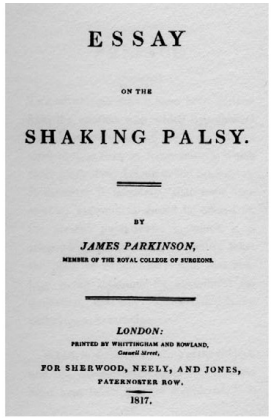
Neurocentro della Svizzera Italiana NSI

Facolta' di Biomedicina USI Lugano

18.04.2024

La Malattia di Parkinson: una Storia Affascinante….

- 1817: la prima descrizione clinica complete di James Parkinson in: “The shaking palsy”


ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Cannon Street,

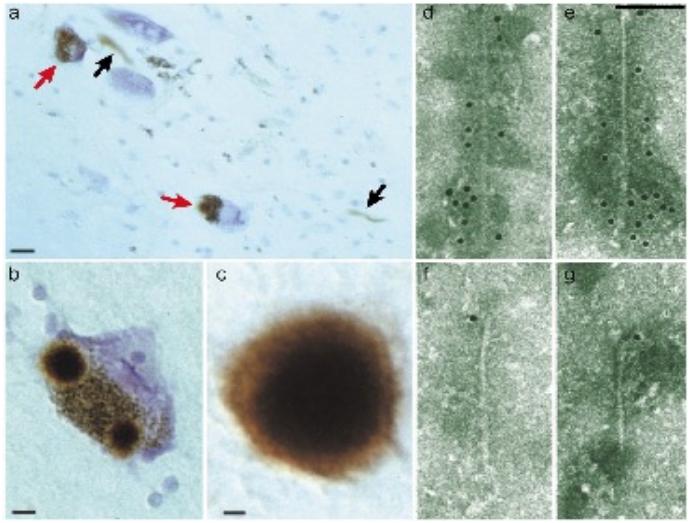
FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.


Paralysis Agitans. *(After St. Leger.)*

- 1967: la terapia con levodopa cura i sintomi del PD: “Risvegli”, libro di Oliver Sacks’, film di Penny Marshall

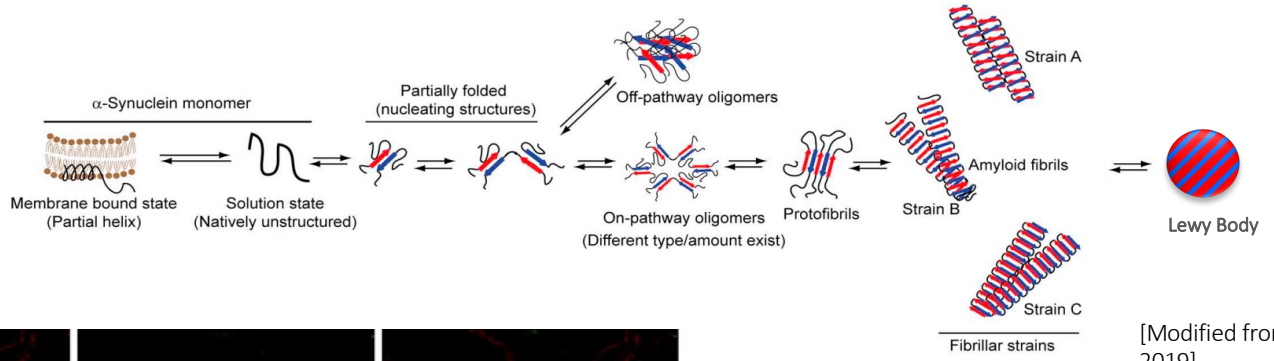


- 1997: M.G. Spillantini et al dimostrano che i corpi e i neuriti di Lewy sono fatti della proteina alpha-synuclein

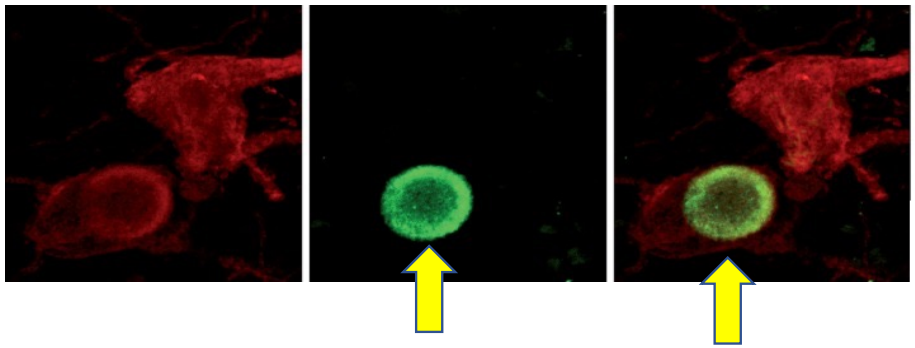
Polymeropoulos et al. mostrano la presenza di una mutazione (A53T) nel gene per alpha-synuclein, in 3 famiglie greche con PD

[M. Goedert 2001]

Alpha-Synucleinopathies: *Malattia di* Parkinson, Dementia con Corpi di Lewy e Atrofia MultiSistemica



[Modified from Mehra, BBA 2019]

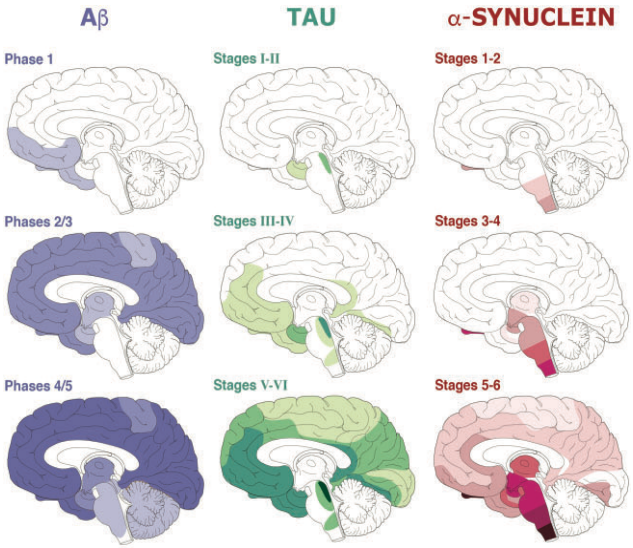


IF con tyrosine hydroxylase (rosso) and α-synuclein (verde), cervello di un soggetto con PD: tipico corpo di Lewy intra-neuronale.

Corpi e Neuriti di nei neuroni: Malattia di Parkinson; Dementia con Corpi di Lewy

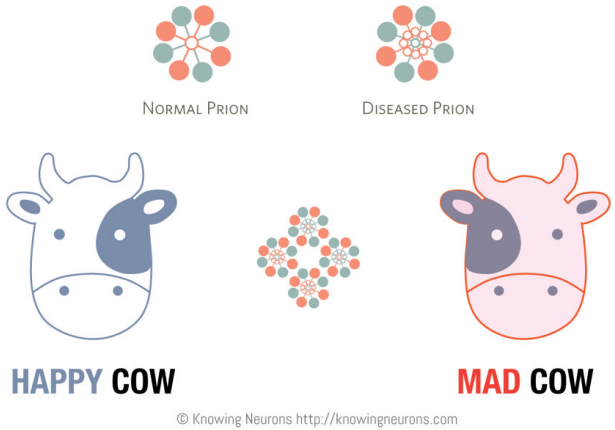
Glial Cytoplasmic Inclusions (GCI) negli oligodendrociti: Atrofia Multisitemica

alpha-synucleina si propaga nel Sistema Nervoso

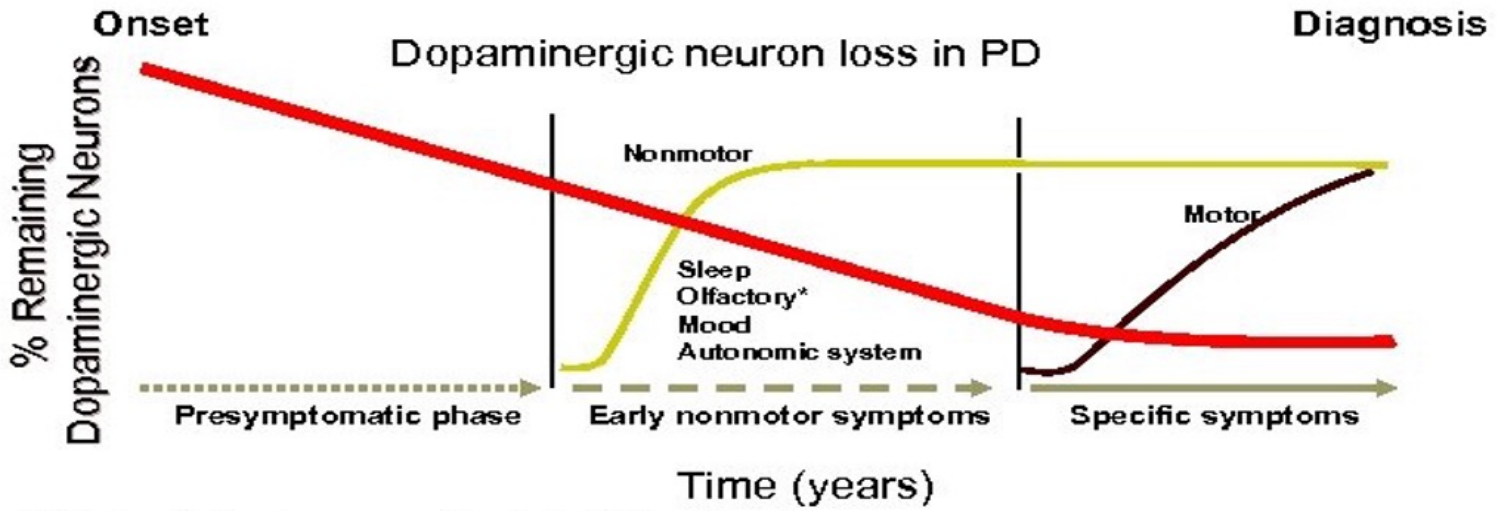


- 2003: Prof. Heiko Braak ipotizza che accumuli di alpha-syn compaiono prima nel bulbo olfattivo e nel nucleo del nervo vago: PD origina nei nervi periferici e poi invade il cervello

- 2016: prion like" behaviour degli aggregati di alpha-syn e tau: le malattie neurodegenerative sono una malattia prionica?"



“Time is Brain” …anche nella malattia di Parkinson



*Olfactory dysfunction may predate clinical PD by at least 4 years.

Halperin et al. *Neurotherapeutics*. 2009;6:128-140.
Lang. *Neurology*. 2007;68:948-952.
Ross et al. Ann *Neurol*. 2008;63:167-173.
Adapted image reprinted from *Neurotherapeutics*, Vol. 6, Halperin I, Morelli M, Korczyn AD, Youdim MB, Mandel SA. Biomarkers for evaluation of clinical efficacy of multipotential neuroprotective drugs for Alzheimer's and Parkinson's diseases, pages 128-140, Copyright 2009, with permission from Elsevier.

Parkinson's disease

- Seconda malattia neurodegenerativa nell'anziano
- > 5 milioni di pazienti nel mondo
- Non abbiamo terapia efficaci

PERCHE'?

1) NON ESISTONO TEST DIAGNOSTICI PRECOCI: la diagnosi e' solo clinica basata su sintomi/segni tardivi

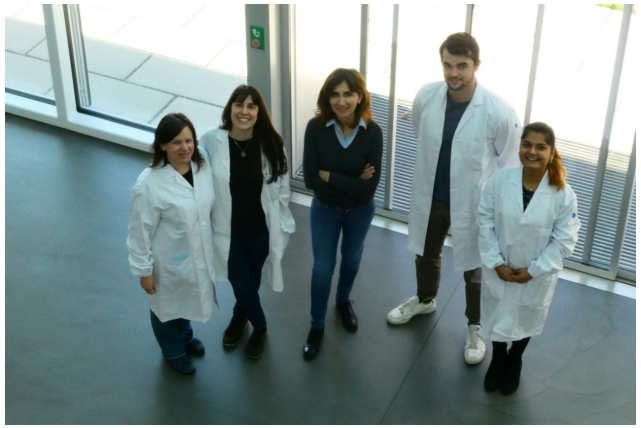
2) Eterogeneita' clinica e sintomi simili a molte malattie neurodegerative

⇨ **I Tessuti Periferici** sono uno strumento diagnostico per le malattie neurodegenerative del cervello

Lab Malattie Neurodegenerative
LRT-EOC Bellinzona

-Identificare/sviluppare **biomarcatori precoci** e non invasivi per la malattia di Parkinson e altre malattie neurodegenerative

- Capire quale ruolo giocano l'**infiammazione** e le cellule immunitarie nel sangue circolante nel causare la morte dei neuroni e la infiammazione cerebrale

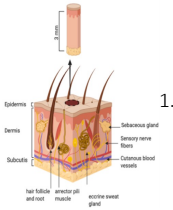


-Prelievi di **pelle e sangue**

-Tecniche avanzate di **Imaging** (microscopia elettronica e confocale) e **Analisi di proteine/acidi nucleici**

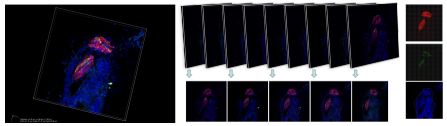
- Modelli di malattia: linee cellulari umane and **iPSCs** per lo sviluppo di organoidi cerebrali

Research flow chart

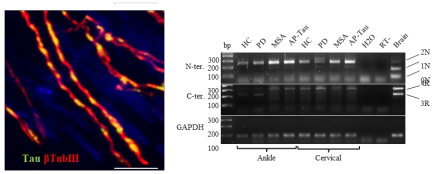


1. Skin biopsy collection

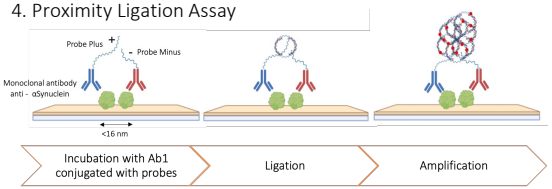
2. Quantification of somatosensory and autonomic innervation

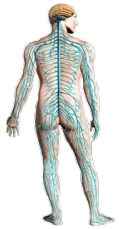


3. Detection and quantification of pathologic proteins



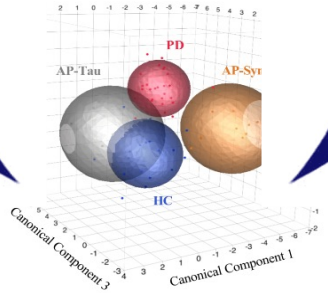
4. Proximity Ligation Assay





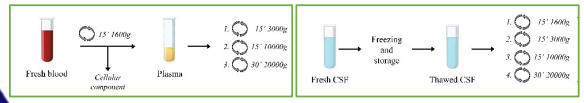
Recruitment of patients with: **Parkinson's Disease, Multiple system Atrophy, Tauopathies, Small fiber neuropathy**

Lugano Cohort (since 2015)
Biobank and clinical database

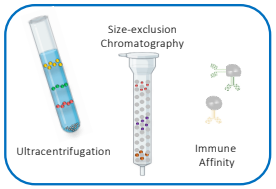


Diagnostic Modeling

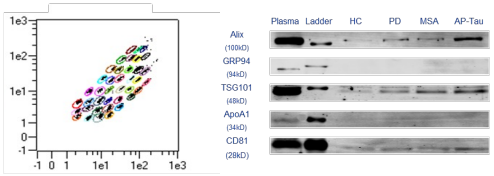
1. Plasma and Cerebrospinal fluid collection



2. Isolation of Extracellular Vesicles

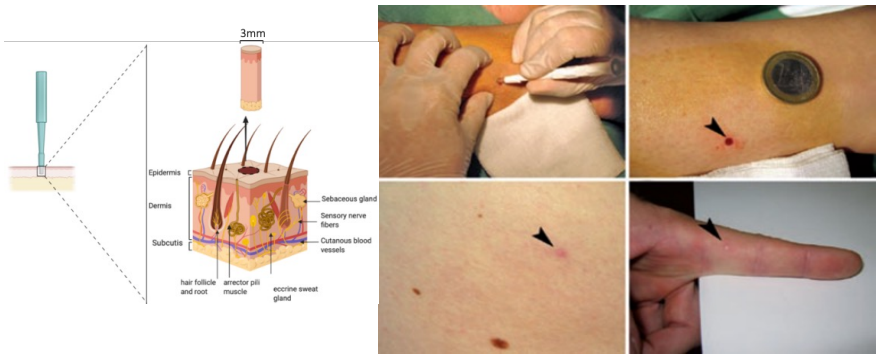


3. Characterisation of Extracellular Vesicles



Lab for Neurodegenerative diseases LRT EOC Bellinzona

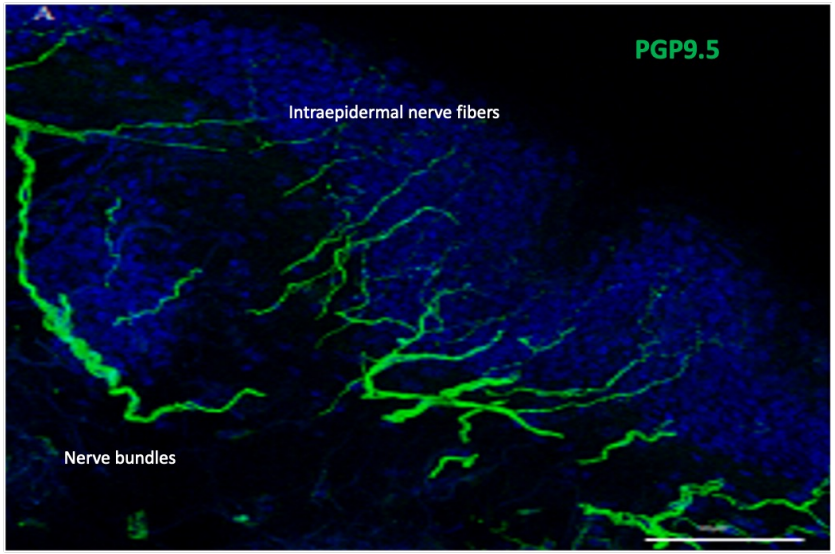
Biopsia di Cute



Sandra Pinton

➢ Punch (3 mm diametro):

- **Caviglia (10 cm sopra il malleolo laterale)**
- **Area Cervicale (C7)**



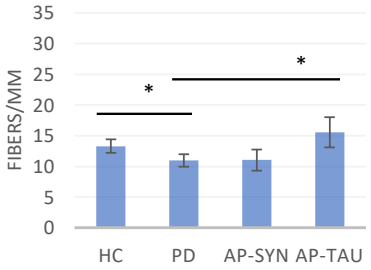
1) **Facile, non invasivo e basso costo**

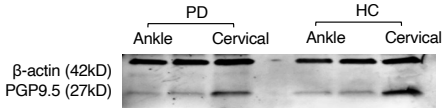
2) **Gold standard** per la diagnosi di **neuropatia delle piccolo fibre sensitive**

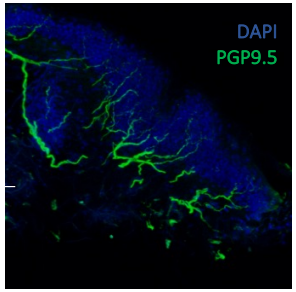
3) **Follow-up** per monitoaggio della **progressione di malattia**

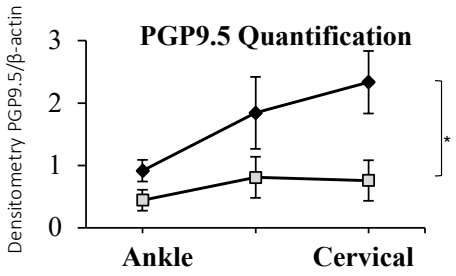
PD hanno una riduzione delle terminazioni nervosa cutanee che correla alla durata di malattia

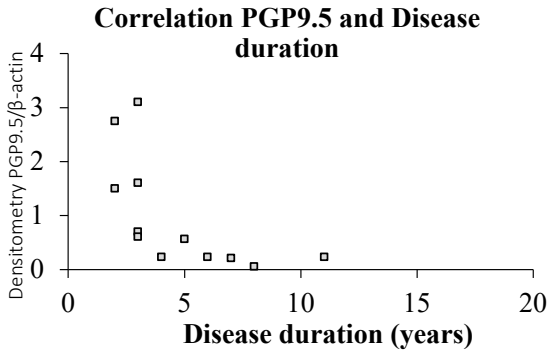
Elena Vacchi

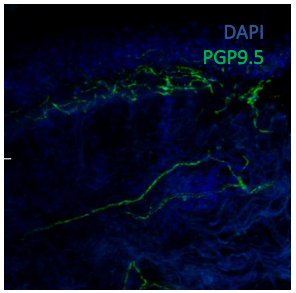










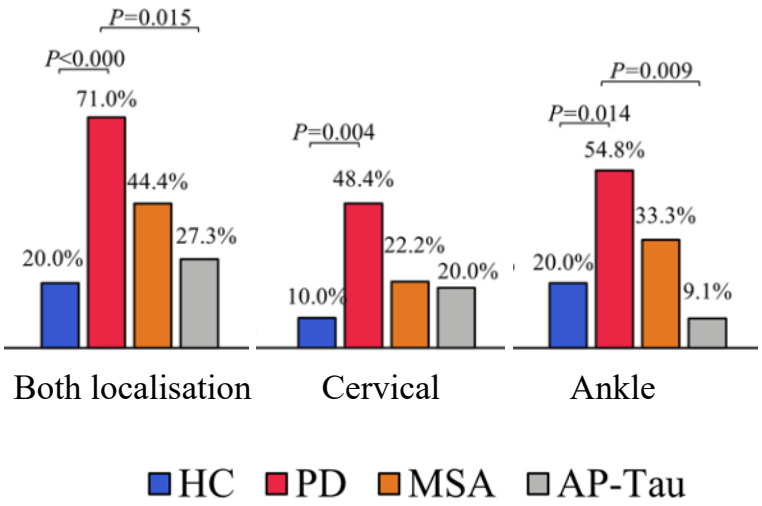


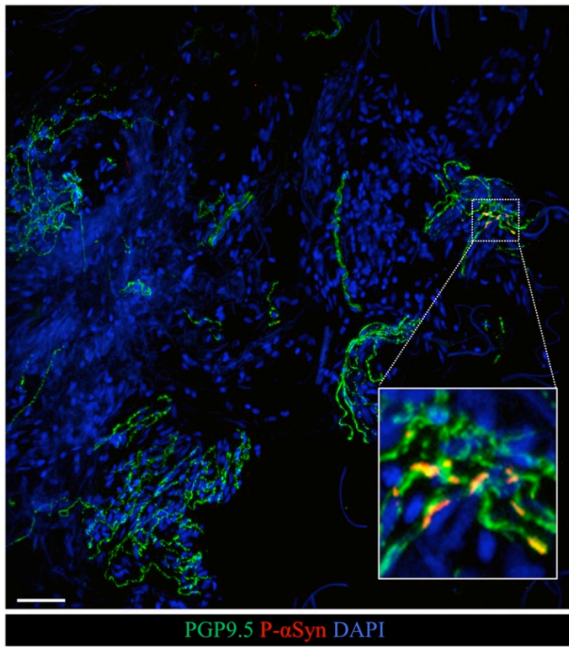
[Melli, ACTN 2018]

Phosphorylated αSyn (P-αSyn) e’ aumentata nella pelle dei Pazienti con PD

Elena Vacchi

The 90% of insoluble αSyn in Lewy Bodies, Lewy neurites, and glial cytoplasmic inclusion is phosphorylated at Serine 129.



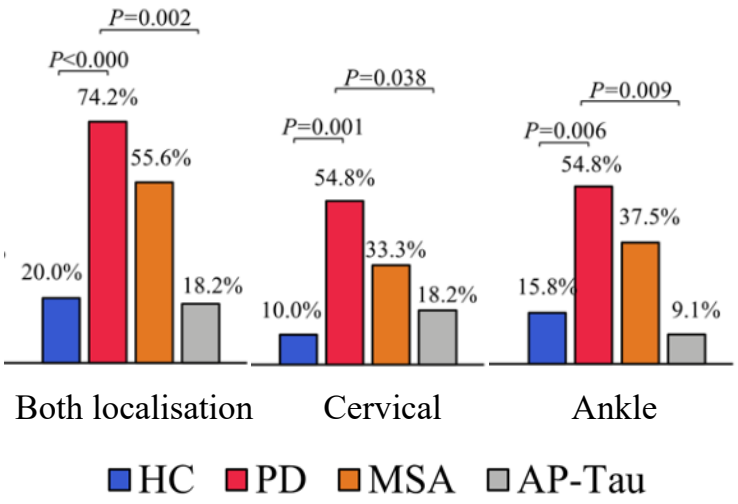


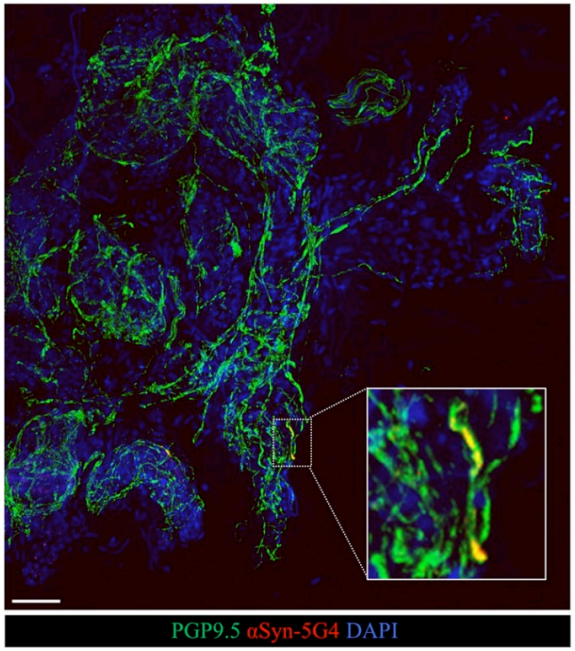
[Vacchi et al., npj PD 2021]

αSyn aggregata (αSyn-5G4) e’ aumentata nella pelle dei Pazienti con PD

Elena Vacchi

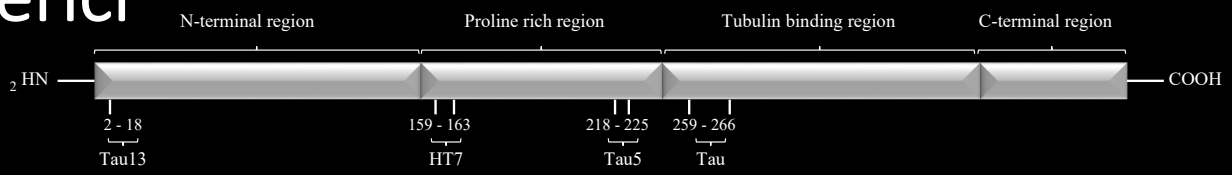
5G4 antibody is conformation-specific monoclonal antibody with high reactivity for aggregated forms of αSyn, and low reactivity for monomeric αSyn*.

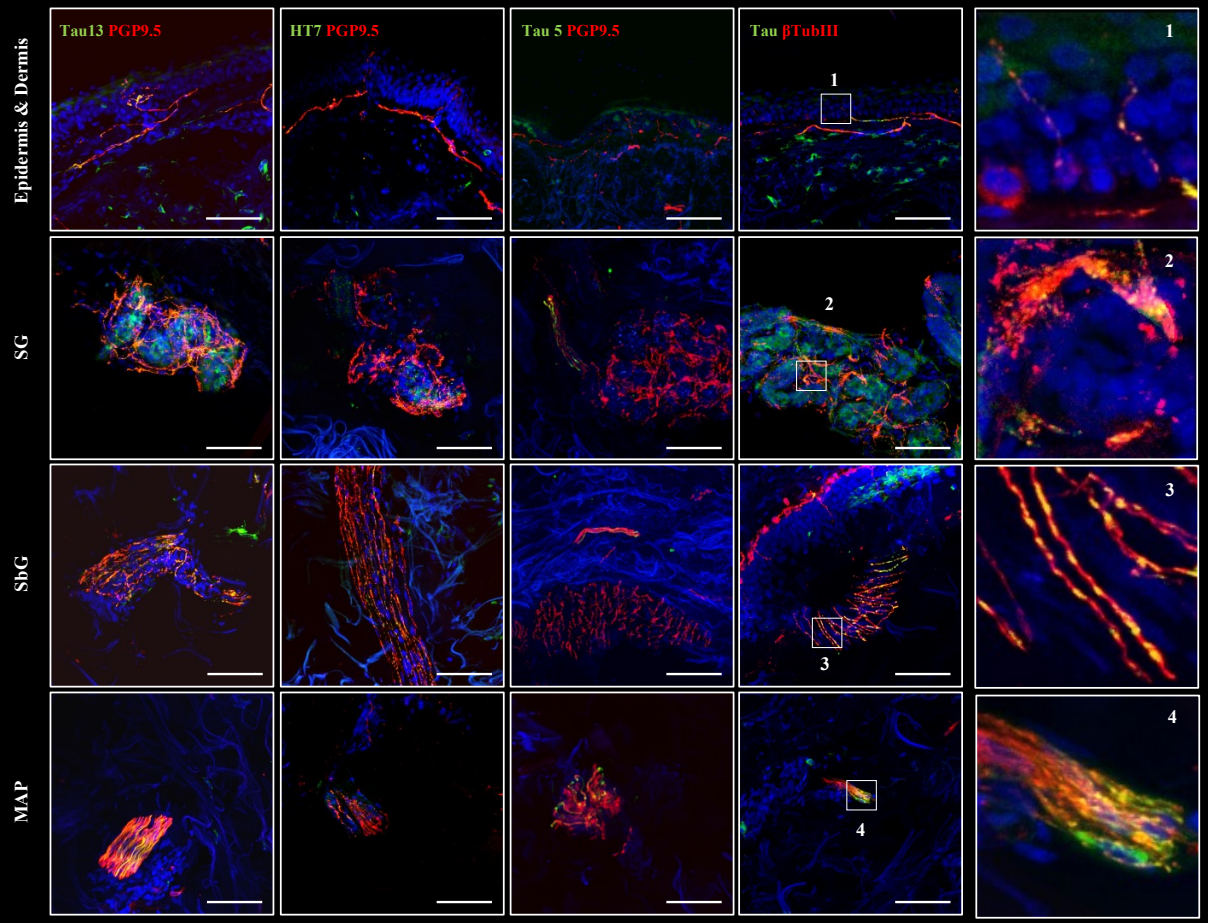


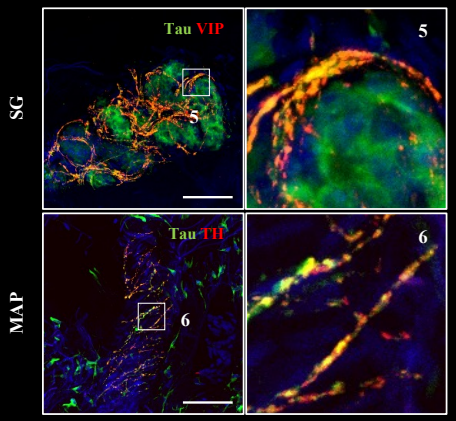


[Vacchi et al., npj PD 2021]

Tau e’ presente nei nervi periferici

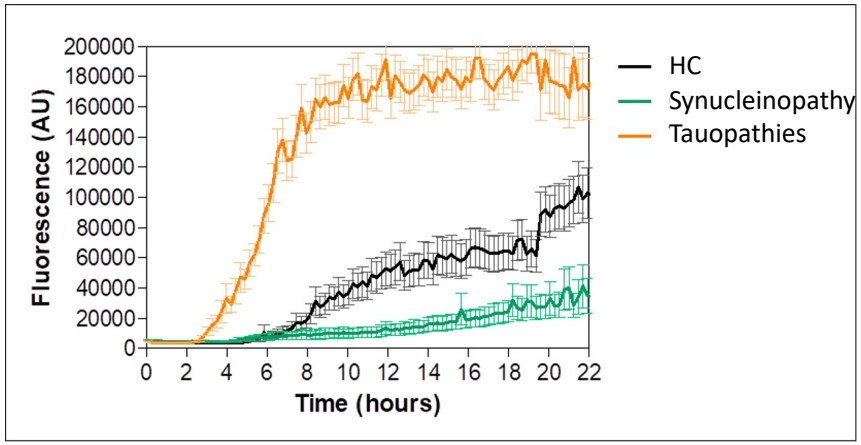






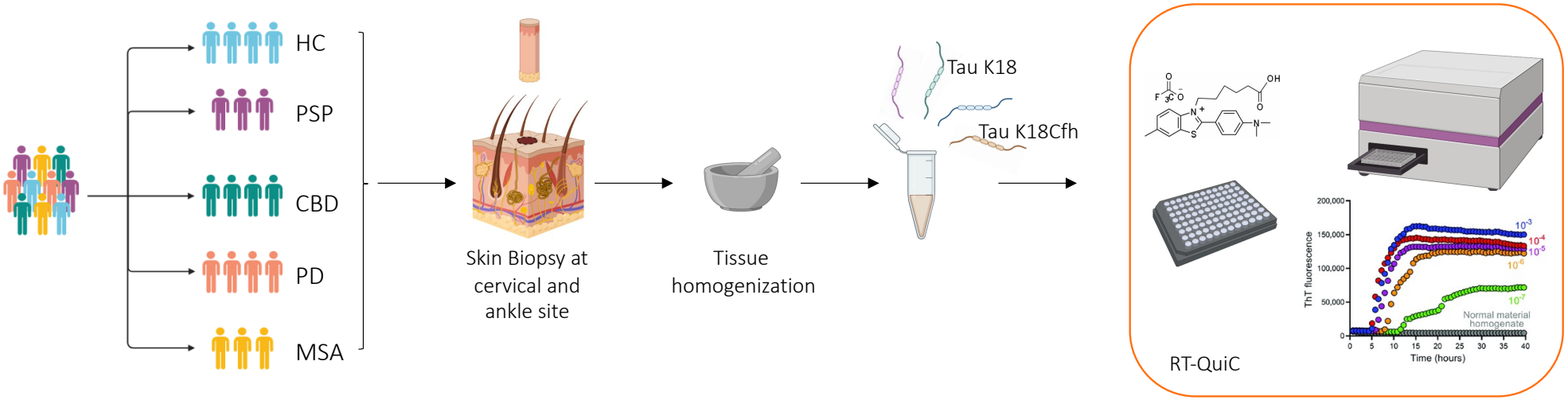
[Vacchi et al., Brain 2022]

Tau K18 RT-QuIC nella pelle per la diagnosi delle Tauopatie



-24 TAUOPATHIES (18 PSP, 6 CBD)
-14 HEALTHY CONTROLS
-20 SYNUCLEINOPATHIES (15 PD, 5 MSA)

DEMENTIA RESEARCH
SYNAPSIS FOUNDATION SWITZERLAND



Le Vescicole Extracellulari (EVs)

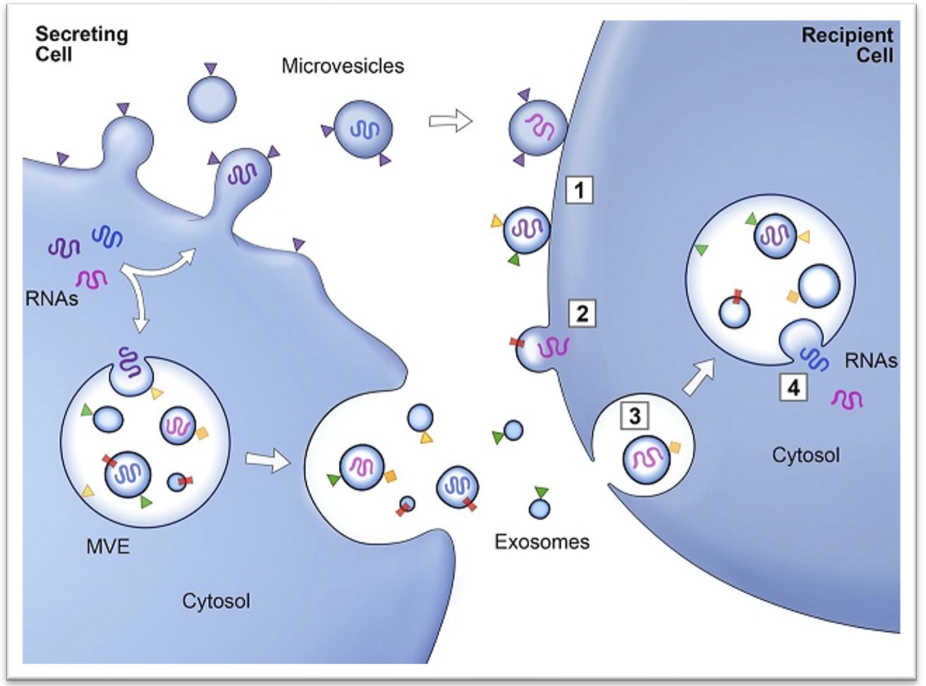
- Particelle circondate da una membrana lipidica

- I recettori di membrana determinano l'entrata nelle cellule;

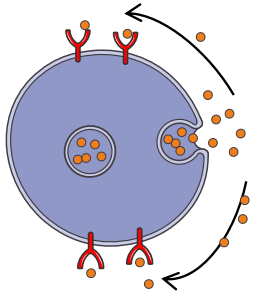
- Transportano proteins e RNA

- Sono rilasciate nei fluidi corporei

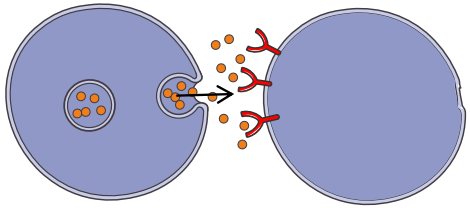
- Il contenuto influenza la fisiologia delle cellule.



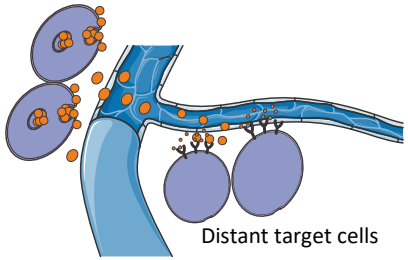
SELF-SIGNALING



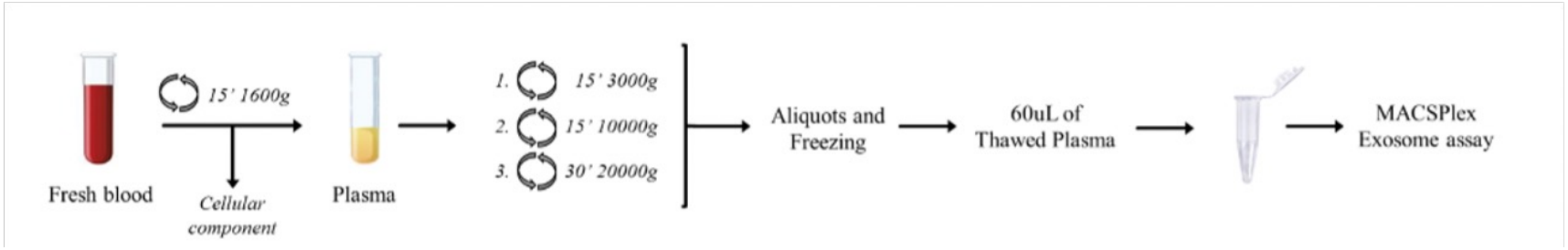
ADJACENT SIGNALING

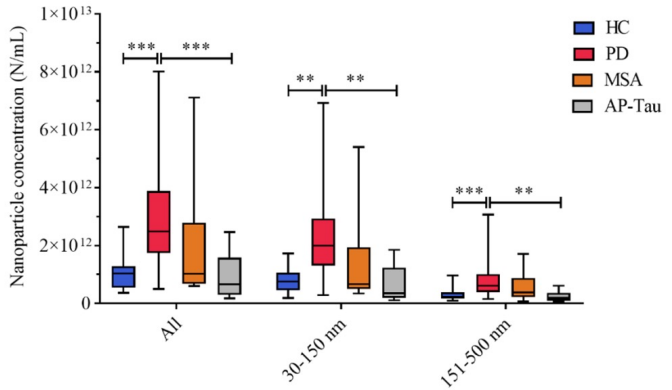


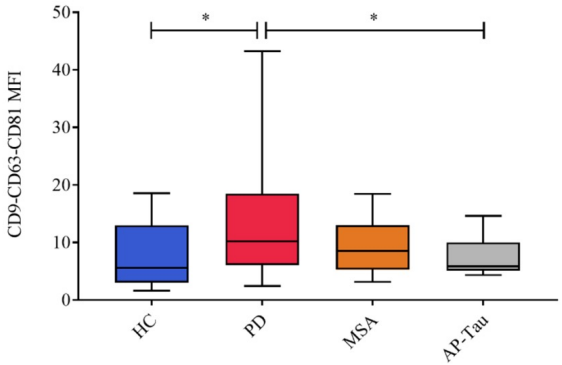
DISTANT SIGNALING



Nel sangue dei pazienti con PD vi e' una concentrazione maggiore di EVs







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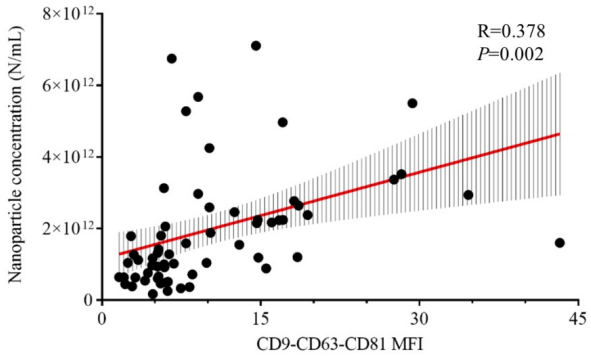
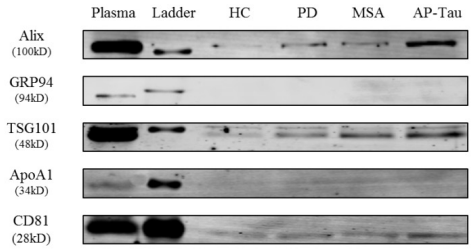


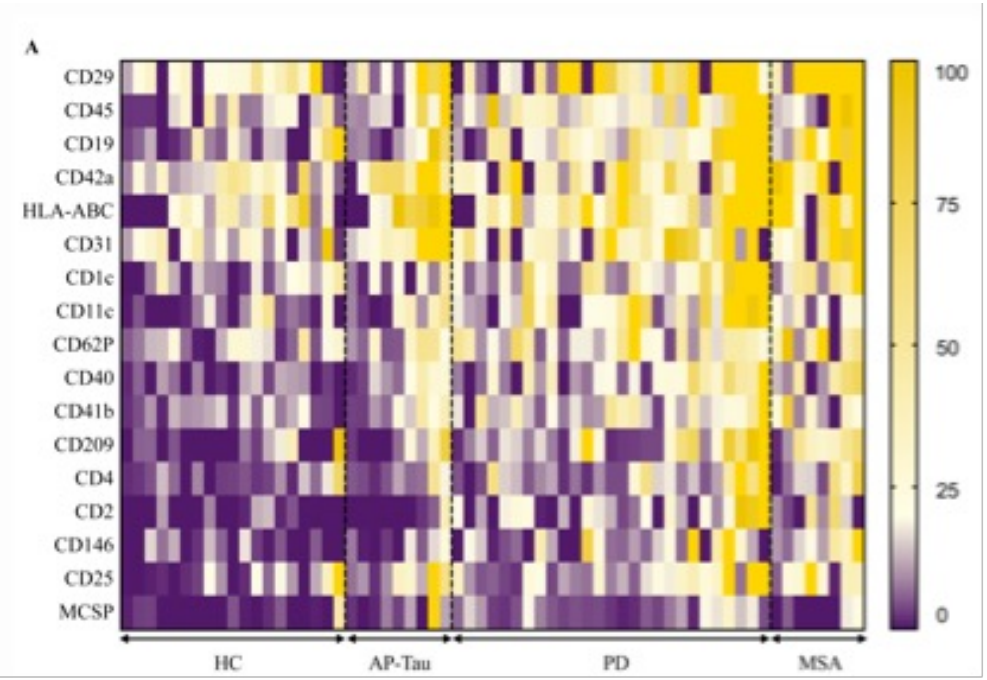
E

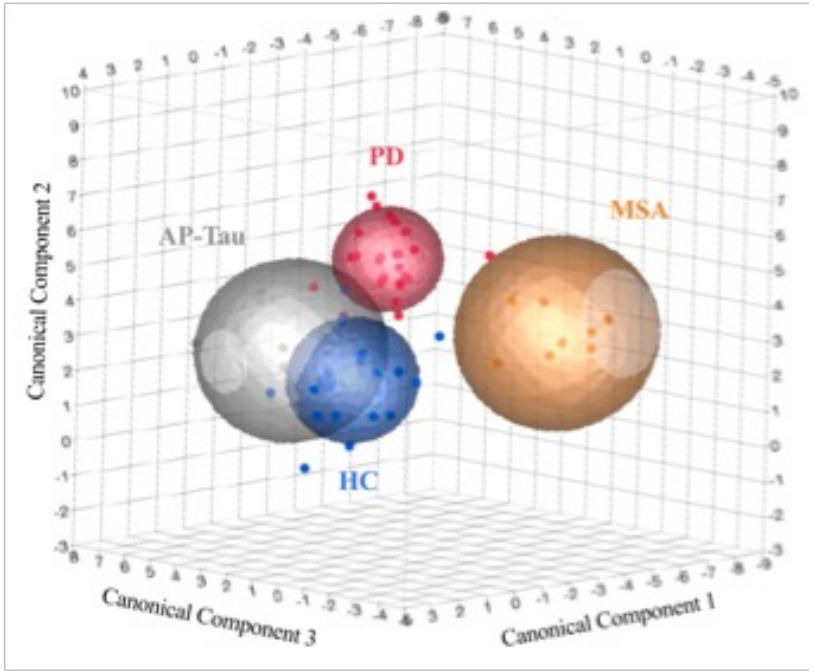


[Vacchi E. Neurol Neuroimmunol Neuroinflamm. 2020]

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

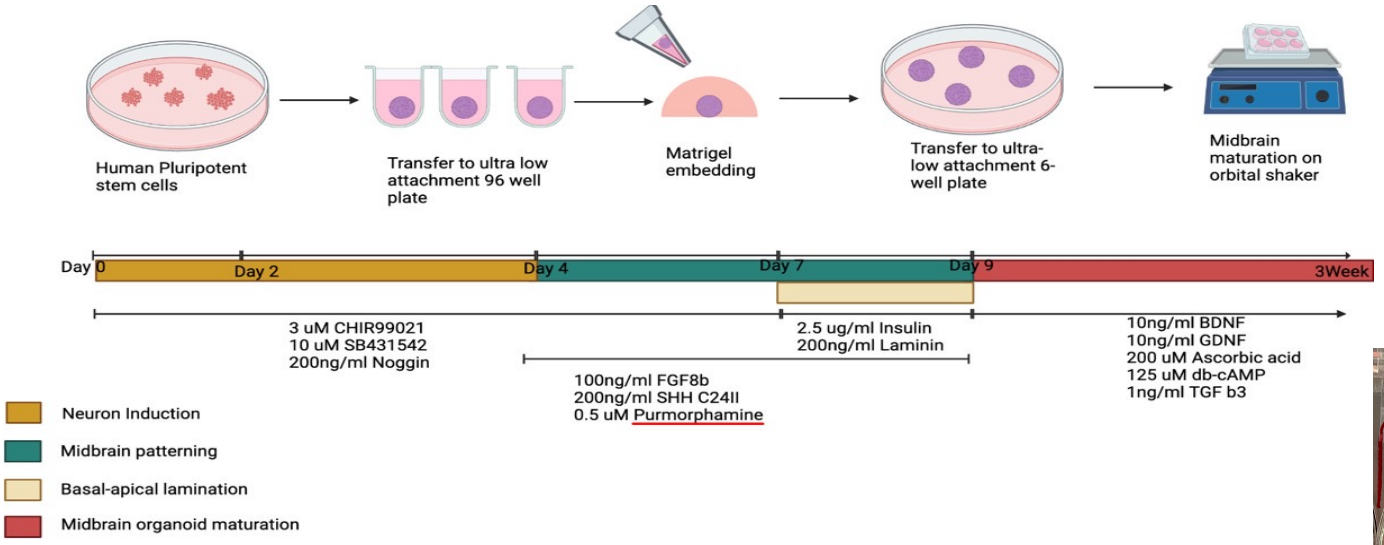
Il profilo dei recettori di superficie delle EVs e' differente e specifico nelle malattie neurodegenerative

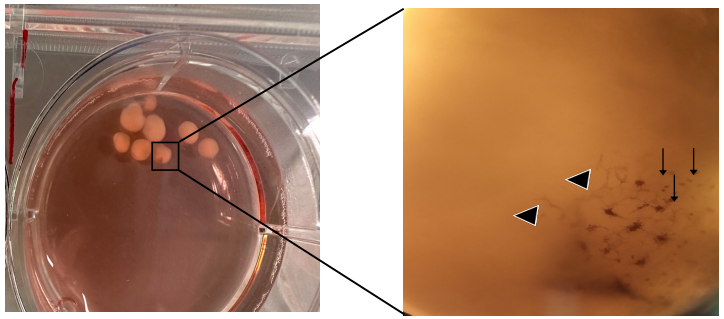


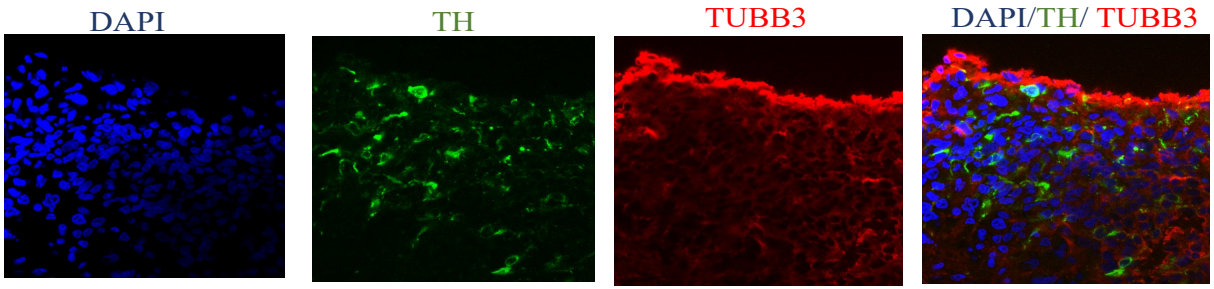


[Vacchi E. Neurol Neuroimmunol Neuroinflamm. 2020]

Generazione di organoidi cerebrali derivati da IPS umane per studiare la neuroinfiammazione nella malattia di Parkinson







Grazie

Lab for Neurodegenerative diseases (LRT-EOC)

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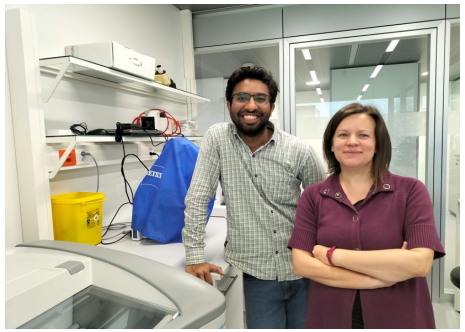
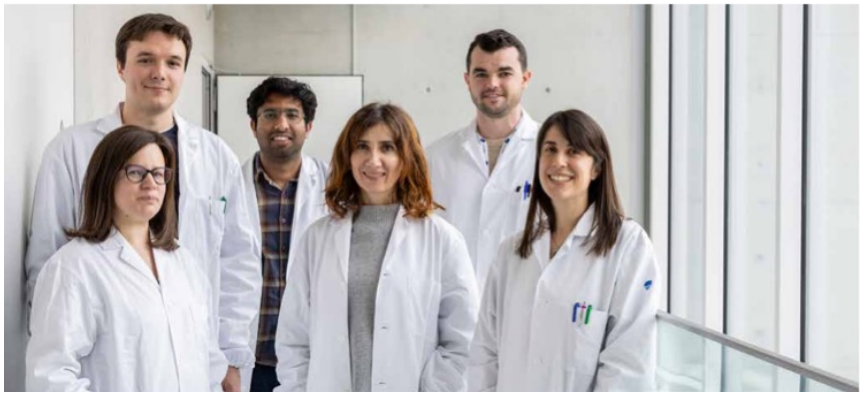
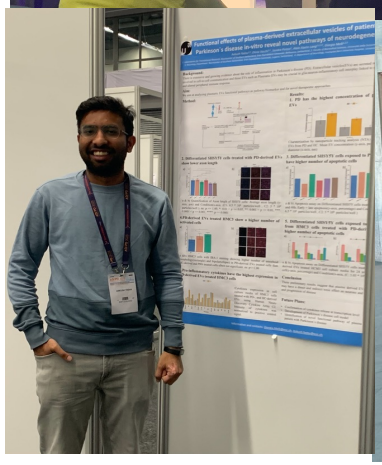
Rudolf Kaelin
Master student @USI

Paolo Barbaglia
Master Student

Nicole Vago &
Mara Kuster







Thanks to our Collaborators and Funders

Neurodegenerative Diseases Lab.
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Elena Vacchi, PostDoc
Ankush Yadav, Ph.D. Student
Sandra Pinton, Research Assistant
Paolo Barbaglia Master Student

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Salvatore Galati, Clinical Neurologist
Nicole Vago Caputo, Research Nurse
Mara Kuster, Research Nurse

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Stefano Panella, Research Assistant

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Alberto Romagnolo, Clinical Neurologist
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Inigo Ruiz Barrio, Clinical Neurologist
Javier Pagonabarraga, Clinical Neurologist
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Anna Müller, Project Menager
Schmidt Christian, Research Nurse

Bios+
Andrea Raimondi, PhD TEM
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David Jarrossay, Ph.D., FACS Facility

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Presentazione 2

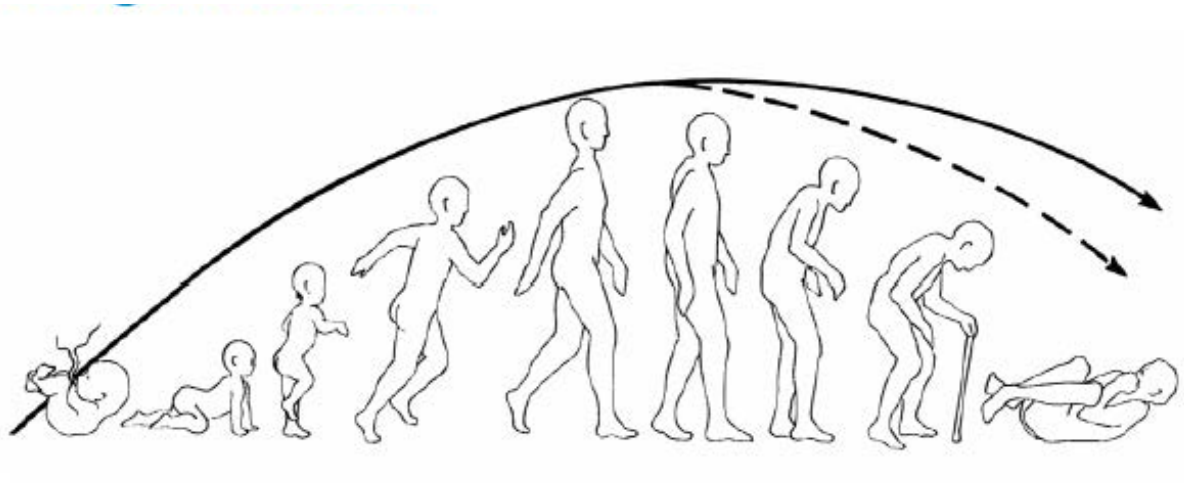
Ente Ospedaliero Cantonale

La ricerca scientifica traslazionale per le malattie neurodegenerative nella Svizzera italiana

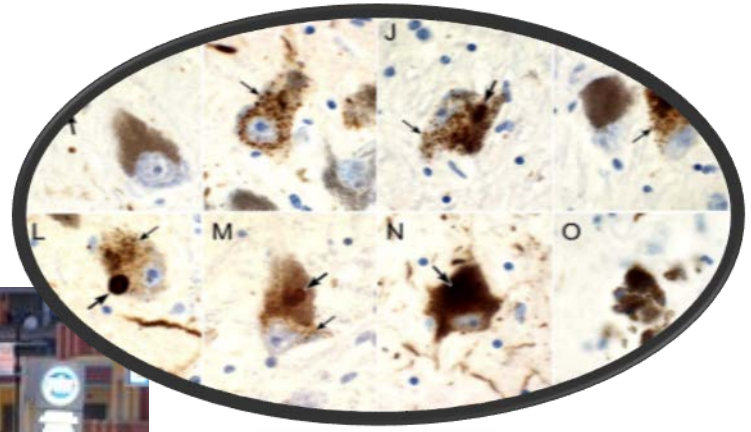
Direttore Medico e Scientifico Istituto di Neuroscienze Cliniche della Svizzera Italiana, Professore Ordinario USI

Lugano, 18.04.2024

Neurodegenerazione: perdita progressiva di neuroni

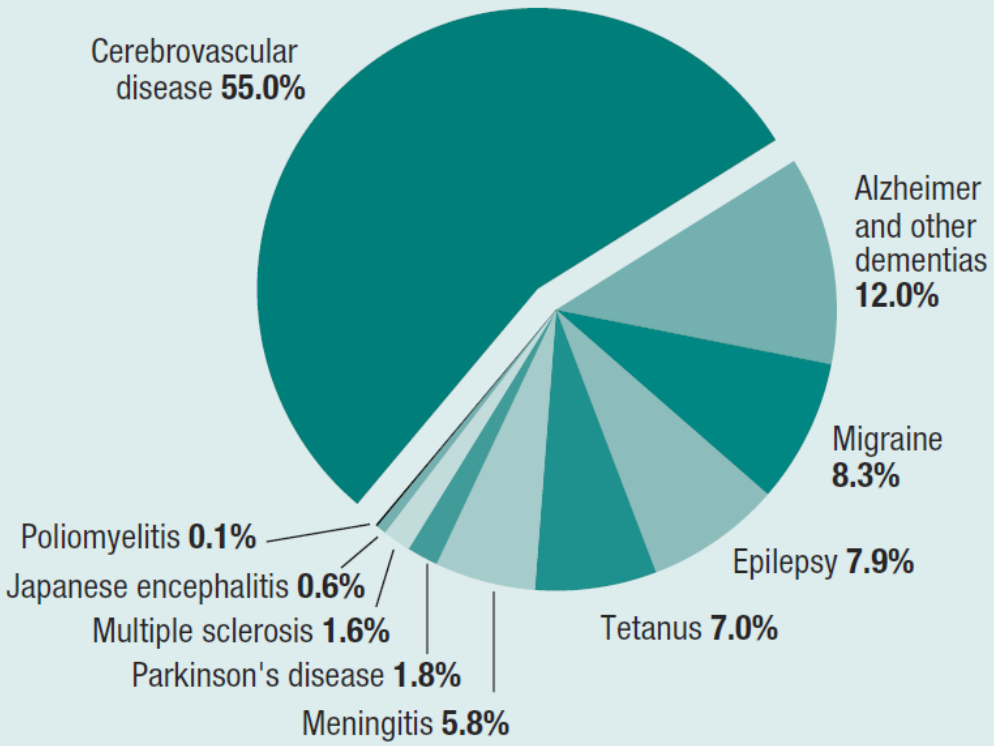


Proteine patologiche non eliminate si accumulano: *ma perché muoiono i neuroni?*



http://www.zollikofen.ch/de/images/4190686f0e864.jpg

Figure 2.2 DALYs for individual neurological disorders as percentage of total neurological disorders



(DALY: „disability adjusted life year“= disease burden; WHO 2012)

Figure 2.4 DALYs per 100 000 population associated with neurological disorders by WHO region and mortality stratum, 2005

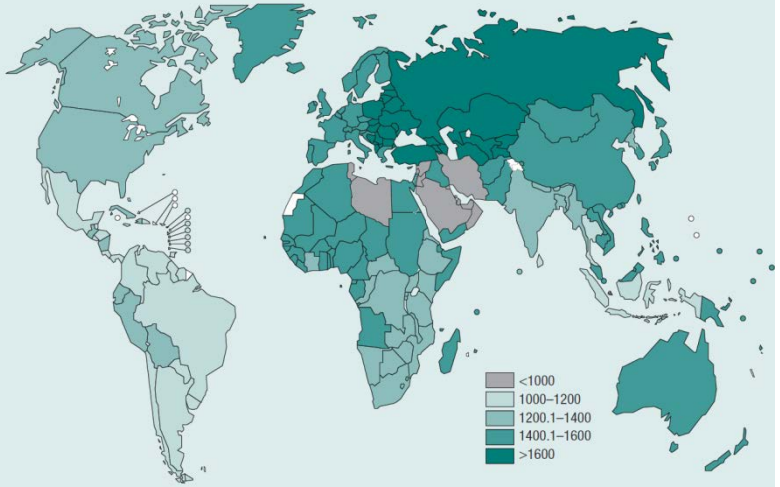
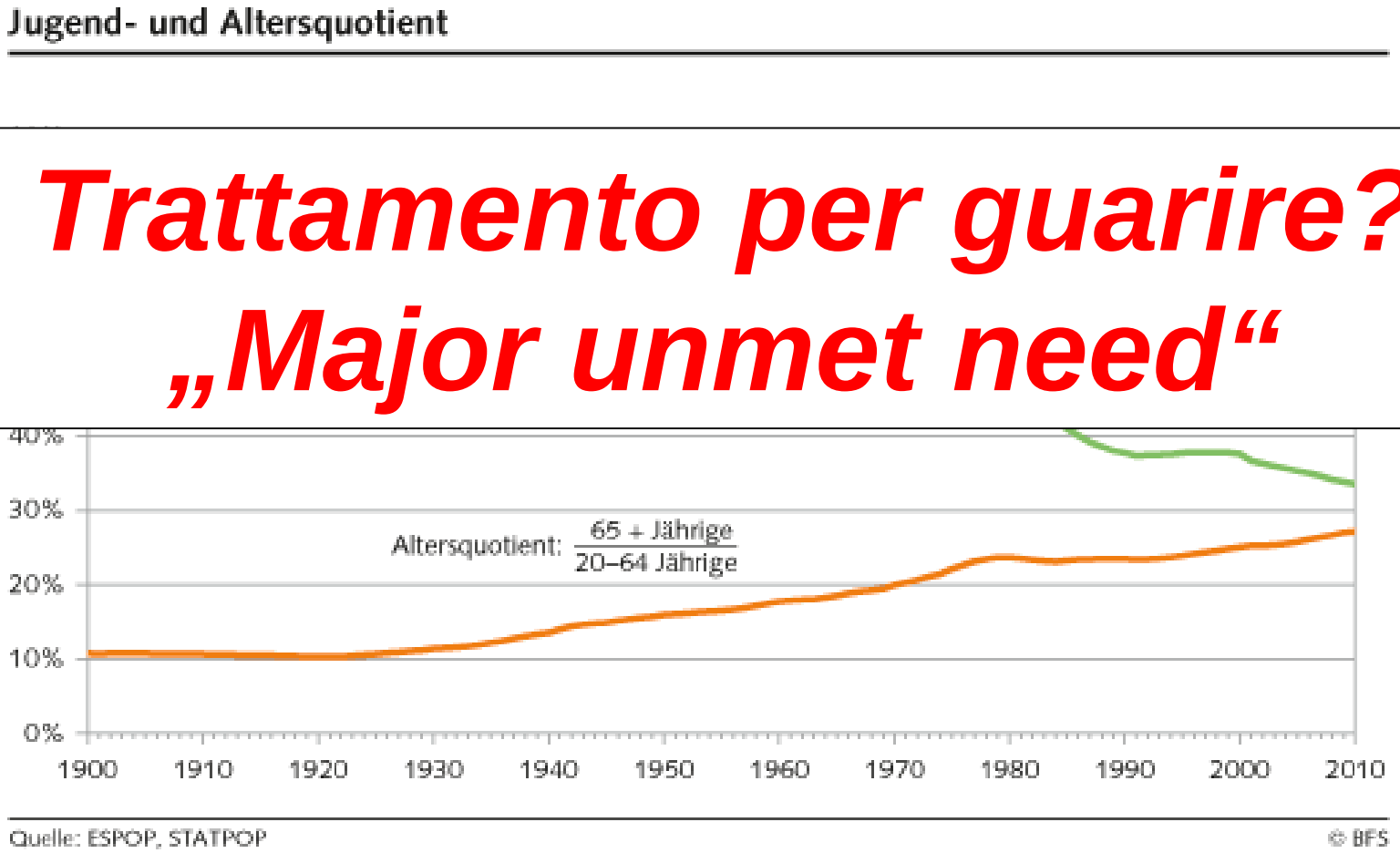


Table 2.6 Neurological disorders as percentage of total DALYs by WHO region, 2005

Cause category	World (%)	WHO region					
		AFR (%)	AMR (%)	SEAR (%)	EUR (%)	EMR (%)	WPR (%)
Epilepsy	0.50	0.46	0.73	0.46	0.40	0.54	0.44
Alzheimer and other dementias	0.75	0.10	1.47	0.26	2.04	0.42	1.32
Parkinson's disease	0.11	0.02	0.22	0.07	0.30	0.06	0.15
Multiple sclerosis	0.10	0.03	0.17	0.08	0.20	0.09	0.15
Migraine	0.52	0.13	0.97	0.41	0.80	0.51	0.73
Cerebrovascular disease	3.46	1.11	3.10	1.93	7.23	2.69	6.81
Poliomyelitis	0.01	0.00	0.00	0.01	0.00	0.01	0.01
Tetanus	0.44	0.77	0.01	0.81	0.00	0.54	0.10
Meningitis	0.36	0.24	0.39	0.81	0.24	0.43	0.24
Japanese encephalitis	0.04	0.00	0.00	0.05	0.00	0.06	0.09
Total	**6.29**	**2.86**	**7.06**	**4.90**	**11.23**	**5.34**	**10.04**

Sfida per la società

Malattia di Parkinson: 1% > 65 y, in aumento continuo

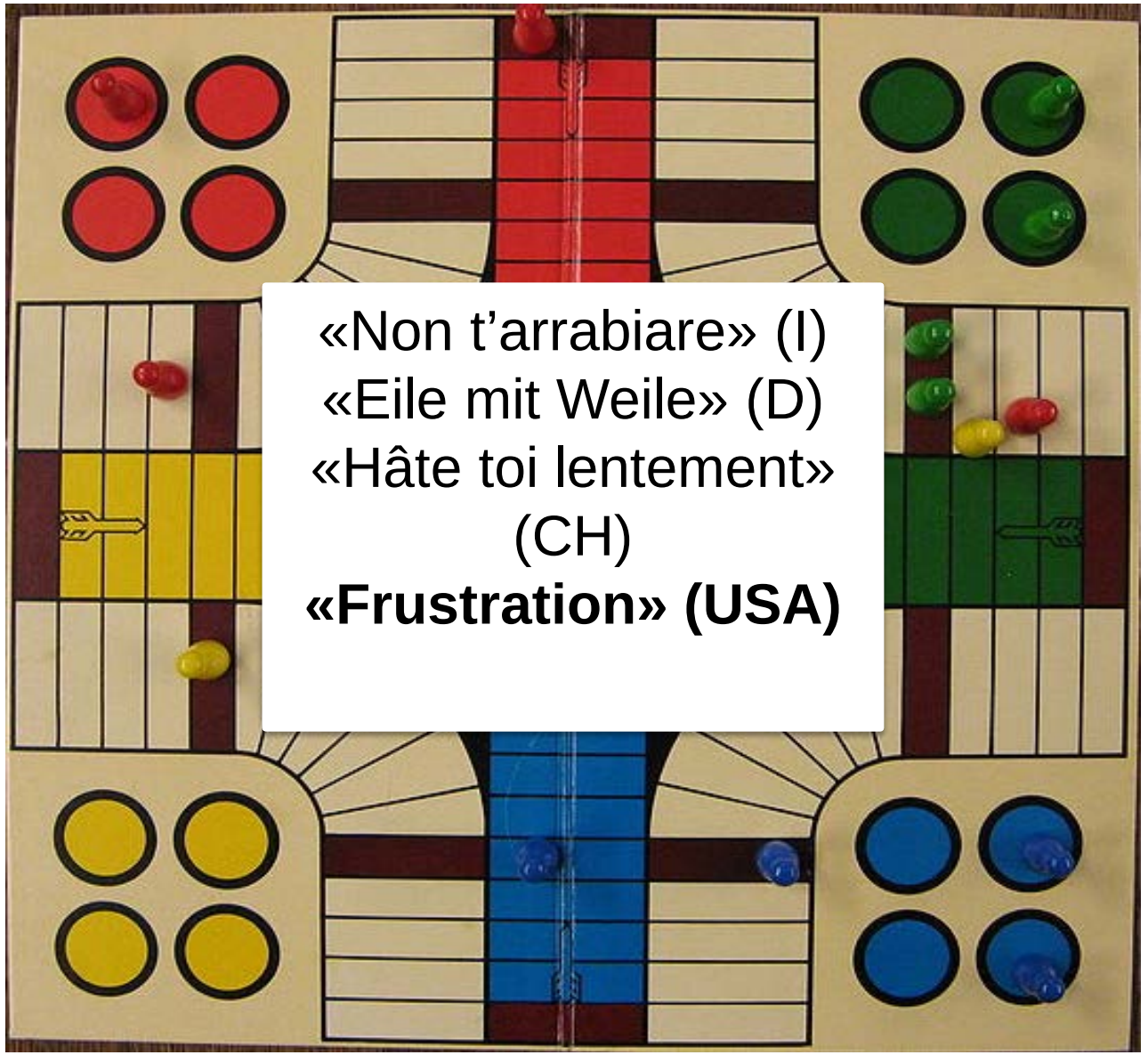


Trattamento per guarire?

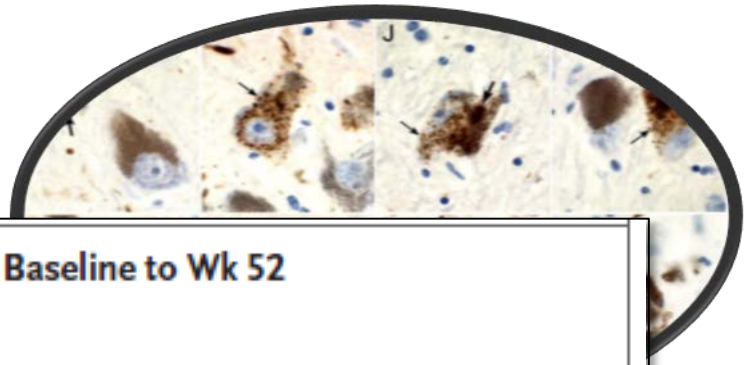
„Major unmet need“

(Ufficio federale della stat. 2012)

Ricerca? Difficile…



Nuovi sviluppi: Terapia con anticorpi?



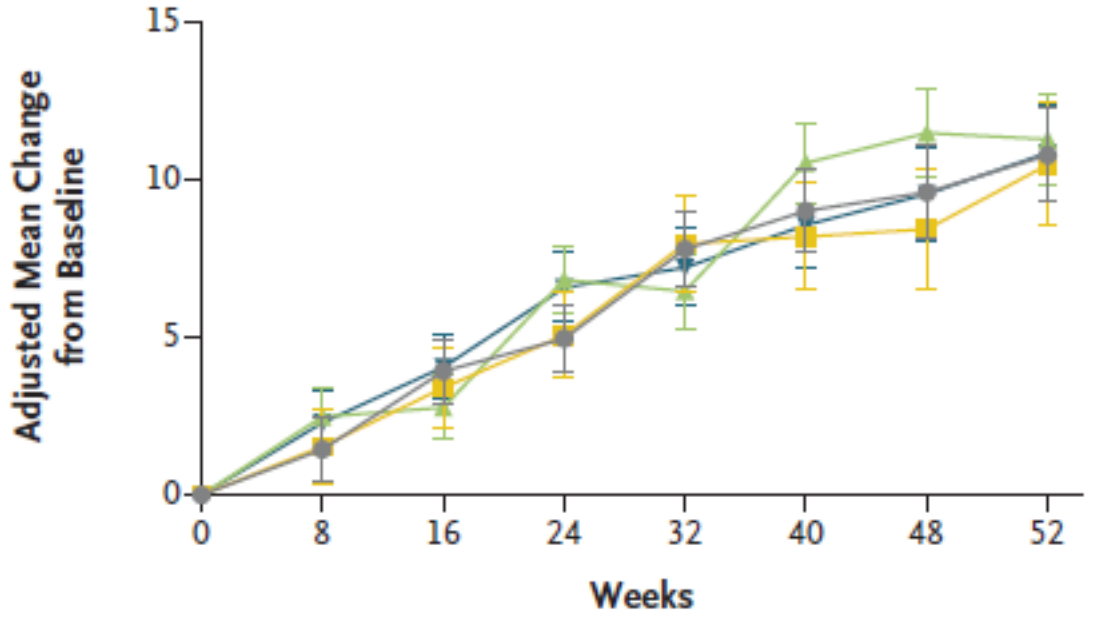
The NEW ENGLAND JOURNAL of M

ORIGINAL ARTICLE

Trial of Cinpanemab in Earl Disease

A.E. Lang, A.D. Siderowf, E.A. Macklin, W. Poewe, D.J
O. Rascol, N. Giladi, F. Stocchi, C.M. Tanner, R.B.
E. Tolosa, B. Mollenhauer, J.M. Cedarbaum, K. Fra
D.L. Graham, I. Sapir, J. Inra, R.M. Hutchison
S. Budd Haeberlein, and T. Dam, for the SPA

A Change in Total MDS-UPDRS Score from Baseline to Wk 52

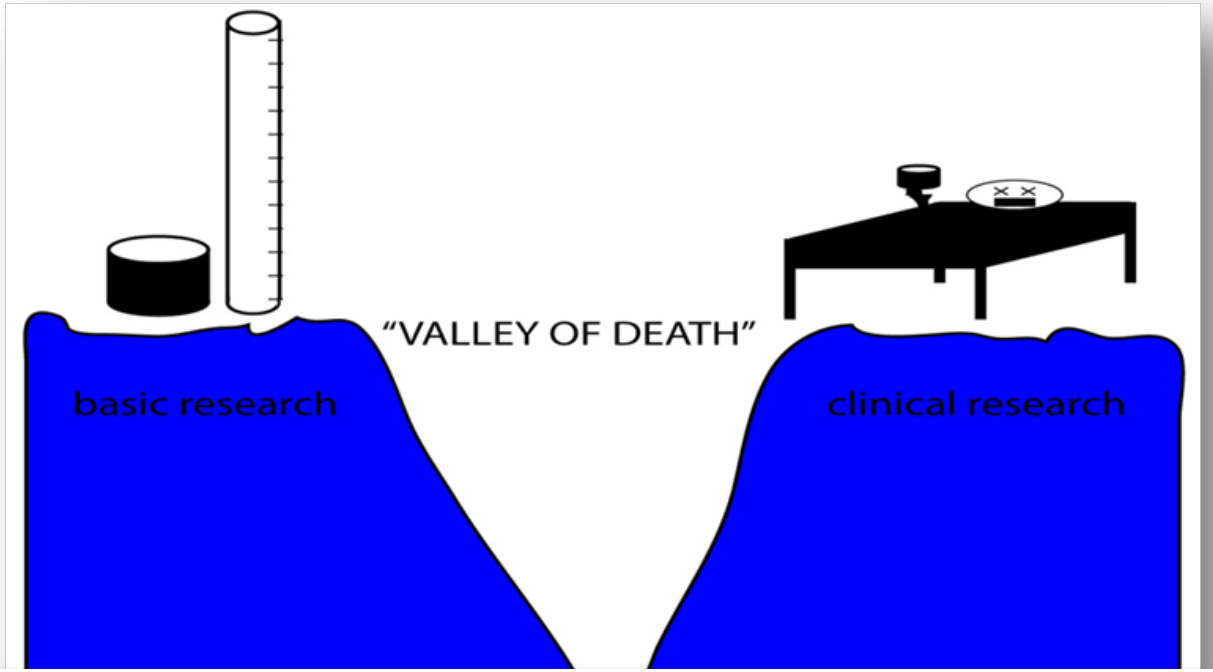


No. of Participants

Control	100	97	95	92	74	61	49	53
Cinpanemab, 250 mg	55	52	51	53	41	35	28	29
Cinpanemab, 1250 mg	102	98	96	95	69	64	51	57
Cinpanemab, 3500 mg	100	97	96	90	69	59	49	51

(NEJM 2022)

«La valle della morte» tra ricerca e cura



Esempio:

Parkinson's Disease Gene Therapy: Success by Design Meets Failure by Efficacy

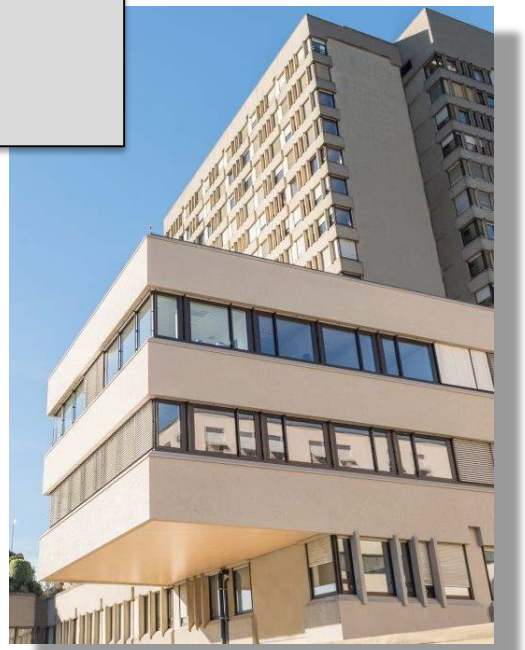
Raymond T Bartus[1,2], Marc S Weinberg[3] and R. Jude Samulski[3,4]

[1]Ceregene, Inc., San Diego, California, USA; [2]RTBioconsultants, Inc., San Diego, California, USA; [3]Gene Therapy Center, University of North Carolina, Chapel Hill, North Carolina, USA; [4]Department of Pharmacology, University of North Carolina, Chapel Hill, North Carolina, USA

Istituto di Neuroscienze Cliniche della Svizzera Italiana- «Neurocentro»

2009:

*«Il NSI permette di rispondere all'esigenza di **sinergia** fra le diverse specialità offrendo ai pazienti un approccio e un trattamento a**ll'avanguardia e sicuri** supportati da una **ricerca di punta»***



Perché far ricerca?

La ricerca non è un lusso ma una necessità

„Research enhances the vitality of teaching, teaching lifts the standards of service and service opens new avenues of investigation“

Jack Masur

(citazione sulla parete, Building 10, NIH, Bethesda, MD, USA)

https://www.biomed.usi.ch/en

Sinergia USI-EOC in Ticino

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La Facoltà di scienze biomediche: un nuovo indirizzo e "lievito" universitario

I primi professori della Facoltà: da sinistra, Luca

Servizio comunicazione e media
23/01/2017

Si è tenuta questa mattina nell'au
Facoltà di scienze biomediche de
l'innovazione Mauro Dell'Ambrog
illustrato nel dettaglio la struttura

Università della Svizzera italiana

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Presentato l'accordo di collaborazione USI-EOC per la ricerca in scienze biomediche

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Studiare medicina all'USI

La Facoltà di scienze biomediche dell'Università della Svizzera italiana

La Facoltà di scienze biomediche dell'USI è nata nel 2014 con l'obiettivo di contribuire alla soluzione di un importante problema nazionale: la penuria di medici formati in Svizzera. A questo scopo la Facoltà offre un Master in medicina umana. Inoltre la Facoltà offre anche programmi di dottorato, post-lauree e nell'ambito dell'imprenditoria biomedica.

Seit 2020 wird an der Tessiner Universität ein Masterstudiengang in Medizin angeboten.
Università della Svizzera italiana

Echo der Zeit > | Sendung vom 19.05.2023 >

Tessiner Medizinstudiengang ist gefragt

Der Schweiz fehlt es an Ärztinnen und Ärzten. Mit der Schaffung neuer Ausbildungsplätze versucht der Bund Gegensteuer zu geben. So auch im Tessin: Seit 2020 gibt es dort die Möglichkeit, ein Masterstudium in Medizin zu absolvieren. Der Studiengang lockt mit grosser Praxisnähe.

Come organizzare la ricerca?

Modello Neurocentro:

- Ricerca traslazionale di qualità
- Priorità e focus chiari
- Sinergia EOC-USI
- Sinergia clinica-lab
  (p.es.: biobanca pazienti con PD la più grande della CH dopo pochi anni)

Gruppi di ricerca nelle malattie neurodegenerative:

- Prof. Giorgia Melli: Ricerca traslazionale sulla Malattia di Parkinson; «groupe leader» nei Laboratori a Bellinzona

- PD Dr. Leonardo Sacco: ricerca clinica sulle demenze

- PD Dr. Salvatore Galati: ricerca clinica e traslazionale sulla malattia di parkinson e il sonno

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Centro di eccellenza della Svizzera italiana per le malattie neurodegenerative

Forma-zione

Ricerca Clinica

Ricerca Spe-rimentale

RICERCA DEMENZE
FONDAZIONE SYNAPSIS SVIZZERA

La cura e i bisogni del paziente definiscono le priorità

Grazie

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FONDAZIONE SYNAPSIS SVIZZERA

Presentazione 3

Università
della
Svizzera
italiana

Facoltà
di
scienze
biomediche

Stato attuale della ricerca sulle demenze

PD Dr. Med. Leonardo Sacco

Head of the Memory Clinic and Neuropsycological and Speech therapy Unit

Neurocenter of Southern Switzerland EOC

Domains of cognition

Cognition is not a unitary construct; it consists of a number of domains [1]

Complex attention	Sustained attention, divided attention, selective attention, processing speed, learning
Executive functions	Planning, decision-making, working memory, responding to feedback, inhibition, flexibility
Learning & memory	Free recall, cued recall, recognition memory, semantic and autobiographical long-term memory, implicit learning, language
Language	Object naming, word finding, fluency, grammar and syntax, receptive language
Perceptual-motor	Visual perception, visuoconstructional reasoning, perceptual–motor coordination
Social cognition	Recognition of emotions, theory of mind, insight

1. Sachdev PA et al., Classifying neurocognitive disorders: the DSM-5 approach, Nat. Rev. Neurol. 10, 634–642 (2014)

Domains of cognition, social cognition

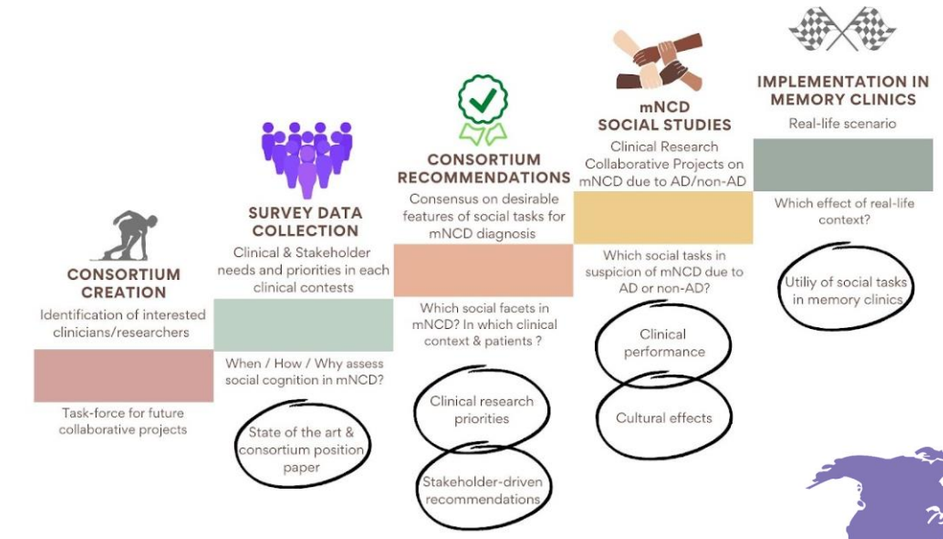
Beaudoin C, Beauchamp MH. Social cognition. Handb Clin Neurol. 2020;173:255-264

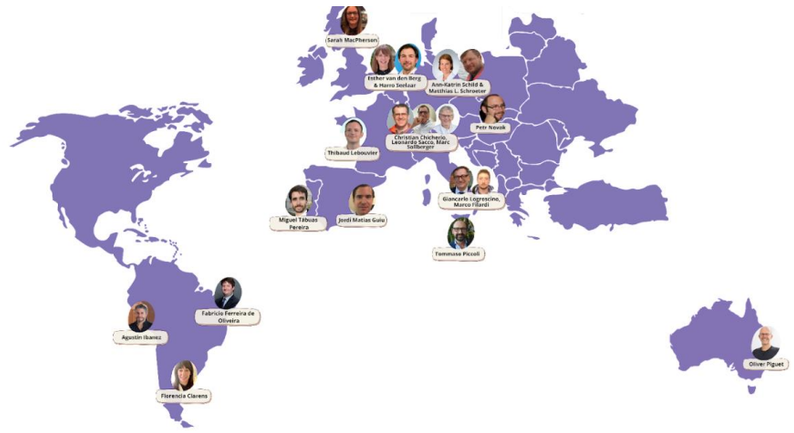
Facoltà di scienze biomediche

Social Cognition Measures For mild Neurocognitive Disorder

Social Cognition Measures

- Ekman 60 Faces Test [1-3]
- Mini-SEA Mini Socio-Emotional Assessment Battery [4-5]
- Faux-pas Test [6]
- Story-Based Empathy Task (SET) [7-8]
- TOM-15 False Belief Task [9]
- Reading the Mind in the Eyes Test (RMET) [10-12]
- Happe's Strange Stories [13]
- NEPSY II Affects Recognition and Theory of Mind [14-15]
- The Awareness of Social Inference Test (TASIT) [16-17]
- Sally-Anne Test [18]
- Edinburgh Social Cognition Test (ESCOT) [19-20]
- Florida Affect Battery [21]
- Interpersonal Reactivity Index (IRI) [22-23]
- Self-Monitoring Scale (SMS - RSMS) [24-25]
- FACE test [26]





Boccardi M, Monsch AU, Ferrari C, Altomare D, Berres M, Bos I, Buchmann A, Cerami C, Didic M, Festari C, Nicolosi V, Sacco L, Aerts L, Albanese E, Annoni JM, Ballhausen N, Chicherio C, Démonet JF, Descloux V, Diener S, Ferreira D, Georges J, Gietl A, Girtler N, Kilimann I, Klöppel S, Kustyniuk N, Mecocci P, Mella N, Pigliautile M, Seeher K, Shirk SD, Toraldo A, Brioschi-Guevara A, Chan KCG, Crane PK, Dodich A, Grazia A, Kochan NA, de Oliveira FF, Nobili F, Kukull W, Peters O, Ramakers I, Sachdev PS, Teipel S, Visser PJ, Wagner M, Weintraub S, Westman E, Froelich L, Brodaty H, Dubois B, Cappa SF, Salmon D, Winblad B, Frisoni GB, Kliegel M; Consortium for the Harmonization of Neuropsychological Assessment for Neurocognitive Disorders (https://nextcloud.dzne.de/index.php/s/EwXjLab9caQTbQe). Harmonizing neuropsychological assessment for mild neurocognitive disorders in Europe. Alzheimers Dement. 2022 Jan;18(1):29-42. doi: 10.1002/alz.12365. Epub 2021 May 13. PMID: 33984176; PMCID: PMC9642857.

Dodich A, Boccardi M, Sacco L, Monsch AU, Démonet JF, Filardi M, Logroscino G, Salmon DP, Weinbtraub S, Dubois B, Cappa SF, Cerami C; Consortium for the Harmonization of Neuropsychological Assessment for Neurocognitive Disorders. Answer to "Social cognition assessment for mild neurocognitive disorders". Alzheimers Dement. 2022 Jul;18(7):1441-1442. doi: 10.1002/alz.12664. Epub 2022 Apr 8. PMID: 35394112

Basit ER Italian Version

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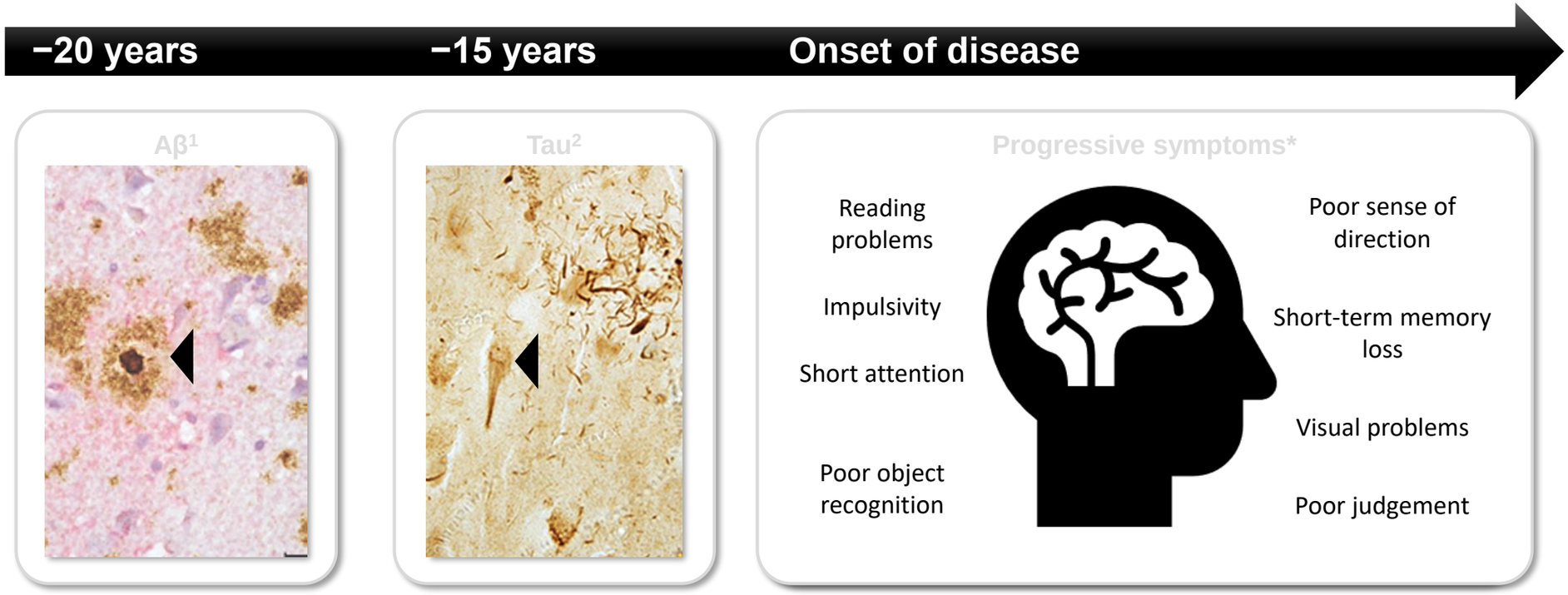
The Alzheimer’s disease (AD) continuum

Cognitively normal	Preclinical-Subjective cognitive decline	Minor cognitive disorder: Mild cognitive impairment (MCI)	Major cognitive disorder : Mild-to-moderate AD dementia	Major cognitive disorder: Severe AD dementia

As the underlying neurodegenerative disease progresses, with greater destruction of brain tissue, an individual will progress from cognitively normal to MCI and then to dementia[4]

1. Dubois B, et al., Timely Diagnosis for Alzheimer's Disease: A Literature Review on Benefits and Challenges. J Alzheimers Dis 2016;49:617–631; 2. Aisen PS, et al., On the path to 2025: understanding the Alzheimer's disease continuum. Alzheimers Res Ther 2017;9:60; 3. Dixon RA et al., Cognitively elite, cognitively normal, and cognitively impaired ageing. J Clin Exp Neuropsychol 2014;36(4):418–430; 4. University of California San Francisco. Available from https://memory.ucsf.edu/dementia-overview (Accessed February 11 2019); 5. Kazim SF, Iqbal K., Neurotrophic factor small-molecule mimetics mediated neuroregeneration and synaptic repair: an emerging therapeutic modality for Alzheimer's disease. Mol Neurodegener 2016;11:50; 6. Jack CR Jr, et al., Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:257-262; 7. Roberts R, Knopman DS., Classification and epidemiology of MCI. Clin Geriatr Med 2013;29:753–772

Alzheimer's disease pathology is thought to begin 15–20 years before clinical presentation



- AD pathologic changes in the brain start 15–20 years before the development of symptoms[3,4]
- AD is now considered a continuum, consisting of a preclinical stage and progressing to AD dementia[3]
- Disease-modifying therapies aiming to interfere with the underlying pathophysiologic mechanisms of the disease process that lead to cell death may need to be initiated early in the course of disease[4]

1. Mathur R, et al., A reduced astrocyte response to β-amyloid plaques in the ageing brain associates with cognitive impairment. PLoS One 2015;10:e0118463;
2. Day RJ, et al., Caspase-Cleaved Tau Co-Localizes with Early Tangle Markers in the Human Vascular Dementia Brain. PLoS One 2015;10:e0132637;
3. Jack CR, et al., NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535–562;
4. Bateman RJ, et al., Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795–804;

Definition of Subjective Cognitive Decline

Subjective cognitive decline (SCD) refers to a perceived decline in cognitive ability in the absence of objective findings (Jessen et al., 2014, 2020).

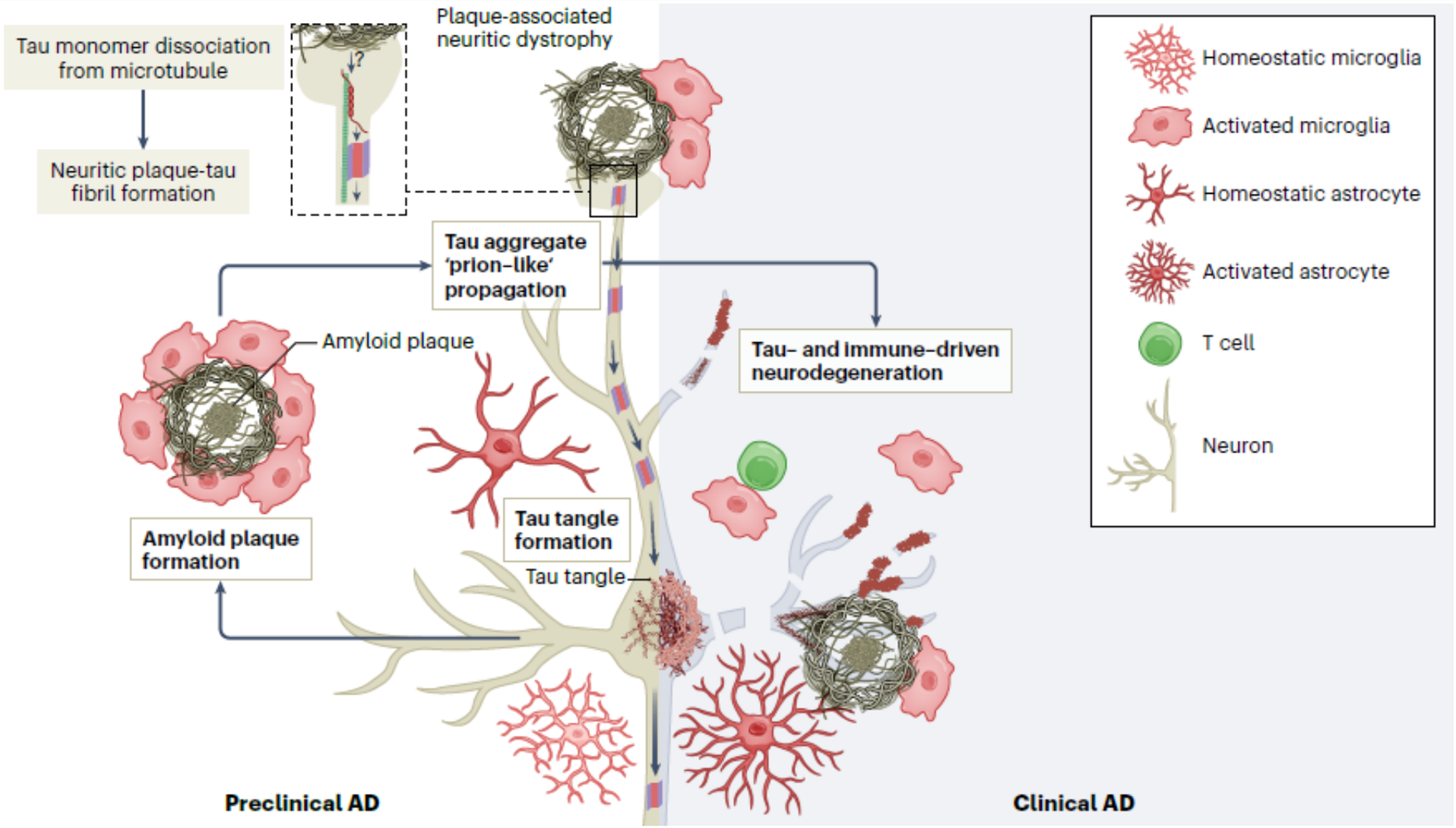
1st criteria

Self-experienced persistent decline in cognitive capacity, compared with a previously normal cognitive status, which is unrelated to an acute event.

2nd criteria

An objective unaltered cognition obtained by normal performances on standardized cognitive tests.

Pathogenesis of Alzheimer's disease



Self WK, Holtzman DM. Emerging diagnostics and therapeutics for Alzheimer disease. Nat Med. 2023 Sep;29(9):2187-2199. doi: 10.1038/s41591-023-02505-2. Epub 2023 Sep 4. PMID: 37667136.

Considerations around tau propagation: extracellular tau

The increased presence of tau in the extracellular space, CSF, and interstitial fluid in AD has long been thought to be a result of secretion from dying cells[1]

However, it has recently been shown that **functional neurons secrete tau** through a number of pathways in both physiological and pathological conditions[1]

Increasing evidence implies that extracellular tau has a role in the **propagation of tau** pathology[1,2]

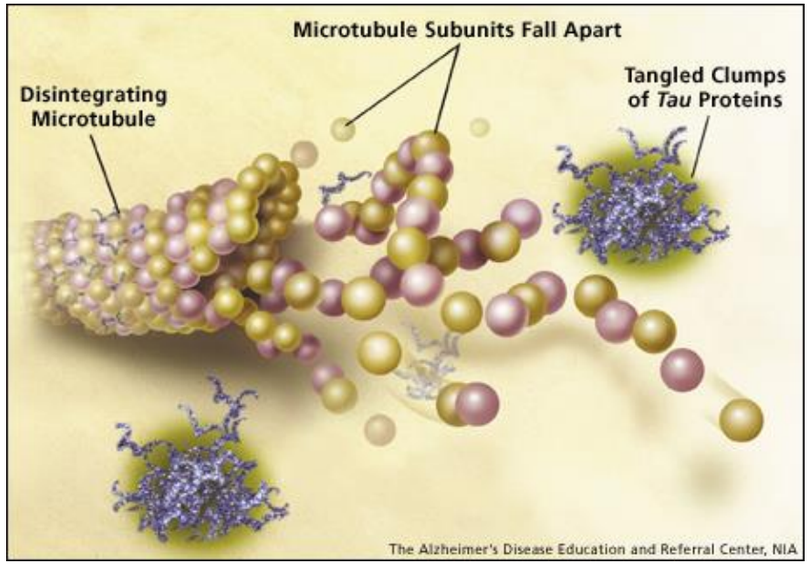
Extracellular tau is also believed to contribute to **loss of synaptic function and has neurotoxic effects**[3]

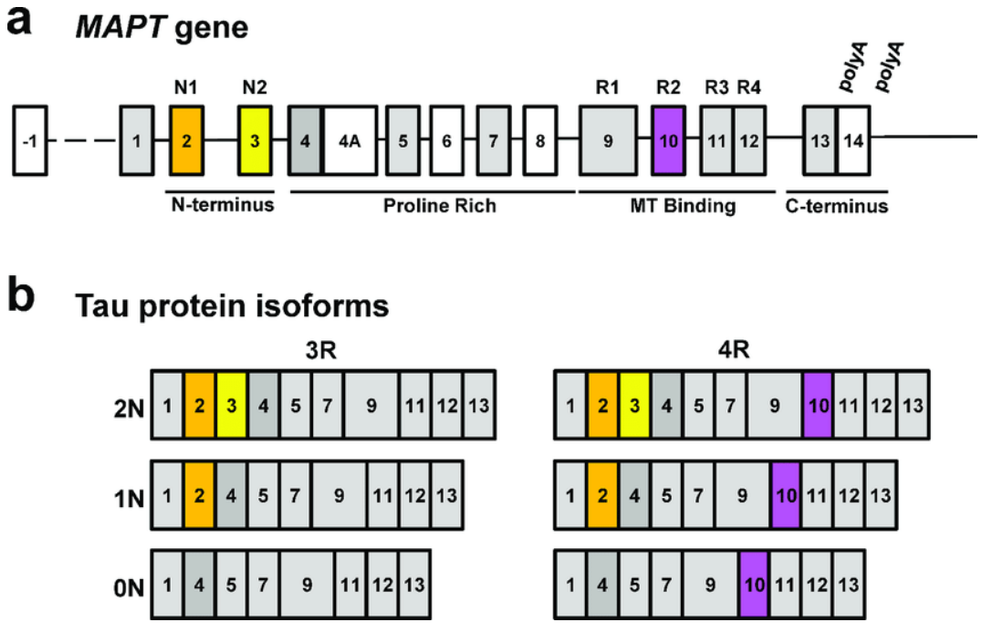
New therapeutic approaches are targeting extracellular tau in attempts to prevent tau propagation, including immunotherapy[3]

Medina M, Avila J., The role of extracellular Tau in the spreading of neurofibrillary pathology. Front Cell Neurosci 2014;8:113; 2. Yamada K., Extracellular Tau and Its Potential Role in the Propagation of Tau Pathology. Front Neurosci 2017;11:667; 3. Sebastián-Serrano A, et al.
The Neurotoxic Role of Extracellular Tau Protein. Int J Mol Sci 2018;19:998

Ongoing Phase 2 clinical trials-Anti Tau therapy

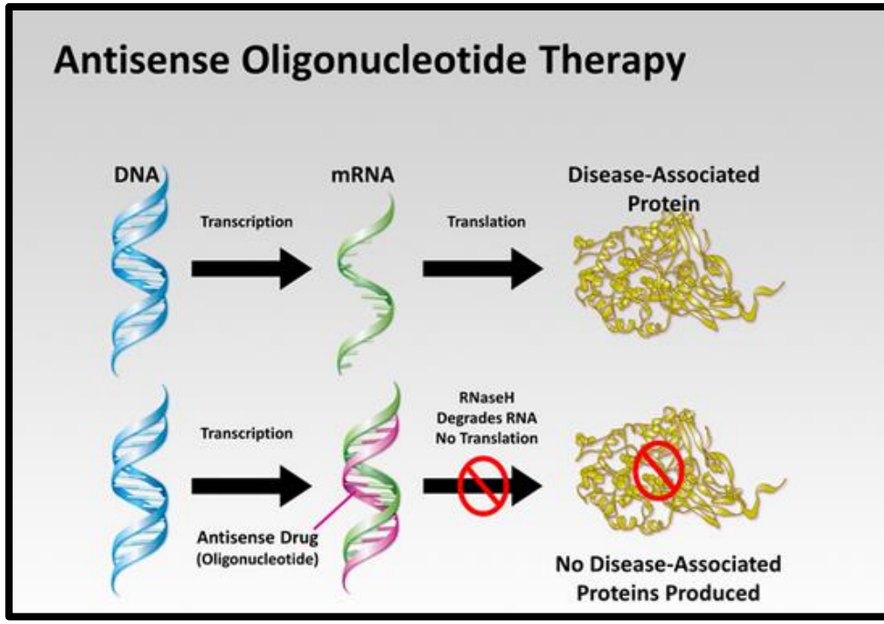
- Tau is considered to be a key secondary effector of the disease process in AD. In AD, the highly soluble, natively unfolded tau protein forms intracellular fibrillar structures of aggregated, abnormally modified tau that results in a toxic-gain-of-function associated with synaptic and neuronal loss.
- There is a critical role for tau in contributing to Aβ-linked neurotoxicity. Based upon the close links between tau pathology, neurodegeneration, and clinical features consistent with AD, coupled with the evidence that tau pathology can spread via neuronal release and uptake of pathological tau species, decreasing tau protein synthesis is expected to effectively address this disease mechanism.





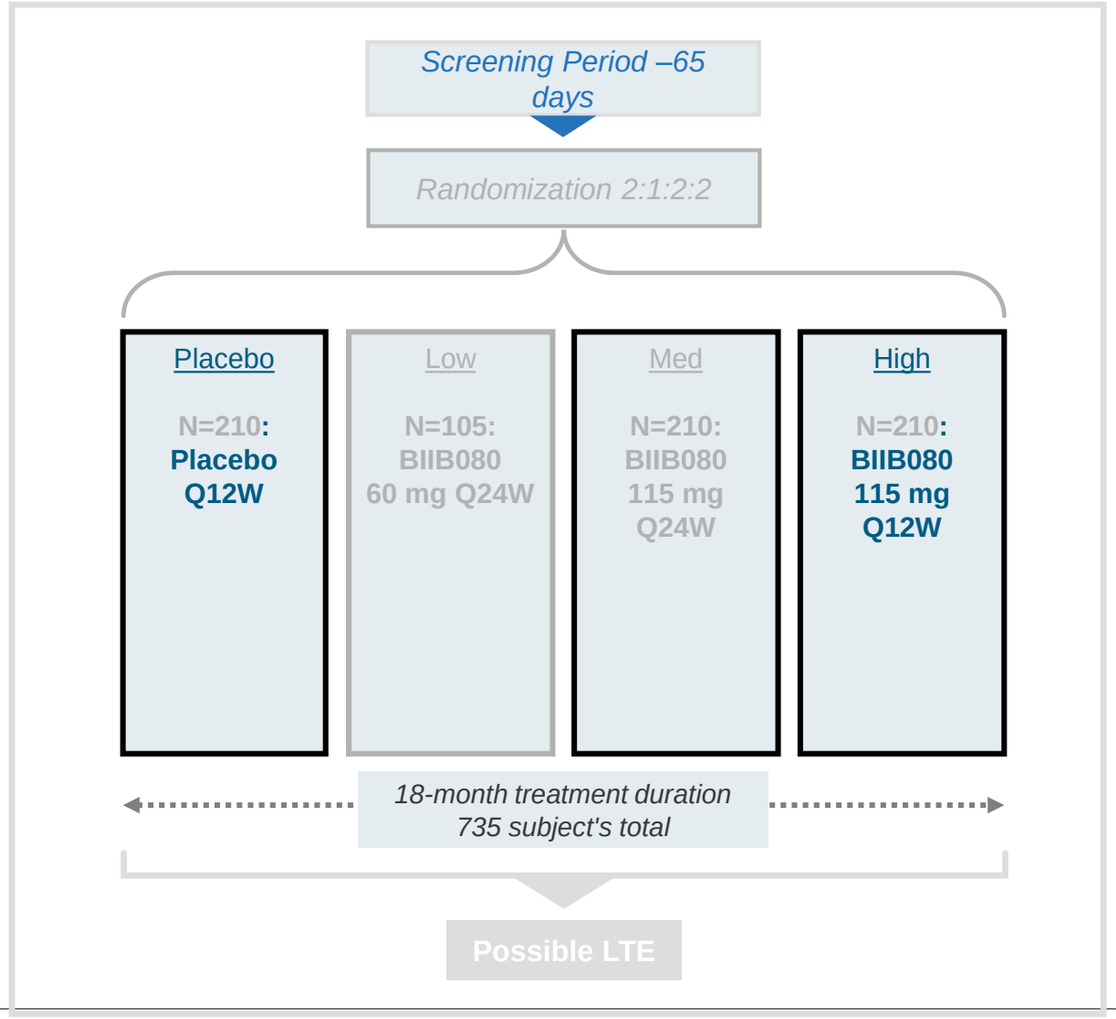
BIIB080

- BIIB080 is an 18-nucleotide chimeric 2'-MOE/DNA modified ASO that selectively reduces MAPT mRNA.
- BIIB080 is designed to bind to MAPT pre-mRNA and prevent translation of tau protein by promoting the degradation of the MAPT-encoded RNA
- BIIB080 has previously been evaluated in ISIS 814907-CS1, a Phase 1, placebo-controlled, double-blind MAD clinical trial with a 12-week treatment period and 24-week follow-up period followed by an open-label LTE period composed of a 48-week treatment period with 16-week follow-up (23-week follow-up period in the UK).
- BIIB080 has been generally well tolerated.
- Mouse models showed that MAPT mRNA reduction may reverse neurofibrillary tangle pathology and extend survival



- Mummery CJ, Börjesson-Hanson A, Blackburn DJ, Vijverberg EGB, De Deyn PP, Ducharme S, Jonsson M, Schneider A, Rinne JO, Ludolph AC, Bodenschatz R, Kordasiewicz H, Swayze EE, Fitzsimmons B, Mignon L, Moore KM, Yun C, Baumann T, Li D, Norris DA, Crean R, Graham DL, Huang E, Ratti E, Bennett CF, Junge C, Lane RM. Tau-targeting antisense oligonucleotide $MAPT_{Rx}$ in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. Nat Med. 2023 Jun;29(6):1437-1447. doi: 10.1038/s41591-023-02326-3. Epub 2023 Apr 24. Erratum in: Nat Med. 2024 Jan;30(1):304. PMID: 37095250; PMCID: PMC10287562

Study Overview



POPULATION

- Age 50–80 years
- MCI (40-50%); Mild AD (50-60%)
- CDR Global Score: 0.5-1
- MMSE score 22–30
- Objective cognitive impairment
- Evidence of amyloid pathology (PET or CSF)

ENDPOINTS

Primary:

- CDR-SB (every 6 months, Q6M)

Secondary (Q6M):

- Safety & tolerability
- ADCS-ADL-MCI
- ADAS-Cog13
- MMSE
- ADCOMS
- Modified iADRS

Exploratory Endpoints

Sub Studies

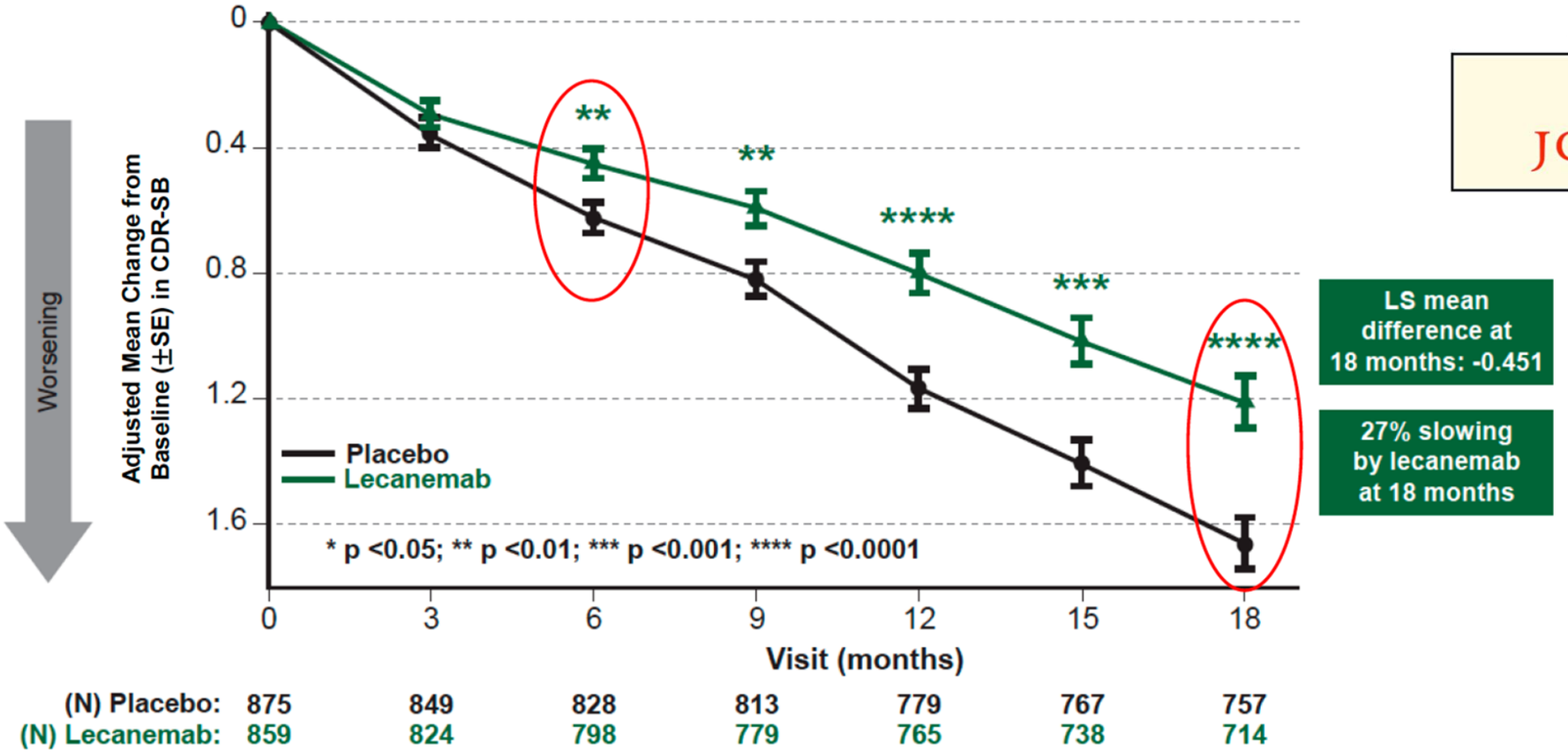
Tau PET Sub Study

- ~400 subjects, mandatory at sites with capability

MET-ID Sub Study

- , 8 US sites, 21 subjects only

Disease modifying therapy for Alzheimer's disease



LS mean difference at 18 months: -0.451

27% slowing by lecanemab at 18 months

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Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

Anti amyloid Therapy

Monoclonal antibody (RCT)	Trial endpoint (weeks)	Number of trial participants	Amyloid negative in treatment group at end (%)[a]	Dose	Cognitive benefit compared to placebo	ARIA-E (% treatment greater than placebo)	ARIA-H (% treatment greater than placebo)	Aβ target
Solanezumab (Expedition 1,2)[69]	80	2,052	-	400 mg	No	0.5	−0.7	Soluble monomer
Crenezumab (CREAD 1,2)[70]	102	1,619	-	60 mg/kg	No	0.1	0.5	Soluble oligomers
Gantenerumab (Graduate 1,2)[134]	116	1,965	27	1,020 mg	No	-	-	Insoluble fibrils
Aducanamab (EMERGE)[64]	78	1,638	48	10 mg/kg[b]	Yes	33.0	13.0	Insoluble fibrils
Aducanamab (ENGAGE)[64]	78	1,647	31	10 mg/kg[b]	No	33.0	13.0	Insoluble fibrils
Donanemab (TRAILBLAZER-ALZ 2)[4]	76	1,736	76	700 mg first 3 doses, 1,400 mg	Yes	21.9	17.8	Plaque-associated Aβ
Lecanemab (Clarity AD)[3]	78	1,734	81	10 mg/kg	Yes	10.9	6.3	Protofibrils

Self WK, Holtzman DM. Emerging diagnostics and therapeutics for Alzheimer disease. Nat Med. 2023 Sep;29(9):2187-2199. doi: 10.1038/s41591-023-02505-2. Epub 2023 Sep 4. PMID: 37667136.

Summary of established and emerging fluid biomarkers

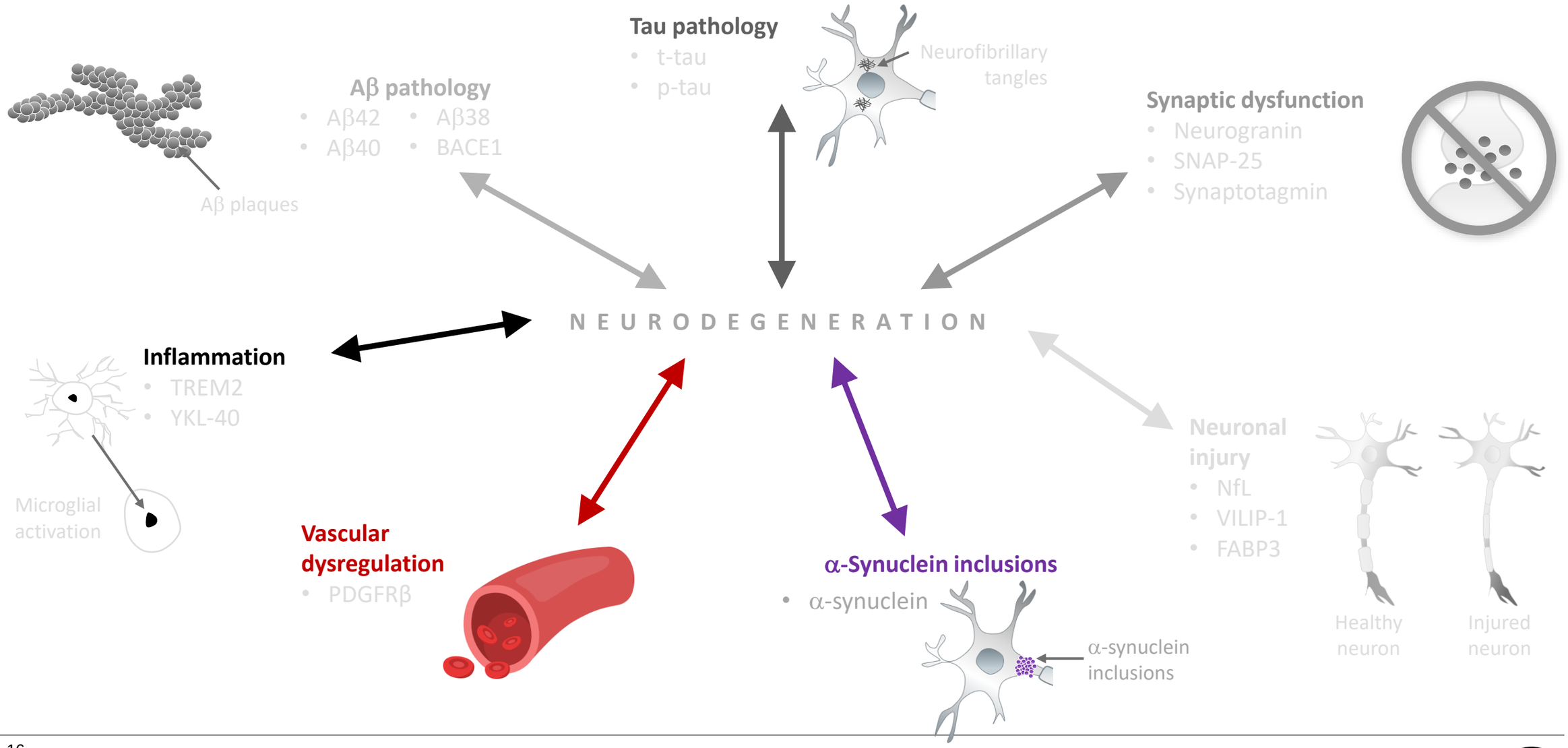

Image modified from Molinuevo JL et al., Current state of Alzheimer's fluid biomarkers. Acta Neuropathol 2018;136:821–853

Thank you for your attention