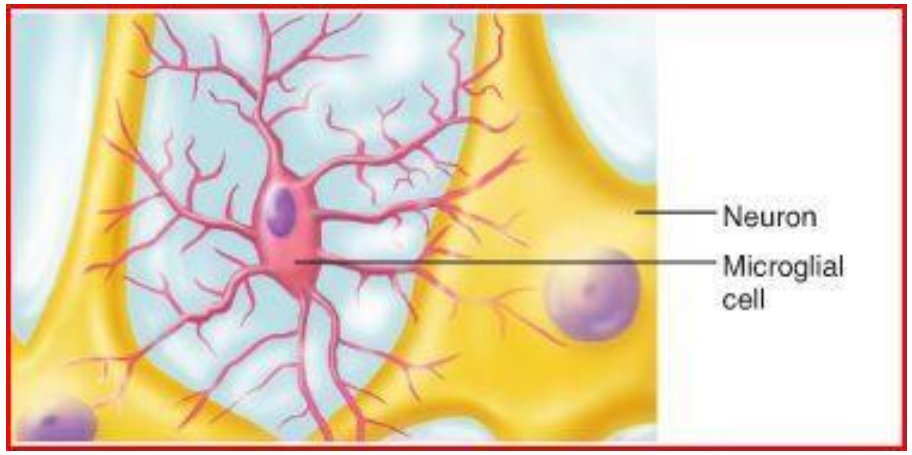
Inflammation, Immunity & Neurodegeneration

Elisa Conti
University of Milano-Bicocca
School of Medicine & Milan Center for Neuroscience (NeuroMI)

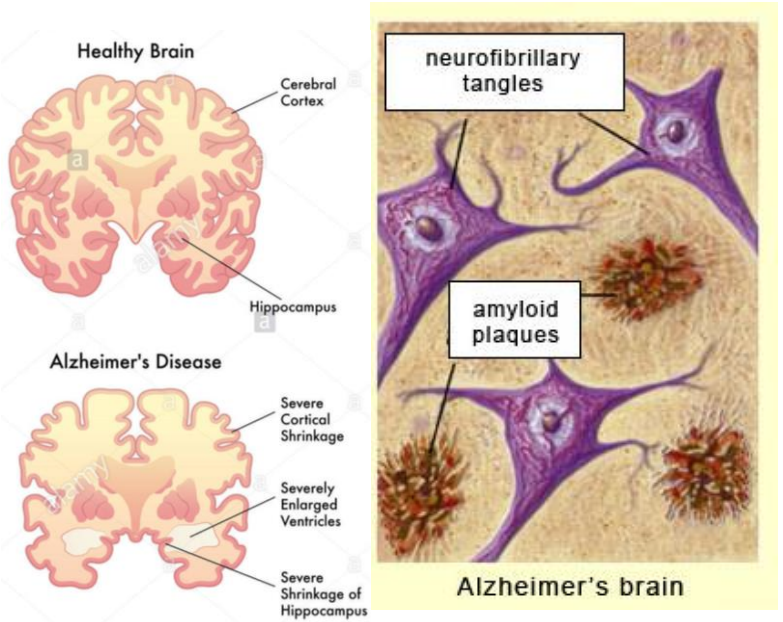
Dr. Alois Alzheimer

The presence of **"activated" microglia** were first described in the AD brain by Alois Alzheimer himself in his original report on **Auguste D. in 1907**. Alzheimer reported the presence of **"gliose" associated with the plaques and tangles**, which are the pathological hallmarks of AD



MICROGLIA

- Represents about 5-20% of glial cells
- Both at cerebral and spinal level



Two important functions:

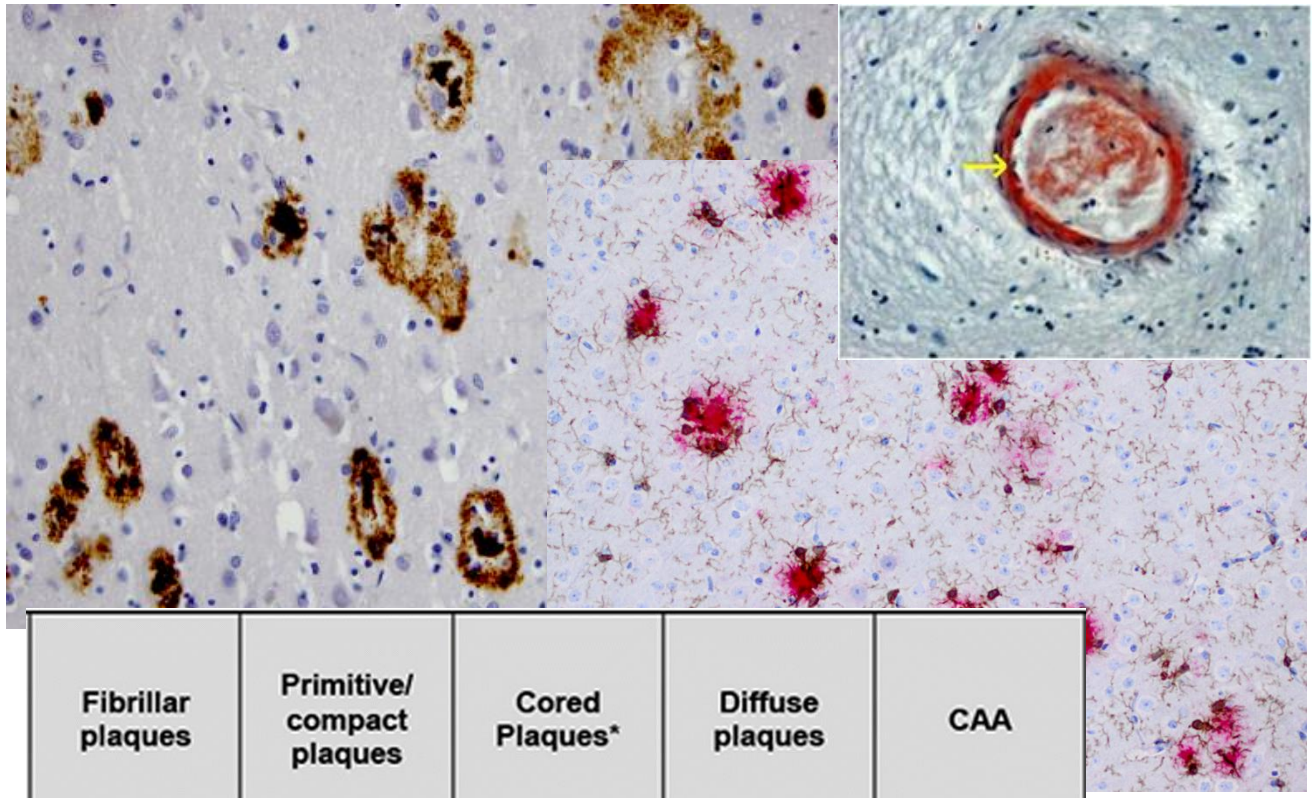
IMMUNE DEFENCE

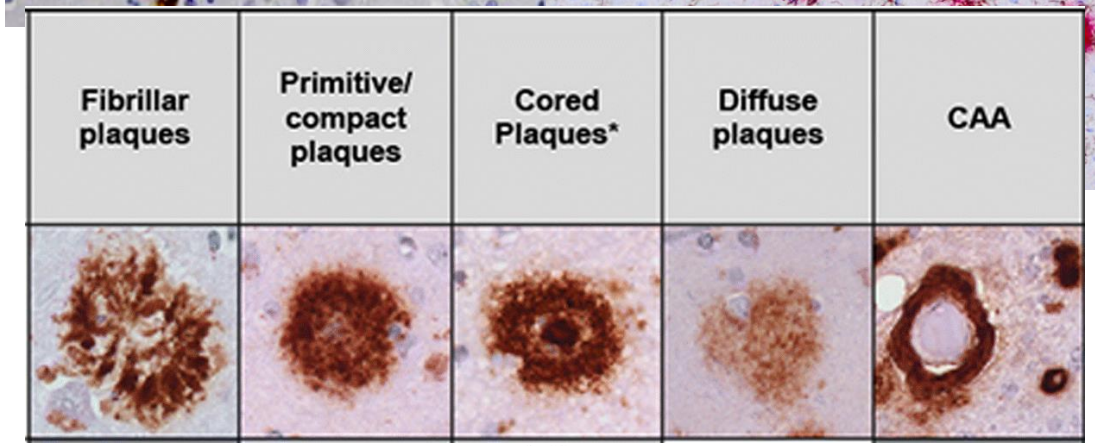
- Phagocytosis
- Cytotoxicity

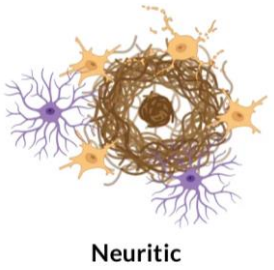
CNS HOMEOSTASIS MAINTENANCE

Plaque progression

Rozemuller JM, Eikelenboom P, Stam FC, Beyreuther K, Masters CL (1989) A4 protein in Alzheimer's disease: primary and secondary cellular events in extracellular amyloid deposition. *J Neuropathol Exp Neurol* **48**, 674-91.







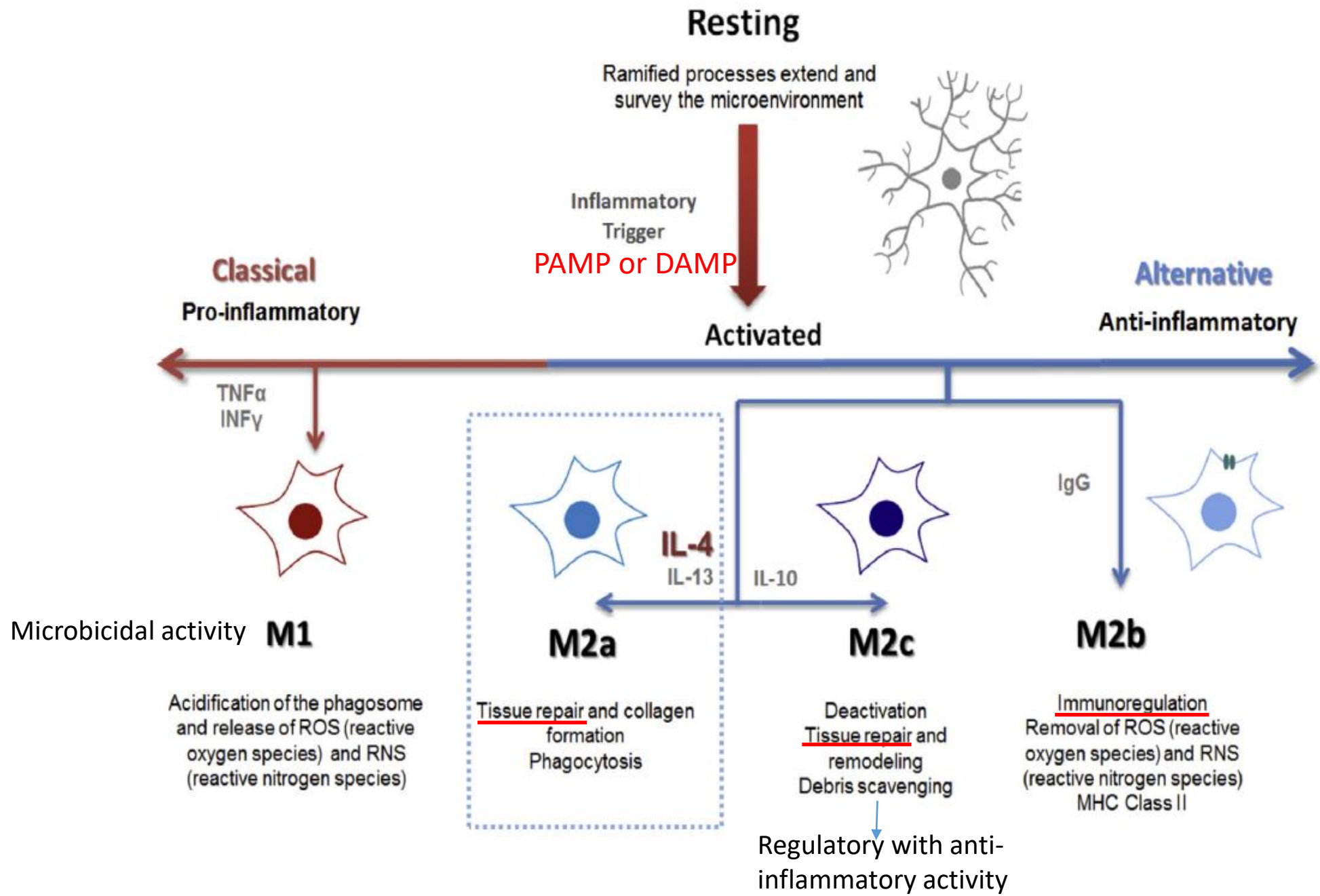
Abeta deposition is associated to:

1. Dystrophic neurites
2. Neuron loss
3. **Microglial activation**
4. Astrocytes activation

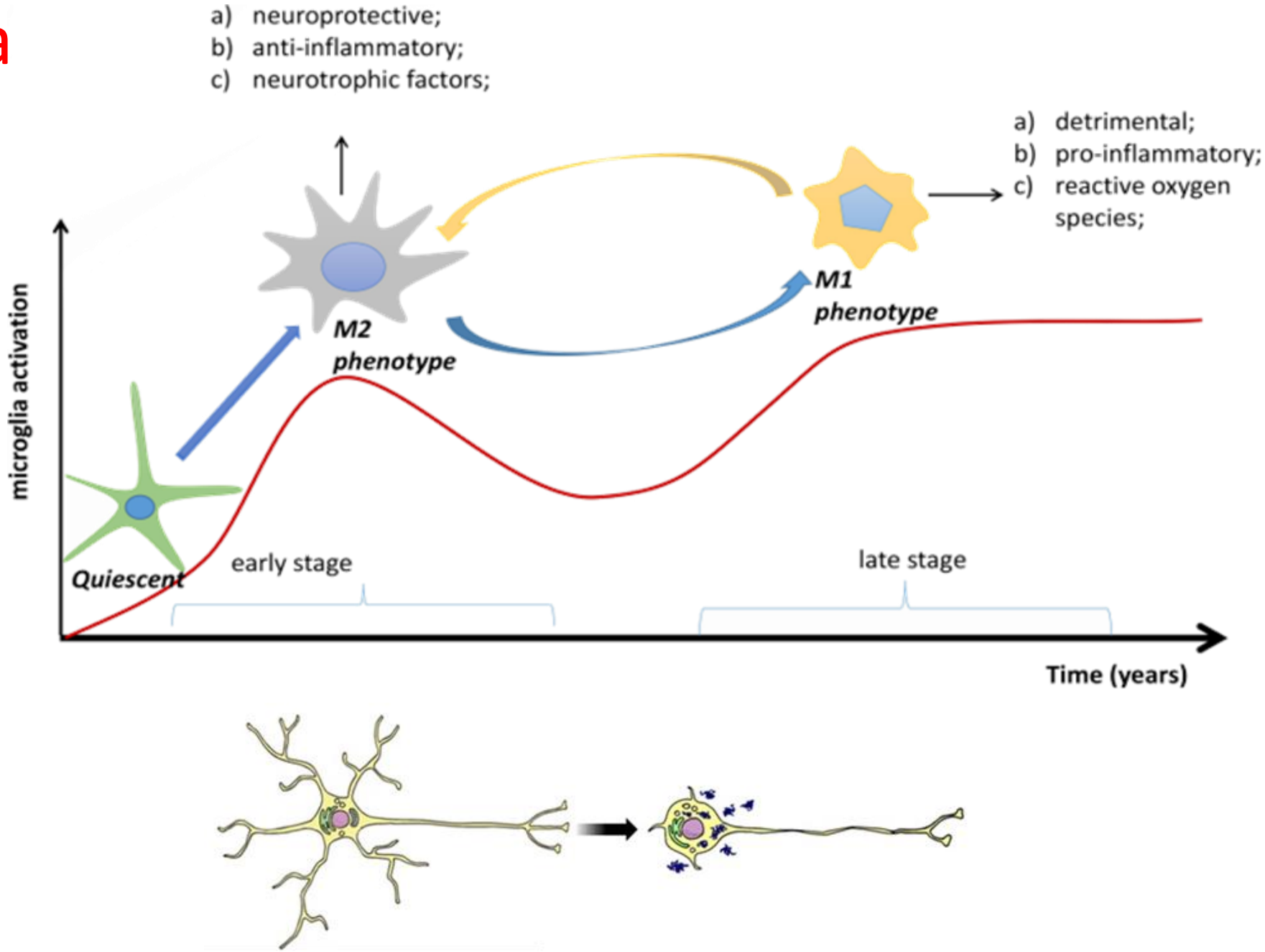
Consequence or cause?

AD could have a possible «immunological or inflammatory» component...

At later stages, associated with degenerating axons and dendrites.


Resting
Ramified processes extend and survey the microenvironment
Inflammatory Trigger
PAMP or DAMP
Classical
Pro-inflammatory
Activated
Alternative
Anti-inflammatory
TNFα
INFγ
IL-4
IL-13
IL-10
IgG
M1
M2a
M2c
M2b
Microbicidal activity
Acidification of the phagosome and release of ROS (reactive oxygen species) and RNS (reactive nitrogen species)
Tissue repair and collagen formation
Phagocytosis
Deactivation
Tissue repair and remodeling
Debris scavenging
Immunoregulation
Removal of ROS (reactive oxygen species) and RNS (reactive nitrogen species)
MHC Class II
Regulatory with anti-inflammatory activity

Microglia nell'AD



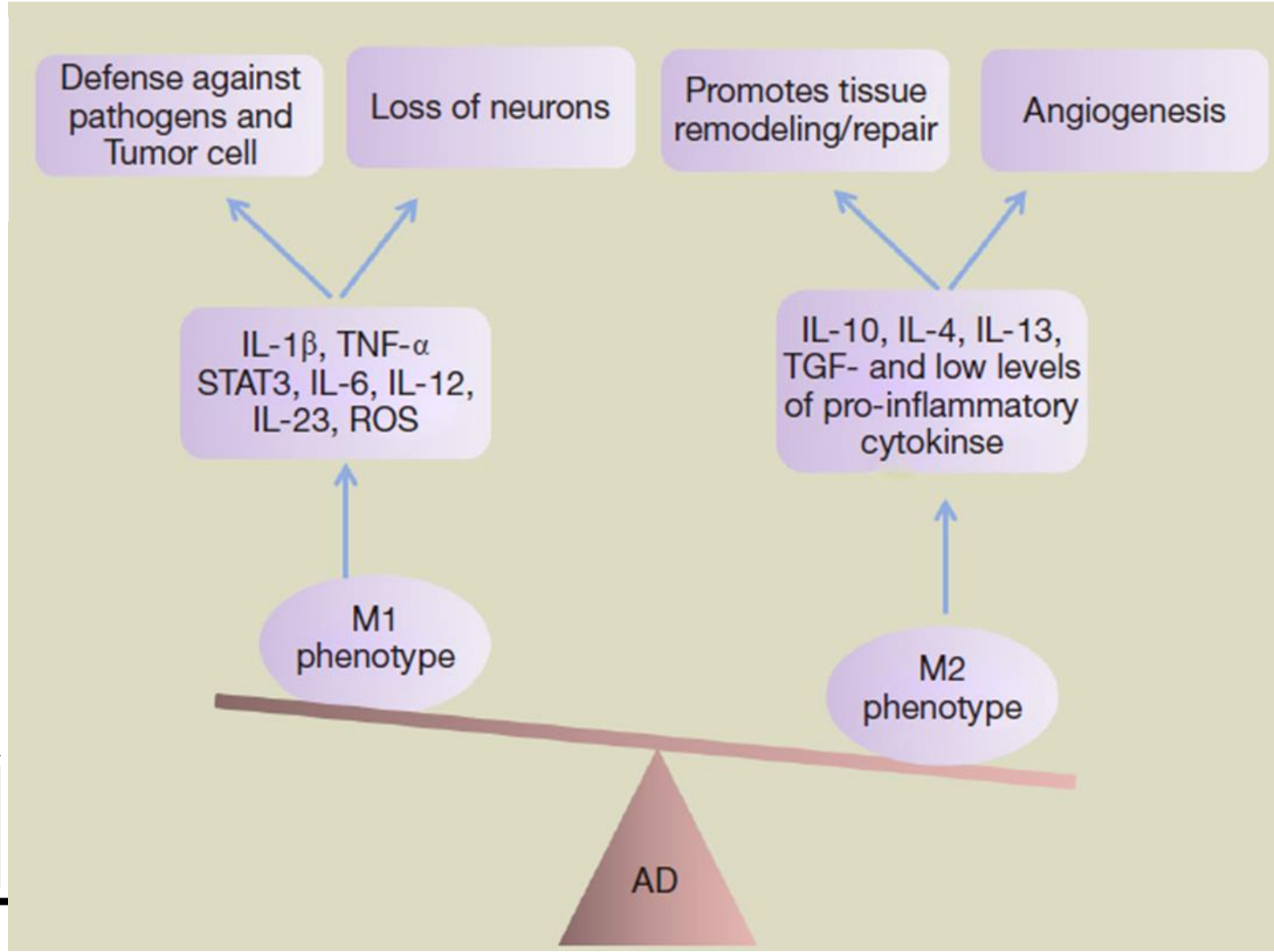
Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 7611–7615, October 1989
Neurobiology

Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease

(glia/trisomy 21/temporal lobe/neurodegenerative disorders)

W. Sue T. Griffin*†‡, Laura C. Stanley†, Chen Ling*, Lanya White*, Veronica MacLeod*, Linda J. Perrot*, Charles L. White III§, and Carlos Araoz¶

In 1989 Griffin demonstrates that Abeta plaque associated microglia express IL1, which in turn regulates APP synthesis. This is the first demonstration of immunological properties of microglia.



Neurobiology of Aging 60 (2017) 173–182

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Anti-inflammatory (M2) macrophage media reduce transmission of oligomeric amyloid beta in differentiated SH-SY5Y cells

Valerie Sackmann[a,b], Anna Ansell[a,b], Christopher Sackmann[a,b], Harald Lund[c], Robert A. Harris[c], Martin Hallbeck[a,b], Camilla Nilsberth[b,d,*]

La capacità di fagocitare Abeta da parte della microglia si riduce nelle fasi avanzate di malattia

ELSEVIER

Neurobiology of Aging 34 (2013) 128–136

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Microglial activation in Alzheimer's disease: an (*R*)-[^{11}C]PK11195 positron emission tomography study

Alie Schuitemaker[a,b,*], Marc A. Kropholler[b], Ronald Boellaard[b], Wiesje M. van der Flier[a,c], Reina W. Kloet[b], Thalia F. van der Doef[b,e], Dirk L. Knol[c], Albert D. Windhorst[b], Gert Luurtsema[b], Frederik Barkhof[d], Cees Jonker[a], Adriaan A. Lammertsma[b], Philip Scheltens[a], Bart N.M. van Berckel[b]

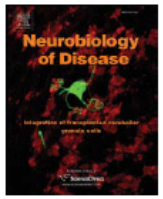
Neurobiology of Disease 32 (2008) 412–419

ELSEVIER

Contents lists available at ScienceDirect

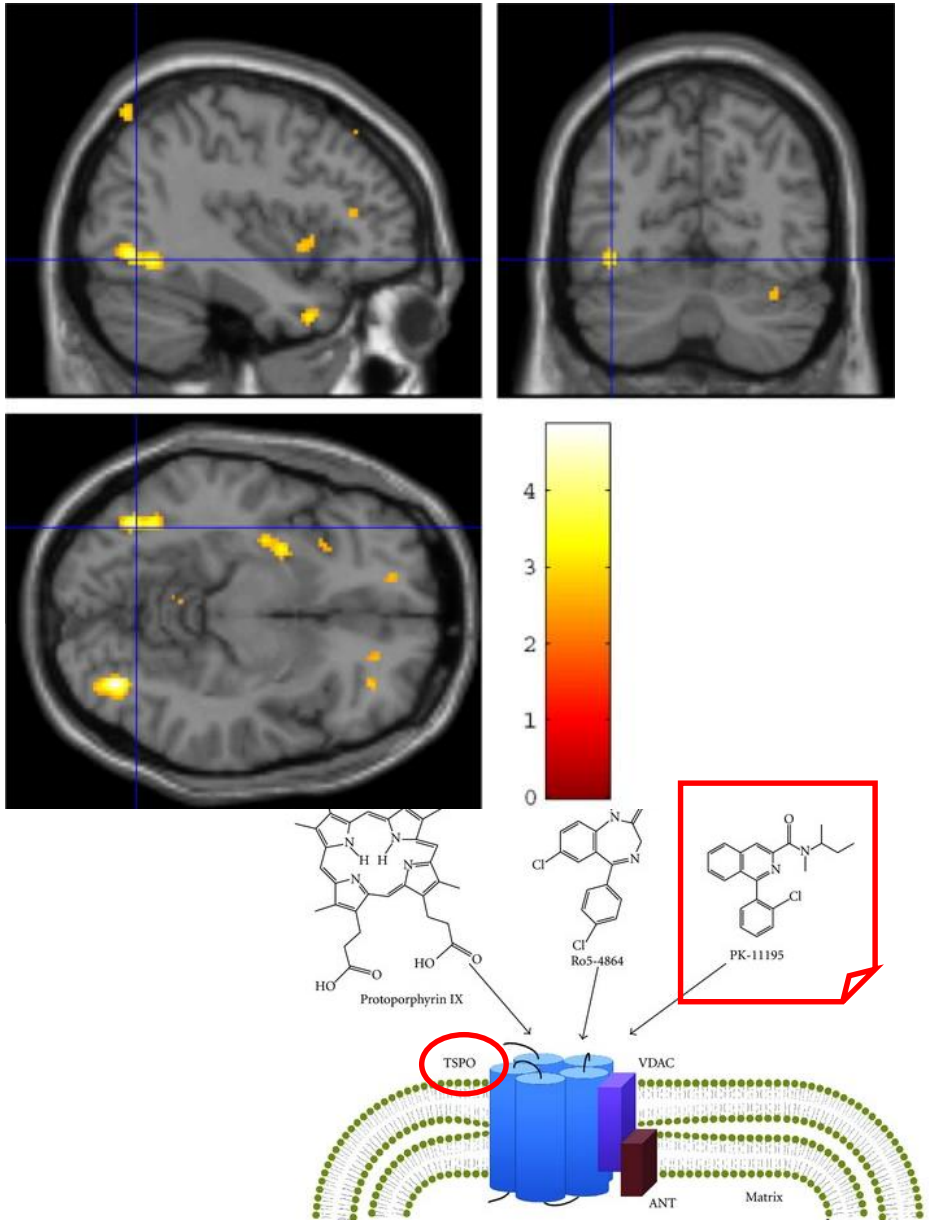
Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study

Paul Edison [a,*], Hilary A. Archer [b], Alexander Gerhard [a,d], Rainer Hinz [c,d], Nicola Pavese [a], Federico E. Turkheimer [a], Alexander Hammers [a], Yen Fong Tai [a], Nick Fox [b], Angus Kennedy [a], Martin Rossor [a,b], David J. Brooks [a,c]



MMSE scores in AD subjects **correlated with levels of cortical microglial activation but not with amyloid load**. The inverse correlation between MMSE and microglial activation is compatible with a role of microglia in neuronal damage.

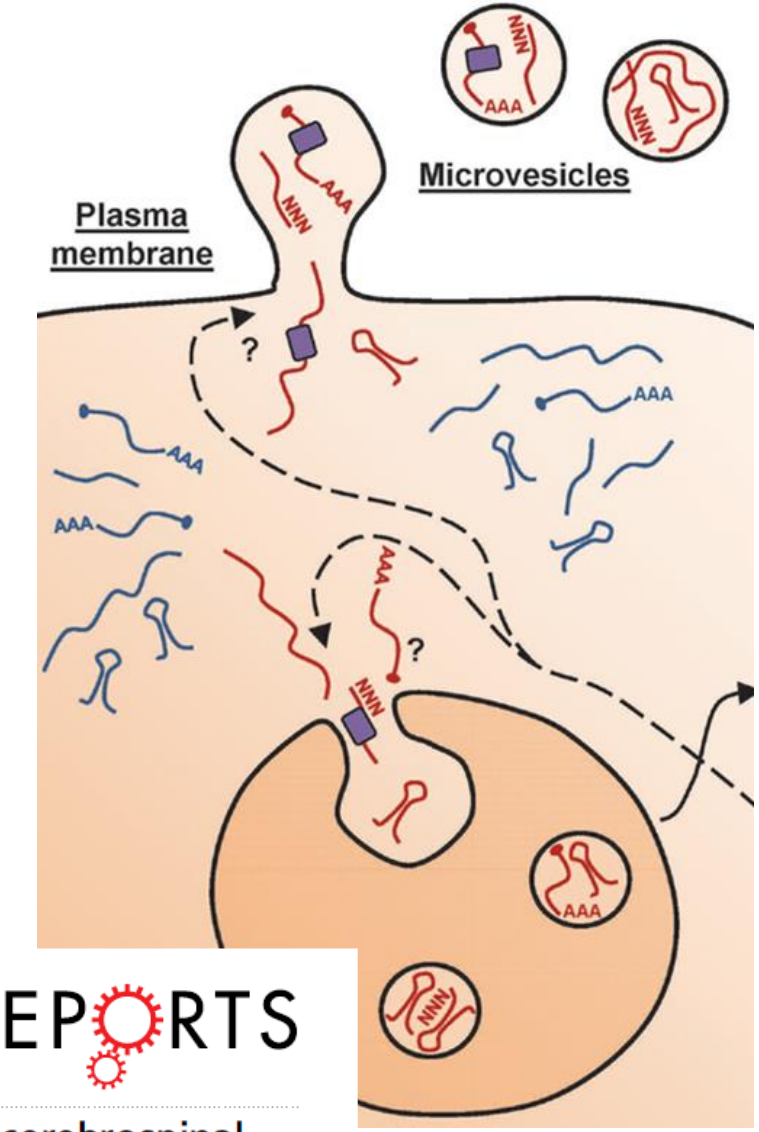
JLB

Activated macrophages release microvesicles containing polarized M1 or M2 mRNAs

Livia Garzetti, Ramesh Menon,* Annamaria Finardi,* Alessandra Bergami,* Antonio Sica,† Gianvito Martino,* Giancarlo Comi,* Claudia Verderio,†,‡ Cinthia Farina,* and Roberto Furlan*,1*

*Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Milano, Italy; †Humanitas Clinical and Research Center, Rozzano, Italy; and ‡Consiglio Nazionale delle Ricerche, Institute of Neuroscience, Milano, Italy

RECEIVED SEPTEMBER 5, 2013; REVISED DECEMBER 11, 2013; ACCEPTED DECEMBER 19, 2013. DOI: 10.1189/jlb.0913485



ANN NEUROL 2014;76:813–825

Myeloid Microvesicles in Cerebrospinal Fluid Are Associated with Myelin Damage and Neuronal Loss in Mild Cognitive Impairment and Alzheimer Disease

Federica Agosta, MD, PhD,[1] Dacia Dalla Libera, MD,[1] Edoardo Gioele Spinelli, MD,[1] Annamaria Finardi, BSci,[1] Elisa Canu, PhD,[1] Alessandra Bergami, MLT,[1] Luisella Bocchio Chiavetto, PhD,[2] Manuela Baronio, MD,[3] Giancarlo Comi, MD,[1,4] Gianvito Martino, MD,[1] Michela Matteoli, PhD,[5,6] Giuseppe Magnani, MD,[1] Claudia Verderio, PhD,[5,6] and Roberto Furlan, MD, PhD[1]

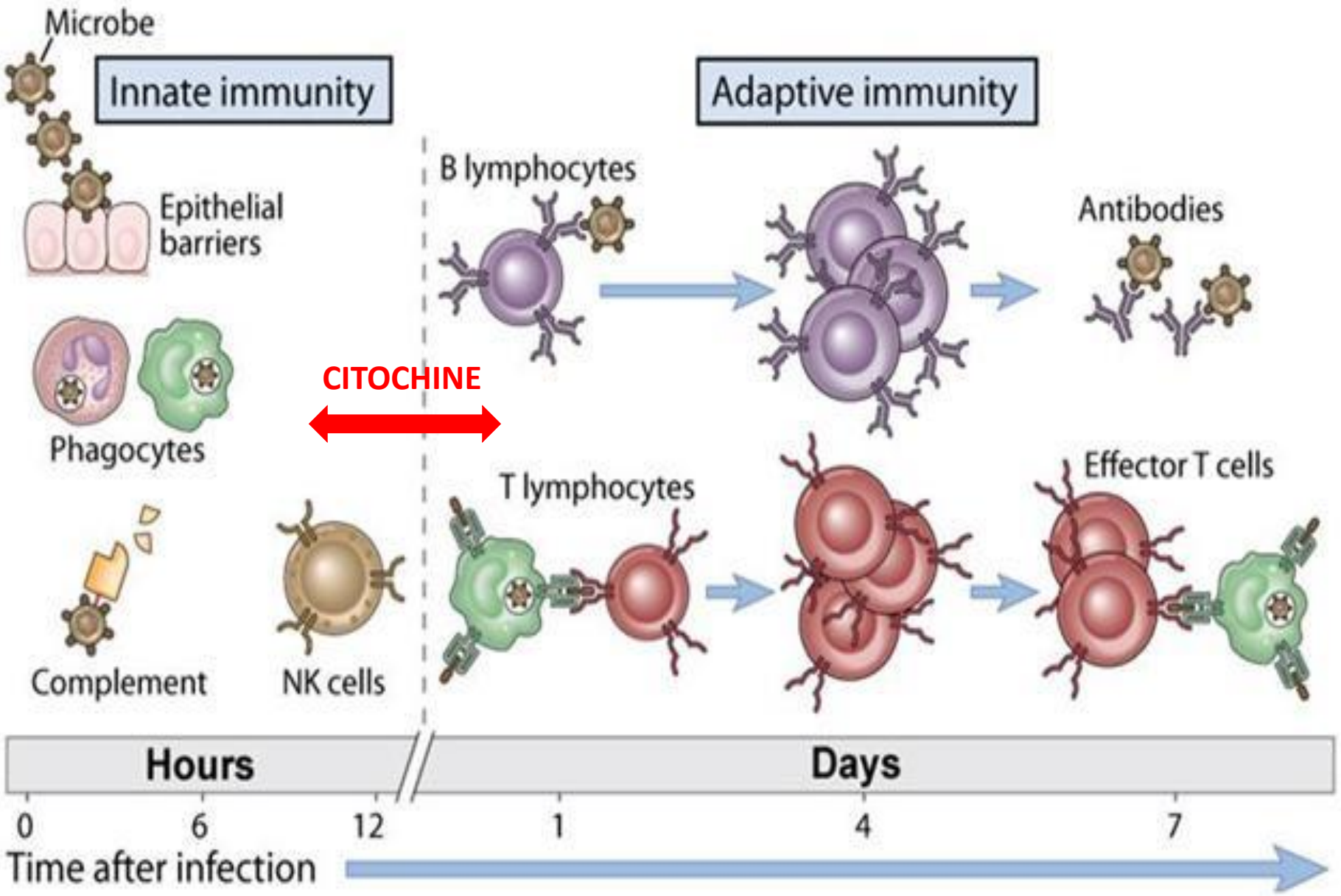
Received: 20 July 2018
Accepted: 27 April 2019
Published online: 08 May 2019

SCIENTIFIC REPORTS

OPEN

Microvesicles from cerebrospinal fluid of patients with Alzheimer's disease display reduced concentrations of tau and APP protein

Philipp Spitzer[1], Linda-Marie Mulzer[1], Timo Jan Oberstein[1], Luis Enrique Munoz[2], Piotr Lewczuk[1,3], Johannes Kornhuber[1], Martin Herrmann[2] & Juan Manuel Maler[1]



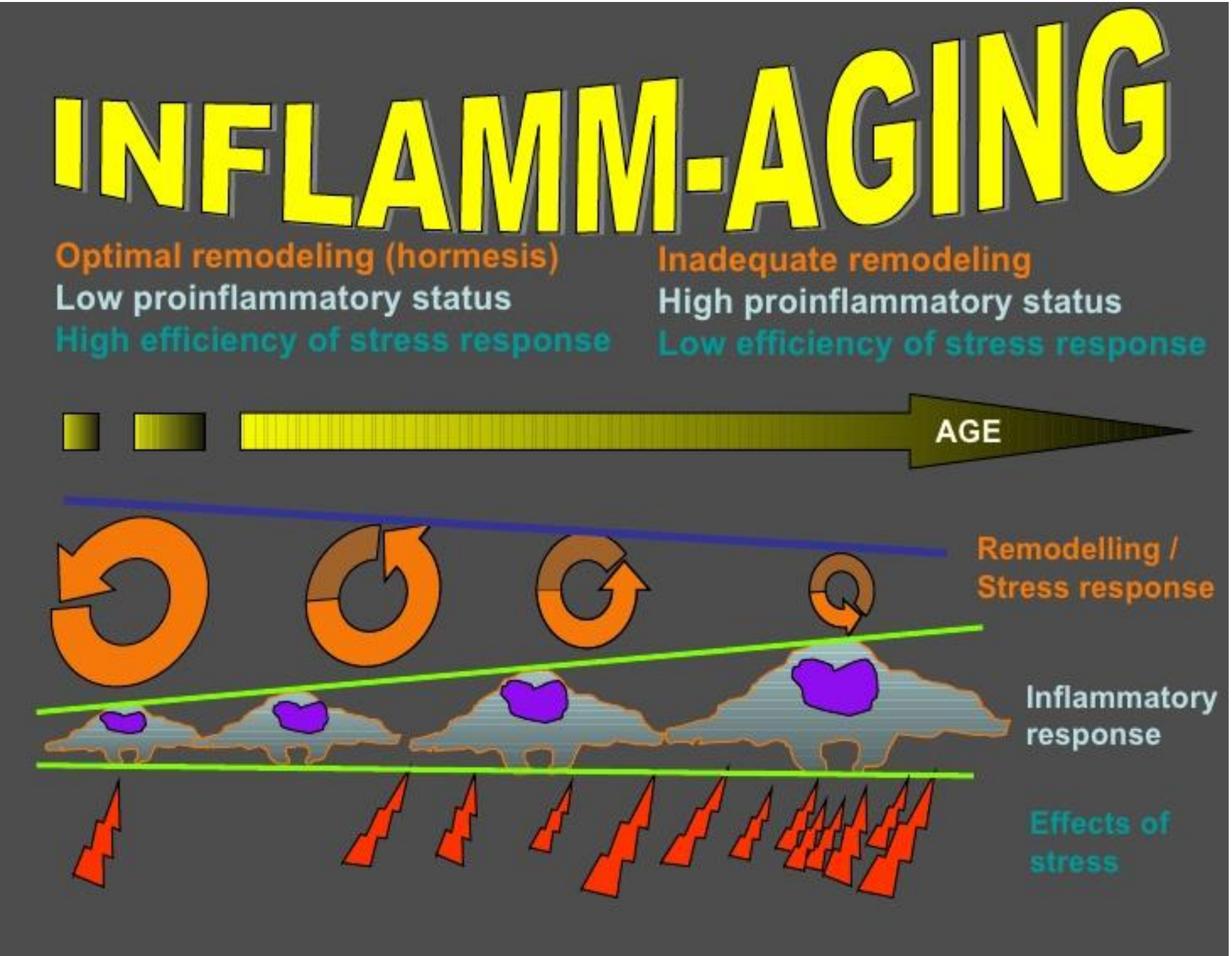
Innate immunity

- No time lag
- Not antigen specific
- No memory

Le citochine fanno da tramite fra immunità innata ed adattativa.

Adaptive immunity

- A lag period
- Antigen specific
- Development of memory



INFLAMMAGING

(Franceschi)

Progressiva perdita di competenza immunologica.

Stato Infiammatorio:

1. Di basso grado
2. Controllato
3. Asintomatico
4. Cronico
5. Sistemico

- **Declino immunità adattativa:** riduzione dei linfociti T naive e risposta Th2
- **Aumento immunità innata** sostenuta da fagociti

Journal of Neuroinflammation

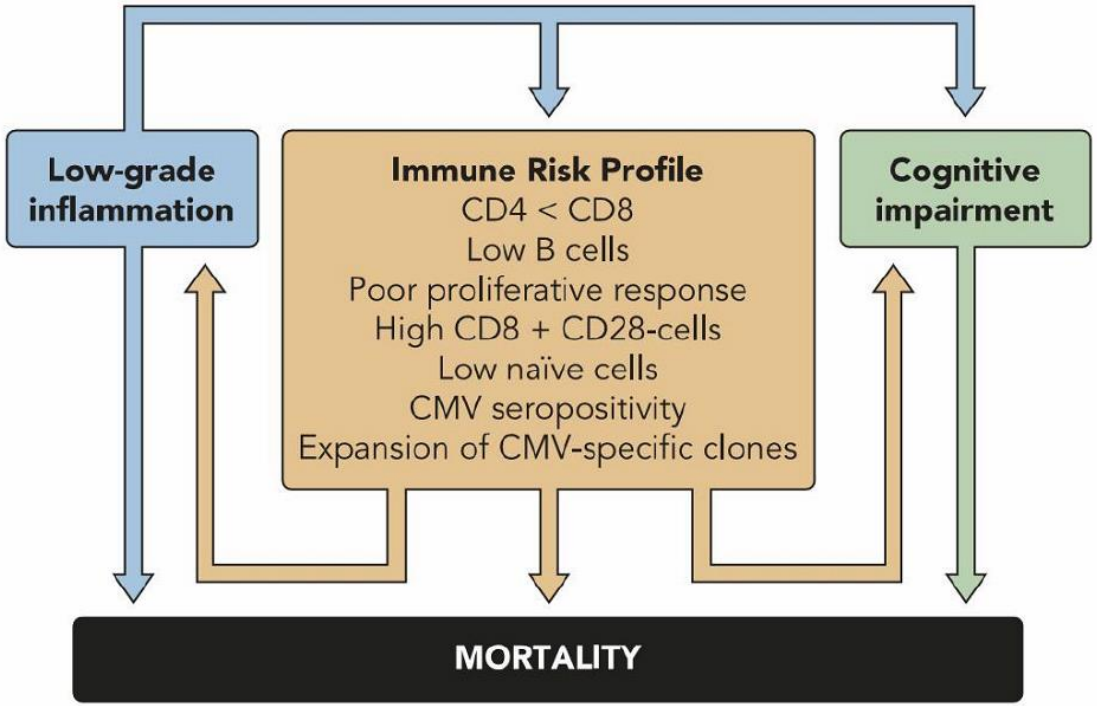
BioMed Central

Review

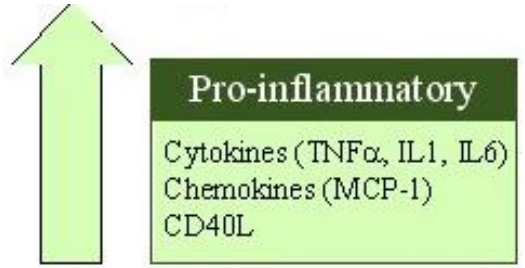
Open Access

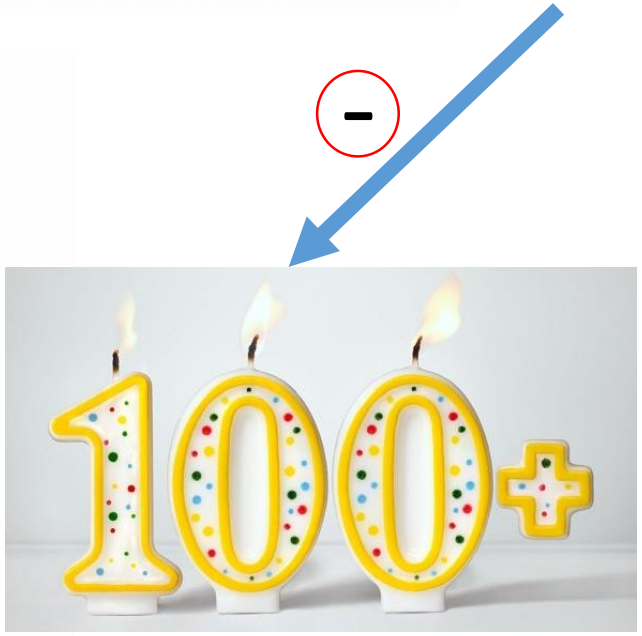
Inflammaging as a prodrome to Alzheimer's disease

Brian Giunta*[1], Francisco Fernandez[1,2], William V Nikolic[2], Demian Obregon[2], Elona Rrapo[1], Terrence Town[3,4,5] and Jun Tan[2]



Interplay between the IRP, low grade inflammation, and cognitive impairment in mortality





frontiers in
CELLULAR NEUROSCIENCE

REVIEW ARTICLE
published: 07 November 2014
doi: 10.3389/fncel.2014.00380

Versatility of the complement system in neuroinflammation, neurodegeneration and brain homeostasis

*Franca Orsini[1], Daiana De Blasio[1,2], Rosalia Zangari[1,3], Elisa R. Zanier[1] and Maria-Grazia De Simoni[1]**

[1] Department of Neuroscience, IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy
[2] Department of Experimental and Clinical Sciences, University of Chieti, Pescara, Italy
[3] Department of Anesthesia and Critical Care Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

NEUROINFIAMMAZIONE: risposta infiammatoria all'interno del cervello e del midollo spinale. I mediatori dell'infiammazione sono prodotti sia da cellule residenti che da cellule periferiche.

Journal of Neurochemistry JNC

JOURNAL OF NEUROCHEMISTRY | 2016 doi: 10.1111/jnc.13607

PAST TO FUTURE

Neuroinflammation: the devil is in the details

Damon J. DiSabato,* Ning Quan† and Jonathan P. Godbout*,‡

Lancet Neurol 2015; 14: 388–405

...us, Ohio, USA
..., Ohio, USA

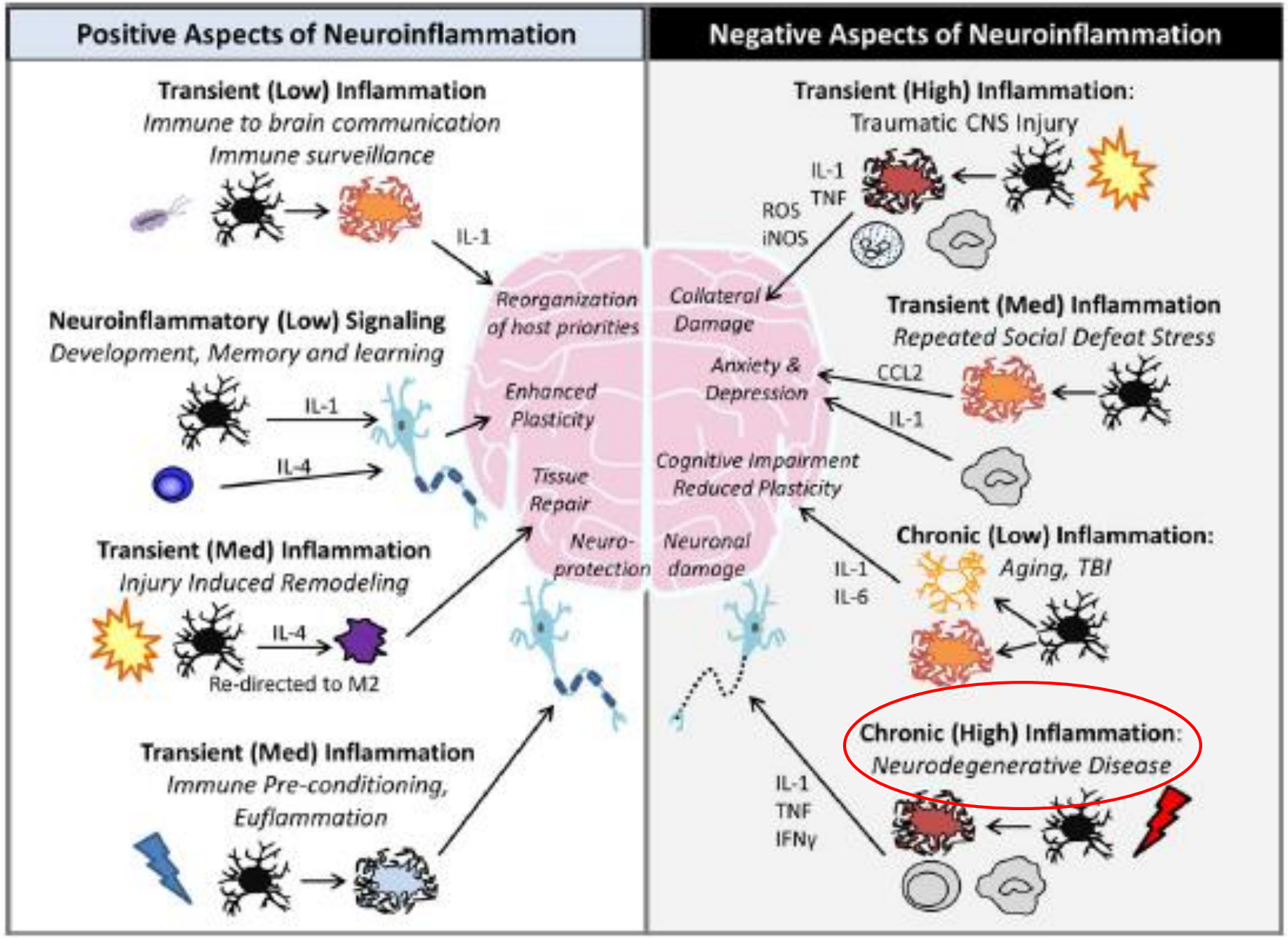
pod cast CrossMark

Neuroinflammation in Alzheimer's disease

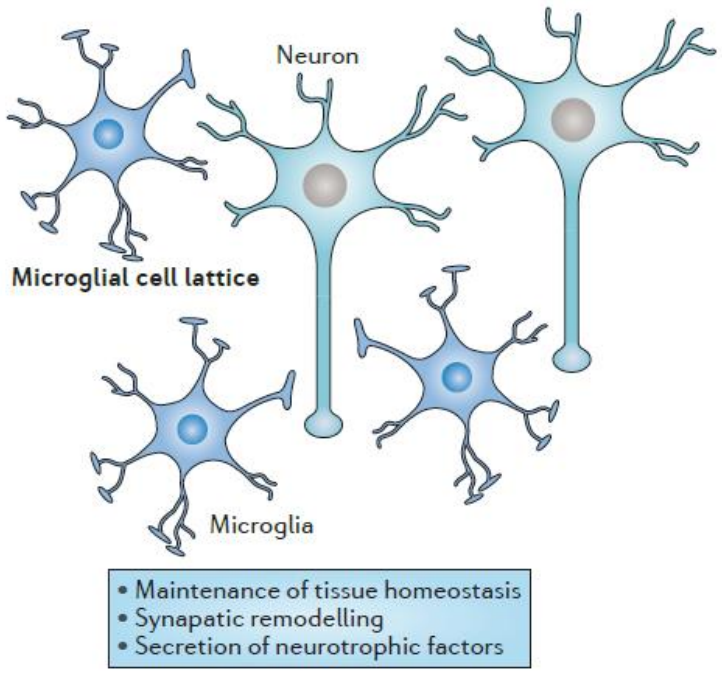
Michael T Heneka, Monica J Carson, Joseph El Khoury, Gary E Landreth, Frederic Brosseron, Douglas L Feinstein, Andreas H Jacobs, Tony Wyss-Coray, Javier Vitorica, Richard M Ransohoff, Karl Herrup, Sally A Frautschy, Bente Finsen, Guy C Brown, Alexei Verkhratsky, Koji Yamanaka, Jari Koistinaho, Eicke Latz, Annett Halle, Gabor C Petzold, Terrence Town, Dave Morgan, Mari L Shinohara, V Hugh Perry, Clive Holmes, Nicolas G Bazan, David J Brooks, Stéphane Hunot, Bertrand Joseph, Nikolaus Deigendesch, Olga Garaschuk, Erik Boddeke, Charles A Dinarello, John C Breitner, Greg M Cole, Douglas T Golenbock, Markus P Kummer

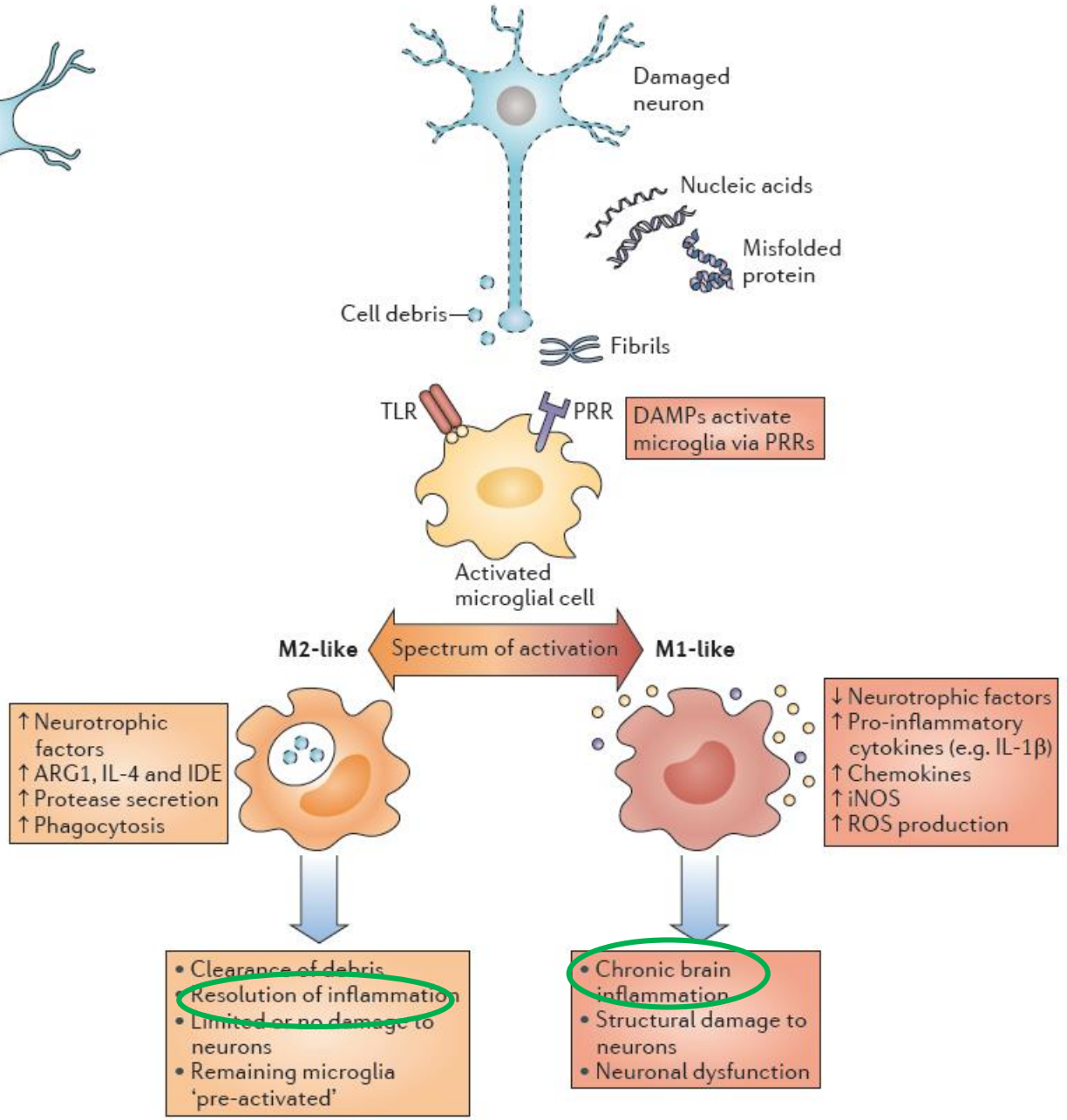
Da metà anni '90 si inizia a parlare di «NEUROINFIAMMAZIONE»

- Intensity
- Duration

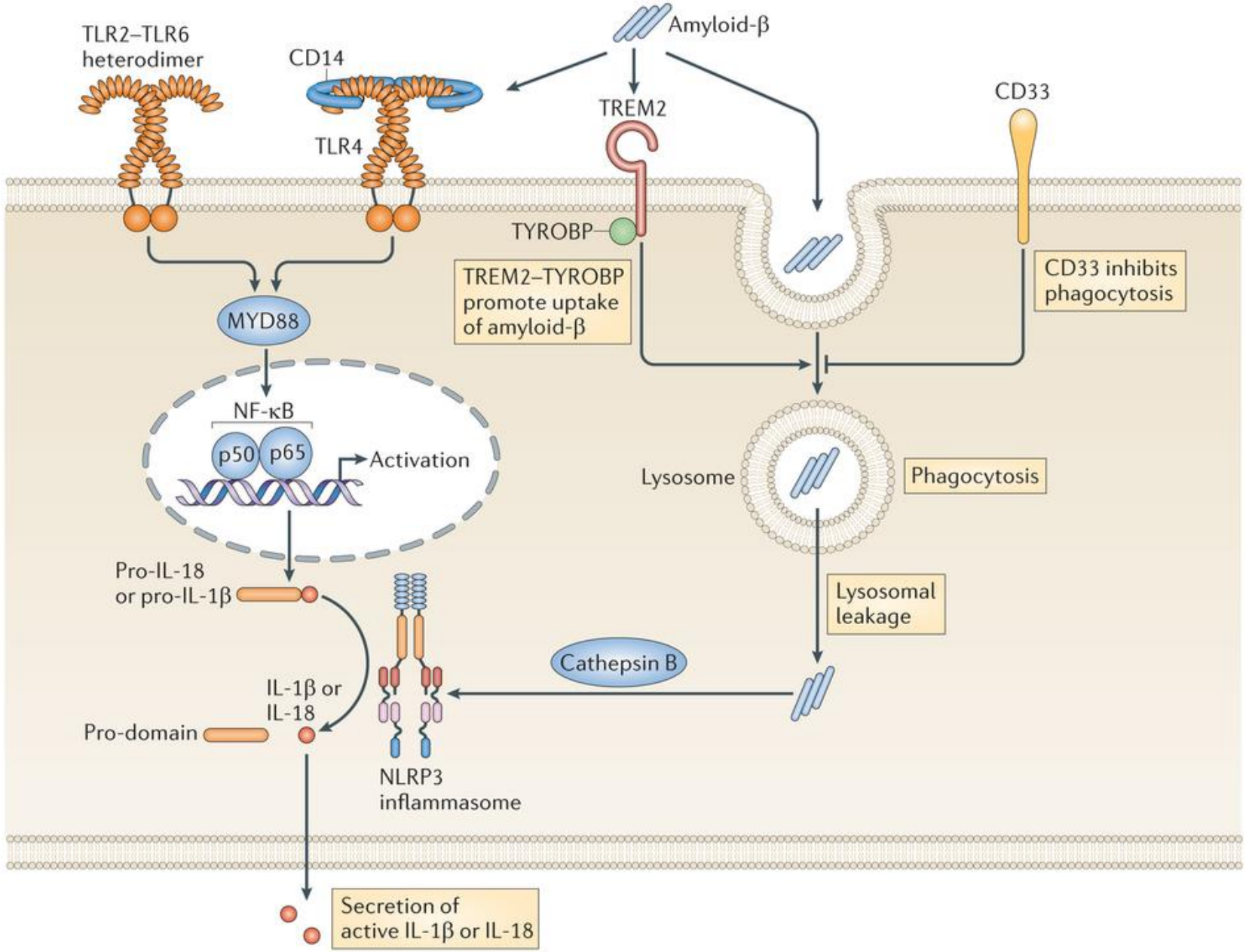


J. Neurochem. (2016) 10.1111/jnc.13607





PRR, pattern recognition receptors (TLR2, TLR4,TLR6)
…able to *trigger inflammatory pathways*
DAMP, danger-associated molecular patterns
…i.e., *misfolded proteins*
PAMP, pathogen-associated molecular patterns
…i.e., *microbial molecules*

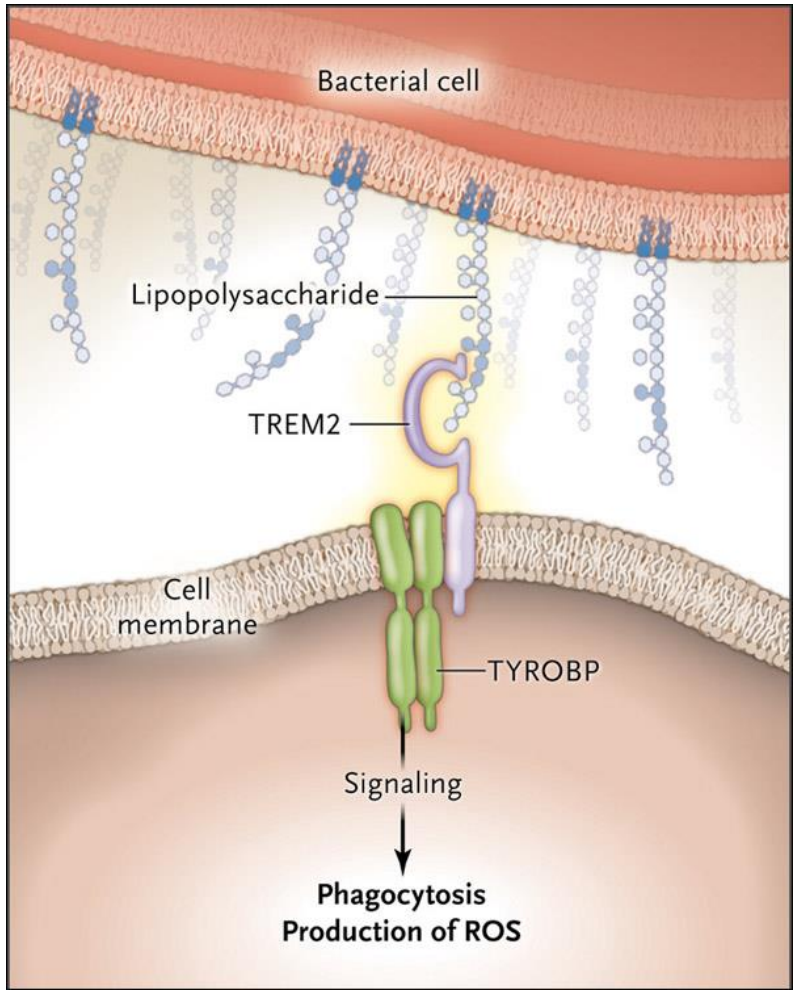


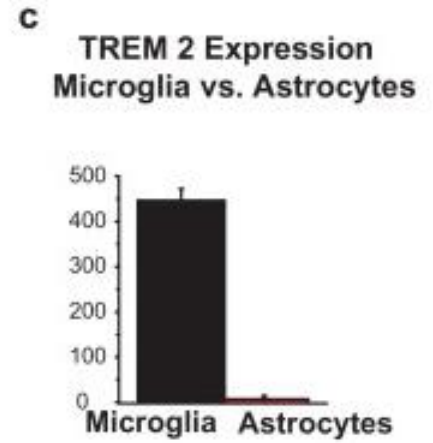
In AD the immune response could reduce microglial Abeta clearance favouring AD progression.

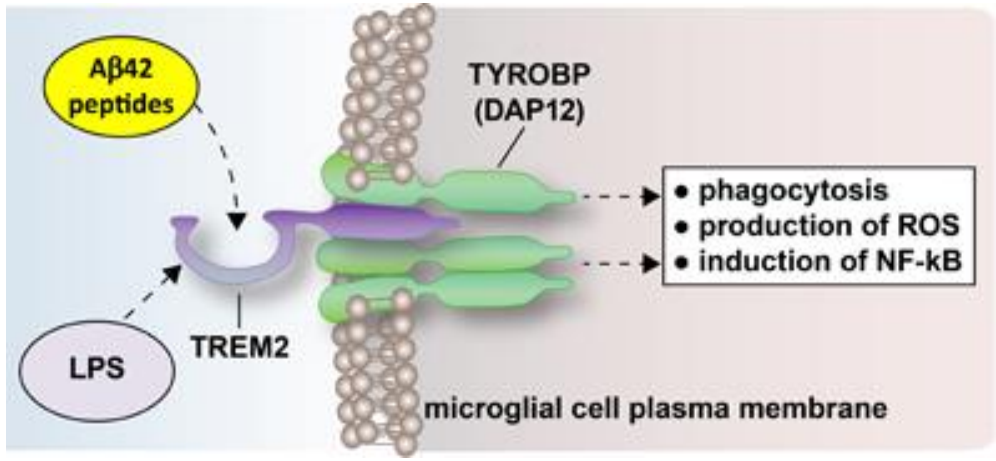
Triggering receptor expressed on myeloid cells 2

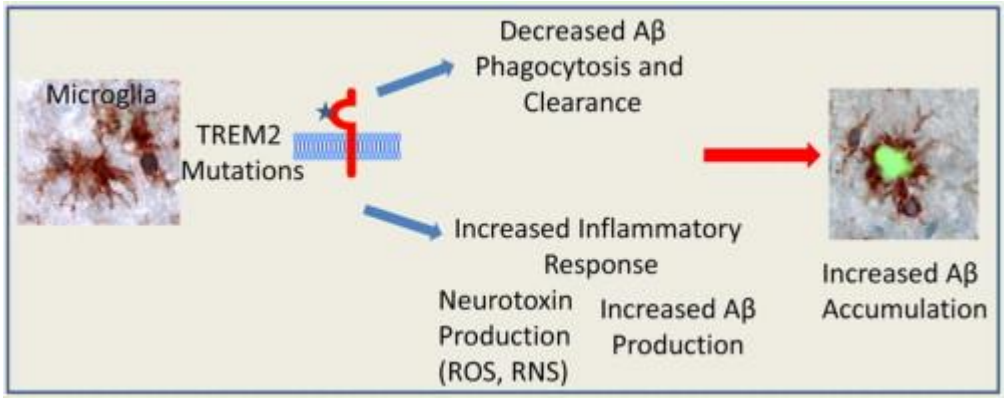
Mutazione omozigote = NHD (demenza)

Missenso rs75932628-T → R47H ↑ rischio LOAD *(Guerriero et al.2013)*









TREM2 and Risk of Alzheimer's Disease — Friend or Foe?

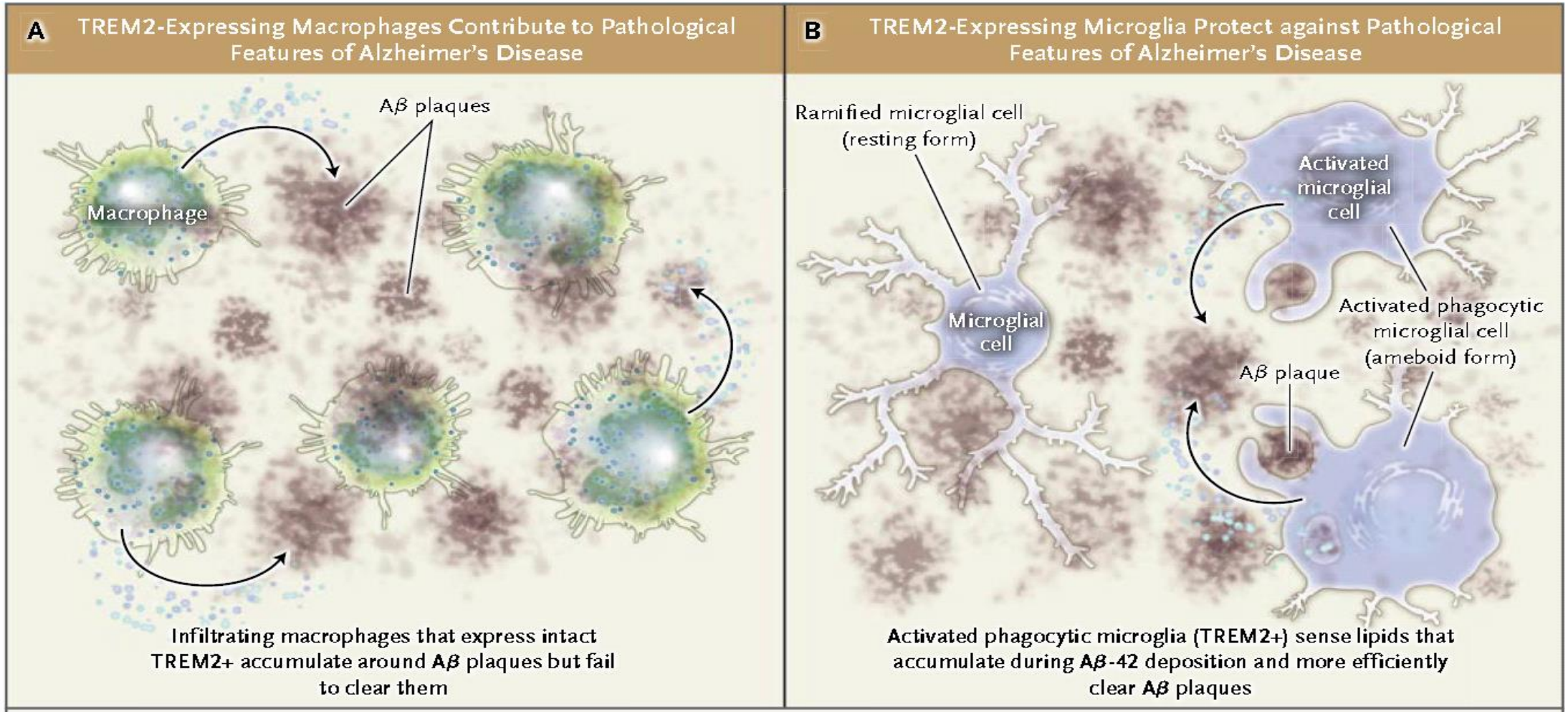


Figure 1. Different Takes on TREM2.

How variant *TREM2*, the gene encoding the triggering receptor expressed on myeloid cells 2 protein, confers susceptibility to Alzheimer's disease is not clear. Experiments with the use of mouse models indicate different potential mechanisms. Jay et al.[4] recently found that infiltrating macrophages in the brain (Trem2+ and CD45+) accumulate around amyloid-beta (Aβ) plaques but fail to efficiently clear them — that is, macrophages expressing intact TREM2 may contribute to the pathological features of the disease. In contrast, Wang et al.[5] found that TREM2+ microglia, resident in the brain, sense lipids that accumulate during Aβ-42 deposition and thereby more efficiently clear pathologic plaques.

Rudolph E. Tanzi, Ph.D.

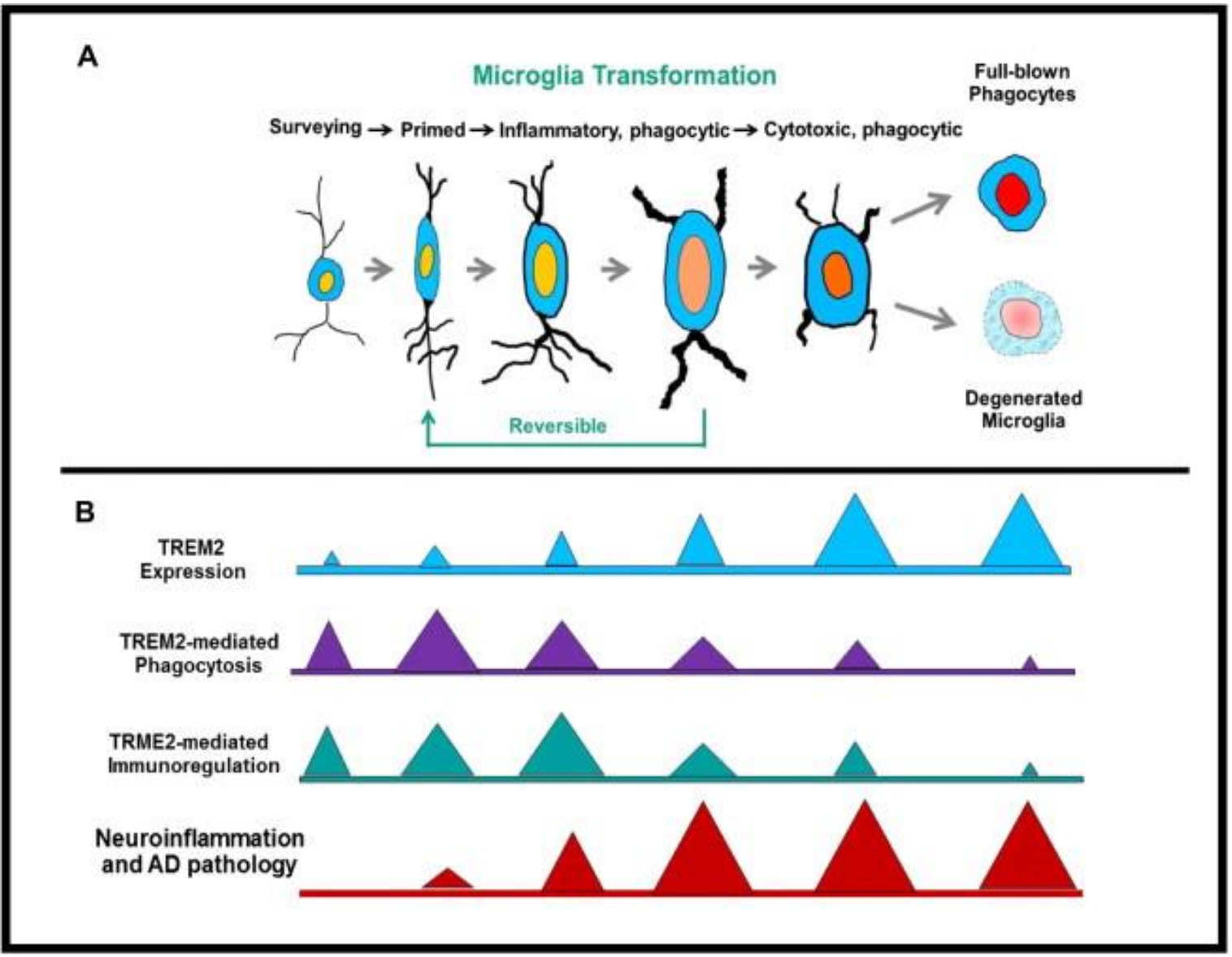


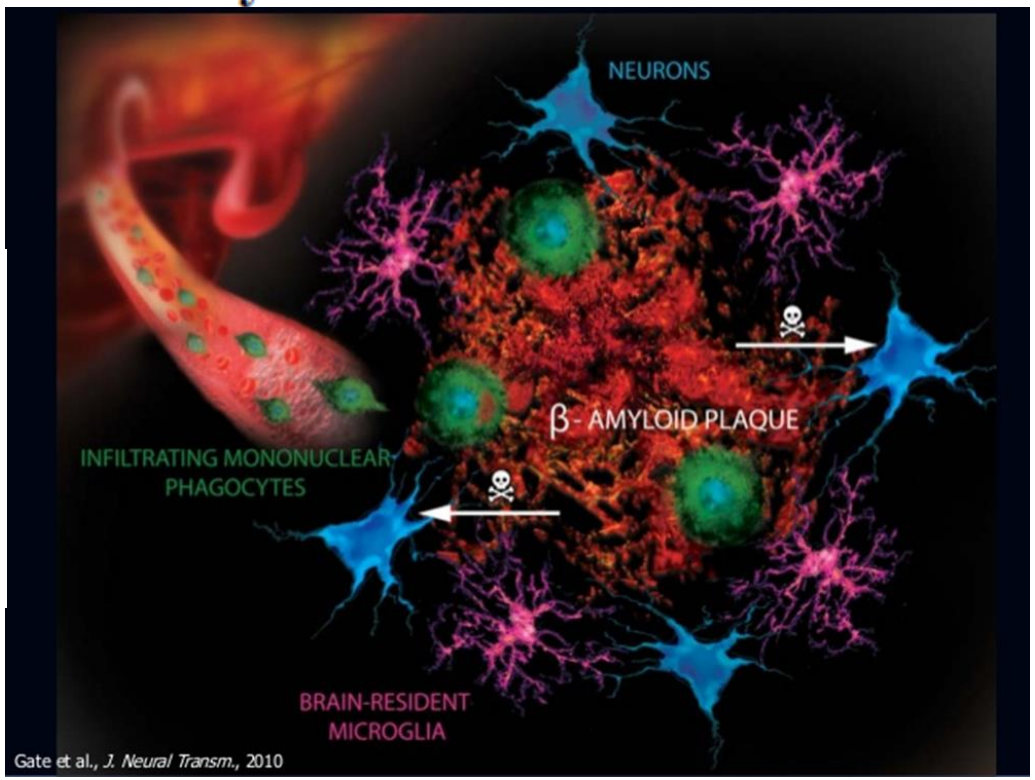
Fig. 1. Scheme showing possible relationship between microglia phenotypes and TREM2. (A) Microglia activation is characterized by the transformation of morphology. The main function and properties corresponding to morphology are surveying, primed, inflammatory, phagocytic, and cytotoxic. We propose that microglia could return to a less inflammatory state before becoming cytotoxic or turning into macrophage-like cells and eventually degenerated. (B) We hypothesize the changes of TREM2 expression and function according to microglia transformation stages and AD pathology. The magnitude of the changes is reflected by the size of the triangles. At an early stage of the transformation, microglia perform TREM2-mediated phagocytosis and immunoregulation. It is possible that if TREM2 function is insufficient at early stages of the disease, as disease progresses, regardless of TREM2 expression, loss of function of TREM2 occurs, which could result in failure to regulate microglia inflammatory properties. Upregulation of TREM2 could be a response to increased presence of ligands as a result of neuronal loss. Loss of TREM2 function could also be due to impaired ligand binding and signaling. All of these could increase microglial activation and chronic inflammation, which in turn exacerbate neurodegeneration.

J Neural Transm (2010) 117:961–970
DOI 10.1007/s00702-010-0422-7

BASIC NEUROSCIENCES, GENETICS AND IMMUNOLOGY - REVIEW ARTICLE

Macrophages in Alzheimer's disease: the blood-borne identity

David Gate · Kavon Rezai-Zadeh · Dominique Jodry · Altan Rentsendorj · Terrence Town



Gate et al., *J. Neural Transm.*, 2010

Neurobiology of Disease

Invasion of Hematopoietic Cells into the Brain of Amyloid Precursor Protein Transgenic Mice

Anna K. Stalder,[1,2,3] Florian Ermini,[1] Luca Bondolfi,[2] Werner Krenger,[3] Guido J. Burbach,[4] Thomas Deller,[4] Janaky Coomaraswamy,[1] Matthias Staufenbiel,[5] Regine Landmann,[3] and Mathias Jucker[1,2]

The Journal of Neuroscience, November 30, 2005 • 25(48):11125–11132 • 11125

Only a subpopulation of amyloid deposits was surrounded by invading cells. This suggests that not all amyloid plaques are a target for invading cells or, alternatively, all amyloid plaques attract invading cells but only for a limited time, possibly at an early stage of plaque evolution.

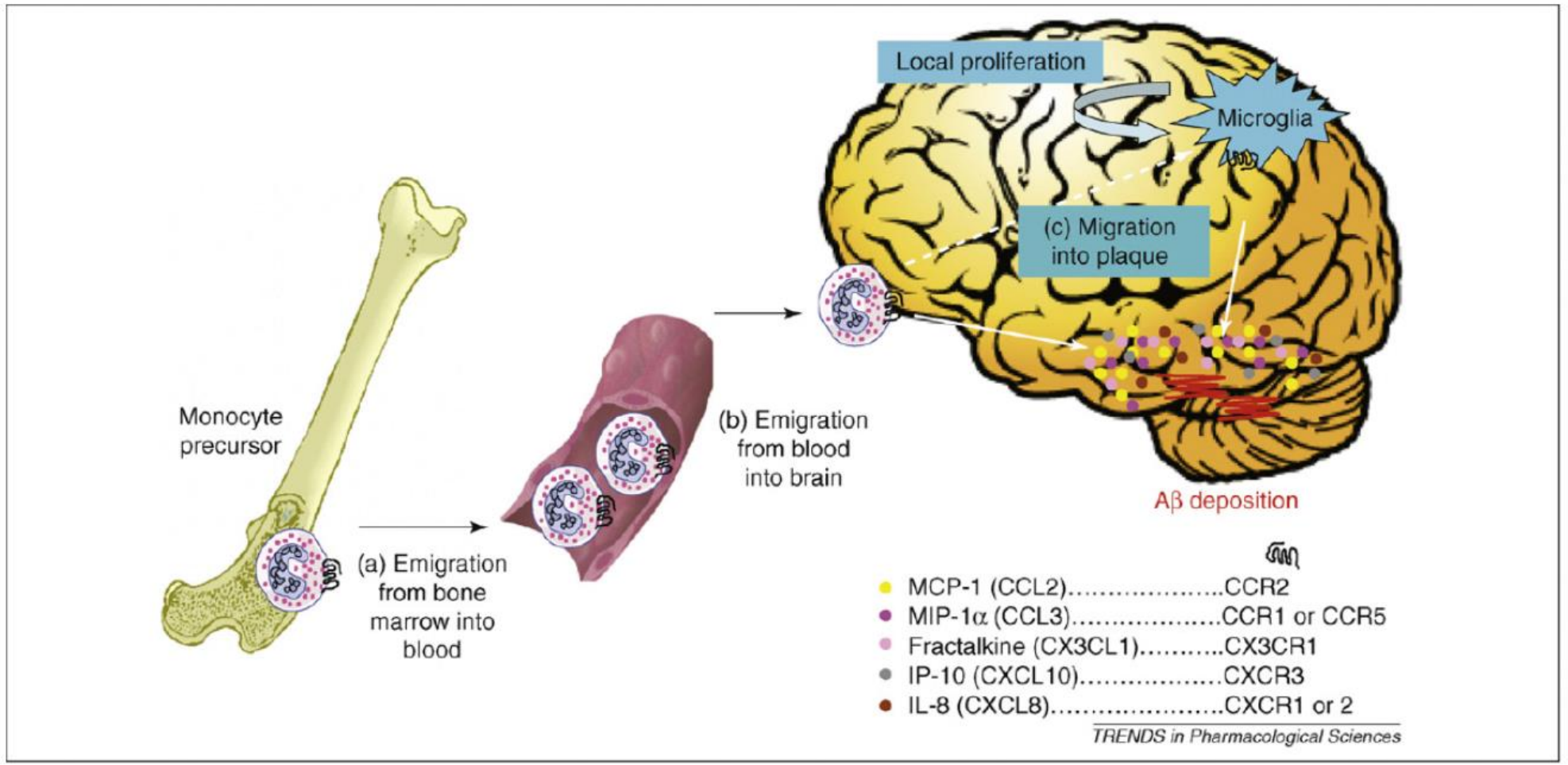
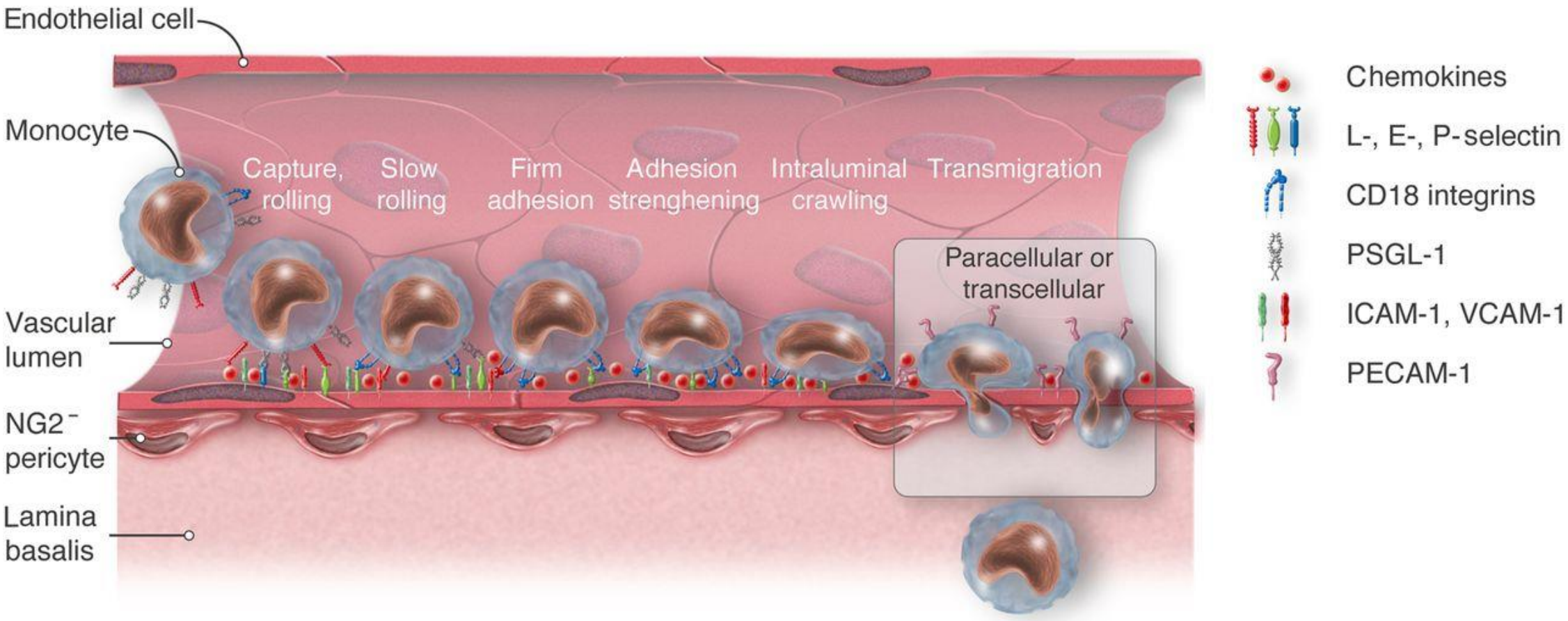


Figure 4. A proposed model for microglia accumulation in AD highlighting the potential role of both local proliferation and the recruitment of bone-marrow-derived cells in this process. Local microglia, in response to Aβ accumulation, produce growth factors that stimulate microglia proliferation. In addition, these local microglia produce several chemokines that will recruit cells from **(a)** bone marrow → blood **(b)** blood → brain **(c)** brain → plaque. This is likely to be controlled by distinct subsets of chemokine-receptor pairs that act at one or more steps in this multistep process. The chemokine/chemokine receptor pairs implicated in microglial trafficking into the AD brain are indicated.

CHEMOTAXIS AND CELL INVASION

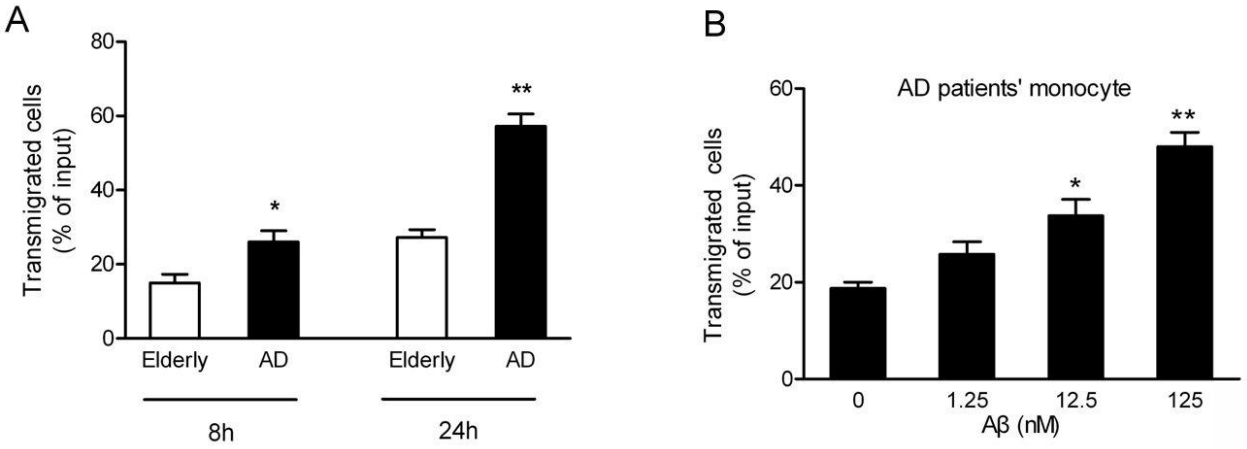


OPEN ACCESS Freely available online

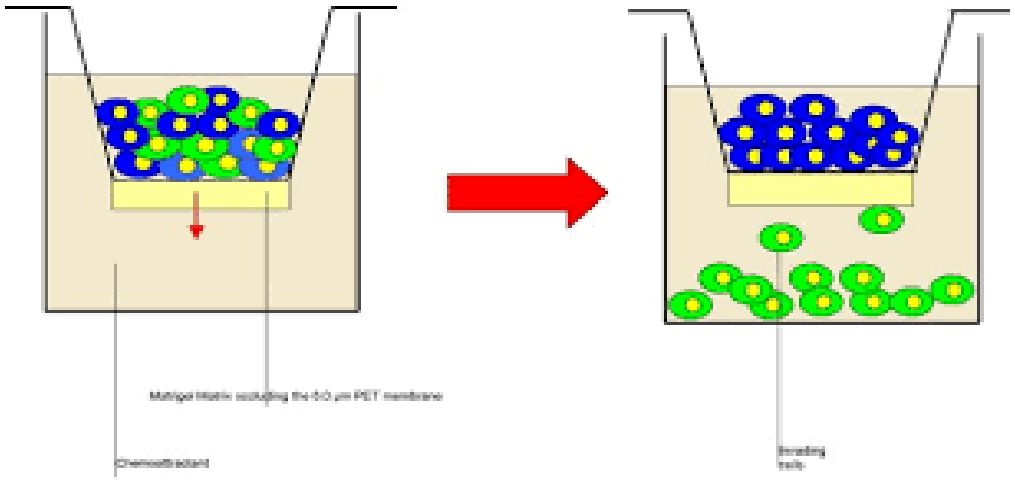
PLOS ONE

CXCL1 Contributes to β-Amyloid-Induced Transendothelial Migration of Monocytes in Alzheimer's Disease

Ke Zhang[1], Li Tian[1], Li Liu[2], Yu Feng[2], Yan-Bin Dong[1], Bo Li[1], De-Shu Shang[1], Wen-Gang Fang[1], Yun-Peng Cao[2], Yu-Hua Chen[1*] 2013



Non physiological **nanomolar** concentrations!



Munawara *et al. Immunity & Ageing* (2021) 18:29
https://doi.org/10.1186/s12979-021-00236-x

Immunity & Ageing

RESEARCH Open Access

Hyperactivation of monocytes and macrophages in MCI patients contributes to the progression of Alzheimer's disease

Usma Munawara[1], Michael Catanzaro[1,2], Weili Xu[3], Crystal Tan[3], Katsuiku Hirokawa[4], Nabil Bosco[5], David Dumoulin[6], Abdelouahed Khalil[1], Anis Larbi[1,3], Simon Lévesque[7], Charles Ramassamy[8], Annelise E. Barron[9], Stephen Cunnane[10], Pascale B. Beauregard[6], Jean-Pierre Bellenger[11], Serafim Rodrigues[12,13*], Mathieu Desroches[14,15], Jacek M. Witkowski[16], Benoit Laurent[17], Eric H. Frost[7] and Tamas Fulop[1*]

Increased monocytes chemotaxis to MCP-1

Our Aim:

To verify if patho-physiological Abeta 1-42 levels (125 pM) are able to induce monocyte chemotaxis in AD patients. Possible mechanisms?

Journal of Alzheimer's Disease 95 (2023) 549–559
DOI 10.3233/JAD-230239
IOS Press

TSPO Modulates Oligomeric Amyloid-β-Induced Monocyte Chemotaxis: Relevance for Neuroinflammation in Alzheimer's Disease

Elisa Conti[a,b], Denise Grana[a,b], Federica Angiulli[a,b], Aristotelis Karantzoulis[b,c], Chiara Villa[a,b], Romina Combi[a,b], Ildebrando Appollonio[a,b,c], Carlo Ferrarese[a,b,c], ImmunAD-Brianza Network[a,b,c,1] and Lucio Tremolizzo[a,b,c,*]

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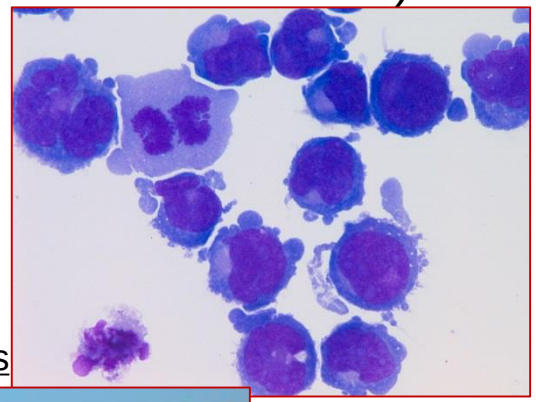
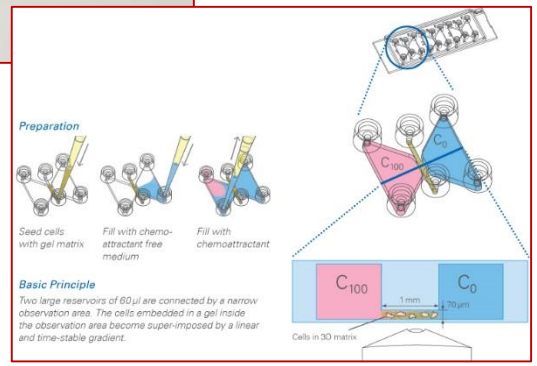
[c]*Memory Clinic, Neurology Unit, IRCCS "San Gerardo dei Tintori", Monza, Italy*

Cellule THP-1
(leucemia mieloide acuta)

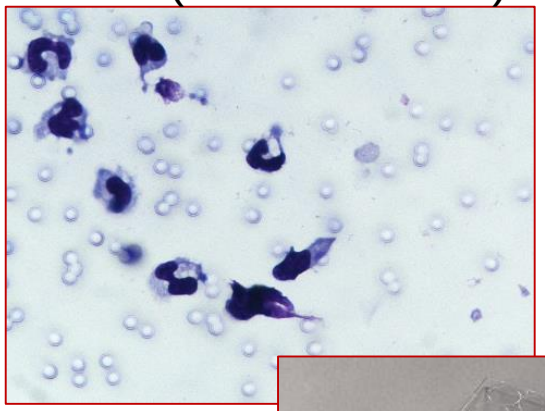


µ-slide chambers



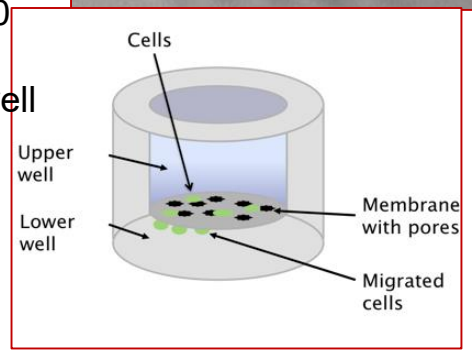
- ✓ Incubazione 24 h
- ✓ Immagini acquisite ogni 4 minuti

Monociti umani
(da CTRL e AD)

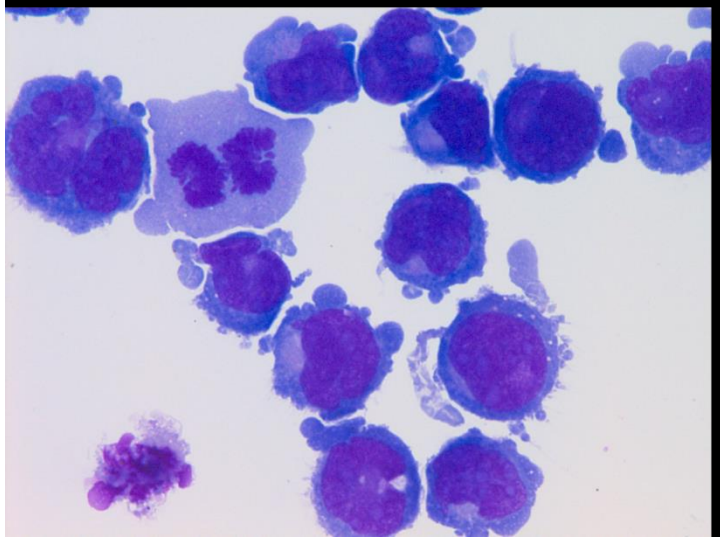


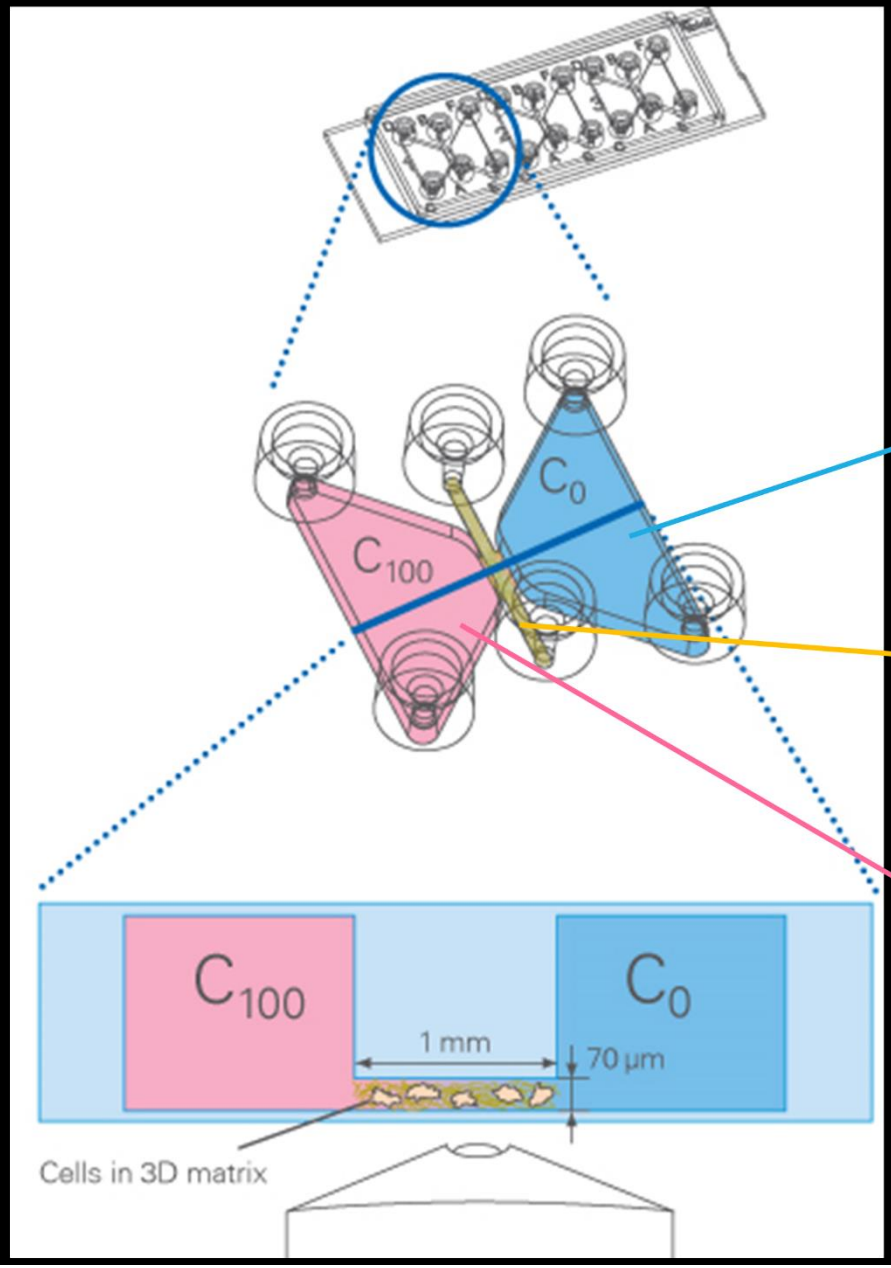
Boyden chambers

- ✓ Incubazione 90 minuti
- ✓ 50˙000 cellule/well



Ibidi Chambers



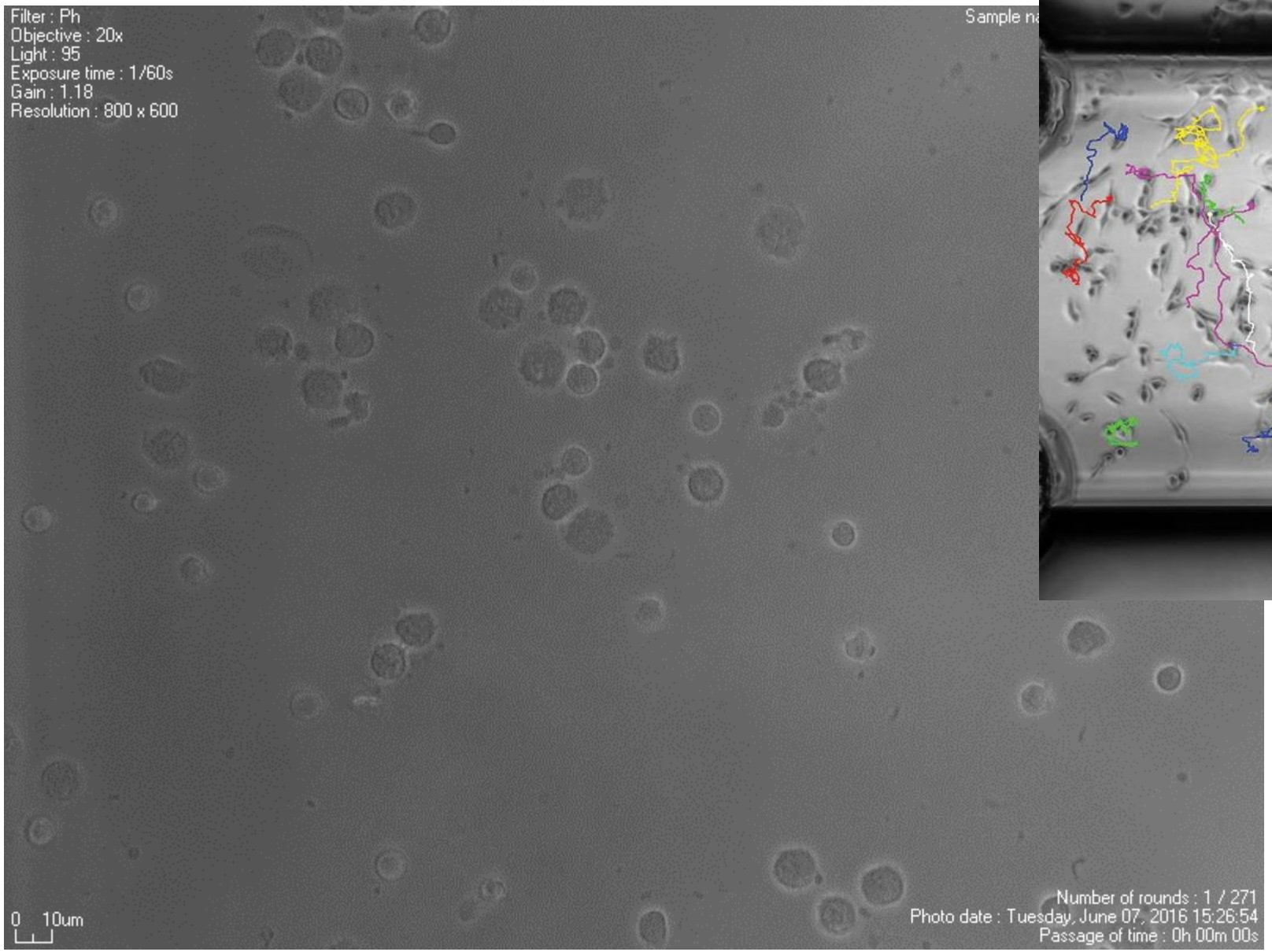


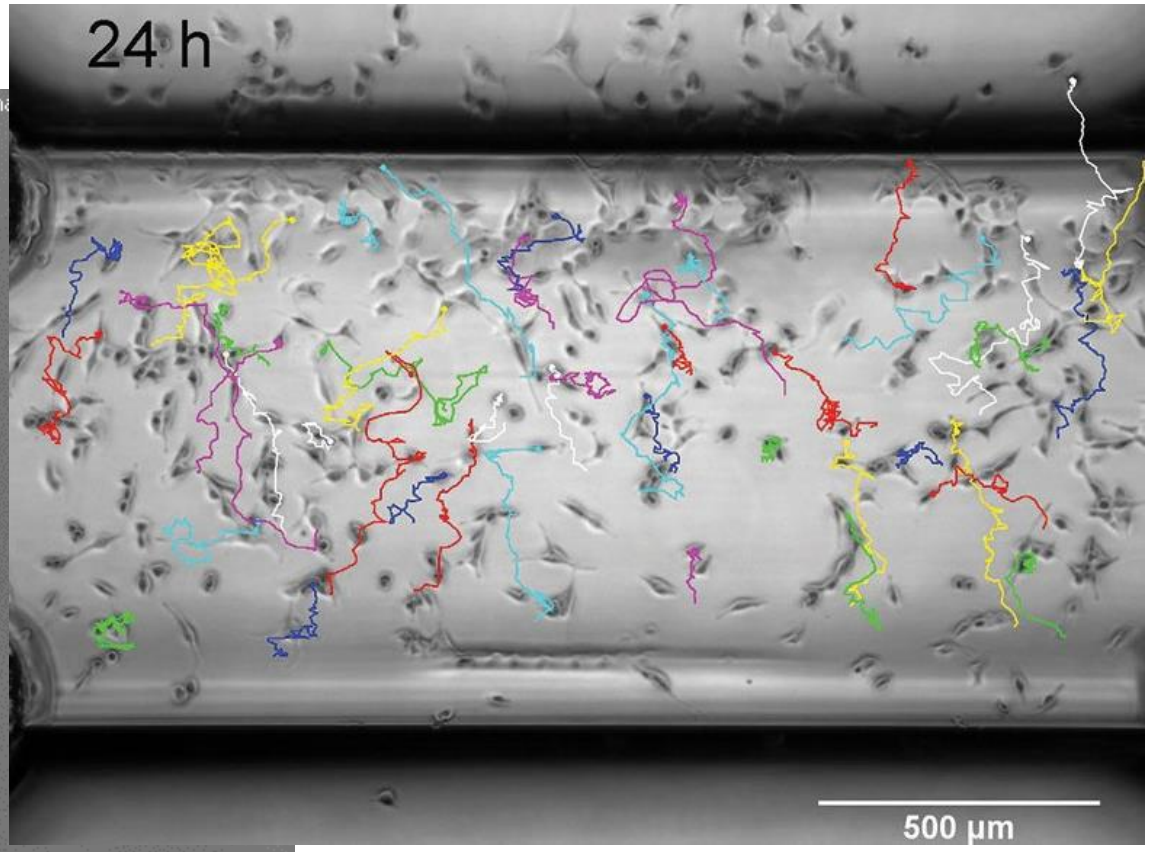
Basale
(RPMI con FBS 2%)

Cellule
(3*10⁶/ml)

Chemoattraente
(MCP-1 10 ng/ml
Abeta 125 nM)

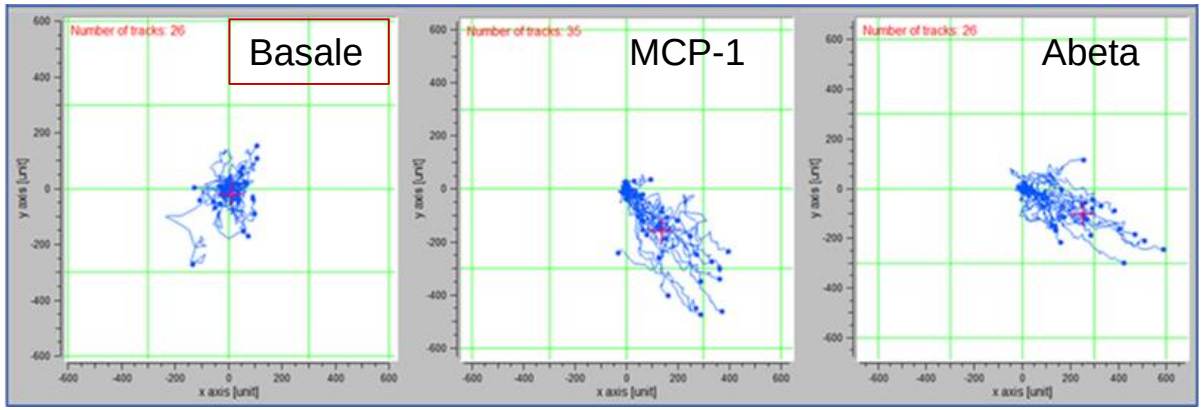
Time- lapse microscopy

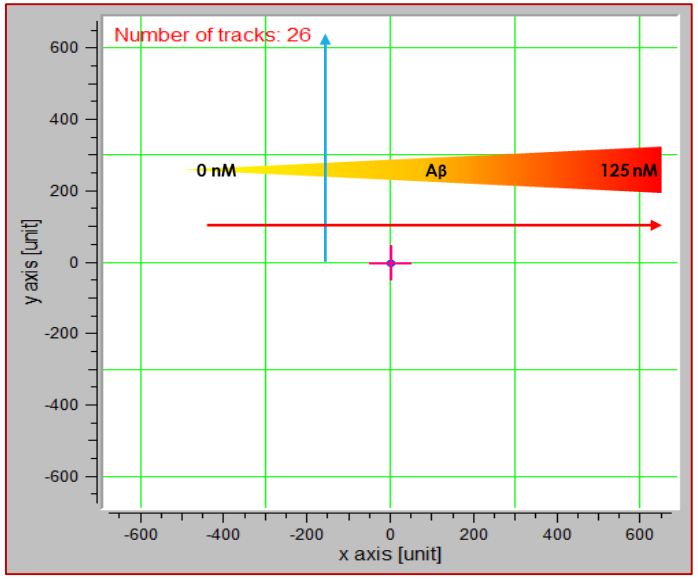


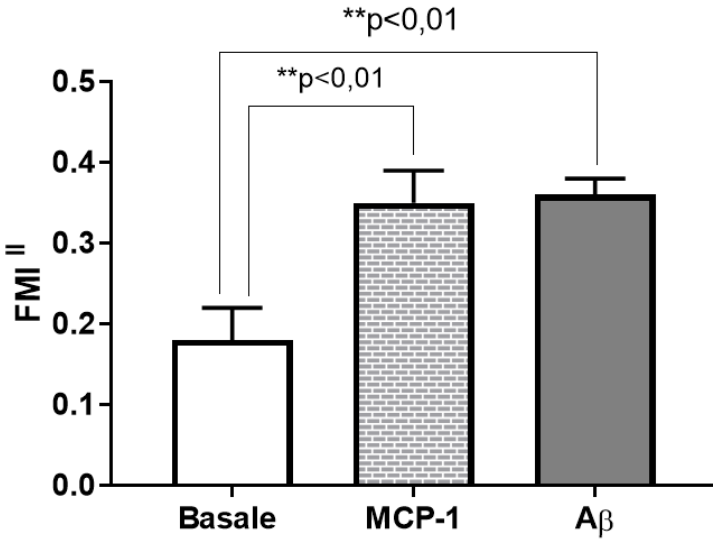


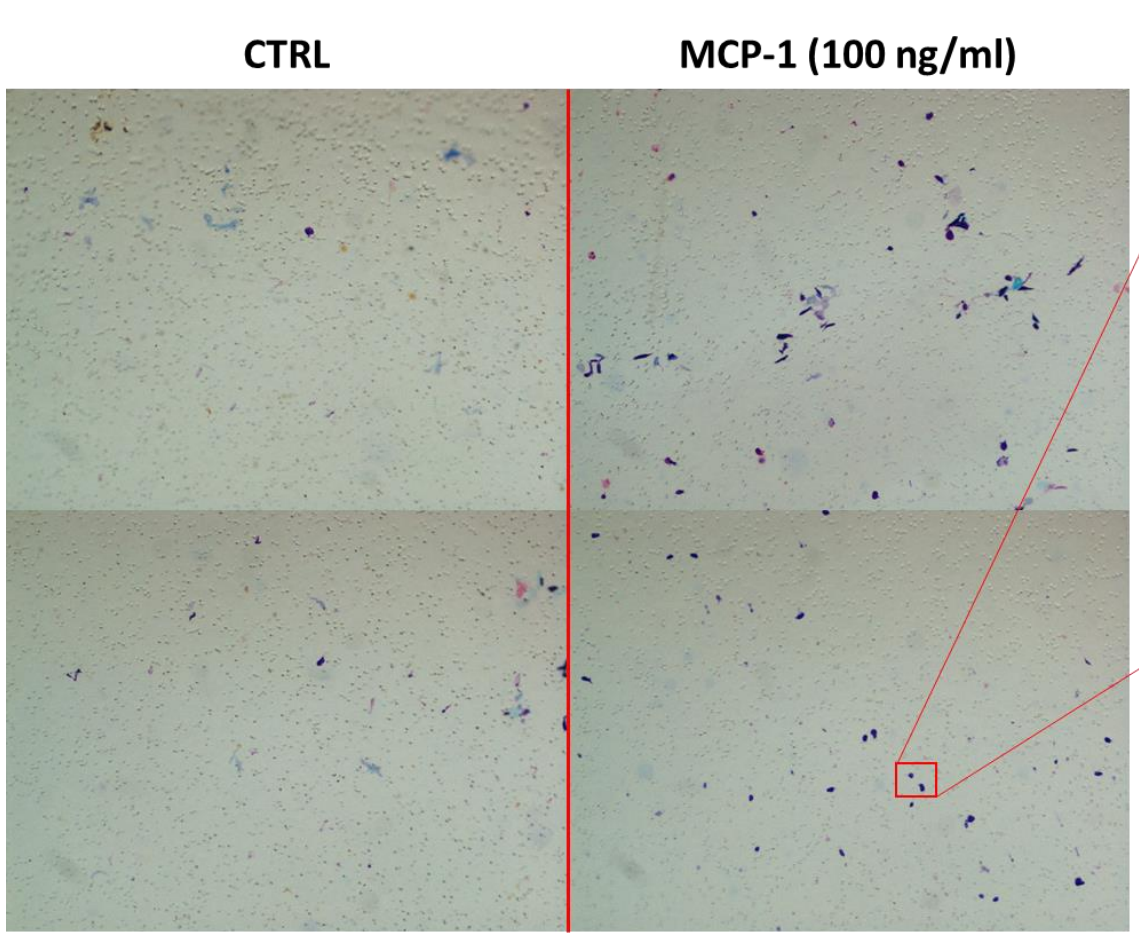
Results: Abeta induces chemotaxis

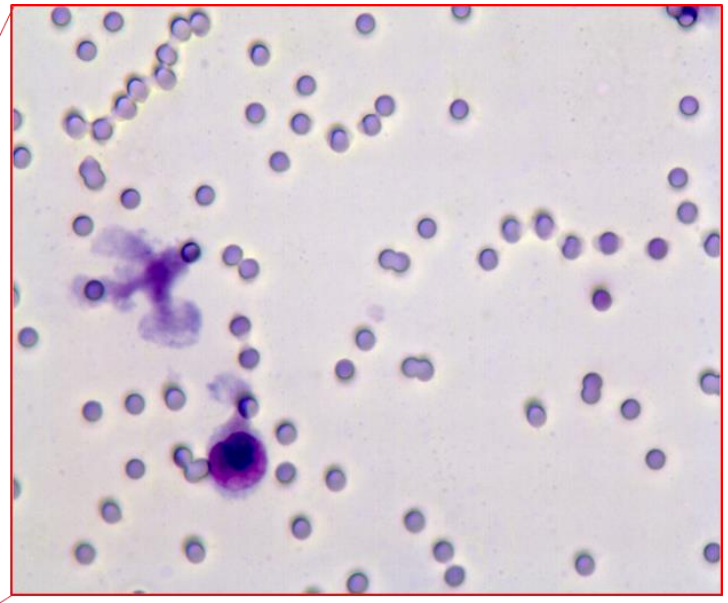
THP-1







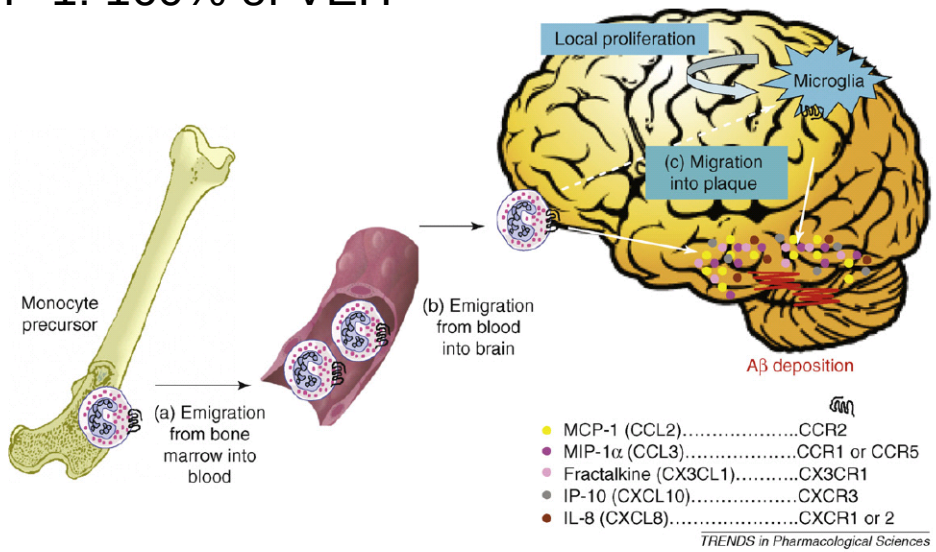




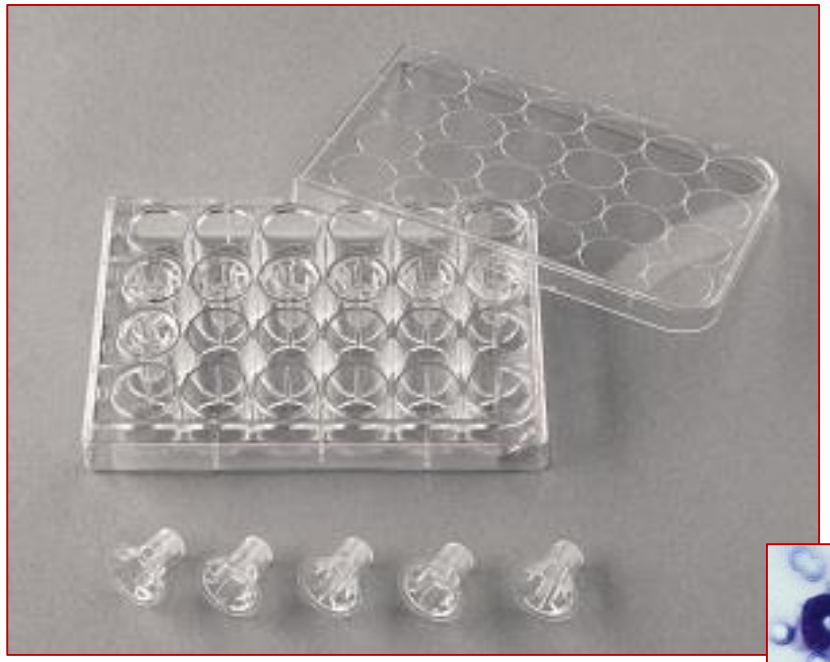
MCP-1: 160% of VEH

Monocyte Chemotaxis

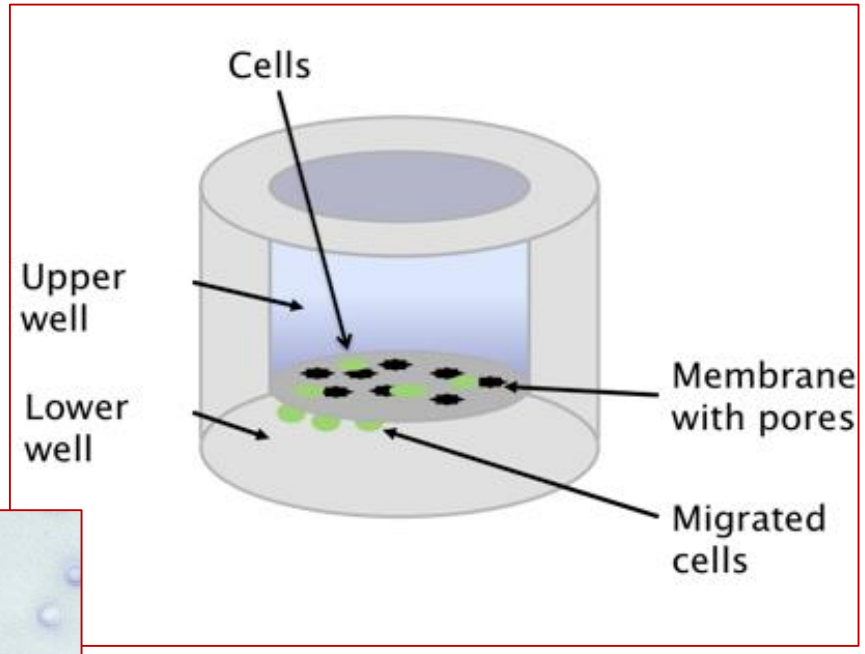
- MCP-1 (CCL-2) ⟶ CCR2
- TSPO receptor



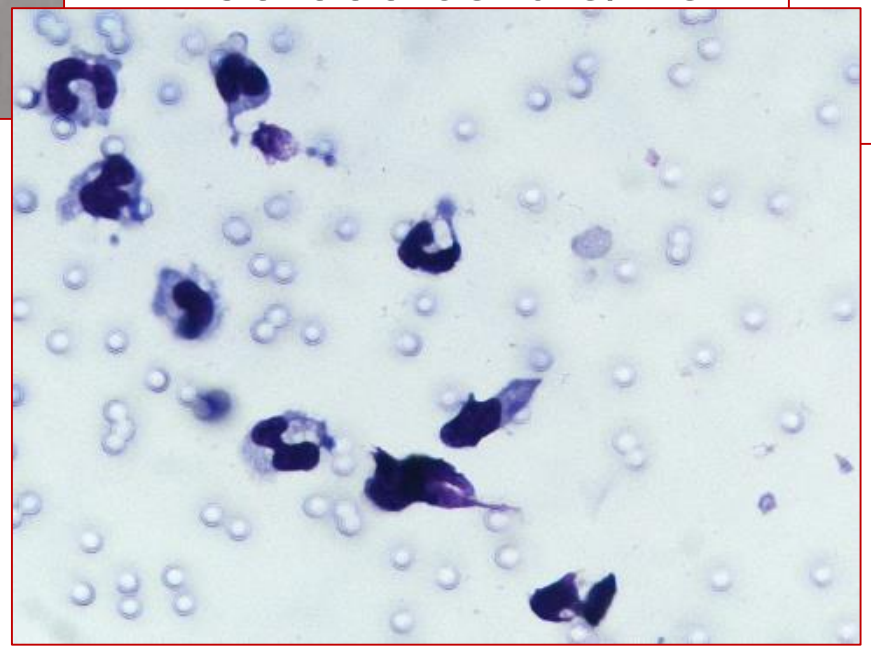
Monociti umani
(da CTRL e AD)



Boyden chambers

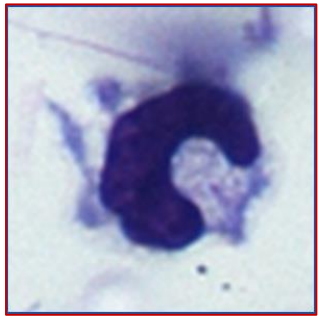


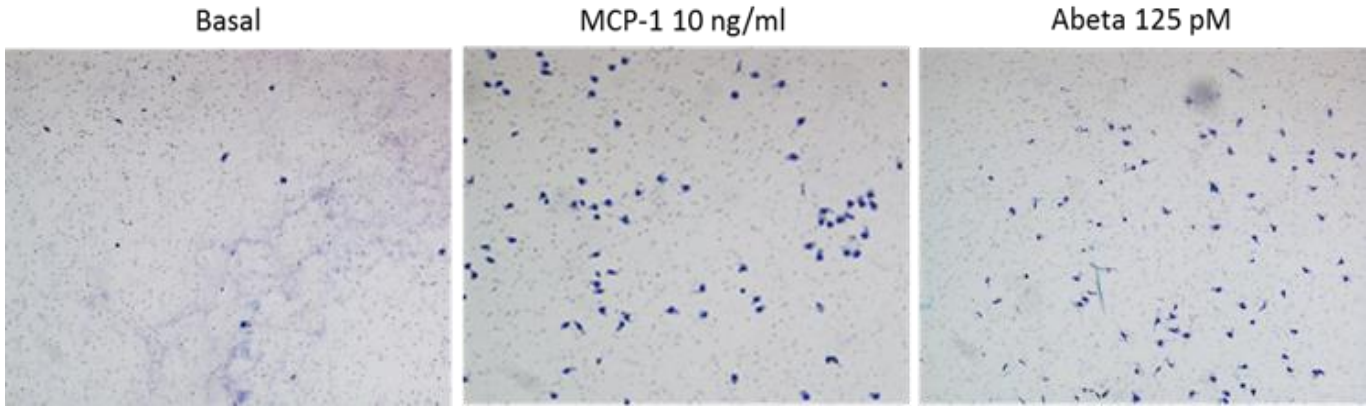
✓Incubazione 90 minuti
✓50˙000 cellule/well

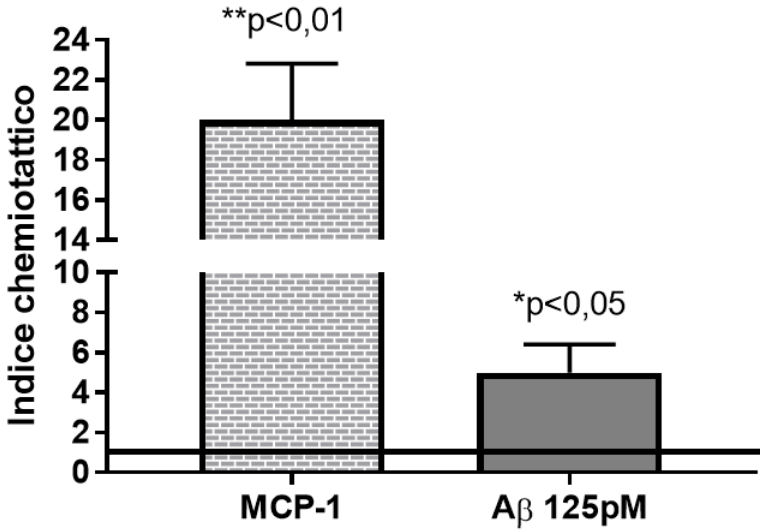


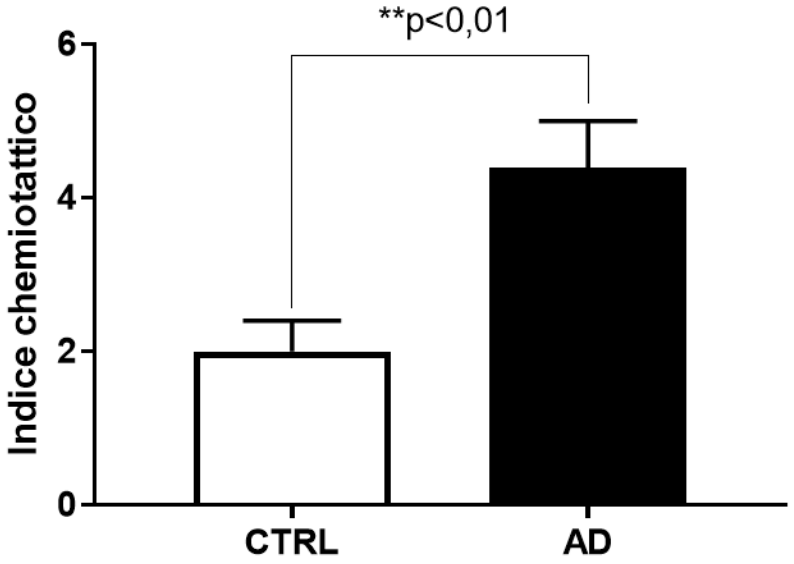
Results: Abeta induces chemotaxis

Human monocytes

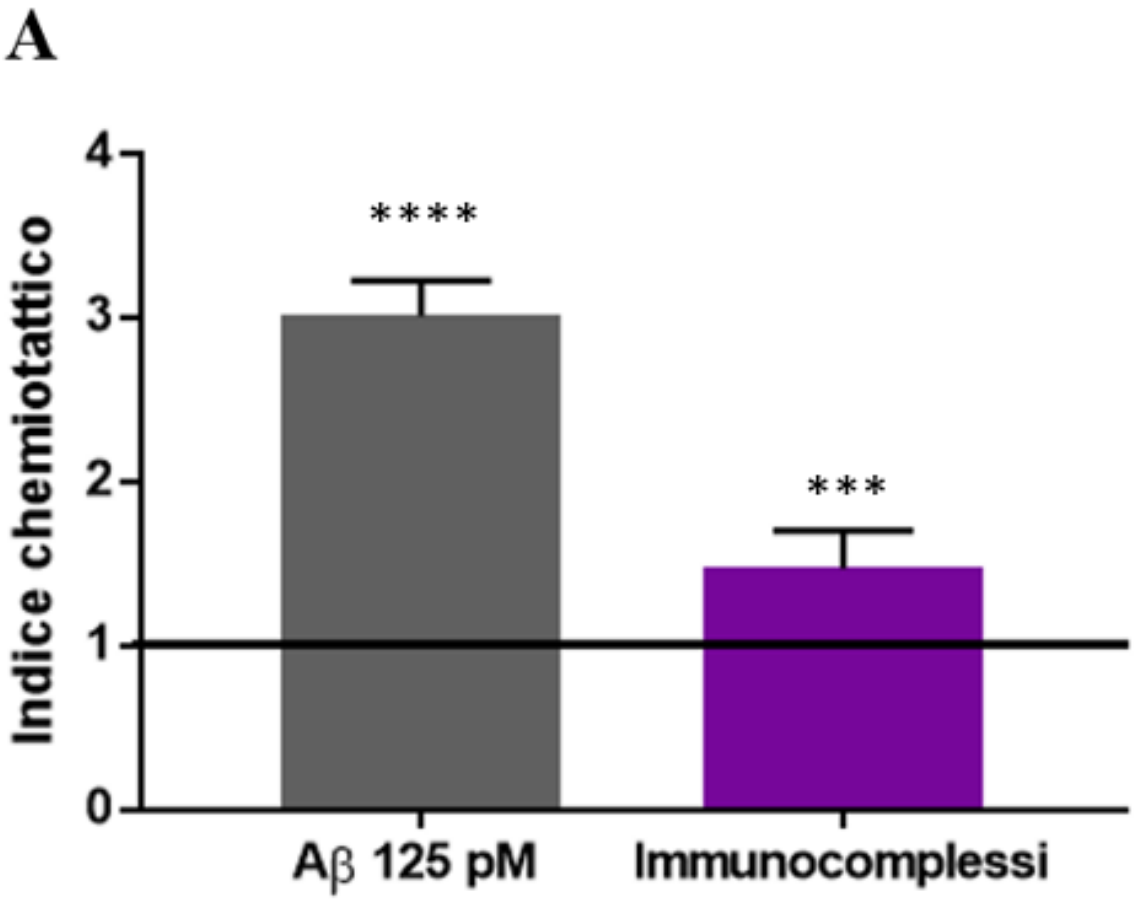




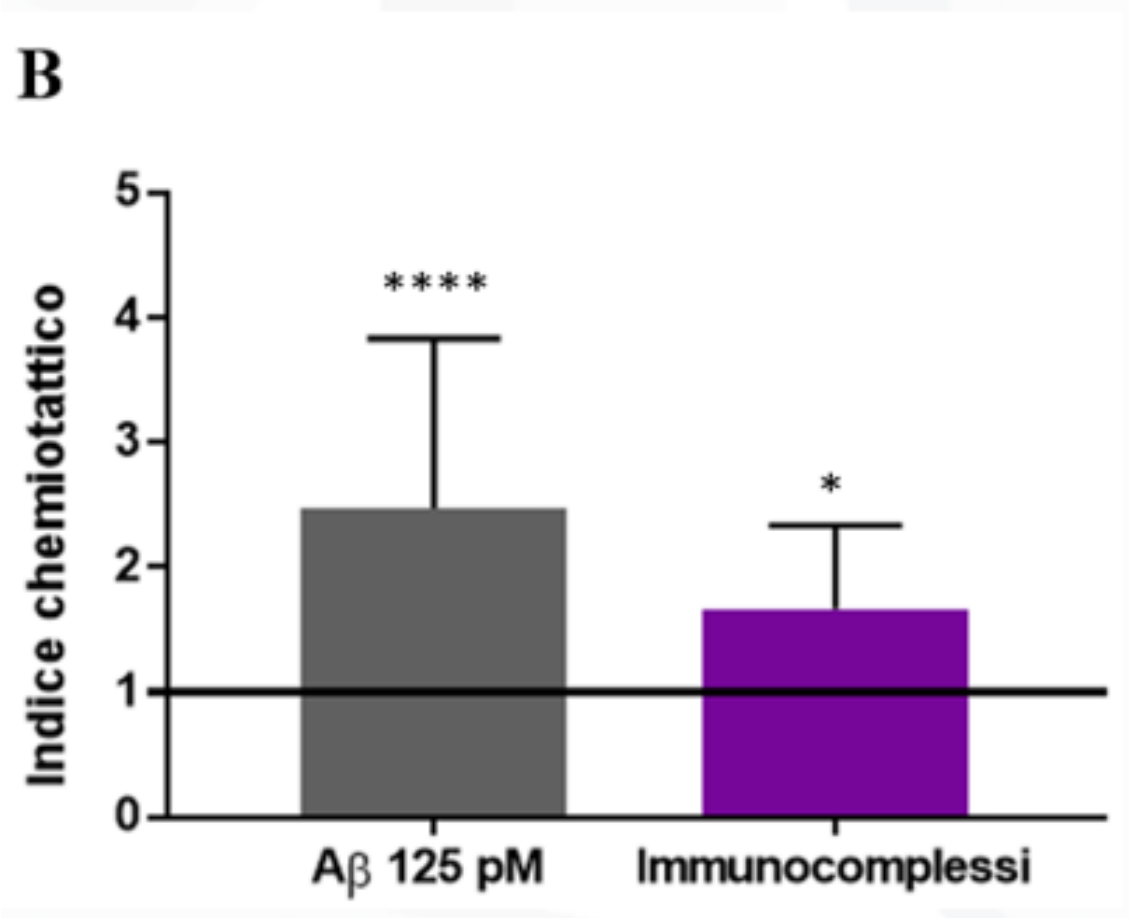




Results: anti Abeta antibodies block chemotaxis in cell line and human monocytes

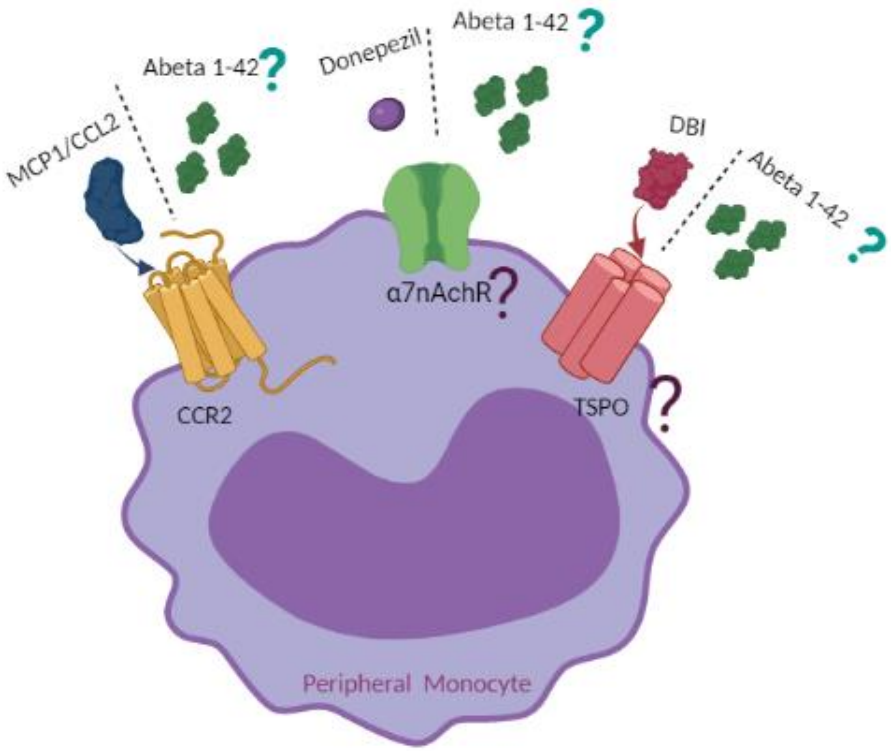


U937

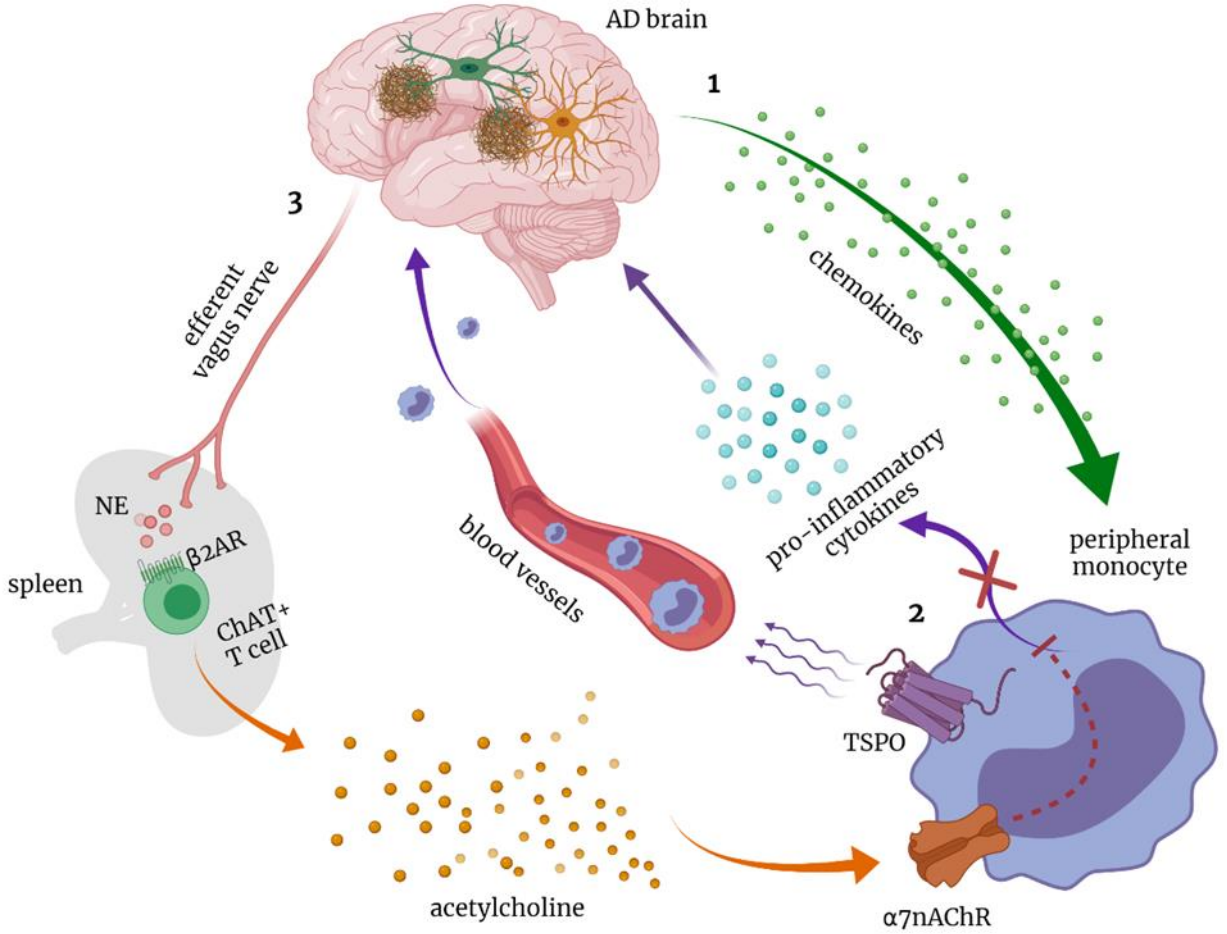


AD Monocytes

Which receptors may be involved in Abeta-induced chemotaxis?



Created with BioRender.com



diagnostics

MDPI

Review

Biomarkers of neuroinflammation in Alzheimer's disease: a central role for periphery?

Federica Angiulli,[1,2,3] Elisa Conti,[1,2] Chiara Paola Zoia,[1,2] Fulvio Da Re,[4] Ildebrando Appollonio,[1,2,4] Carlo Ferrarese,[1,2,4] Lucio Tremolizzo[1,2,4]


tspo
neuroinflammation
microglia
pet
program
tracer
month
trainee
training
clinical
neuroscience
quantification
pk11195
brain
surged
supervised
novel
neurodegenerative
pathogenic
alzheimer
marker
positron
diseased
disease
probe
phase
elaboration
proponent
competent
gsk
mild
last
injury
state
imperial
immune
regarded
wealth
chronic
release
datum
amongst
industrial
resident
parkinson
participating
inform
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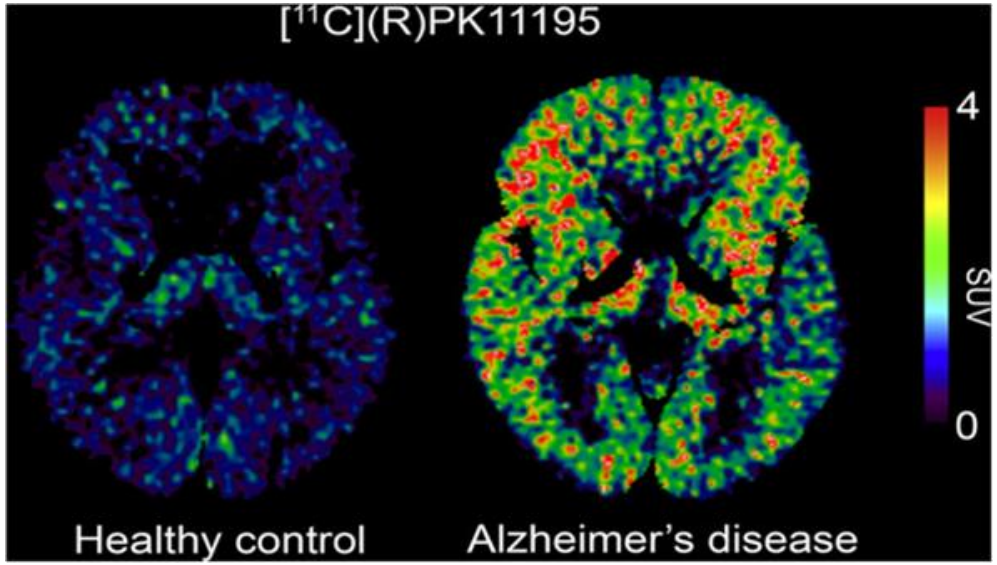
shape
metric
kinetic
nervou
sensitivity
labelled
started
graduate
characterize
pro
project
consistently
validation
normal
quantitative
imaging
breadth
acute
agent
content
immuno
emitter
partnership
define
expressed
referred
pathology
believe
academic
inflammatory
dependently
antagonist
exceptionally
sustain
look
centre
initiate
stage
sensitive
consist
vivo
strength
ligand
supply
year
mathematical
generally
candidate
post
pre
basic

Microglial activation is revealed by PK11195 binding to TSPO receptor



Zimmer *et al. Journal of Neuroinflammation* 2014, **11**:120

Brain (2000), **123**, 2321–2337

The peripheral benzodiazepine binding site in the brain in multiple sclerosis

Quantitative *in vivo* imaging of microglia as a measure of disease activity

R. B. Banati,[1,10] J. Newcombe,[4] R. N. Gunn,[1] A. Cagnin,[1] F. Turkheimer,[1] F. Heppner,[3,11] G. Price,[7] F. Wegner,[9] G. Giovannoni,[5] D. H. Miller,[5] G. D. Perkin,[3] T. Smith,[4,6] A. K. Hewson,[4,8] G. Bydder,[2] G. W. Kreutzberg,[10] T. Jones,[1] M. L. Cuzner[4] and R. Myers[1]

In-vivo measurement of activated microglia in dementia

THE LANCET • Vol 358 • August 11, 2001

Annachiara Cagnin, David J Brooks, Angus M Kennedy, Roger N Gunn, R Myers, Federico E Turkheimer, Terry Jones, Richard B Banati

Clinical Trial › Neurology. 2006 Jun 13;66(11):1638-43.
doi: 10.1212/01.wnl.0000222734.56412.17.

Microglial activation correlates with severity in Huntington disease: a clinical and PET study

N Pavese [1], A Gerhard, Y F Tai, A K Ho, F Turkheimer, R A Barker, D J Brooks, P Piccini

ORIGINAL ARTICLES Ann Neurol 2005;57:168–175

Microglial Activation and Dopamine Terminal Loss in Early Parkinson's Disease

Yasuomi Ouchi, MD, PhD,[1] Etsuji Yoshikawa, BA,[2] Yoshimoto Sekine, MD, PhD,[1,2] Masami Futatsubashi, BA,[2] Toshihiko Kanno, RT,[1] Tomomi Ogusu, MA,[2] Tatsuo Torizuka, MD, PhD[1]

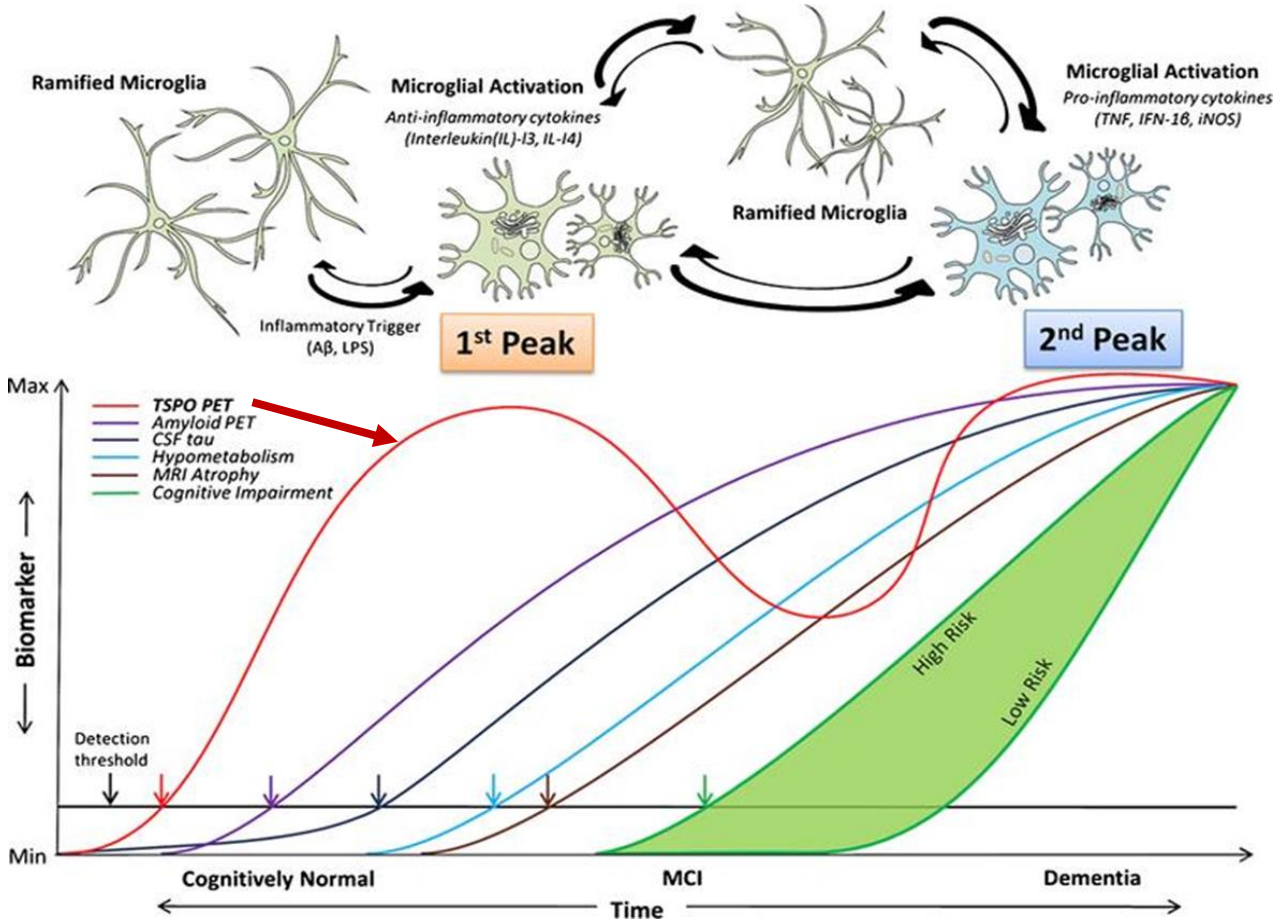
Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [11C](R)-PK11195 positron emission tomography study

Neurobiology of Disease 15 (2004) 601–609

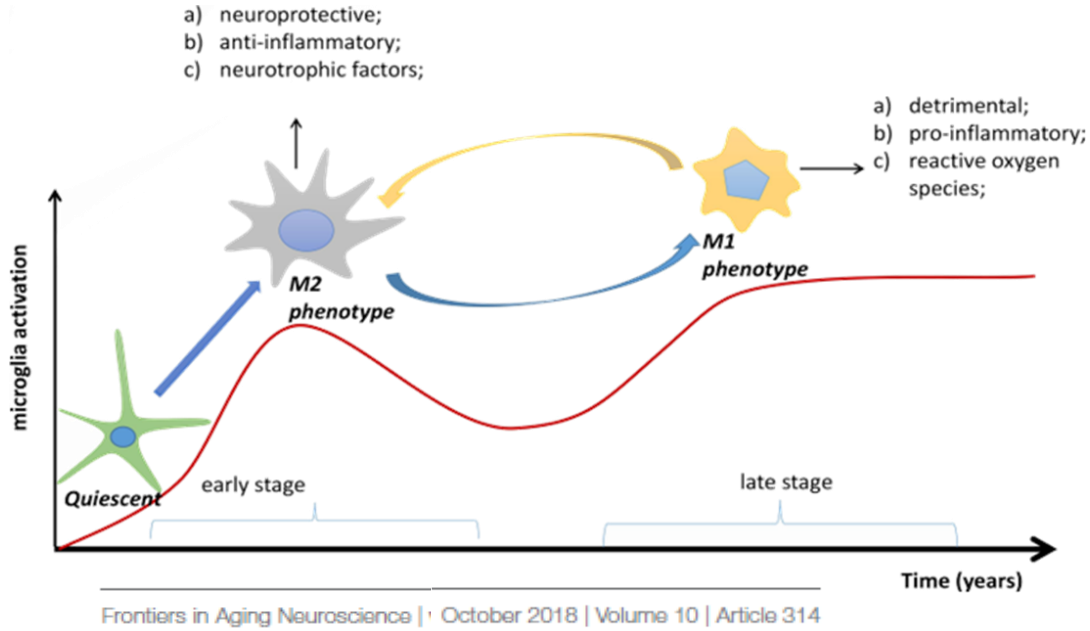
M.R. Turner,[a,b,*] A. Cagnin,[c] F.E. Turkheimer,[b,d] C.C.J. Miller,[a] C.E. Shaw,[a] D.J. Brooks,[b,e] P.N. Leigh,[a] and R.B. Banati[b,d]

Role of Neuroinflammation in the Trajectory of Alzheimer's Disease and *in vivo* Quantification Using PET

Paul Edison[a,*] and David J. Brooks[b,c]



P. Edison and D.J. Brooks Journal of Alzheimer's Disease 64 (2018) S339–S351



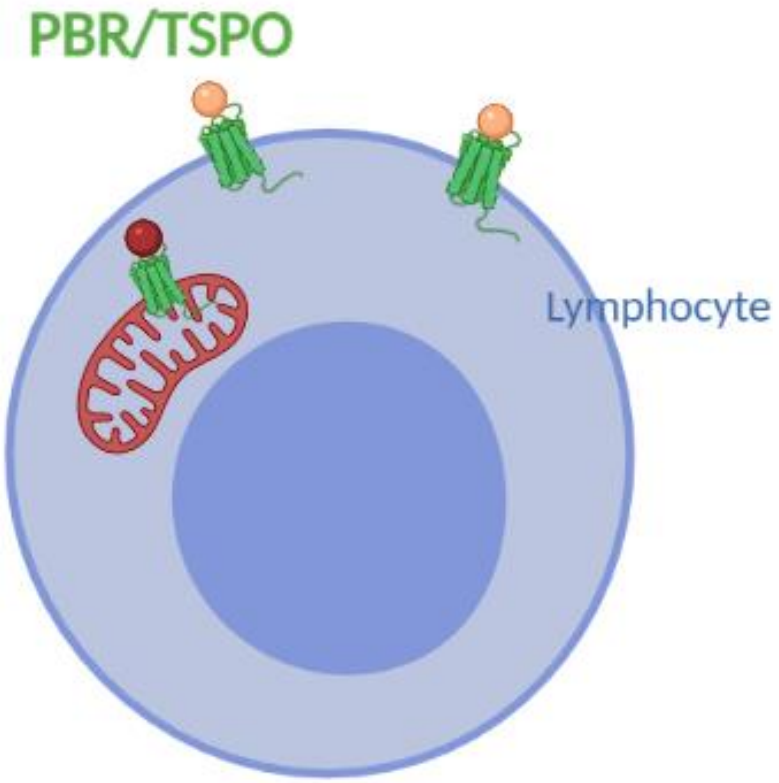
Frontiers in Aging Neuroscience | October 2018 | Volume 10 | Article 314

TSPO is a negative regulator of microglial activation and it reduces inflammation. An up-regulation of TSPO in activated microglia correspond to an adaptive response to reduce inflammation

Life Sciences
Volume 52, Issue 15, 1993, Pages 1265-1277

Topology of two DBI receptors in human lymphocytes

Alla Berkovich, Carlo Ferrarese, Guido Cavaletti, Hannu Alho, Claudia Marzorati, Graziella Bianchi, Alessandro Guidotti, Erminio Costa

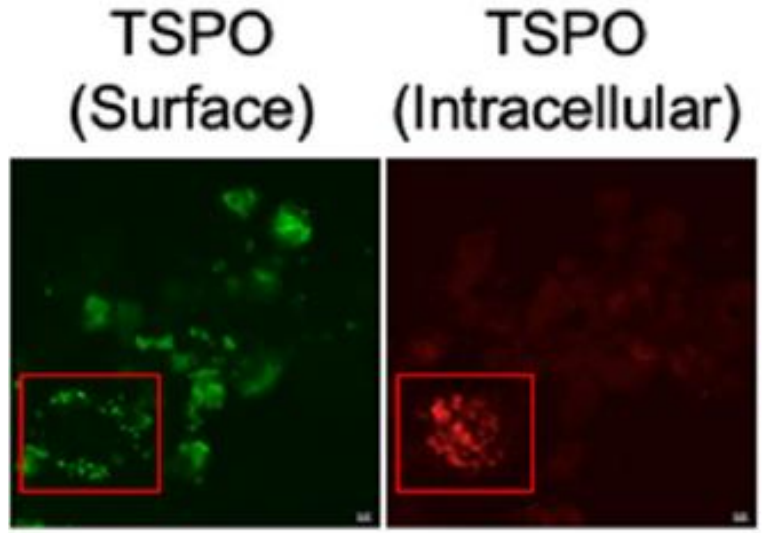


PBR/TSPO is present on mitochondrial and plasma membrane

Surface translocator protein 18 kDa (TSPO) localization on immune cells upon stimulation with LPS and in ART-treated HIV+ subjects

J Leukoc Biol. 2021;110:123–140.

Lance K. Blevins[1] | Robert B. Crawford[1] | Diana J. Azzam[2] | Tomás R. Guilarte[2] | Norbert E. Kaminski[1]

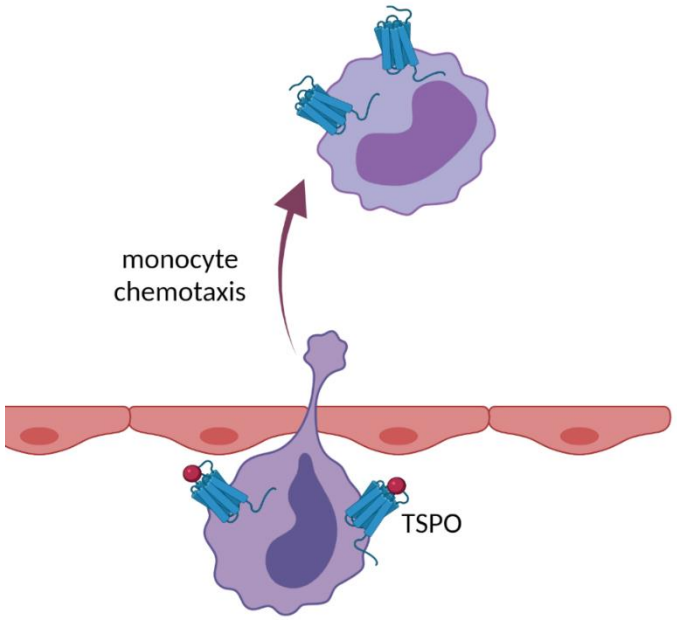


Life Sciences, Vol. 53, pp. 653-658 1993
Printed in the USA

Pergamon Press

BENZODIAZEPINE INDUCED CHEMOTAXIS OF HUMAN MONOCYTES: A TOOL FOR THE STUDY OF BENZODIAZEPINE RECEPTORS

Paola Sacerdote, Luisa D.Locatelli,
Alberto E.Panerai



Acta Psychiatr Scand. 1990 Aug;82(2):169-73.

Decreased density of benzodiazepine receptors in lymphocytes of anxious patients: reversal after chronic diazepam treatment.

Ferrarese C, Appollonio I, Frigo M, Perego M, Piolti R, Trabucchi M, Frattola L.

PERGAMON

PNEC

Psychoneuroendocrinology 24 (1999) 243–249

Benzodiazepine-induced chemotaxis is impaired in monocytes from patients with generalized anxiety disorder

P. Sacerdote [a,*], A.E. Panerai [a], L. Frattola [b], C. Ferrarese [b]

Journal of Cerebral Blood Flow & Metabolism (2013) 33, 53–58

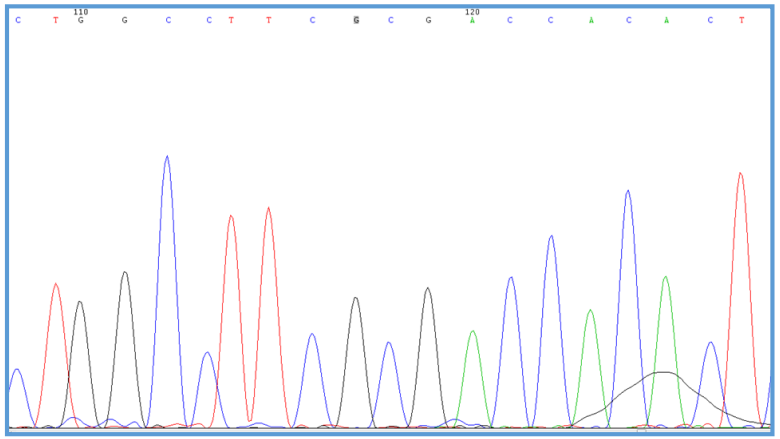
www.jcbfm.com

ORIGINAL ARTICLE

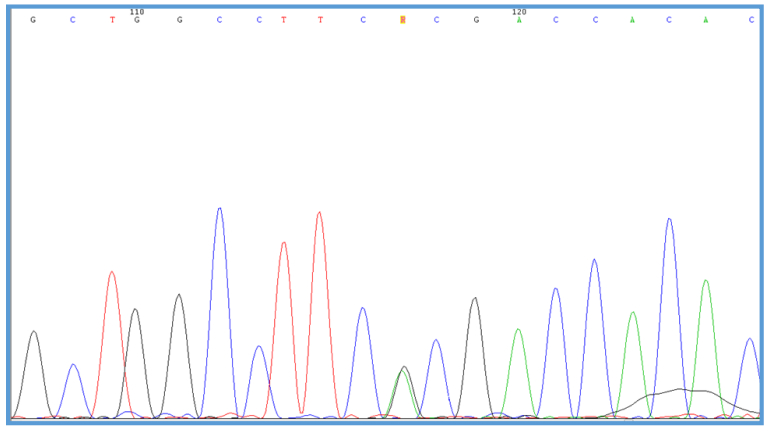
A genetic polymorphism for translocator protein 18 kDa affects both *in vitro* and *in vivo* radioligand binding in human brain to this putative biomarker of neuroinflammation

Second-generation radioligands for translocator protein (TSPO), an inflammation marker, are confounded by the codominant rs6971 polymorphism that affects binding affinity. The resulting three groups are homozygous for high-affinity state (HH), homozygous for low-affinity state (LL), or heterozygous (HL). We tested if *in vitro* binding to leukocytes distinguished TSPO

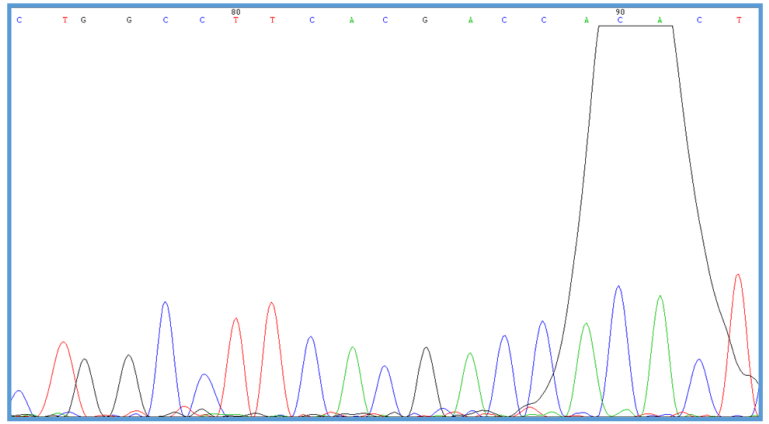
G/G H/H 49%



A/G L/H 42%



A/A L/L 9%



Mechanisms involved in Abeta induced chemotaxis:
Possible role of PBR/TSPO receptor?

Neuropharmacology Vol. 29, No. 4, pp. 375–378, 1990
Printed in Great Britain.

CHARACTERIZATION OF PERIPHERAL BENZODIAZEPINE RECEPTORS IN HUMAN BLOOD MONONUCLEAR CELLS

C. FERRARESE,[1,*] I. APPOLLONIO,[1] M. FRIGO,[1] M. PEREGO,[1] C. PIERPAOLI,[1] M. TRABUCCHI[2] and L. FRATTOLA[1]

Opinion TRENDS in Pharmacological Sciences Vol.27 No.8

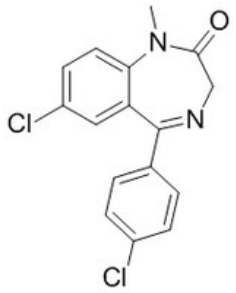
Translocator protein (18 kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function

Vassilios Papadopoulos[1], Mario Baraldi[2], Tomás R. Guilarte[3], Thomas B. Knudsen[4], Jean-Jacques Lacapère[5], Peter Lindemann[6], Michael D. Norenberg[7], David Nutt[8], Abraham Weizman[9], Ming-Rong Zhang[10] and Moshe Gavish[11]

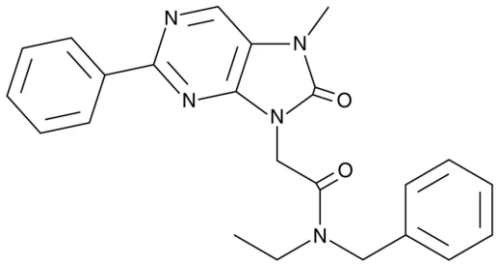
Exogenous PBR (TSPO) ligands

Agonists

- Ro5-4864

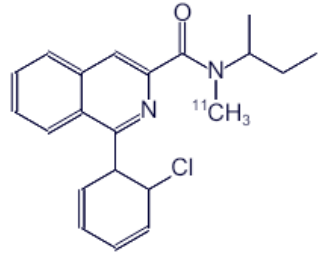


- Emapunil (XBD-173)



Antagonist

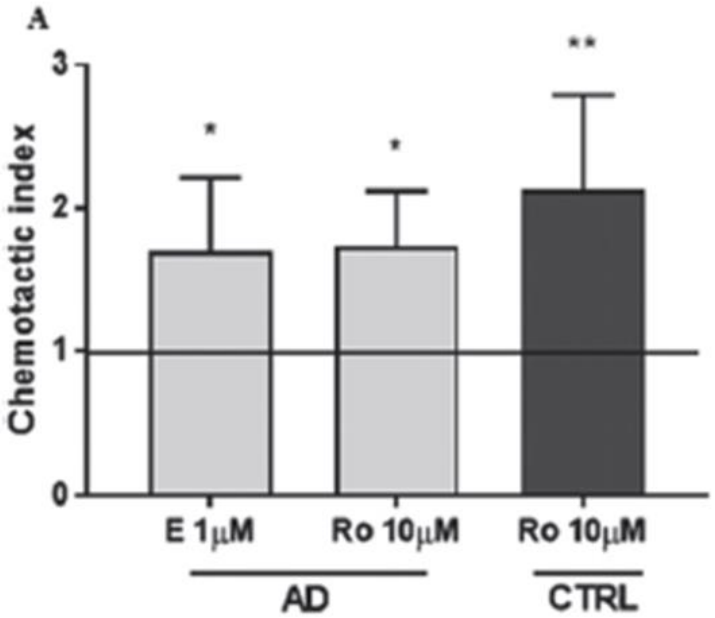
- PK11195

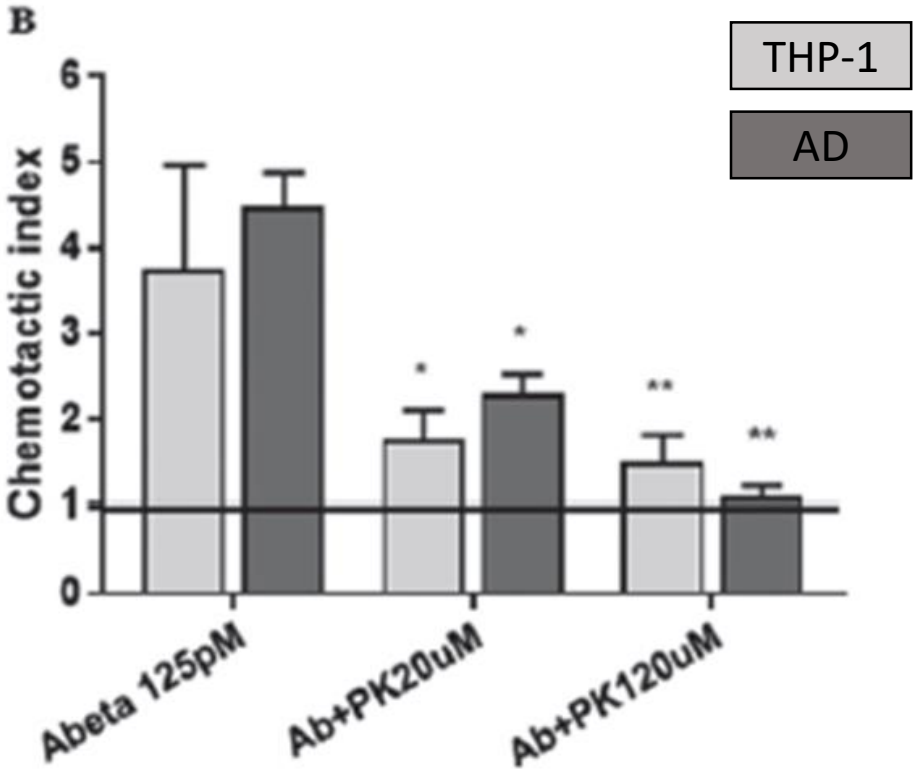


Results: TSPO pharmacological modulation

TSPO Agonist: **Ro5-4864 (10 µM) and Emapunil stimulate monocyte chemotaxis**

TSPO Antagonist: **PK-11195 blocks Abeta induced chemotaxis**



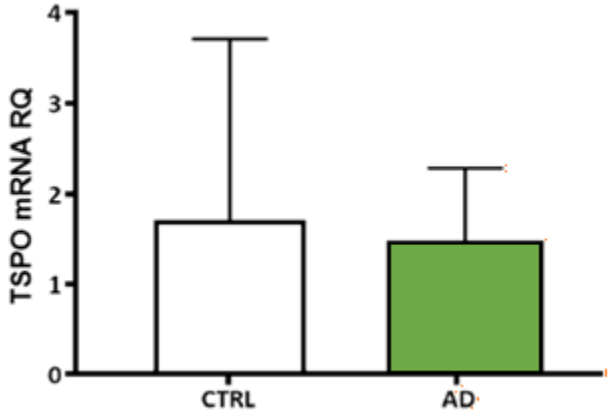


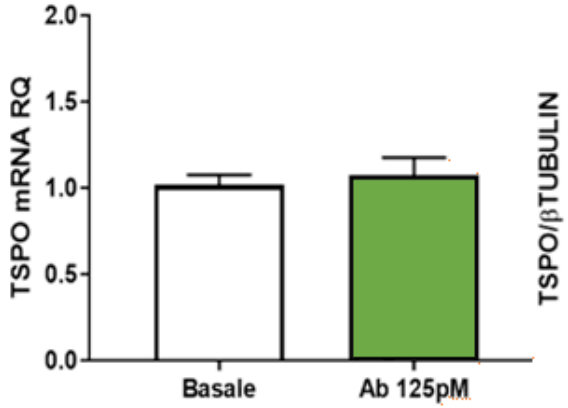
Results: TSPO and CCR2 expression

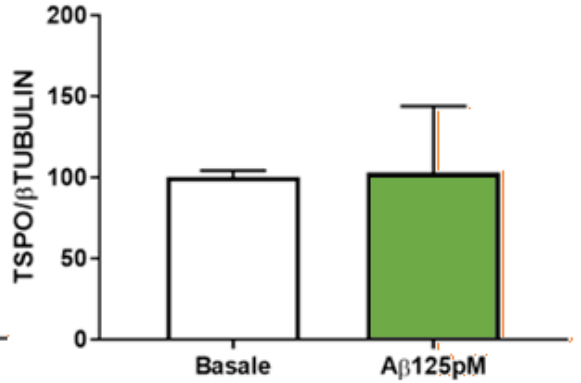
Human monocytes

THP-1:with Aβ 125pM

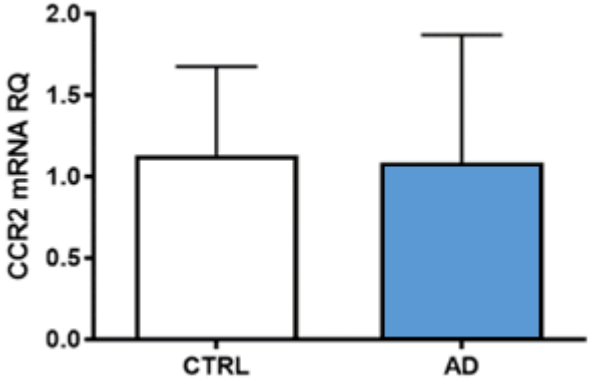
TSPO

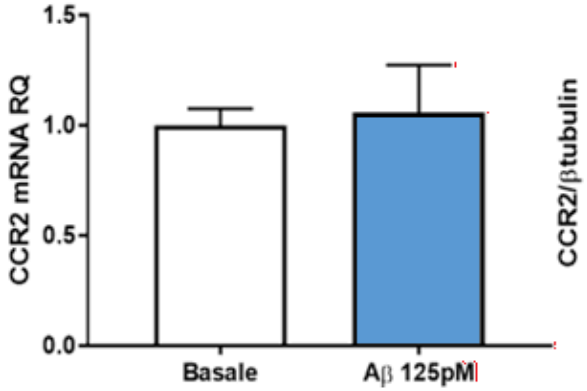


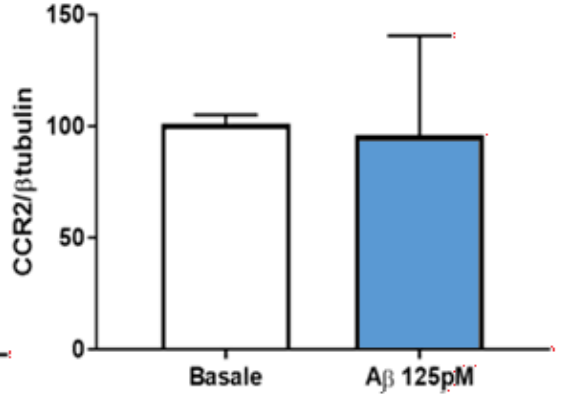




CCR2





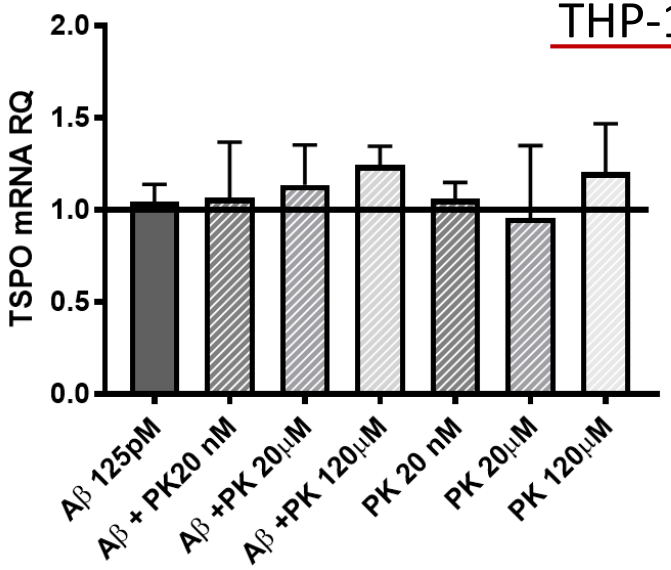


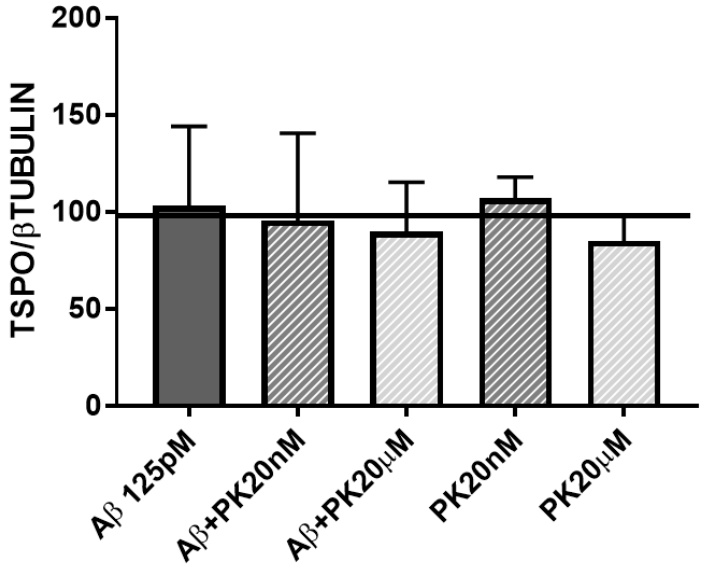
Results: TSPO pharmacological modulation

TSPO ligands: receptor expression

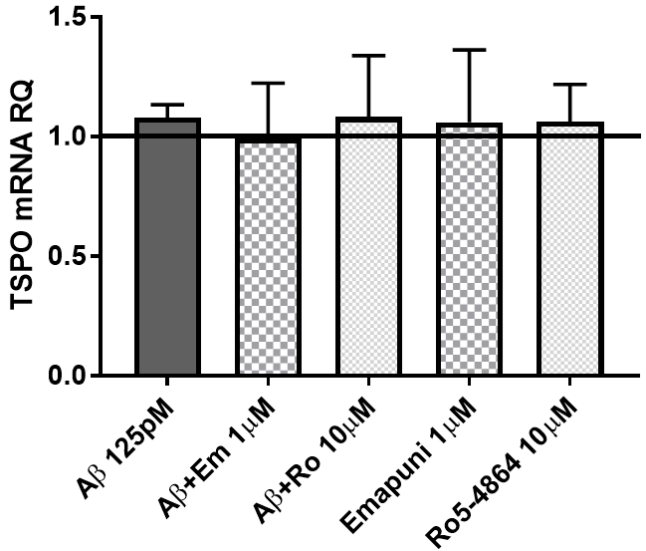
PK-11195

THP-1



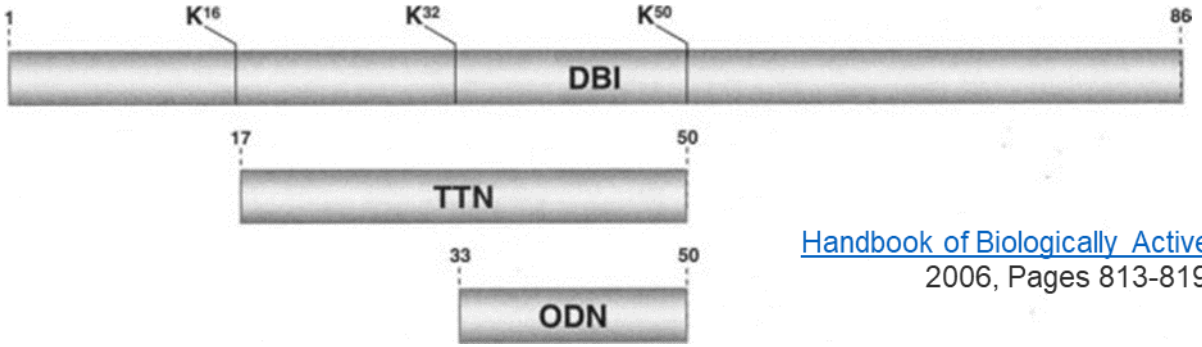


Emapunil, Ro5-4864



Abeta could increase soluble mediator levels but not levels of receptors.

Endogenous PBR/TSPO ligands: DBI (Diazepam Binding Inhibitor)



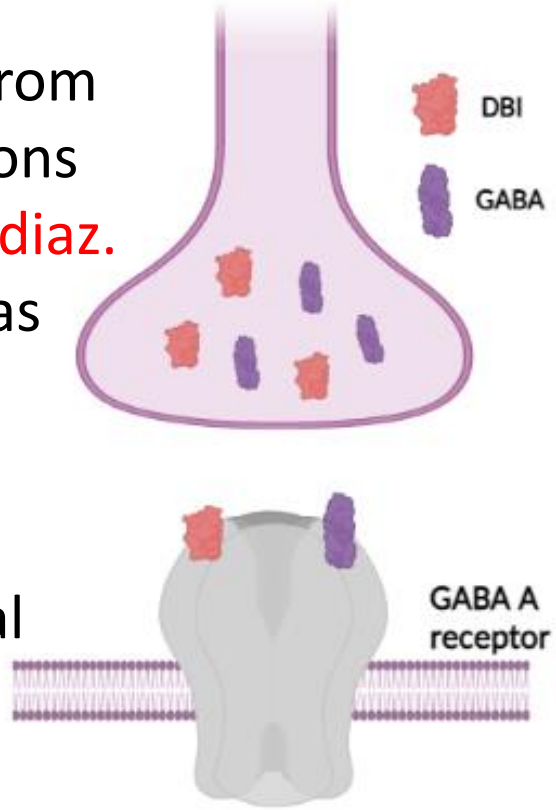
PROCESSING OF DBI (biologically active peptides):
- triakontatetraneuropeptide TTN (DBI17–50)
- octadecaneuropeptide ODN (DBI33–50)

Handbook of Biologically Active Peptides
2006, Pages 813-819

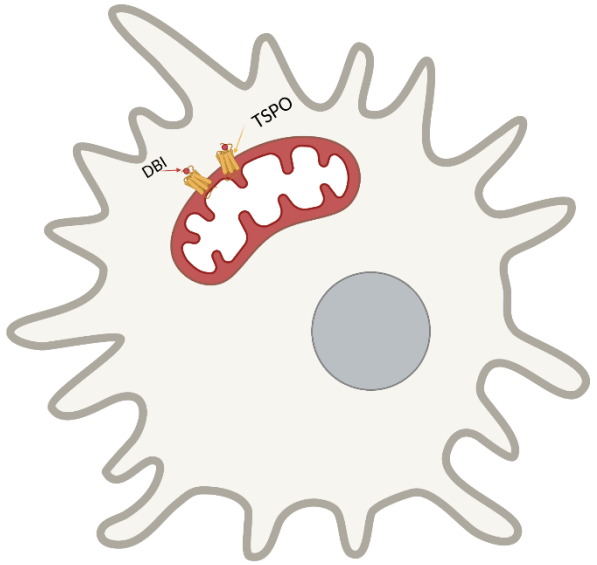
1. DBI is released from GABAergic neurons

Binds Central Benzodiaz. Receptors and acts as negative allosteric modulator

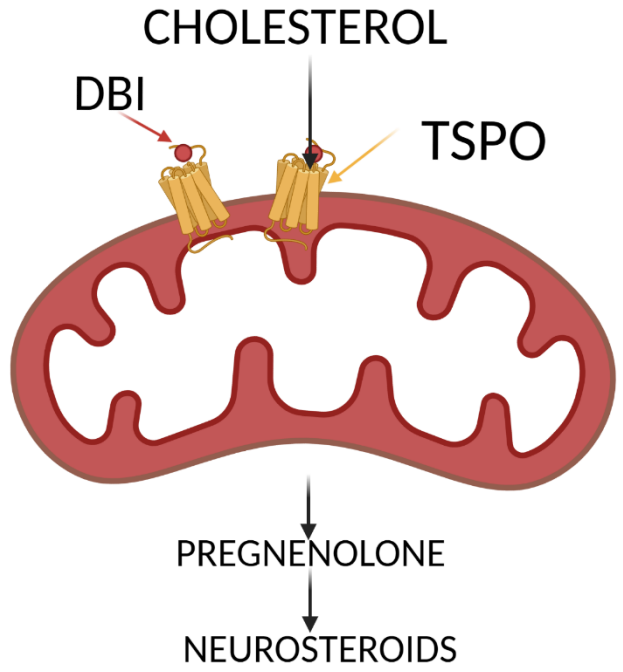
→ansiogenic and epileptogenic clinical effect



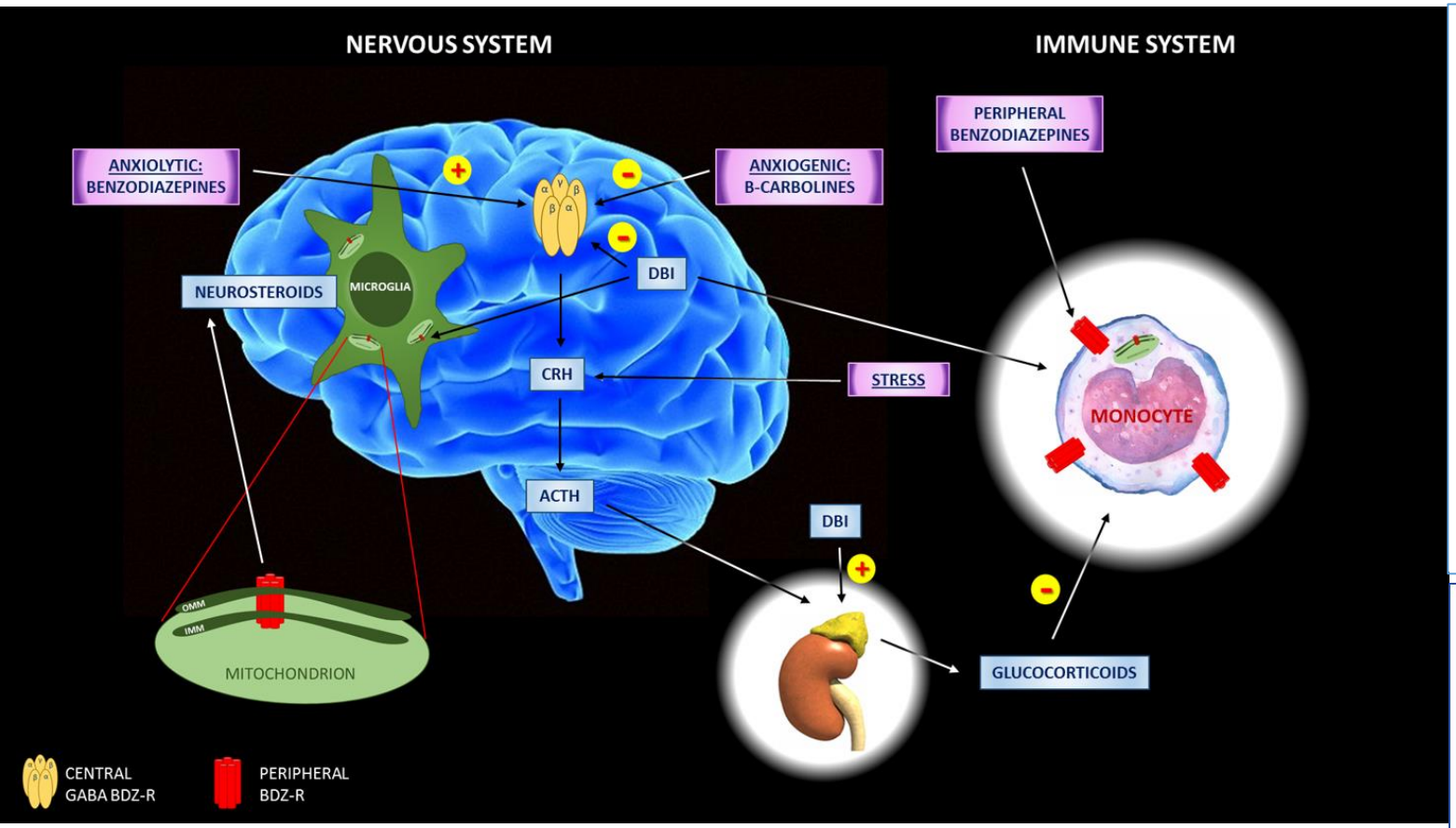
2. DBI binds PBR/TSPO in mitochondria of glial cells/steroidogenic glands and lymphomonocytes

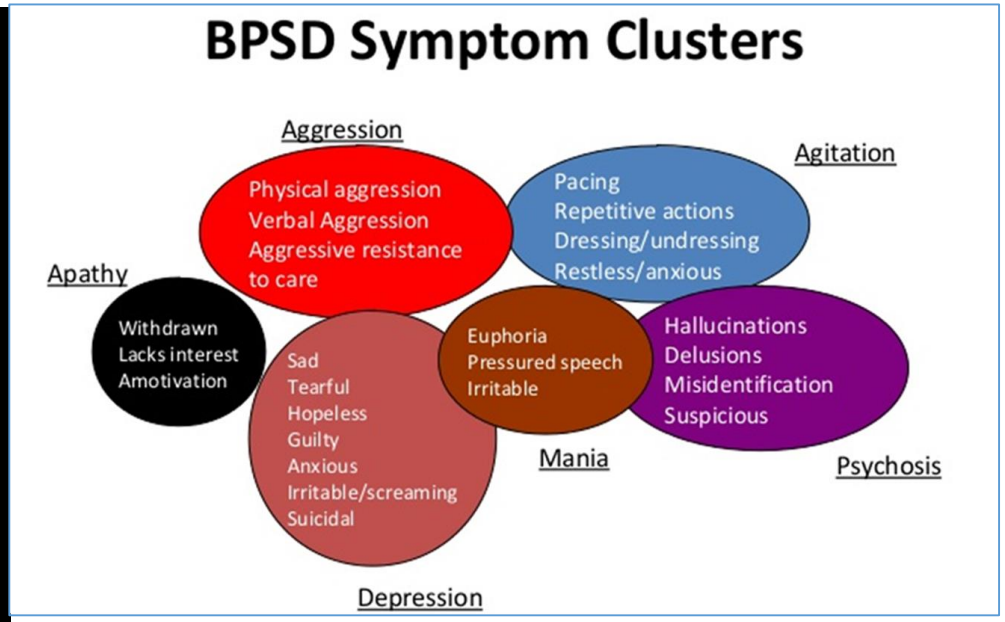


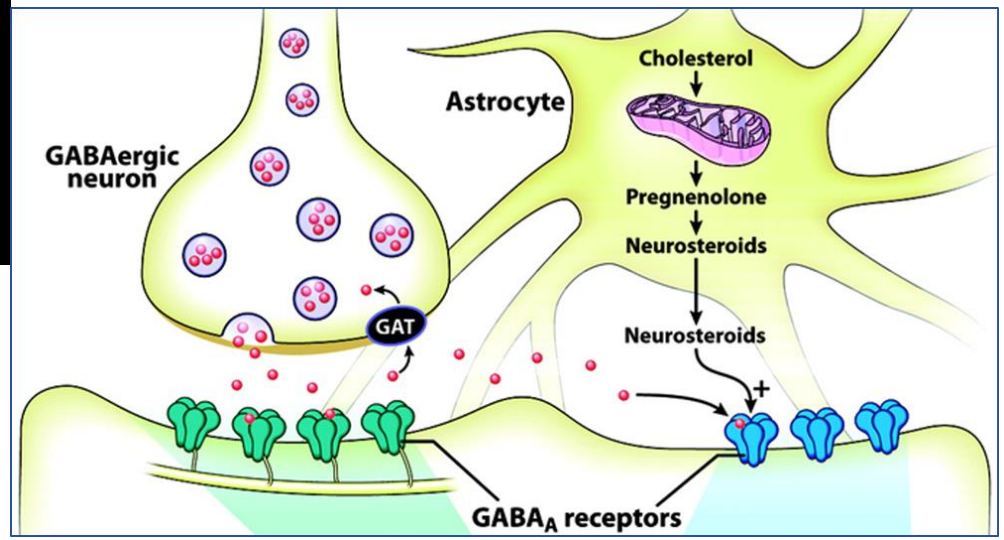
Glial cells, steroidogenic glands



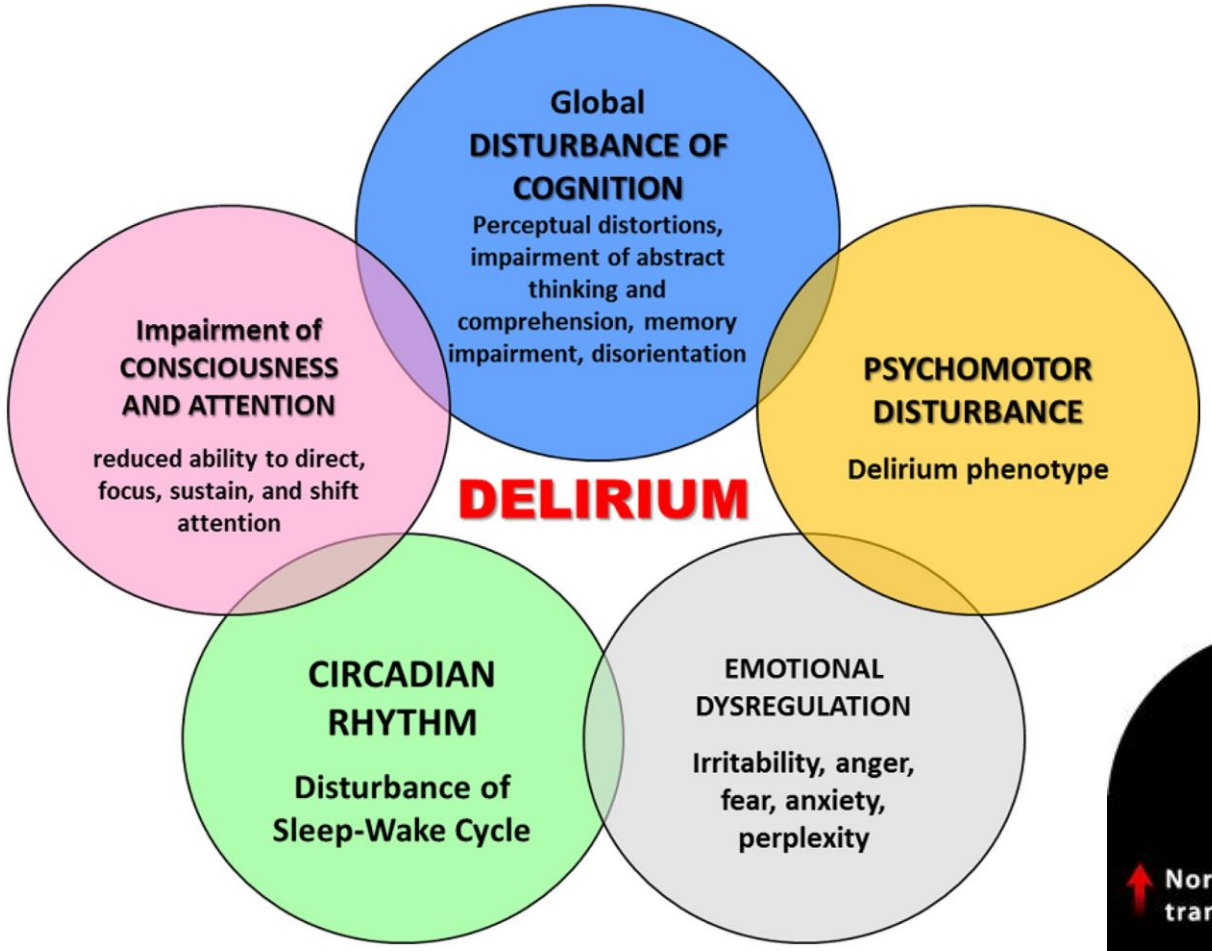
Neurinflammation oltre il piano cognitivo sul piano comportamentale?



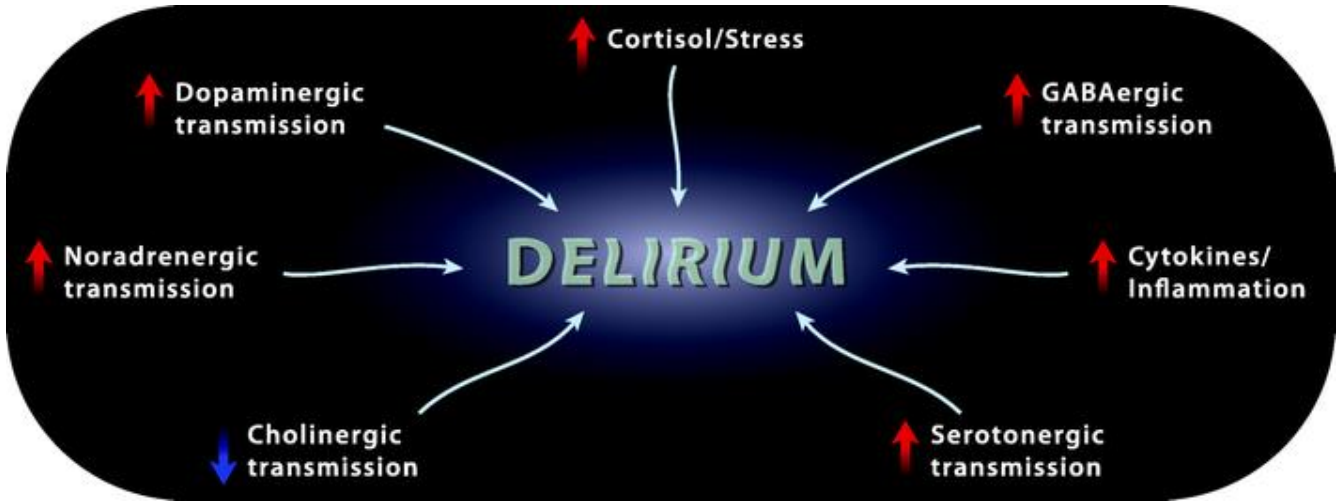




DELIRIUM



E’ un deficit acuto dell’attenzione e delle funzioni cognitive (soprattutto memoria, orientamento, identificazione delle persone).
E’ presente disorganizzazione di comportamento, comunicazione, ritmo sonno-veglia.

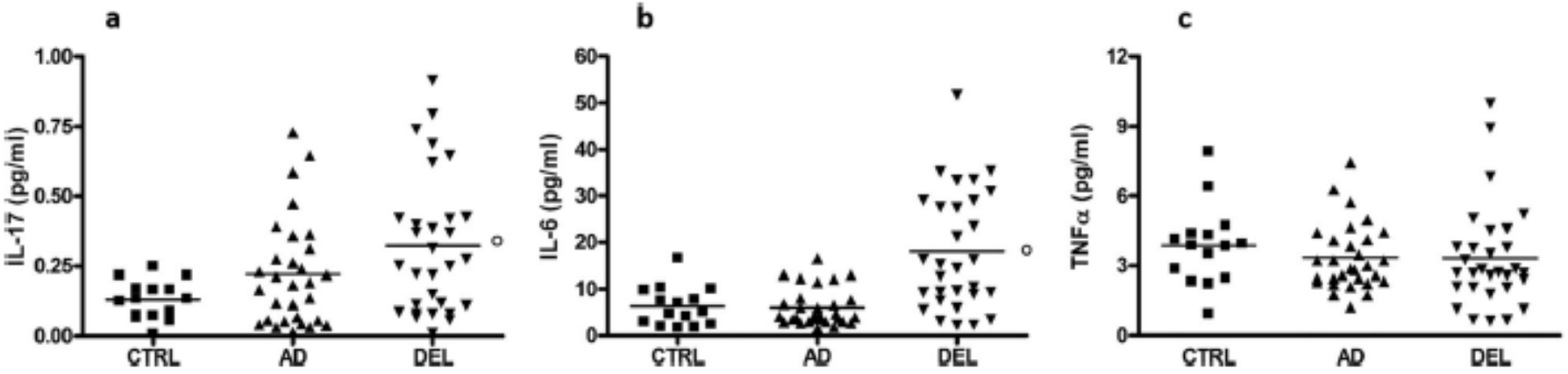


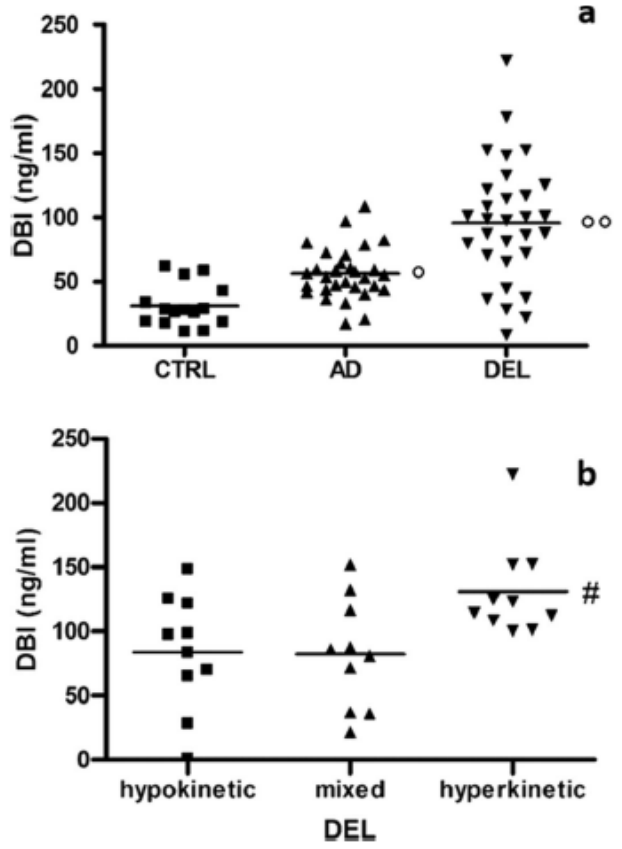
Neurological Sciences
https://doi.org/10.1007/s10072-020-04608-x

ORIGINAL ARTICLE

Serum DBI and biomarkers of neuroinflammation in Alzheimer's disease and delirium

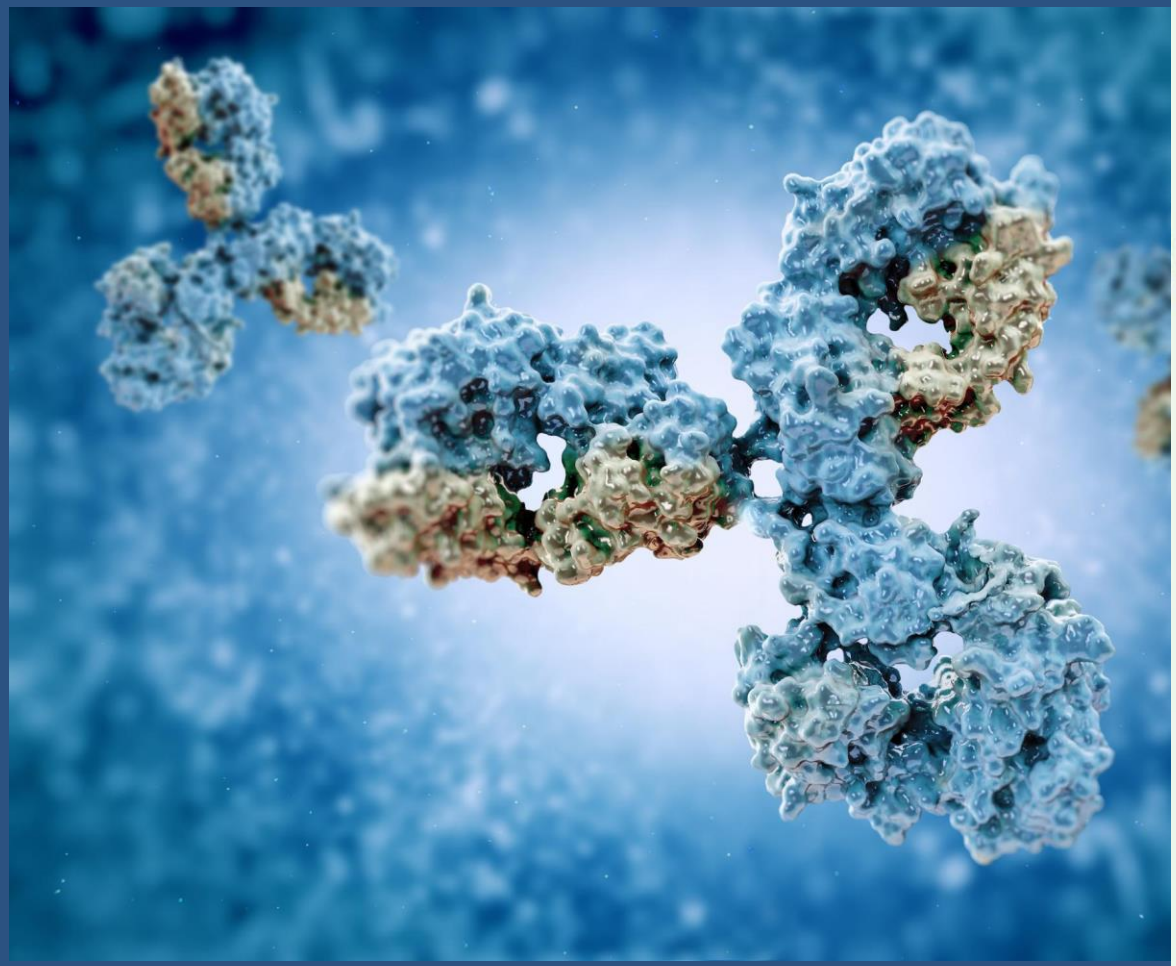
Elisa Conti[1] · Simona Andreoni[1] · Davide Tomaselli[1] · Benedetta Storti[1,2] · Francesco Brovelli[1,2] · Roberto Acampora[1,2] · Fulvio Da Re[1,2] · Ildebrando Appollonio[1,2] · Carlo Ferrarese[1,2] · Lucio Tremolizzo[1,2]

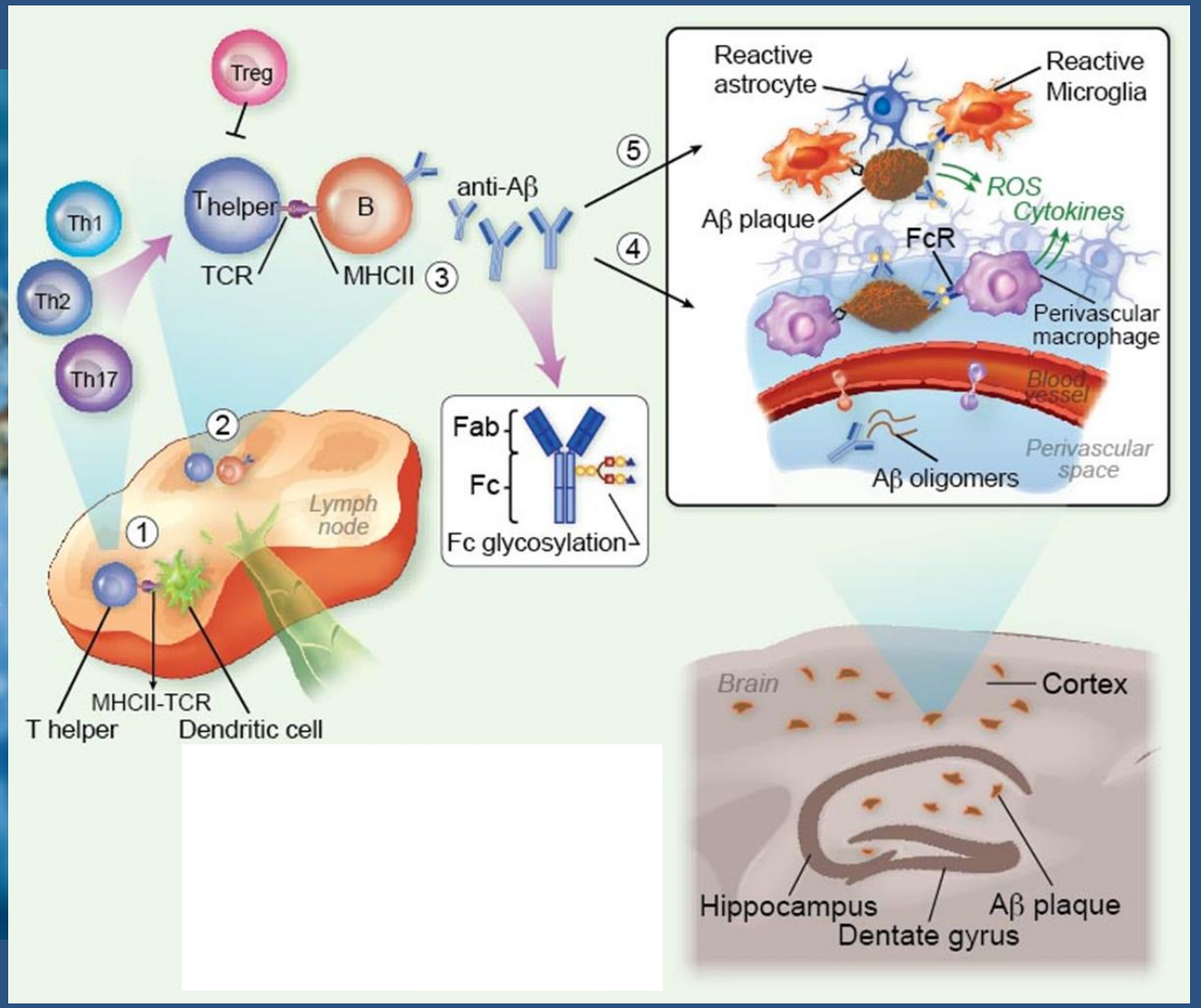




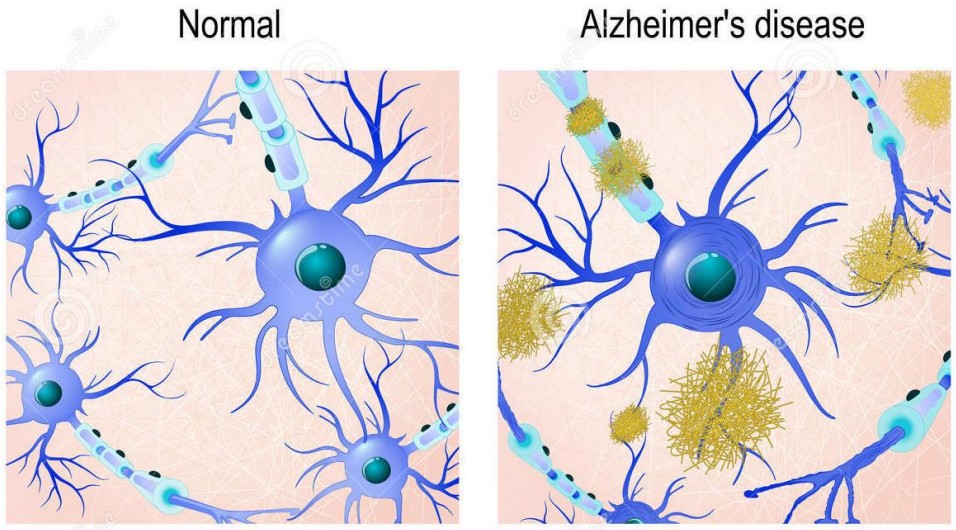
In conclusion, DBI may be a very promising candidate for marking the psychomotor cluster of BPSD in AD patients, perhaps offering in the future a valuable helping tool to practicing physicians. As a final point, the DBI rise in DEL offers novel cues for a better comprehension of the pathogenesis of this potentially fatal condition.

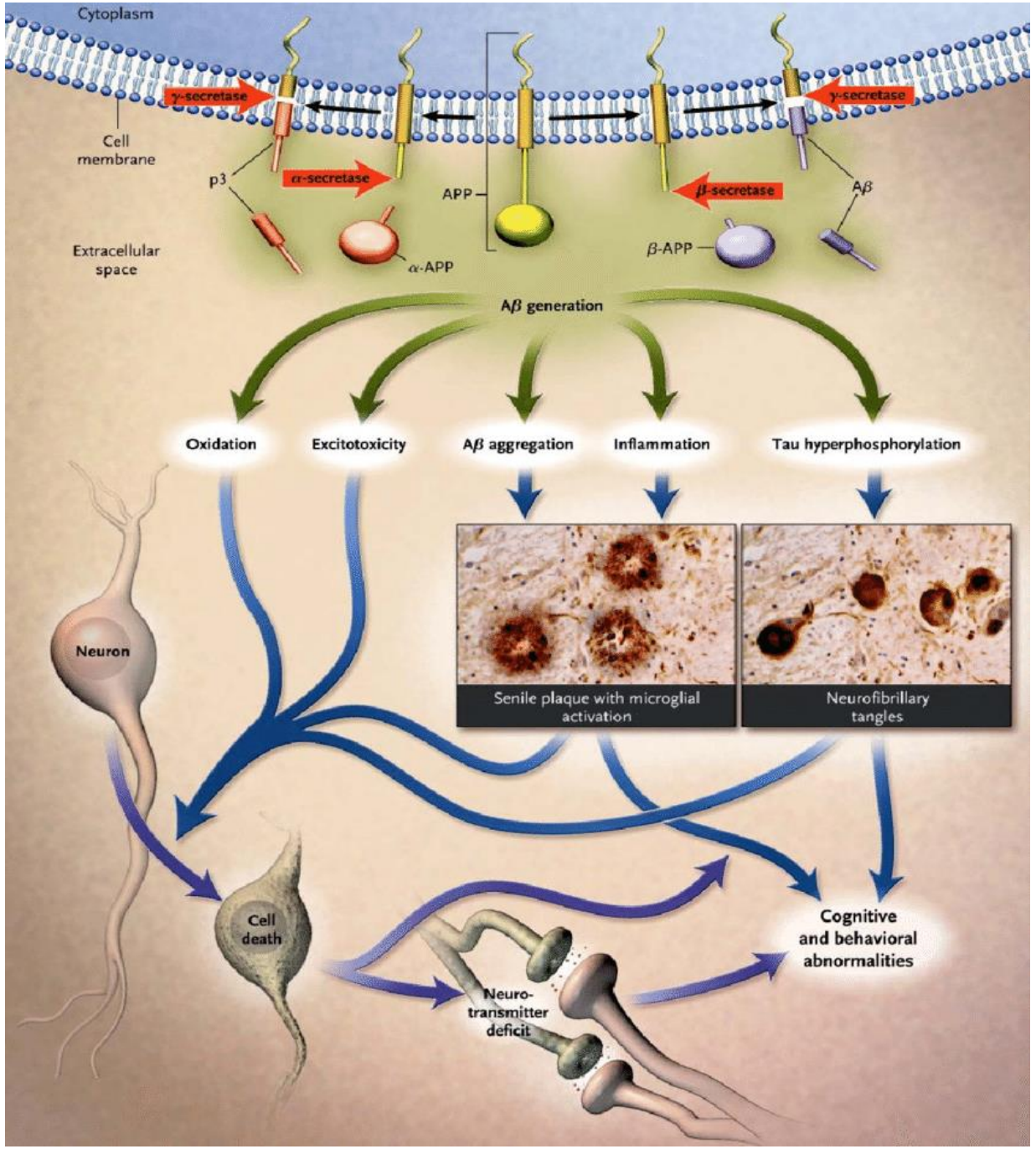
Adaptive immunity



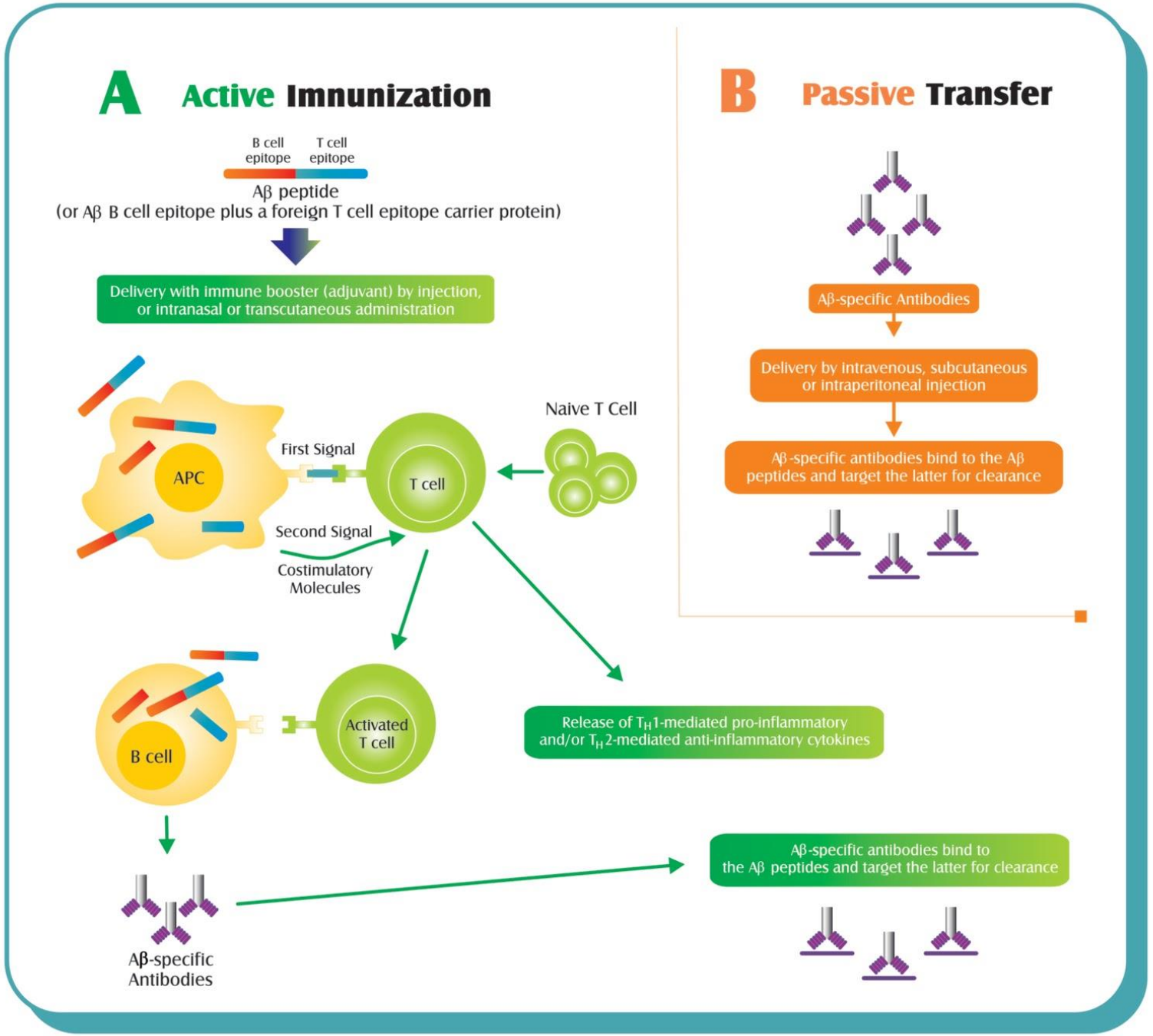


The amyloidogenic hypothesis of Alzheimer’s disease

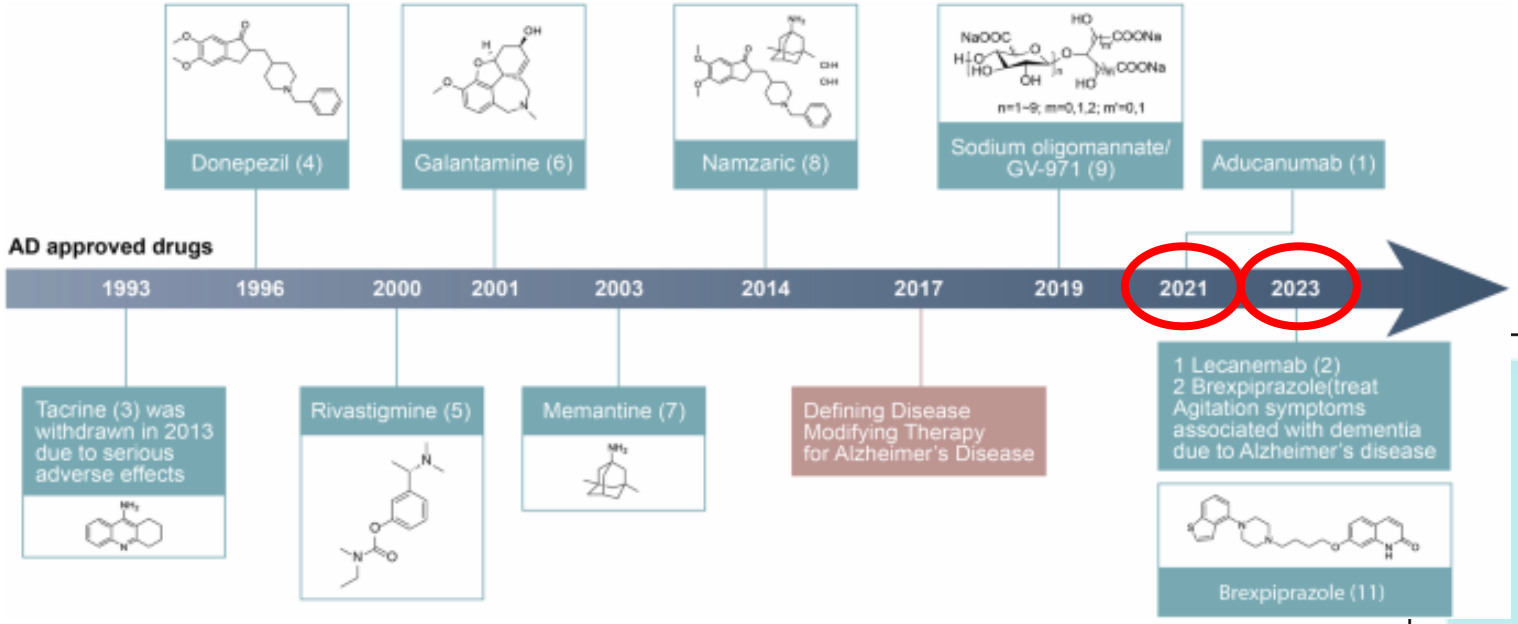


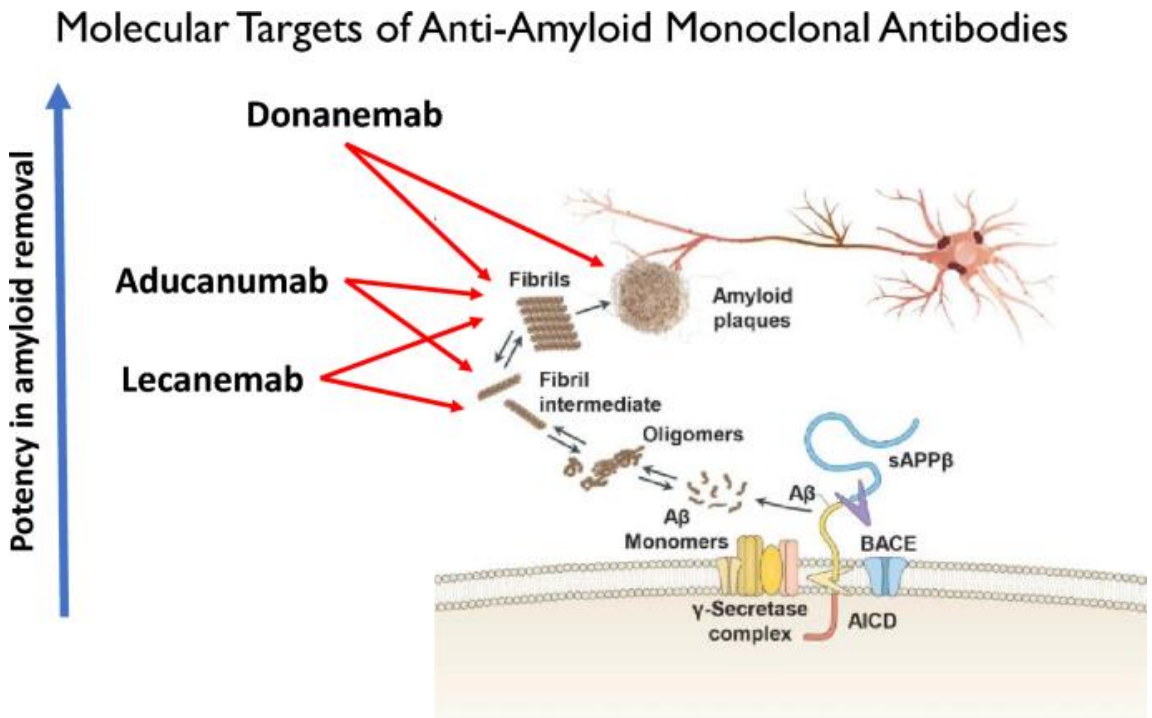


Vaccination in Alzheimer's disease



Compound	Mechanism of action	Relevant clinical outcome	Fluid biomarker outcome
AN1792	Active immunization against full-length Aβ42	PII: halted because of the development of meningoencephalitis (169)	PII: reduction in CSF tau; no change in CSF Aβ42 (169)
CAD106	Active immunization against Aβ fragment	PI: well tolerated in subject with AD (176)	PI: no changes in CSF Aβ40, Aβ42, p-tau, or t-tau; increase in total serum plasma Aβ and decrease in free Aβ (176)
Bapineuzumab	Monoclonal antibody directed against N-terminus of Aβ	PII: *post hoc* analysis showed effect on cognition in APOE ε4 non-carriers (185) PIII: two separate studies (one with APOE ε4 carriers and one with non-carriers) failed to reach clinical endpoints (70) Development of MRI changes in ~20% of treated patients (210)	PII: reduction in CSF p-tau and t-tau; no effect on CSF Aβ40 or 42 (186) PIII: decrease in CSF p-tau (carriers); no effect on any CSF measures (Aβ42, p-tau, t-tau) in non-carriers; no effect on Aβ42 in carriers (70)
Solanezumab	Monoclonal antibody against middle portion of Aβ	PIII: two large trials failed to reach clinical endpoints. A pooled analysis of the two trials demonstrated an effect on cognition in subjects with mild dementia (142)	PII: increase in serum and CSF Aβ40 and 42 (190) PIII: increase in both CSF Aβ40 and 42; no effect on CSF p-tau or t-tau; increases in serum Aβ40 and 42 (142)
Crenezumab	Monoclonal antibody against middle portion of Aβ; built on IgG1 backbone	PI: well tolerated in subjects with mild to moderate AD (211)	PI: increase in serum Aβ levels (211)
Gantenerumab	Entirely humanized monoclonal antibody binds the N-terminus of Aβ fibrils	PIII: results not yet published, trial discontinued	No fluid biomarker data have been reported
Ponezumab	Humanized monoclonal antibody binds the C-terminus of Aβ	PI: well tolerated in subjects with AD (212–214)	PI: increase in serum and CSF Aβ levels w/single dose (212)
Tramiprosate	Molecule that binds Aβ and prevents aggregation	PIII: no benefit on clinical endpoints (215)	PII: reduction in CSF Aβ42 (216)
Avagacestat	Gamma secretase inhibitor	PII: well tolerated at low doses; at doses found to have CSF effects, a trend worsening cognition was detected (109)	PII: at higher, poorly tolerated doses, reductions in CSF Aβ 38, 40, and 42 were reported. Non-significant trend toward reduction in CSF p-tau and t-tau at all doses No changes in CSF Aβ at lower doses (109)
Semagacestat	Gamma secretase inhibitor	PIII: preplanned analysis showed an association with worsening cognitive and functional outcomes resulting in early termination (71)	PII: no effect on CSF Aβ40 or 42; reduction in plasma Aβ40 (201) PI: dose-dependent reduction in Aβ production as measured by SILK (18) PIII: no changes in CSF Aβ or t-tau; p-tau remained the same (increased in placebo) dose-dependent reduction in serum Aβ40 and 42 (71)





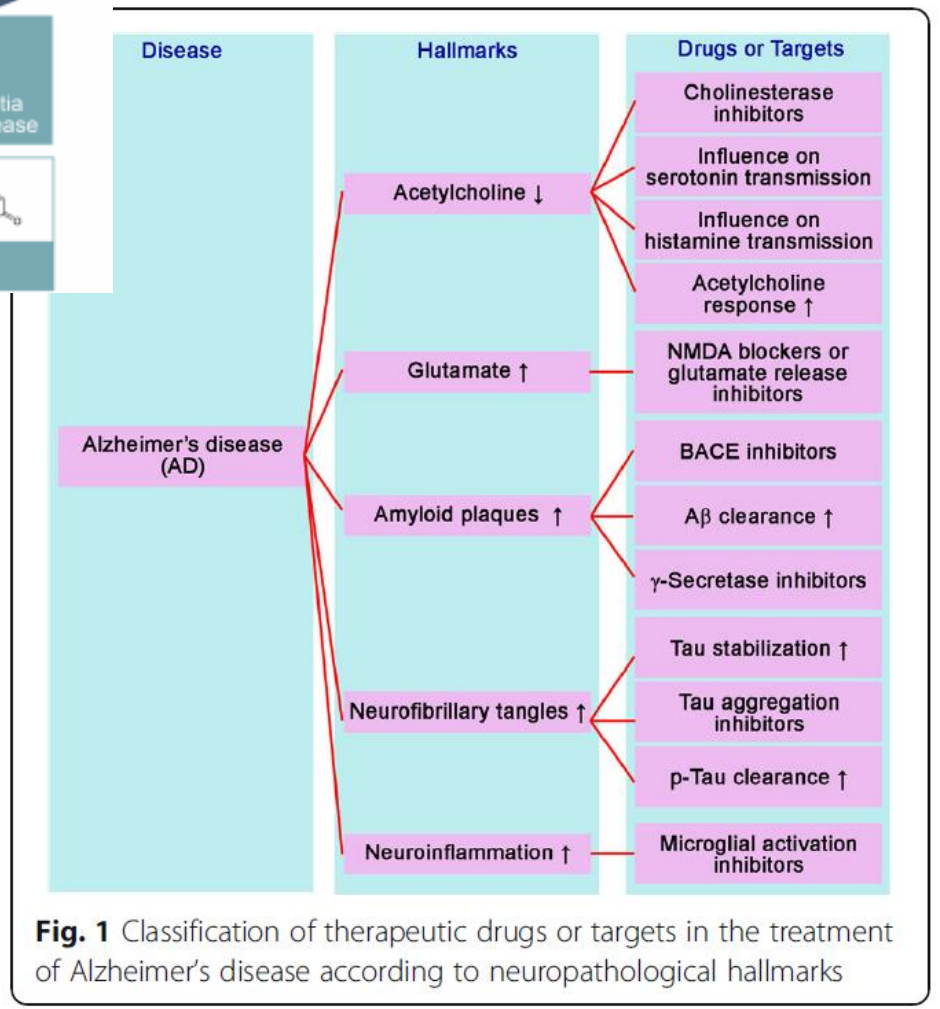
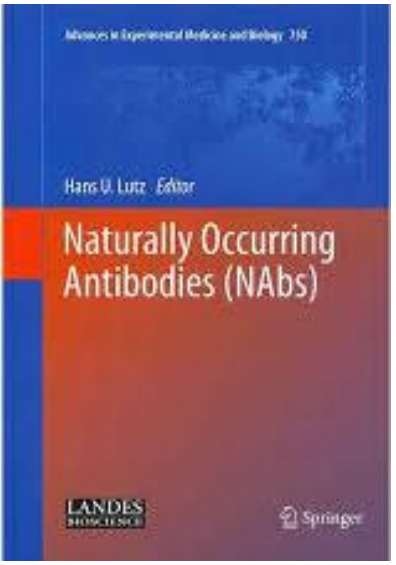


Fig. 1 Classification of therapeutic drugs or targets in the treatment of Alzheimer's disease according to neuropathological hallmarks



CHAPTER 7

NATURALLY OCCURRING AUTOANTIBODIES AGAINST β-AMYLOID

Jan-Philipp Bach and Richard Dodel*
Department of Neurology, Philipps-University Marburg, Germa
**Corresponding Author: Richard Dodel—Email: dodel@med.un*

J Clin Immunol (2010) 30 (Suppl 1):S37–S42
DOI 10.1007/s10875-010-9413-6

Anti-amyloidogenic Activity of IgGs Contained in Normal Plasma

Brian O'Nuallain · Angela D. Williams · Helen P. McWilliams-Koeppen · Luis Acero · Alfred Weber · Hartmut Ehrlich · Hans P. Schwarz · Alan Solomon

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ScienceDirect

Biochemical and Biophysical Research Communications 361 (2007) 800–804

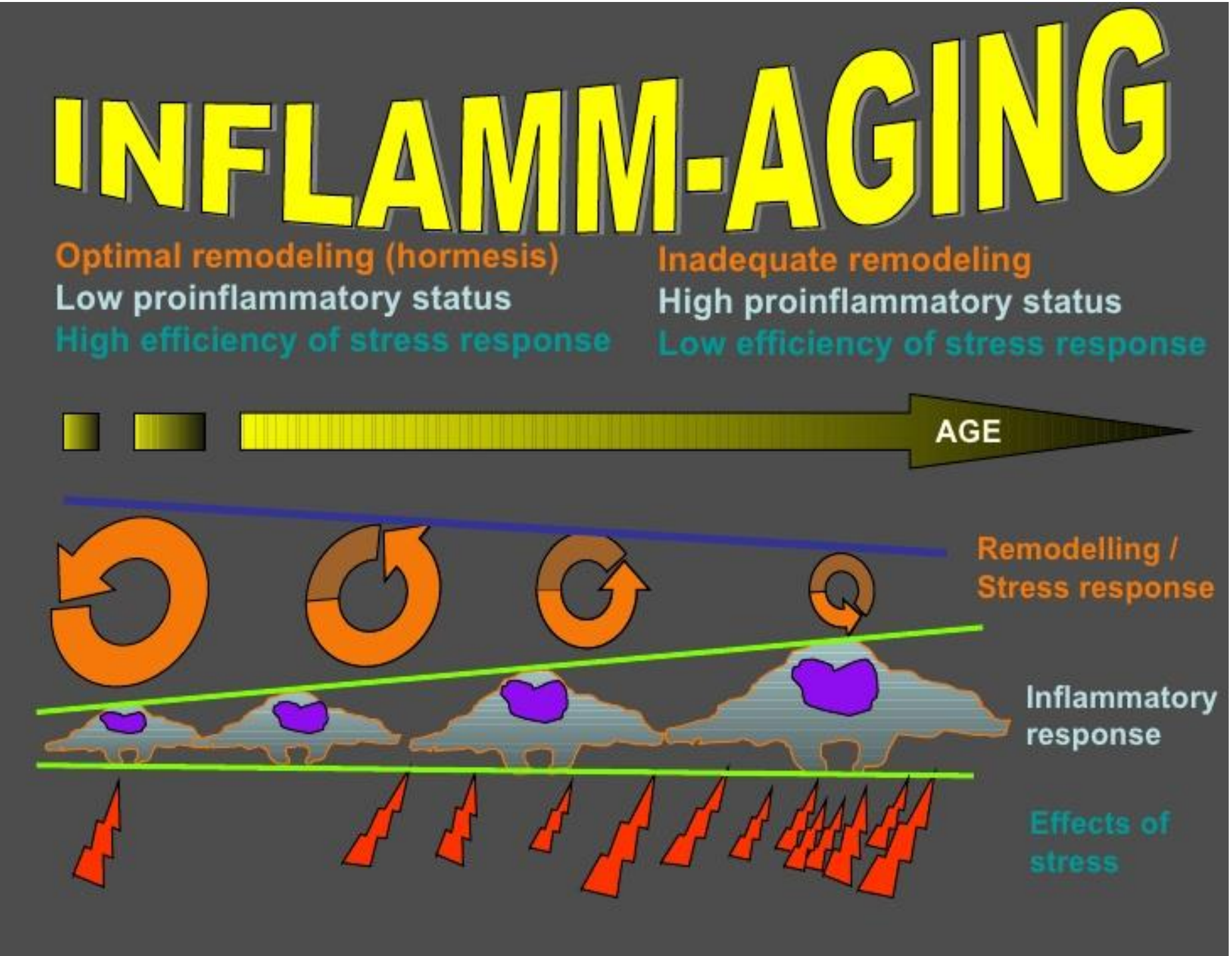
BBRC

www.elsevier.com/locate/ybbrc

Reduced serum level of antibodies against amyloid β peptide is associated with aging in Tg2576 mice

Ji-Hoon Sohn [a,1], Jung On So [a,1], Hee Kim [b], Eun Joo Nam [b], Hee Jin Ha [b], Young Ho Kim [b], Inhee Mook-Jung [a,*]

[a] *Department of Biochemistry and Cancer Research Institute, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-799, Republic of Korea*
[b] *Digital Biotech Inc., R&D, Ansan, Kyungi-do 425-839, Republic of Korea*



INFLAMMAGING

(Franceschi)

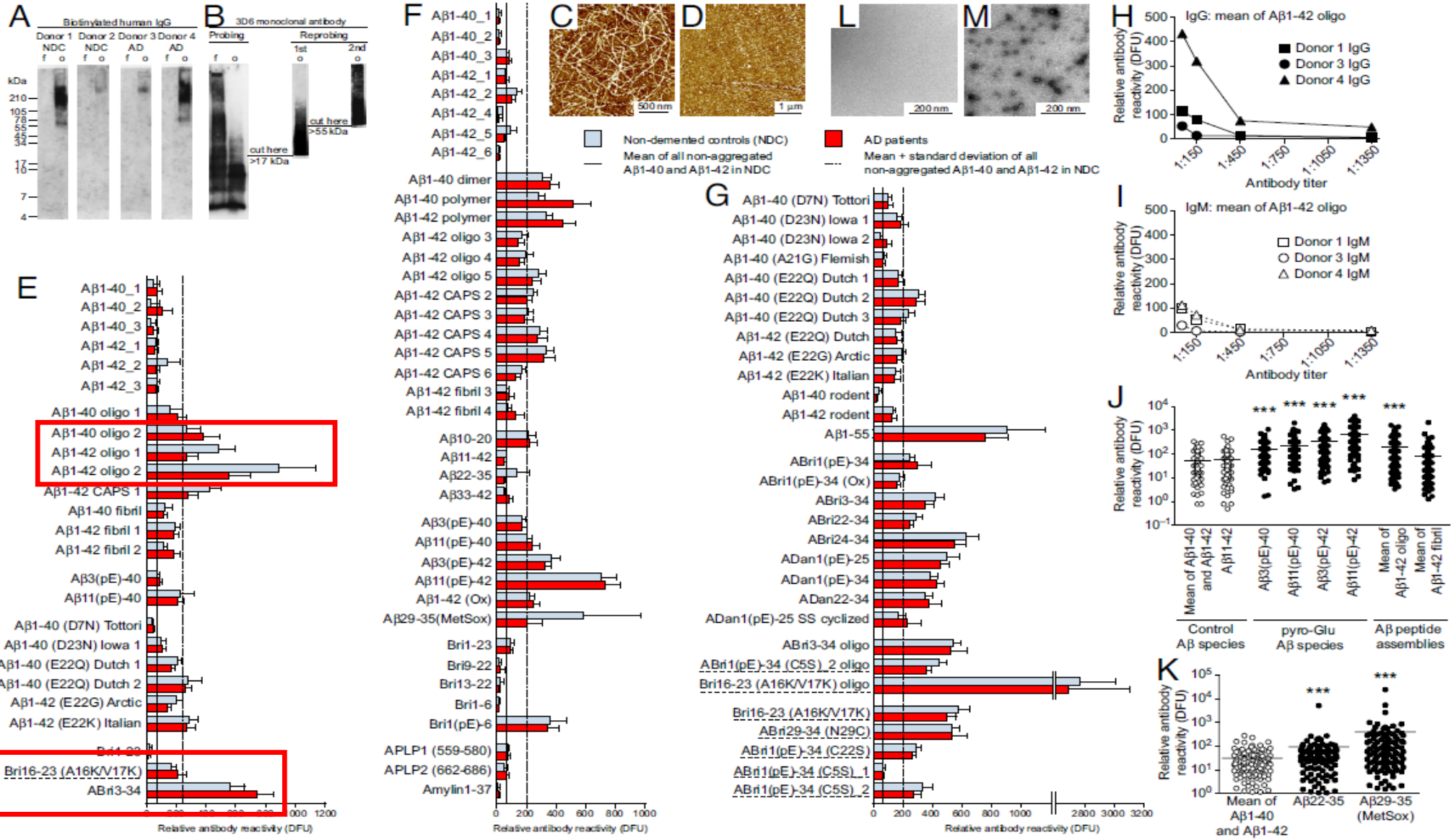
Progressiva perdita di competenza immunologica.

Stato Infiammatorio:

1. Di basso grado
2. Controllato
3. Asintomatico
4. Cronico
5. Sistemico

- **Declino immunità adattativa** e risposta Th2
- **Aumento immunità innata** sostenuta da fagociti

Neuroprotective natural antibodies to assemblies of amyloidogenic peptides decrease with normal aging and advancing Alzheimer's disease



Elevation of β-Amyloid 1-42 Autoantibodies in the Blood of Amnestic Patients With Mild Cognitive Impairment

Daniela Storace, PhD; Sergio Cammarata, MD; Roberta Borghi, PhD; Roberta Sanguineti, PhD; Luca Giliberto, MD; Alessandra Piccini, PhD; Valeria Pollero, BSc; Cristina Novello, BSc; Carlo Caltagirone, MD; Mark A. Smith, PhD; Paola Bossù, PhD; George Perry, PhD; Patrizio Odetti, MD; Massimo Tabaton, MD

Journal of Alzheimer's Disease 48 (2015) 63–72
DOI 10.3233/JAD-150236
IOS Press

Increased Number of Plasma B Cells Producing Autoantibodies Against $A\beta_{42}$ Protofibrils in Alzheimer's Disease

Sofia Söllvander[a], Frida Ekholm-Pettersson[a,1], Rose-Marie Brundin[a], Gabriel Westman[b], Lena Kilander[a], Staffan Paulie[c], Lars Lannfelt[a] and Dag Sehlin[a,*]
[a]*Department of Public Health & Caring Sciences/Molecular Geriatrics, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden*
[b]*Department of Medical Sciences, Uppsala University, Uppsala, Sweden*
[c]*Mabtech AB, Nacka Strand, Sweden*

Cholinesterase inhibitor use is associated with increased plasma levels of anti-Abeta 1–42 antibodies in Alzheimer's disease patients☆

Elisa Conti[a,*,1], Gloria Galimberti[a,1], Lucio Tremolizzo[a], Alessandro Masetto[a], Diletta Cereda[a], Clara Zanchi[a], Fabrizio Piazza[a], Marco Casati[b], Valeria Isella[a], Ildebrando Appollonio[a], Carlo Ferrarese[a]

[a] *Department of Neuroscience and Biomedical Technologies, University of Milano-Bicocca, San Gerardo Hospital, Via Cadore 48, 20052 Monza (MI), Italy*
[b] *Laboratory of Chemical and Clinical Analyses, San Gerardo Hospital, Monza (MI), Italy*

Neuroscience Letters 486 (2010) 193–196

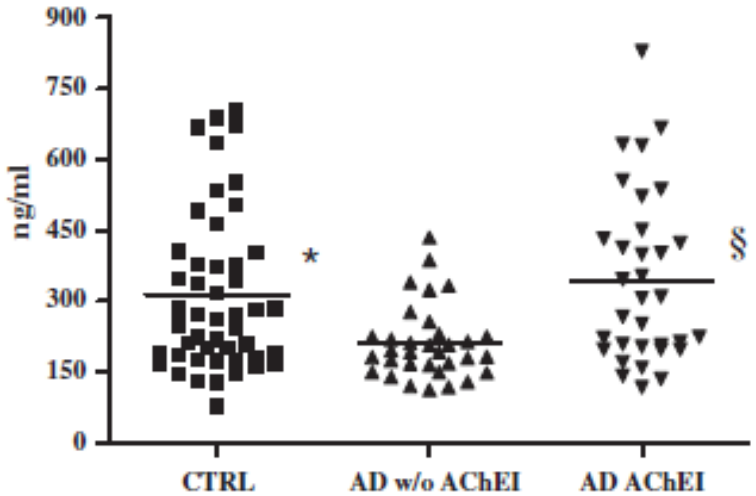
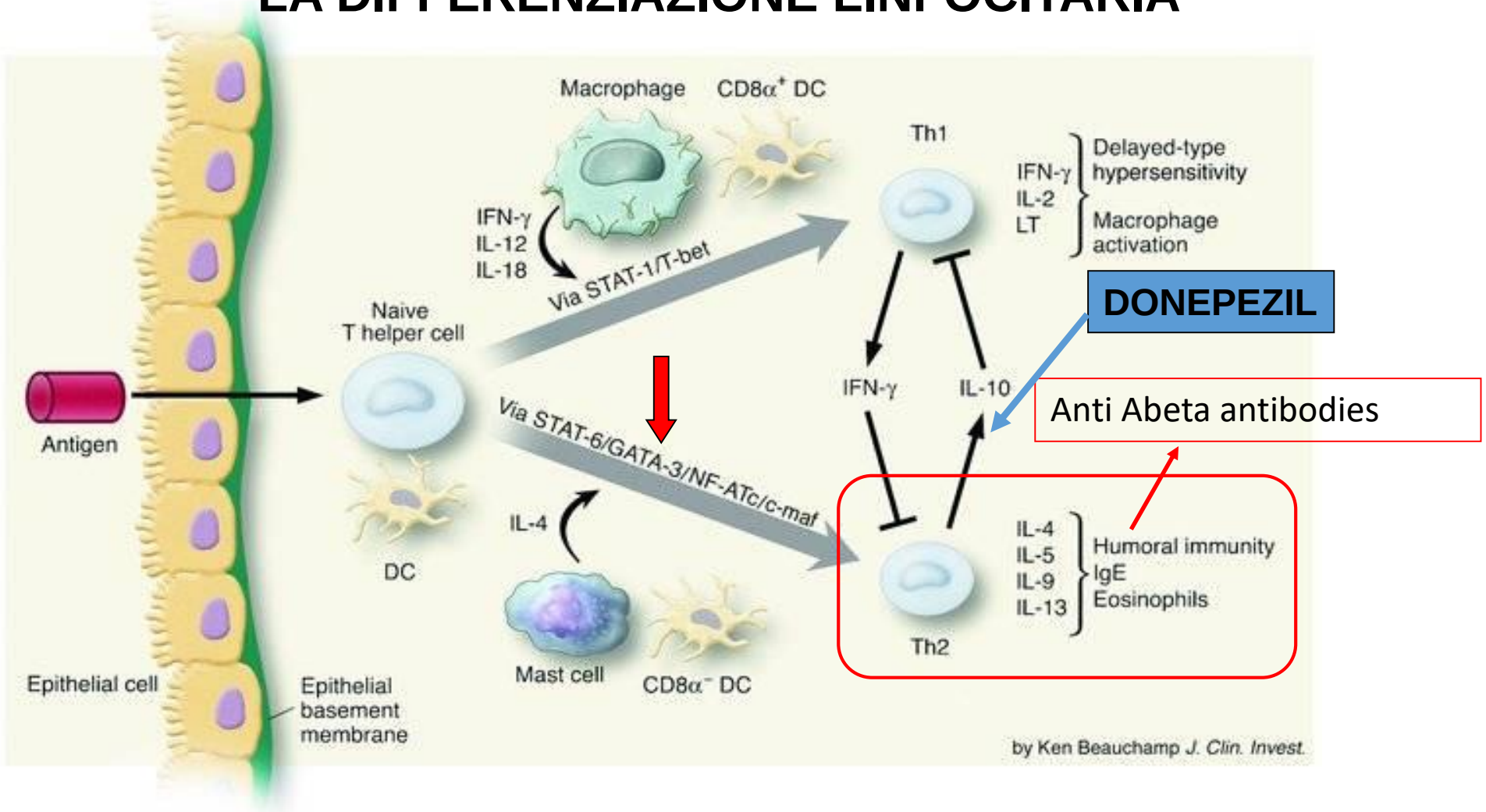


Fig. 1. Anti-Abeta 1–42 plasma levels in controls (CTRL), AD patients not receiving AChEI (AD w/o AChEI) and AD patients receiving AChEI (AD AChEI). §$p < 0.01$ AD AChEI vs. AD w/o AChEI, *$p < 0.01$ CTRL vs. AD w/o AChEI.

The acetylcholinesterase inhibitor, Donepezil, regulates a Th2 bias in Alzheimer's disease patients

Marcella Reale[a,*], Carla Iarlori[a], Francesco Gambi[a], Claudio Feliciani[b], Lucci Isabella[a], Domenico Gambi[a,c]

LA DIFFERENZIAZIONE LINFOCITARIA



CONTRO: evidenza che gli AChEI sono una terapia sostanzialmente sintomatica

Potremmo osservare un effetto biologico del farmaco che non raggiunge la soglia di significatività clinica?

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Life Sciences 74 (2003) 675–696
Life Sciences
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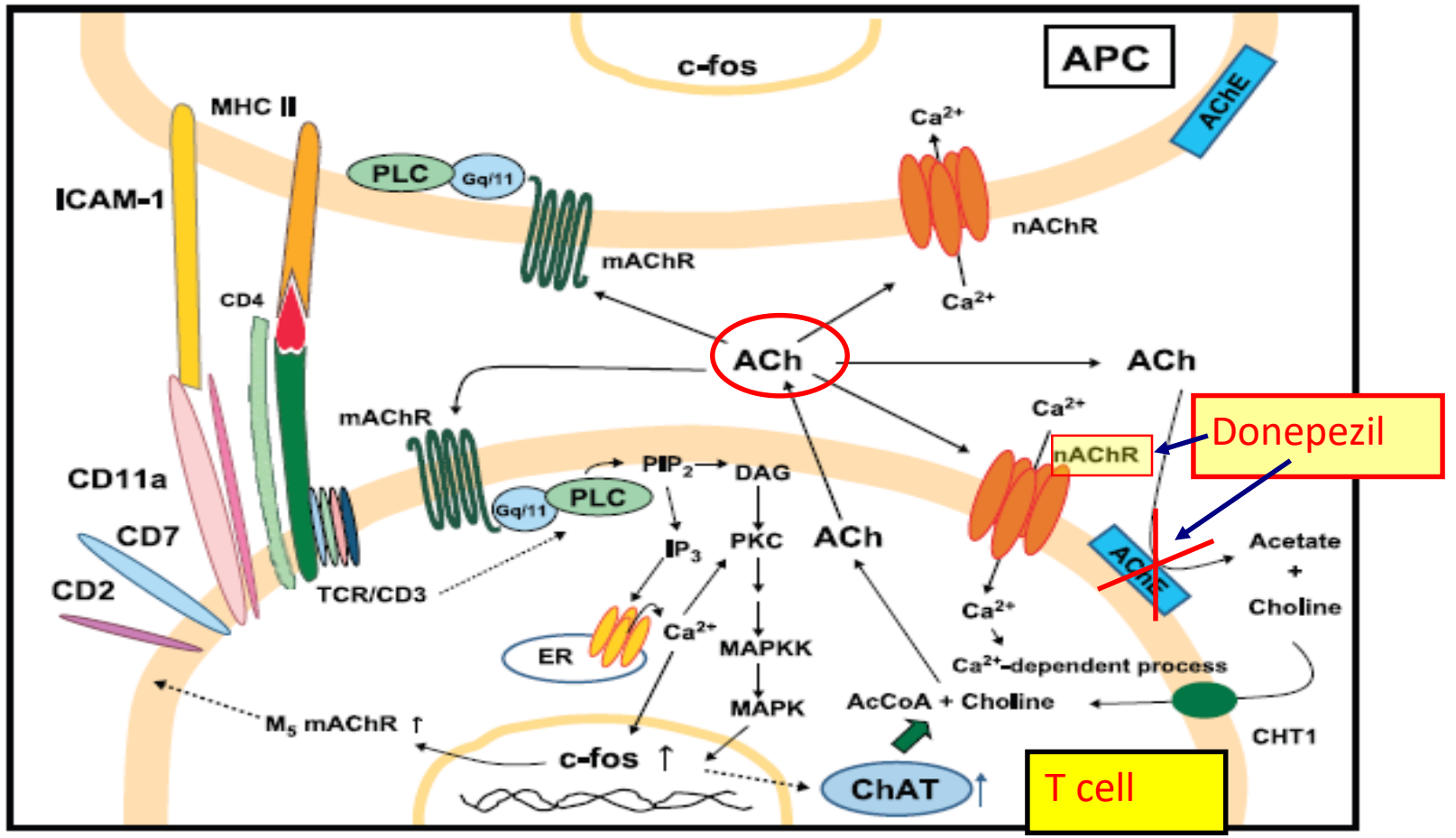
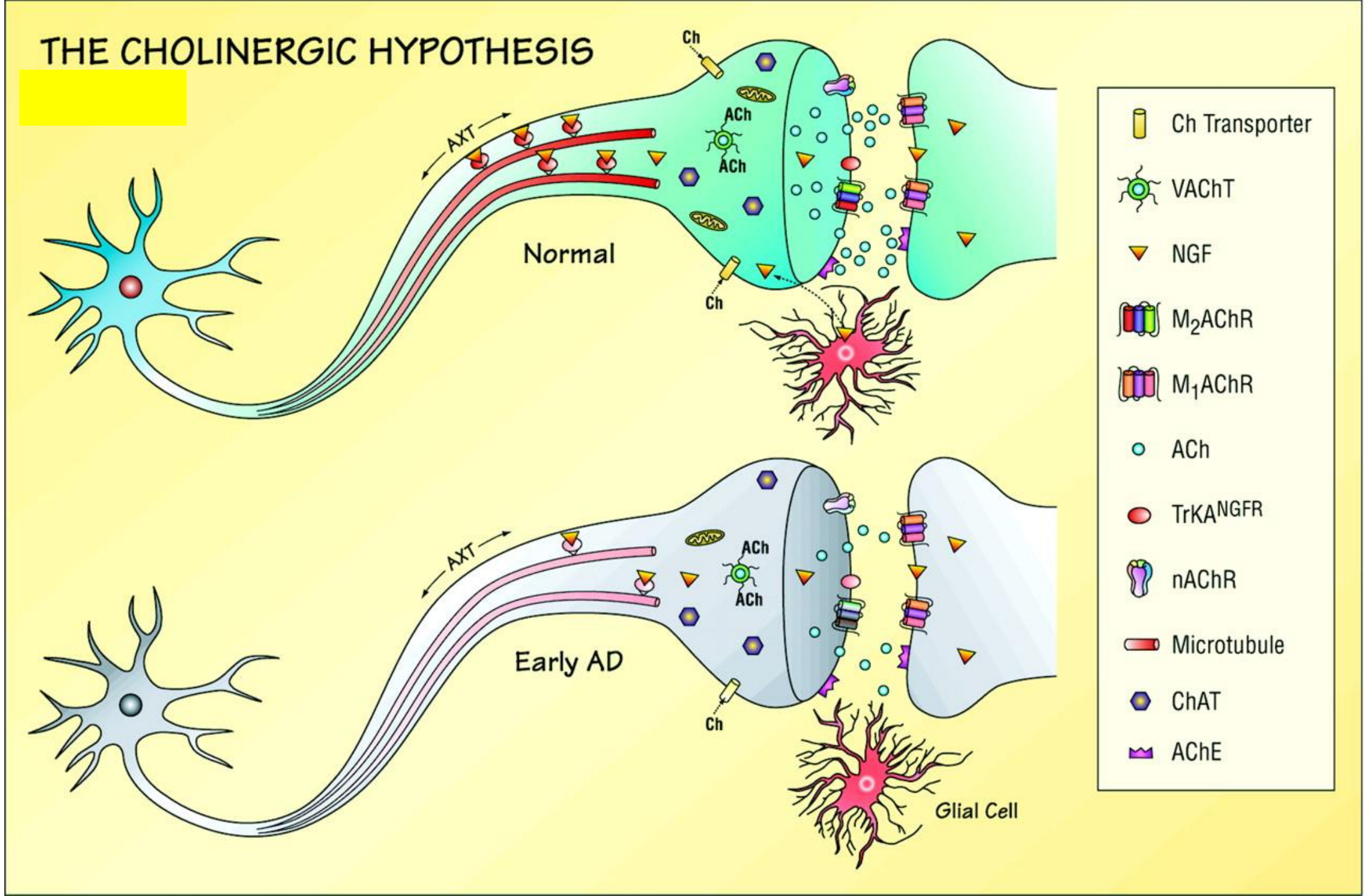
Minireview

The lymphocytic cholinergic system and its contribution to the regulation of immune activity

Koichiro Kawashima*, Takeshi

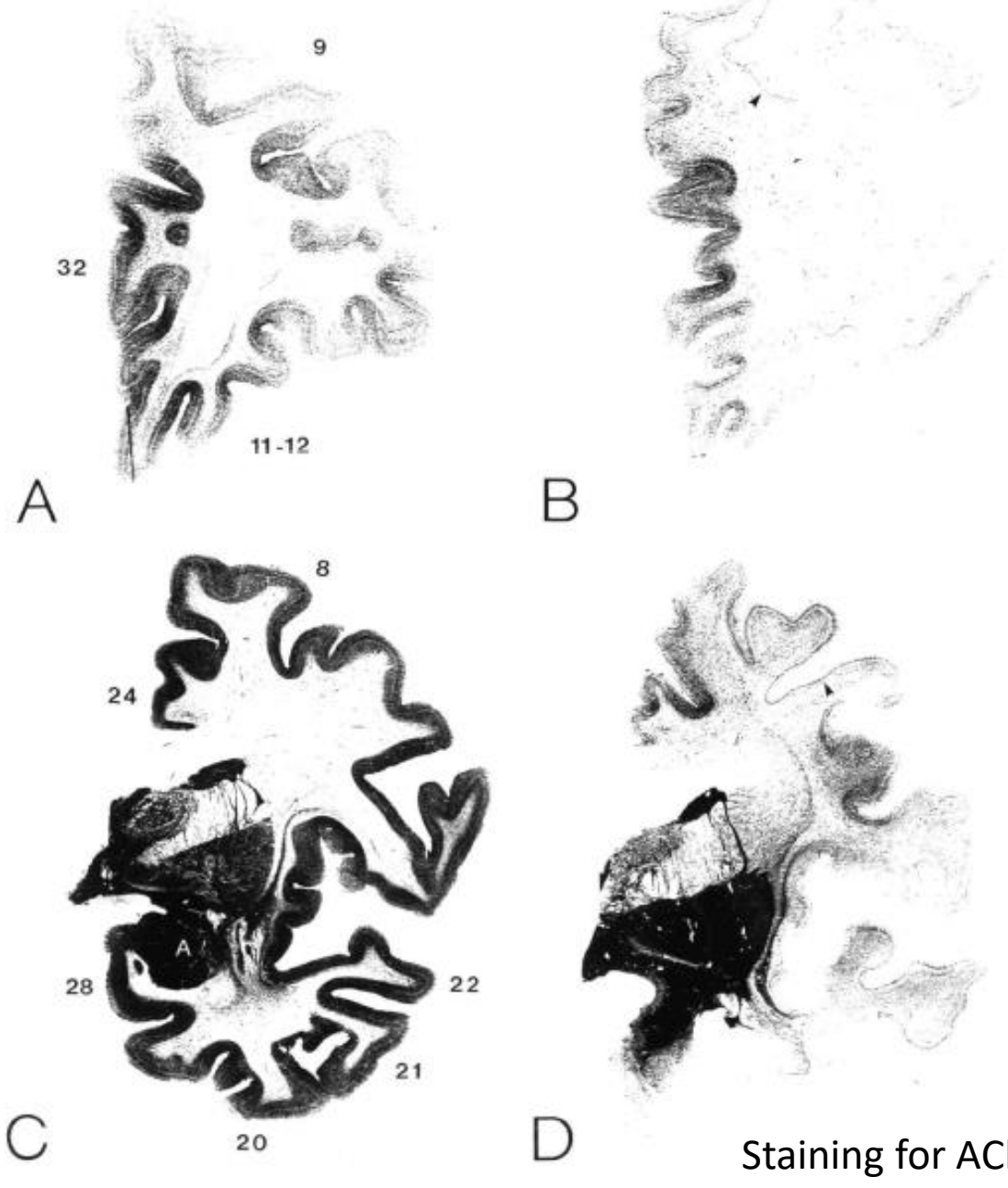
Department of Pharmacology, Kyoritsu College of Pharmacy, 1-5-30 Shiba




THE CHOLINERGIC HYPOTHESIS
Ch
ACh
ACh
AXT
Normal
Ch
AXT
ACh
ACh
Early AD
Ch
Glial Cell
Ch Transporter
VAChT
NGF
M2AChR
M1AChR
ACh
TrKANGFR
nAChR
Microtubule
ChAT
AChE

Normal

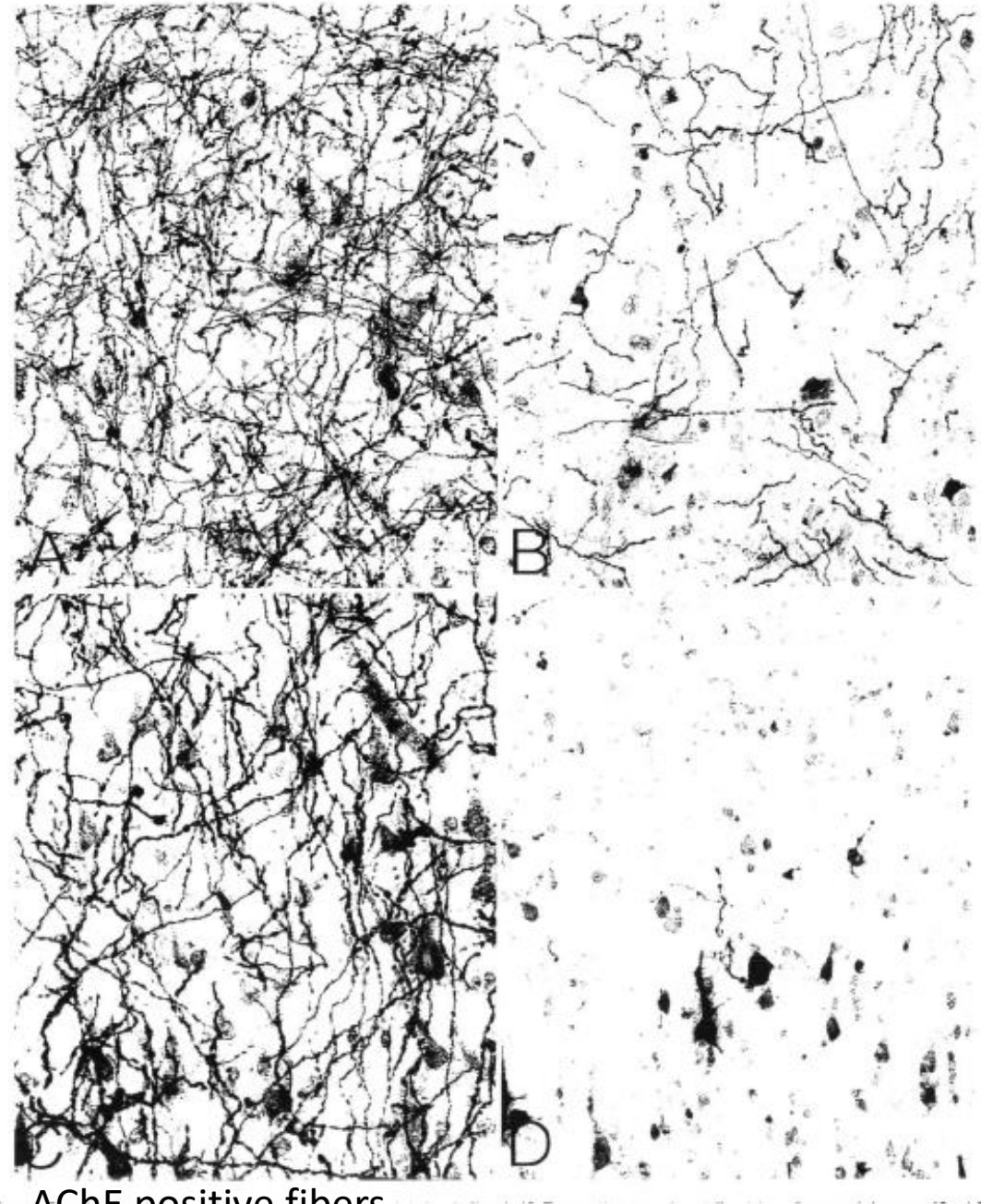
AD



Staining for AChE

Normal

AD



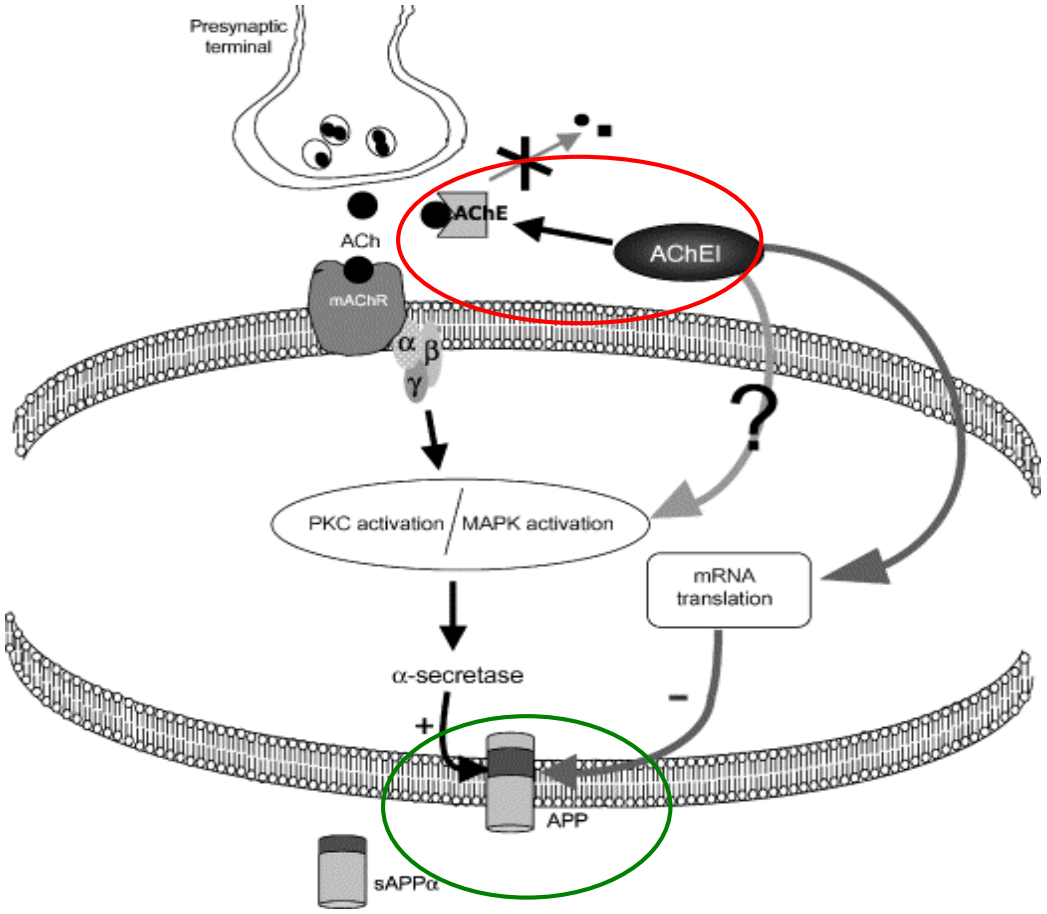
AChE positive fibers

BASI MOLECOLARI DELLA TERAPIA ANTICOLINESTERASICA

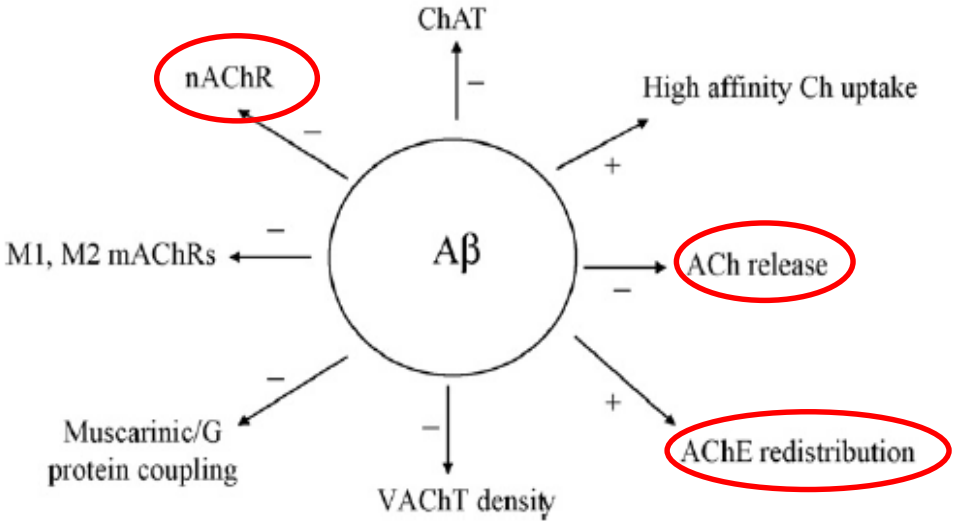
IPOTESI AMILOIDOGENICA ⟷ IPOTESI COLINERGICA

Amplificazione della funzionalita' colinergica

Promozione del metabolismo non amiloidogenico di APP



Interazioni fra meccanismi amiloidogenici e colinergici nell'AD



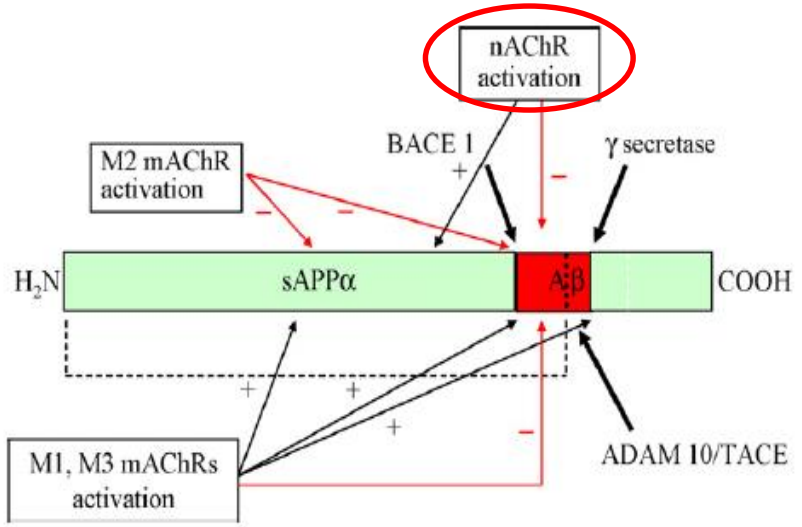


Fig. 1. Schematic representation of the known changes in cholinergic neurons that may be due to the action of Aβ.

Different mechanisms of AChE inhibitors on the release of sAPPα

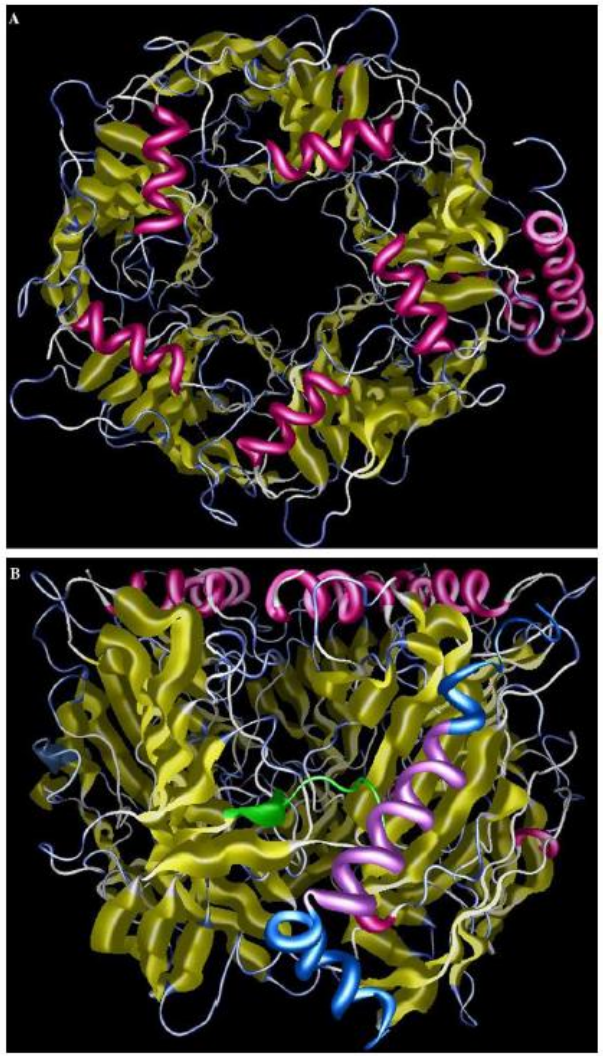
AchE inhibitor	Change	Cholinergic mechanism	Other mechanism	Reference
Tacrine	Decrease	–	nt	Lahiri et al. (1994); Lahiri et al. (1996)
Metrifonate	Increase	+	nt	Pakaski et al. (2000, 2001); Racchi et al. (2001)
Ambenonium	Increase	+	nt	Pakaski et al. (2001)
Ganstigmine	Increase	+	nt	Mazzucchelli et al. (2003)
Ladostigil	Increase	+	MAP-kinase or tyrosin kinase-dependent pathway	Yogev-Falach et al. (2002)
Donepezil	Increase	+	Enhancing trafficking and activity of ADAM 10	Zimmermann et al. (2004)
Phenserine	Decrease	–	Inhibition of APP mRNA translation	Lahiri et al. (2000); Shaw et al. (2001)
Galantamine	Increase	+	nt	Lenzken et al. (2007)

The table summerizes some of the effects of AChE inhibitors on the APP processing and their possible mechanisms. The symbol (nt) indicates that the parameter has not been tested. Different mechanisms of action AChE inhibitors on the release of sAPPα, relating to some of the effects of AChE inhibitors on APP processing and their possible mechanisms. The symbol (nt) indicates that the parameter has not been tested.

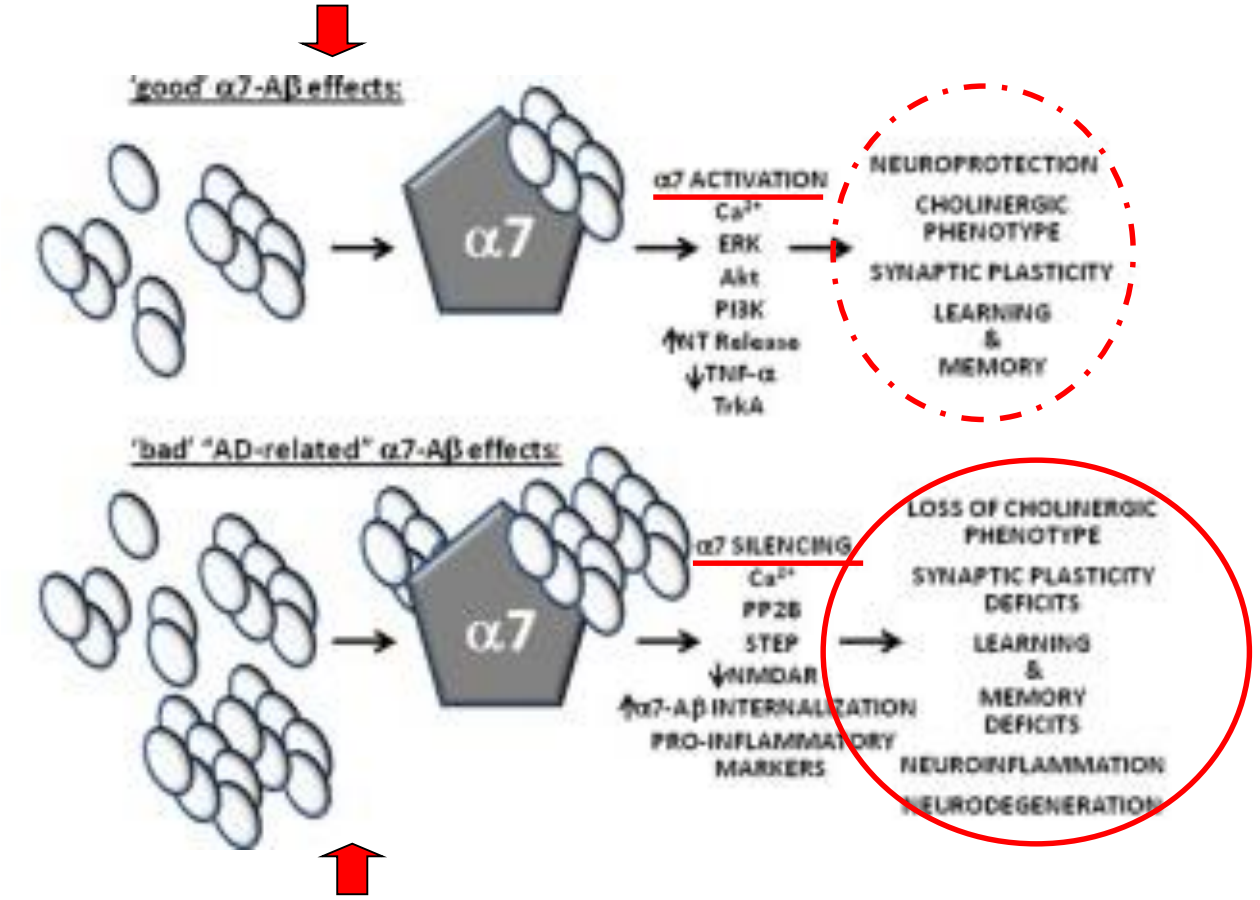
Base docking model of the homomeric α7 nicotinic receptor–β-amyloid$_{1-42}$ complex

L. Michel Espinoza-Fonseca*

Biochemical and Biophysical Research Communications 320 (2004) 587–591



Physiological conditions: Abeta in picomolar range

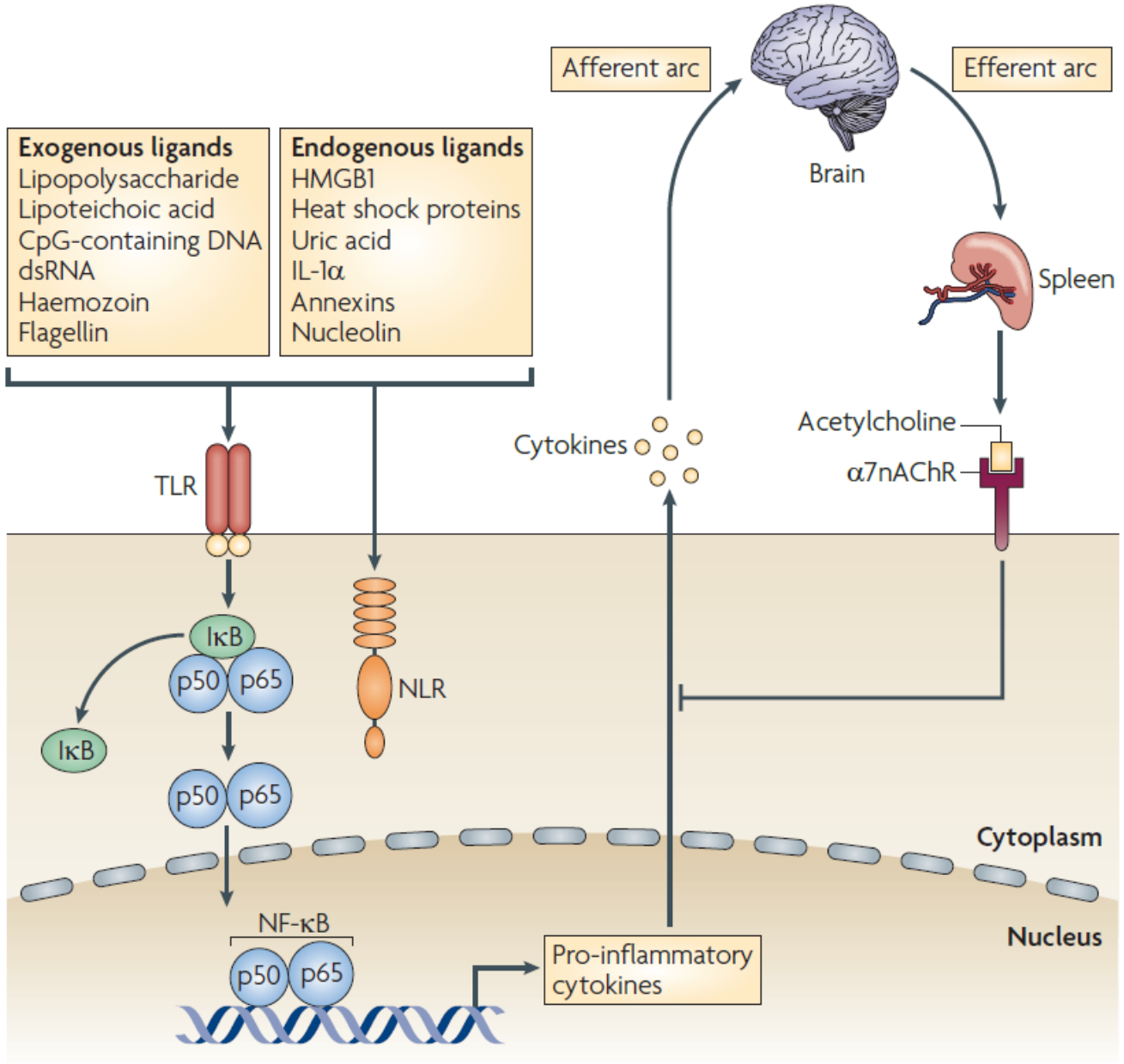


Pathological conditions: Abeta in nanomolar range

Neural circuit that controls cytokine production in spleen. Action potentials transmitted via the **vagus nerve** to **spleen** mediate the release of **acetylcholine**, the neurotransmitter which **inhibits cytokine release** by interacting with **alpha7 nicotinic acetylcholine receptors** expressed on cytokine-producing cells. The **motor arc of the inflammatory reflex** is termed the

CHOLINERGIC ANTI-INFLAMMATORY PATHWAY.

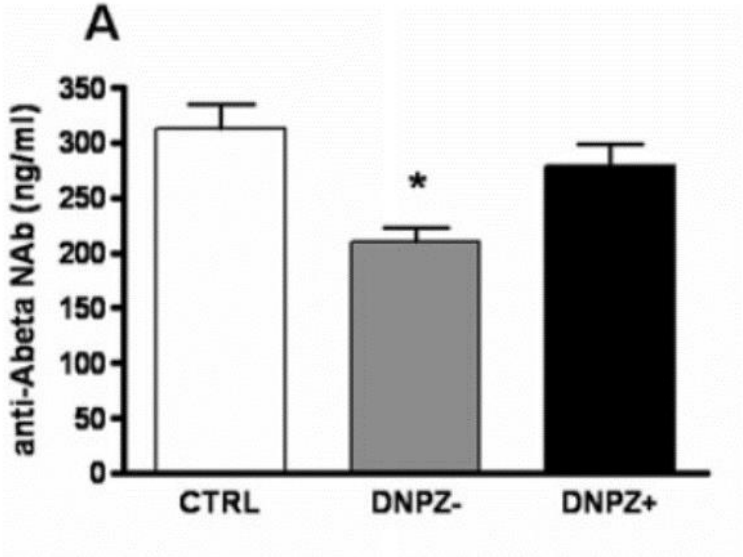
A cholinergic system is expressed by immune cells.

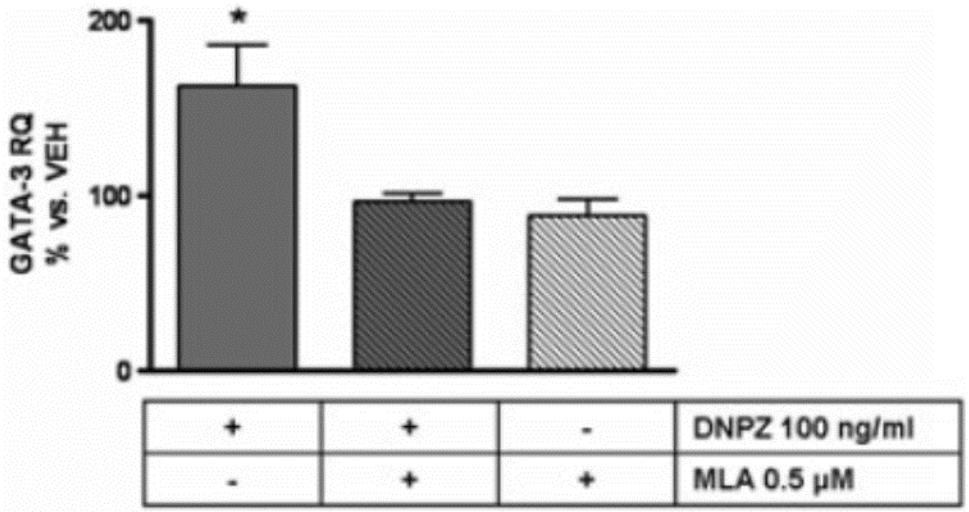


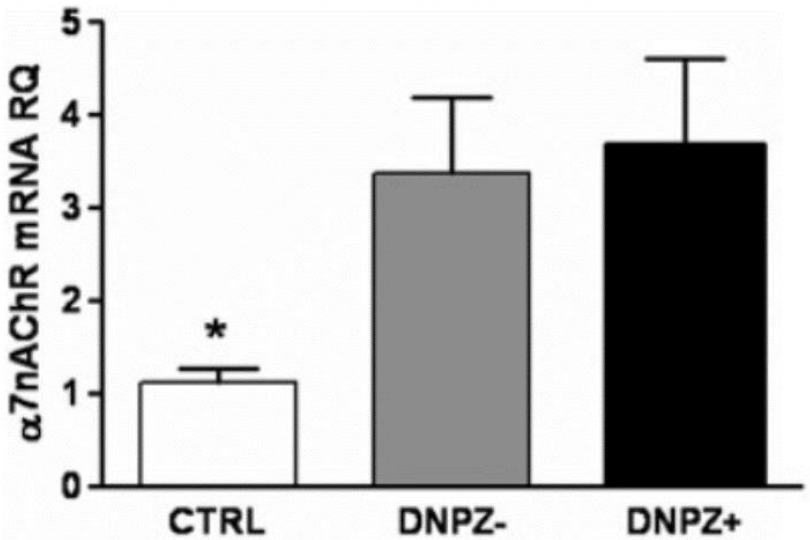
HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2016
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2538

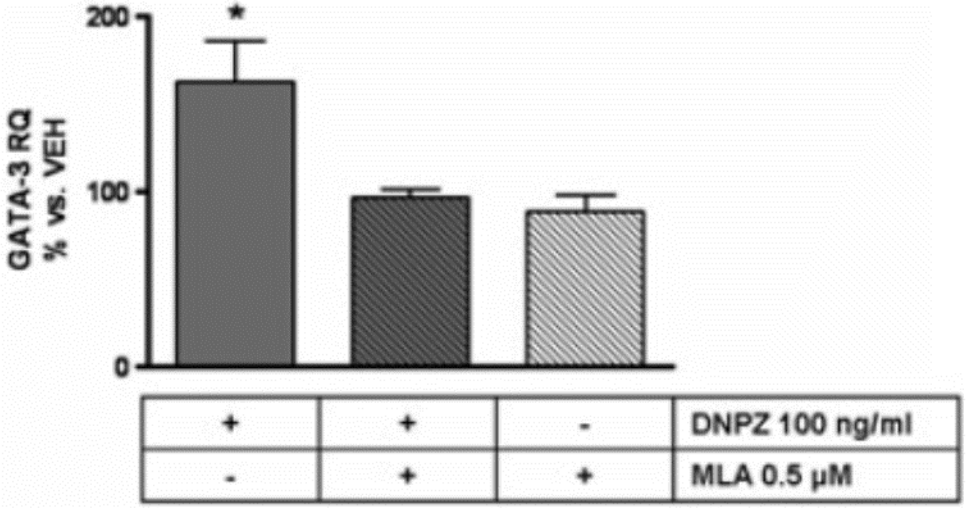
Donepezil modulates the endogenous immune response: implications for Alzheimer's disease

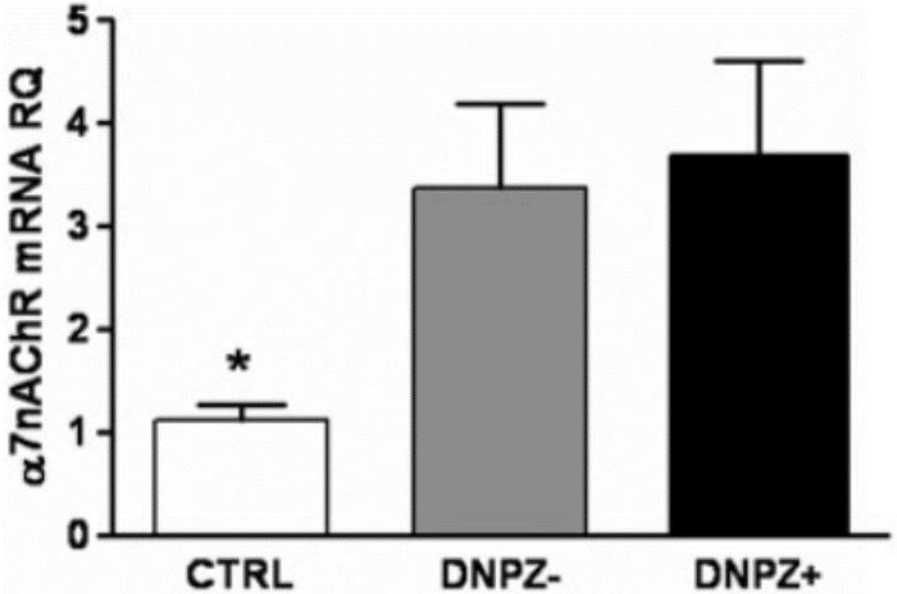
Elisa Conti[1], Lucio Tremolizzo[1,2]*, Marta Elena Santarone[1], Marco Tironi[1], Isabella Radice[1], Chiara Paola Zoia[1], Angelo Aliprandi[3], Andrea Salmaggi[3], Roberto Dominici[4], Marco Casati[5], Ildebrando Appollonio[1,2] and Carlo Ferrarese[1,2]







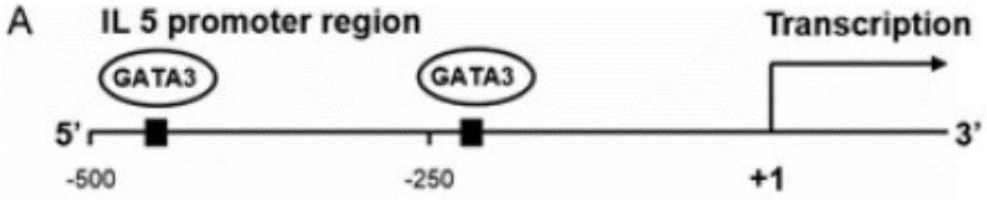


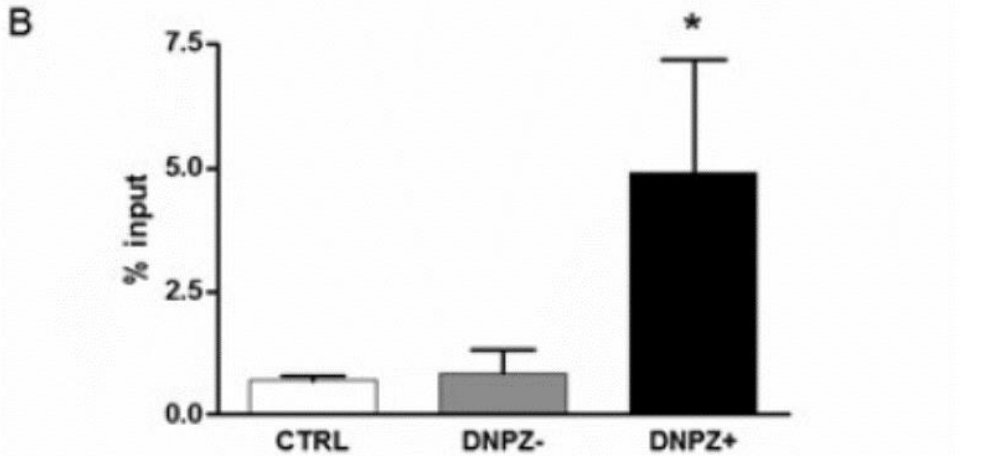


Neuroprotection by donepezil against glutamate excitotoxicity involves stimulation of α7 nicotinic receptors and internalization of NMDA receptors

H Shen[1]*, T Kihara[1]*, H Hongo[1], X Wu[1], WR Kem[2], S Shimohama[3], A Akaike[4], T Niidome[1] and H Sugimoto[1]

British Journal of Pharmacology (2010) **161** 127–139 127





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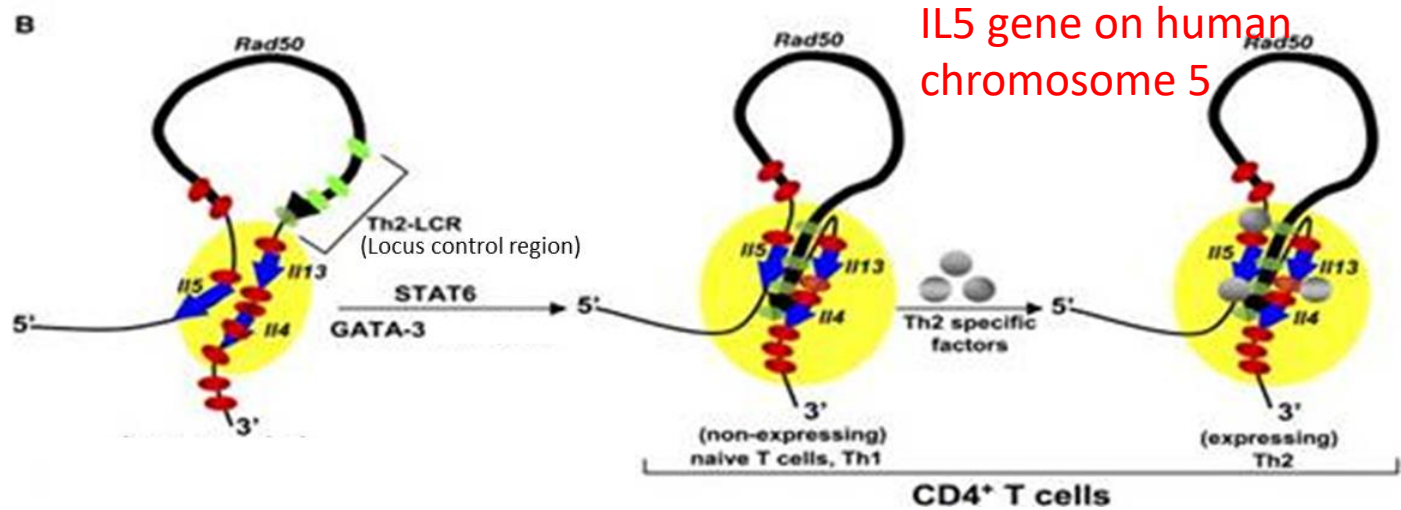
GATA-3 Has Dual Regulatory Functions in Human Interleukin-5 Transcription*

Received for publication, August 15, 2001, and in revised form, September 11, 2001
Published, JBC Papers in Press, September 28, 2001, DOI 10.1074/jbc.M107836200



IL5 gene on human chromosome 5

Cyclic AMP-induced Chromatin Changes Support the NFATc-mediated Recruitment of GATA-3 to the Interleukin 5 Promoter*

Received for publication, July 31, 2008 Published, JBC Papers in Press, September 4, 2008, DOI 10.1074/jbc.M805929200

Stefan Klein-Hessling[‡1], Tobias Bopp[§], Mithilesh K. Jha[‡], Arthur Schmidt[‡], Shoichiro Miyatake[¶], Edgar and Edgar Serfling[‡2]

Nicotinic acetylcholine receptor α_7 regulates cAMP signal within lipid rafts

Jin Oshikawa,[1] Yoshiyuki Toya,[1] Takayuki Fujita,[1] Masato Egawa,[2] Junichi Kawabe,[3] Satoshi Umemura,[1] and Yoshihiro Ishikawa[1,3]

Am J Physiol Cell Physiol 285: C567–C574, 2003.

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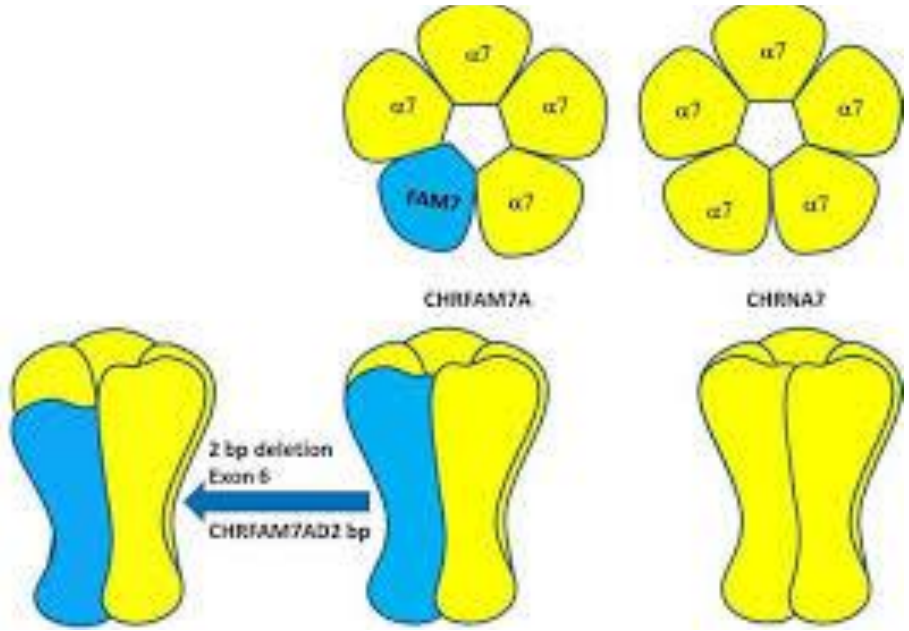
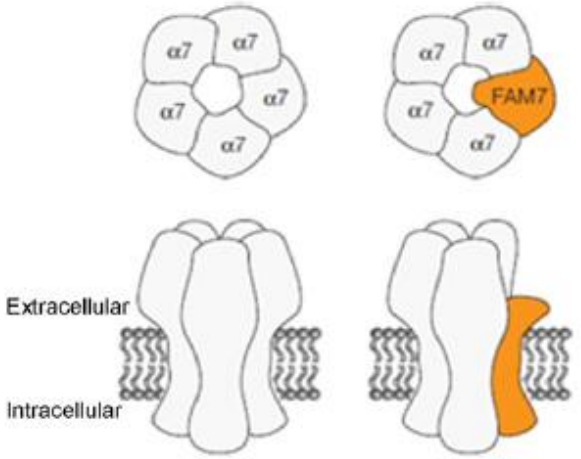
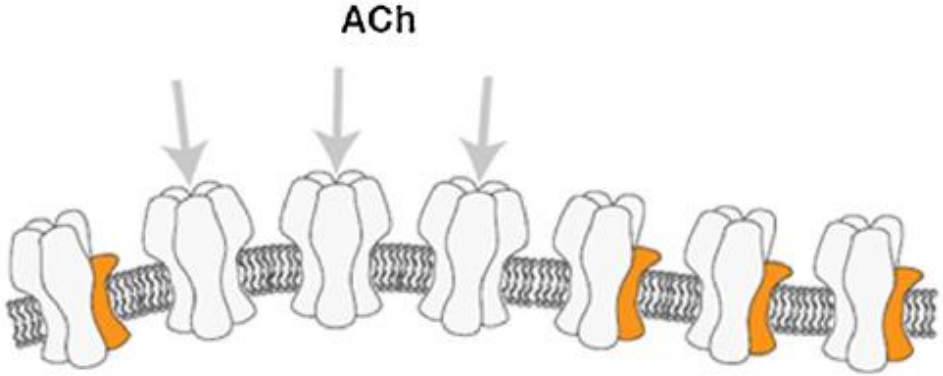
journal homepage: www.elsevier.com/locate/biochempharm

The chimeric gene *CHRFAM7A*, a partial duplication of the *CHRNA7* gene, is a dominant negative regulator of α7*nAChR function

Tanguy Araud [d], Sharon Graw [b], Ralph Berger [b], Michael Lee [b], Estele Neveu [a], Daniel Bertrand [a], Sherry Leonard [b,c,*]







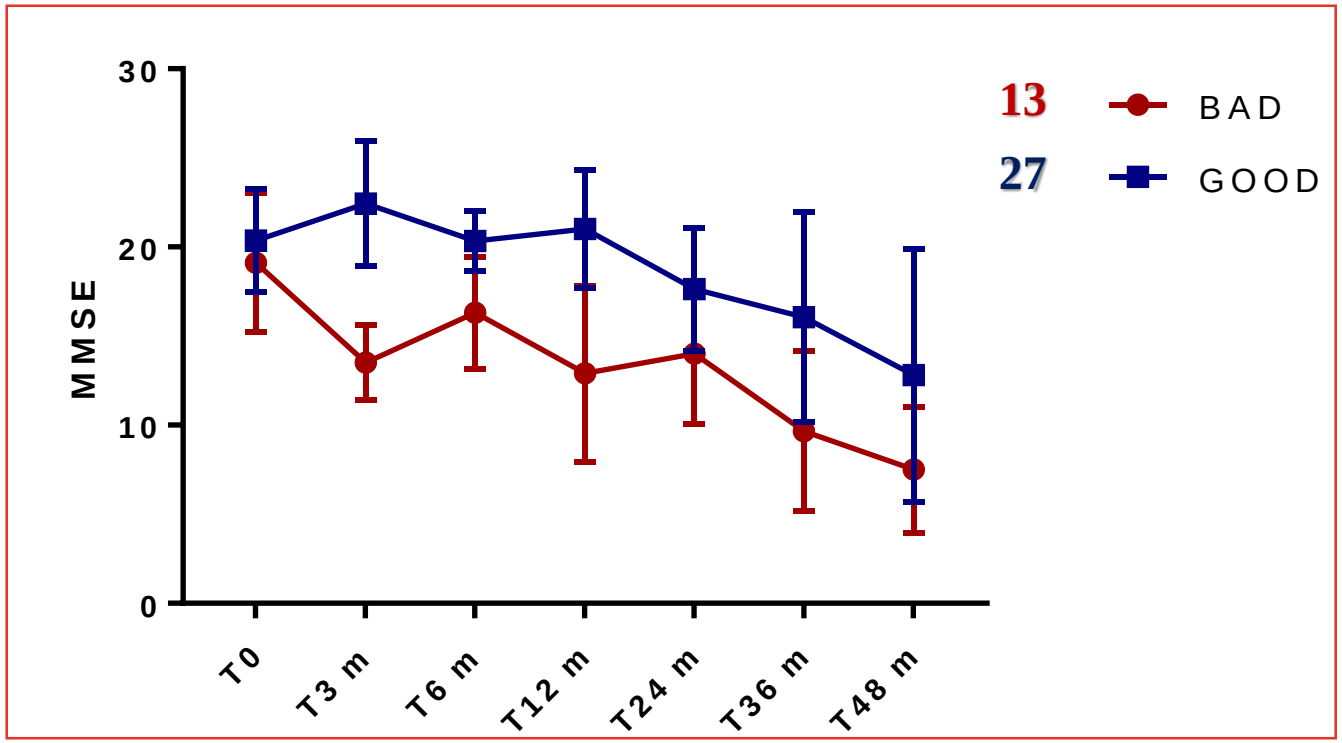
Alfa7 duplicato: Roberta Benfante @CNR

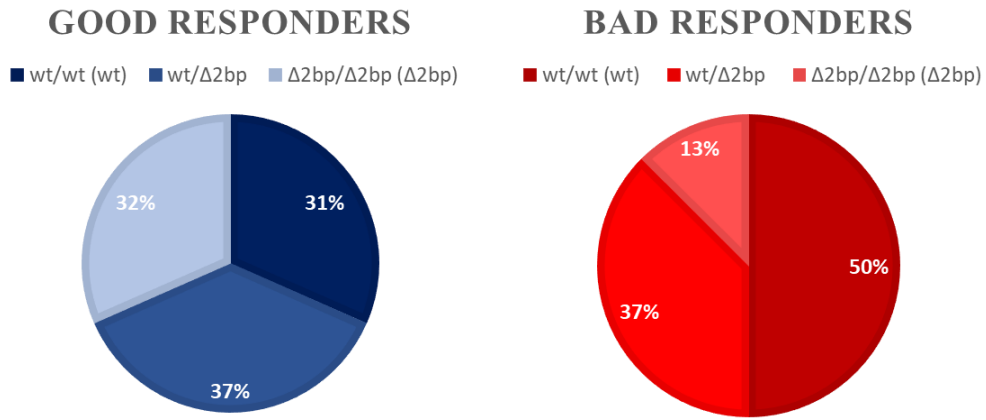
- CHRNA7/FAM7A FUSION GENE; CHRFAM7A
- The CHRFAM7A gene on chromosome 15 is a hybrid consisting of a partial duplication of the CHRNA7 gene fused to a copy of the FAM7A gene (Riley et al., 2002). CHRFAM7A had a dominant-negative effect on the amplitude of ACh-elicited CHRNA7 currents, which was due to reduced surface expression of CHRNA7. Stimulation of CHRNA7 in macrophages induces an antiinflammatory response.

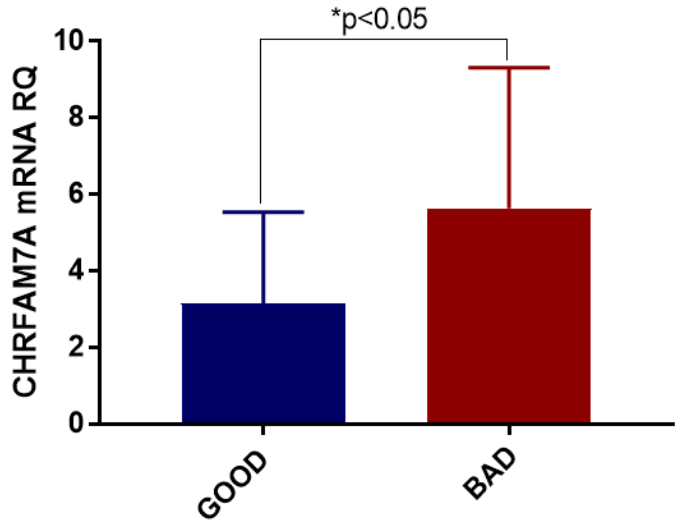
Risposta alla terapia e CHRFAM7A

Suddivisione in Good e Bad Responders

- Valutazione retrospettiva del **MMSE**, Mini Mental State Evaluation
- ***Coefficiente di progressione di malattia*** → cut-off = $\frac{\text{-3 punti MMSE}}{\text{12 mesi}}$ = **-0,25**

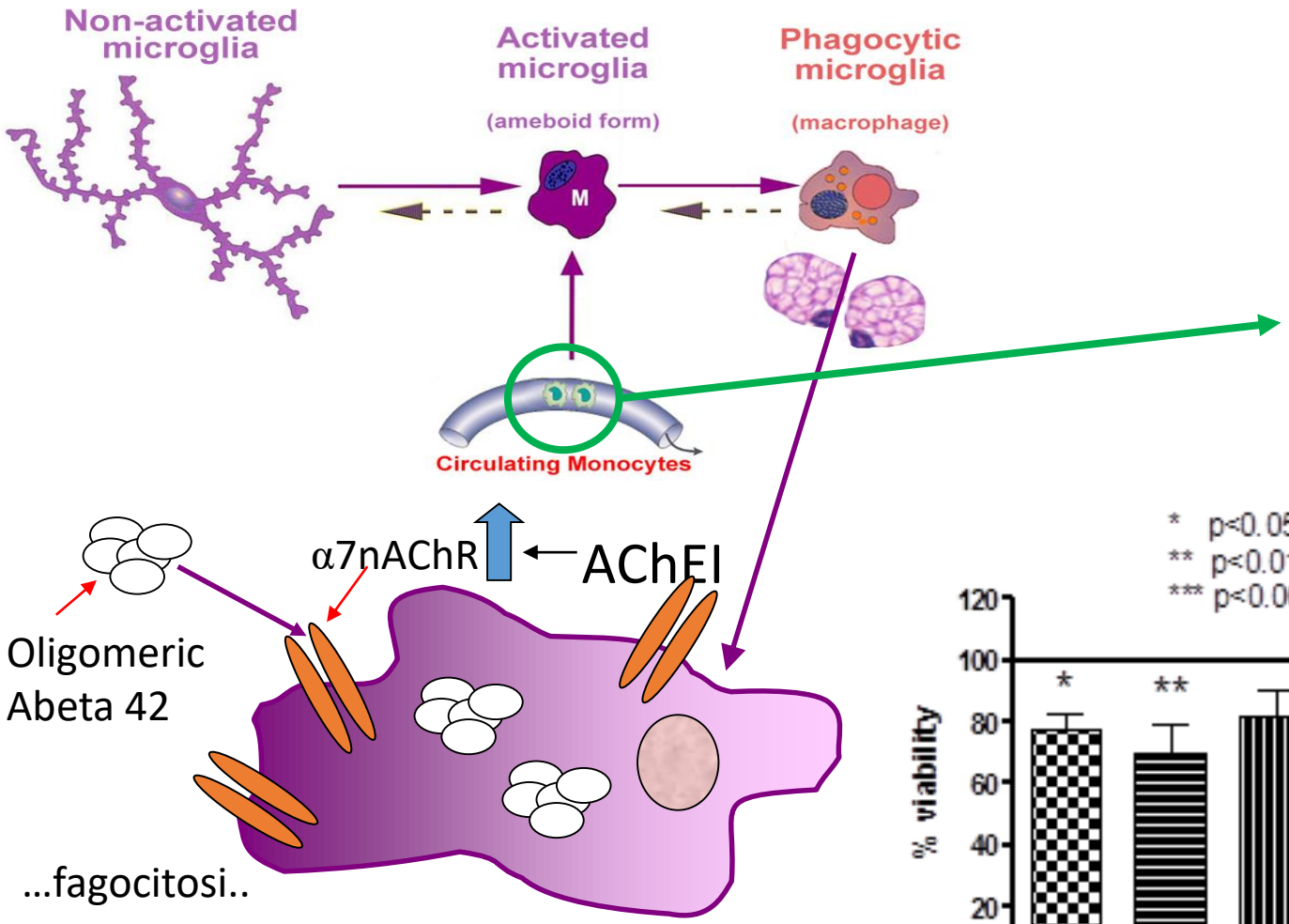




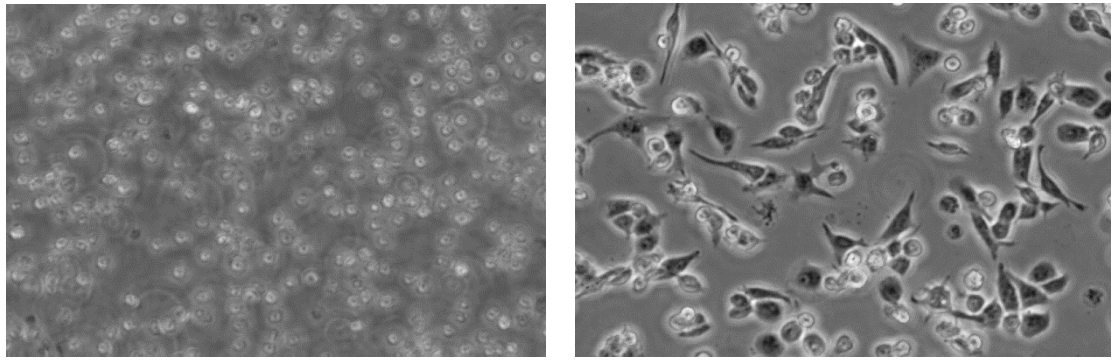


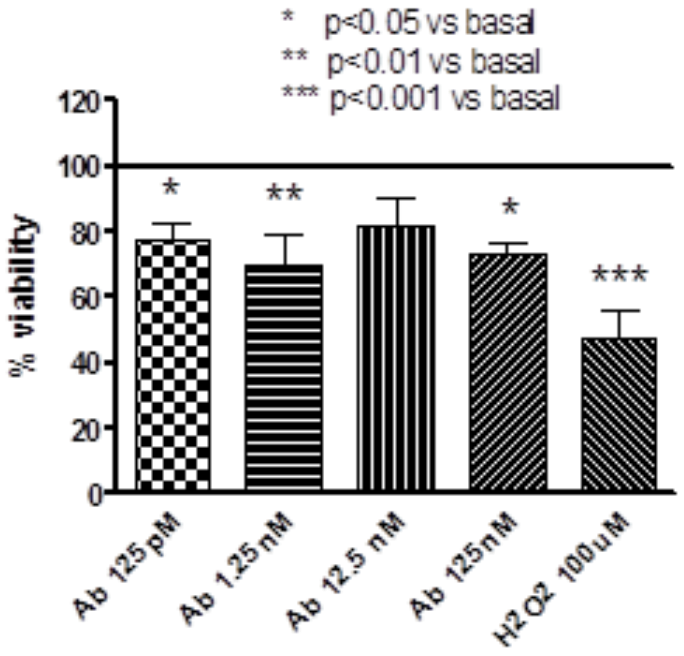
In collaborazione con Dott.ssa Benfante

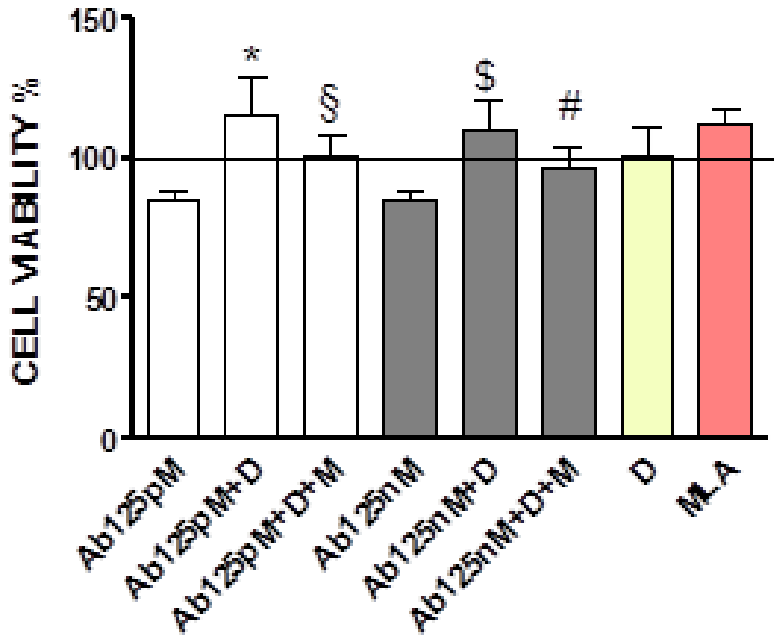
CLEARANCE DI ABETA



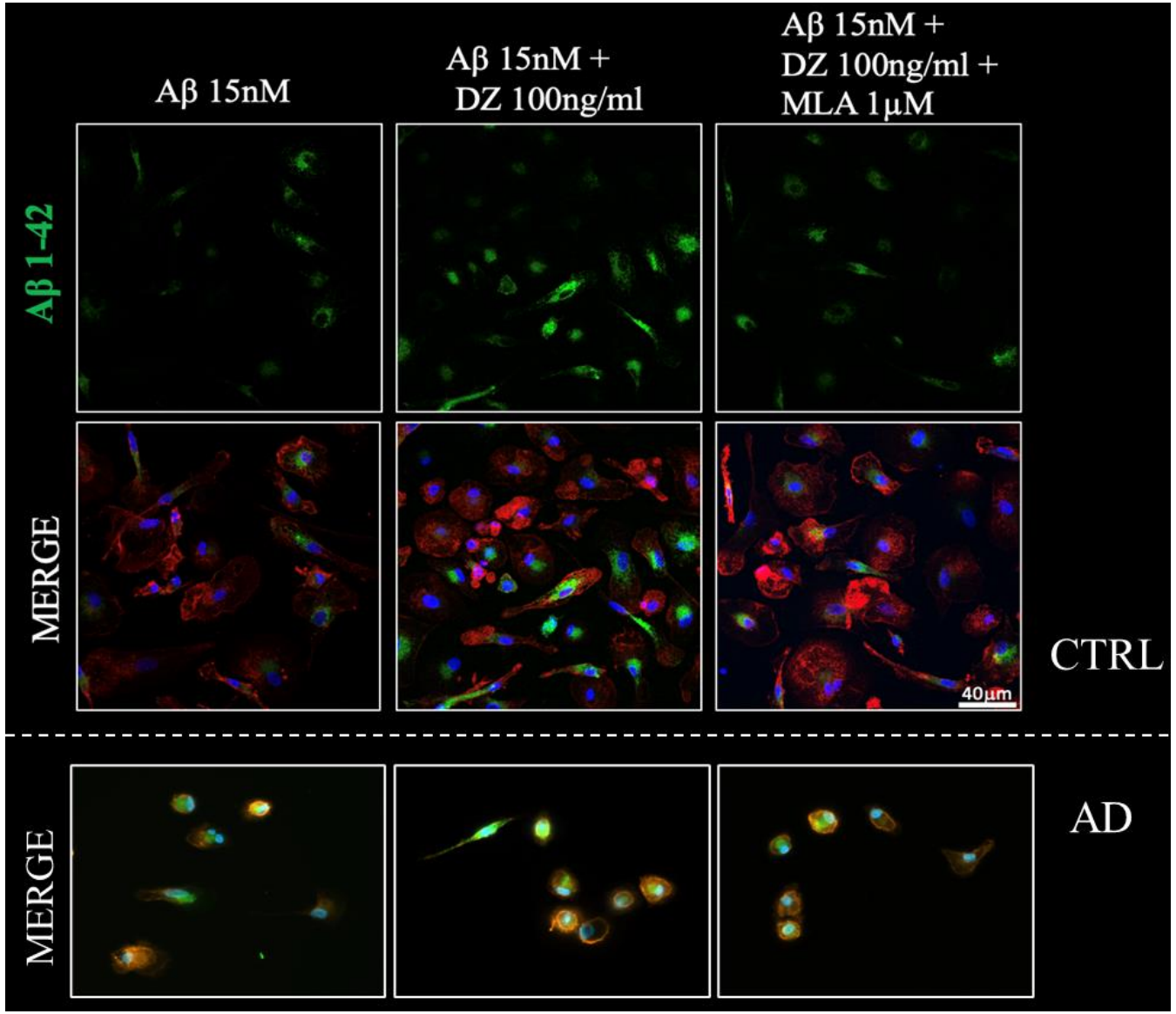
THP1 differenziate a macrofagi con 25ng/ml PMA per 48 ore

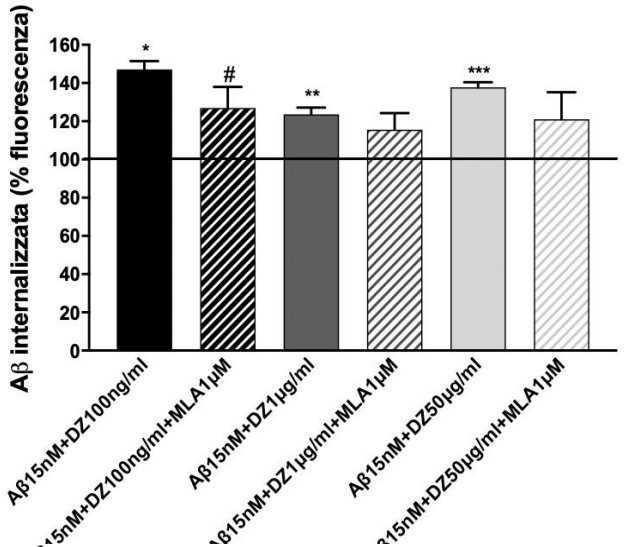


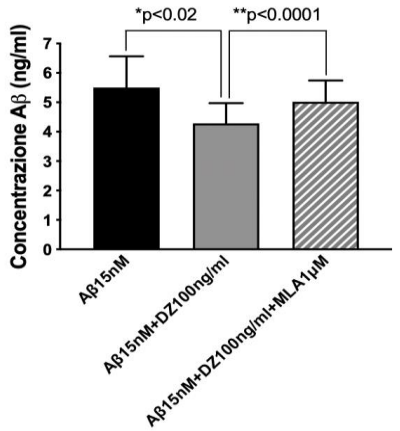




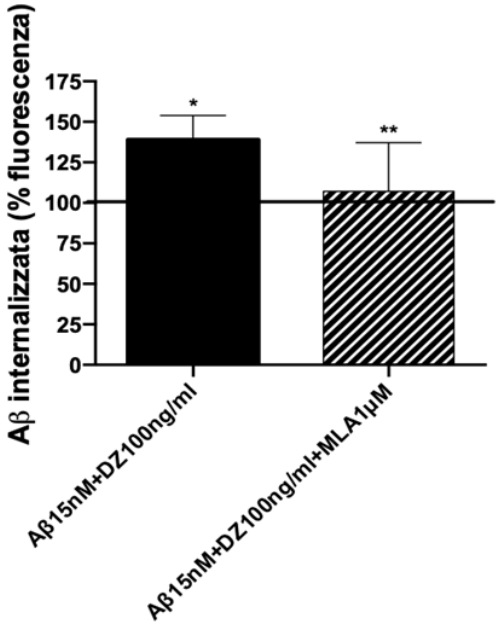
L'interazione *Donepezil-α7nAChR favorisce la fagocitosi di Aβ*

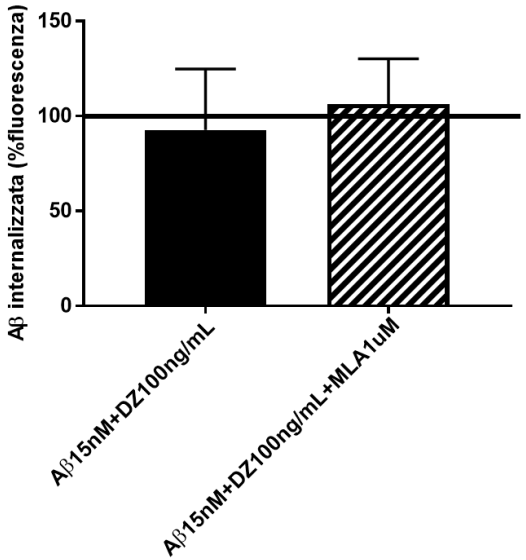






Cellule U937





Differenziamento per 7 giorni con M-CSF

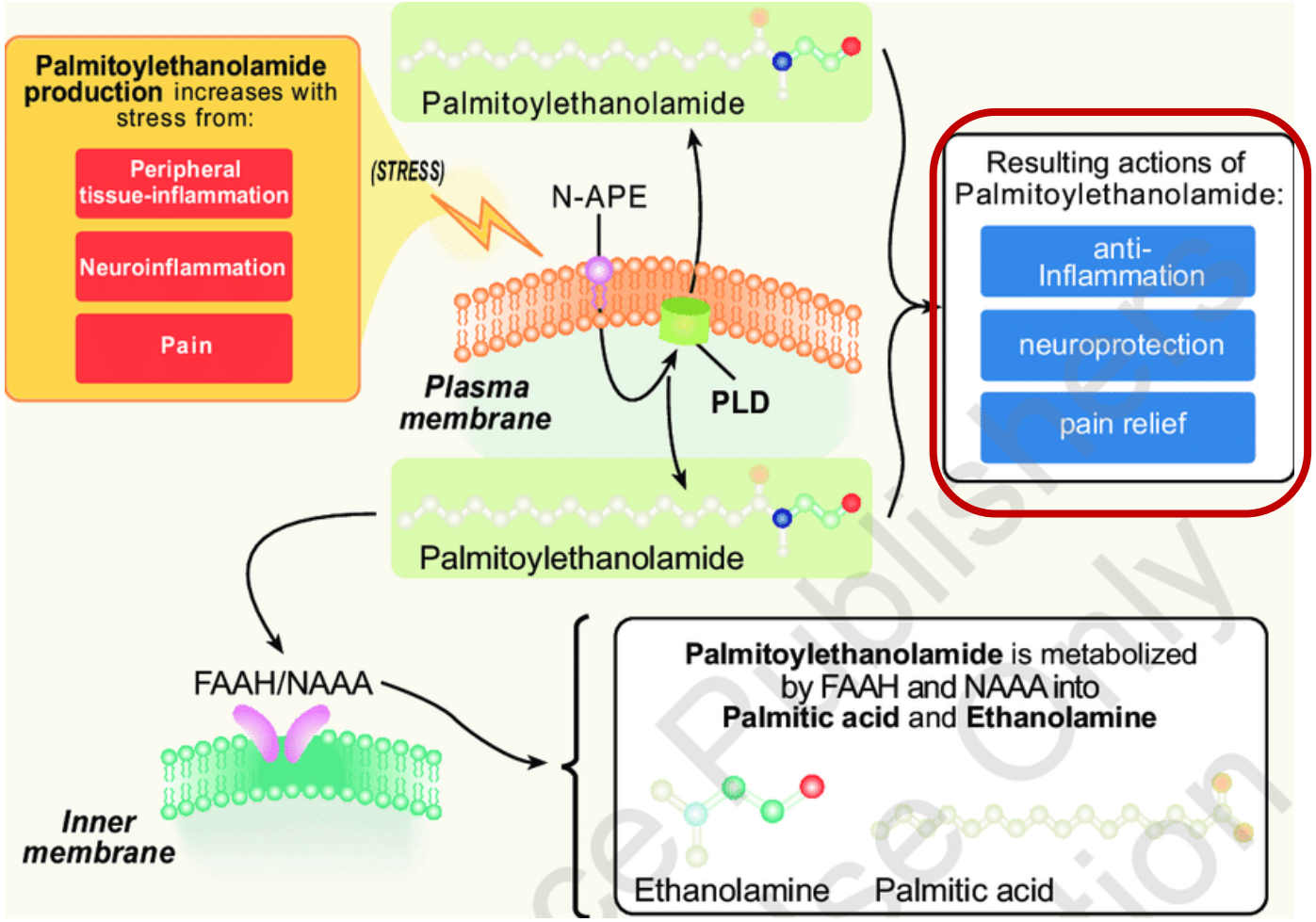
Macrofagi CTRL

Macrofagi AD

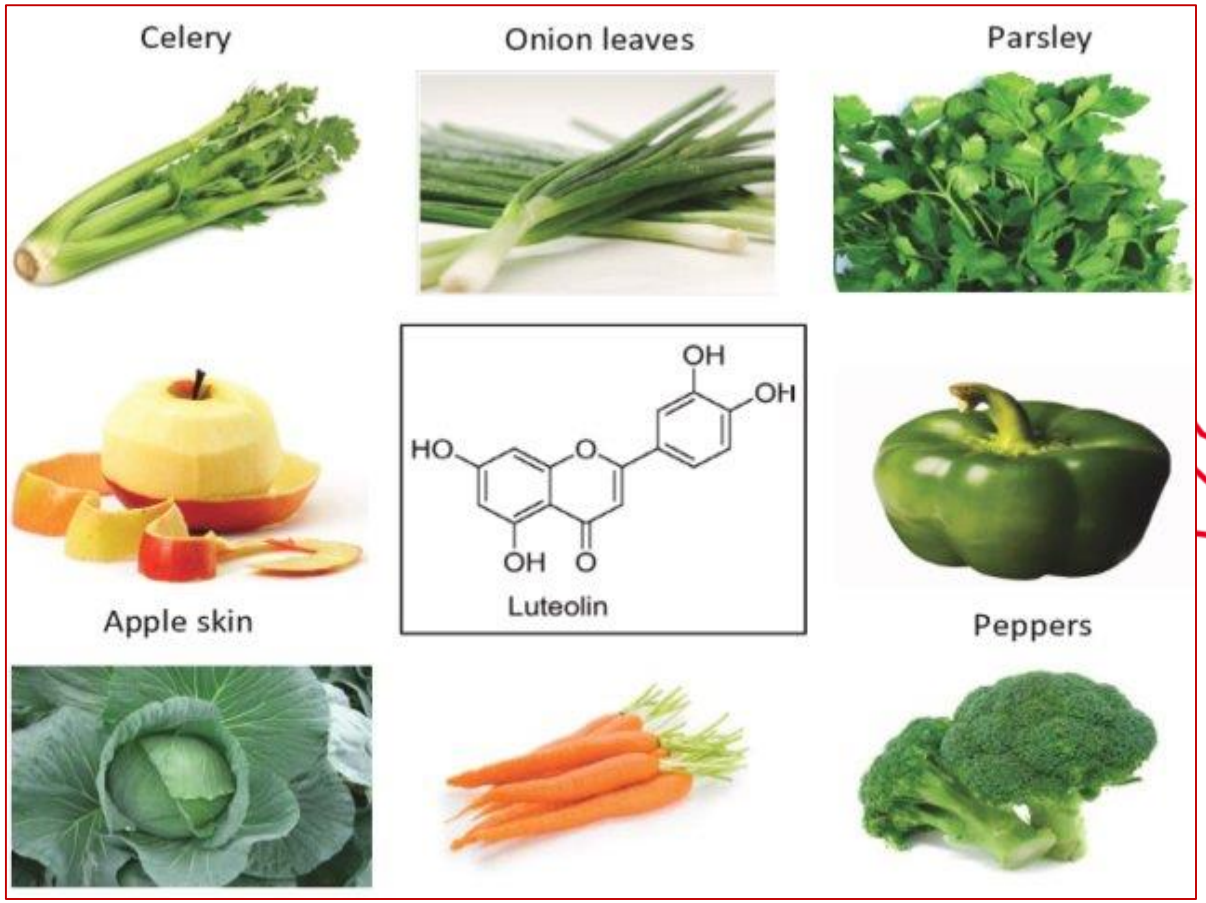
In collaborazione con Dott.ssa Rodriguez Menendez

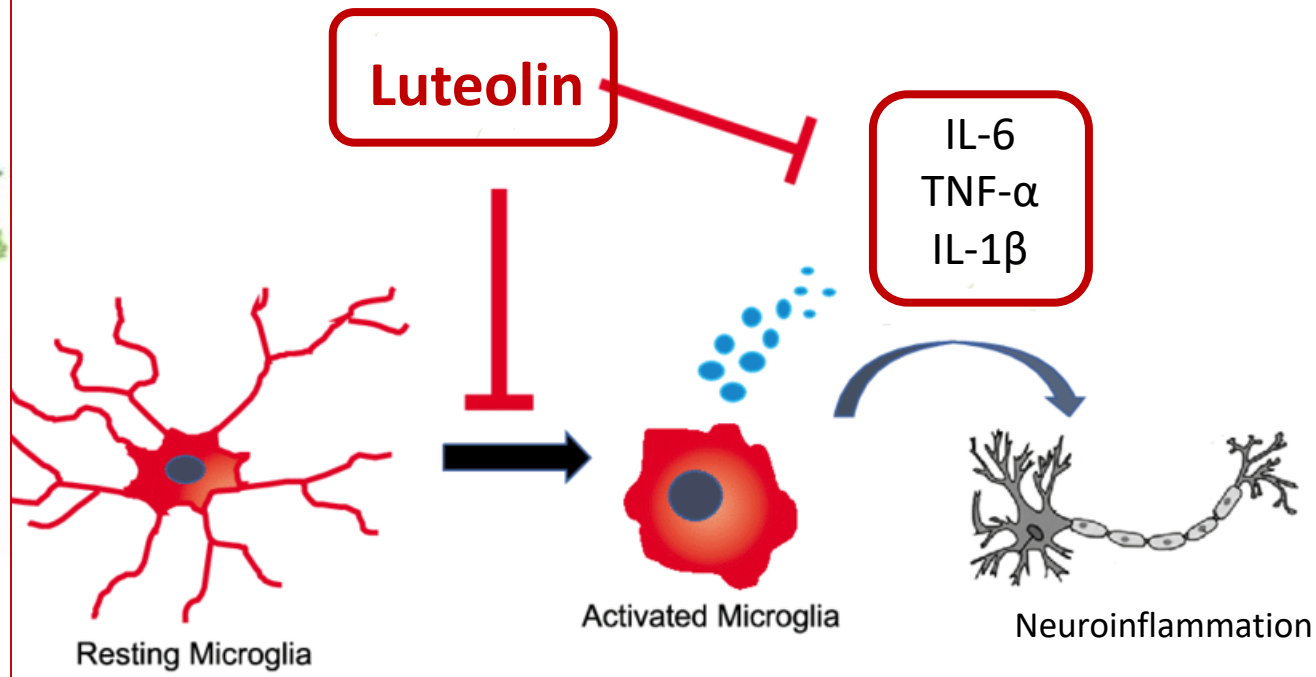
Altre sostanze sono in grado di contrastare la chemiotassi Abeta indotta?

PEA è l'ammide di un acido grasso di natura endogena e si trova in diversi tessuti umani. La sua produzione è indotta in mastociti e cellule microgliali in presenza di danno.



Luteolina





Research Article

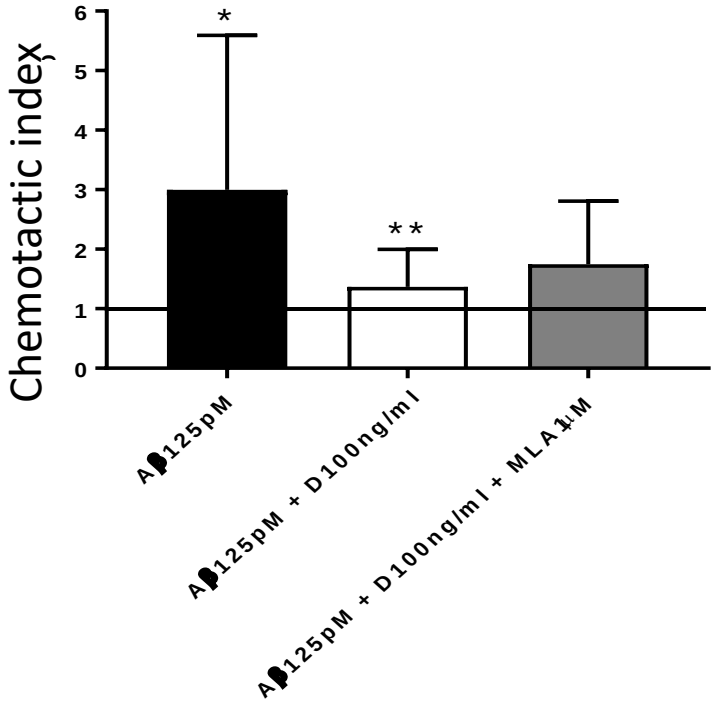
Luteolin Inhibits Microglial Inflammation and Improves Neuron Survival Against Inflammation

Li-Hong Zhu, Wei Bi, Ren-bin Qi, Hua-dong Wang & Da-xiang Lu

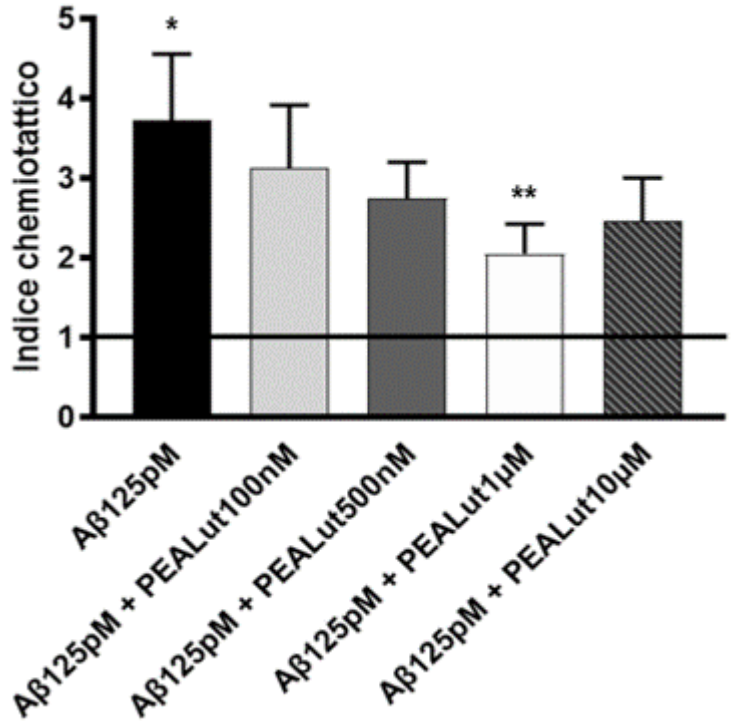
Pages 329-336 | Received 28 Dec 2010, Published online: 01 Jun 2011

Journal
International Journal of Neuroscience ›
Volume 121, 2011 - Issue 6

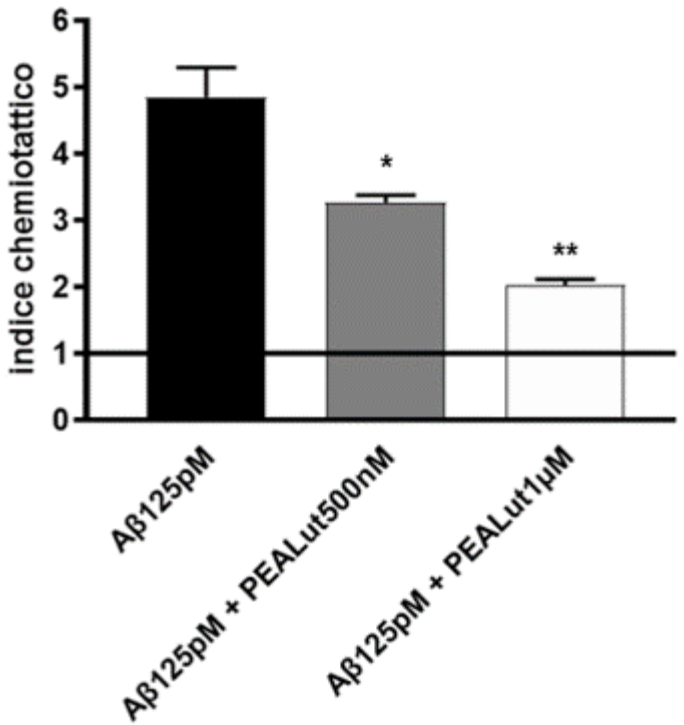
Donepezil e Co-ultraPEALut contrastano la chemiotassi Aβ-indotta



Monociti AD



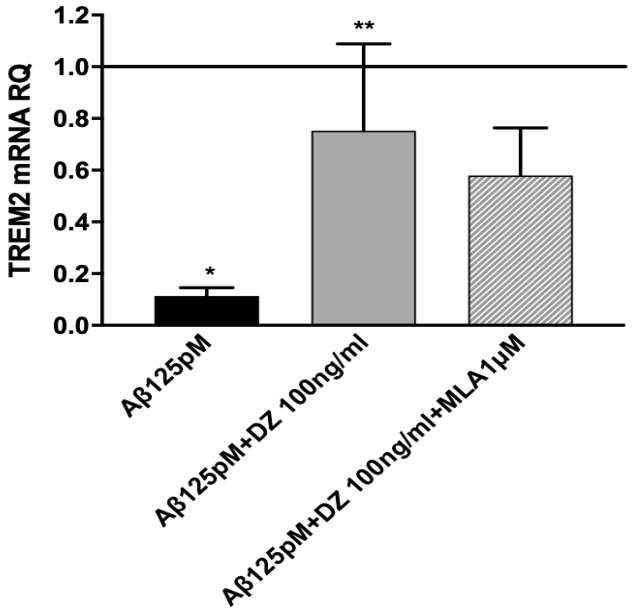
U937



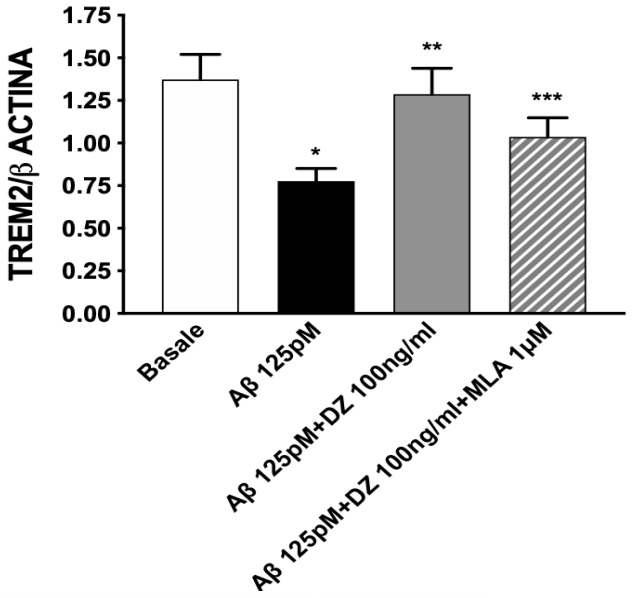
Monociti AD

Donepezil e Co-ultraPEALut aumentano l'espressione di TREM2

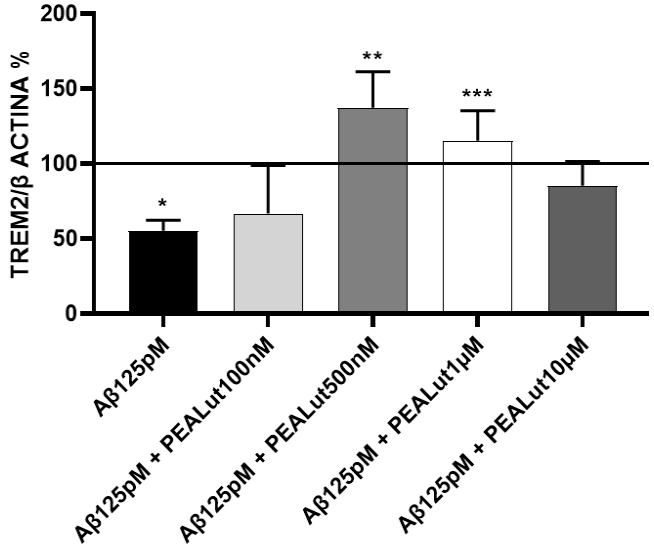
U-937 differenziate



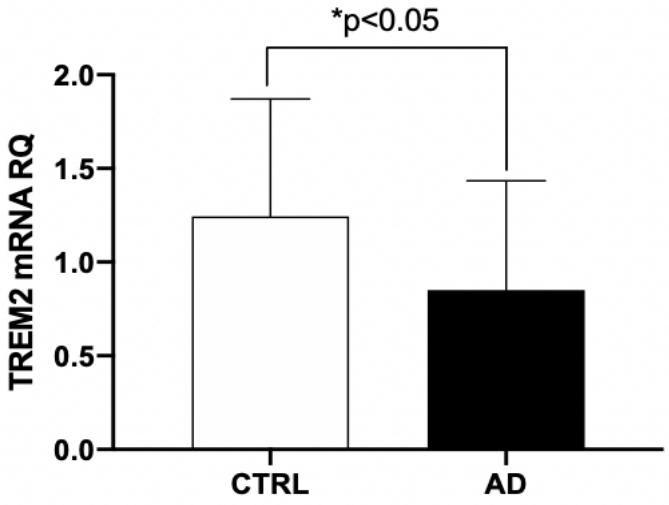
Donepezil

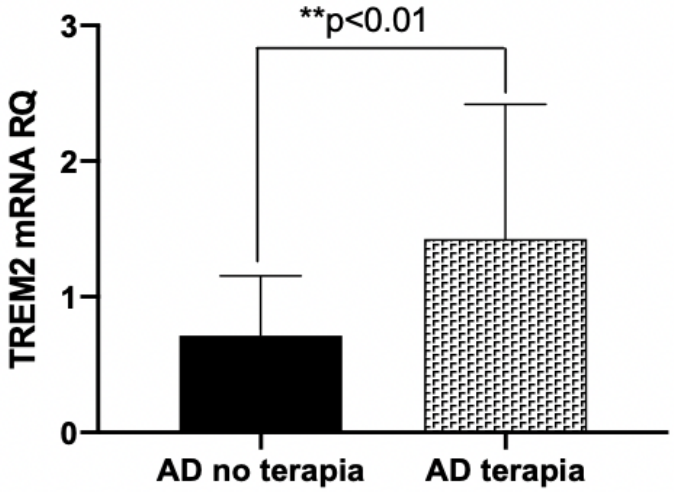


Co-ultraPEALut

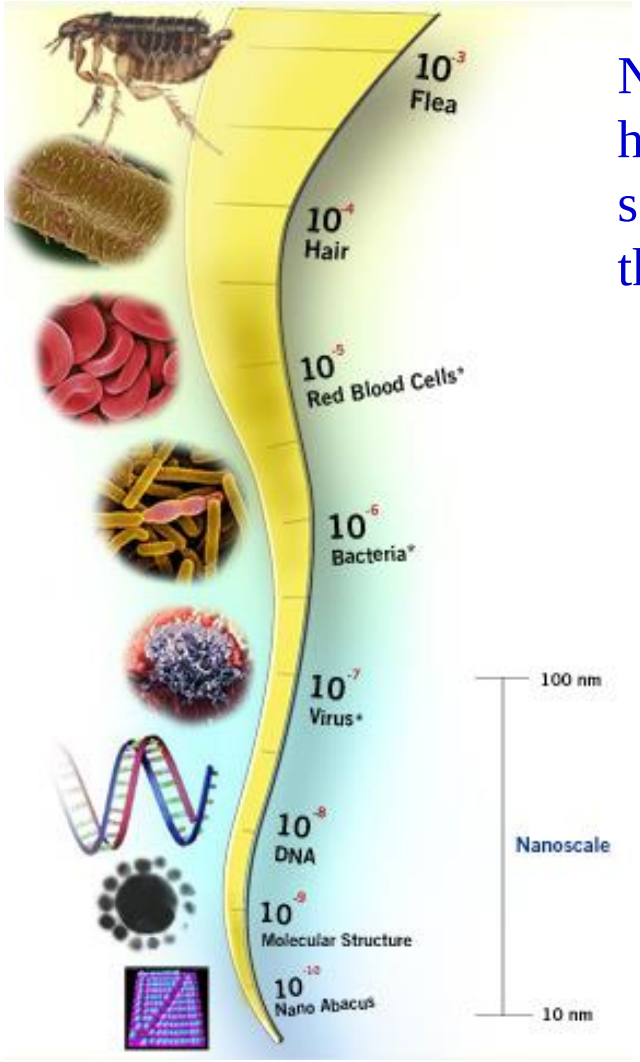


Monociti Umani (Donepezil)

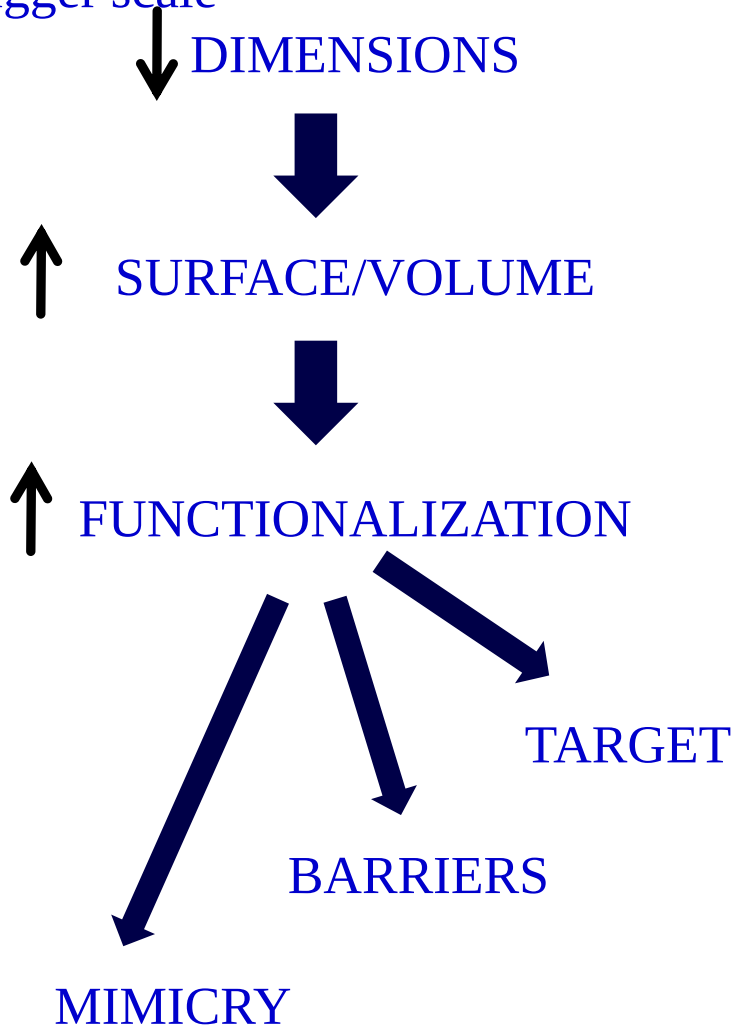




Nanomedicine



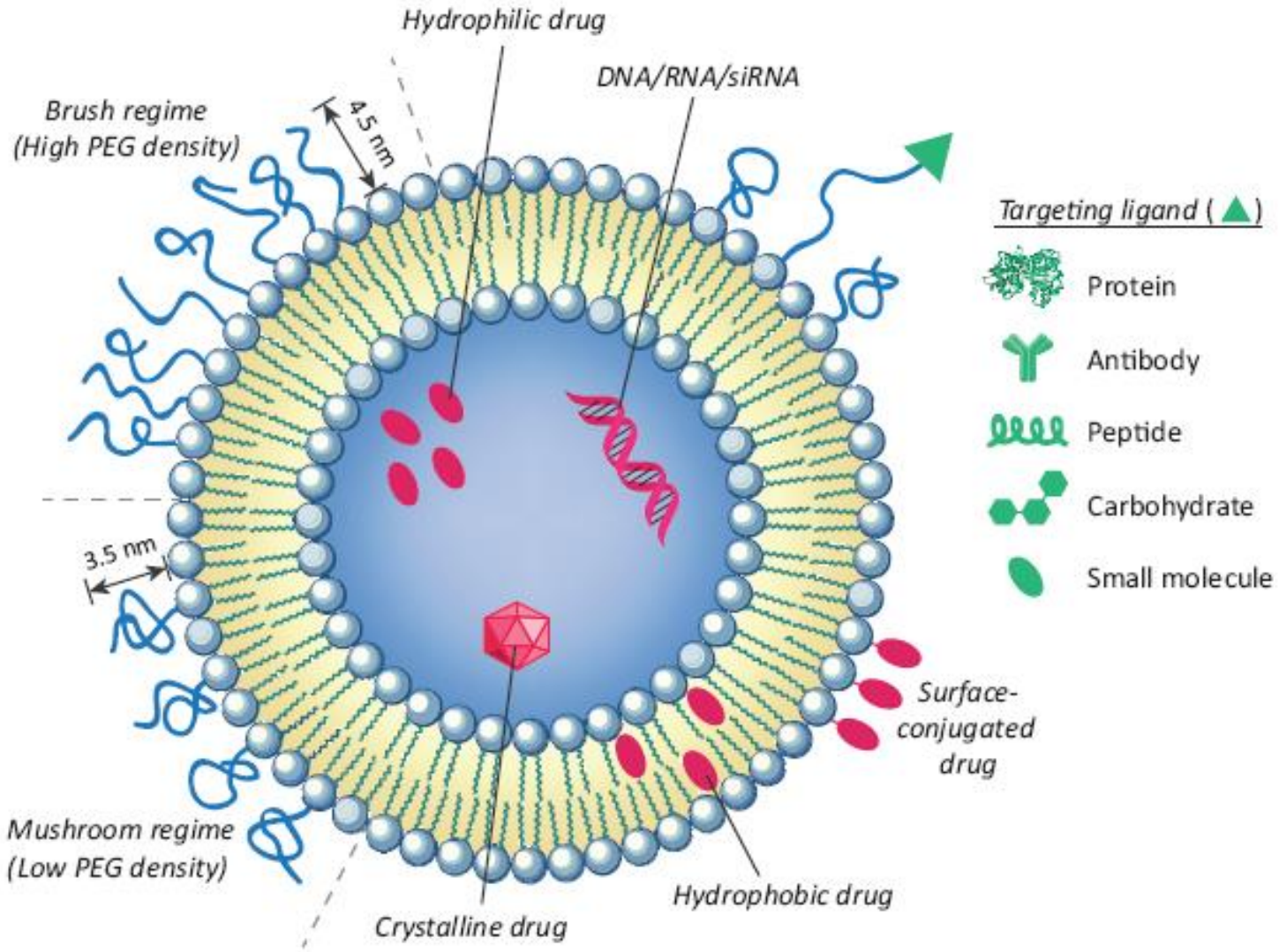
Nanomedicine is the application of nanotechnology to achieve innovation in healthcare. It uses the properties developed by a material at its nanometric scale 10-9 m which often differ in terms of physics, chemistry or biology from the same material at a bigger scale



USED IN:

- DIAGNOSTIC,
- DRUG DELIVERY,
- REGENERATIVE MEDICINE

LIPOSOMES

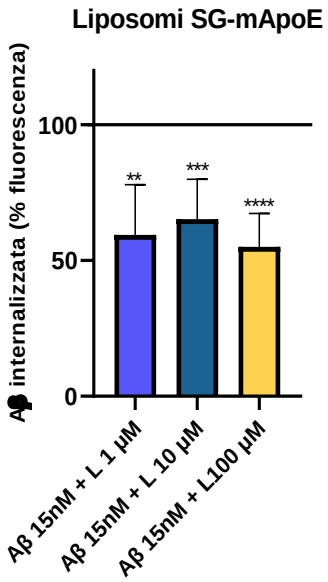


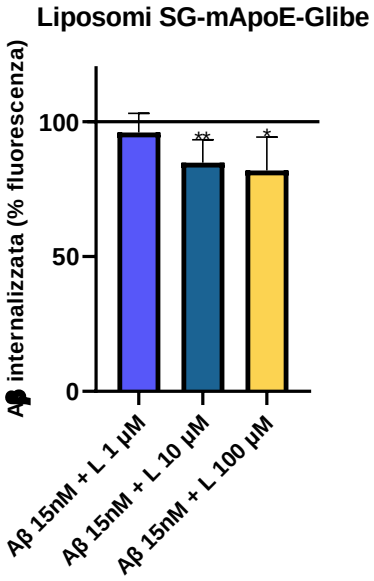
Matrice di sm/chol (1:1) con:

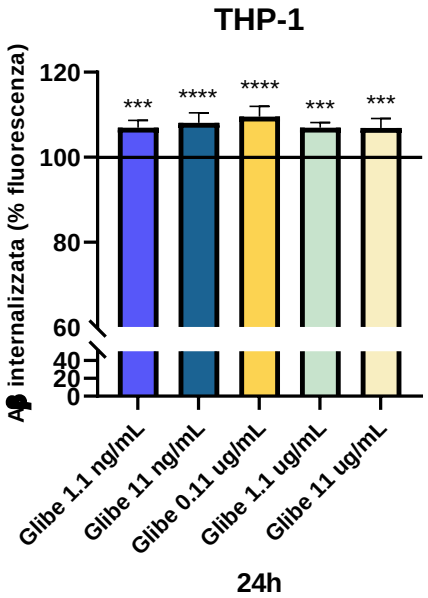
- *MApoE: monomero di ApoE*
- *SG17*
- *glibenclamide*

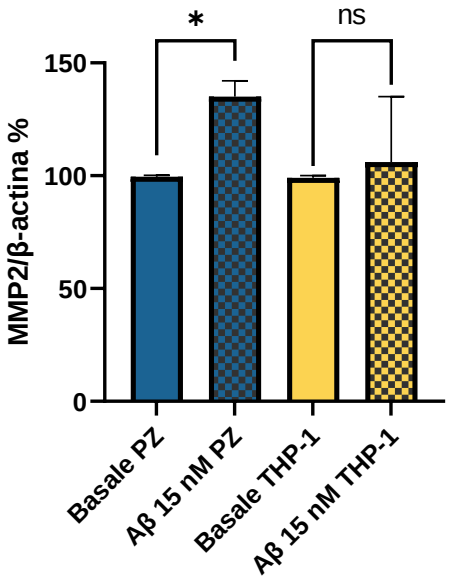
Liposomi: modulano in maniera diversa l'internalizzazione di Aβ

THP-1

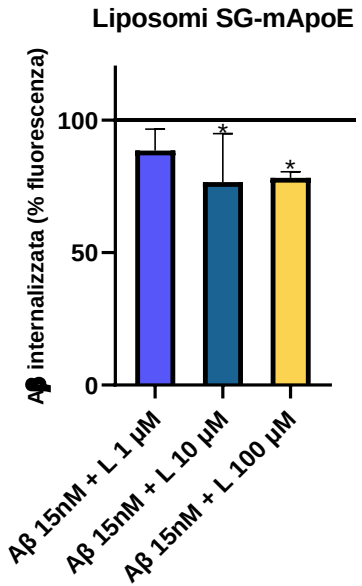


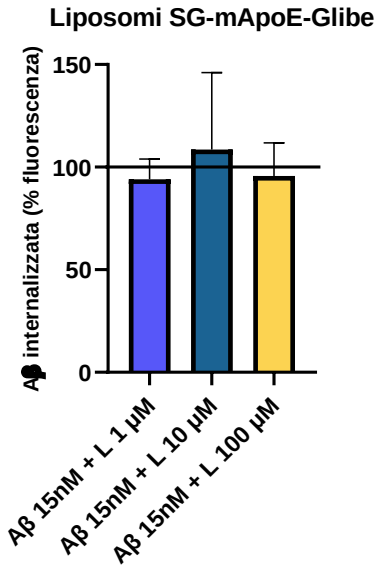


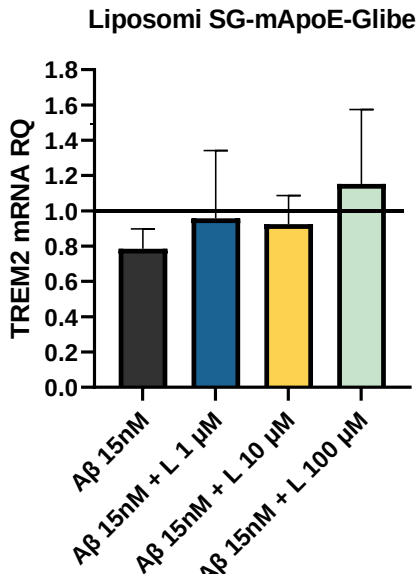




AD

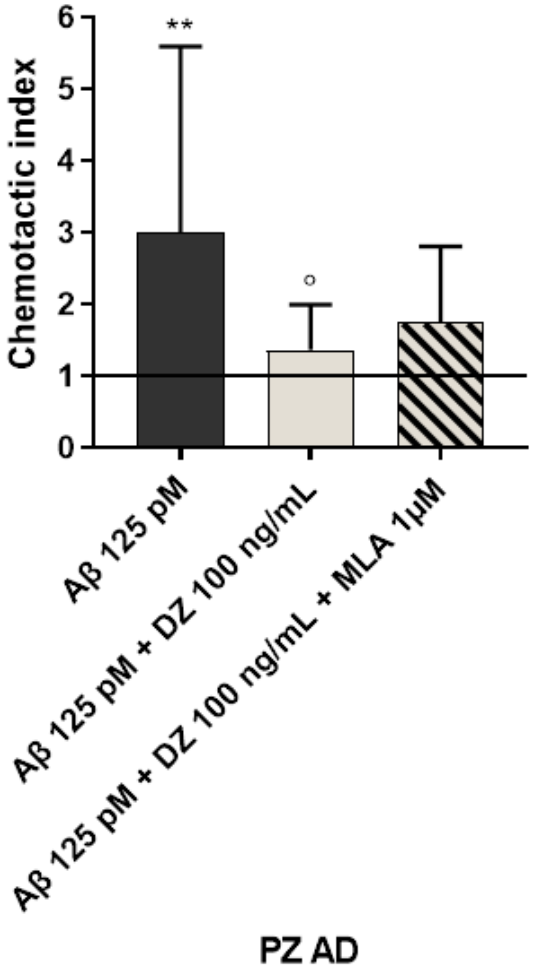






I trattamenti: modulano la chemiotassi monocitaria Aβ-indotta

Donepezil



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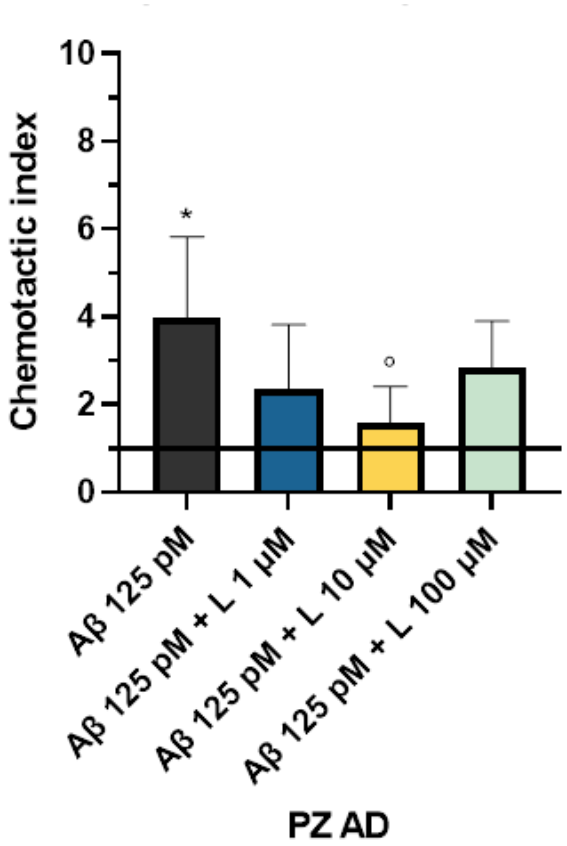

Co-ultraPEALut