DNSRO
UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II
Dipartimento di Neuroscienze e
Scienze Riproduttive ed Odontostomatologiche

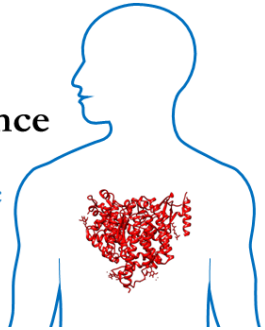
Biological Aspects of New Molecular Therapies for Neuropathologies

Ilaria Piccialli, PhD

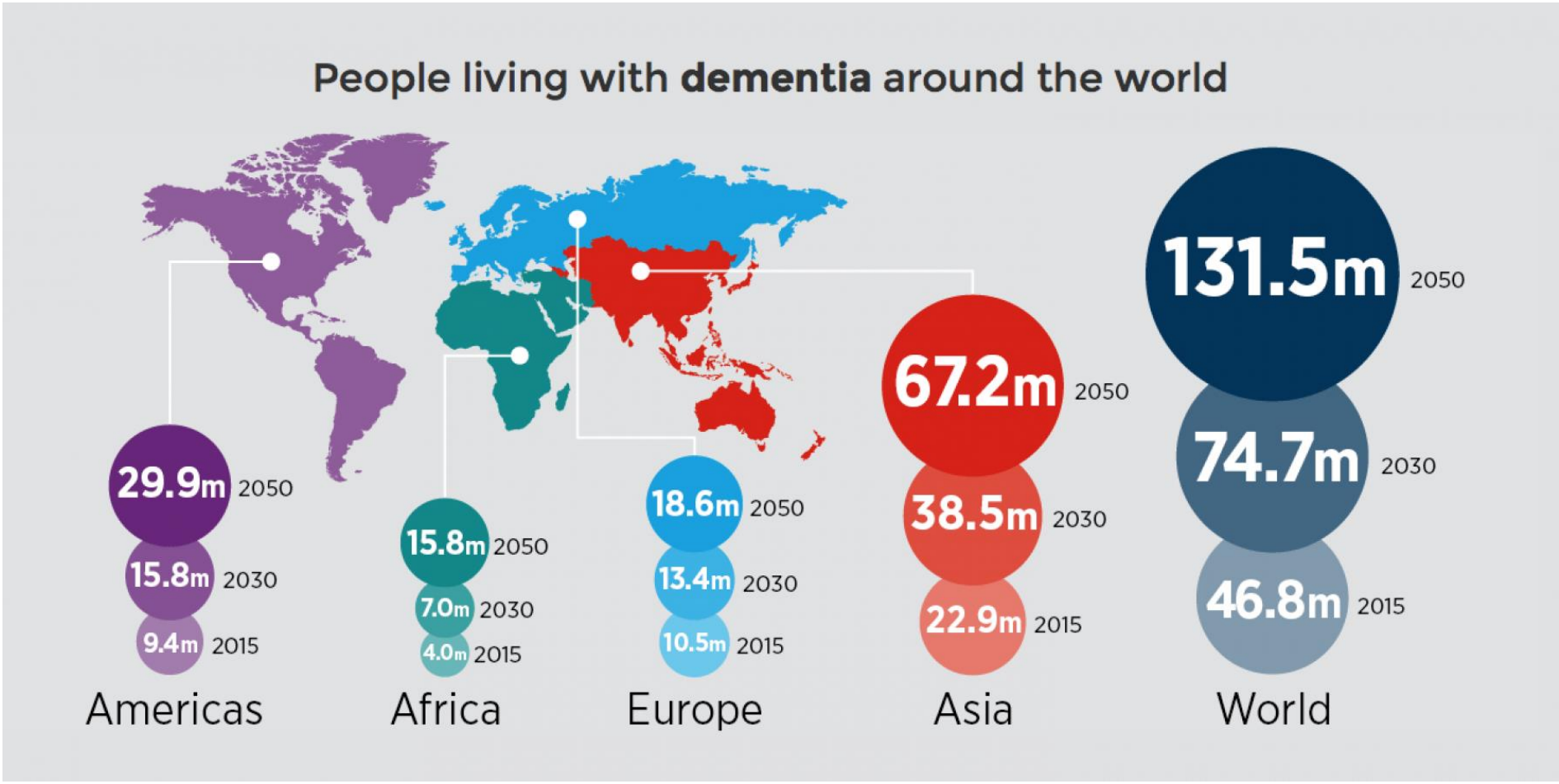
Department of Neuroscience, Reproductive and Dentistry Sciences,
Division of Pharmacology, School of Medicine

2024 April 19th

MRTBS 2024
1st International Conference
Modern research trends in biomedical sciences: a holistic approach to health care
Opole, Poland, 17-19.04.2024

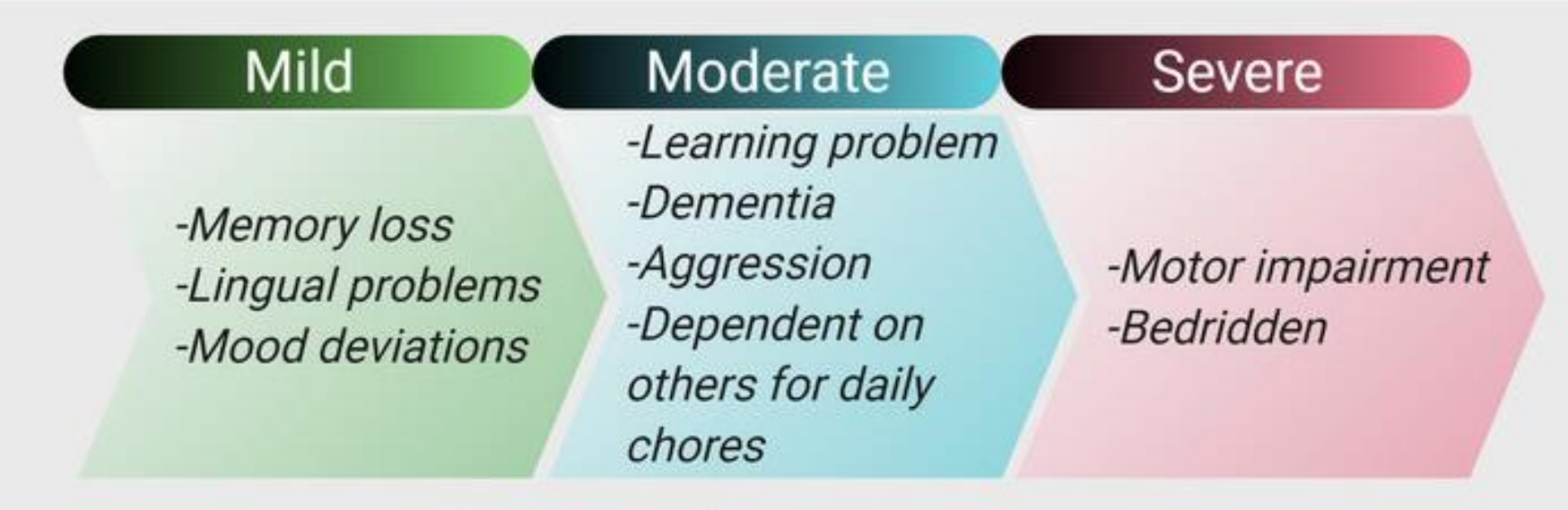


World Alzheimer's report 2015

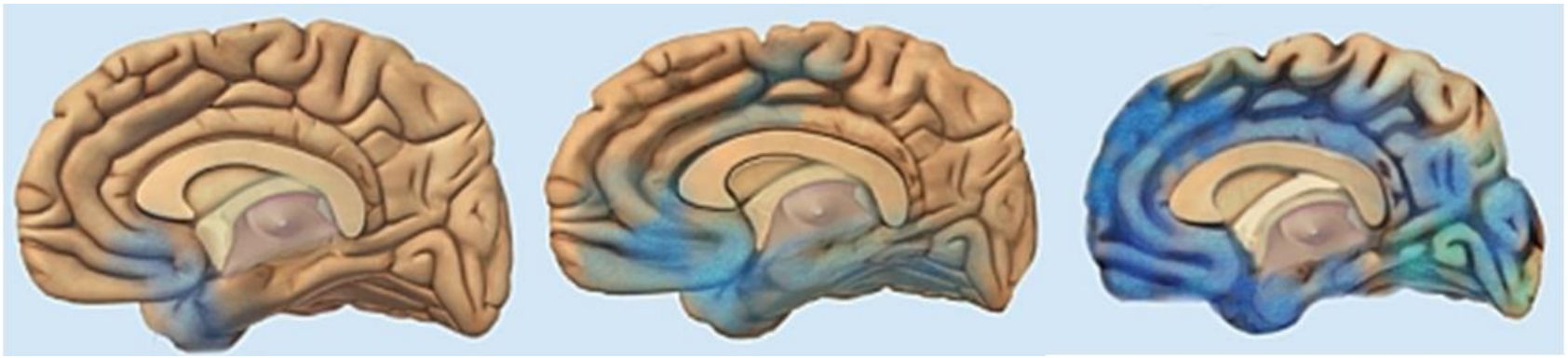


© https://ncdalliance.org/news-events/news/world-alzheimer-report-2015-launched

Alzheimer's disease symptoms

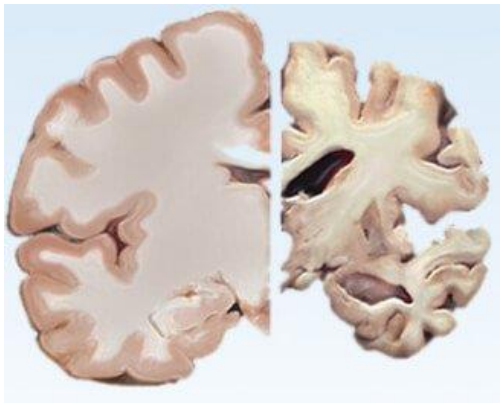


PRECLINICAL AD **MILD TO MODERATE AD** **SEVERE AD**

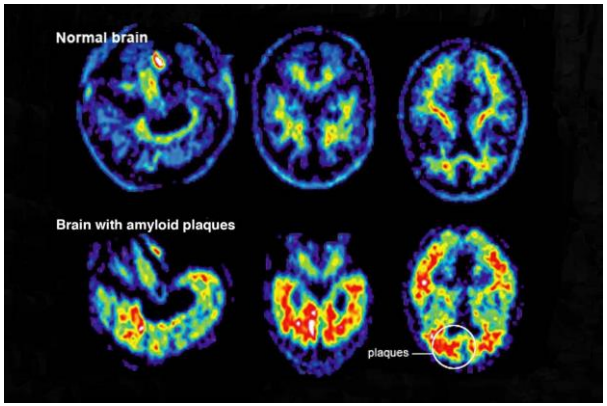


Aβ plaques and NFTs: the main hallmarks of Alzheimer's Disease

HEALTHY **AD**



Aβ PLAQUES (PET SCANS)



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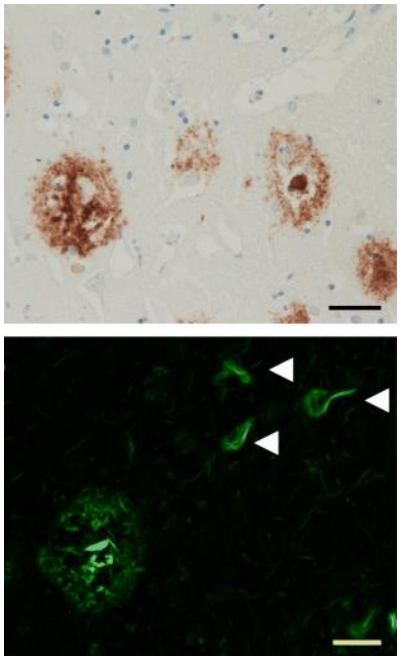
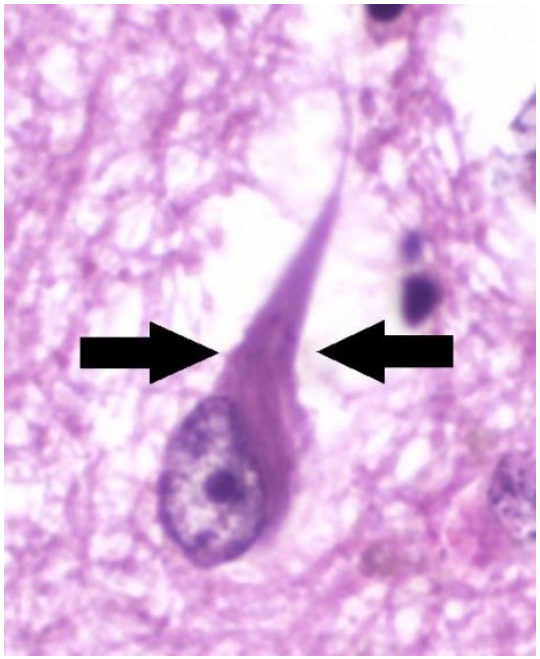
Aβ PLAQUES



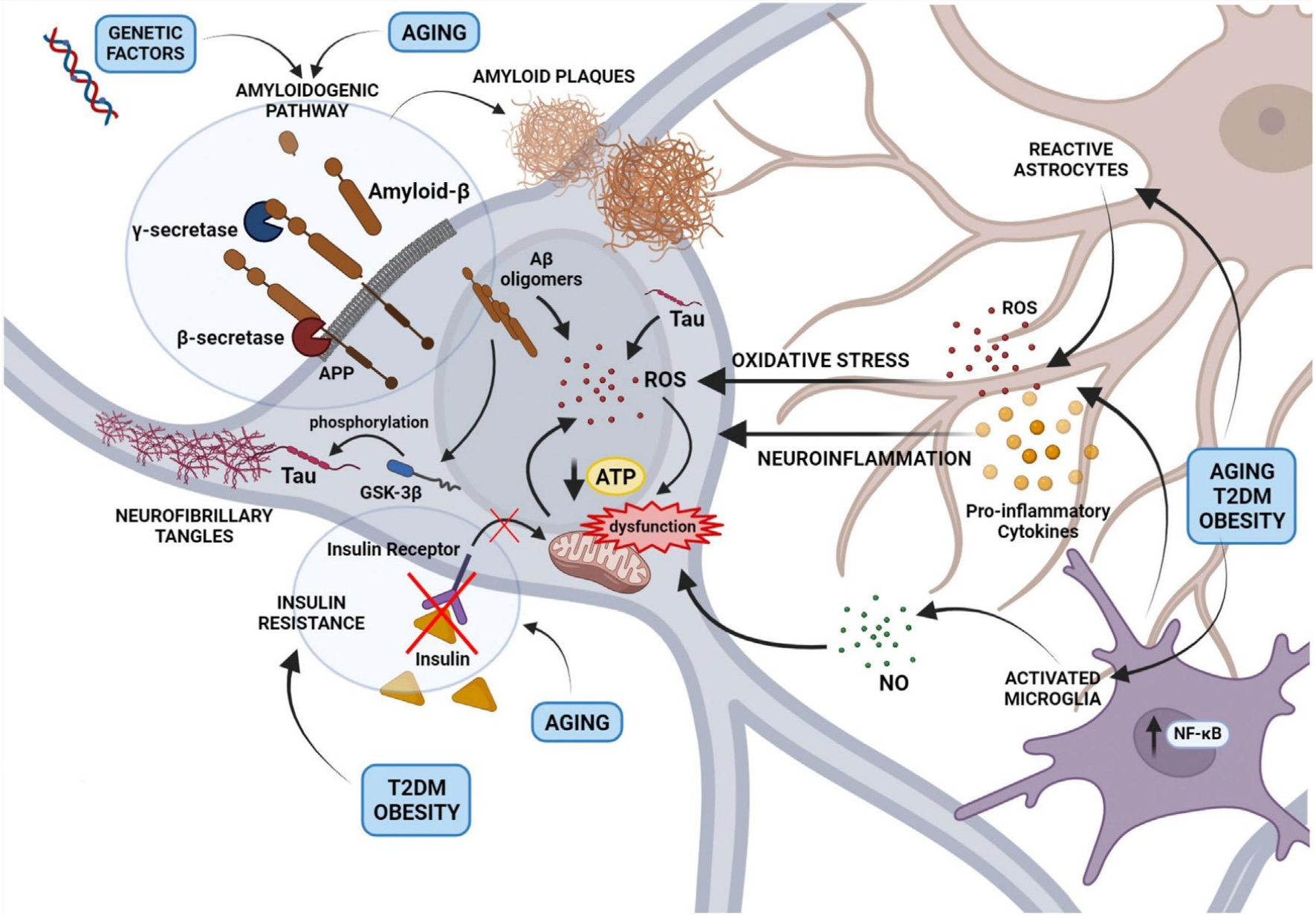
©DeTure and Dickson, 2019. *Molecular Neurodegeneration*

NEUROFIBRILLARY TANGLES



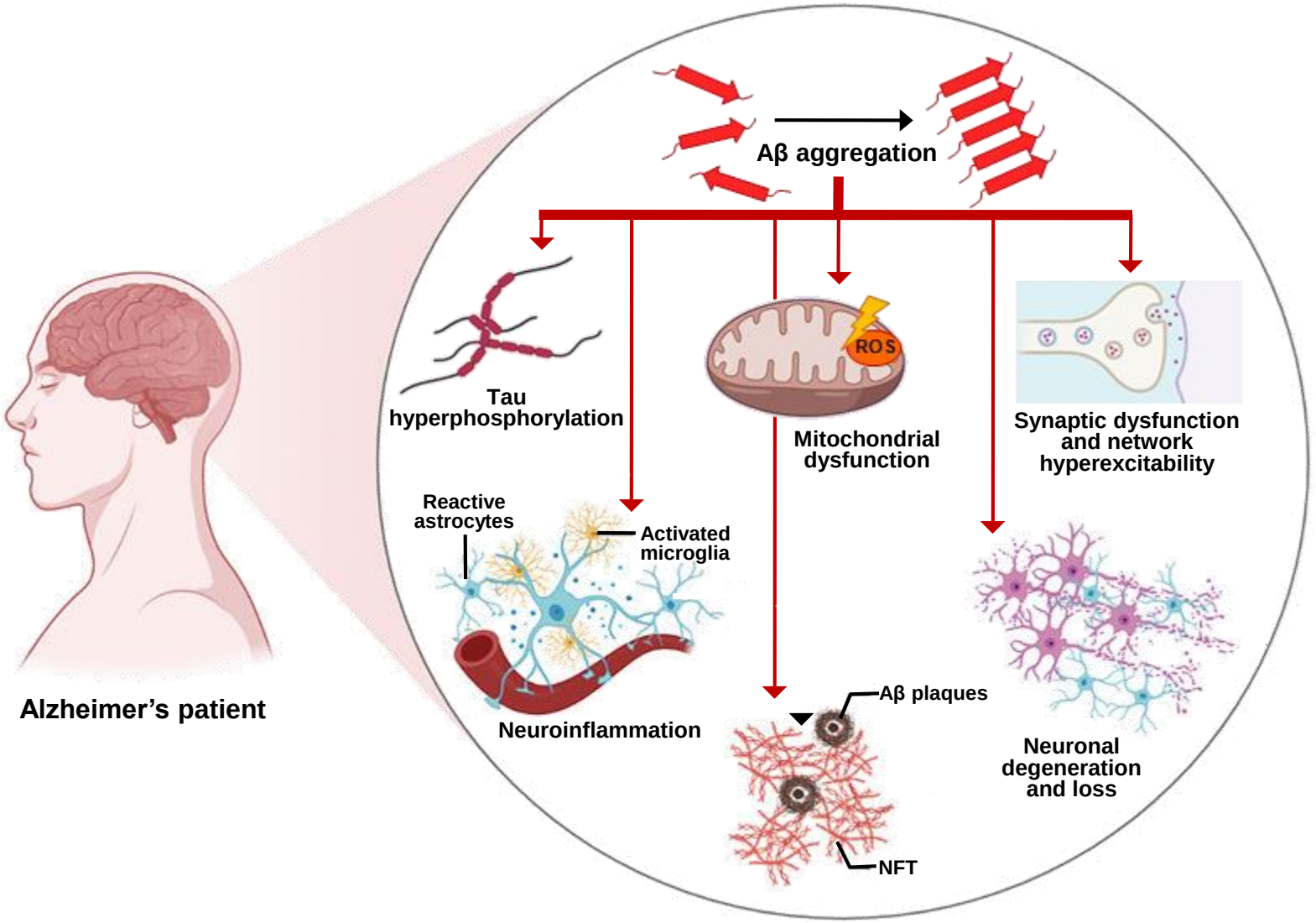
©https://en.wikipedia.org/wiki/Neurofibrillary_tangle

Alzheimer's Disease: a multifaceted pathology



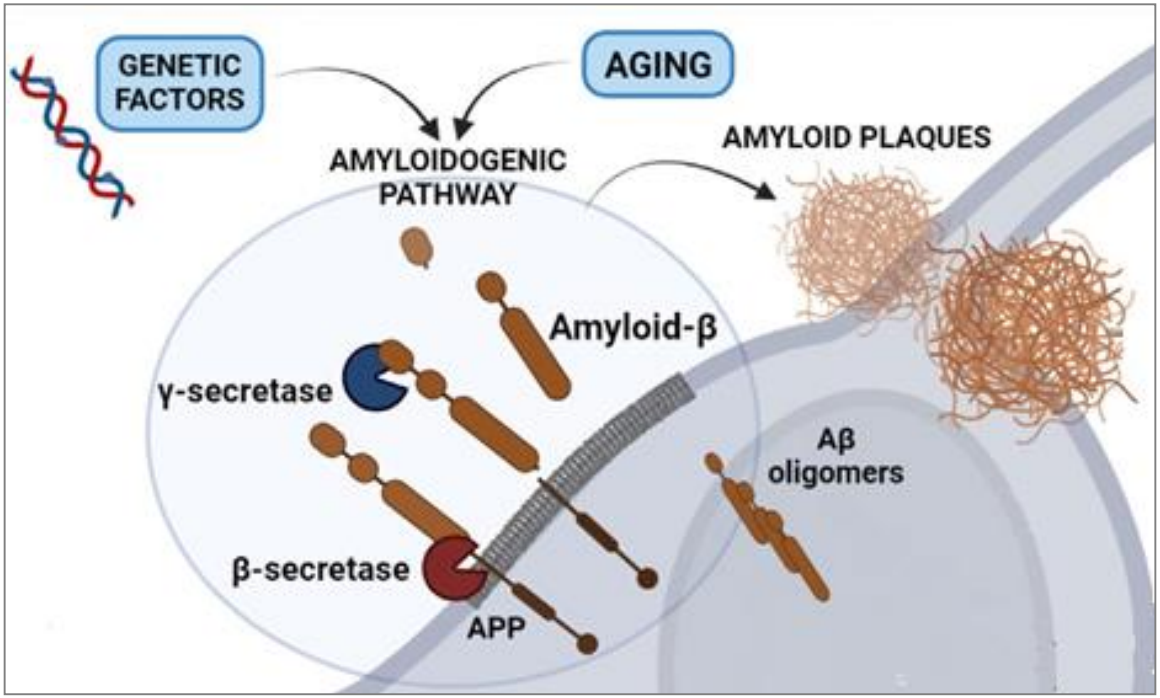
Piccialli *et al.*, 2022 *Frontiers in Pharmacology*

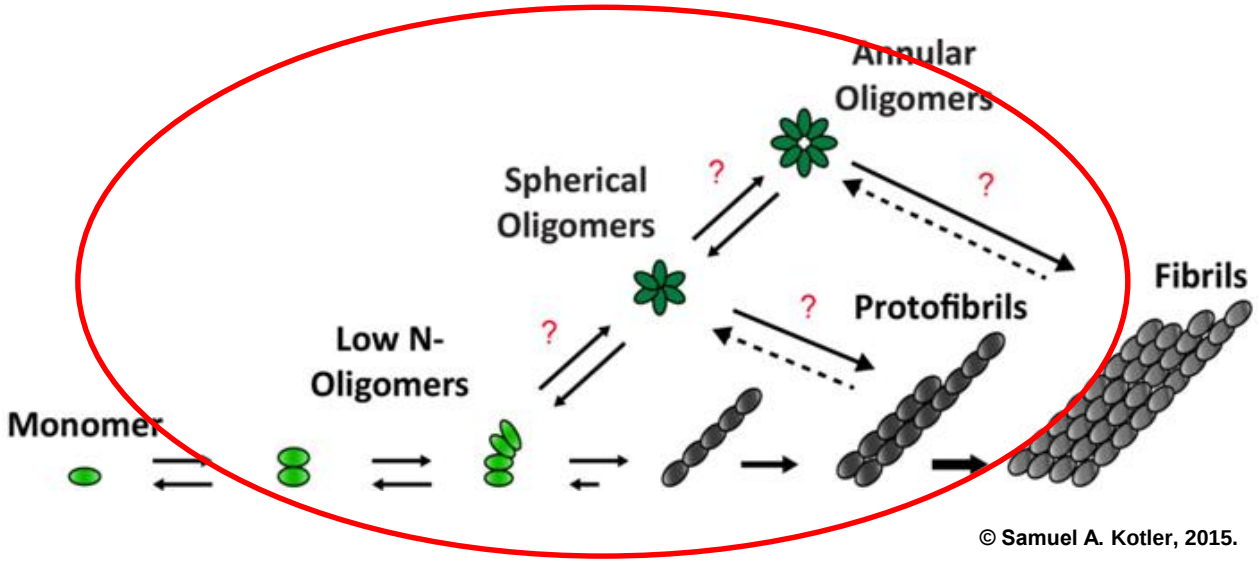
The Amyloid Hypothesis



Modified from Xia *et al.*, 2023 *Frontiers in Genetics*

The Amyloid-β processing



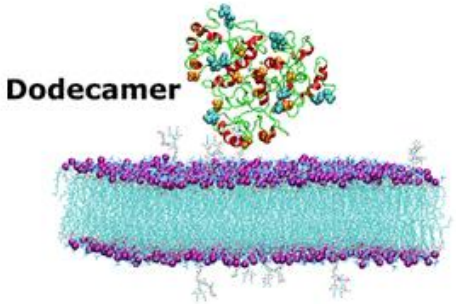


Aβ Oligomers: the main culprit in AD pathogenesis

THE JOURNAL OF PHYSICAL CHEMISTRY B
pubs.acs.org/JPCB
Article

Amyloid β Dodecamer Disrupts the Neuronal Membrane More Strongly than the Mature Fibril: Understanding the Role of Oligomers in Neurotoxicity

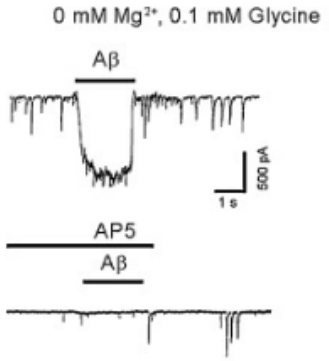
Hoang Linh Nguyen, Huynh Quang Linh, Pawel Krupa, Giovanni La Penna, and Mai Suan Li*



Cell Calcium 47 (2010) 264–272
Contents lists available at ScienceDirect
Cell Calcium
journal homepage: www.elsevier.com/locate/ceca

Amyloid β oligomers induce Ca^{2+} dysregulation and neuronal death through activation of ionotropic glutamate receptors

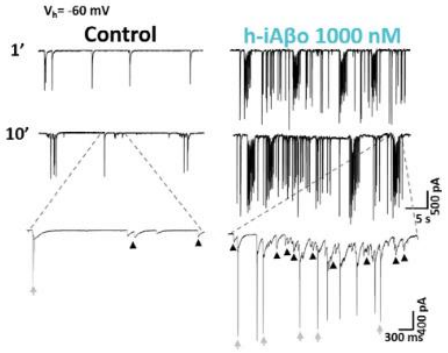
Elena Alberdi[a], Mª Victoria Sánchez-Gómez[a], Fabio Cavaliere[a], Alberto Pérez-Samartín[a], José Luis Zugaza[b], Ramón Trullas[c], María Domercq[a], Carlos Matute[a,*]



ORIGINAL PAPER
Aging Cell
WILEY

Synaptic dysregulation and hyperexcitability induced by intracellular amyloid beta oligomers

Eduardo J. Fernandez-Perez[1] | Braulio Muñoz[1] | Denisse A. Bascuñan[1] | Christian Peters[1] | Nicolas O. Riffo-Lepe[1] | Maria P. Espinoza[1] | Peter J. Morgan[2] | Caroline Filippi[2] | Romain Bourboulou[2] | Urmi Sengupta[3,4] | Rakez Kayed[3,4] | Jérôme Epsztein[2] | Luis G. Aguayo[1]



Aβ oligomers alter Na^+ and K^+ currents and increase neuronal excitability

frontiers in Chemistry

ORIGINAL RESEARCH
published: 09 July 2019
doi: 10.3389/fchem.2019.00479

Synthesis and Pharmacological Evaluation of a Novel Peptide Based on *Anemonia sulcata* BDS-I Toxin as a New $K_V3.4$ Inhibitor Exerting a Neuroprotective Effect Against Amyloid-β Peptide

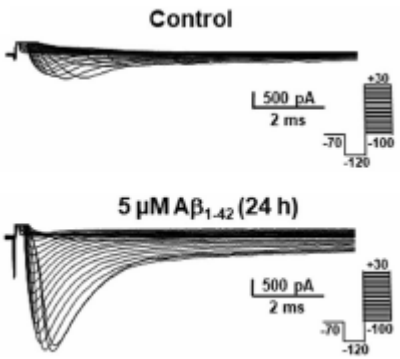
SCIENTIFIC REPORTS
nature research

Amyloid β-Induced Upregulation of $Na_v1.6$ Underlies Neuronal Hyperactivity in Tg2576 Alzheimer's Disease Mouse Model

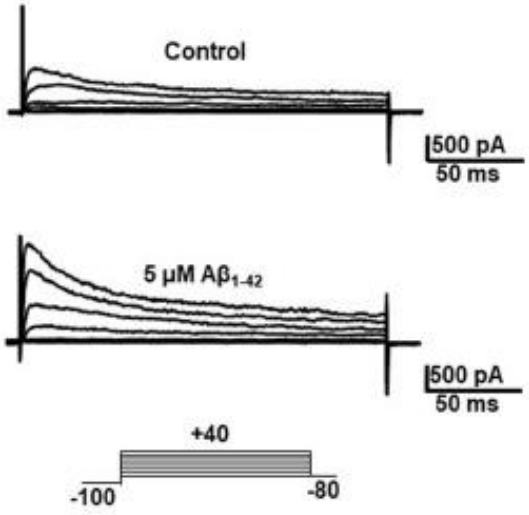
Roselia Ciccone[1], Cristina Franco[1,2], Ilaria Piccialli[1], Francesca Boscia[1], Antonella Casamassa[1], Valeria de Rosa[1], Pasquale Cepparulo[1], Mauro Cataldi[1], Lucio Annunziato[3] & Anna Pannaccione[1]

NEURONAL CELLS

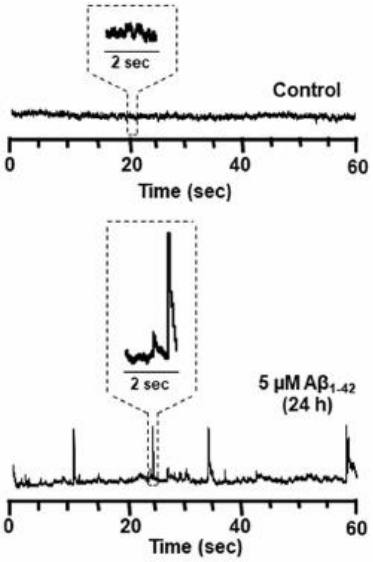
Na^+ currents



K^+ currents



Neuronal spikes



Aβ oligomers induce astrocyte activation and neuroinflammation

Contents lists available at ScienceDirect

Neurobiology of Aging

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

The expression and activity of $K_V3.4$ channel subunits are precociously upregulated in astrocytes exposed to Aβ oligomers and in astrocytes of Alzheimer's disease Tg2576 mice

Francesca Boscia [a,1], Anna Pannaccione [a,1], Roselia Ciccone [a,1], Antonella Casamassa [a], Cristina Franco [a], Ilaria Piccialli [a], Valeria de Rosa [a], Antonio Vinciguerra [a], Gianfranco Di Renzo [a], Lucio Annunziato [a,b,*]

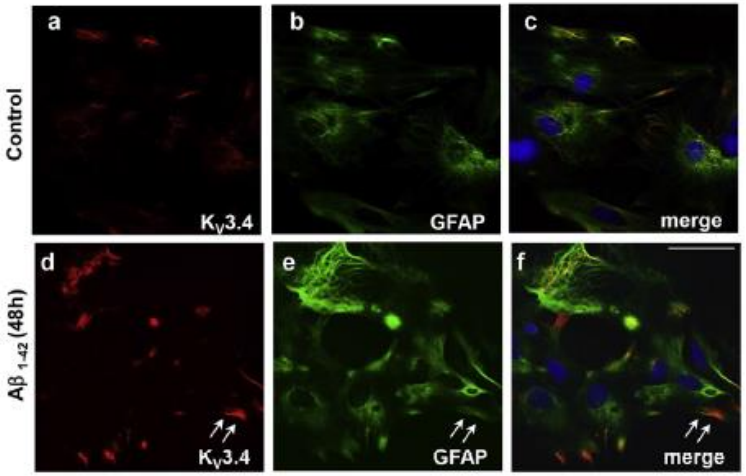
toxins

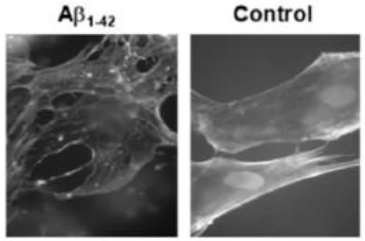
MDPI

Article

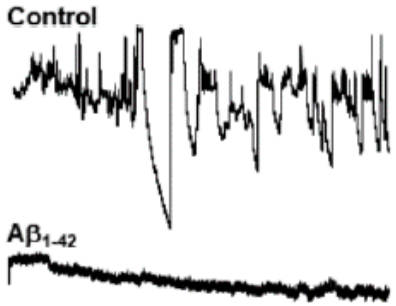
The *Anemonia sulcata* Toxin BDS-I Protects Astrocytes Exposed to $A\beta_{1–42}$ Oligomers by Restoring $[Ca^{2+}]_i$ Transients and ER Ca^{2+} Signaling

Ilaria Piccialli [1,†], Valentina Tedeschi [1,†], Francesca Boscia [1], Roselia Ciccone [1], Antonella Casamassa [1], Valeria de Rosa [1], Paolo Grieco [2], Agnese Secondo [1,*] and Anna Pannaccione [1,*]

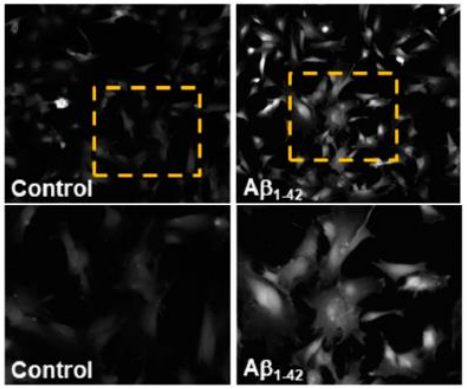




MEMBRANE EXCITABILITY



INTRACELLULAR ROS



The β-sheet conformation is critical for Aβ oligomer toxicity

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Review

β-Sheet interfering molecules acting against β-amyloid aggregation and fibrillogenesis

Antonio Francioso [a,*], Pasqualina Punzi [b], Alberto Boffi [a], Clori
Maria D'Erme [a], Luciana Mosca [a]

RSC Advances

ROYAL SOCIETY OF CHEMISTRY

PAPER

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Cite this: RSC Adv., 2021, 11, 23557

Destabilization potential of beta sheet breaker peptides on Abeta fibril structure: an insight from molecular dynamics simulation study†

Vinod Jani, Uddhavesh Sonavane and Rajendra Joshi *

Biochem. J. (2009) 421, 415–423 (Printed in Great Britain) doi:10.1042/BJ20090379

Antiparallel β-sheet: a signature structure of the oligomeric amyloid β-peptide

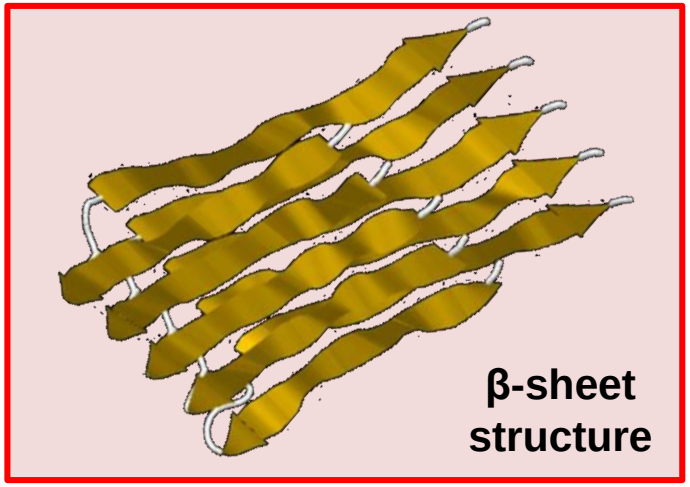
Emilie CERF*[1], Rabia SARROUKH*[1], Shiori TAMAMIZU-KATO†, Leonid BREYDO‡, Sylvie DERCLAYE§, Yves F. DUFRÊNE§, Vasanthy NARAYANASWAMI†||, Erik GOORMAGHTIGH*, Jean-Marie RUYSSCHAERT* and Vincent RAUSSENS*[2]

ACS Chemical Neuroscience

Cite This: ACS Chem. Neuro

Toxic Amyloid Tape: A Novel Mixed Antiparallel/Parallel β-Sheet Structure Formed by Amyloid β-Protein on GM1 Clusters

Yuki Okada,[†] Kaori Okubo,[†] Keisuke Ikeda,[‡] Yoshiaki Yano,[†] Masaru Hoshino,[†] Yoshio Hayashi,[§,∥] Yoshiaki Kiso,[§,⊥] Hikari Itoh-Watanabe,[#] Akira Naito,[#] and Katsumi Matsuzaki*[,†]



β-sheet structure

ISOAC1: a new Aβ aggregation inhibitor

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Development of multifunctional, heterodimeric isoindoline-1,3-dione derivatives as cholinesterase and β-amyloid aggregation inhibitors with neuroprotective properties

Natalia Guzior [a], Marek Bajda [a], Mirosław Skrok [a], Katarzyna Kurpiewska [b], Krzysztof Lewiński [b], Boris Brus [c], Anja Pišlar [d], Janko Kos [d, e], Stanislav Gobec [c], Barbara Malawska [a, *]

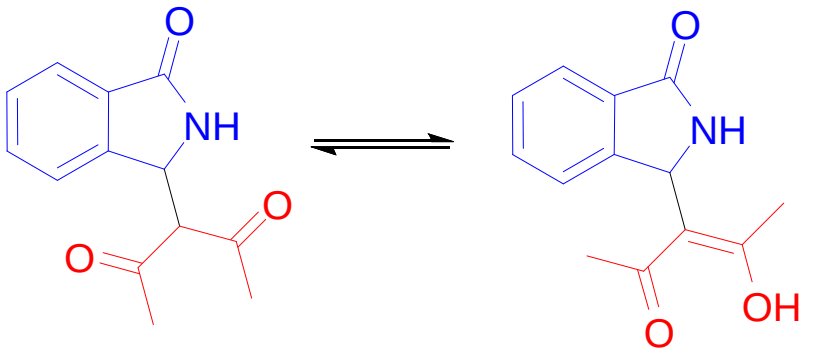
Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis of new *N*-benzylpiperidine derivatives as cholinesterase inhibitors with β-amyloid anti-aggregation properties and beneficial effects on memory in vivo

Anna Więckowska [a], Krzysztof Więckowski [b], Marek Bajda [a], Boris Brus [c], Kinga Sałat [d], Paulina Czerwińska [a], Stanislav Gobec [c], Barbara Filipek [d], Barbara Malawska [a,*]



ISOINDOLINONE

β-DIKETON

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

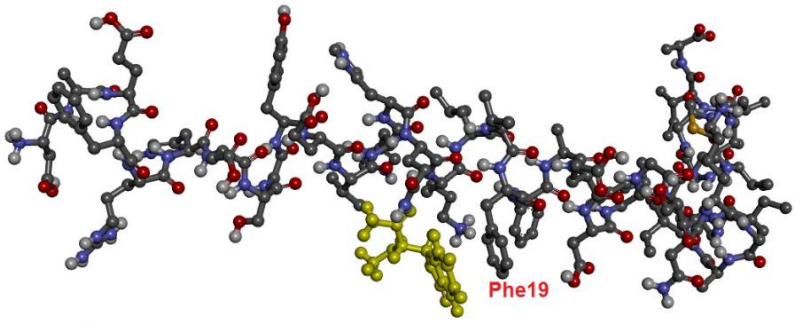
journal homepage: www.elsevier.com/locate/biopha

The 3-(3-oxoisoindolin-1-yl)pentane-2,4-dione (ISOAC1) as a new molecule able to inhibit Amyloid β aggregation and neurotoxicity

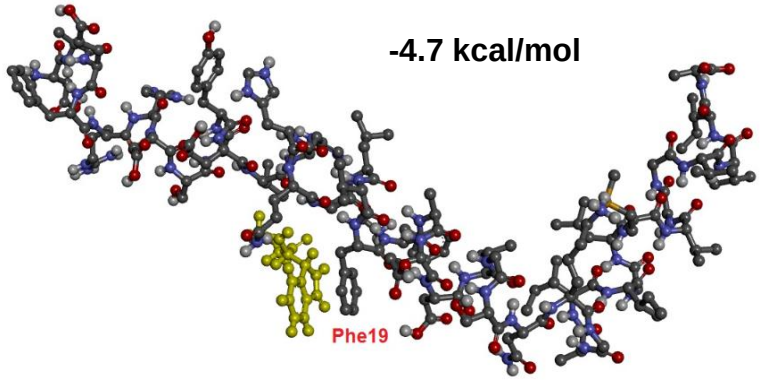
Ilaria Piccialli [a], Francesca Greco [b], Giovanni Roviello [c], Maria Josè Sisalli [a], Valentina Tedeschi [a], Antonia di Mola [d], Nicola Borbone [b], Giorgia Oliviero [e], Vincenzo De Feo [f], Agnese Secondo [a], Antonio Massa [d, *], Anna Pannaccione [a, *]

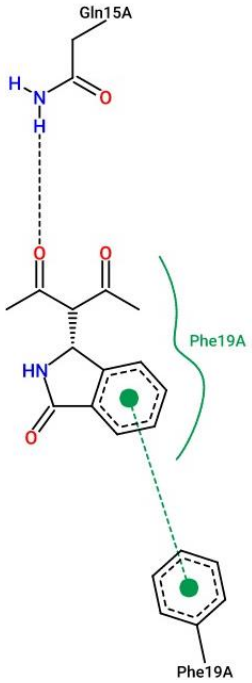
ISOAC1 Binds to Both Monomeric and Protofibrillar Aβ

$A\beta_{1-42}$ monomer (PDB ID: 1IYT)

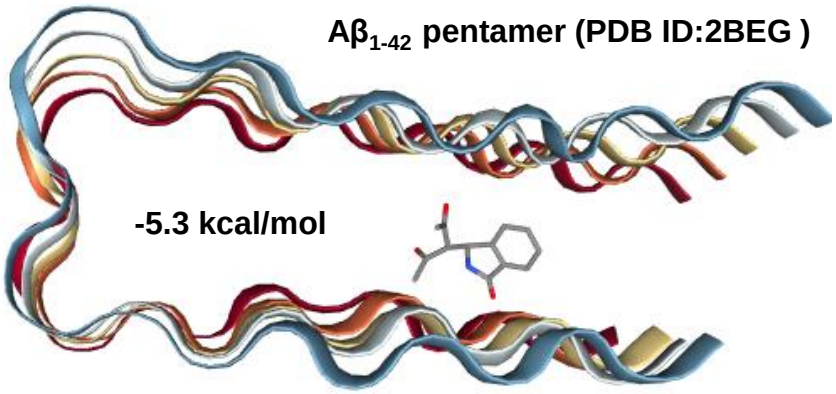


-4.7 kcal/mol

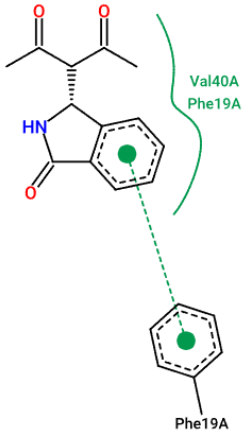


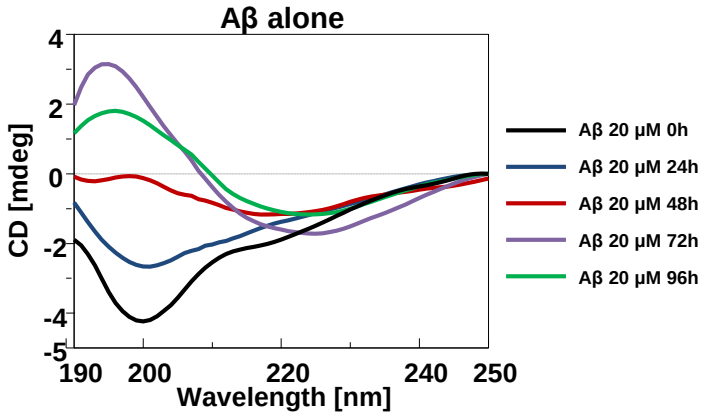


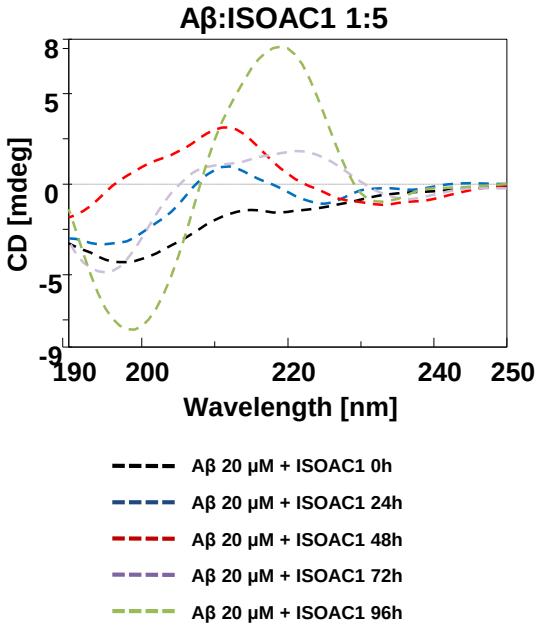
$A\beta_{1-42}$ pentamer (PDB ID:2BEG)



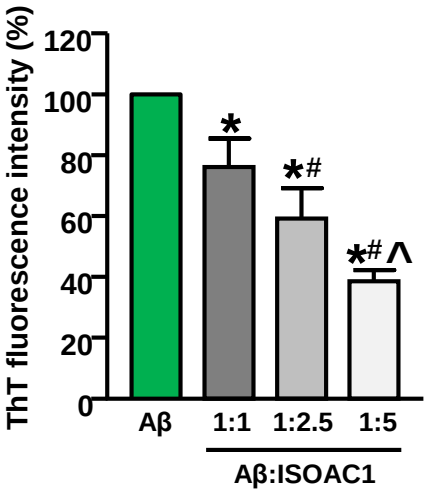
-5.3 kcal/mol

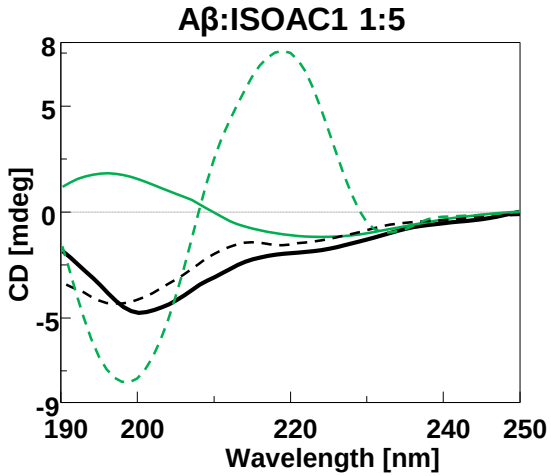


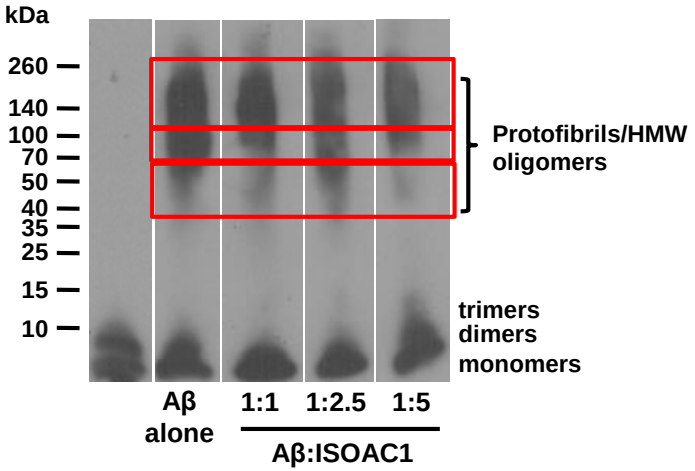


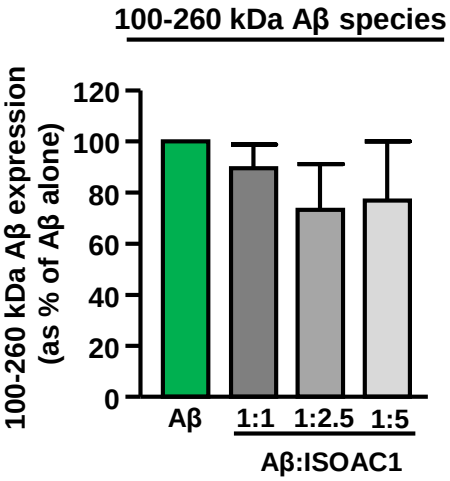


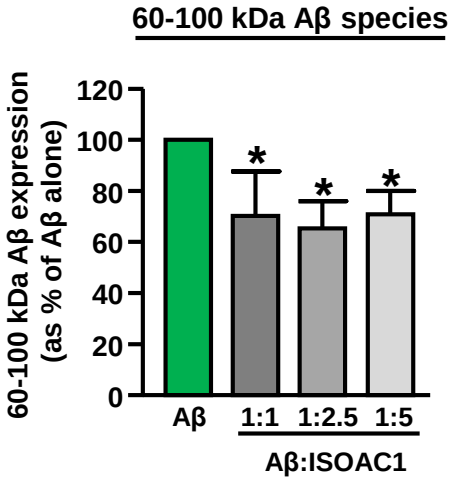
ISOAC1 Remodels the Aβ Aggregation Process

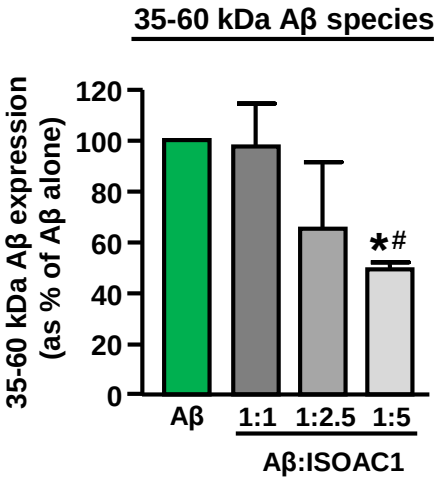




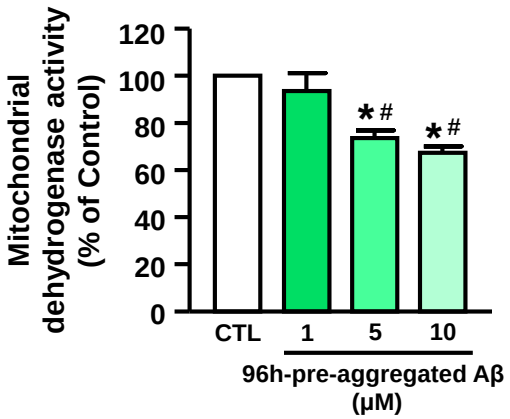


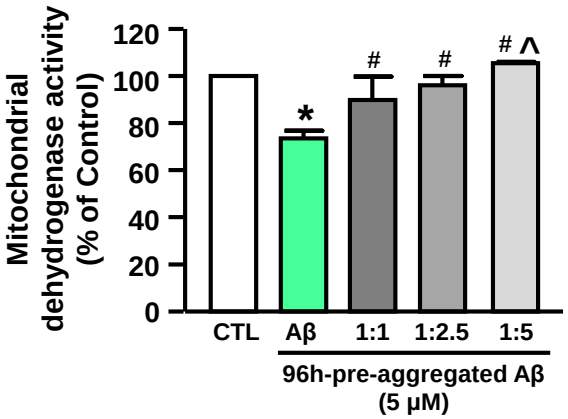


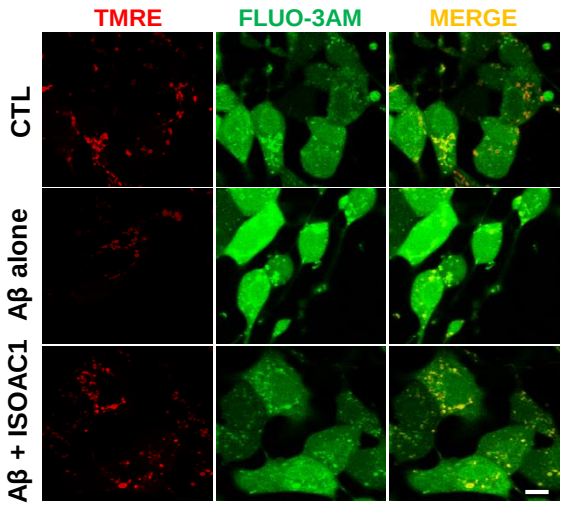


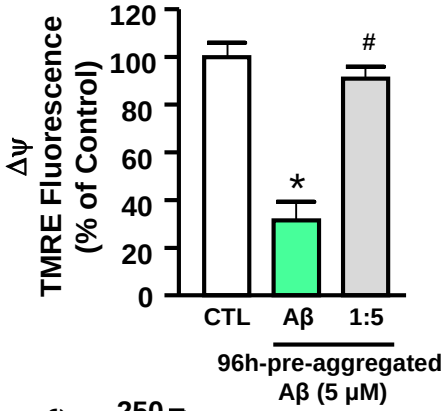


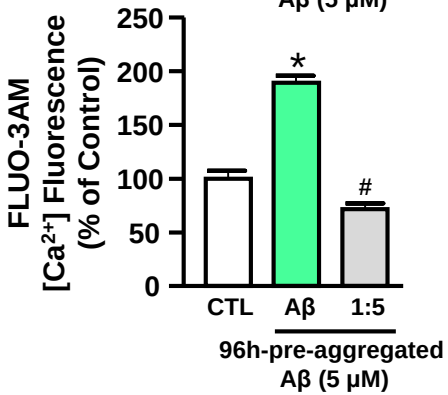
ISOAC1 Reduces the Toxicity of the Aβ Aggregates

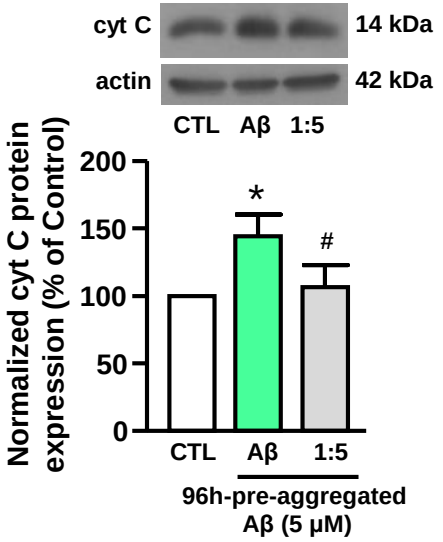




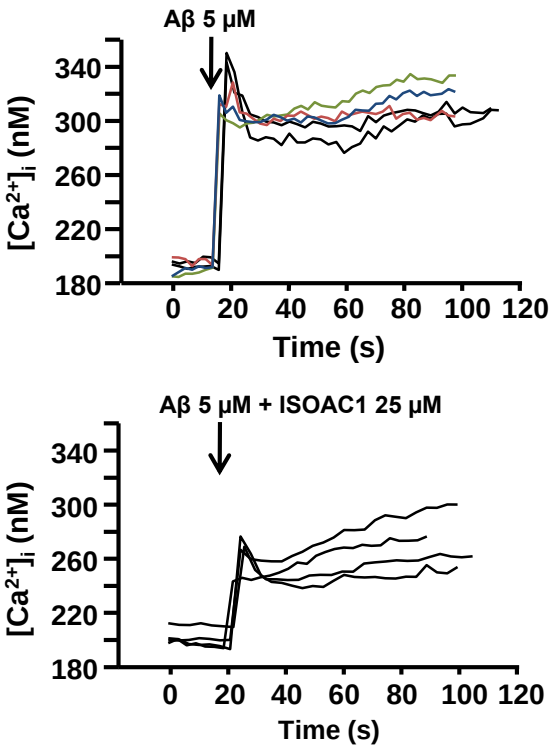


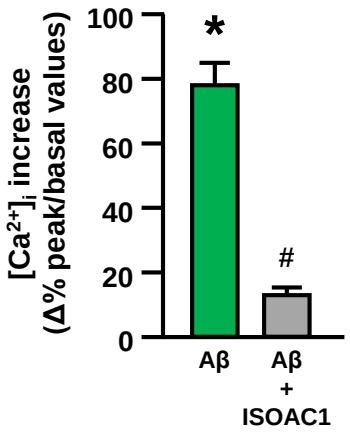


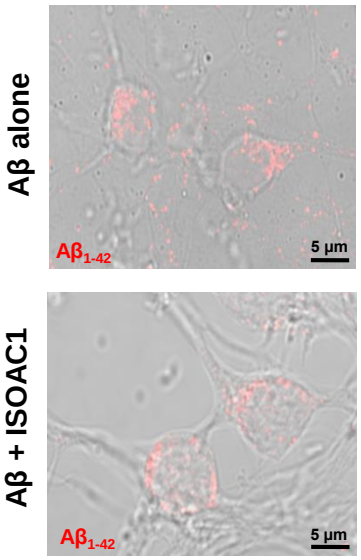


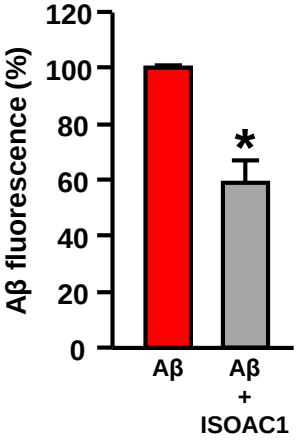


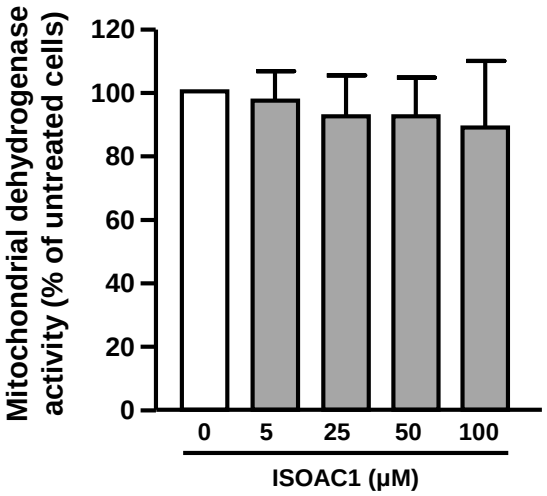
ISOAC1 Protects Primary Neurons from Aβ Toxicity

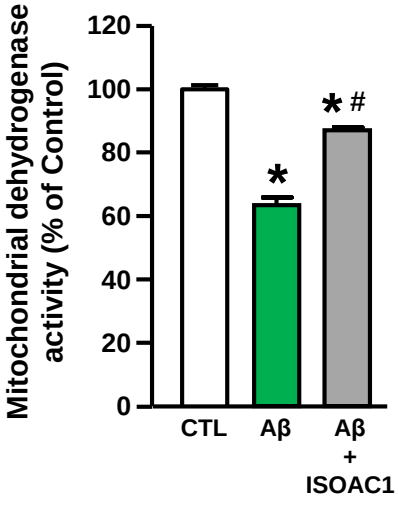


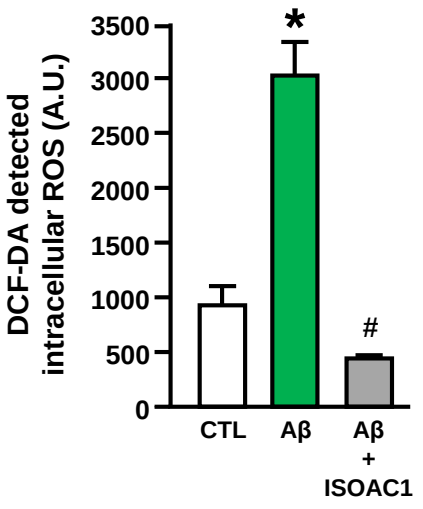












Conclusions

- **ISOAC1 is able to inhibit the aggregation of $A\beta_{1-42}$ by blocking the conversion from its native conformation to β-sheet secondary structures**
- **$A\beta_{1-42}$ samples aggregated in the presence of ISOAC1 were less toxic at the mitochondrial level than those incubated alone**
- **ISOAC1 is able to protect primary cortical neurons from the $A\beta_{1-42}$ injury by counteracting the early steps of $A\beta_{1-42}$ toxicity, such as intracellular Ca^{2+} level elevations, mitochondrial activity reduction, and increase of ROS production, as well as by reducing $A\beta_{1-42}$ accumulation**

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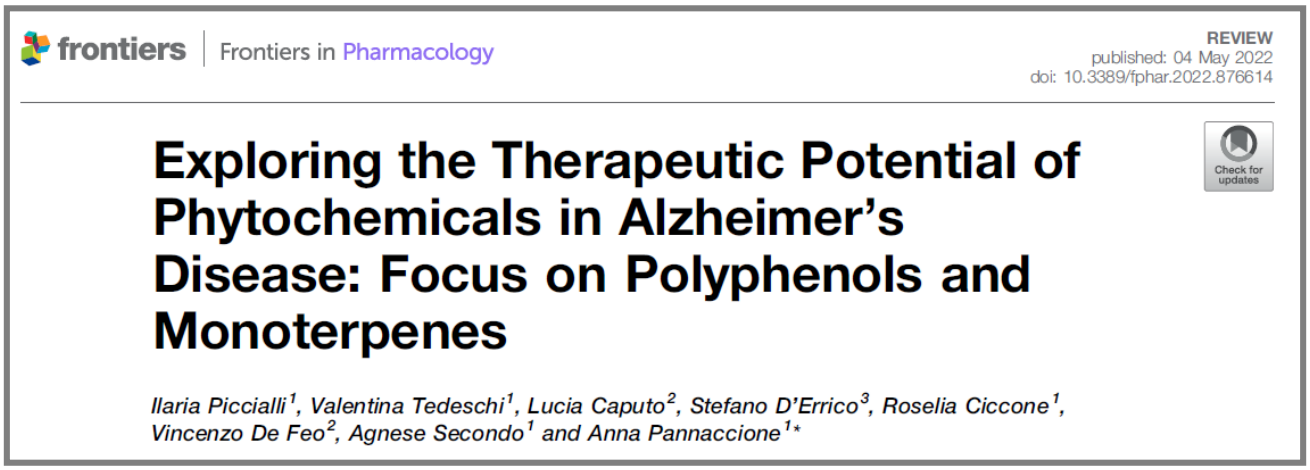
The 3-(3-oxoisoindolin-1-yl)pentane-2,4-dione (ISOAC1) as a new molecule able to inhibit Amyloid β aggregation and neurotoxicity

Ilaria Piccialli [a], Francesca Greco [b], Giovanni Roviello [c], Maria Josè Sisalli [a], Valentina Tedeschi [a], Antonia di Mola [d], Nicola Borbone [b], Giorgia Oliviero [e], Vincenzo De Feo [f], Agnese Secondo [a], Antonio Massa [d,*], Anna Pannaccione [a,*]

Future Perspectives



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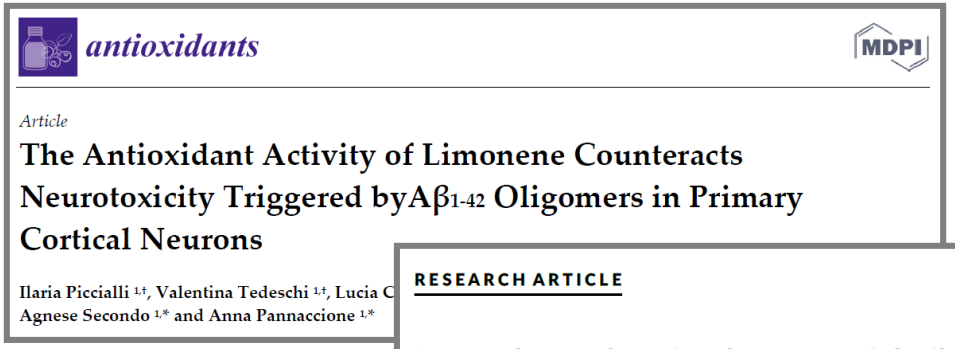
Exploring the Therapeutic Potential of Phytochemicals in Alzheimer's Disease: Focus on Polyphenols and Monoterpenes

*Ilaria Piccialli[1], Valentina Tedeschi[1], Lucia Caputo[2], Stefano D'Errico[3], Roselia Ciccone[1], Vincenzo De Feo[2], Agnese Secondo[1] and Anna Pannaccione[1]**

To investigate the anti-Aβ activity of NATURAL COMPOUNDS



antioxidants

MDPI

Article

The Antioxidant Activity of Limonene Counteracts Neurotoxicity Triggered byAβ1-42 Oligomers in Primary Cortical Neurons

Ilaria Piccialli [1,†], Valentina Tedeschi [1,†], Lucia C
Agnese Secondo [1,*] and Anna Pannaccione [1,*]

RESEARCH ARTICLE

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Lavender and coriander essential oils and their main component linalool exert a protective effect against amyloid-β neurotoxicity

Lucia Caputo[1] | Ilaria Piccialli[2] | Roselia Ciccone[2] | Paolo de Caprariis[1] | Antonio Massa[3] | Vincenzo De Feo[1] | Anna Pannaccione[2]

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Division of Pharmacology, Departement of neuroscience, reproductive and dentistry sciences, Federico II University of Naples

Prof. Anna Pannaccione
Prof. Agnese Secondo
Prof. Maria Josè Sisalli
Dr. Valentina Tedeschi

Division of Pharmacy, Federico II University of Naples

Prof. Nicola Borbone
Dr. Francesca Greco

Department of Molecular Medicine and Medical Biotechnologies, Federico II University of Naples

Prof. Giorgia Oliviero

Department of Chemistry and Biology "A. Zambelli", University of Salerno, Fisciano, SA, Italy

Prof. Antonio Massa
Dr. Antonia di Mola

Division of Pharmacy, University of Salerno, Fisciano, SA, Italy

Prof. Vincenzo De Feo

Thank you for your attention!