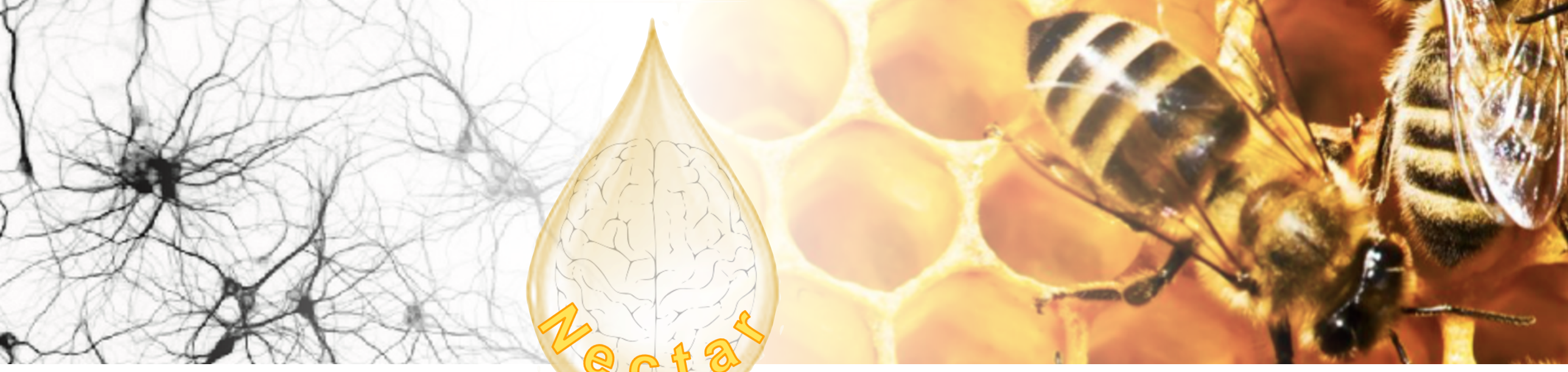


A new perspective for NCT: besides cancer, can it be effectively used for Alzheimer's disease?

N.Protti on behalf of NECTAR Consortium

nicoletta.protti@unipv.it

fisica.unipv.it/NECTAR-EU-FETOpen/index.html

Collegium Maius & Collegium Novodvorscianum
Krakow, 10-15 July 2022

4th Jagiellonian Symposium
on Advances in Particle Physics and Medicine

H2020-FETOPEN-2018-2020
grant agreement #964934

The funding scheme

European Commission H2020 call "Future and Emerging Technologies - FET Open: novel ideas for radically new technologies": FET-Open supports early stage science and technology research exploring new foundations for radically new future technologies by challenging current paradigms and venturing into unknown areas.

huge emphasis on technological transfer, IPs and patents creations leading to positive side effect on EU society, economy, etc... => great attention since the very beginning of the project of research community <-> industry relationships (+ SME involvement in projects)

NECTAR consortium:

UNIVERSITÀ DI PAVIA

UNIVERSITA DEGLI STUDI DI TORINO

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

RAYLAB DETECTING INNOVATION

spin off® POLITECNICO DI MILANO

IRSN INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

Stockholm University

Universitätsklinikum Essen

UNIVERSITÄTS KLINIKUM jena

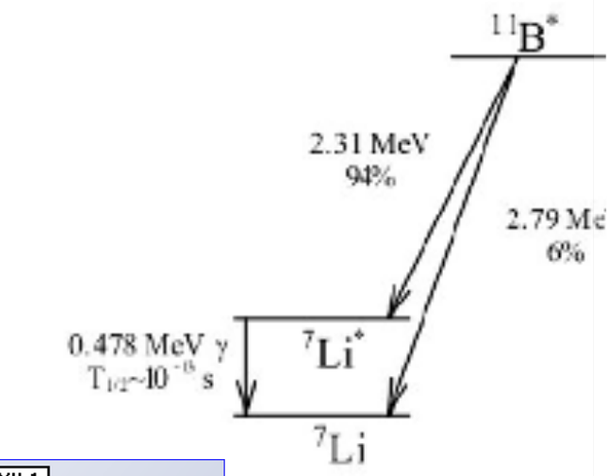
Summary

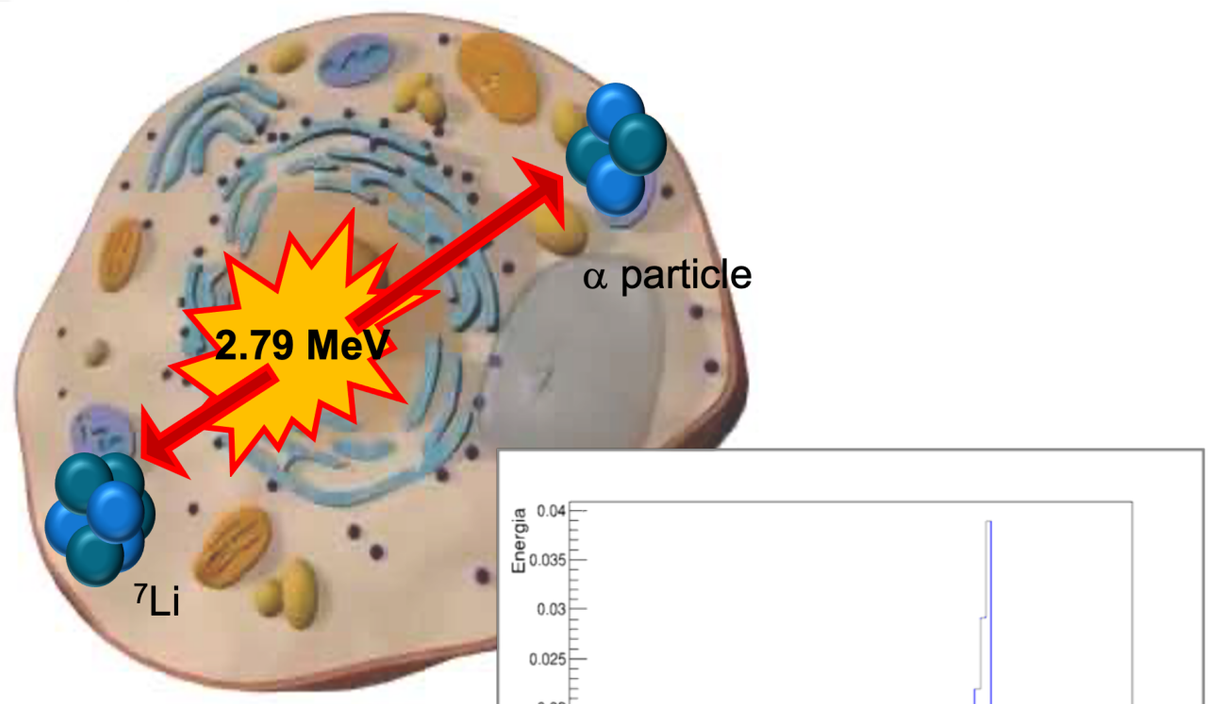
1. Neutron Capture Therapy (NCT) principles
2. AD: impact and pathological hallmarks
3. NCT 4 AD?
4. Preliminary results

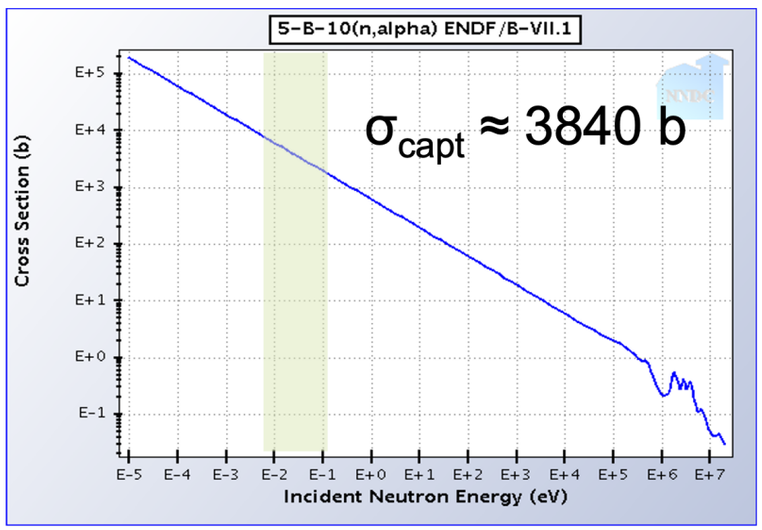
-> more details in prof. Altieri's speech scheduled in the "Particle Therapy" session of Thursday 14/07

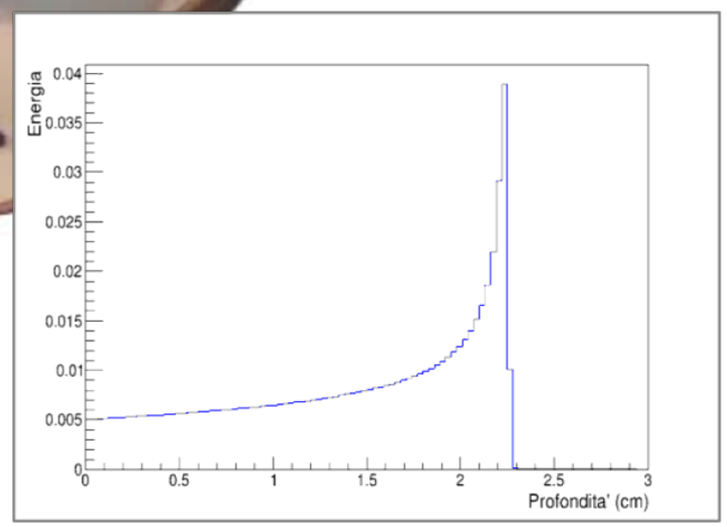
(Boron) Neutron Capture Therapy

Boron Neutron Capture Therapy is a **cell-level selective hadrontherapy** whose biological efficacy relies on the high LET, short range, charged secondaries produced by the neutron capture reaction $^{10}B(n,\alpha)^{7}Li$ induced by low energy neutrons.





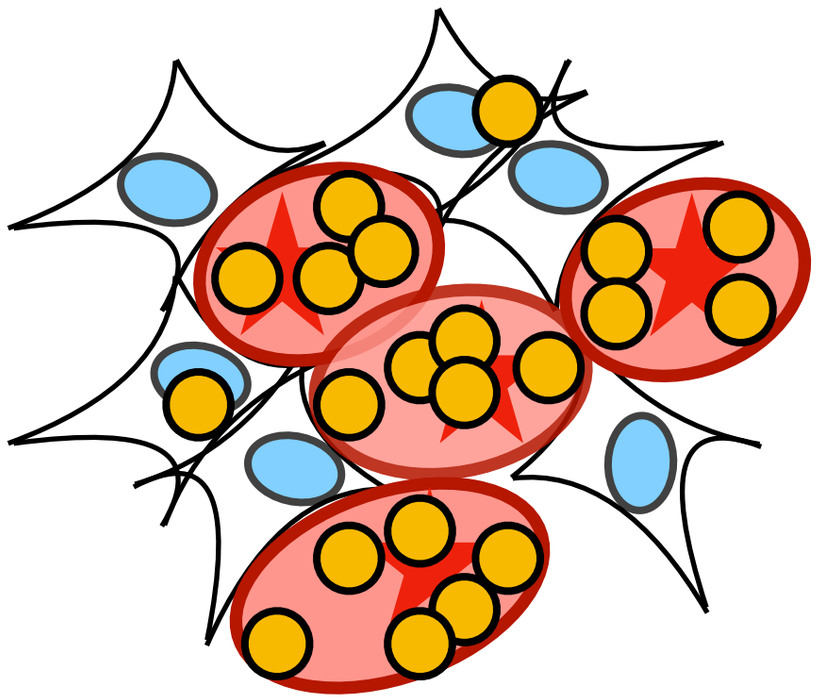


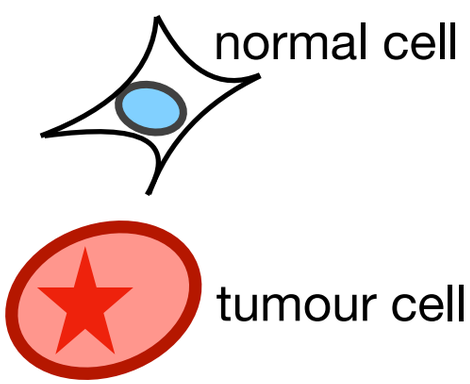


	E (MeV)		R (μm)
α	1.47	1.78	~ 10
^{7}Li	0.84	1.01	~ 5
γ	0.48	—	—

(Boron) Neutron Capture Therapy

BNCT main application as **cancer treatment**. Modest development and spread of Gd-NCT based on Gd-157 neutron capture reaction (biological effect through ICE and Auger electrons)





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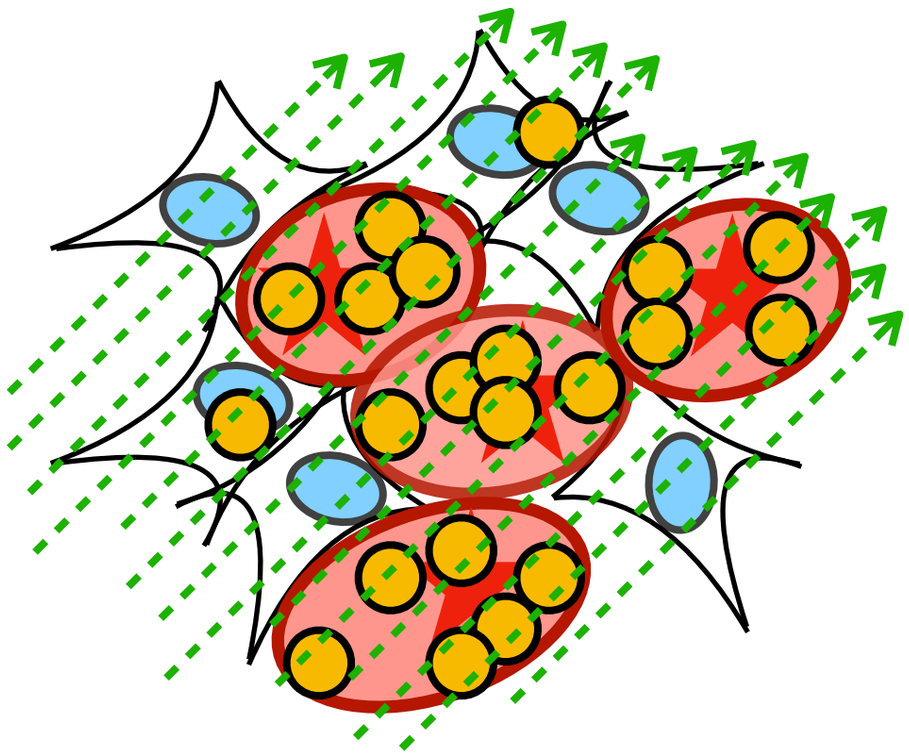

^{10}B-enriched drug

neutron irradiation

normal cell

tumour cell

(Boron) Neutron Capture Therapy

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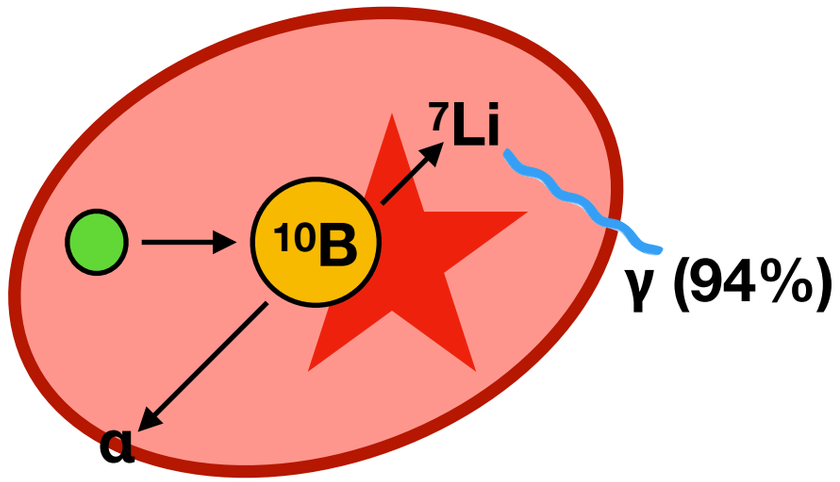

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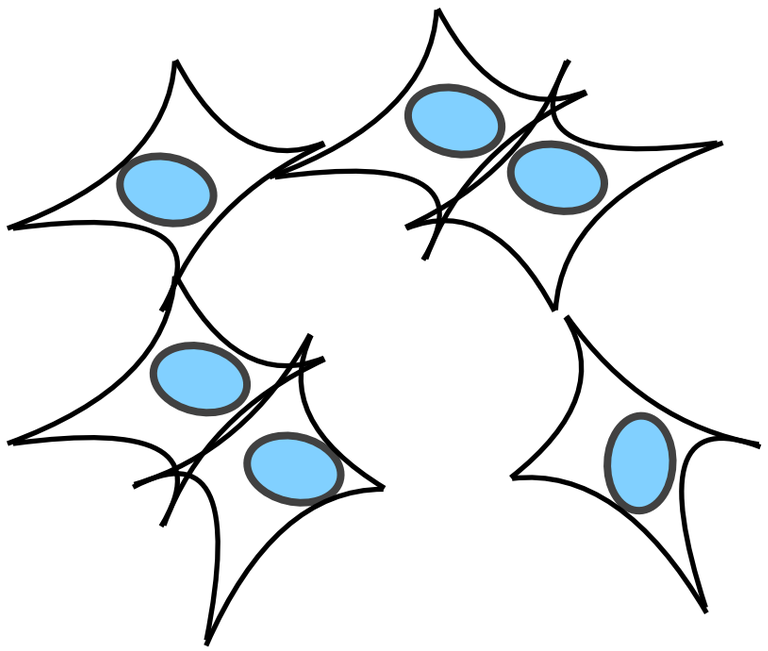
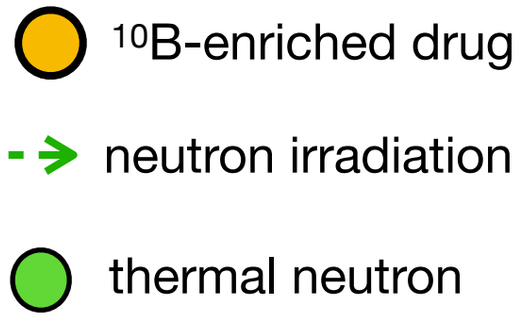
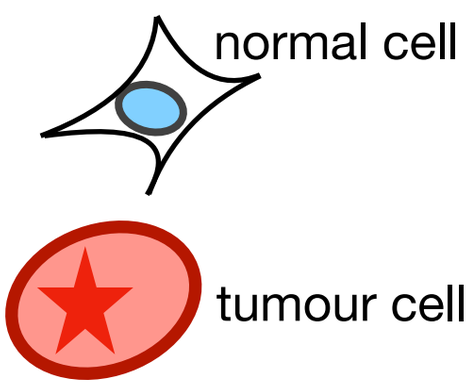






Dementia and AD numbers (* taken from ADI website: https://alzint.org)

- 55 million people worldwide live with dementia nowadays; this number is expected to rise up to 139 million for 2050.

-The total estimated **cost of dementia** in 2015 was US$ 818 billion; in 2018 costs reached a trillion dollars and will rise to US$ 2 trillion by 2030.

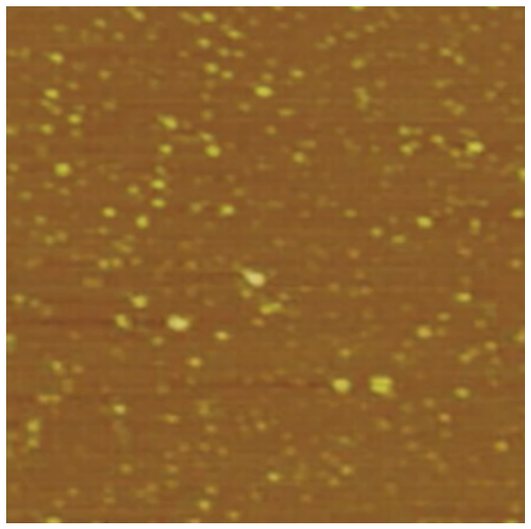
- If global dementia care were a country, it would be the 14th largest economy in the world.

- **Alzheimer's disease (AD) is the most common form of dementia**; 46.8 million people live with AD worldwide, equivalent to **1 new case every 3.2 seconds**.

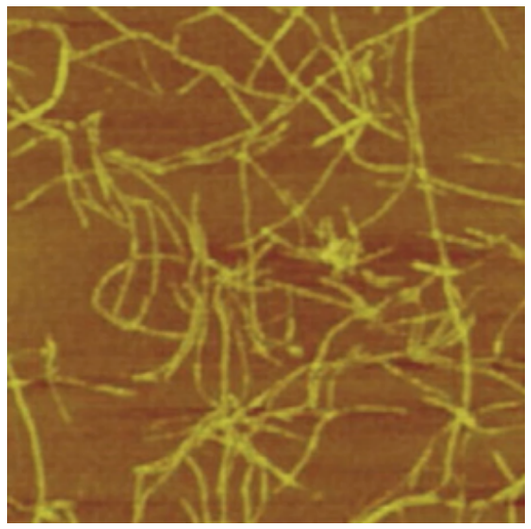
- In June 2021 USA FDA approved Biogen aducanumab as AD drug effective against AD; anyway European Community didn't allow trials with aducanumab due to controversies on its actual efficacy thus **AD treatment is still a symptomatic treatment** aiming only to mitigate the progressive loss of cognitive and functional abilities.

The pathological hallmarks in AD

- Despite a huge scientific debate, Aβ peptide is considered to be the main culprit of the neuropathological process of AD (Aβ Cascade Hypothesis, ACH)
- The toxic peptide is characterised by a progressive aggregation: oligomers (fen nm) -> fibrils (few nm x tens-hundreds μm) -> plaques (tens of μm)

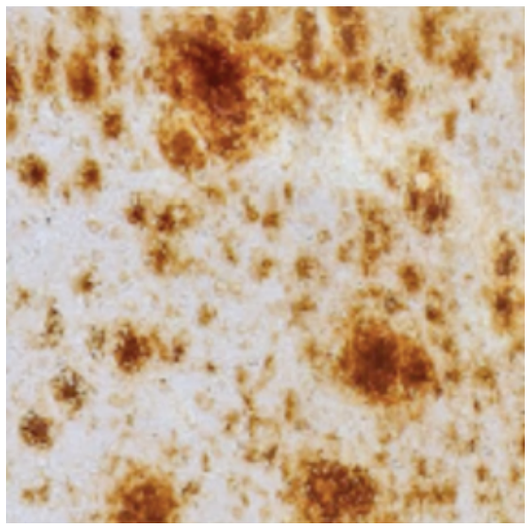


monomers & oligomers



protofibrils & fibrils

(images taken by AFM @ IRFMN)



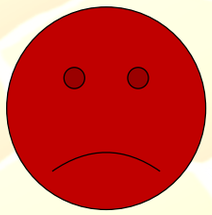
plaques

Why and how NCT could play in the match against AD?!

- ^{10}B and ^{157}Gd charged secondaries from neutron capture reactions (NCR) possess ranges in tissues which match very well the mean dimensions of the Aβ aggregates

=> (1) could the high LET secondary radiations trigger a local depolymerisation of Aβ aggregates?

... but the gammas?!



- Both B10 and Gd157 NCR lead to high energy, highly penetrating photons which induced radiobiological effects in distant targets/regions!

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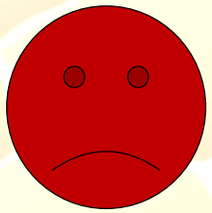

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- Evidences of effectiveness of conventional RadioTherapy (RT) by high energy photons (X-rays) in:

TracheoBronchial Amyloidosis (TBA)

AD transgenic mice

Advanced AD patients (CT scans)

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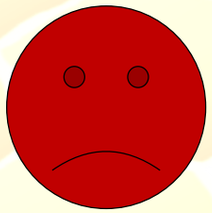

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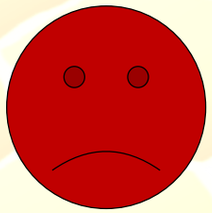

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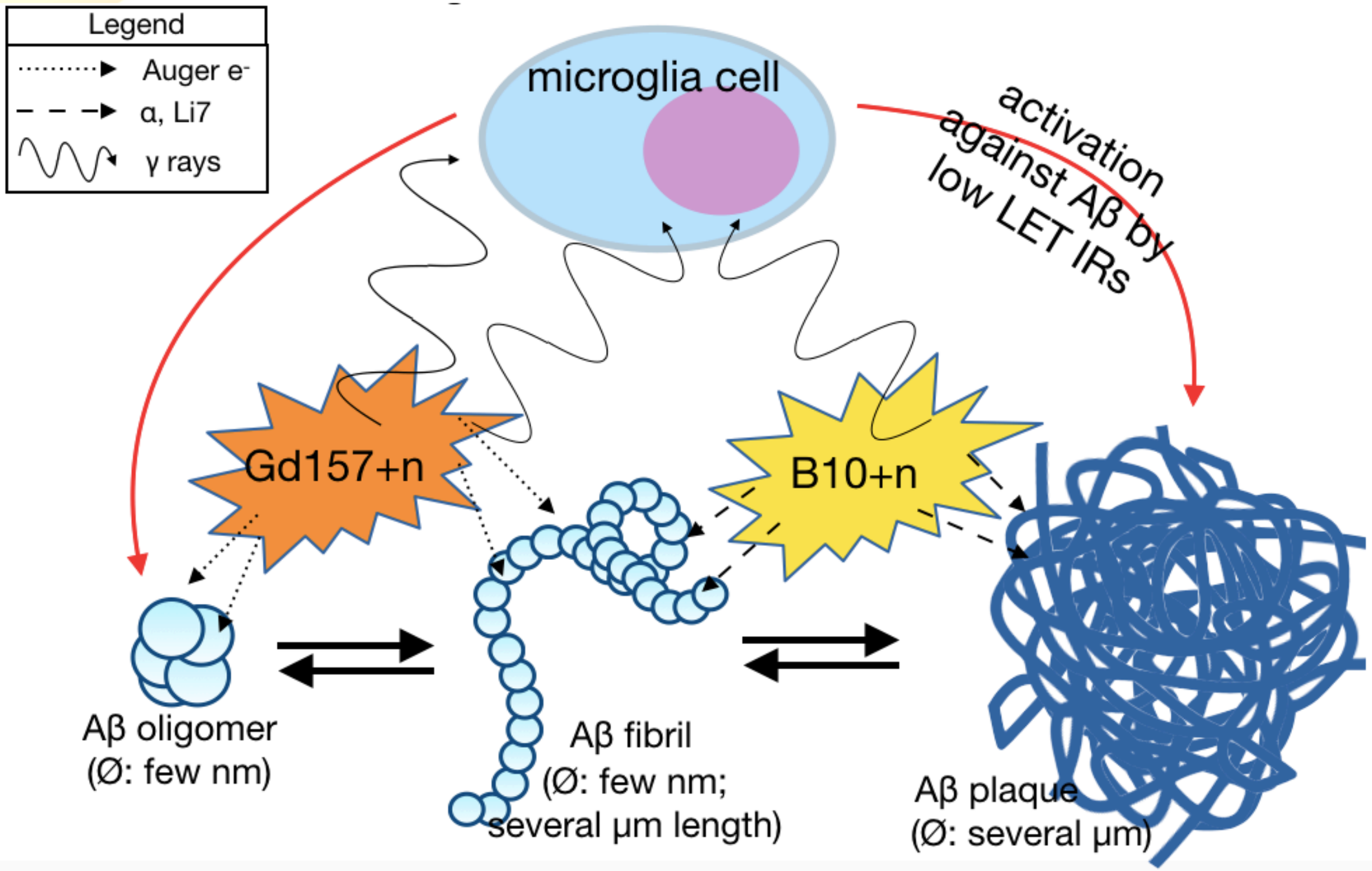
NECTAR scientific background

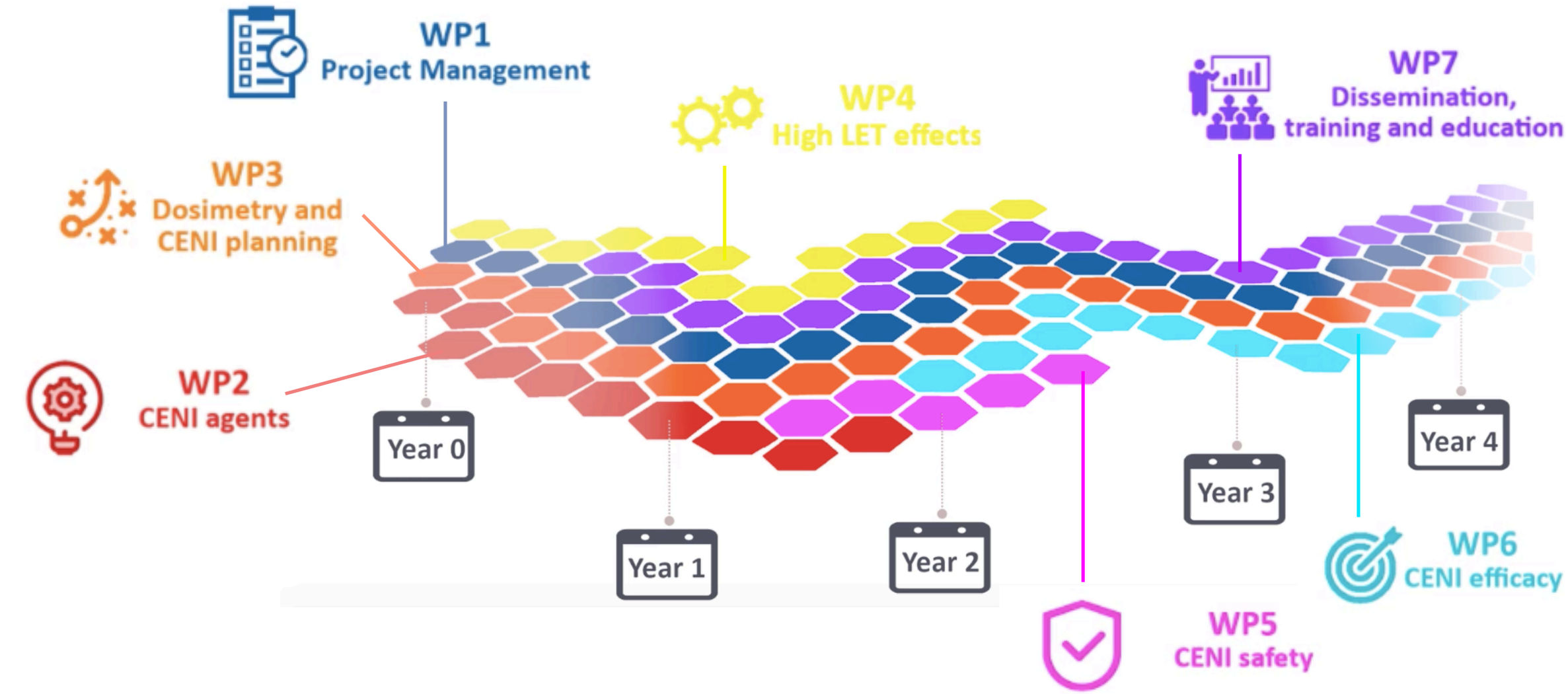
- Microglia brain cells protect neurons from physical and chemical damage and are responsible for clearing foreign substances and cellular debris from the brain =>

(2) could AD neutron mediated irradiation activate microglia cells by low LET gammas to promote depolymerised Aβ aggregates phagocitosis?

An NCR-driven bimodal treatment



Aim of NECTAR = to evaluate the preclinical feasibility, safety and effectiveness of a **Capture Enhanced Neutron Irradiation** (CENI) mediated by B10 and Gd157 to affect the neurotoxic aggregates of the beta-amyloid protein (Aβ) involved in Alzheimer's disease (AD) pathology



So, why do not simply say:

NCT for AD

?

Yes but:

NCT = cancer treatment (scope = eradication) with high doses and high dose rates (typically 1-2 "fractions")

ON THE CONTRARY NECTAR must focus on low doses and low dose rates treatment to fight a chronic (degenerative) disease affecting the whole brain

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This means a COMPLETELY NEW VISION both in term of AD treatments & NCT basic principles application and exploitation

NECTAR positive conclusion = weekly long-term low-dose per fraction irradiation protocol induces useful effects on Aβ aggregates and/or brain immune system (glia cells) to slow down/ stop AD neuronal degeneration

- Bistolfi 2008: glucosamminoglycans (GAGs) invariably involved in Aβ folded structure are known to be radiosensitive =>

Aβ aggregates unfolding and further improved clearance from extracellular space triggered by the radiation effects on GAGs already active at low doses and low dose rates?

NECTAR objectives and roadmap

- Synthesis of biocompatible radiation enhancer probes targeting selectively Aβ protein and aggregates and capable of passing health BBB
- In vitro Aβ depolimerization through high LET radiations
- n/μ-dosimetric field quantities charcaterization
- In vitro and in vivo CENI proof of concept (safety and effectiveness) using native and transgenic AD mouse models
- Preliminary evaluation on TPS of CENI treatment using brain scans of human AD cases

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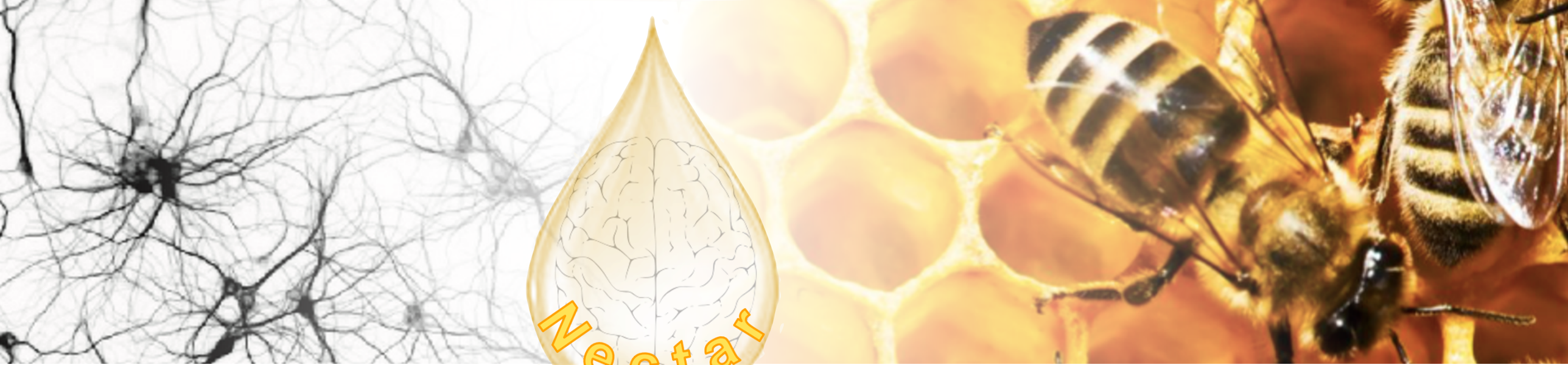
In vitro and in vivo CENI proof of concept (safety and effectiveness) using native and transgenic AD mouse models

Preliminary evaluation on TPS of CENI treatment using brain scans of human AD cases

YEAR 1

- Step 1: B10 or Gd157 enriched molecules able to selectively bind Aβ protein
- Step 2: preliminary tests of neutron irradiation at Pavia University reactor of B10-enriched Aβ aggregates solutions + preliminary characterisation of LENA neutron facilities + Monte Carlo models for dosimetry at μ and n-scales



Thanks for your kind attention

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