# NEUROGENESIS IN THERAPEUTICS

## Developing novel Therapeutics for Neurodegenerative Diseases and Neural Trauma

Novel synthetic compounds with neuroprotective, neurogenic and anti-neuroinflammatory actions. (MicroNeurotrophins).

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NeuroCord

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## Developing novel Therapeutics for Neurodegeneration

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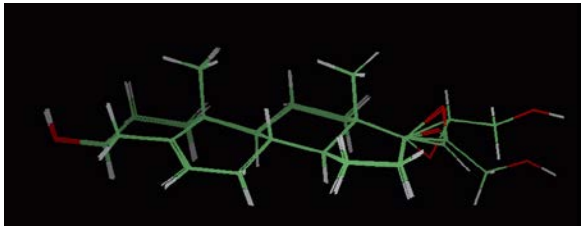
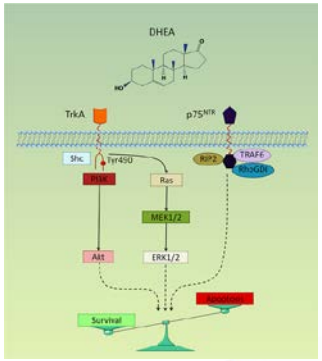
# **DHEA**, a 500.000.000 years old molecule: the **ancestral neurotrophin ??**







Dehydroepiandrosterone and allopregnanolone protect sympathoadrenal medulla cells against apoptosis via antiapoptotic Bcl-2 proteins



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Neurosteroid Dehydroepiandrosterone Interacts with Nerve Growth Factor (NGF) Receptors, Preventing Neuronal Apoptosis

Iakovos Lazaridis[1¤], Ioannis Charalampopoulos[1¤], Vassilia-Ismini Alexaki[2], Nicolaos Avlonitis[3], Iosif Pediaditakis[1], Paschalis Efstathopoulos[1], Theodora Calogeropoulou[3], Elias Castanas[2], Achille Gravanis[1*]

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**Abstract**

The neurosteroid dehydroepiandrosterone (DHEA), produced by neurons and glia, affects multiple processes in the brain, including neuronal survival and neurogenesis during development and in aging. We provide evidence that DHEA interacts with pro-survival TrkA and pro-death $p75^{NTR}$ membrane receptors of neurotrophin nerve growth factor (NGF), acting as a neurotrophic factor: (1) the anti-apoptotic effects of DHEA were reversed by siRNA against TrkA or by a specific TrkA inhibitor; (2) [$^3$H]-DHEA binding assays showed that it bound to membranes isolated from HEK293 cells transfected with the cDNAs of TrkA and $p75^{NTR}$ receptors ($K_D$: 7.4± 1.75 nM and 5.6±0.55 nM, respectively); (3) immobilized DHEA pulled down recombinant and naturally expressed TrkA and $p75^{NTR}$ receptors; (4) DHEA induced TrkA phosphorylation and NGF receptor-mediated signaling; Shc, Akt, and ERK1/2 kinases down-stream to TrkA receptors and TRAF6, RIP2, and RhoGDI interactors of $p75^{NTR}$ receptors; and (5) DHEA rescued from apoptosis TrkA receptor positive sensory neurons of dorsal root ganglia in NGF null embryos and compensated NGF in rescuing from apoptosis NGF receptor positive sympathetic neurons of embryonic superior cervical ganglia. Phylogenetic findings on the evolution of neurotrophins, their receptors, and CYP17, the enzyme responsible for DHEA biosynthesis, combined with our data support the hypothesis that DHEA served as a phylogenetically ancient neurotrophic factor.

**Citation:** Lazaridis I, Charalampopoulos I, Alexaki V-I, Avlonitis N, Pediaditakis I, et al. (2011) Neurosteroid Dehydroepiandrosterone Interacts with Nerve Growth Factor (NGF) Receptors, Preventing Neuronal Apoptosis. PLoS Biol 9(4): e1001051. doi:10.1371/journal.pbio.1001051

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**Competing Interests:** The authors have declared that no competing interests exist.

**Abbreviations:** BDNF, brain-derived neurotrophic factor; CYP17, cytochrome P450 17-hydroxylase/17,20-lyase; DHEA, dehydroepiandrosterone; DHEA-BSA, DHEA–Bovine Serum Albumin; DHEA-BSA-FITC, DHEA-BSA-Fluorescein Isothiocyanate; DHEA-PEG, DHEA–polyethylene glycol amino oxide; DHEAS, dehydroepiandrosterone sulfate; DRG, dorsal root ganglia; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HEK293, human embryonic kidney cell line 293; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NGF, nerve growth factor; $p75^{NTR}$, p75 neurotrophin receptor; PTX, pertussis toxin; RhoGDI, rho GDP dissociation inhibitor; RIP2, receptor-interacting protein 2; SCG, superior cervical ganglia; TRAF6, TNF receptor-associated factor 6; Trk, tropomyosin related kinase

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## Introduction

Dehydroepiandrosterone (DHEA) is a steroid, produced in adrenals, in neurons and in glia [1]. The physiological role of brain DHEA appears to be local, i.e. paracrine, while that produced from adrenals, which represents the almost exclusive source of circulating DHEA, is systemic. The precipitous decline of both brain and circulating DHEA with advancing age has been associated with aging-related neurodegenerative diseases [1,2]. It is experimentally supported that DHEA protects neurons against noxious conditions [3–6]. DHEA exerts its multiple pro-survival effects either directly modulating at micromolar concentrations γ-aminobutiric acid type A ($GABA_A$), N-methyl-D-aspartate (NMDA), or signal receptors, or following its conversion to estrogens and androgens. We have recently shown that nanomolar concentrations of DHEA protect sympathoadrenal cells from apoptosis [7]. PC12 cells do not express functional σ or NMDA receptors and cannot metabolize DHEA to estrogens and androgens [8]. The anti-apoptotic effect of DHEA in PC12 cells is mediated by high affinity ($K_D$ at nanomolar levels) specific membrane binding sites [9]. Activation of DHEA membrane binding sites results in an acute, transient, and sequential phosphorylation of the pro-survival MEK/ERK kinases, which, in turn, activate transcription factors CREB and NFκB, which afford the transcriptional control of anti-apoptotic Bcl-2 proteins. In parallel, activation of DHEA membrane binding sites induces the phosphorylation of PI3K/Akt kinases, leading to phosphorylation/deactivation of the pro-apoptotic Bad protein and protection of PC12 cells from apoptosis [10].

In fact, the anti-apoptotic pathways in sympathoadrenal cells initiated by DHEA at the membrane level strikingly resemble those sensitive to neurotrophin nerve growth factor (NGF). NGF promotes survival and rescues from apoptosis neural crest–derived neurons (including their related sympathoadrenal cells) and neurons involved in nonception. NGF binds ($K_D$: 0.01 nM) to transmembrane tyrosine kinase





Dehydroepiandrosterone: An Ancestral Ligand of Neurotrophin Receptors

Iosif Pediaditakis, Ioannis Iliopoulos, Ioannis Theologidis, Nickoleta Delivanoglou, Andrew N. Margioris, Ioannis Charalampopoulos, and Achille Gravanis

Institute of Molecular Biology and Biotechnology (I.P., A.G.), Foundation of Research and Technology-Hellas; and Departments of Pharmacology (I.P., N.D., I.C., A.G.), Biology (I.I., I.T.), and Clinical Chemistry (A.N.M.), School of Medicine, University of Crete, Heraklion 71110, Greece

Dehydroepiandrosterone (DHEA), the most abundant steroid in humans, affects multiple cellular functions of the endocrine, immune, and nervous systems. However, up to quite recently, no receptor has been described specifically for it, whereas most of its physiological actions have been attributed to its conversion to either androgens or estrogens. DHEA interacts and modulate a variety of membrane and intracellular neurotransmitter and steroid receptors. We have recently reported that DHEA protects neuronal cells against apoptosis, interacting with TrkA, the high-affinity prosurvival receptor of the neurotrophin, nerve growth factor. Intrigued by its pleiotropic effects in the nervous system of a variety of species, we have investigated the ability of DHEA to interact with the other two mammalian neurotrophin receptors, ie, the TrkB and TrkC, as well as their invertebrate counterparts (orthologs) in molluscs Lymnaea and Aplysia and in cephalochordate fish Amphioxus. Amazingly, DHEA binds to all Trk receptors, although with lower affinity by 2 orders of magnitude compared with that of the polypeptidic neurotrophins. DHEA effectively induced the first step of the TrkA and TrkC receptors activation (phosphorylation at tyrosine residues), including the vertebrate neurotrophin nonresponding invertebrate Lymnaea and Aplysia receptors. Based on our data, we hypothesize that early in evolution, DHEA may have acted as a nonspecific neurotrophic factor promoting neuronal survival. The interaction of DHEA with all types of neurotrophin receptors offers new insights into the largely unidentified mechanisms of its actions on multiple tissues and organs known to express neurotrophin receptors. (*Endocrinology* 156: 16–23, 2015)

Polypeptide neurotrophins (NTs) and their high-affinity tyrosine kinase membrane receptors (tropomyosin related kinase [Trks]) are key effectors of neuronal differentiation, growth and survival (1, 2). Most vertebrates express three types of transmembrane Trk receptors, namely the TrkA, TrkB, and TrkC, all sharing a common structural organization of their extra- and intracellular domains (3), although they do exhibit differences in their affinity toward the polypeptide neurotrophic ligands. More specifically, TrkA is primarily activated by nerve growth factor (NGF), TrkB mainly by brain-derived neurotrophic factor (BDNF) and the NT-4/5, whereas the TrkC receptor is preferentially activated by NT-3 (4). Finally, the immature proneurotrophins are selective ligands for the pan-neurotrophin p75 receptor (5). It should be noted here that NT-3 can also bind to TrkA and TrkB receptors (6, 7).

Although Trk receptors are evolutionarily conserved, they are missing in some species including *Caenorhabditis elegans* and *Drosophila melanogaster*, which do not have the genes encoding the Trk receptors and their ligands (8, 9). Based on these observations, it has been speculated that an alternative form of neurotrophic signaling should be present in invertebrates, possibly including several Trk-related receptors like the mollusk *Lymnaea stagnalis* (Ltrk) (5), the marine mollusk *Aplysia californica* (ApTrk)

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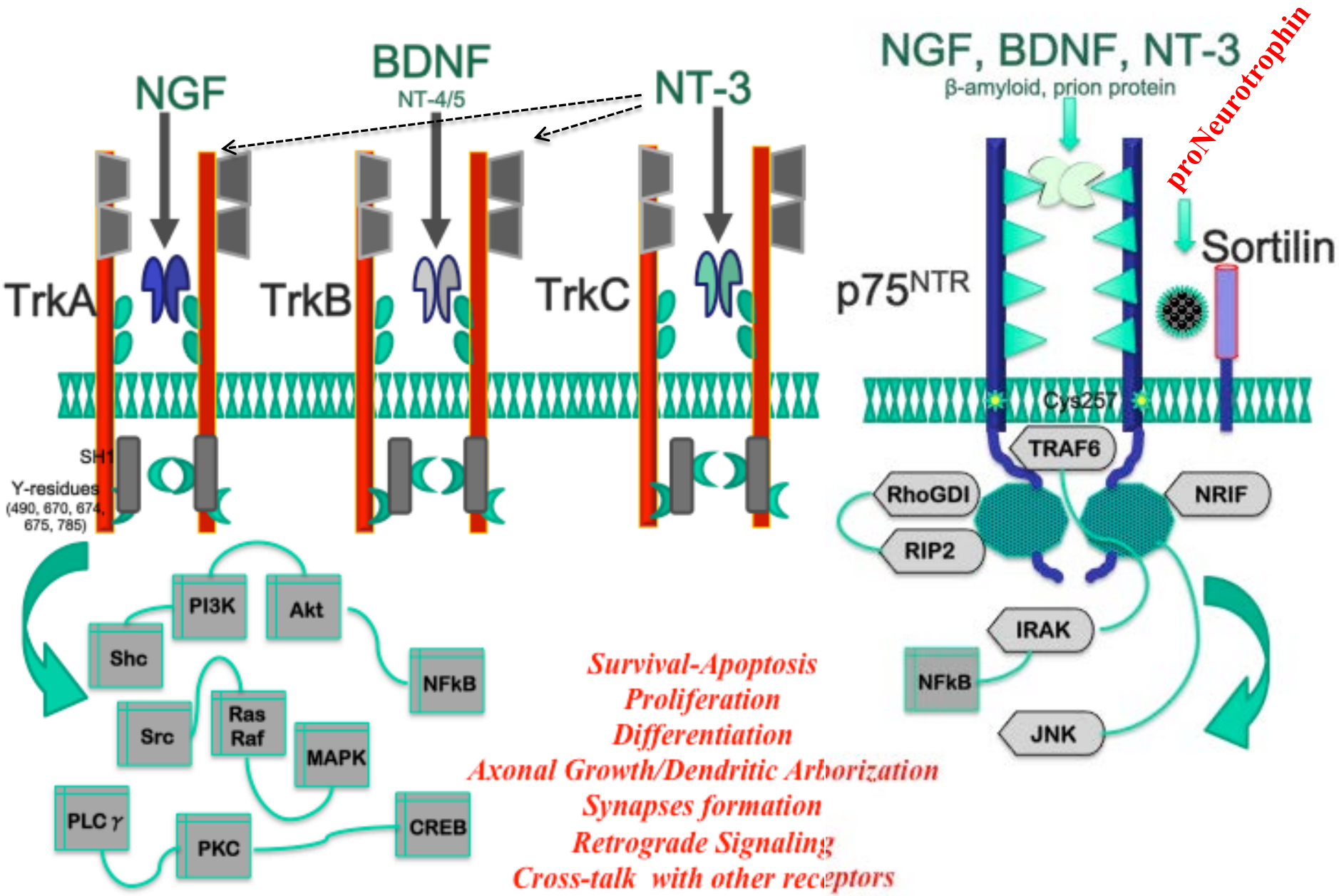
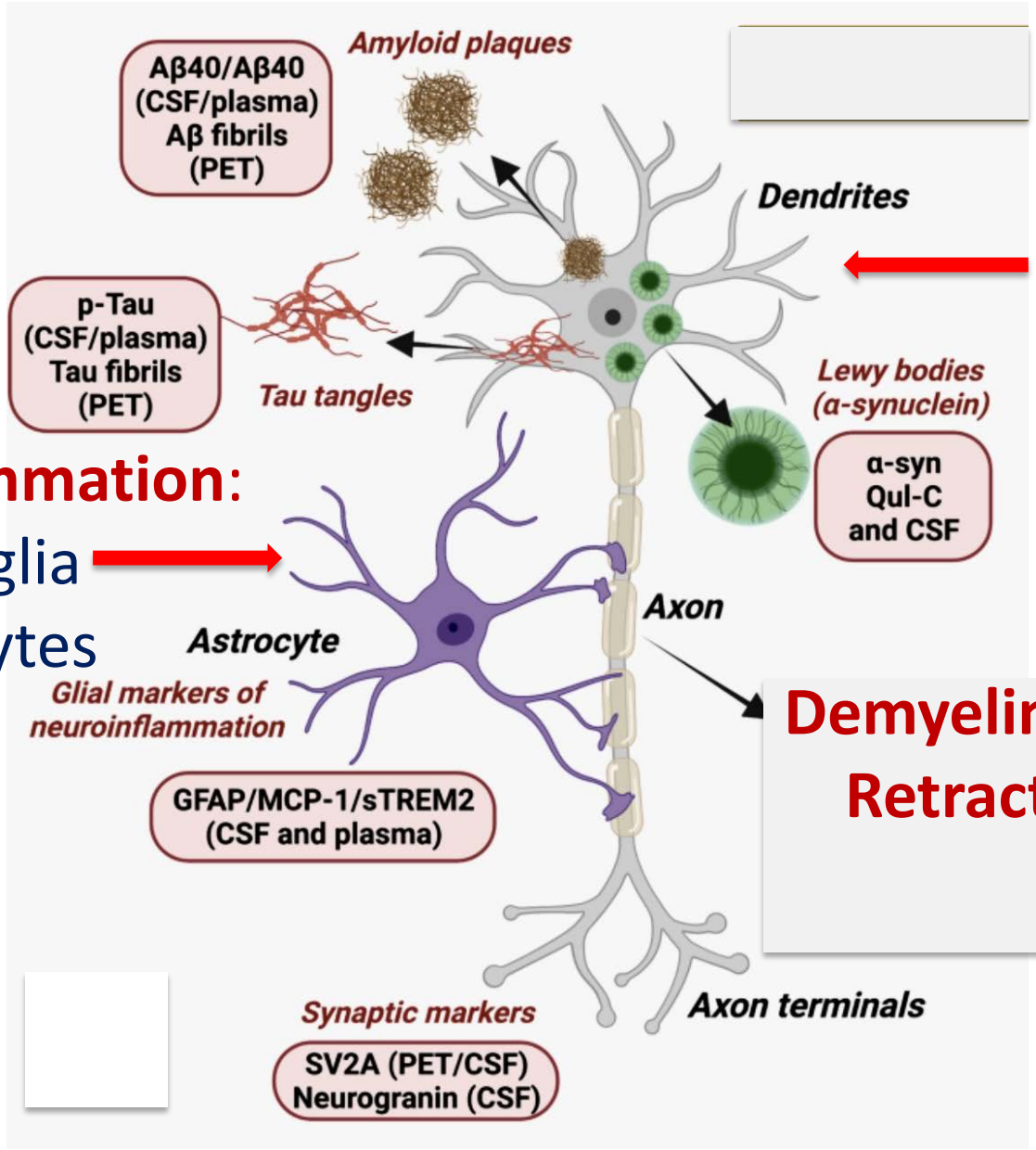
# Neurotrophin receptors & signaling




Gravanis et al., Science Signaling. 2012

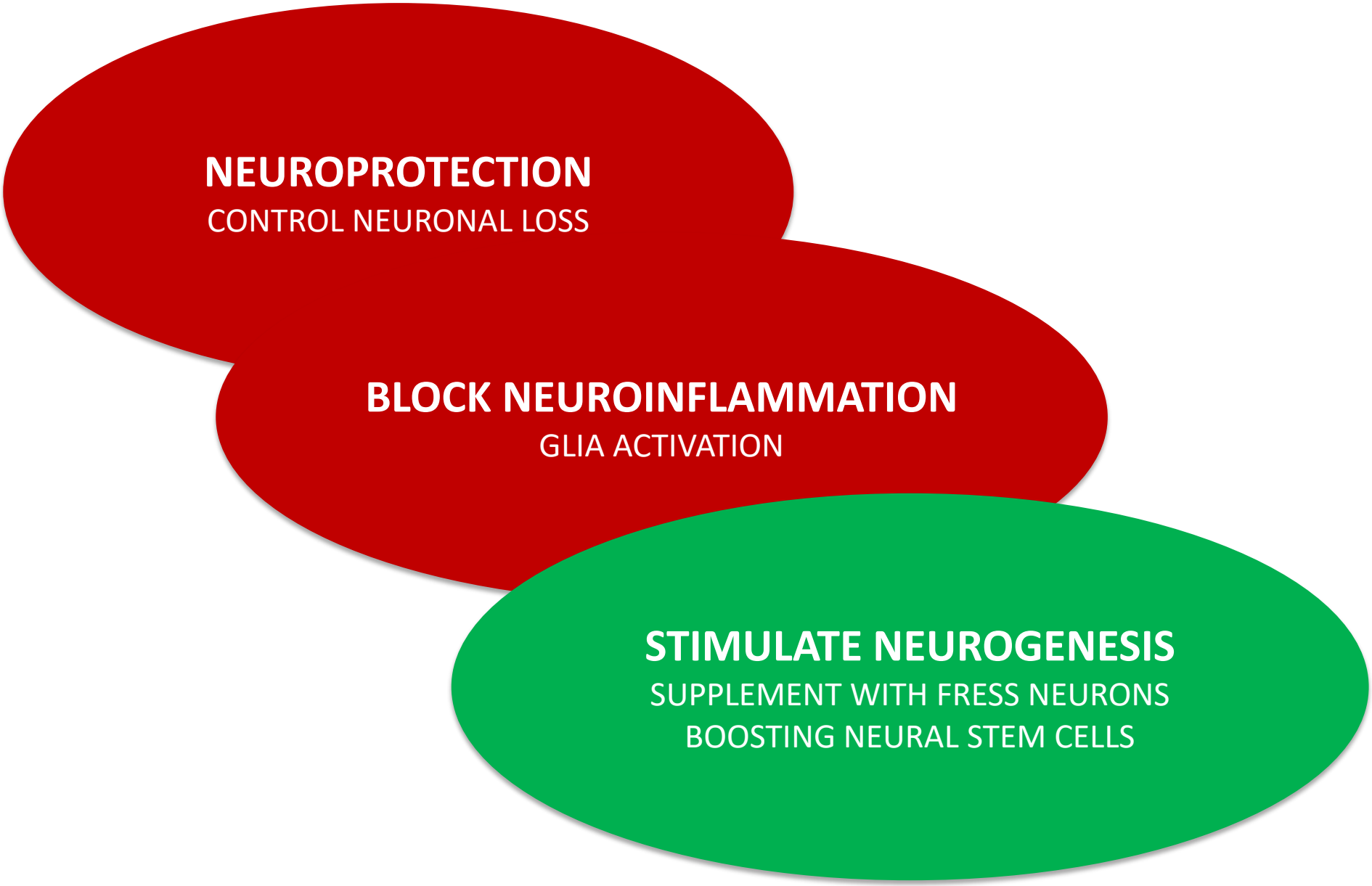
# Mechanisms of Neurodegeneration



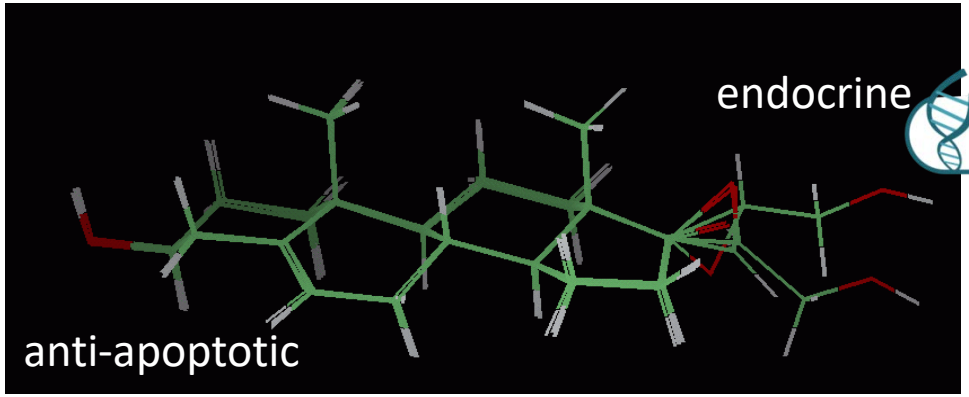

**Cell Death:**
Apoptosis
Necrosis
Autophagy

**Neuroinflammation**:
Microglia
Astrocytes

# Pharmacology focusing on symptoms



# Synthetic 17-spiro-steroid analogs, NGF receptor modulators

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BIOMEDICAL RESEARCH & DEVELOPMENT

Journal of Medicinal Chemistry Article

*J. Med. Chem.* **2009,** *52,* 6569–6587 **6569**
DOI: 10.1021/jm900468p

## Novel Dehydroepiandrosterone Derivatives with Antiapoptotic, Neuroprotective Activity

Theodora Calogeropoulou,*,† Nicolaos Avlonitis,† Vassilios Minas,‡ Xanthippi Alexi,§ Athanasia Pantzou,† Ioannis Charalampopoulos,‡ Maria Zervou,† Varvara Vergou,‡ Efrosini S. Katsanou,§ Iakovos Lazaridis,‡ Michael N. Alexis,§ and Achille Gravanis‡

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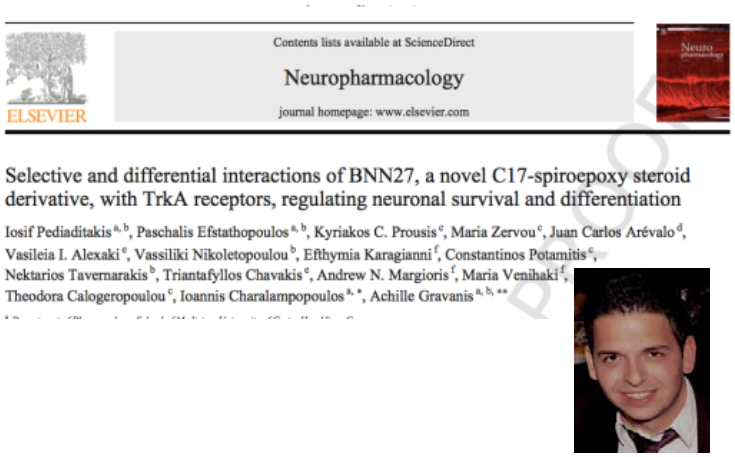
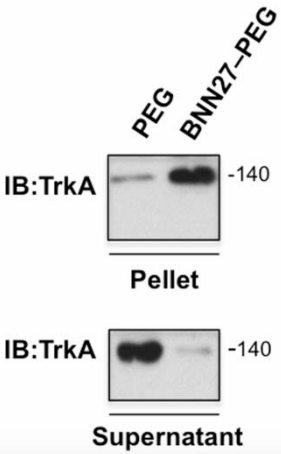
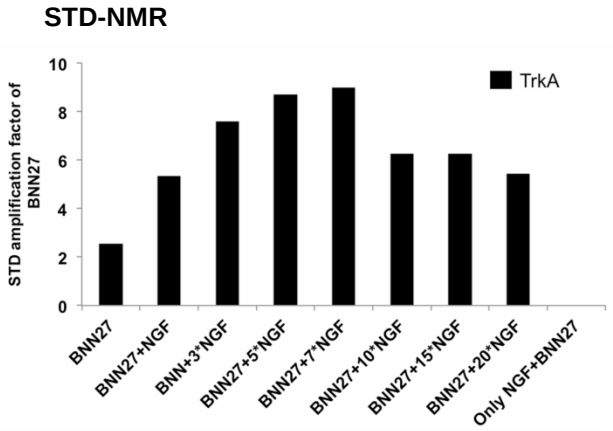
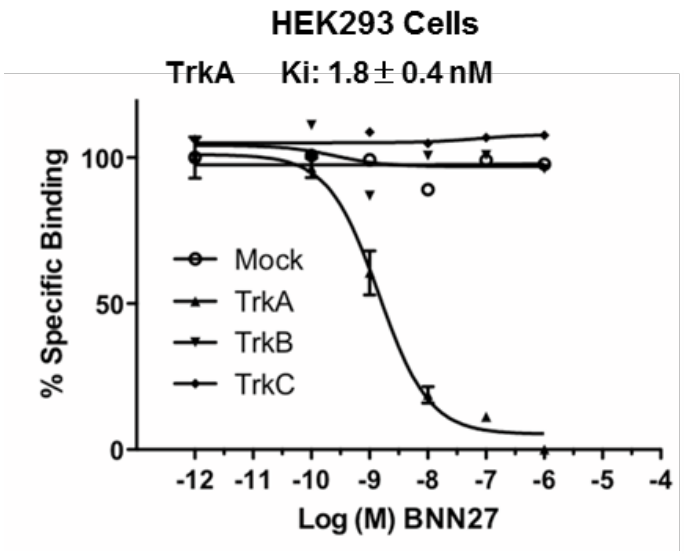
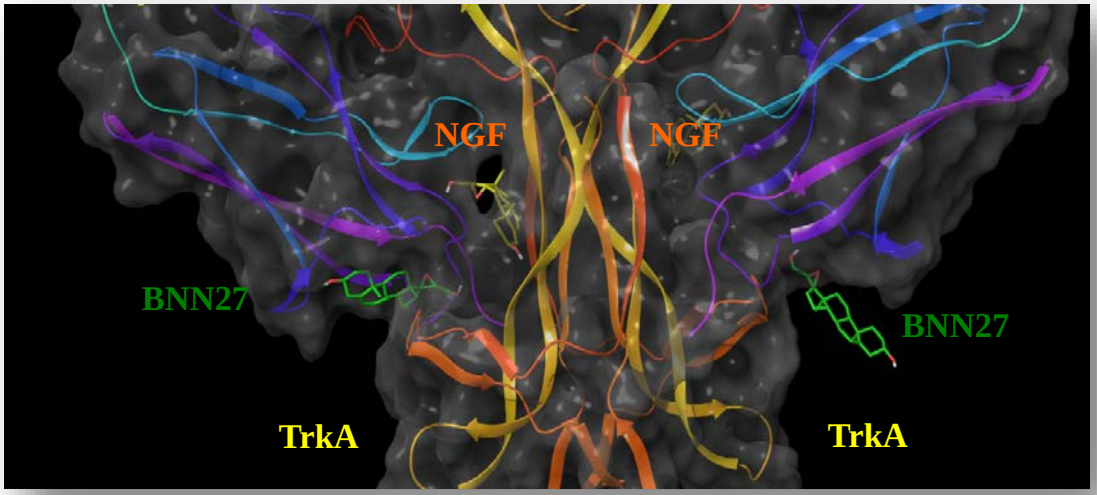
# BNN27 specifically interacts with TrkA receptor

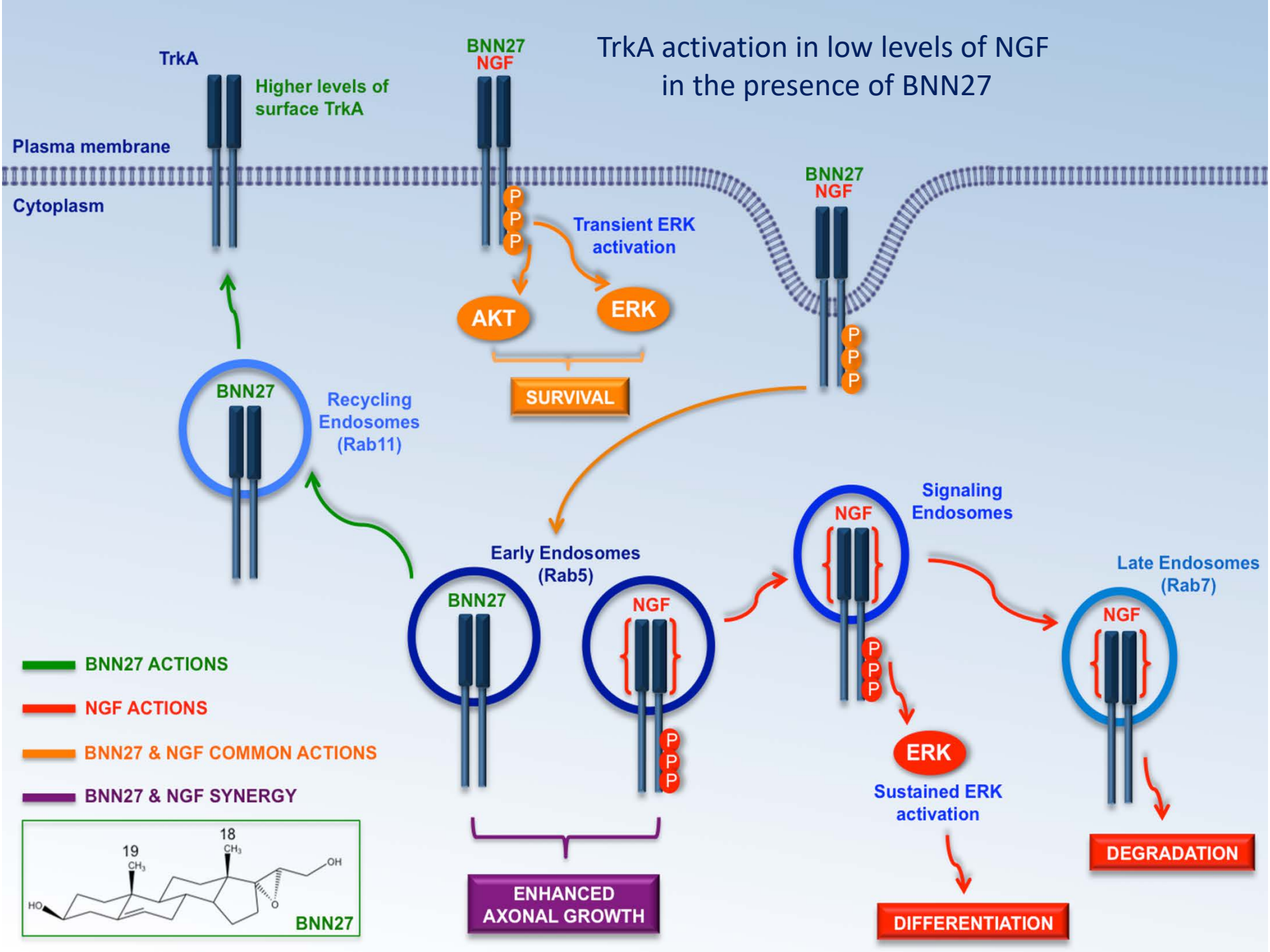


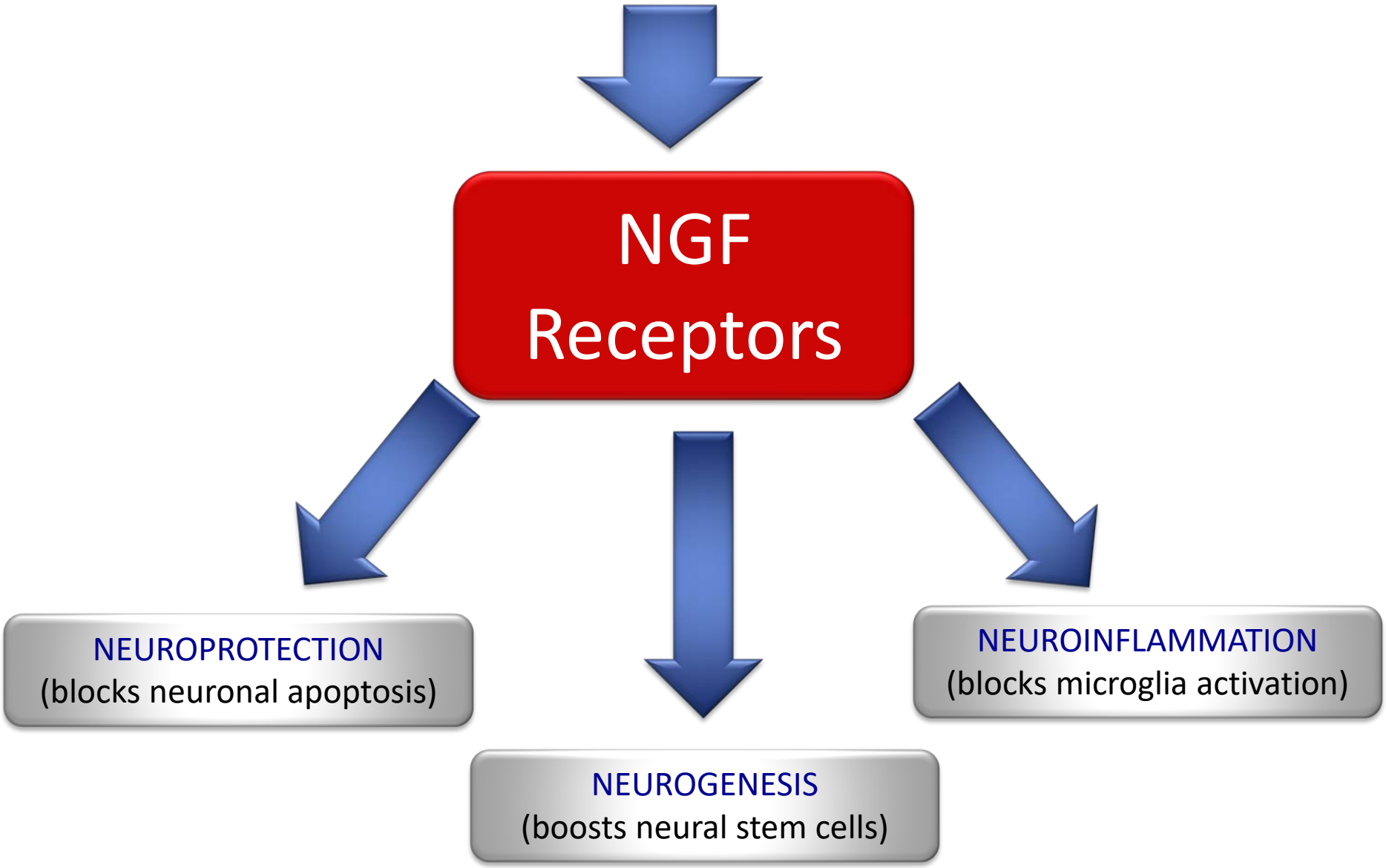



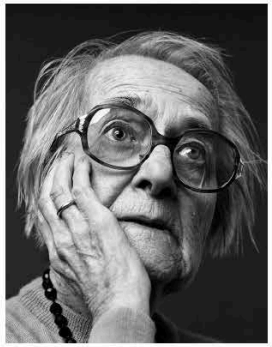

TrkA activation in low levels of NGF
in the presence of BNN27
TrkA
Higher levels of
surface TrkA
BNN27
NGF
Plasma membrane
Cytoplasm
P
P
P
Transient ERK
activation
AKT
ERK
SURVIVAL
BNN27
NGF
P
P
P
BNN27
Recycling
Endosomes
(Rab11)
Early Endosomes
(Rab5)
BNN27
NGF
P
P
P
Signaling
Endosomes
NGF
P
P
P
ERK
Sustained ERK
activation
Late Endosomes
(Rab7)
NGF
DEGRADATION
BNN27 ACTIONS
NGF ACTIONS
BNN27 & NGF COMMON ACTIONS
BNN27 & NGF SYNERGY
ENHANCED
AXONAL GROWTH
DIFFERENTIATION
19
CH3
18
CH3
OH
HO
O
BNN27

# Multidynamic MicroNeurotrophins



BIONATURE

# Neurodegeneration & Brain - Alzheimer's Disease



ALZHEIMER'S DISEASE IS THE
**6TH LEADING CAUSE**
OF DEATH IN THE UNITED STATES

In 2017, Alzheimer's and other dementias will cost the nation $259 billion
By 2050, these costs could rise as high as
**$1.1 TRILLION**

MORE THAN 5 MILLION AMERICANS ARE LIVING WITH ALZHEIMER'S
BY 2050, THIS NUMBER COULD RISE AS HIGH AS 16 MILLION

EVERY
66
SECONDS
someone in the United States develops the disease

**35%** of caregivers for people with Alzheimer's or another dementia report that their health has gotten worse due to care responsibilities, compared to
**19%** of caregivers for older people without dementia

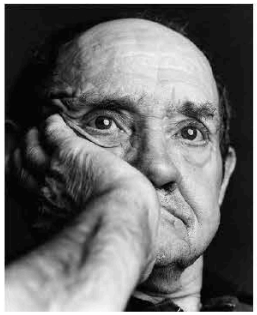
**1 IN 3**
seniors dies with Alzheimer's or another dementia

Since 2000, deaths from heart disease have decreased by 14%
while deaths from Alzheimer's disease have increased by 89%

MORE THAN **15 MILLION AMERICANS** provide unpaid care for people with Alzheimer's or other dementias

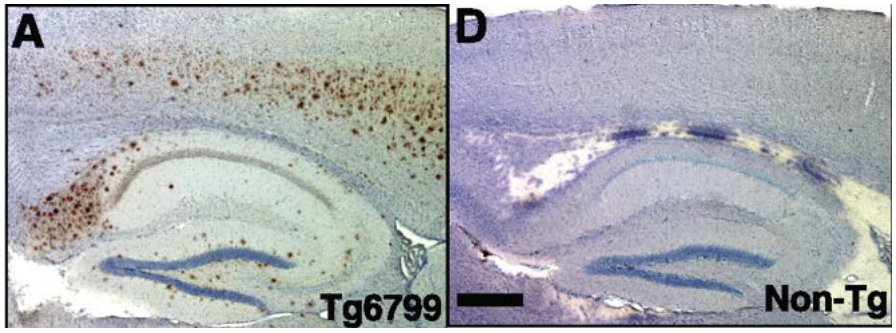
IN 2016 these caregivers provided an estimated **18.2 BILLION HOURS** of care valued at over **$230 BILLION**

IT KILLS MORE THAN
breast cancer and prostate cancer
COMBINED



# Alzheimer's humanized 5xFAD mouse model

- Harbours 5 familial AD mutations
  - human APP with the Swedish (K670N, M671L), Florida (I716V), and London (V717I) mutations
  - human presenilin 1 with two FAD mutations, M146L and L286V.

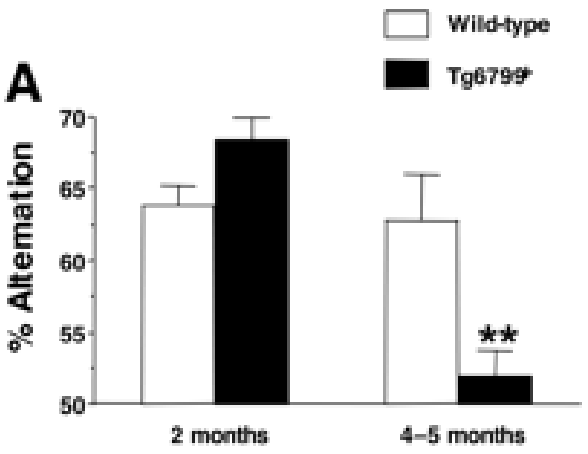



Molecular Psychiatry www.nature.com/mp

ARTICLE OPEN

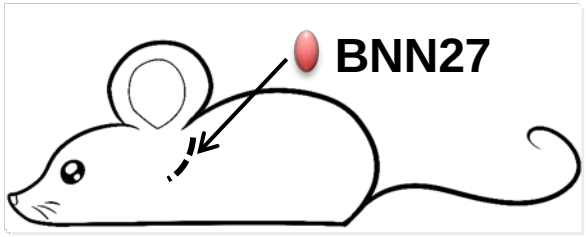
Multimodal beneficial effects of BNN27, a nerve growth factor synthetic mimetic, in the 5xFAD mouse model of Alzheimer's disease

Maria Kokkali[1,2,6], Kanelina Karali[1,2,6], Evangelia Thanou[3], Maria Anna Papadopoulou[1,2], Ioanna Zota[1,2], Alexandros Tsimpolis[1,2], Paschalis Efstathopoulos[1], Theodora Calogeropoulou[4], Ka Wan Li[3], Kyriaki Sidiropoulou[2,5], Achille Gravanis[1,2] and Ioannis Charalampopoulos[1,2]



# BNN27 improves working memory / spontaneous alternation performance

T-maze spontaneous alternation test

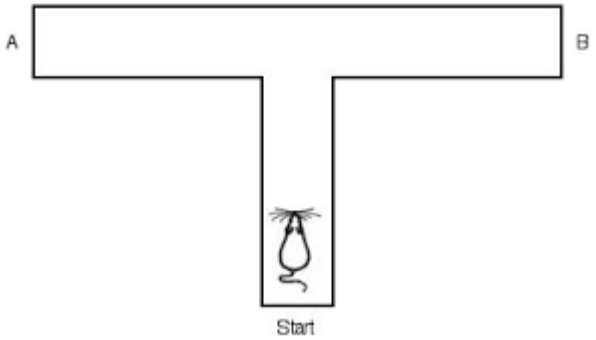


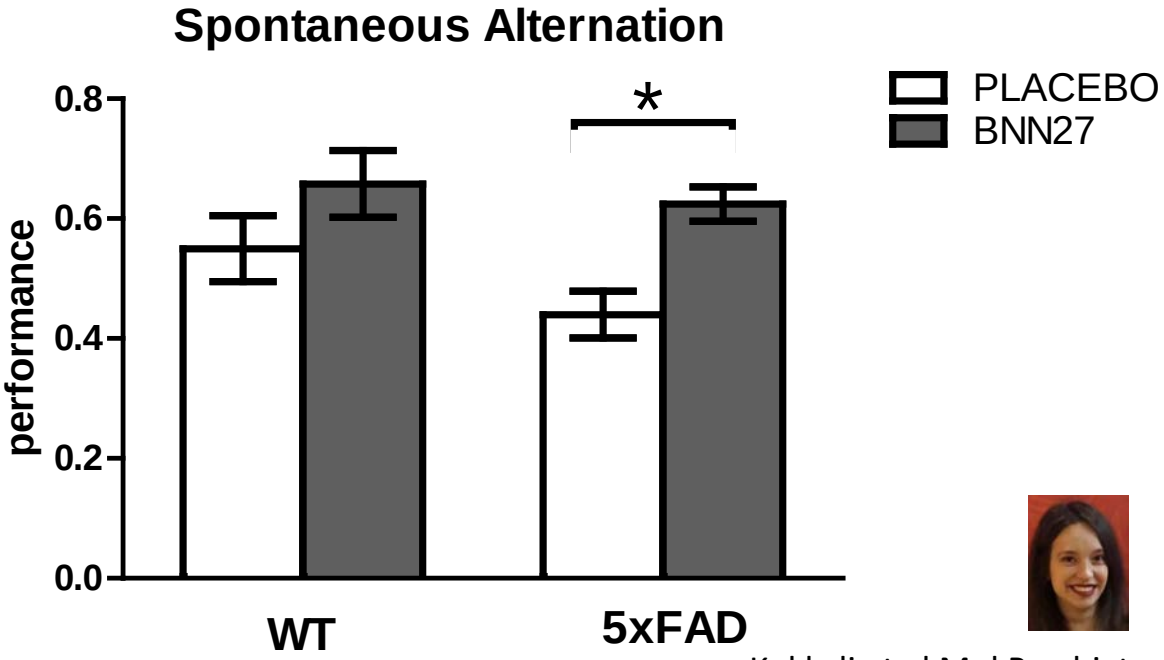

**5xFAD** (1.5 months old)

60 days later

Behavioural TESTING

PERFUSION TISSUE HARVEST



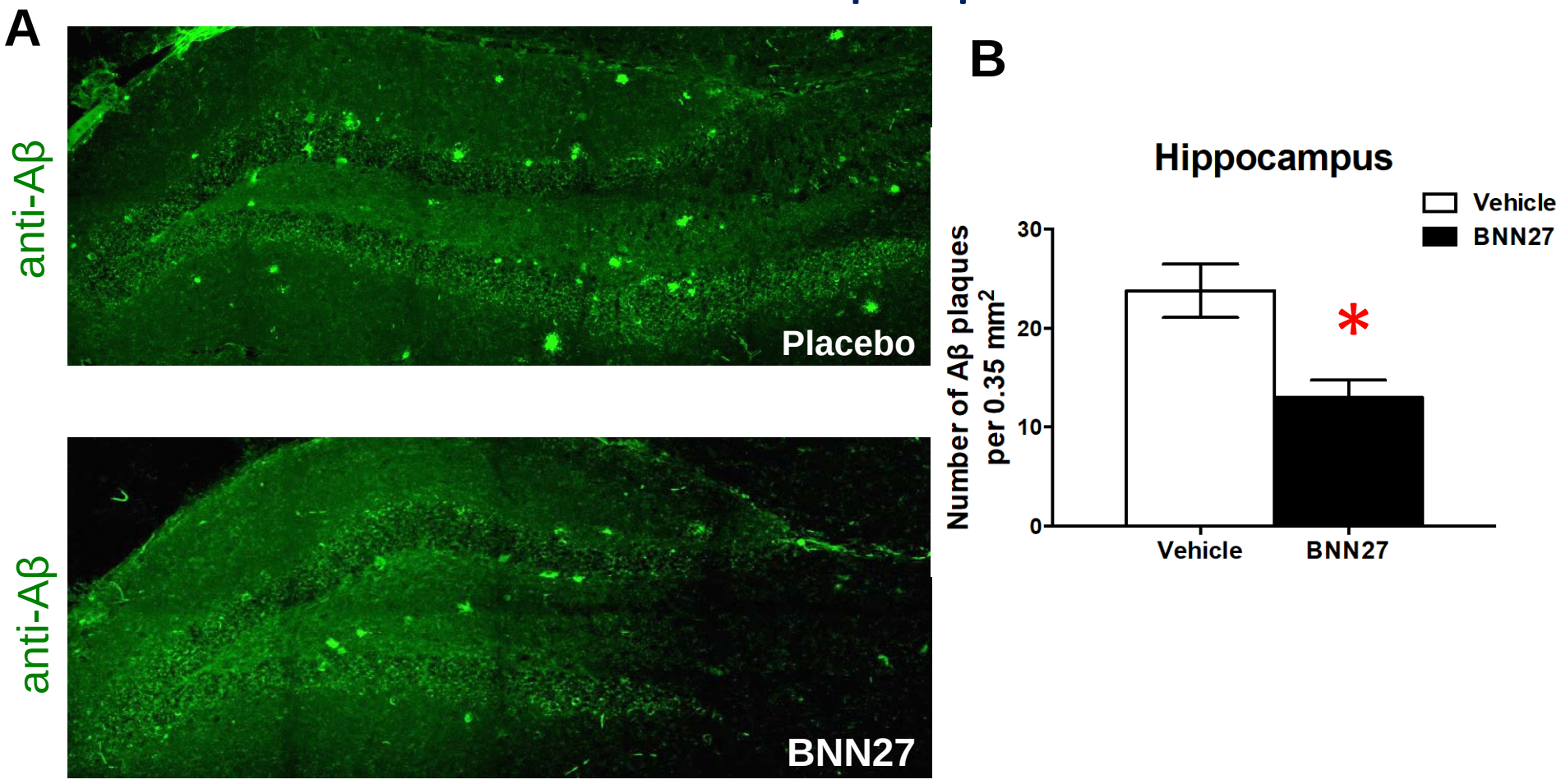

Groups

- 5xFAD BNN27 (n=9)
- 5xFAD placebo (n=5)
- WT BNN27 (n=5)
- WT placebo (n=6)



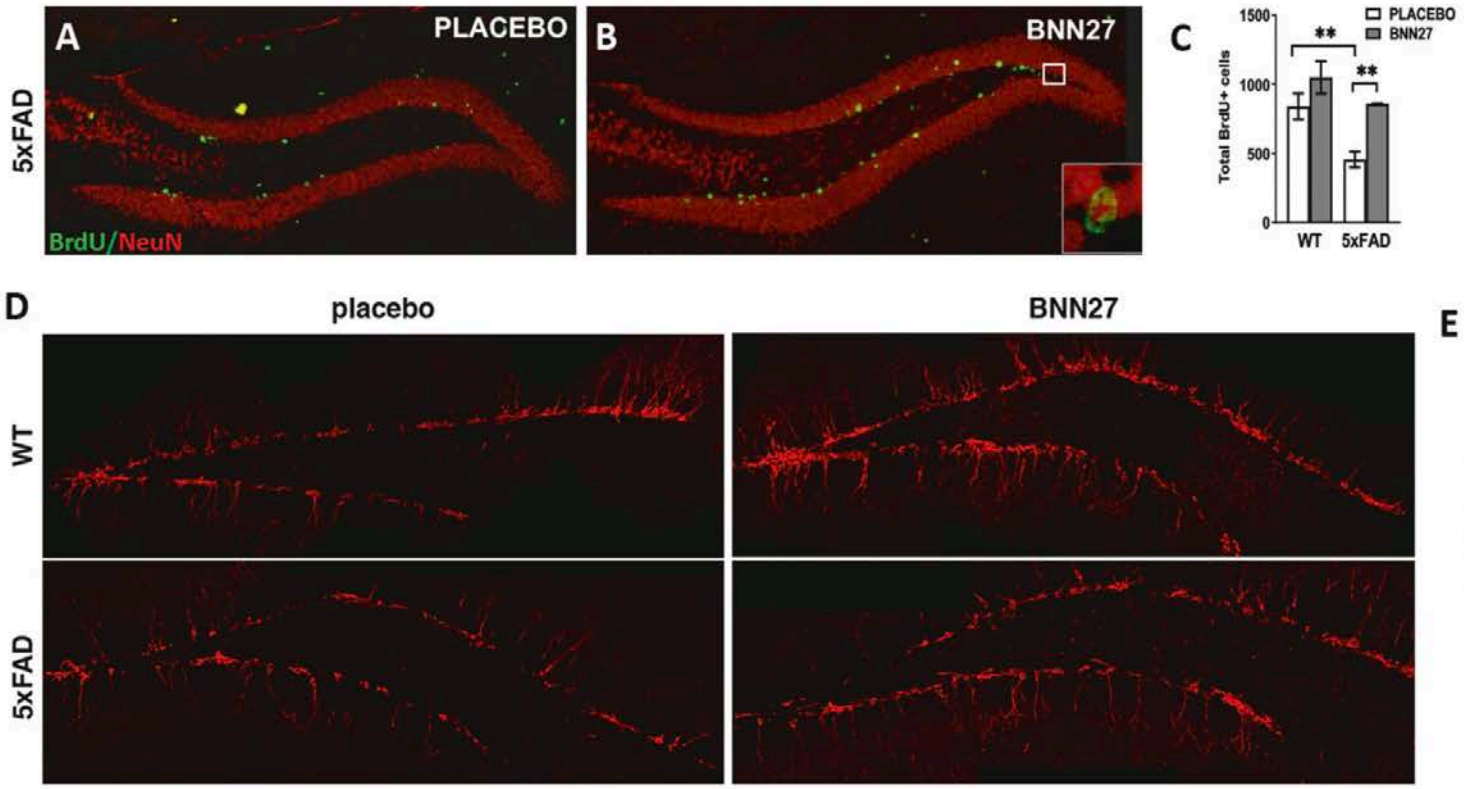
Kokkali et al Mol Psychiatry 2024

# BNN27 slows down plaque formation




**Immunostaining with anti-Aβ.** BNN27 treatment significantly decreased the formation of Aβ plaques within dentate gyrus of the hippocampus [*mean ± SE; n = 8; Student t test **P < 0.01]*

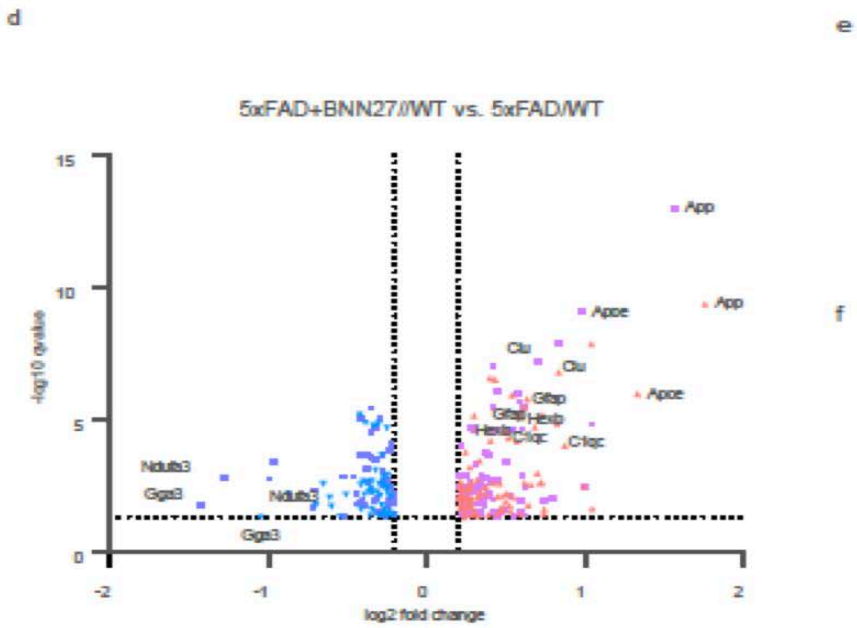
# BNN27 promotes adult hippocampal neurogenesis in the 5xFAD mice.

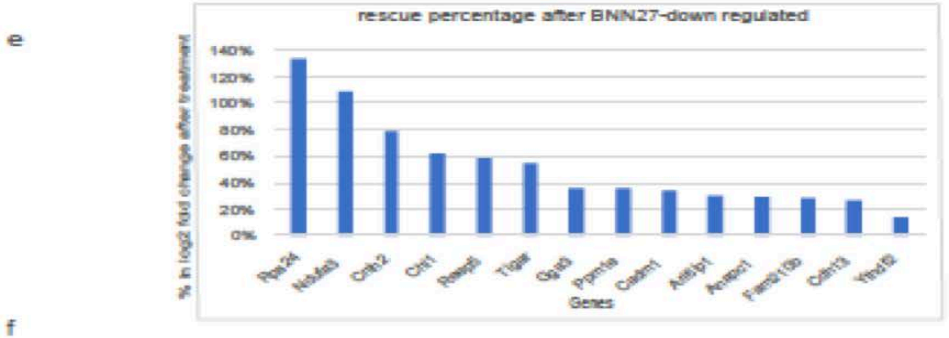


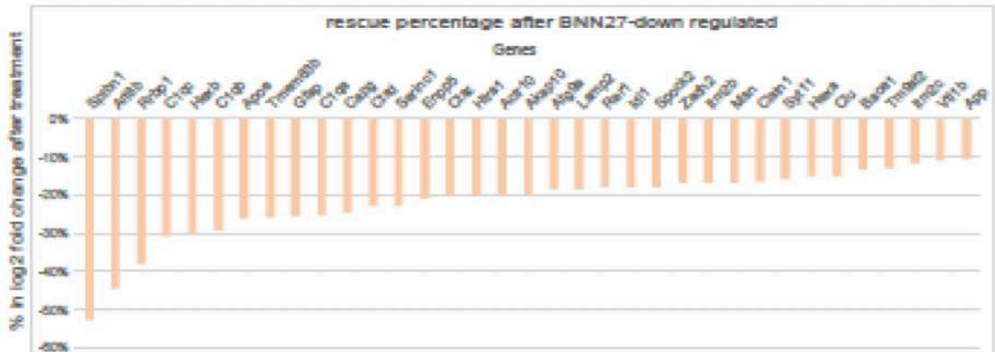

BNN27 significantly increases in the number of BrdU+/NeuN+ neurons and the number of DCX positive newly born neurons in the dentate gyrus of the hippocampus

# Comparative Proteomics Analysis in wt vs 5xFAD vs BNN27 treated animals

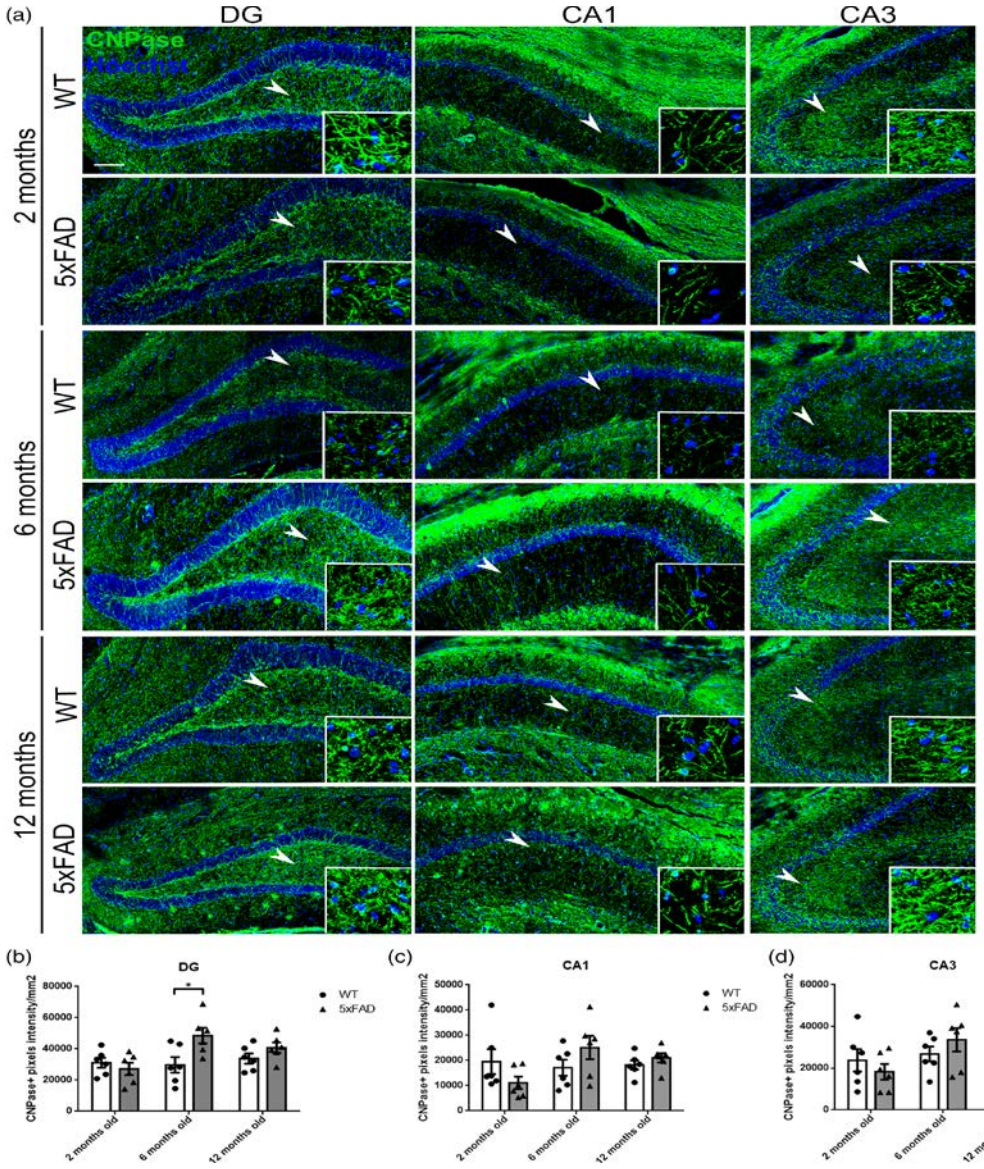
BNN27 treatment rescued 35 (out of 80) up-regulated proteins related to Alzheimer's disease: Apoe, Bace1, App, Aβ binding Apoe, Itm2b, Clu, amyloid precursor protein metabolic process App, Bace1, Syt11, Capg, oxidative damage, macrophage activation C1qa, Syt11, and mental deterioration Hexa, Htra1.



# At the age of 6 months of 5xFAD mice OPCs decline in the DG, extending to all hippocampal regions at 12 months.

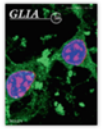



Received: 11 June 2023 | Revised: 8 December 2023 | Accepted: 14 December 2023
DOI: 10.1002/glia.24505
GLIA
WILEY
RESEARCH ARTICLE

## Dynamics of myelin deficits in the 5xFAD mouse model for Alzheimer's disease and the protective role of BDNF

Ioanna Zota[1,2] | Konstantina Chanoumidou[1,2] | Ioannis Charalampopoulos[1,2] | Achille Gravanis[1,2]





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### COVER IMAGE

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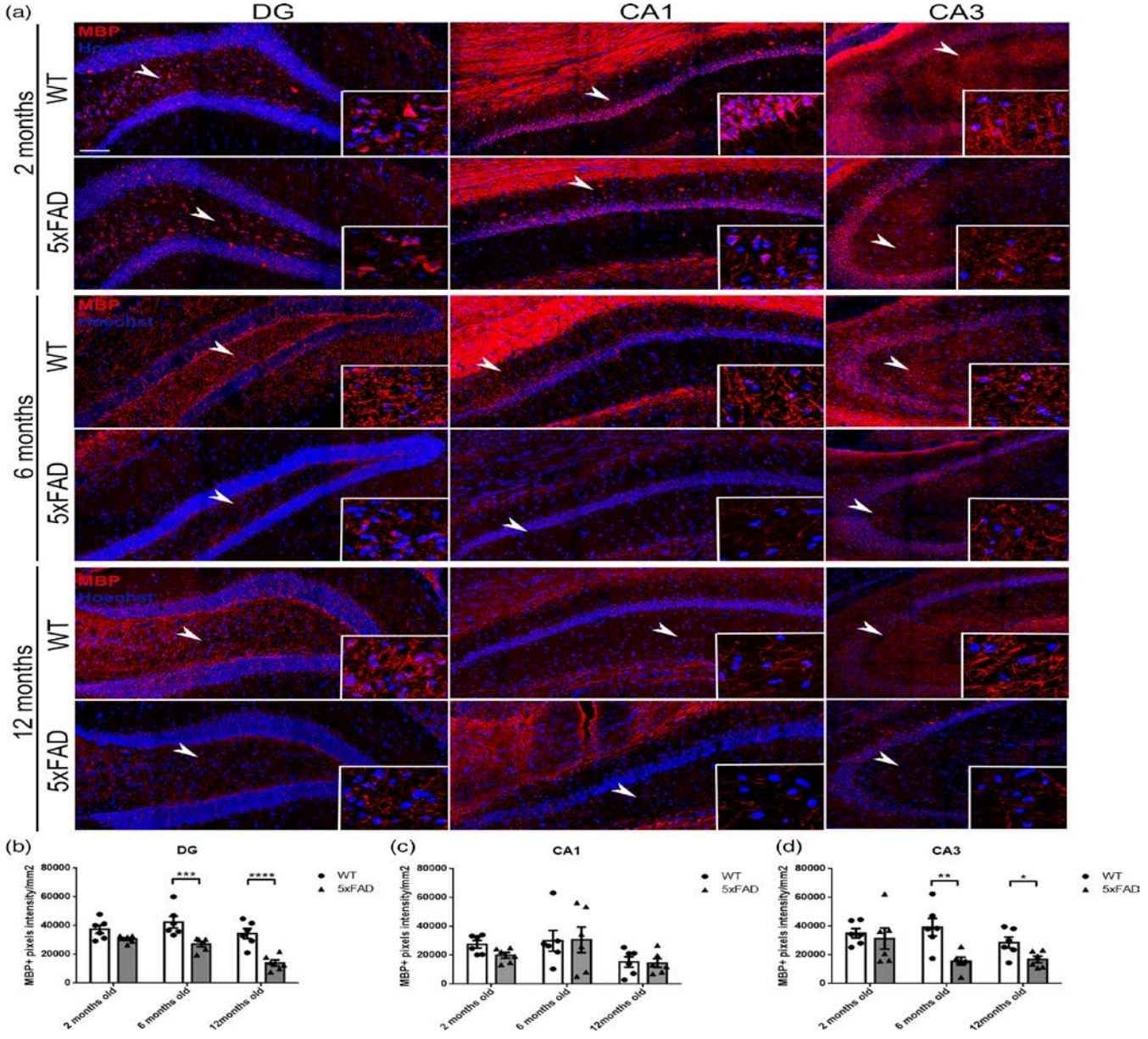
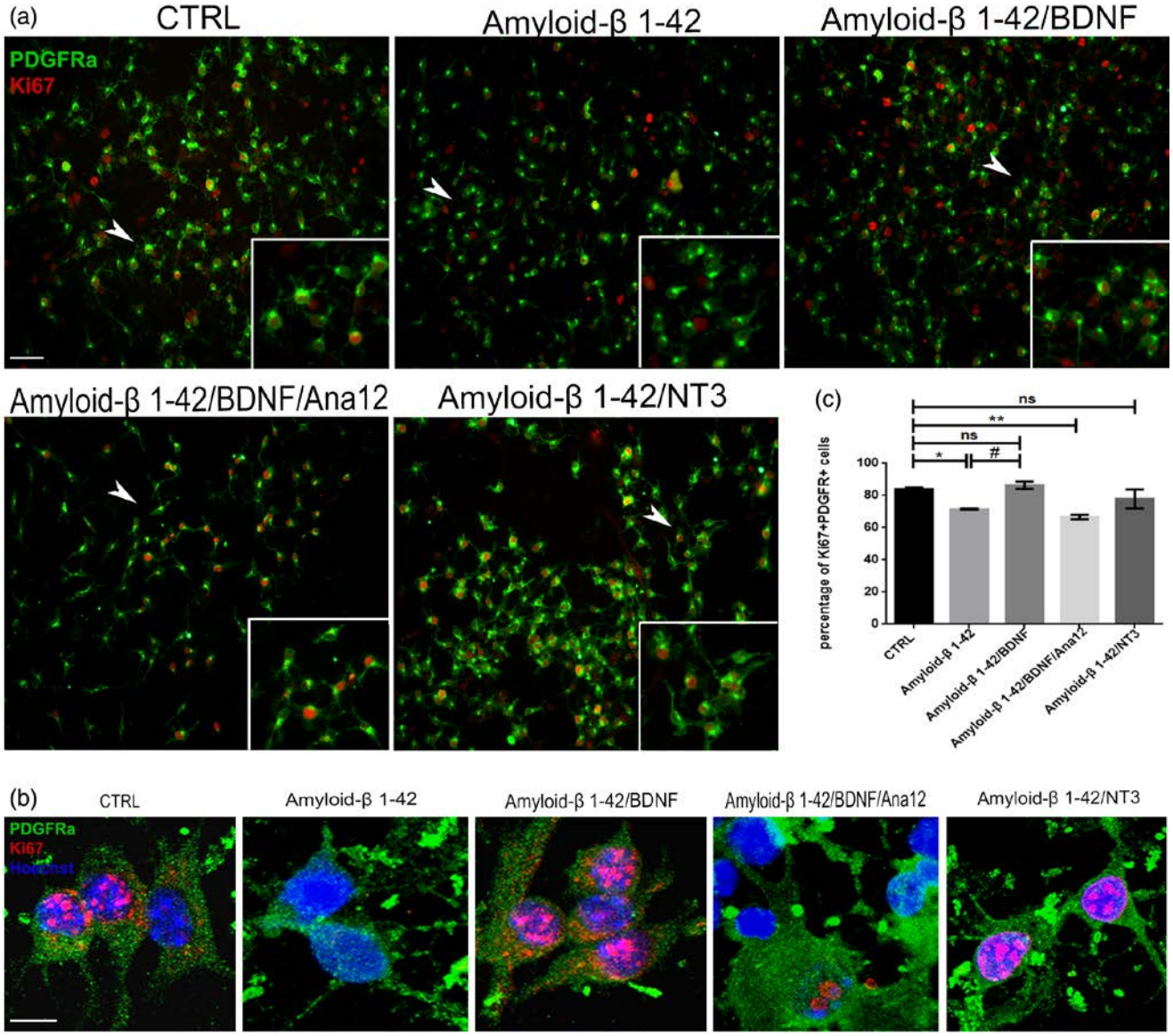
Cover Image, Volume 72, Issue 4

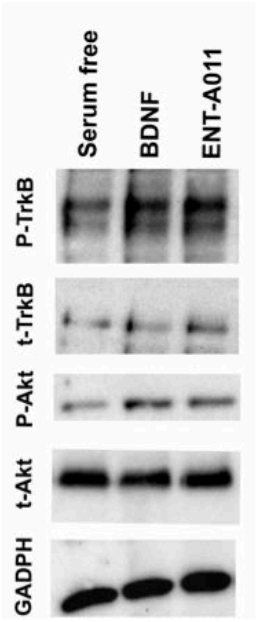
Ioanna Zota, Konstantina Chanoumidou, Ioannis Charalampopoulos, Achille Gravanis

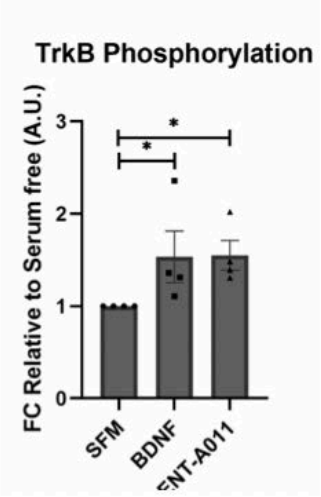
# Levels of myelination were decreased in 5xFAD mice starting from 6 months onwards

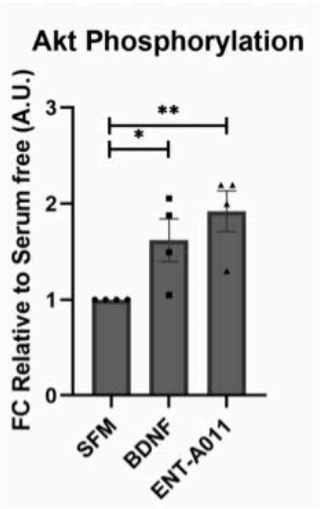


# BDNF reversed the inhibitory effect of Amyloid-β on OPC **proliferation**, in primary OPC cultures isolated from P2 wt mice






Charou *et al. Stem Cell Research & Therapy* (2024) 15:200
https://doi.org/10.1186/s13287-024-03818-w

Stem Cell Research & Therapy

RESEARCH Open Access

# Comprehensive characterization of the neurogenic and neuroprotective action of a novel TrkB agonist using mouse and human stem cell models of Alzheimer's disease

Despoina Charou[1,2], Thanasis Rogdakis[1,2†], Alessia Latorrata[3†], Maria Valcarcel[4], Vasileios Papadogiannis[5], Christina Athanasiou[7,8,9], Alexandros Tsengenes[7,8,9], Maria Anna Papadopoulou[1,2], Dimitrios Lypitkas[1,2], Matthieu D. Lavigne[2], Theodora Katsila[3], Rebecca C. Wade[7,8,10,11], M. Zameel Cader[6], Theodora Calogeropoulou[3], Achille Gravanis[1,2] and Ioannis Charalampopoulos[1,2*]

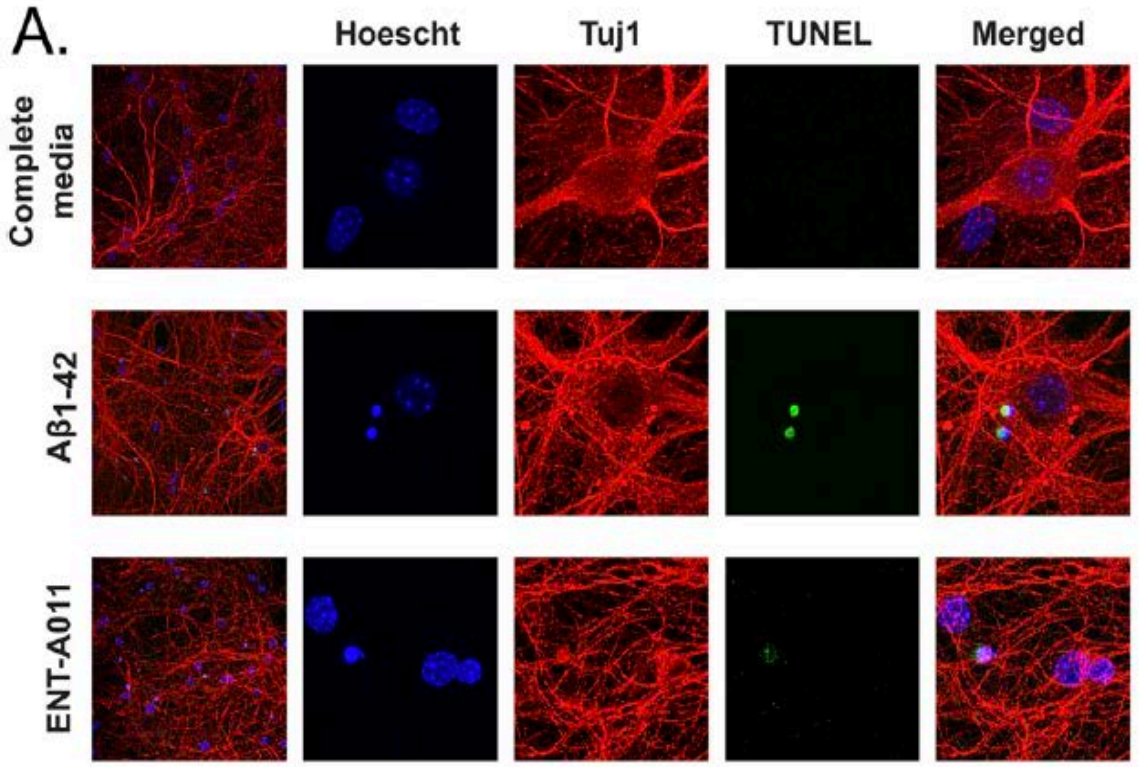


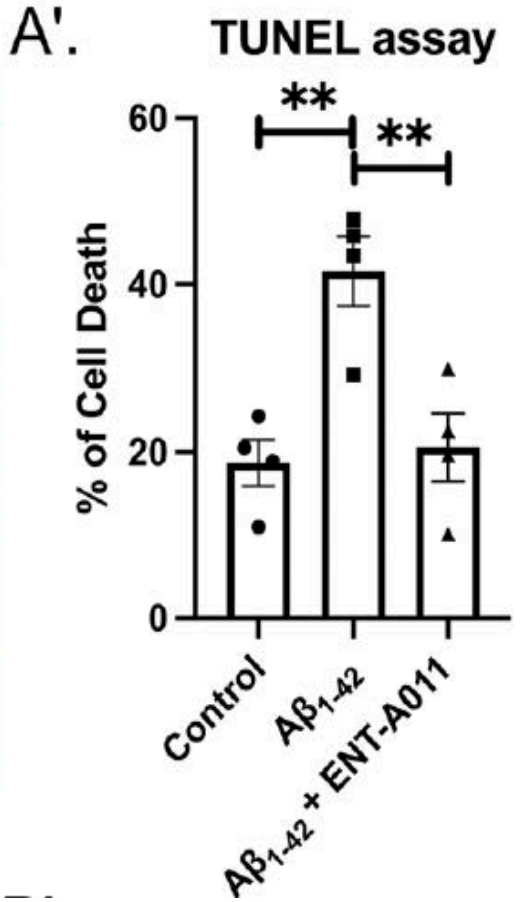
T. Calogeropoulou



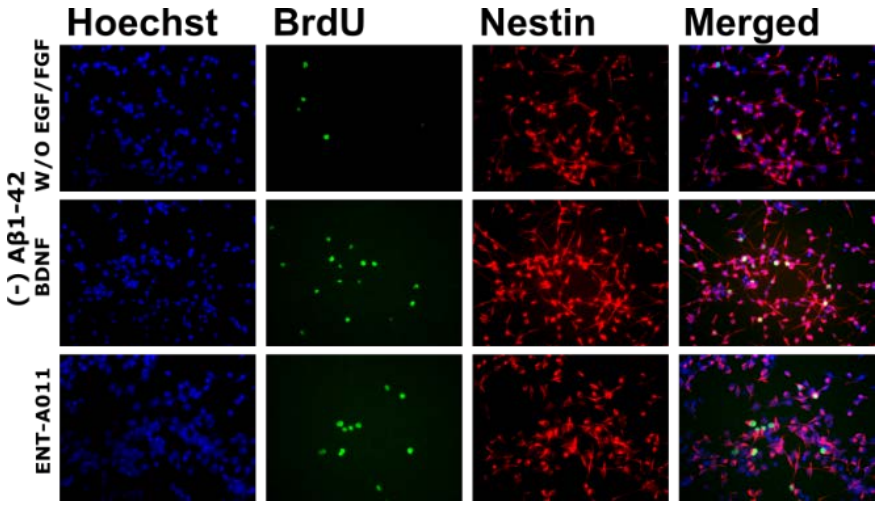
D. Charou

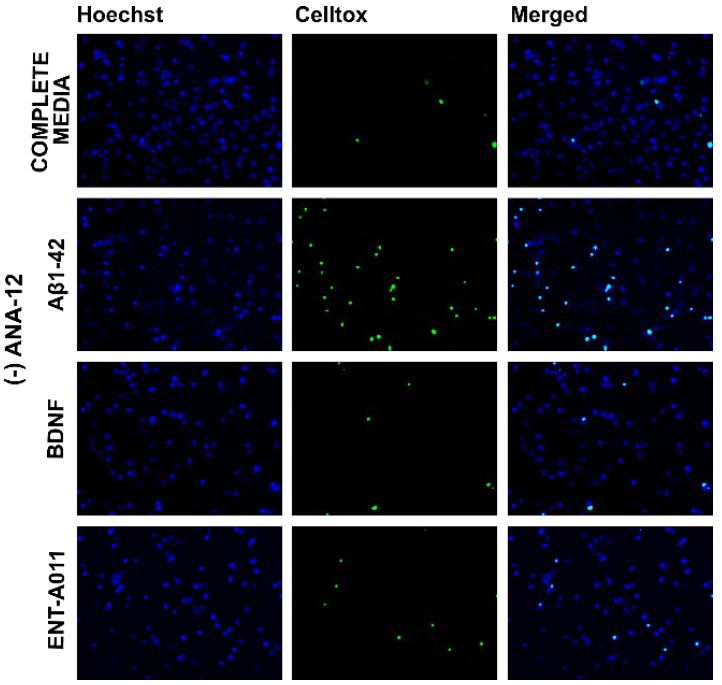
# ENT-A011 protects mouse hippocampal neurons and rat cortical neurons against Aβ42 toxicity

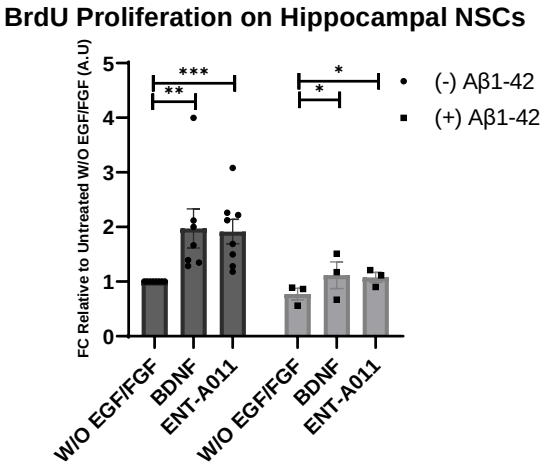


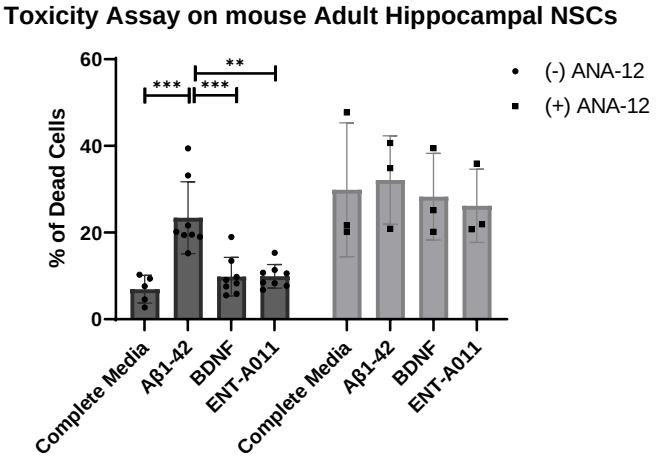



# ENT-A011 increased proliferation and survival of mouse adult hippocampal NSCs in culture

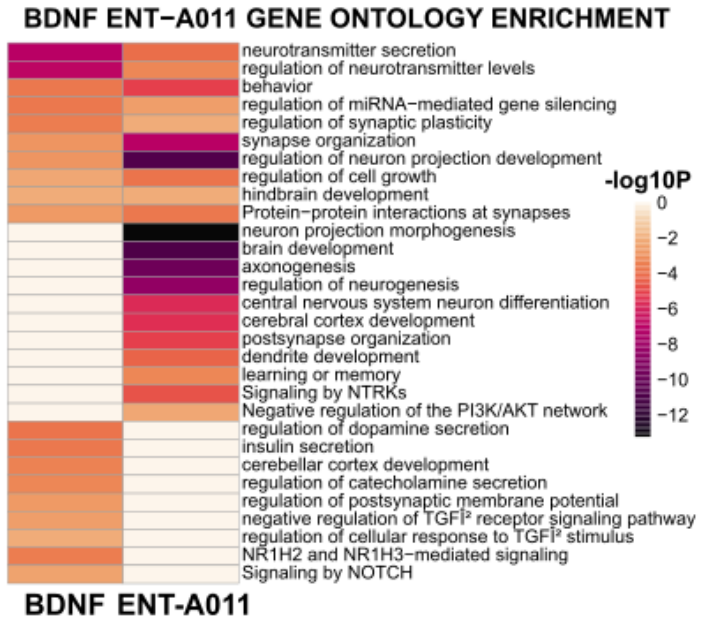


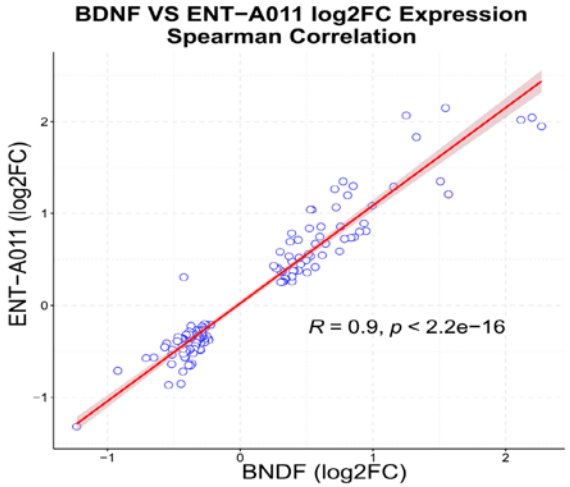



# We compared the effects of ENT-A011 to BDNF on Expression and Gene Ontology enrichment analysis in human Cortical Neural Progenitor Cells



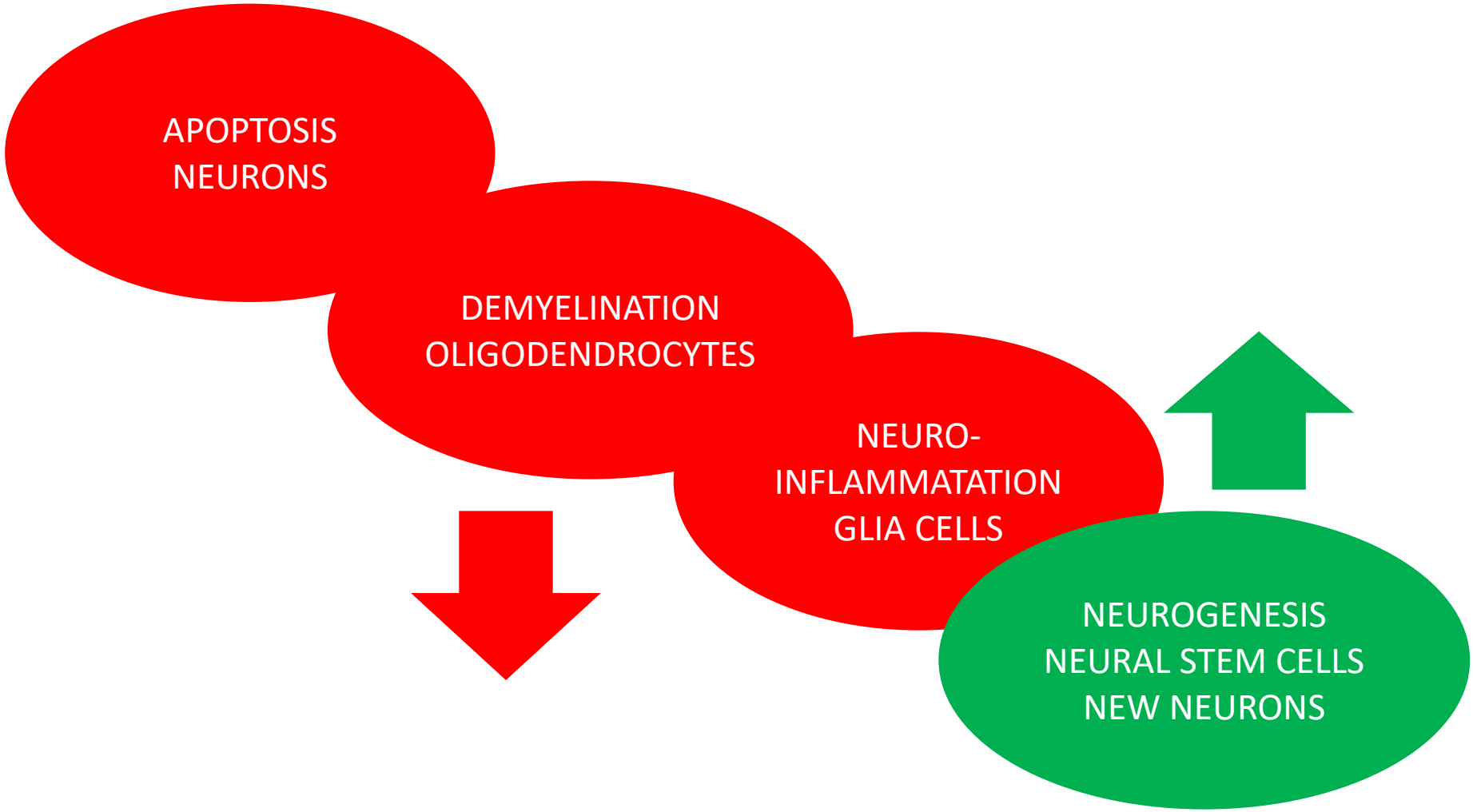




-Genes co-upregulated by both BDNF and ENT-A011 included those **associated with neural development and function, neurotransmitter secretion, synapse organization, and regulation of cell growth**: Complexin 2 (*CPX-2*), cut like homeobox 1 (*CUX1*), presynaptic organizer bassoon (*BSN*), t-Box Brain Transcription Factor 1 (*TBR1*), DMRT Like Family A2 (*DMRTA2*),Tyrosine Phosphatase Receptor Type D (*PTPRD*).

-A **striking target of ENT-A011 was also amyloid Beta Precursor Like Protein 1** (*APLP1*), a member of the amyloid precursor protein family

-ENT-A011 **upregulated BDNF/TrkB signalling members**, such as *DOK5,* NCK Adaptor Protein 2 (*NCK2),* Transcription Factor B (*BCL11B*)

# We propose the combination of multifaceted TrkA (NGF) and TrkB (BDNF) activators in Alzheimer's therapeutics



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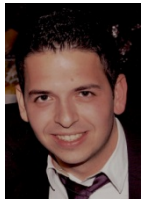
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# NEUROGENESIS IN THERAPEUTICS

## Developing novel Therapeutics for Neural Trauma

Novel neuroimplants for spinal cord injury and reversal of paralysis with 3D scaffolds hosting neural stem cells (brain-on-a-chip technologies)

ReNeuroCell

THERAPEUTICS

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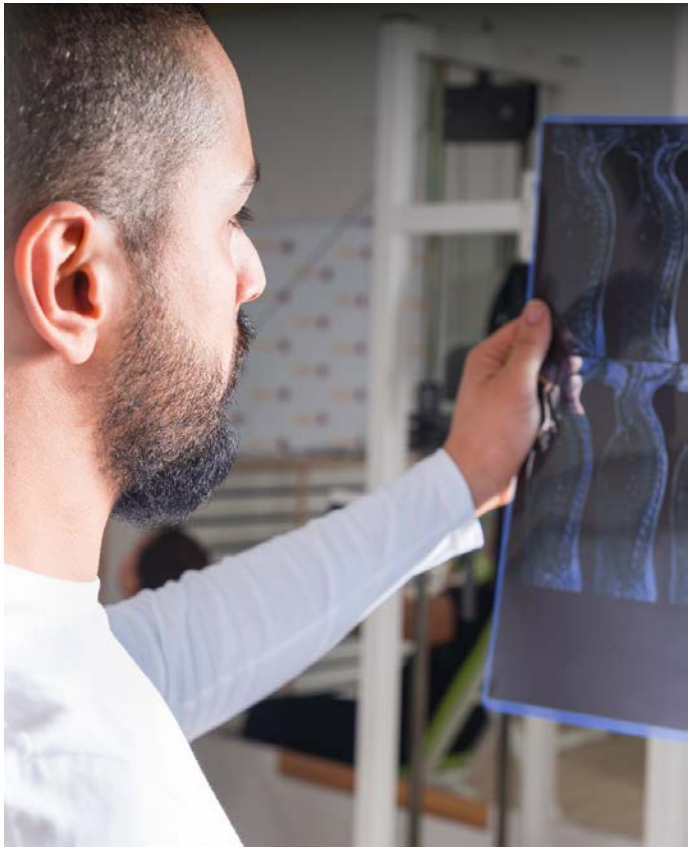
# SCI: an increasing burden on healthcare systems

**There are no effective therapies for SCI**

Clinical treatment for SCI is limited to surgical decompression and anti-inflammatory glucocorticoids

- Minimal recovery
- Treatment aimed solely on inhibiting further damage



# Challenges in Developing Effective SCI Treatments

01 **Replacement of lost neural tissue**

02 **Re-establishment of neural function**
SCI induces loss of precious neural tissue

03 **Engineering the SCI response**
Neuroprotection, Neurogenesis

04 **Limiting neuroinflammation**

05 **Modulation astrogliosis**
Enhancing angiogenesis

06 **Enhancing remyelination**
Neuroprotection, Neurogenesis

07 **Enhancing axon elongation & connectivity**

# The ReNeuroCell Biotechnology Approach

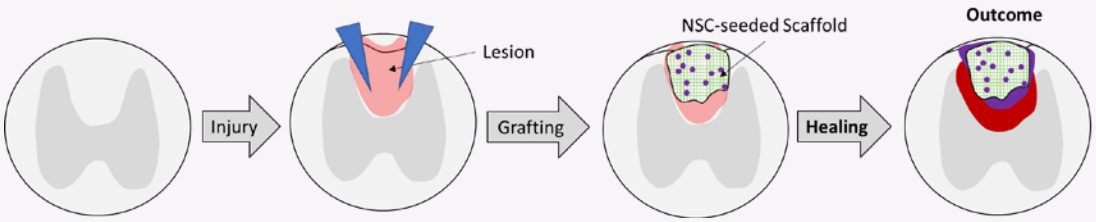
## Develop scaffold carriers of potent stem cells

Rather than injecting a pool of loose cells, graft a system of interacting neural progenitors robustly attached to a biologically-active scaffold

### Advantages

- Enhance stem cell survival
- Localize NSCs/AxSCs in the lesion
- Pre-engineer stem cell fate
- Enhance graft repeatability
- Design graft based the clinical picture of each patient

**Delivery of state-of-the-art NSC treatments via bio-scaffolds in a SCI lesion**



# Engineering Porous Collagen-Based Scaffolds

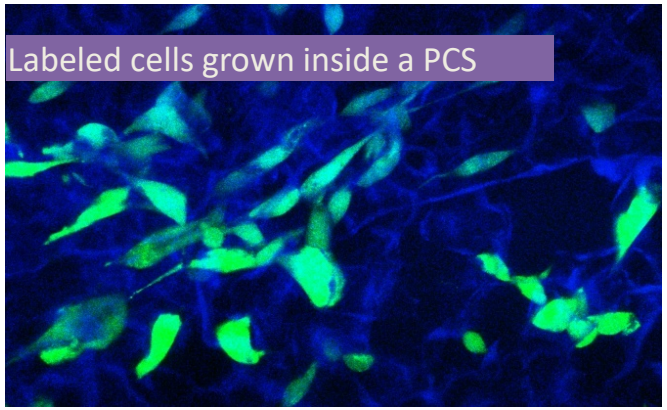
## Adapt & optimize bio-scaffold Technology for SCI

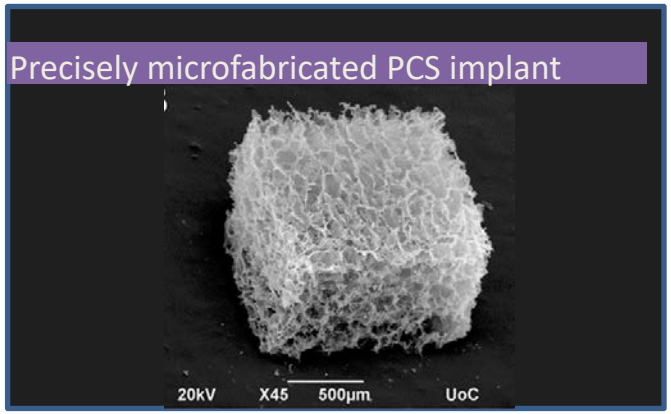
**Optimize graft design via multiple means**

- Scaffolds: composition, pore structure, degradation rate
- progenitor cells: type (AxSCs, NSCs, fate-restricted cells like immature OPCs)
- stem cell maturation prior to implantation
- combine with neuroprotective/neurogenic agents

**Miniaturize implants to smoothly fit in SCI lesions**

- Use state-of-the-art laser microfabrication
- Design patient-tailored implants

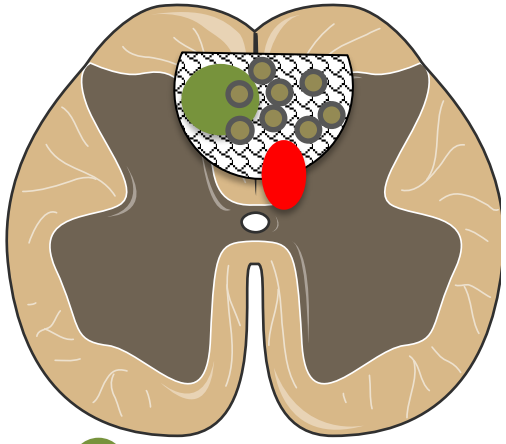


# *In vivo* transplantation of 3D-C-NSCs scaffolds

## Dorsal Column Crash Mouse Model

**T13 spinal cord segment**



**Dorsal columns**

**Rubrospinal**

| GROUPS |
|---|
| Control |
| Crush |
| Treated (collagen scaffold+NSCs) |

| Impairments |
|---|
| Hind-limp stability |
| Coordination |

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ARTICLE OPEN

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Neural stem cell delivery via porous collagen scaffolds promotes neuronal differentiation and locomotion recovery in spinal cord injury

Alexandra Kourgiantaki[1,2,6], Dimitrios S. Tzeranis[2,3,6], Kanelina Karali[1,2,6], Konstantina Georgelou[1,2], Efstathia Bampoula[4], Sotirios Psilodimitrakopoulos[5], Ioannis V. Yannas[3], Emmanuel Stratakis[5], Kyriaki Sidiropoulou[2,4], Ioannis Charalampopoulos[1,2] and Achille Gravanis[1,2]✉

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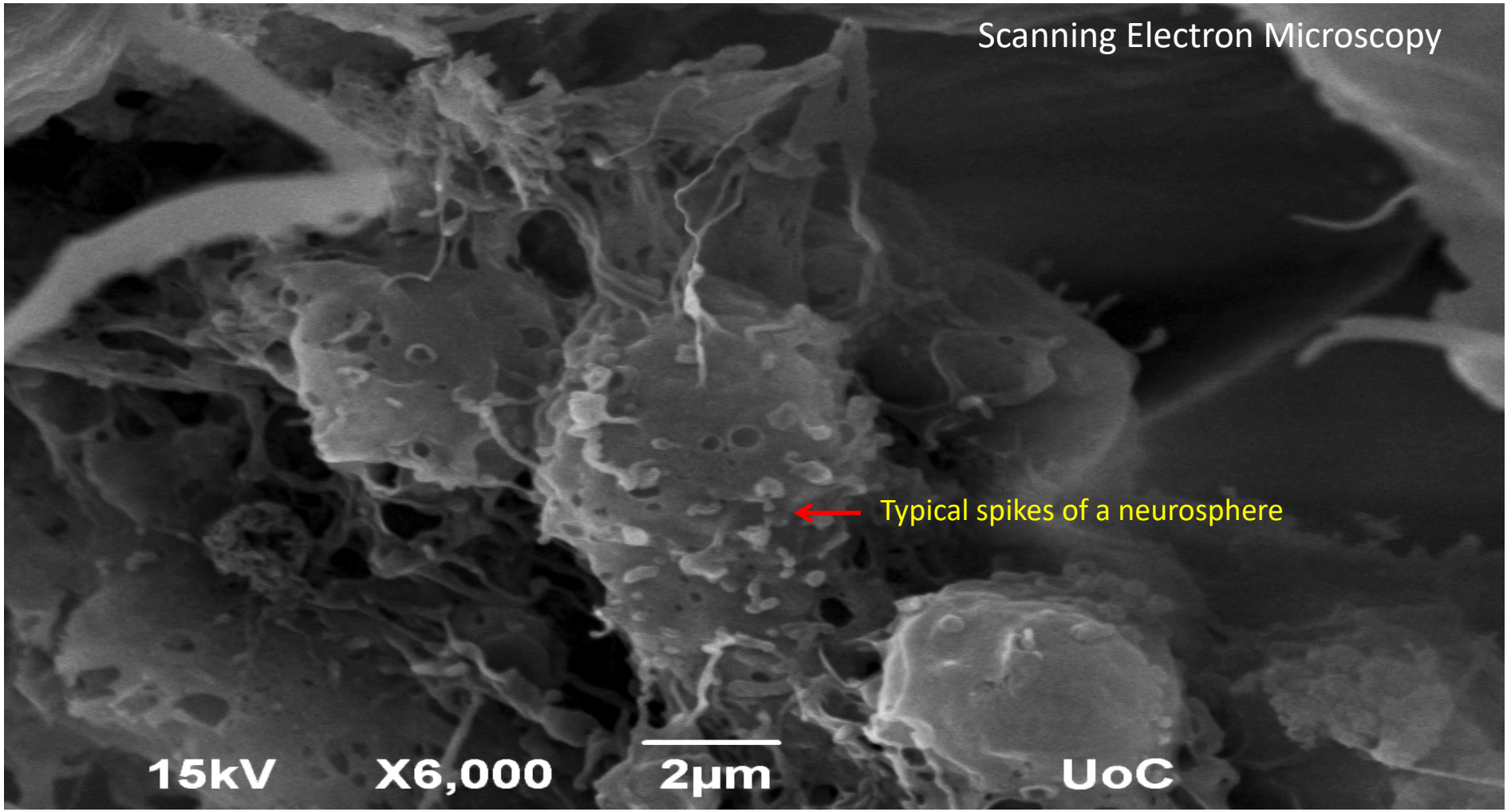
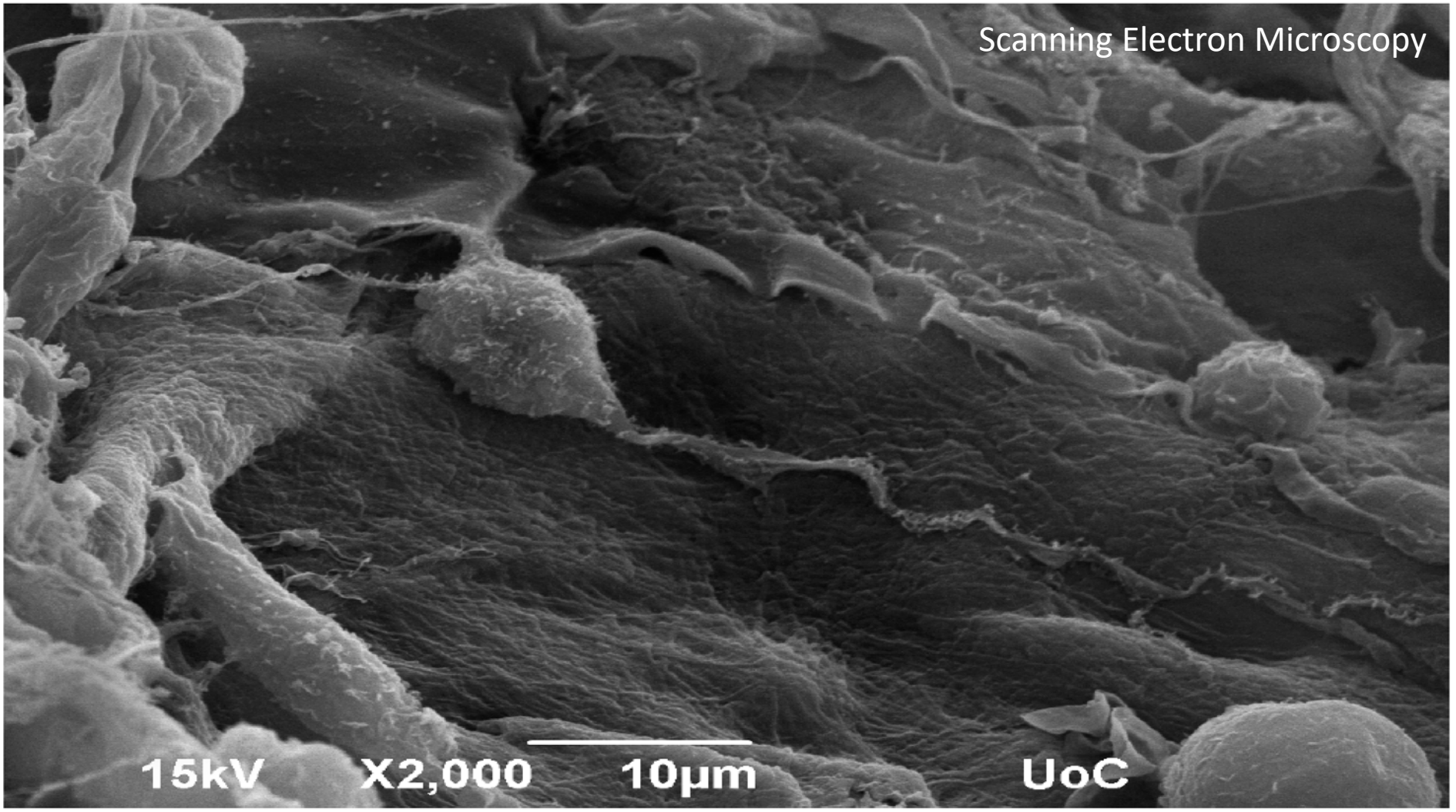
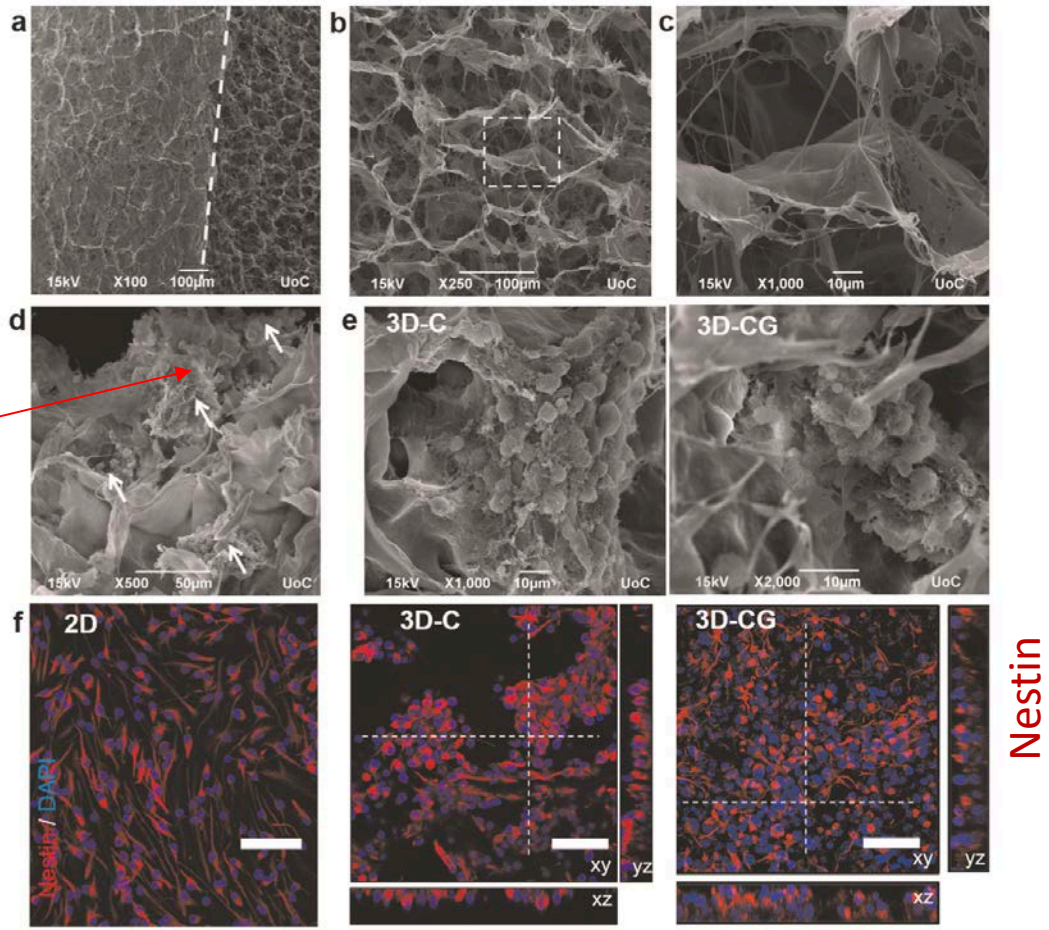

Scanning Electron Microscopy
Typical spikes of a neurosphere
15kV
X6,000
2µm
UoC


Scanning Electron Microscopy
15kV
X2,000
10µm
UoC

# 3D culture of mouse embryonic neural stem cells inside porous collagen-based scaffolds

(Scanning Electron Microscopy)

Separated cells, in 3 days form Neurospheres

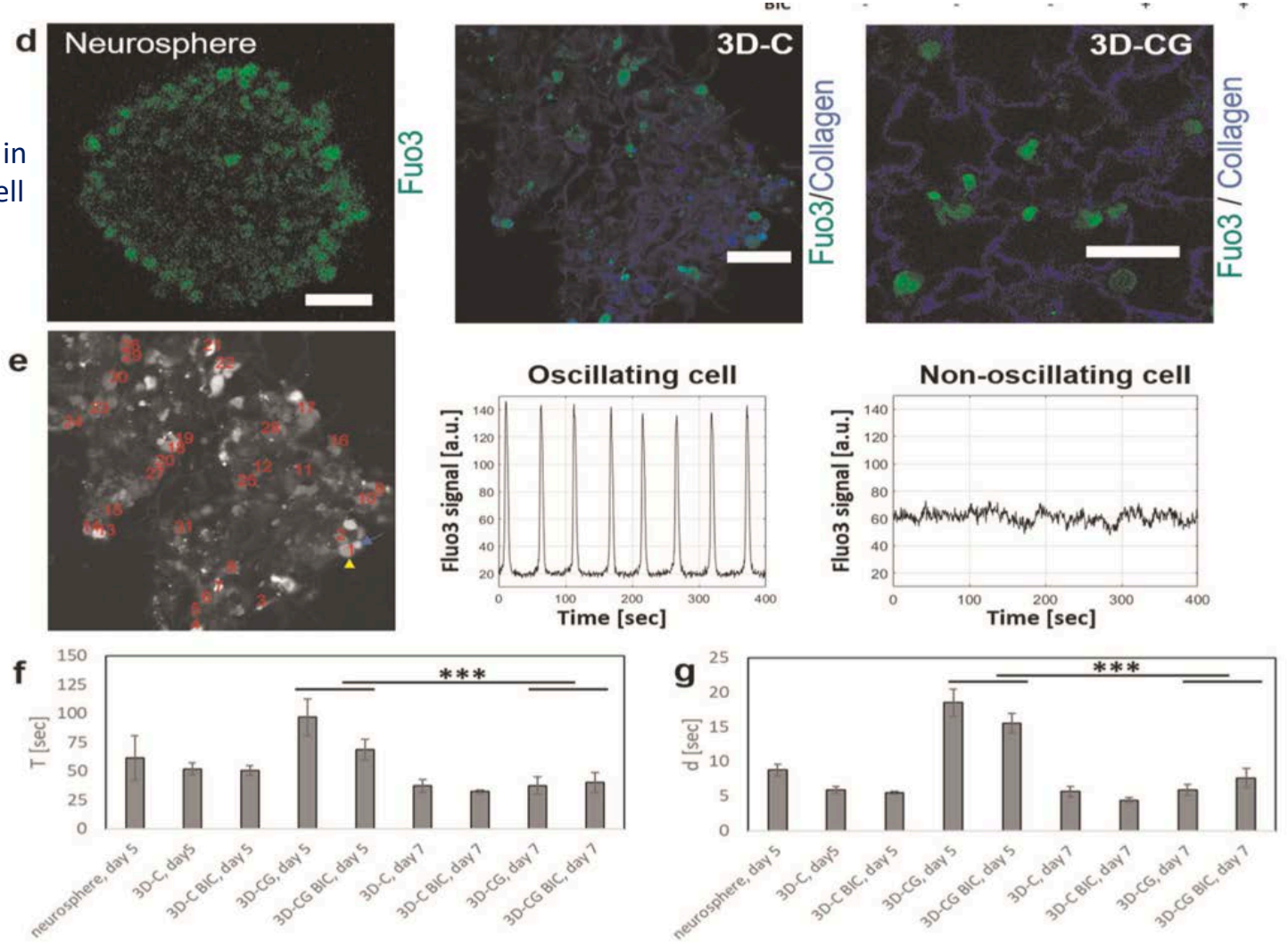





Kourgiantaki et al, NPJ Reg Med 2020

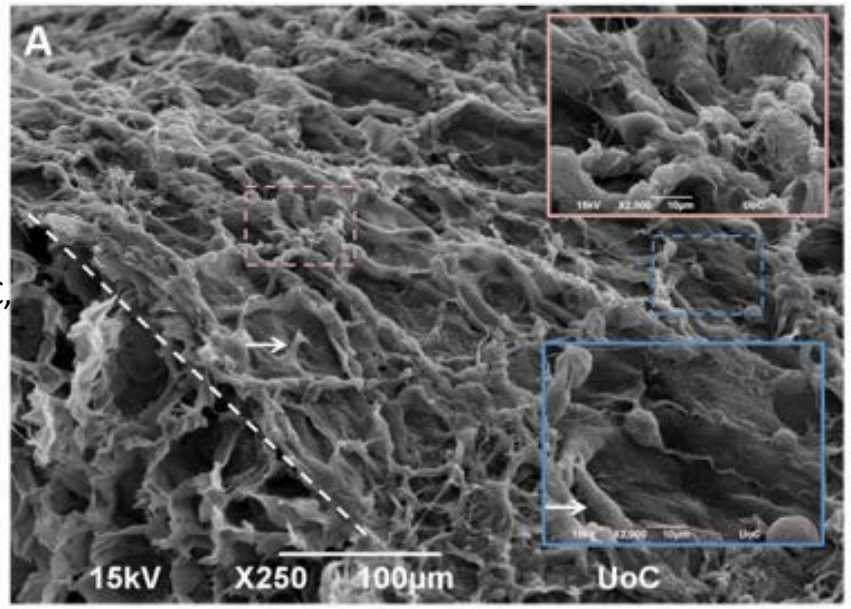
# Porous collagen scaffolds enhance NSC neural differentiation *in vitro (spontaneous activity)*

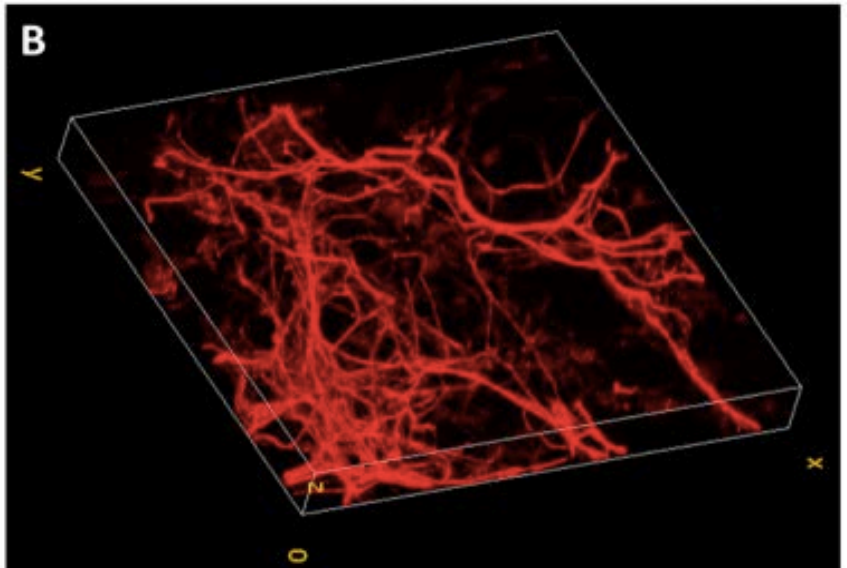
Recording in a single cell



# 3D-C scaffolds supported growth and functional network formation of sensory neurons

3D Scaffolds with NSC, a platform for drug screening!

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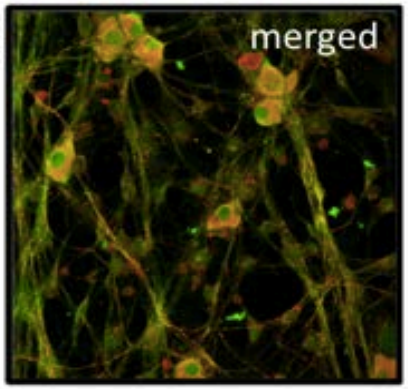
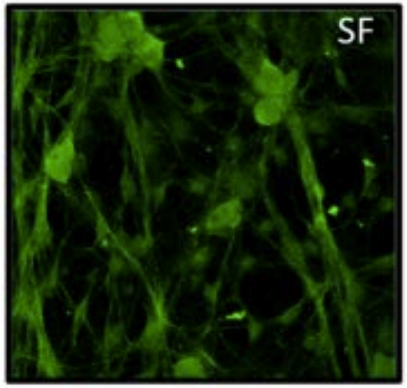
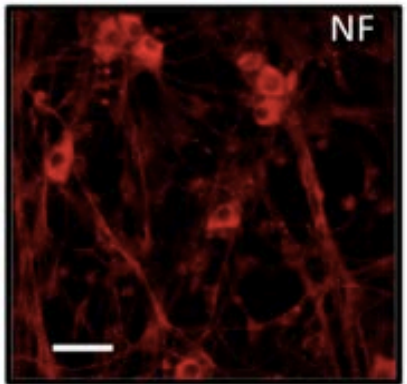
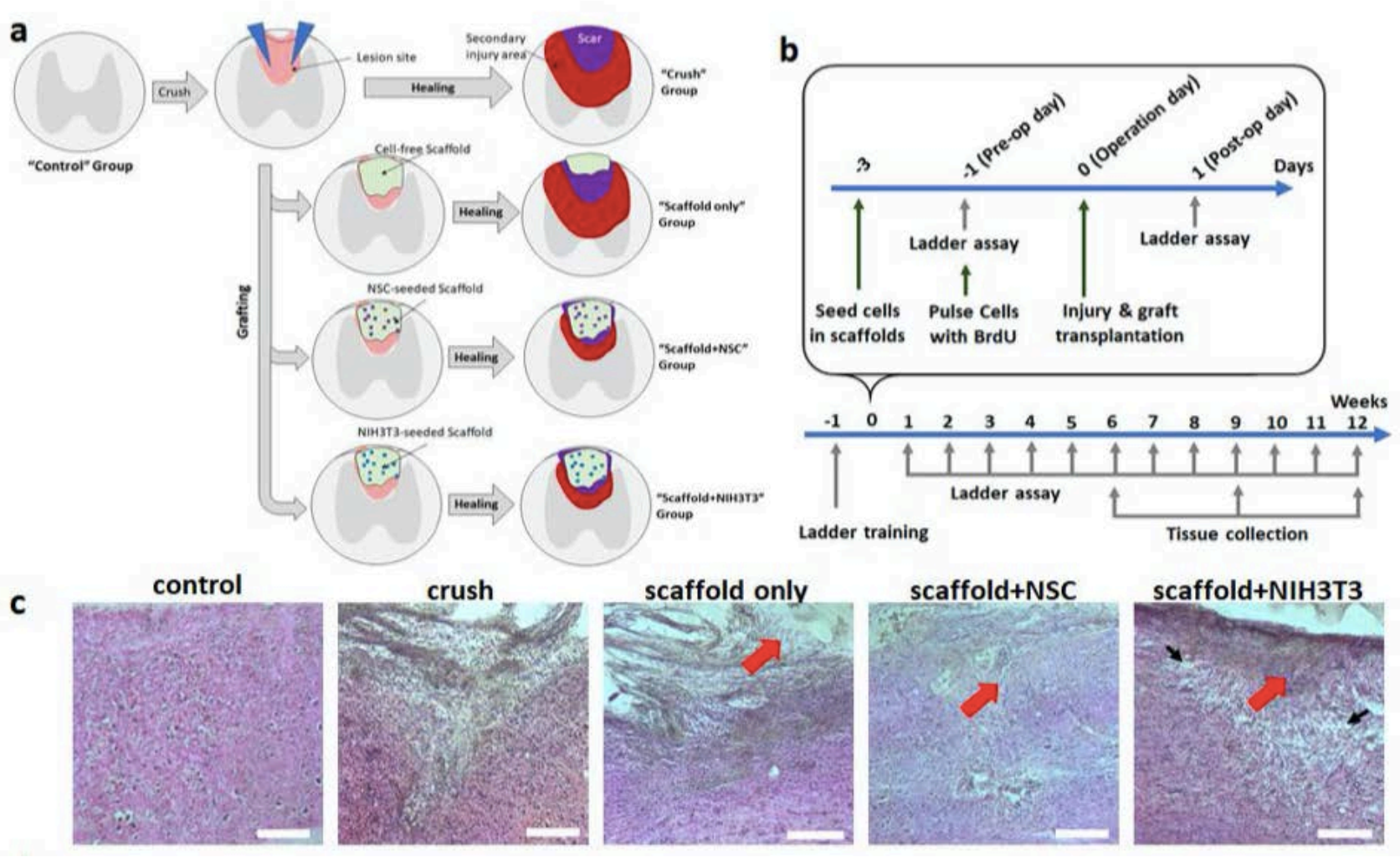


# 3D Collagen scaffold/NSCs treated SCI mice performed equally well to controls in the ladder-walking test 12 weeks after implantation



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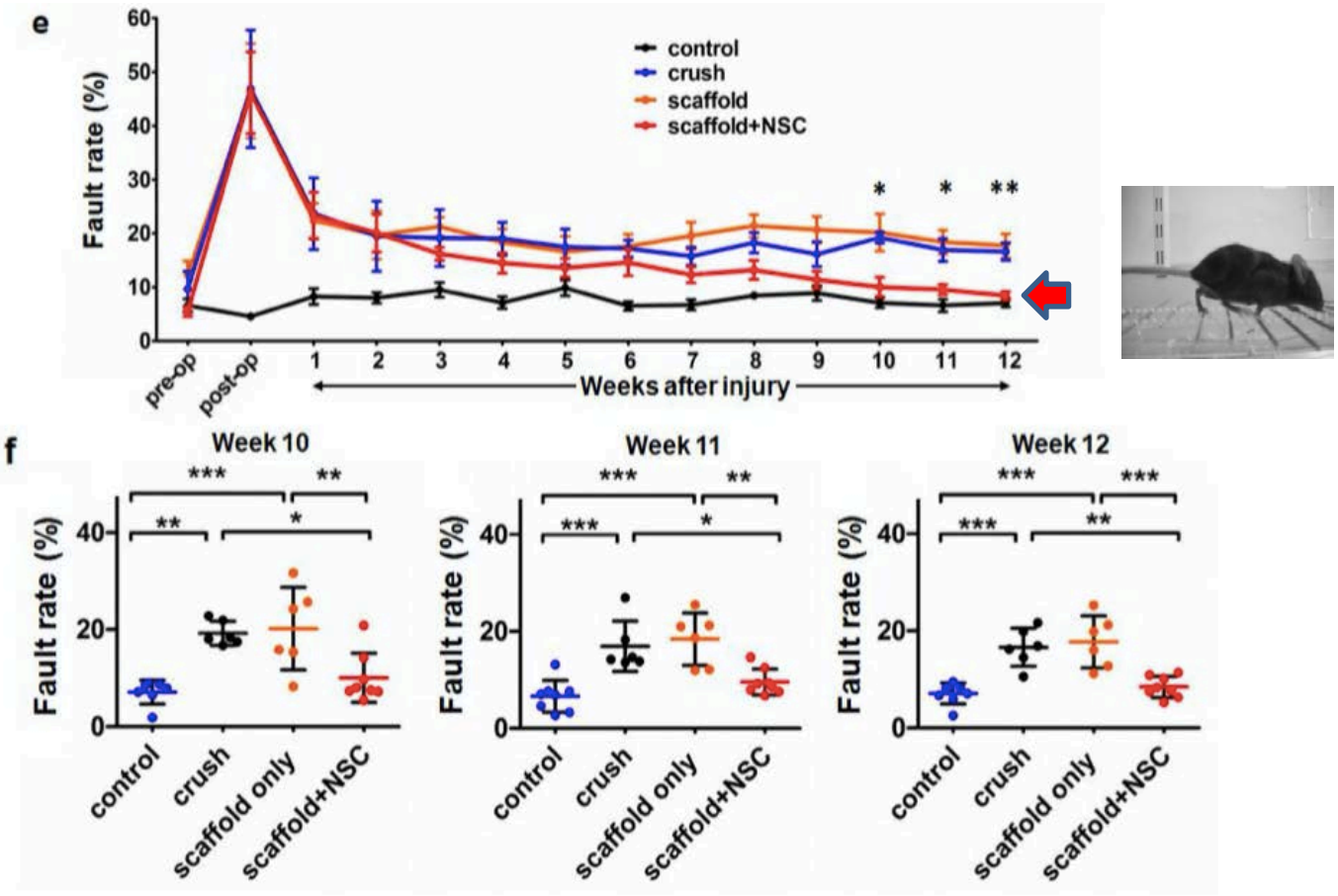
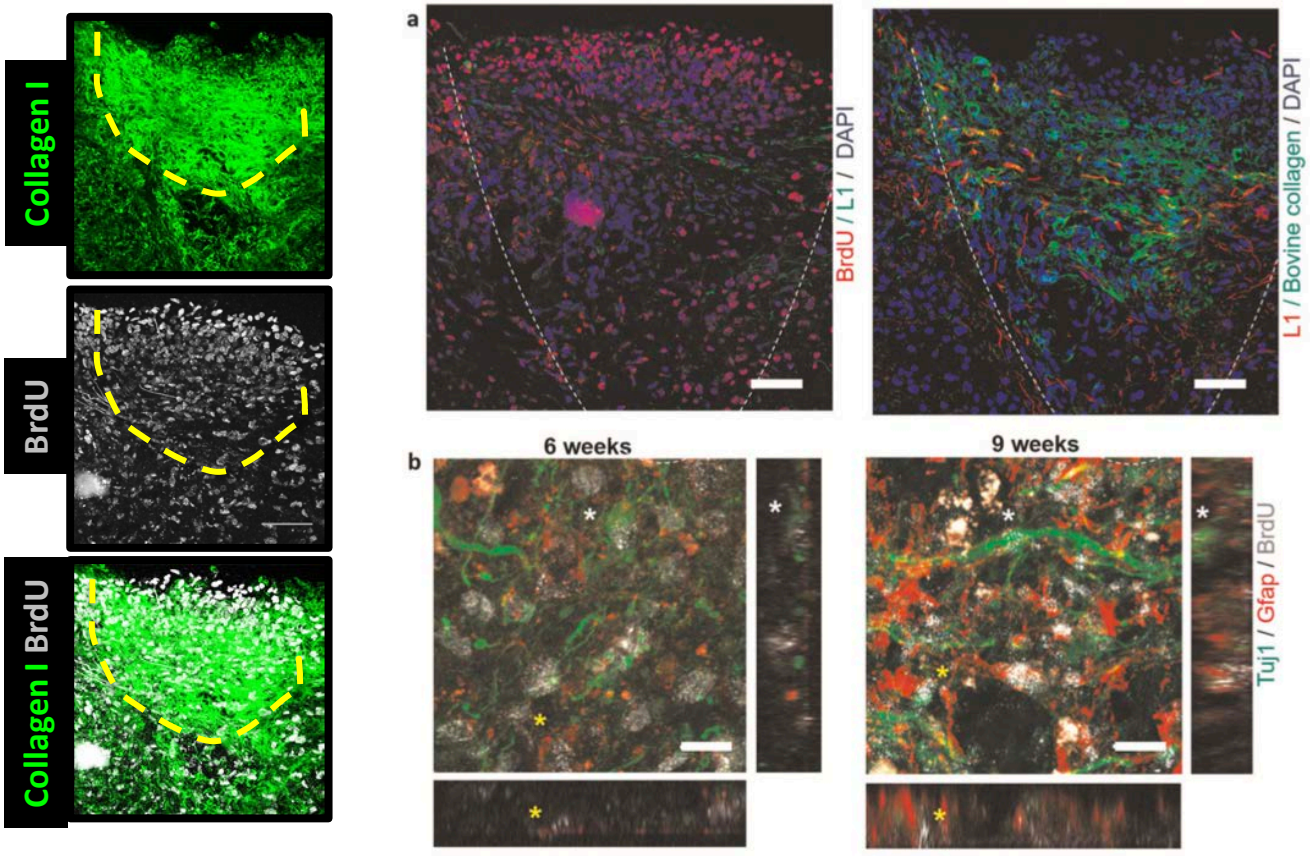


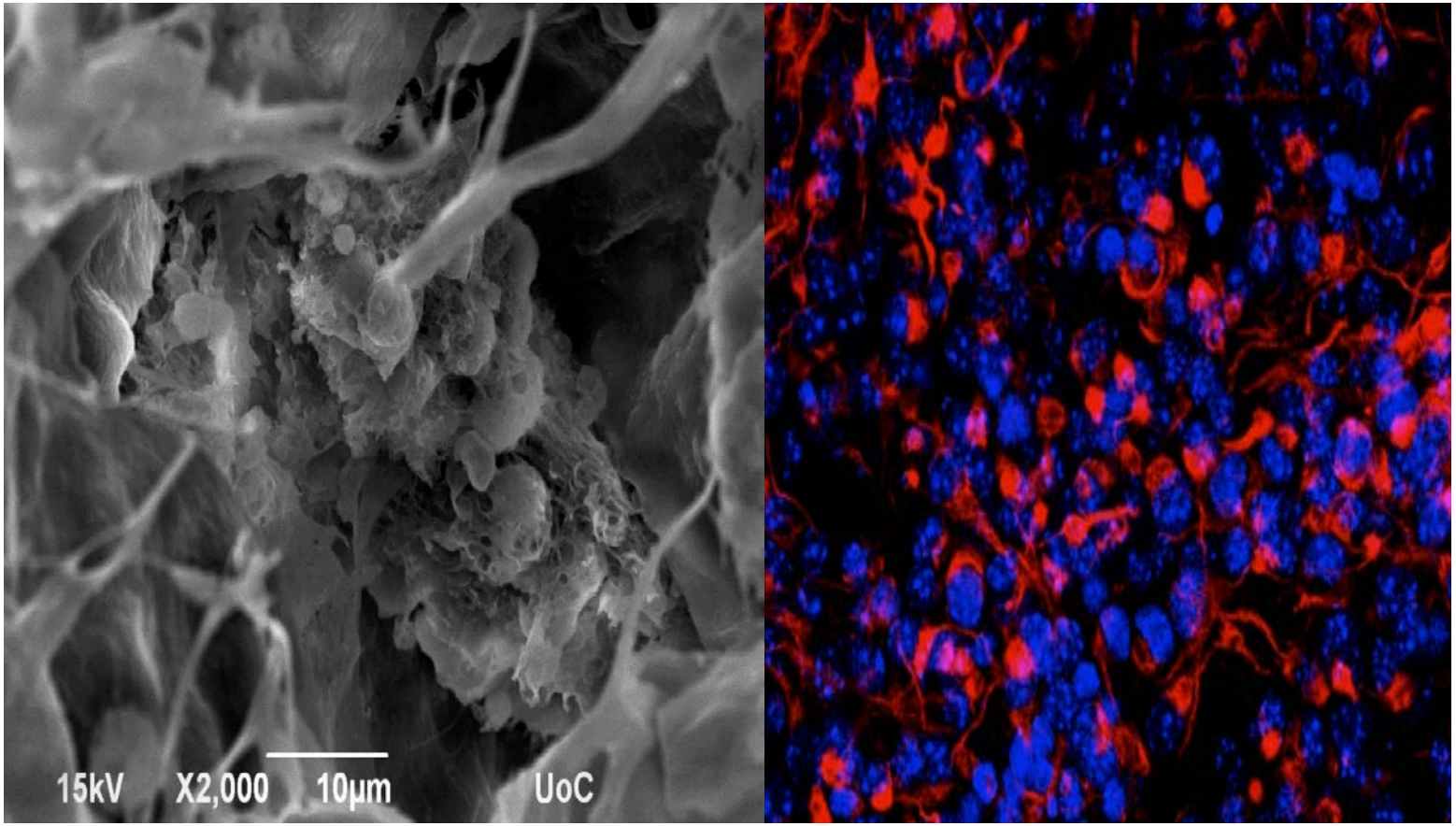
# BrdU-stained NSCs, differentiated in both neurons and astrocytes within the 3D collagen scaffold *in vivo*




- NSC-seeded grafts improved locomotion recovery in a mouse SCI model
- Also they reduced astrogliosis, enhance angiogenesis and axonal elongation
- Grafted NSCs differentiated into both neurons and astrocytes
- Kourgiantaki et al Nature Regen Med 2021

# Porous Scaffolds for NSC Delivery

## **Bio-scaffolds:** Proven Carriers of human Neural Stem Cells



# Translating in humans …..
# Spinal cord injury

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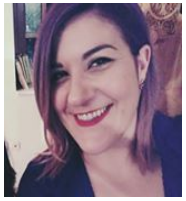
A.Kourgiantaki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