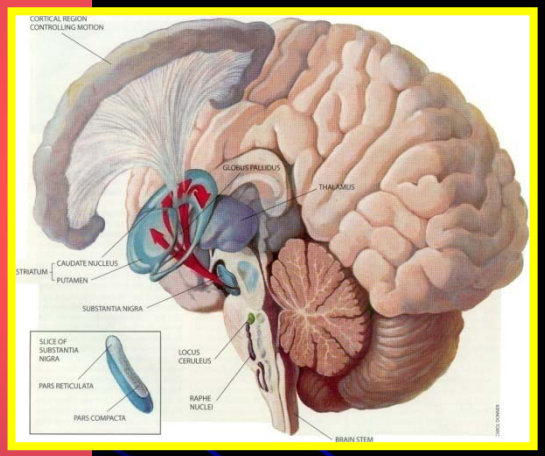
Neuroprotective Strategies in Neurodegenerative Disorders



Silvia A. Mandel

Eve Topf Center of Excellence for Neurodegenerative Diseases Research and Teaching

and

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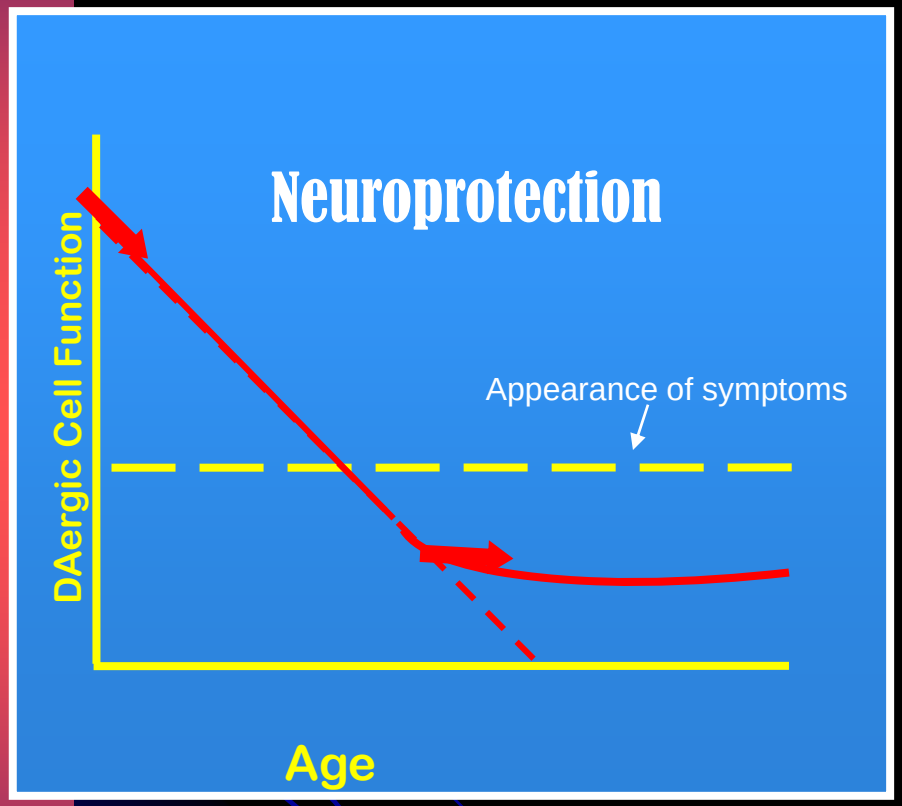
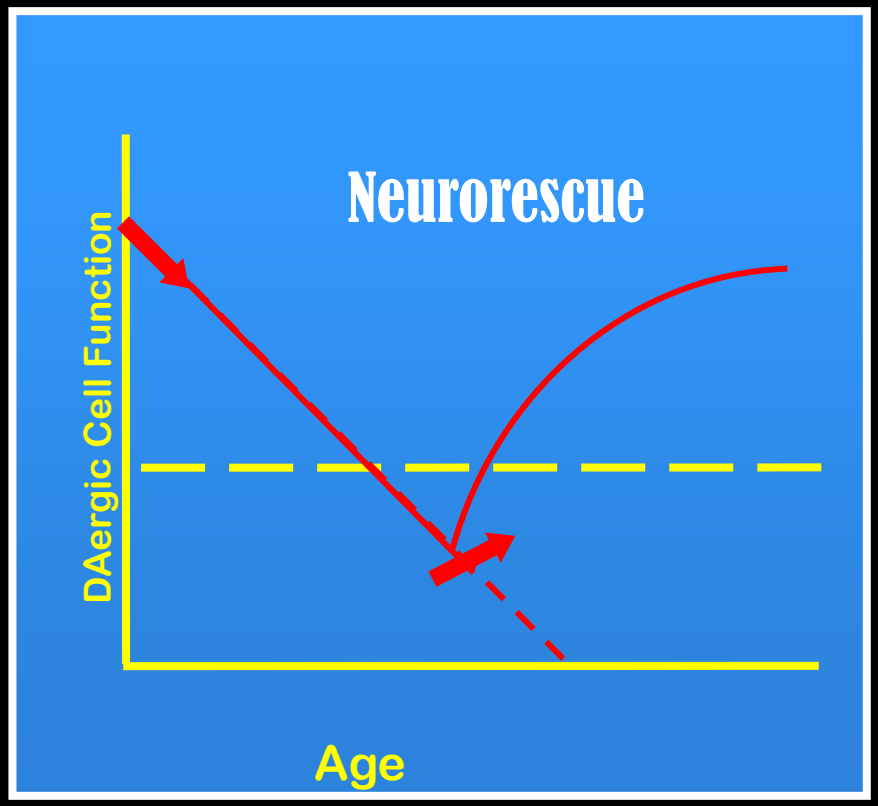
Technion-Rappaport Faculty of Medicine

Haifa, Israel


Neuroprotection
DAergic Cell Function
Appearance of symptoms
Age


Neurorescue
DAergic Cell Function
Age

GRAND CANYON EFFECT

Neuroprotection-Neurorescue In Neurodegenerative Diseases

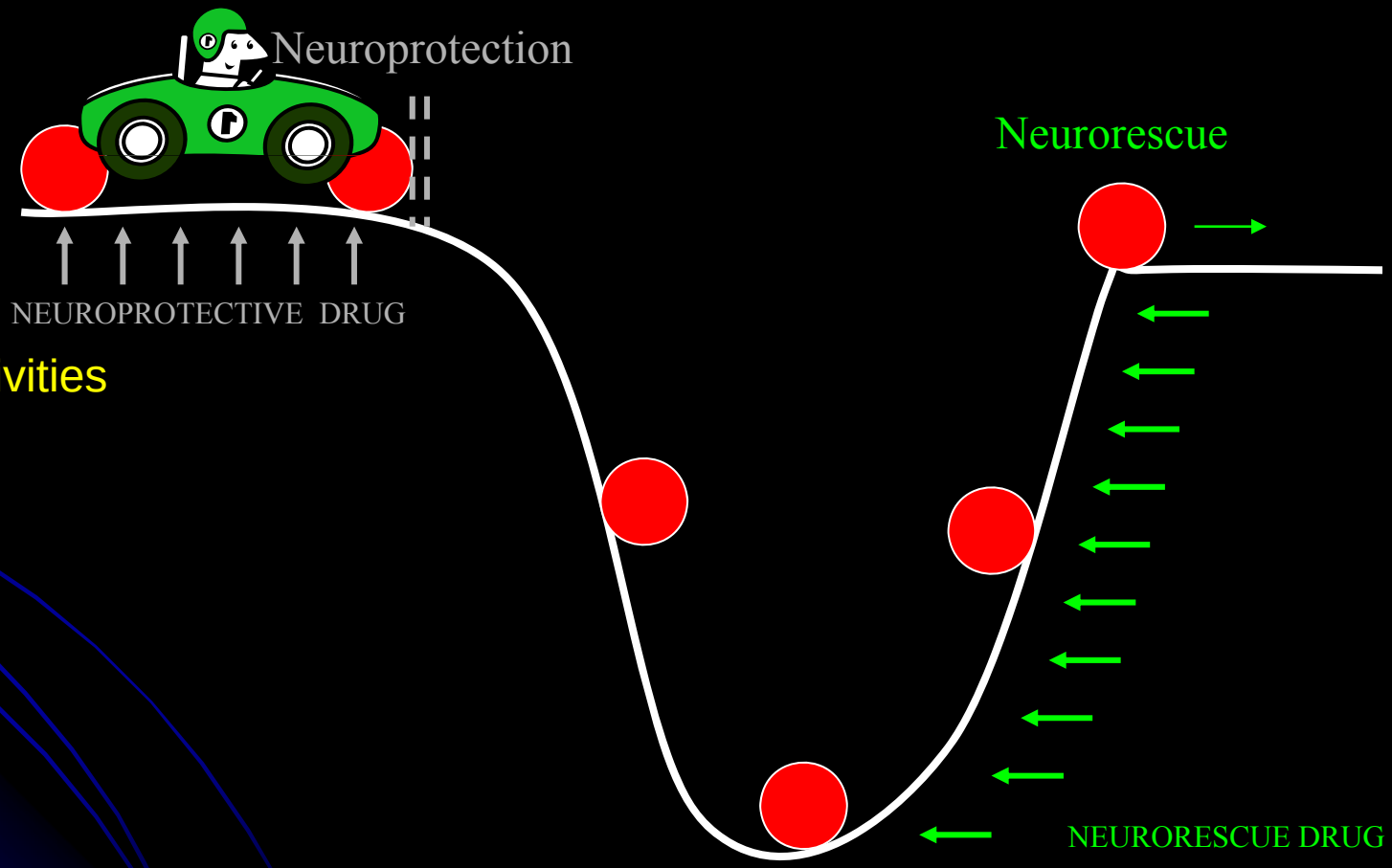
- Healthy food

Green tea

Red wine

Blueberries

- Exercise
- Intellectual activities



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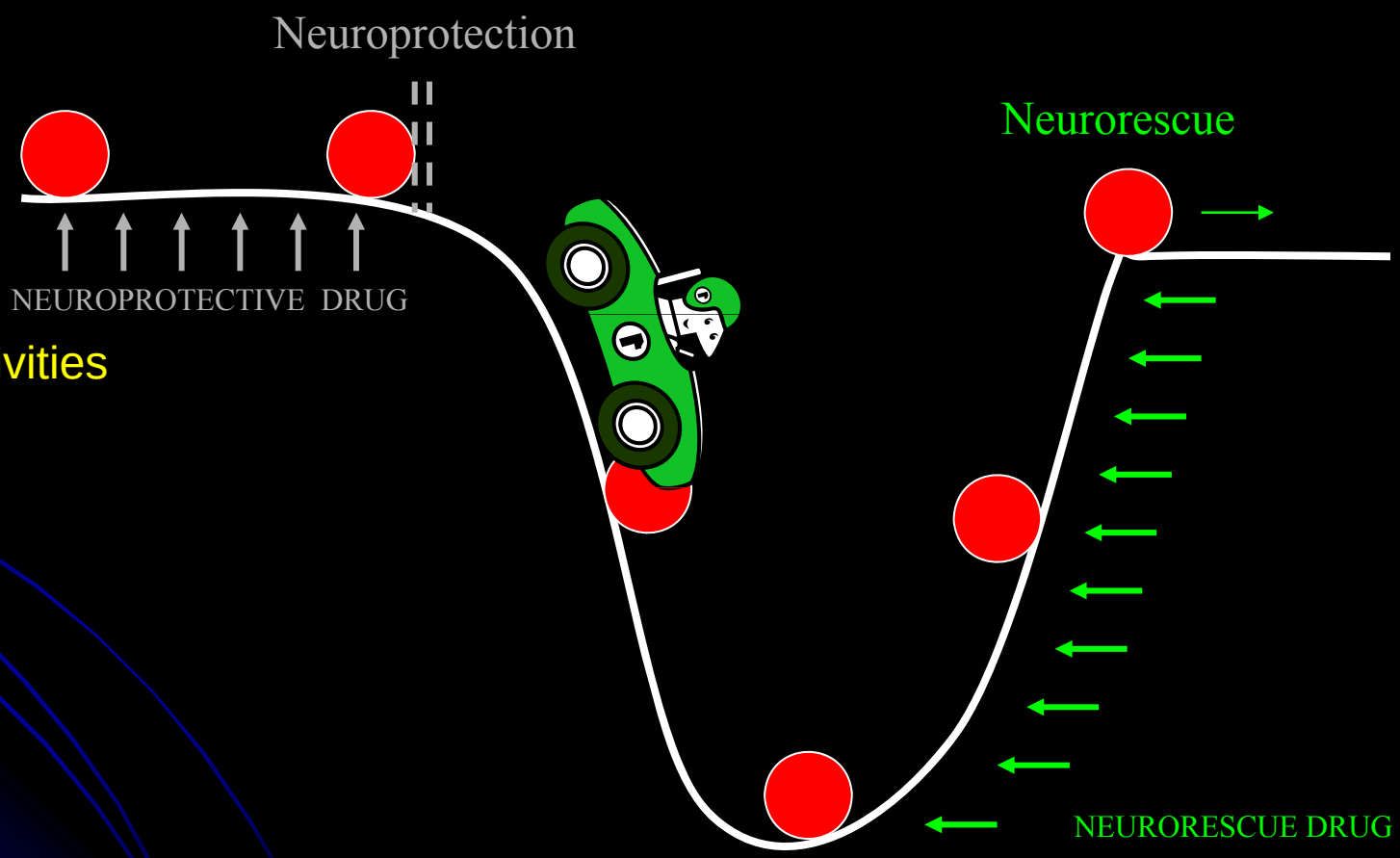

GRAND CANYON EFFECT

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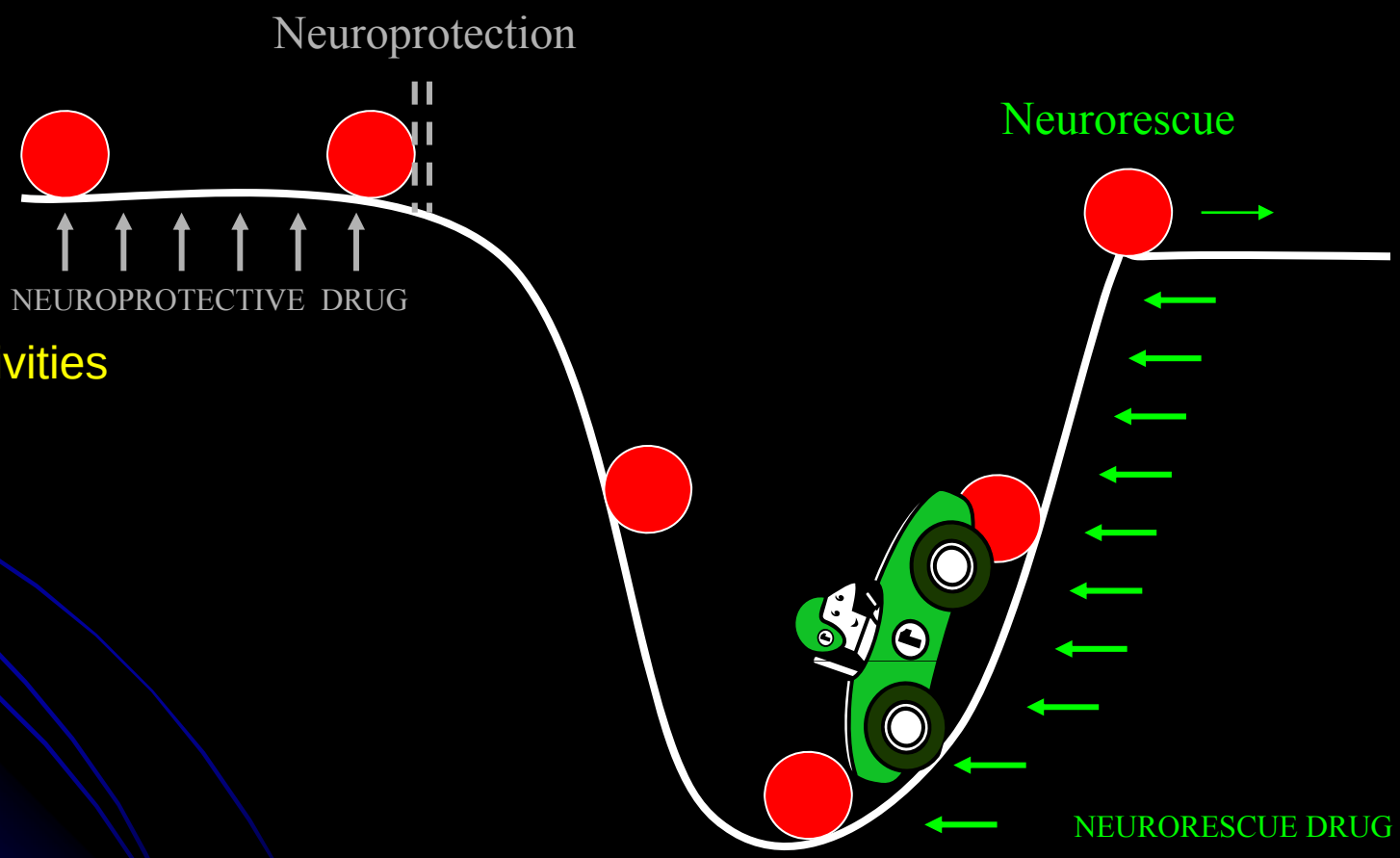


Neurodegeneration

Stroke:
Oxigen deprivation
Glucose deprivation
Glutamate/neurotoxins release

Traumatic brain and spinal-cord injury:
Physical damage
Glutamate/neurotoxin release
Ischemia

Aging
Malnutrition

- inflammation
- accumulation of iron
- increase in reactive oxygen and nitrogen species
- glutamatergic excitotoxicity
- mitochondrial (complex I deficiency)
- ubiquitin-proteasome system dysfunction
- abnormal protein folding and aggregation
- decline in growth factors levels

Oxidative stress
Metabolic impairment
Ion dyshomeostasis
DNA damage

mitochondrial membrane permeabilization

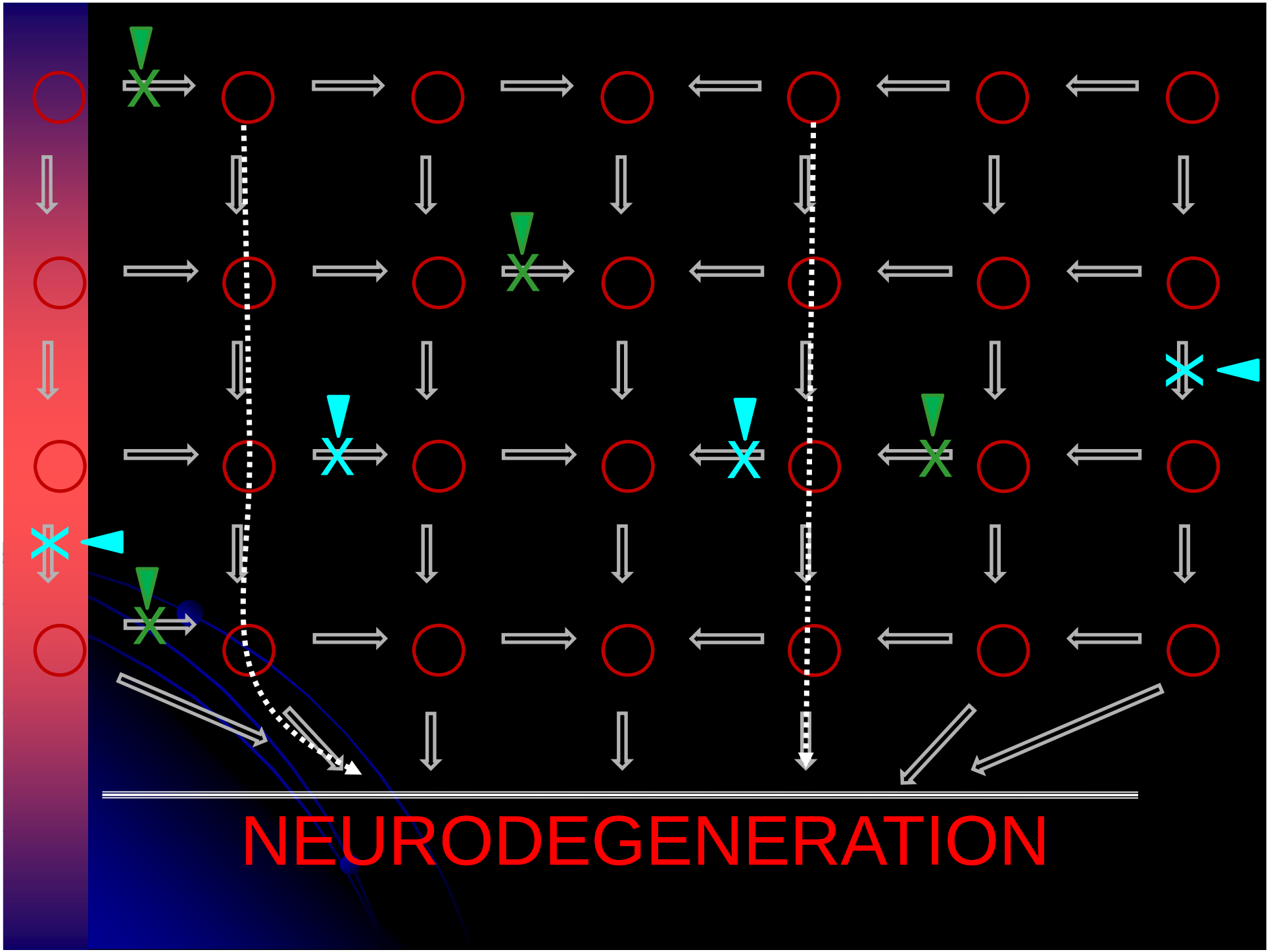
synaptic dysfunction
neuritic degeneration
neuronal death

Alzheimer's disease:
β-amyloid
Presenilins
Apolipoprotein E

Parkinson's disease:
α-synuclein, Parkin, LRRK2 etc
Toxins (rotenone, iron)

Huntington's disease:
Huntingtin (polyglutamine)

Amyotrophic Lateral Sclerosis (ALS)


NEURODEGENERATION

Therapeutic Approaches in Alzheimer’s disease

The main potential therapeutic approaches to multi- factorial AD

1. Cholinesterase inhibitors -Boosting residual cholinergic neurotransmission would reduce symptoms of the illness. Cholinesterase inhibitors are thought to accomplish this by inhibiting acetylcholinesterase.

2. Anti-excitotoxic strategies -Under pathologic conditions, excessive activation of receptors by glutamate kills cells, and there is evidence that the pathologic cascade of AD includes an excitotoxic component.
   Memantine, a non-competitive NMDA antagonist blocks glutamate-mediated excitotoxicity (in case of over-activation of the receptors) without alteration of the physiological activation of the NMDA receptor during neurotransmission.

3. Anti-inflammatory agents -Inhibit chronic inflammatory processes in the AD brain. There is abnormal activity of several aspects of immune function in AD (e.g., reactive microglia surround amyloid plaques, astrocyte proliferation, increased inflammatory cytokines and free radicals).
   Epidemiological evidence suggests that use of nonsteroidal anti-inflammatory medication earlier in life may reduce the risk of developing AD.

4. Antiamyloid Strategies - According to the amyloid hypothesis, inhibition of β- or γ-secretase could reduce Aβ production and diminish subsequent pathologic consequences of its abnormal regulation.

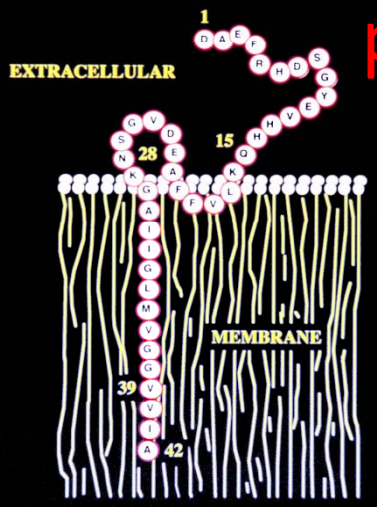
5. Amyloid vaccine - immunization with aggregated Aβ induces antibody response. Elicited antibody binds to and facilitates clearance of Aβ.

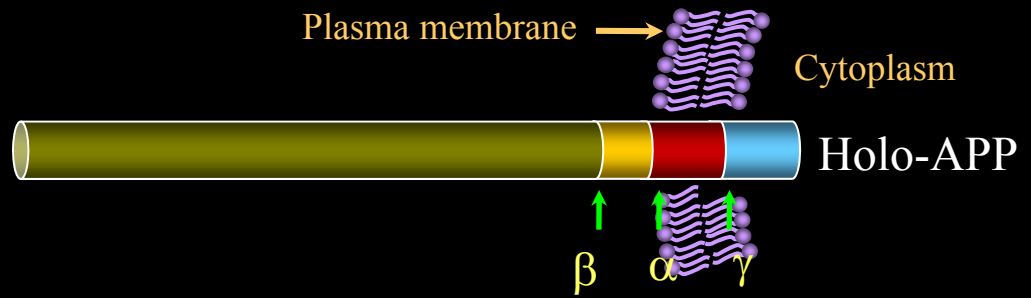
6. Metal complexing agents and antioxidants – There are theoretical reasons as well as clinical data to suggest that free radical damage may cause neuronal degeneration in a range of conditions including aging and AD. Studies have found evidence of increased levels of oxidative damage to neurons, proteins, DNA, and lipids in AD as well as accumulation of iron at sites where neurons degenerate in AD. Thus, treatment with iron- chelators will:

1. Abstract iron, copper and zinc from Aβ plaques.
2. Inhibit iron and copper- dependent neurotoxicity.
3. Facilitate amyloid plaque disaggregation.

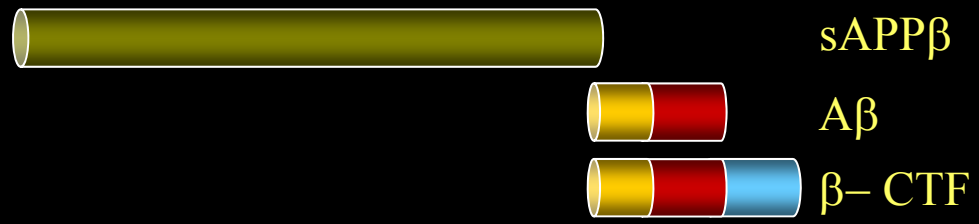
The ClinicalTrials.gov (http://clinicaltrials.gov/) currently contains around 30 registered clinical trials in PD and AD with antioxidants and nutritional supplements (e.g. vitamins E and C, alpha-lipoic acid, creatine, melatonin, omega-3 polyunsaturated fatty acids, CoQ10, curcumin, resveratrol, glucose, malate), individually or in cocktail formulation that are supported by The National Institute of Health (NIH; USA), other federal agencies and private industry.

Therapeutic approaches targeting amyloid β-protein production and oligomerization

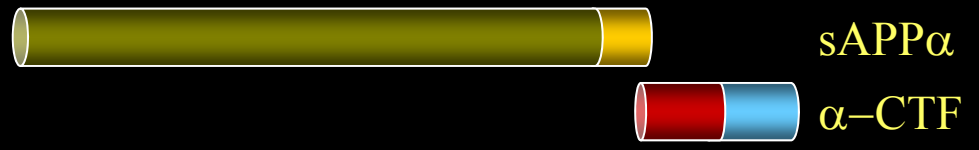




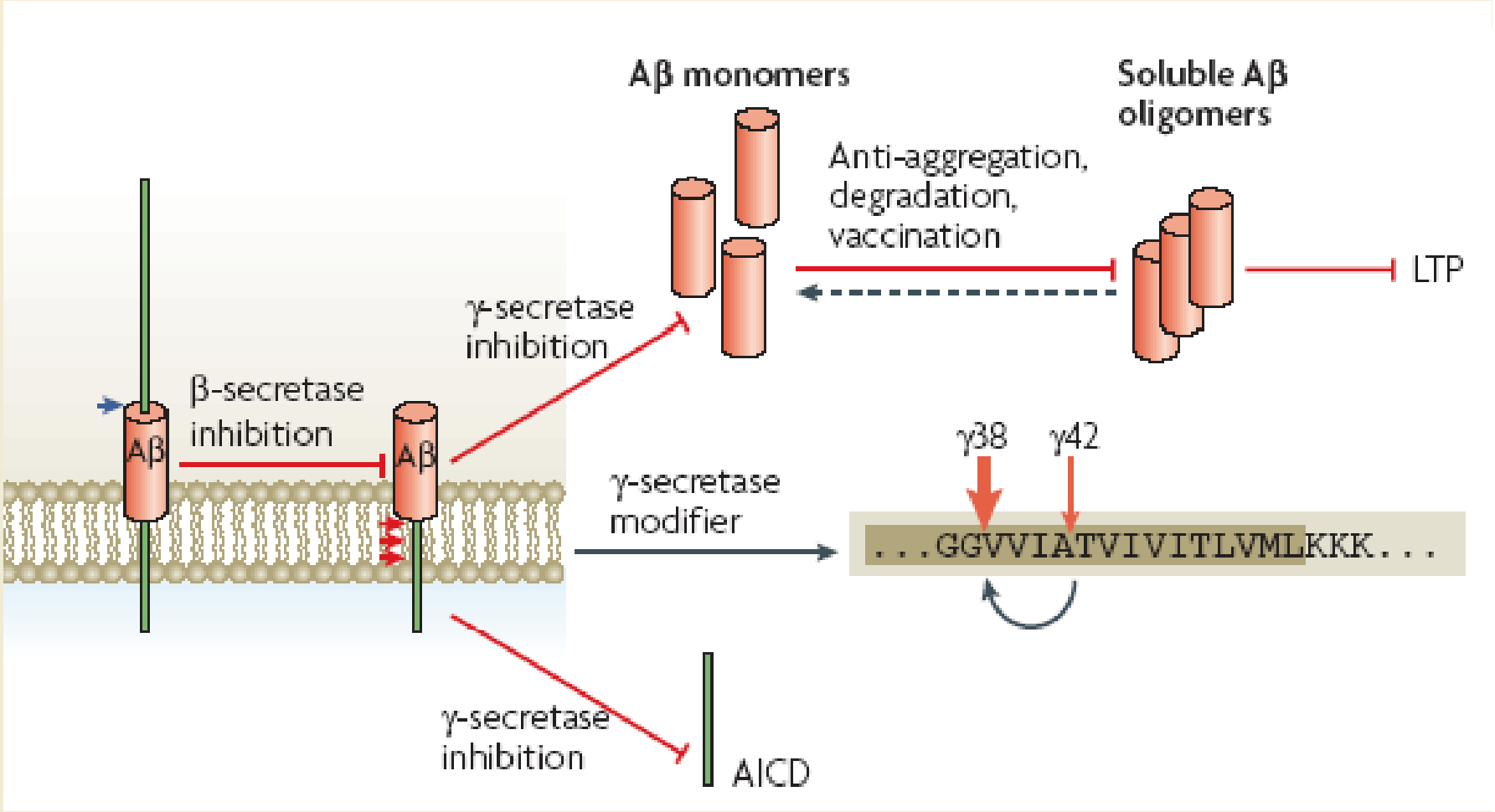
Amyloidogenic derivatives:



Non- amyloidogenic derivatives:



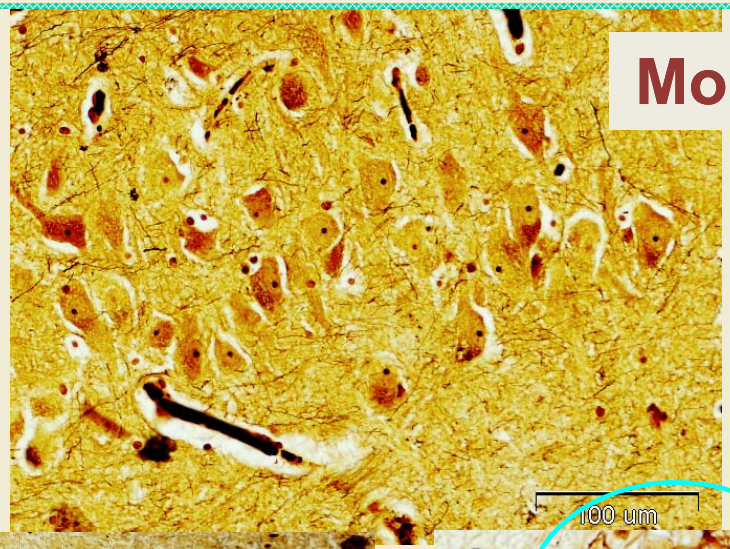
Therapeutic approaches targeting amyloid β-protein production and oligomerization.



Pathologically AD is defined by:

1. Neuronal loss
2. Extracellular insoluble deposition of amyloid or senile plaques (composed mainly of Aβ)
3. Intracellular lesions: neurofibrillary tangles (composed mainly of hyperphosphorylated microtubule associated protein, tau)

Control

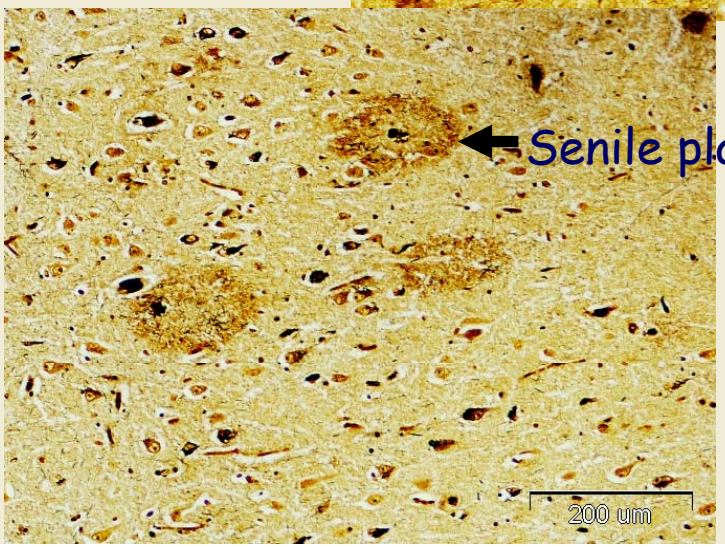


Molecular Hallmarks

β-Amyloid

Tau

Alzheimer's disease



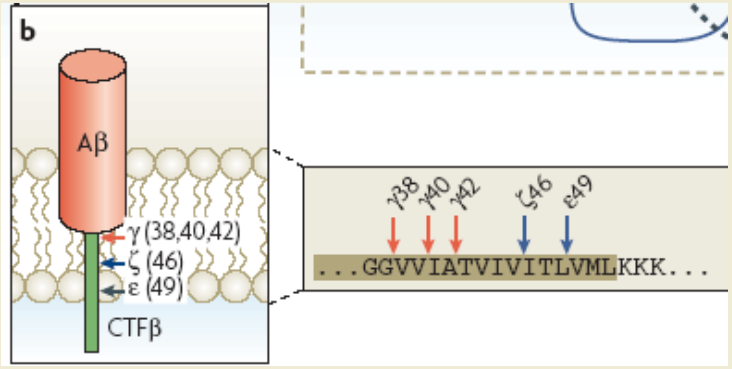
Targeting Aβ oligomers

- γ-secretase modulators
- The non-steroidal anti-inflammatory drugs (NSAIDs) **R-flurbiprofen (Flurizan)**, which lacks cyclo-oxygenase inhibitory activity,

Does not block the γ-secretase cleavage but rather shift its cleavage site from the rapidly aggregating 42-residue variant to the far less amyloidogenic 38-residue form (shaded amino acids are in the transmembrane domain). This shift will not affect potential signalling functions of γ-secretase substrates.

Myriad Genetics: Results of U.S. Phase 3 Trial of Flurizan™ in Alzheimer's Disease:

Did not achieve statistical significance on either of its primary endpoints -- cognition and activities of daily living.



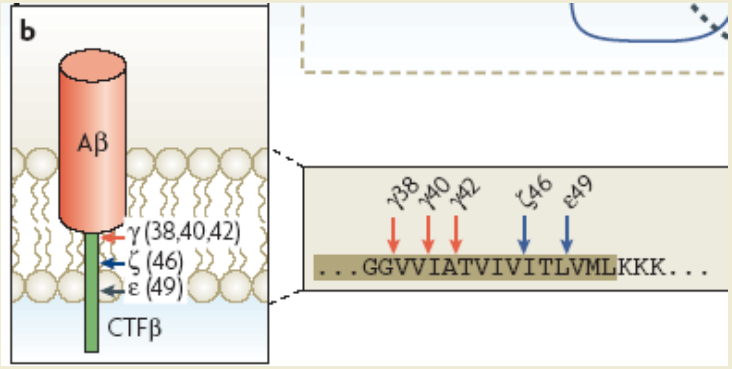
Targeting Aβ oligomers

- γ-secretase modulators

Semagacestat (Eli Lilly & Co.)

Halted in August when preliminary results of an ongoing phase 3 study showed that the drug failed to slow disease progression among more than 2,600 patients with mild to moderate AD, and actually worsened their cognitive decline and ability to perform activities of daily living.

In addition, semagacestat was associated with an increased risk of skin cancer.



Targeting Aβ oligomers

- Active and passive immunization against amyloid-beta (Abeta) are employed to clear and reduce cerebral Abeta towards treatment of AD patients.

- Limitation: A Phase 2 trial of an Aβ1–42 vaccine in patients with AD immunization with Aβ42 (AN1792, Elan Pharmaceuticals) in September, 2000 was associated with the development of a T-cell-mediated, autoimmune meningoencephalitis in 6% of patients, leading to cessation of dosing.

Long-term effects of $A\beta_{42}$ i disease: follow-up of a ran phase I trial

Clive Holmes, Delphine Boche, David Wilkinson, Ghasem Yadeg James W Neal, Elina Zotova, James A R Nicoll

Lancet 2008; 372: 216–23

See Comment page 180

Division of Clinical Neurosciences (Prof C Holmes MRCPsych, D Boche PhD, D Wilkinson FRCPsych, E Zotova BSc, Prof J A R Nicoll FRCPath) and Public Health Sciences and Medical Statistics Group (RDSU), School of Medicine (G Yadegarfar PhD), University of Southampton, Southampton, UK; Moorgreen Hospital, Hampshire Partnership Trust, Southampton, UK (Prof C Holmes, D Wilkinson, V Hopkins RMN); Neuropathology, Department of Cellular Pathology, Southampton University Hospitals NHS Trust, Southampton, UK (Prof J A R Nicoll); Biostat and Epidemiology Department, School of Health Sciences, Isfahan University of Medical Sciences, Isfahan, Iran (G Yadegarfar); Department of Geriatric Medicine and Department of Pathology, University of Wales, Cardiff, UK (A Bayer MRCP, J W Neal FRCPath); Research

Summary

Background Immunisation of patients with Alzhei amyloid plaques from the brain. Our aim was to plaque removal, and long-term clinical outcomes.

Methods In June, 2003, consent for long-term clin both, was sought from 80 patients (or their carers) of immunisation with $A\beta_{42}$ (AN1792, Elan Pharmac in September, 2006. Plaques were assessed in tern (Aβ load) and in terms of characteristic histological until severe dementia or death was assessed with

Findings 20 participants—15 in the AN1792 grou further 22 patients—19 in the AN1792 group, th deceased patients, all in the AN1792 group, had gi die with Alzheimer's disease was excluded. In the who were examined neuropathologically, mean Aβ matched for age at death (2·1% [SE 0·7] in treate 95% CI 0·6–5·4; p=0·02). Although there was co amo nmunised participants, the degree of pla atta during the treatment study period (Krusk und nt post-mortem assessment, including the dem before death. In the whole cohort, there 0·4 1; p=0·86) or of an improvement in the ti gro sus the placebo group.

Interpretation Although immunisation with Aβ, Alzheimer's disease, this clearance did not preven

Funding Alzheimer's Research Trust, Medical Res

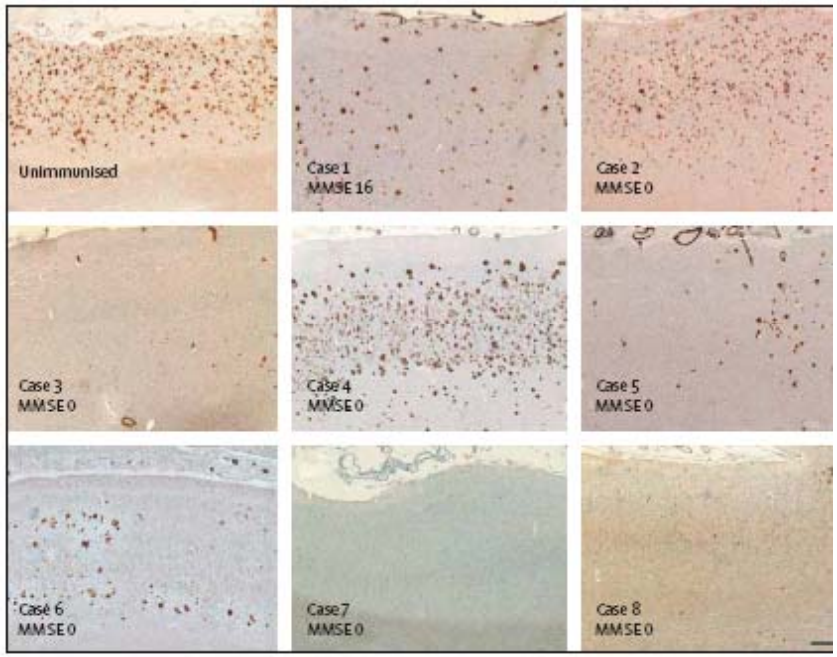


Figure 2: Histological patterns of Aβ in the temporal lobe neocortex after immunisation with AN1792
An unimmunised control (top left) has a high density of plaques. Cases 1–8 are all patients who were immunised with $A\beta_{42}$. Case 1 died 4 months after the first immunisation dose and showed an early stage of A removal. Cases 2–8 survived 20–64 months after first immunisation dose. Case 2 did not develop anti-Aβ antibodies and showed no evidence of plaque clearance. Cases 3–6 showed an intermediate range of plaque clearance. Cases 7 and 8 showed very extensive (case 8) to nearly complete (case 7) removal of Aβ plaques throughout the cerebral cortex. All the long-term survivors (ie, cases 2–8) continued to have progressive dementia with cognitive function declining to an unrecordable level (ie, MMSE=0) before death. Scale bar=0·5 mm.

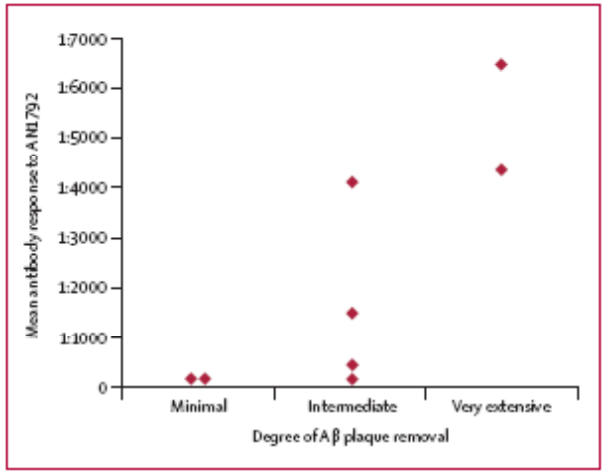


Figure 3: Mean antibody response to AN1792 and Aβ plaque removal

Amyloid-β Immunotherapy continues with more than 13 therapies in clinical trials (http://www.clinicaltrials.gov)

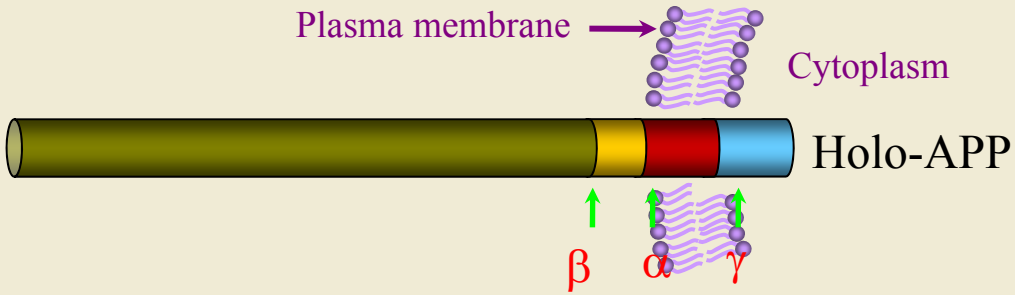
Can Alzheimer Disease Be Prevented by Amyloid-β Immunotherapy?
Cynthia A. Lemere; Eliezer Masliah
Nat Rev Neurol. 2010;6(2):108-119

Targeting Aβ oligomers

- Active and passive immunization against amyloid-beta (Abeta) are employed to clear and reduce cerebral Abeta towards treatment of AD patients. Limitation: A Phase 2 trial of an Aβ1–42 vaccine in patients with AD was associated with the development of a T-cell-mediated, autoimmune meningoencephalitis in 6% of patients, leading to cessation of dosing.

- Inhibition of Abeta production via antibodies against the beta-secretase cleavage site of the amyloid precursor protein (APP).

Solomon B (Tel Aviv univ). anti-APP beta-site antibodies to Tg2576 transgenic mice improved mouse cognitive functions associated with a reduction in both brain inflammation and the incidence of microhemorrhage. Furthermore, antibody treatment did not induce any peripheral autoimmunity responses.



Targeting Aβ oligomers

- Selective degradation of oligomers and fibrils and destabilization of Aβ oligomers.

Proteoglycans and their constituent glycosaminoglycans are associated with amyloid plaques in AD brain tissue and might stabilize the aggregates and make them more resistant to proteolysis.

- One compound ("Alzhemed", tramiprosate,) designed to prevent Aβ from interacting with glycosaminoglycans and proteoglycans

Failed at Phase 3 AD trial

Targeting amyloid-beta

- Progress

Mechanism of action	Product	Company
Aβ Secretase Inhibitors	R-flurbiprofen	Myriad Genetics
	LY450139	Eli Lilly
Aβ Immunization / mAbs	Bapineuzumab (AAB-001)	Elan/Wyeth
	RN1219	Rinat/Pfizer
	CAD-106	Cytos Biotechnology
Aβ Aggregation inhibitors	Tramiprosate	Neurochem
	PBT2	Prana Biotechnology
	AZD-103	Transition Therapeutics/Elan

Failed Ongoing

JANSSEN (TAU) – ApoE4 excluded

Expert Opin. Invest. Drugs 2007, 16(8), 1183-1196

Targeting Tau and Microtubules

- Exciting potential for disease modification
- Fundamental mechanism important across a number of CNS diseases

Mechanism of action	Product	Company	Phase
Microtubule and tau modulators	AL-108	Allon Therapeutics	II
	NP031112	Neuropharma	I
	SAR-502250	Sanofi Aventis	Preclinical
	SRN-003-556	Sirenade	Preclinical

Allon (TAU) continues

Expert Opin. Invest. Drugs 2007, 16(8), 1183-1196

Neuroprotection in Parkinson’s disease

PD Research Portfolio

- Human genetics - Identifying new genes involved in familial PD

- Genomics - Using information from the DNA sequence of the human genome to aid in genetic studies, and to search for the expression of genes associated with the disease

- Animal Models: Transgenic mice, transgenic rats and Drosophila (fruit flies)

- Assay development and high throughput drug screening

- Cell replacement/Stem cell research as potential for replacing dying neurons

- Providing important trophic factors to dying cells and Gene Therapy and Diagnostic Biomarkers

Current treatments for PD

- Levodopa drugs
- Dopamine agonists
- Catechol-O-methyl transferase (COMT) inhibitors
- Anticholinergics
- MAO-B inhibitors
- Amantidine

New PD Treatments on the Horizon

- Symptomatic drugs

Opioid antagonists
NMDA antagonists
Adenosine A2a receptor antagonists. Interact with the specific dopamine receptor subtype D2 in the basal ganglia, making it more sensitive to dopamine. SYN-115 Phase IIa ended

- Neuroprotective agents
- Neural tissue transplants
- Cell implants e.g. genetically engineered dopamine producing cells

Drugs Selected for Investigation In the Neuroprotection Clinical Trial

Drug	Primary Mechanism
Coenzyme Q10	Antioxidant/Mitochondrial Stabilizer
Creatine	Mitochondrial Stabilizer
GPI 1485	Trophic Factor
Minocycline	Anti-inflammatory/Anti-apoptotic
Rasagiline	Anti-oxidant/Anti-apoptotic

Drugs Under Consideration for Future Study

Drug	Primary Mechanism
Amantadine	Glutamate Antagonist
Ascorbic Acid	Antioxidant
Azulenyl Nitrone	Antioxidant
Caffeine	Adenosine Antagonist
COX I-II Inhibitors	Anti-inflammatory
Erythropoietin	Undetermined/Multiple
Estrogen	Undetermined/Multiple
Folate	Undetermined/Multiple
GM-1 ganglioside	Trophic Factor
Modafanil	Unknown
N-acetyl Cysteine	Antioxidant
Nicotine	Unknown
Pramipexole/Ropinirole	Antioxidant/Vesicular Trafficking
Remacemide	Glutamate Antagonist
Selegiline	Antioxidant/Anti-apoptotic

❖Providing important trophic factors to dying cells

Glial-derived neurotrophic factor (GDNF), a protein thought to affect dopamine synthesis, stored and uptake. (Amgen Inc.)

Subjects having pumps inserted in their abdomen and holes drilled in their skull.

Phase II trial. A six-month placebo phase during which time half of the research participants would receive no treatment whatsoever, while the other half received GDNF

In 2004 Amgen received results from certain primate studies on GDNF in which four out of seventy monkeys that were given GDNF suffered cerebellar toxicity at doses 10 times higher than used in humans. Could result of sudden withdrawal of the drug rather than the drug itself ??
Some patients developed antibodies to GDNF

Trial was stopped

Recent lawsuits involving the safety of drugs like Vioxx were a huge factor

❖Vaccination (preclinical)

Triggering the immune system to prevent neuronal death and its manifestation into PD is promising. (Benner et al., PNAS, 2004, 101: 9435-9440)

Ceregene_ A biotechnology company, Gene therapy with GDNF family ligand, **Neurturin**.
In April 2010, the company announced further phase II trials of **Neurturin**, even though previous attempts found no evidence of benefit for Parkinson's disease symptoms in patients*: two autopsies of patients from the first trial suggested that neurturin had failed to stimulate new dopaminergic connections from the substantia nigra. Delivery problem?*

TRANSEURO Europe's premiere clinical study on the treatment of Parkinson's Disease (PD) patients using a cell therapy approach is a 5-year Collaborative Project supported through the FP7 European Commission Health programme, contract number 242003.

Sources for implantable cells

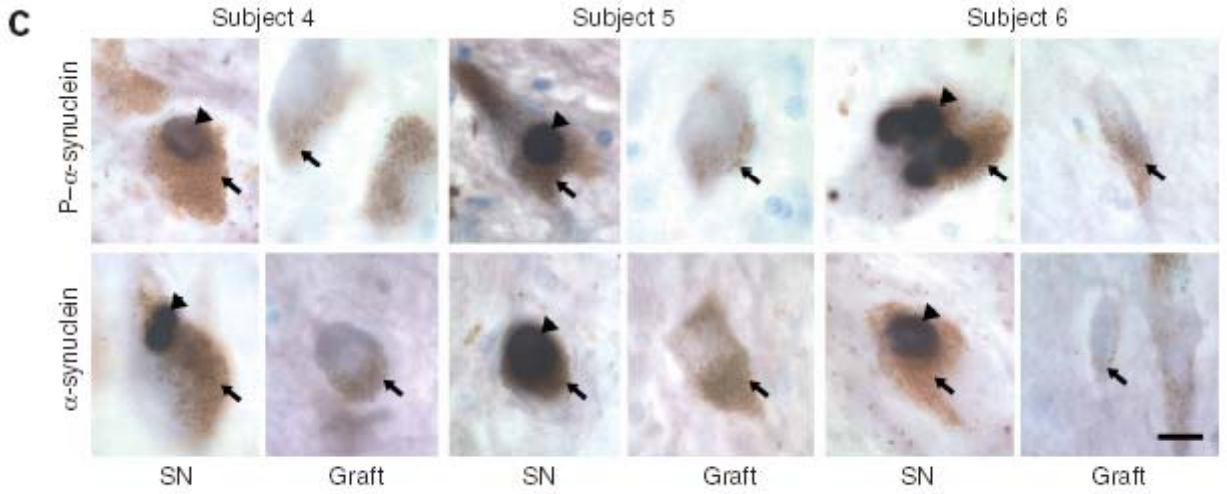
•Fetal tissue and cultured stem cells from embryonic sources
•Cells from the adrenal medulla and retinal pigment epithelium (RPE) as source of DA.

• Recent advances: induced pluripotent stem cells, which are produced by genetic treatment of adult cells from skin or other tissues, may provide cells suitable for therapeutic transplantation, as well as for in vitro drug screening.

DA neurons implanted into people with PD survive without pathology for 14 years

- Postmortem analysis of 5 subjects with PD 9–14 years after transplantation of fetal midbrain cell suspensions revealed surviving grafts that included dopamine and serotonin neurons without pathology despite ongoing degeneration of DA neurons in the host brain.

DA neurons
Lewy bodies →



Mendez I., Viñuela A., Nat Med, 2008

- **Brief Communication**
- *Nature Medicine* **14**, 504 – 506 (2008)

Published online: 6 April 2008 | doi:10.1038/nm1747

Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease

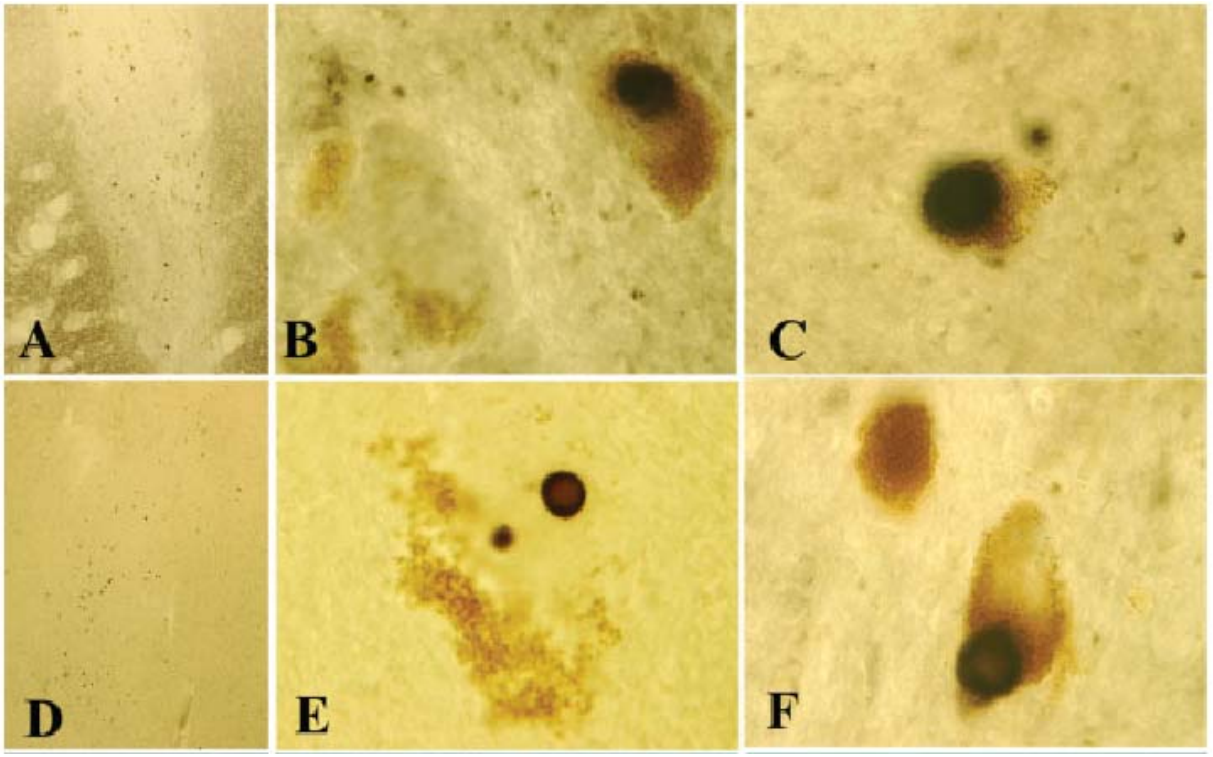
Jeffrey H Kordower[1], Yaping Chu[1], Robert A Hauser[2], Thomas B Freeman[3] & C Warren Olanow[4]

- A case report from 2008 described **pathological changes** within the grafted neurons of a patient with PD who died 14 years posttransplantation (as evidenced by α-synuclein and ubiquitin staining).

Main results

- Some of the grafted neurons were identical in staining pattern and morphology to neurons of the host striatum.

A,B- α-synuclein in transplanted DA neurons. **C**- α-synuclein in host Substantia Nigra. **D,E**- ubiquitin in transplanted neurons. **F**- ubiquitinin host Substantia Nigra.



Kordower JH., Chu Y., Olanow CW., Nature Medicine 14, 2008

- **Brief Communication**
- *Nature Medicine* 14, 501–503 (2008) Published online: 6 April 2008 | doi:10.1038/nm1746
- **Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation**

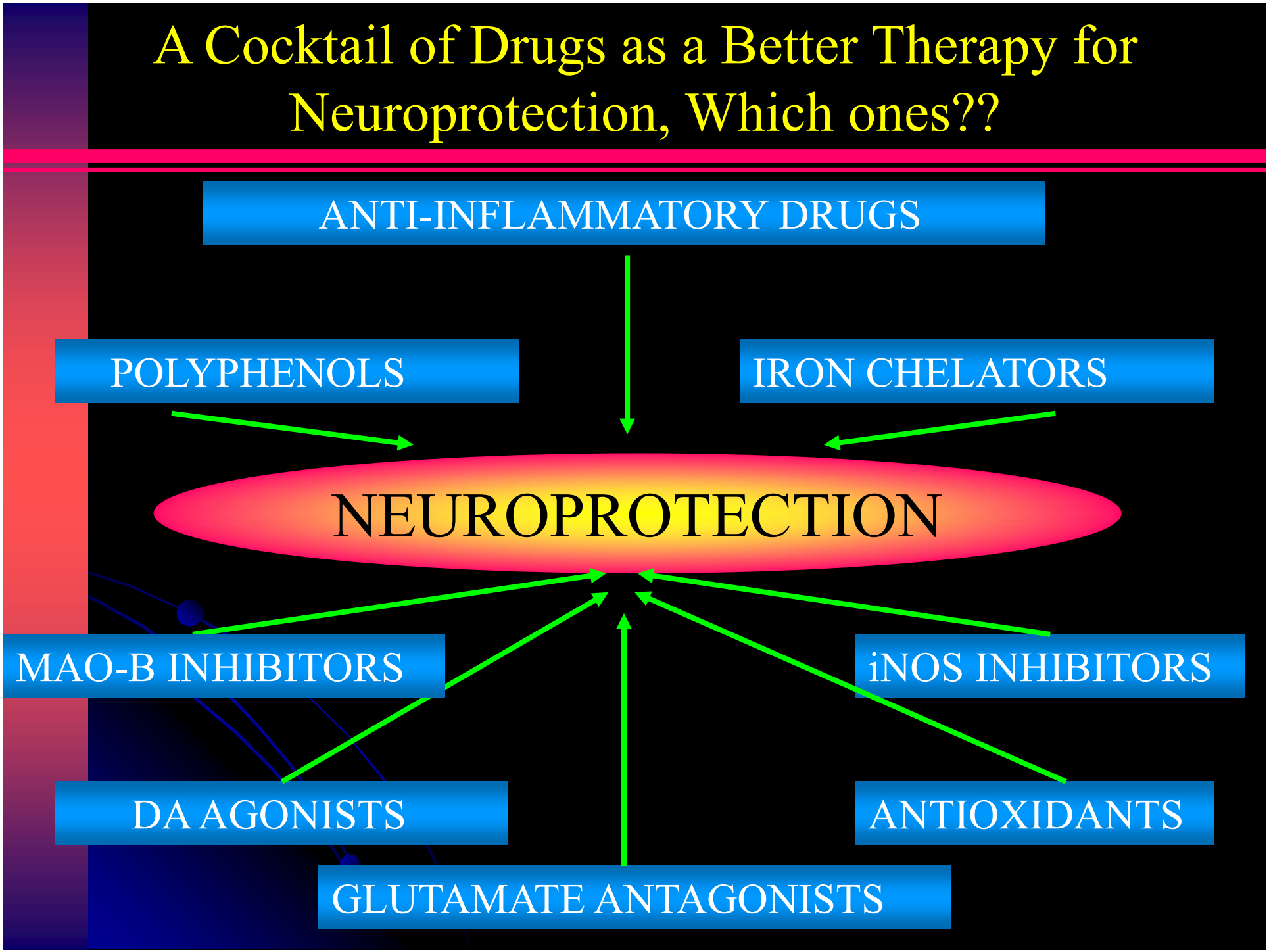
Jia-Yi Li[1], Elisabet Englund[2], Janice L Holton[3], Denis Soulet[1], Peter Hagell[4], Andrew J Lees[3], Tammaryn Lashley[3], Niall P Quinn[5], Stig Rehncrona[6], Anders Björklund[7], Håkan Widner[4], Tamas Revesz[3,9], Olle Lindvall[4,8,9] & Patrik Brundin[1,9]

The disease seems to have spread from the host to the graft.

Curing Parkinson disease with grafted tissue?

Present perception of neurodegeneration: multi-etiological progressive nature involving various pathological and molecular events occurring in parallel or sequentially.

A Cocktail of Drugs as a Better Therapy for Neuroprotection, Which ones??



Novel Pharmacological Strategies for Neuroprotection

Polypharmacology- Cocktail of drugs

Multifunctional Compounds- Drugs acting on various brain targets

Neuroprotection-Neurorescue In Neurodegenerative Diseases

- Healthy food

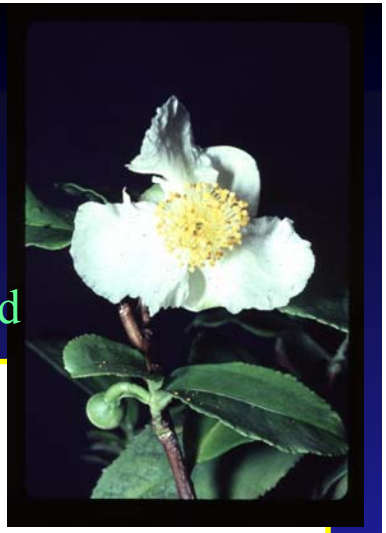
Green tea	Ginko Biloba
Red wine	Pomegranate
Blueberries	Turmeric

- Exercise

- Intellectual activities

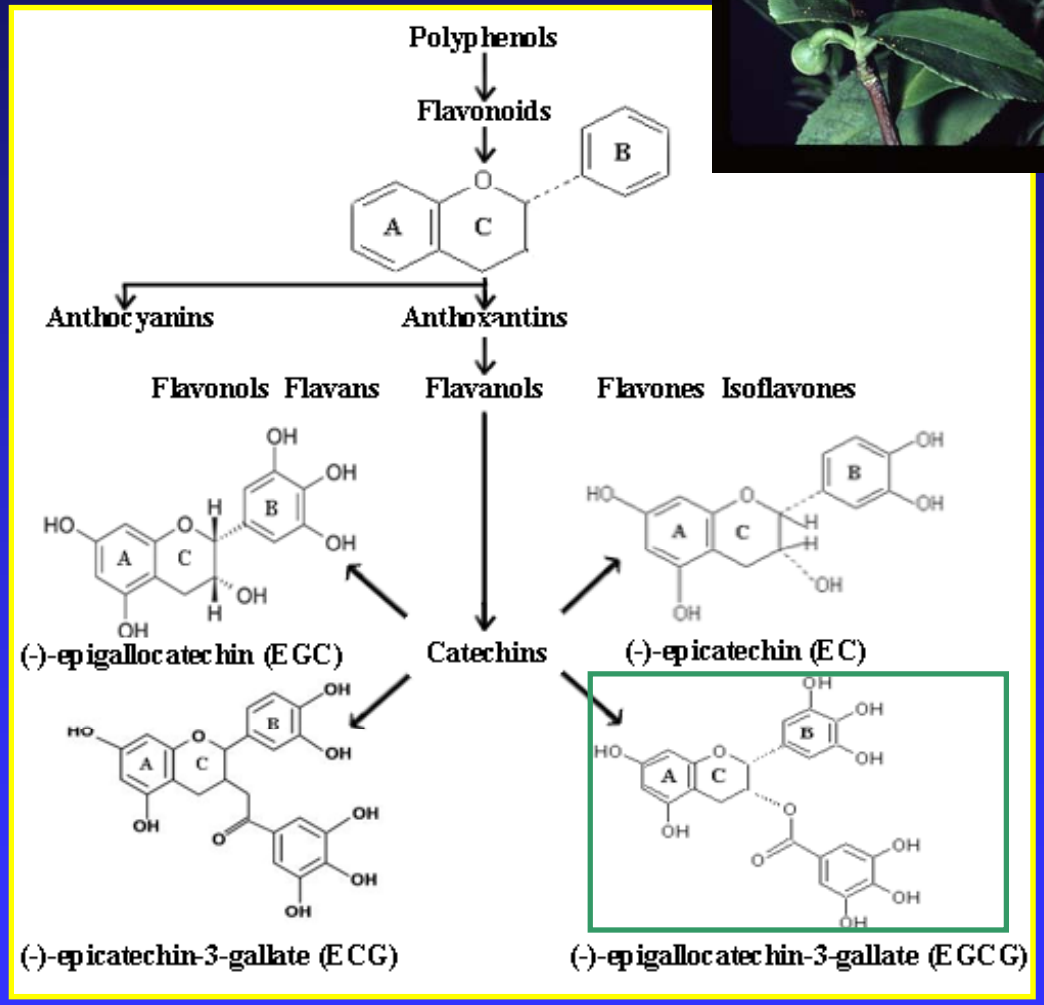
Green tea polyphenols

Green and black teas come from the same plant Camellia sinensis
The differences are in the way they are grown, harvested and processed



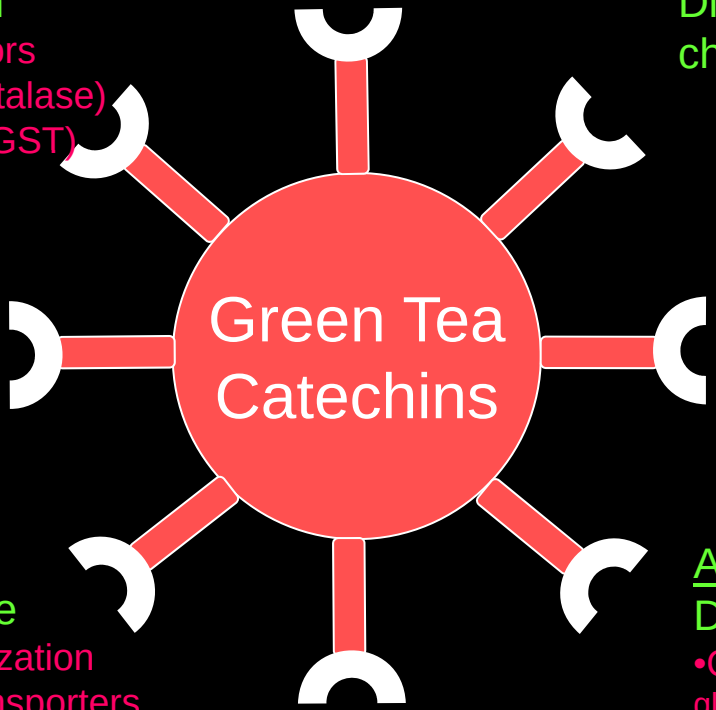
- potent oxygen and nitric radical scavenging
- indirect antioxidant effects through activation of transcription factors and antioxidant enzymes
- iron chelating
- anti-inflammatory activities
- neuroprotective in vitro and in vivo against several neuroroxins

Polyphenol content in green tea extract
EGCG>EGC> EC > ECG



Epidem Brain perm

Multifunctional Activities of Green Tea Catechins



Reactive oxygen and nitric oxide species radical scavengers

Indirect antioxidants through
- activation of transcription factors
- antioxidant enzymes (SOD, catalase)
- Phase II detoxifying enzymes (GST)

Divalent metal (iron, copper) chelators

Anti-inflammatory
Anti-bacterial
Anti-viral
Anti-fungal

Anti-proliferative
Anti-carcinogenic
Anti-angiogenic

Neuroprotective/neurorescue
- Mitochondrial membrane stabilization
- Inhibition of DA presynaptic transporters and catechol-O-methyltransferase (COMT) activity
- Activation of PKC
- Decrease of bad, bax
- Decrease of APP, Aβ and increase of soluble APPα

Cardiovascular system
↓ Oxidized LDL
Artherosclerosis
cholesterol

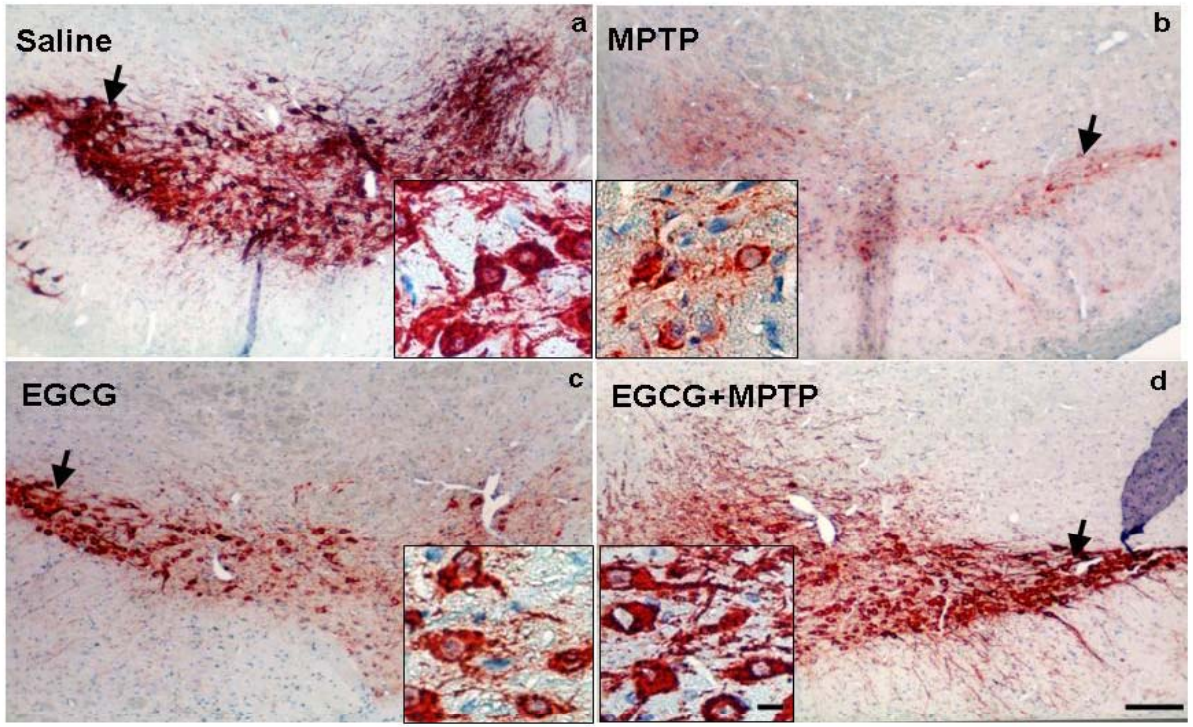
Anti-obesity
Decrease:
- Glucose (activation of glycolitic enzymes)
- triglycerides
- Lipogenesis (inhibition of fatty acid synthase)
- Lipid intestinal absorption

Increase
Fat oxidation
thermogenesis

Prevention of MPTP induced Dopaminergic Neurotoxicity by Green Tea Polyphenol, EGCG. Tyrosine Hydroxylase Immunoreactivity

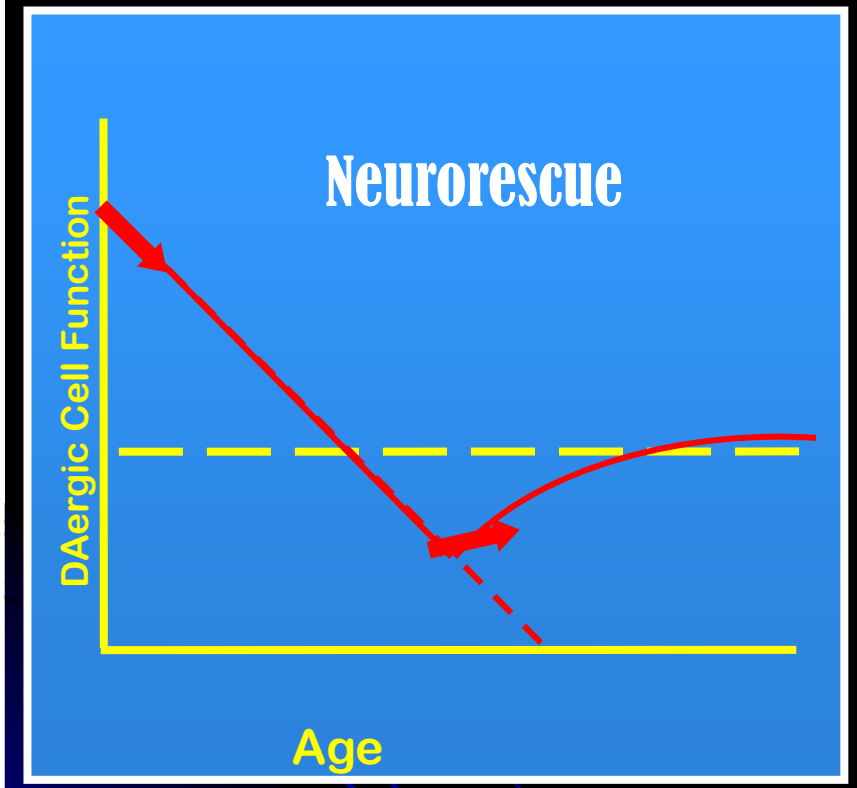
- Rasagiline, deprenyl (MAO-B inhibitors)
- Apomorphine (DA agonist)
- Clioquinol (Iron chelator)
- Melatonin (Antioxidants)
- Mynocyclin

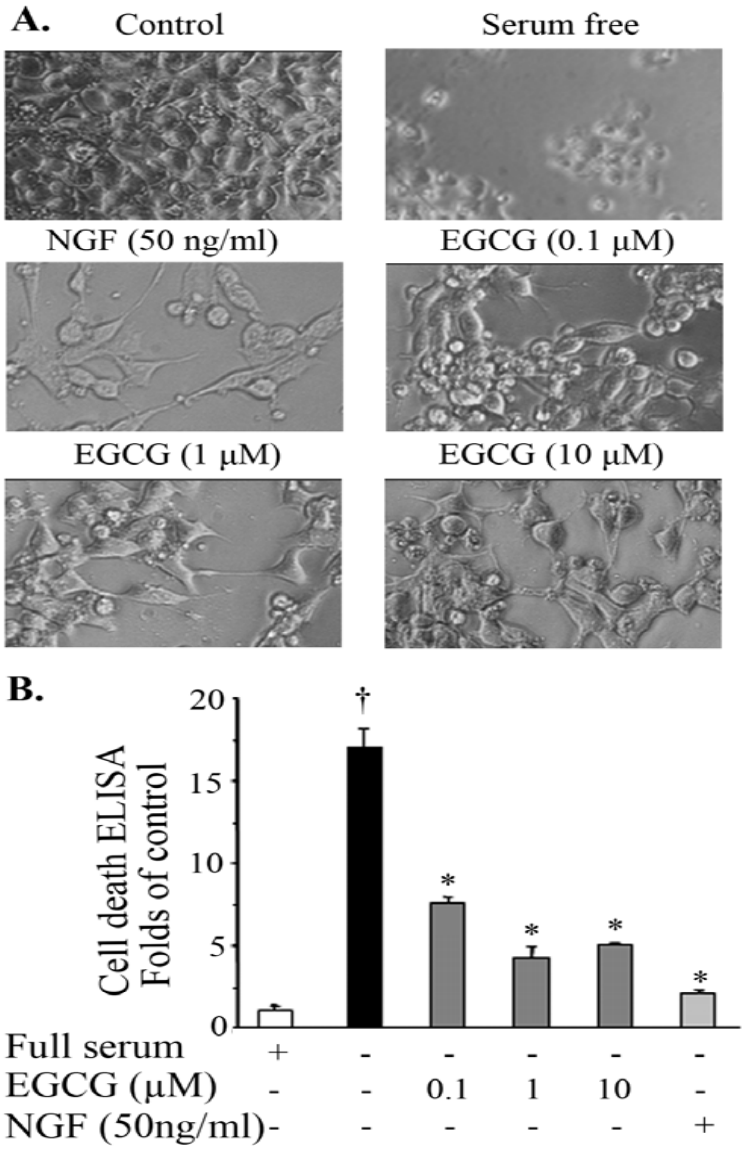
FIG 1



Levites et al., 2001, J. Neurochem
Mandel and Youdim 2004, FRBM
Mandel et al. 2004, J.Neurochem.
Mandel et al. 2004, J. Mol. Neurosci,.

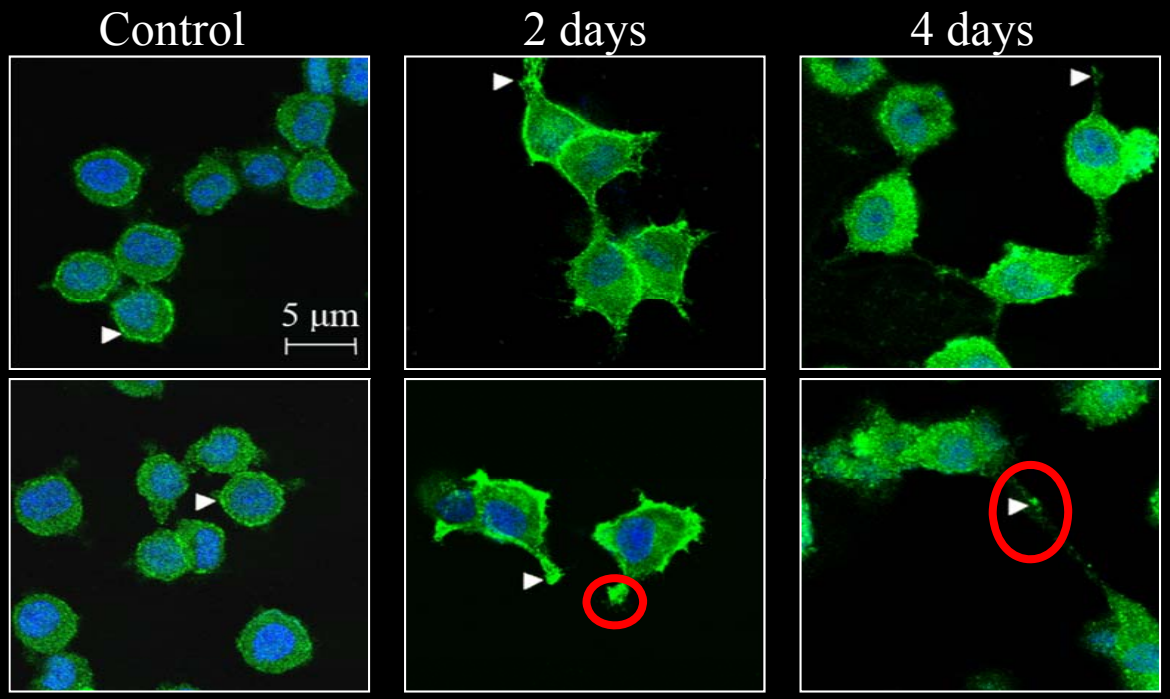
Effect of EGCG After Long-Term (72h, Neurorescue) Serum Starvation Period of PC12 Cells



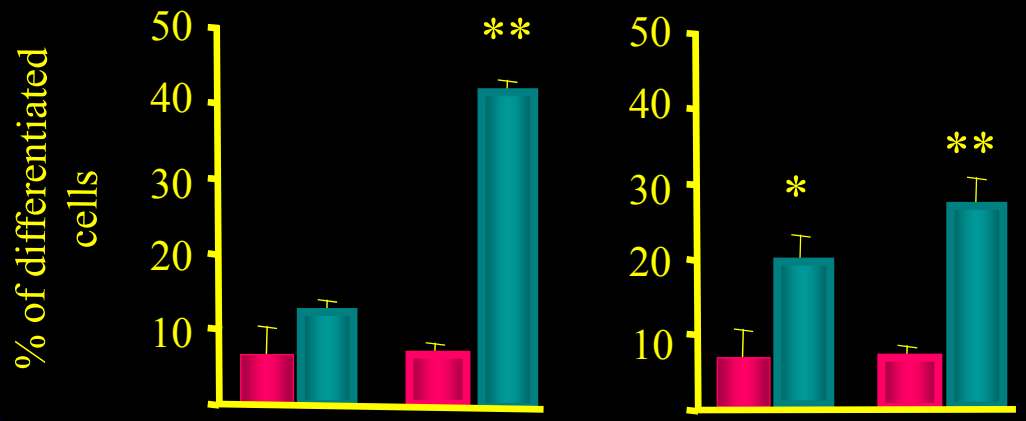


EGCG Promotes Differentiation of PC12 Cells; Expression of GAP43

GAP-43 expression

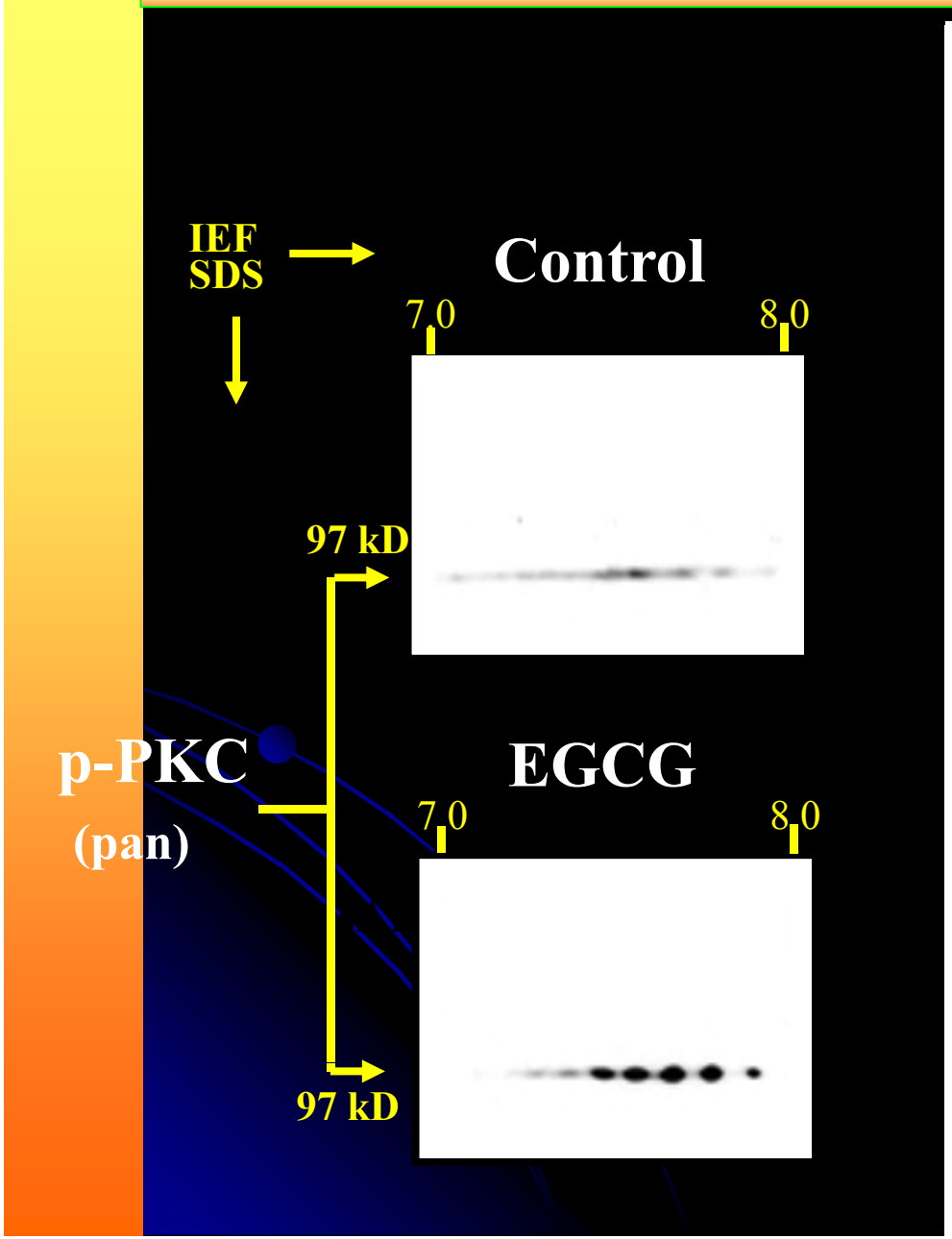


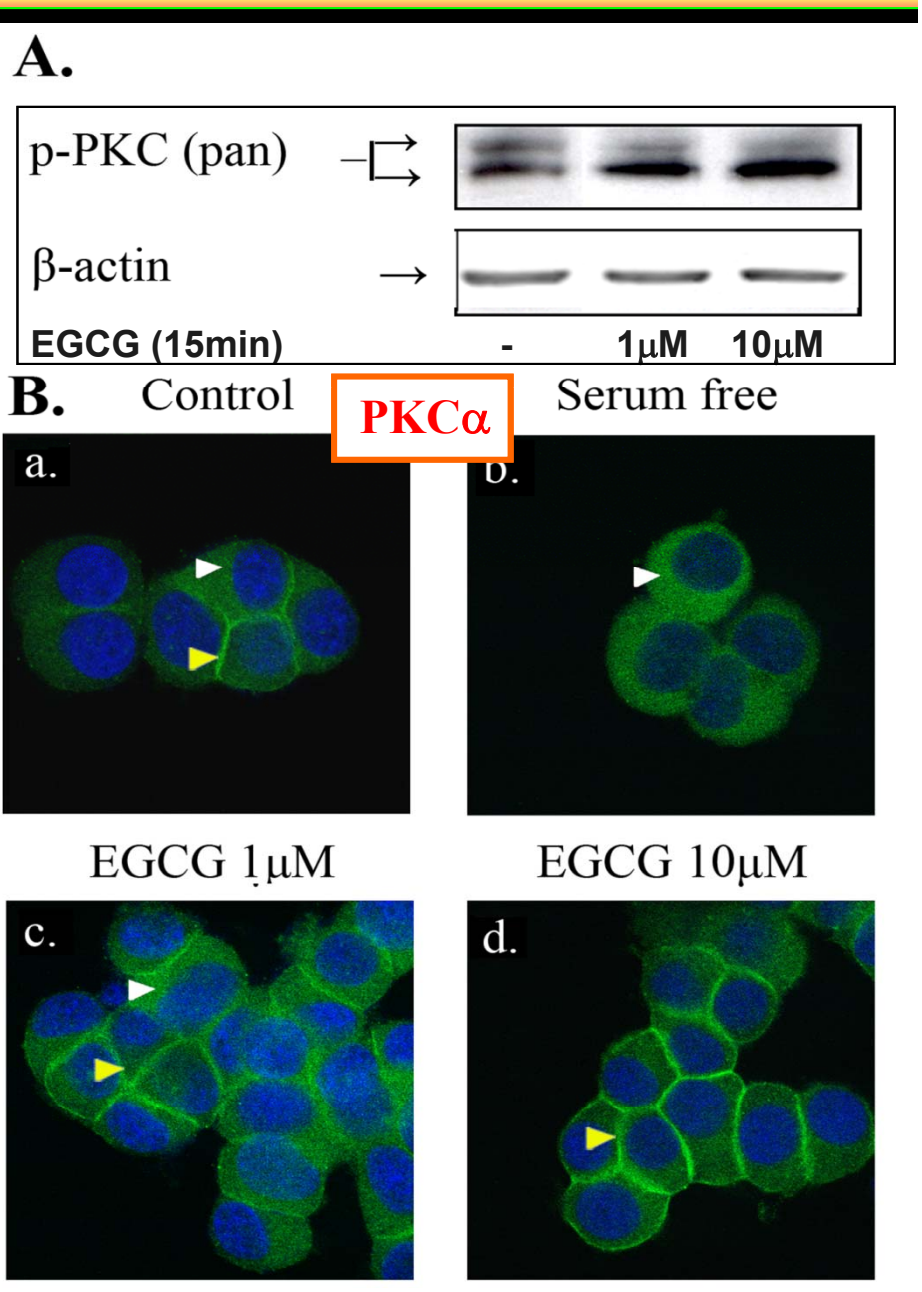
Neurite outgrowth



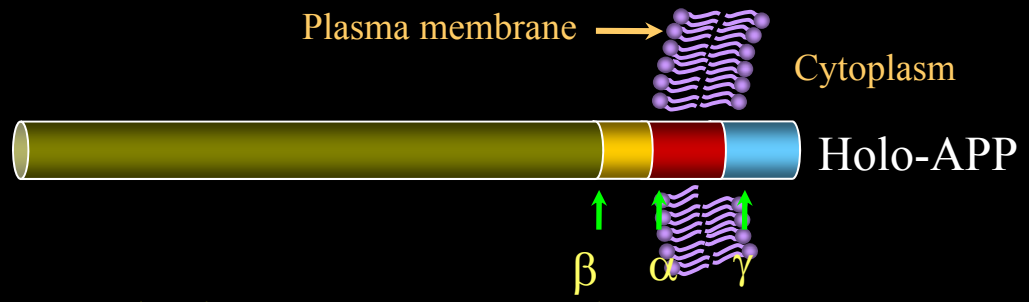
*p<0.05 vs Full Serum 2d
** p<0.01 vs Full Serum 4d
Full Serum
2-4 days EGCG treatment

EGCG Activates PKC Isoforms in Neuroblastoma SH-SY5Y



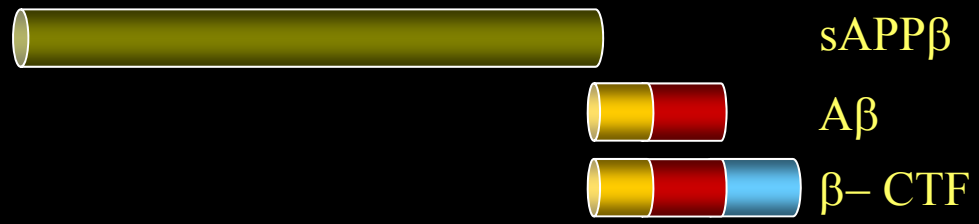


APP processing



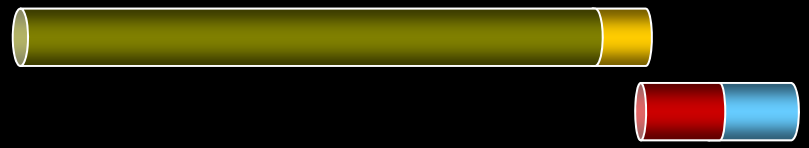
1. EGCG effect on holo-APP expression

Amyloidogenic derivatives:



3. EGCG ability to inhibit Aβ secretion

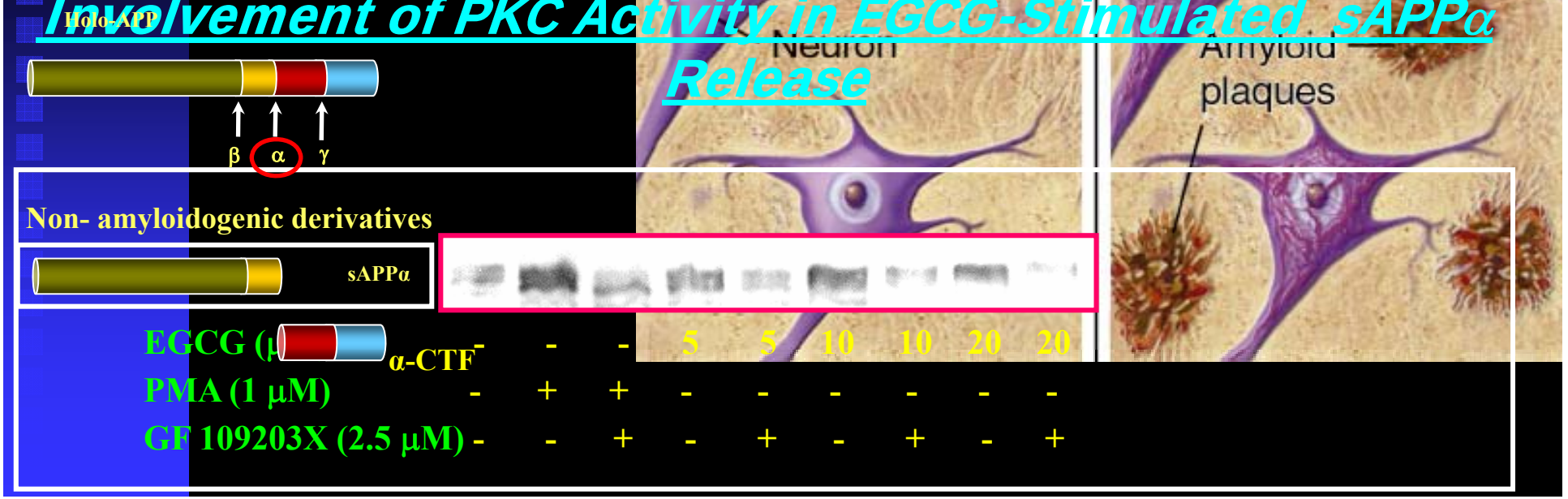
Non- amyloidogenic derivatives:



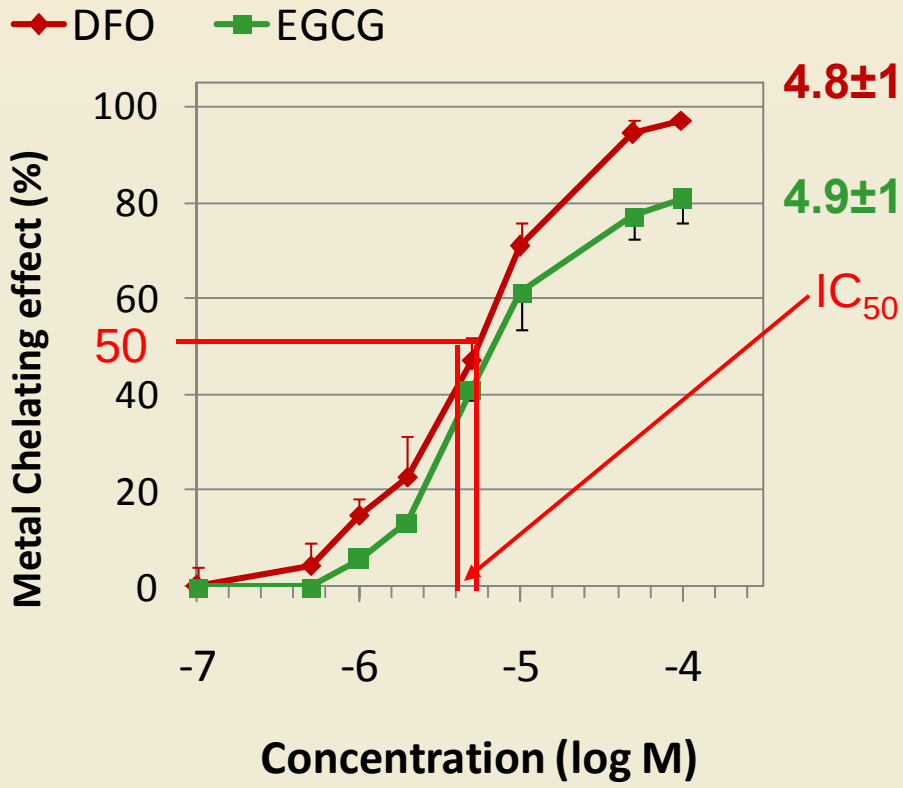
2. EGCG ability to promote non-amyloidogenic pathway

Involvement of α-Secretase in EGCG-Stimulated sAPPα Release

Involvement of PKC Activity in EGCG-Stimulated sAPPα Release



Comparative analysis of the Fe^{2+} chelating potency of EGCG and other iron chelators.

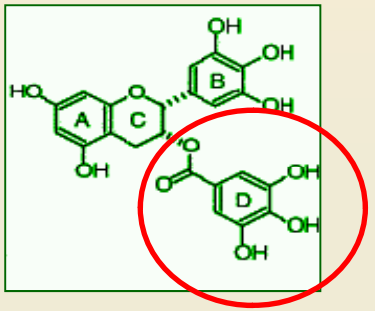


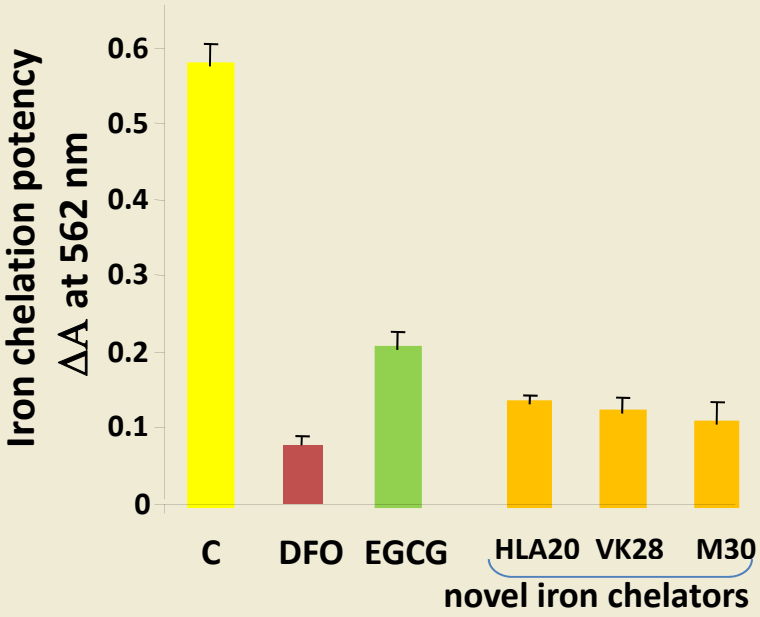
4.8±1.0x10 $^{-6}$ M for DFO

4.9±1.1x10^{-6} M for EGCG

IC_{50}

EGCG





Fe complex

Fe rrozine

Chelating effect (%) = [1-(absorbance of sample at 562 nm)/(absorbance of control, without drugs, at 562 nm)]× 100.

Translational regulation of iron-responsive proteins

IRP1
IRE-BS

IRP2
IRE-BS

Iron chelation
Iron deficiency

IRP1
IRE-BS

IRP2
IRE-BS

5’ Transferrin Receptor IREx5 mRNA 3’

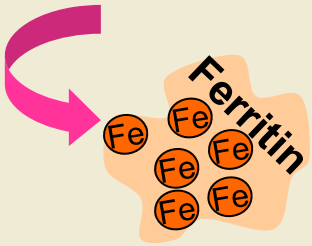
5’ Transferrin Receptor IRP IREx5 mRNA 3’

TfR

IRP

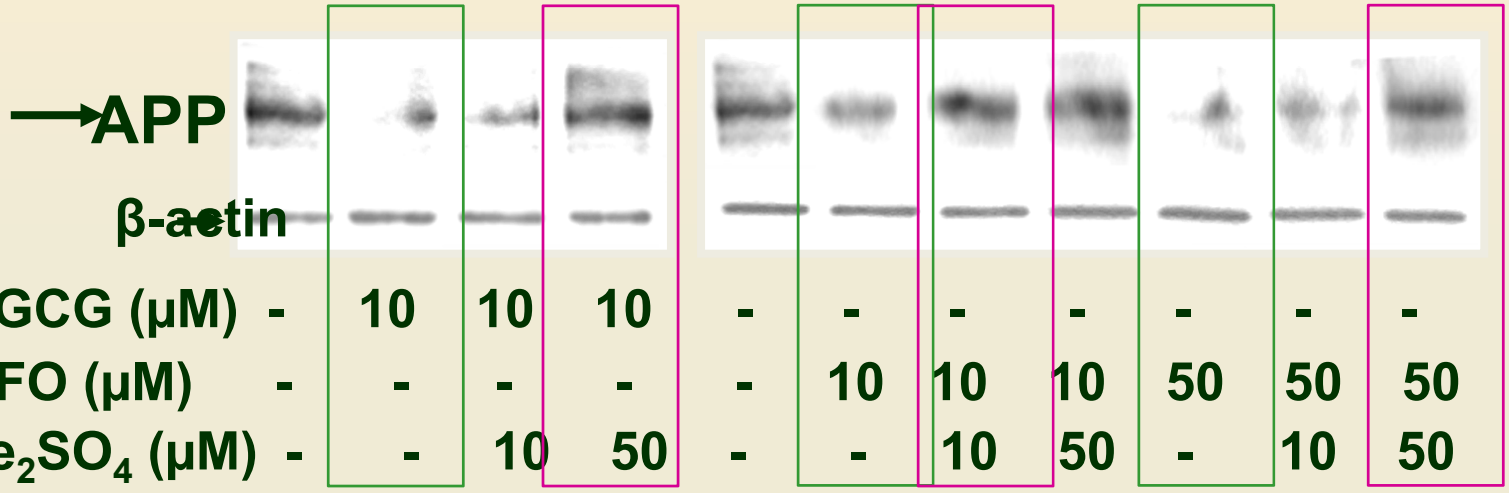
5’ IRE Ferritin mRNA 3’

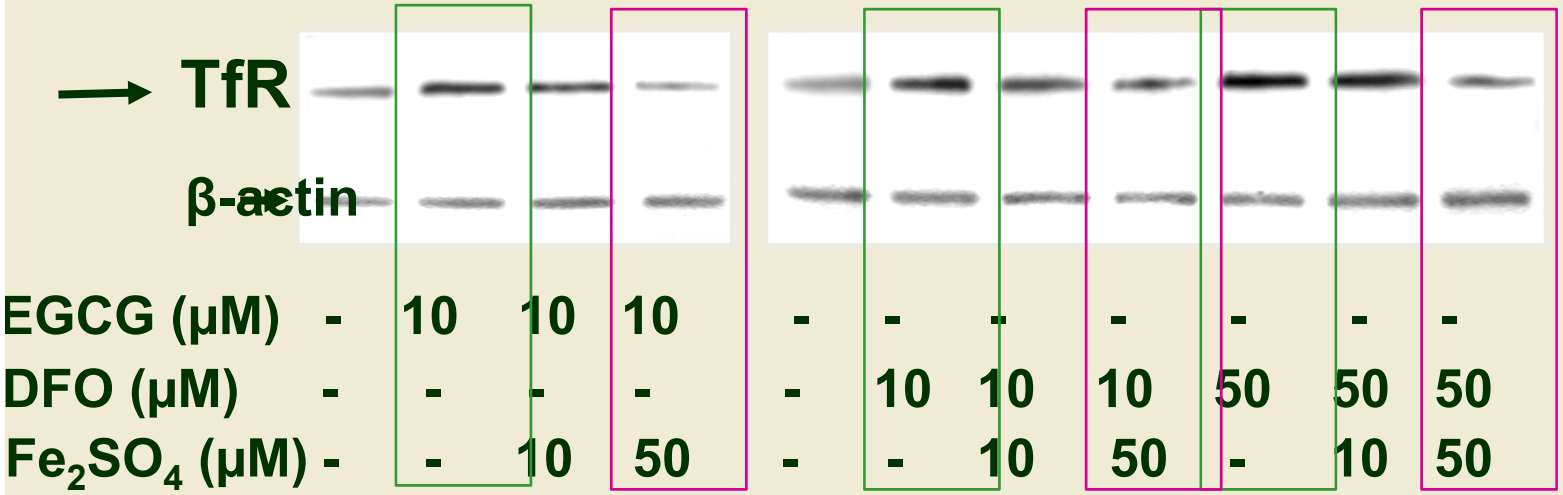
5’ IRE α-synuclein, APP mRNA 3’



Fe metab

Fe(II) abolishes EGCG-induced differential regulation of APP and TfR

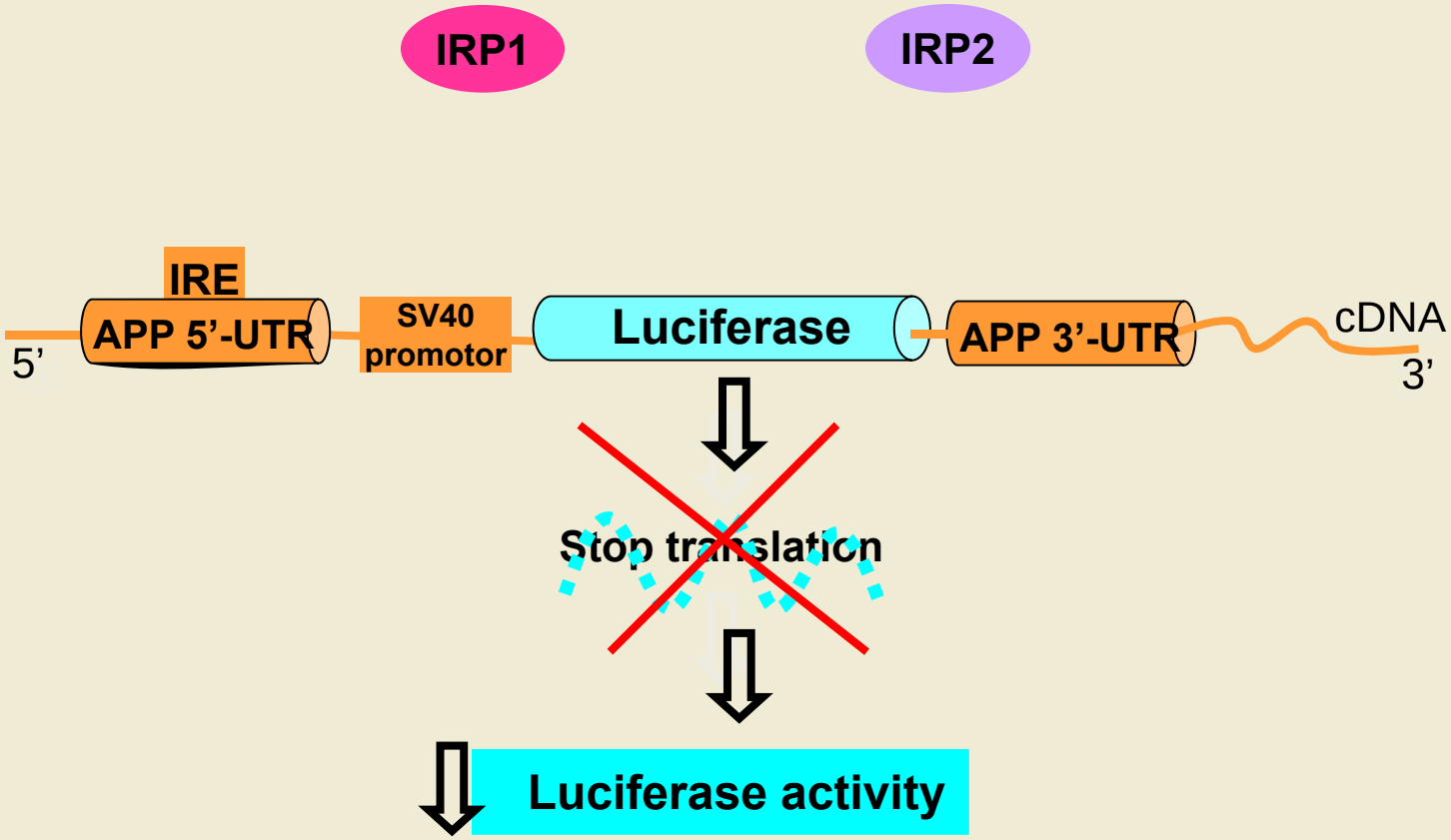




EGCG modulates the translation of a luciferase reporter gene driven by the APP 5'-UTR sequences.

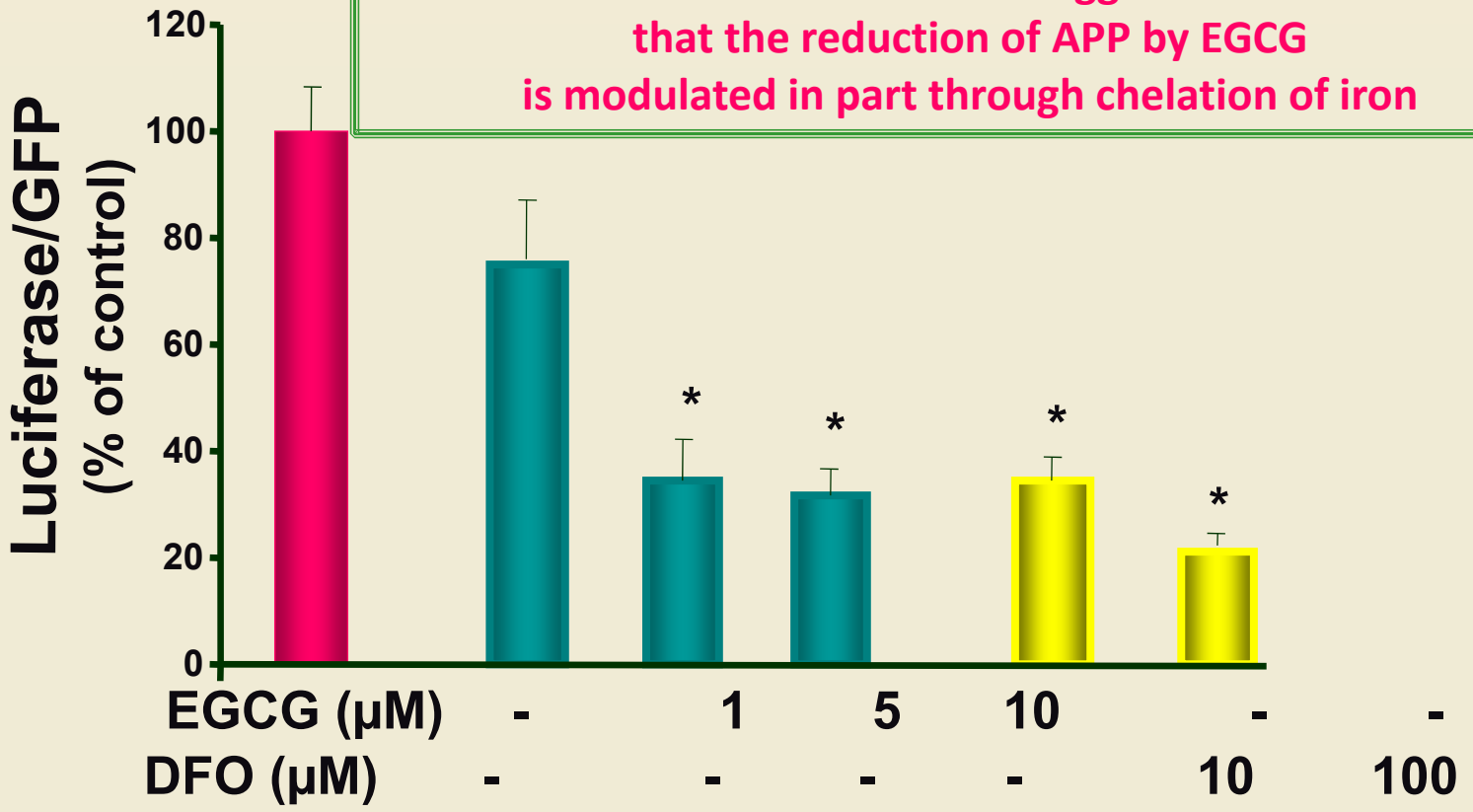
Iron deficiency

Iron chelation



Effect of EGCG on APP 5'-UTR conferred translation of a luciferase reporter mRNA in the human U-87-MG glioma cells

These results suggest
that the reduction of APP by EGCG
is modulated in part through chelation of iron

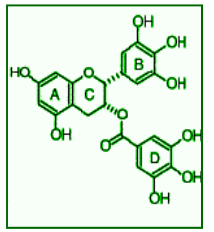


*p< 0.01, vs control

EGCG elevates sAPPα secretion and p-PKC isoforms

1. These results are consistent with previously shown PKC activation by EGCG.
2. EGCG may modulate APP processing via elevation of sAPPα secretion

Proposed Mechanism of EGCG Action for the reduction of Aβ production



EGCG

chelation

Labile Fe(II)

RPs

5’ IRE APP mRNA 3’

APP translation

APP

Destabilization of Aβ fibrils

Aβ

p-PKC-α,-ε

α-secretase

sAPPα

NEUROPROTECTION/NEURORESCUE
NEUROPLASTICITY

GRAND CANYON EFFECT

Neuroprotection-Neurorescue In Neurodegenerative Diseases

- Healthy food

Green tea

Red wine

Blueberries

- Exercise
- Intellectual activities