Neuroprotectin D1 (NPD1) is a Sentinel for Neurodegenerations

Nicolas G. Bazan, M.D., Ph.D.

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2009 Southeast IDeA Regional Meeting
http://www.scepscoridea.org/SoutheastIDeAMeeting

Charleston, SC 2009

LSU Health Sciences Center

Mentoring Neuroscience in Louisiana:

A Biomedical Program to Enhance Neuroscience

First competitive grant of this type in Louisiana

NIH Funding for a Decade to Train Competitive Neuroscience Faculty

2002-2007 (9.8M)
2007-2012 (10.6M)

LSU Health Sciences Center
NEW ORLEANS
Neuroscience Center of Excellence

Tulane University
Health Sciences Center

Xavier University of Louisiana

NICHOLLS
STATE UNIVERSITY

Mentees:

Dr. Royal Saunders

Dr. Gary LaFleur

Dr. Laura Harrison

Dr. Fiona Inglis

Dr. John Doucet

Hamilton Farris, Ph.D.
Neural Mechanisms of Speech Processing

Alberto Musto, M.D., Ph.D.
Inflammatory Signaling in Epileptogenesis

Hugh Xia, Ph.D.
Neurabins/PPI Targeting in Synaptic Plasticity

Laura Schrader, Ph.D.
Regulation of K+currents in Neuronal Excitability

LSU Health Sciences Center NEW ORLEANS

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Tulane University Health Sciences Center

S.U.N. Program Participants 2009
(Funded by NCRR Supplement)

"With our first CoBRE grant, we began establishing a culture of scientific excellence at LSUHSC and other Louisiana institutions of higher education," said Dr. Bazan, "Neurosciences research performed in this environment is greatly synergized with respect to both quality and productivity; the new culture is playing a critical role in innovative and fundamentally important research breakthroughs in the neurosciences at our institutions."

External Advisory Committee, from left to right, Michael Stryker, Ph.D., (UCSF), Colin Barnstable, Ph.D., (Yale), Scott Brady, Ph.D., (Univ. Illinois at Chicago), Randy Blakely, Ph.D., (Vanderbilt), Stuart Lipton, M.D., Ph.D., (Burnham-LaJolla), Robert Murphy, Ph.D., (Univ. Colorado).

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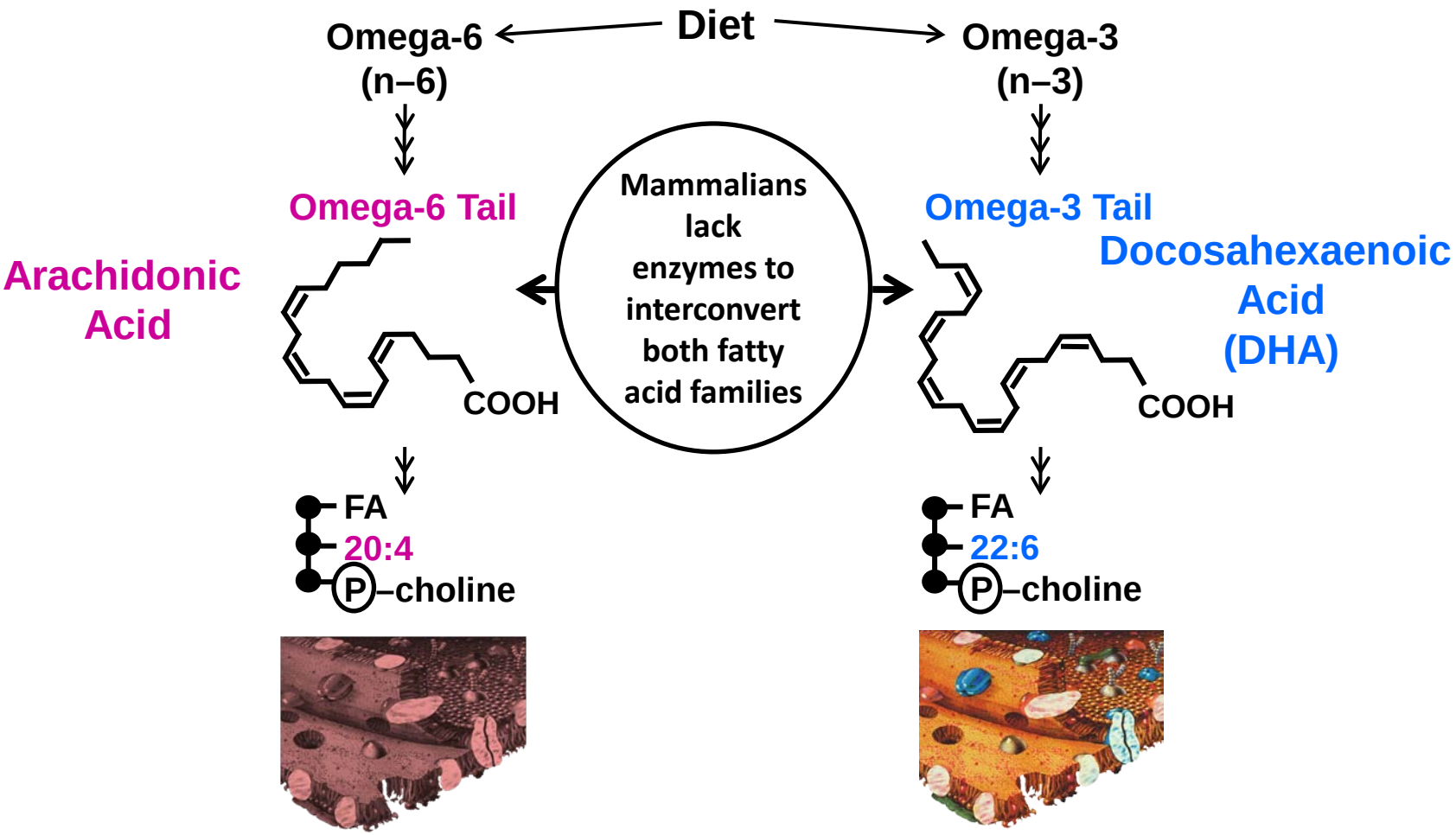
Omega-3 and Omega-6 Essential Fatty Acids



In Cellular Membranes of All Organs and Tissues

Concentrated and avidly retained in Central Nervous System

- **Synaptic Membranes**
- **Photoreceptors**

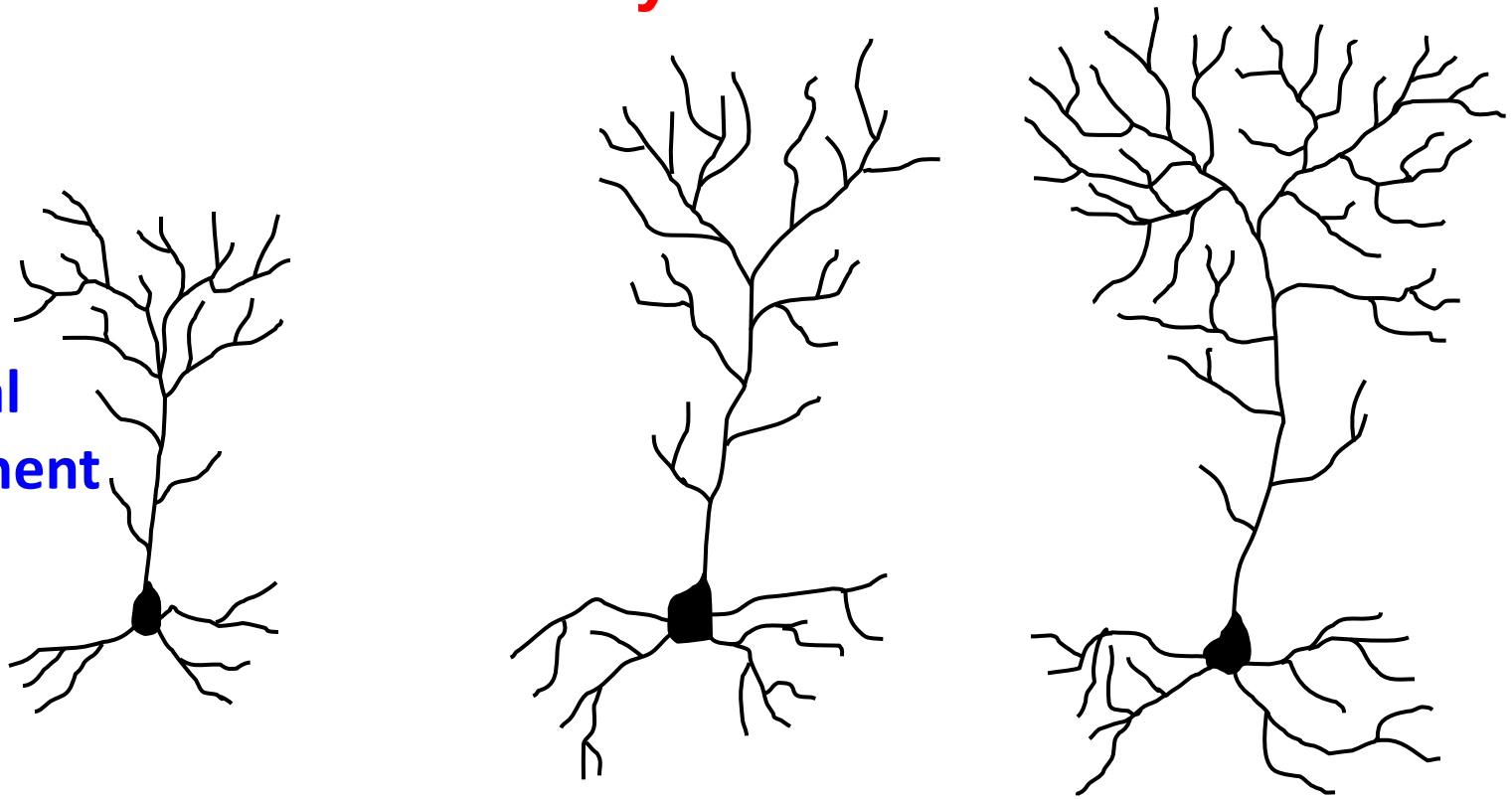
Docosahexaenoic Acid
(DHA 22:6, n-3, Omega-3 Essential Fatty Acid)

Implicated in

- Aging, Memory
- Mild Cognitive Impairments
- Synaptic membrane function
- Photoreceptor biogenesis and function
- Neuroprotection

The Building of the Brain : Why so much DHA? Why DHA is so avidly retained?

Normal Development



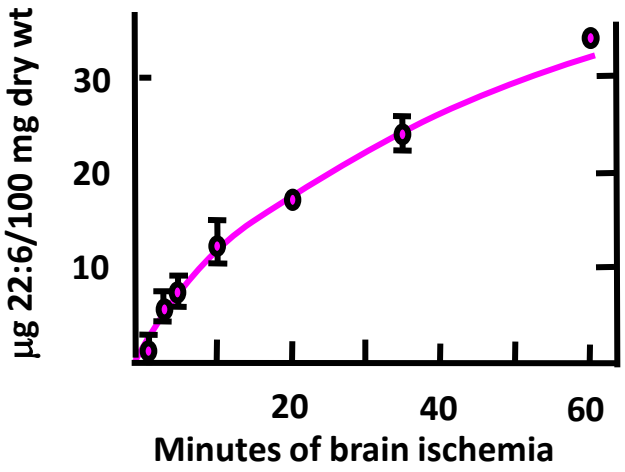
Role in synaptic membrane organization and function

Reservoir of bioactive mediators at the synapse ?

DOCOSANOIDS

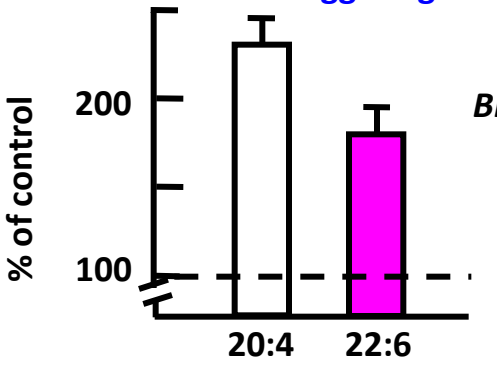
Both?

Arachidonic and Docosahexaenoic Acids are Released in the CNS upon Stimulation : The Advent of Docosanoids



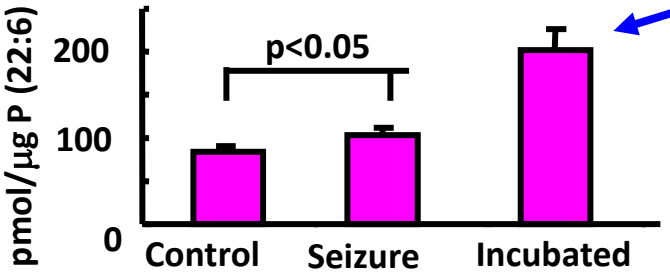
Brain Res. 100:99-110, 1975

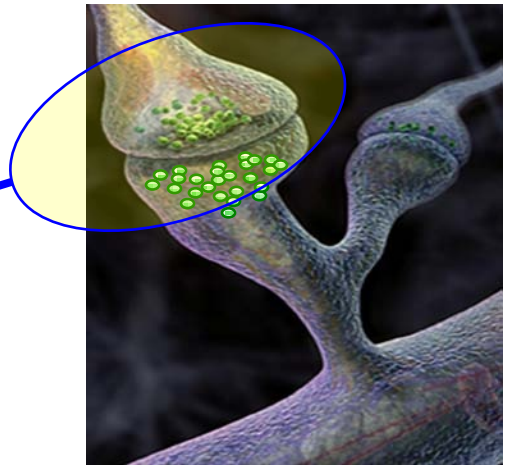
30 sec After Triggering a Seizure



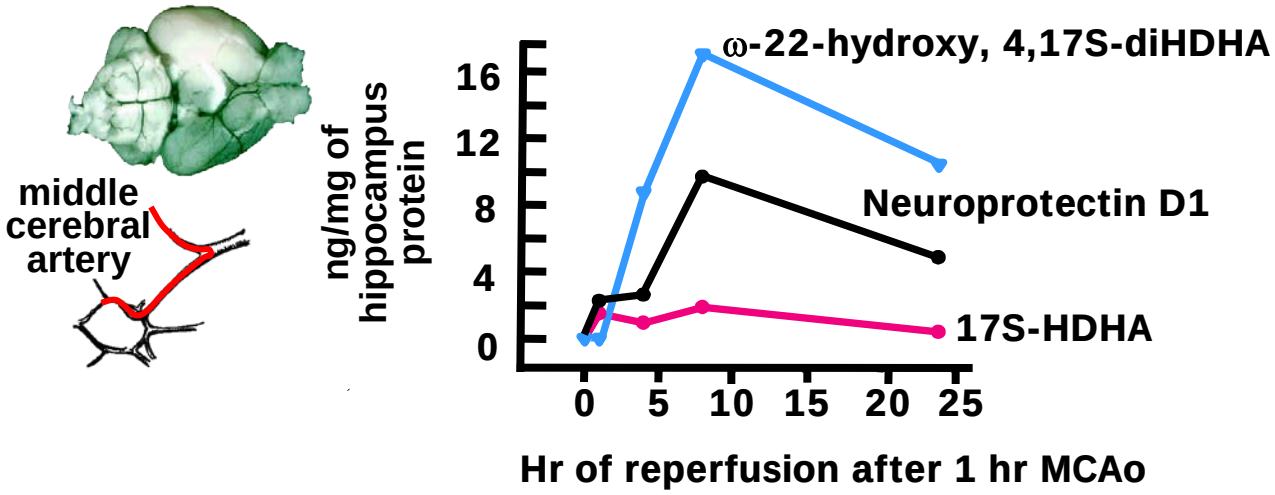
Biochim. Biophys. Acta 218:1-10, 1970

Synaptosomes (1987)





Bazan NG, Birkle DL, Reddy TS: Docosahexaenoic acid is metabolized to lipoxygenase reaction products in the retina. *BBRC* **125:741 747, 1984.**

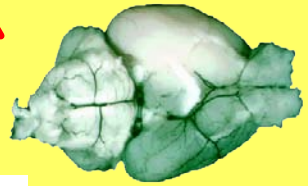


“Natural Forces Within Us Are The True Healers Of Disease”

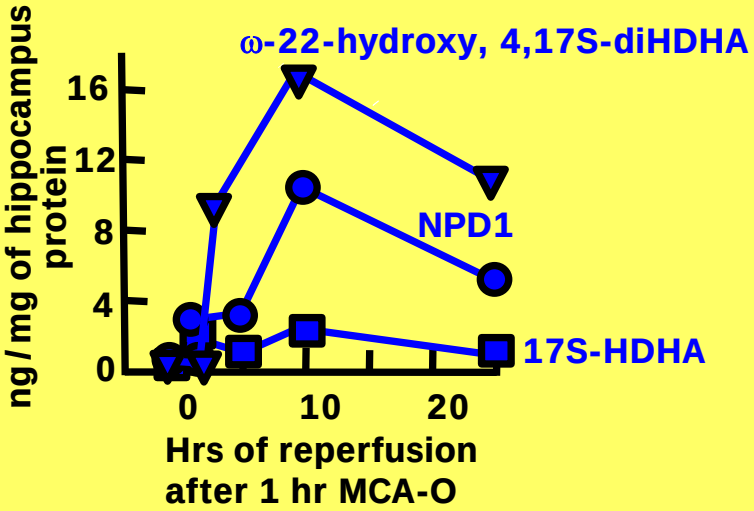
Hippocrates

Ischemia-Reperfusion (MCA-O Model)

1. Endogenous NPD1



middle cerebral artery

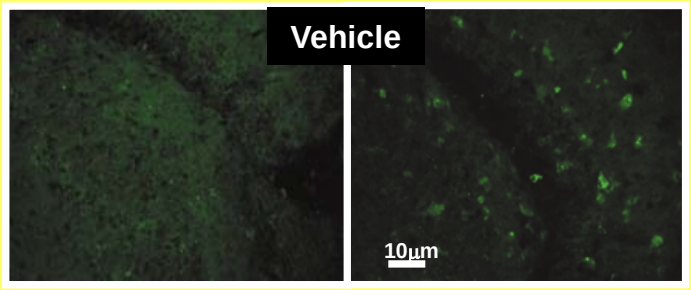


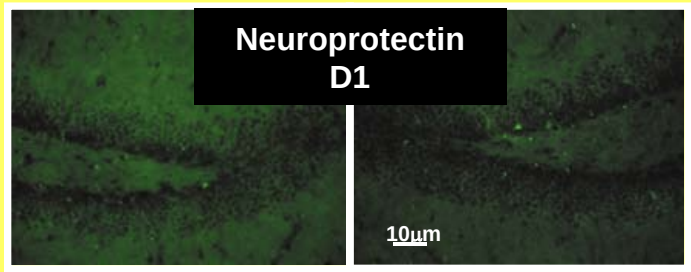
2. NPD1 i.c.v. infused (400 ng/2 days)

↓PMN infiltration

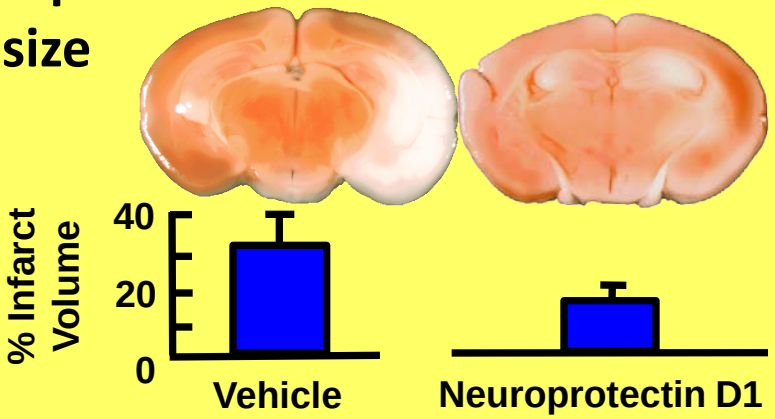
Myeloperoxidase

Contralateral Ipsilateral (MCA-O)





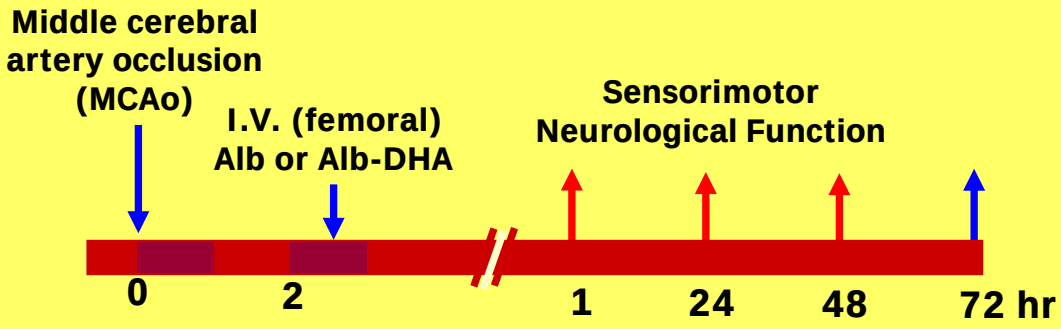
- ↓ NFκB induction
- ↓COX-2 expression
- ↓Stroke size



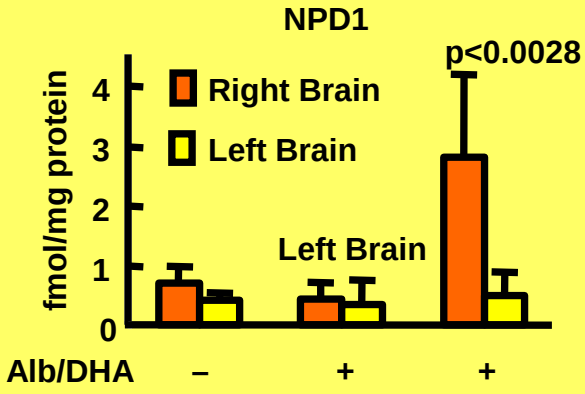
Marcheselli, et.al., JBC (2003)

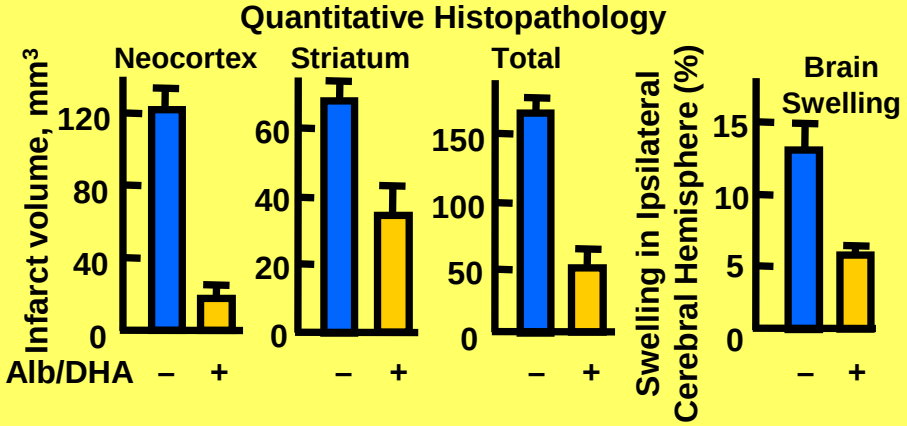
Systemic Docosahexaenoic Acid

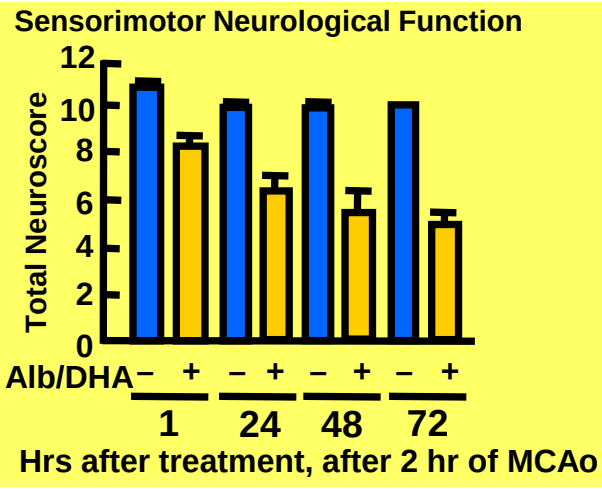
{2 hrs (i.v.) After 2 hrs of MCA-O}



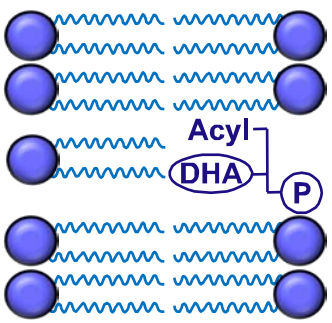
- Cytoprotective (histology)
- Neurobehavioral recovery
- NPD1 synthesis increases





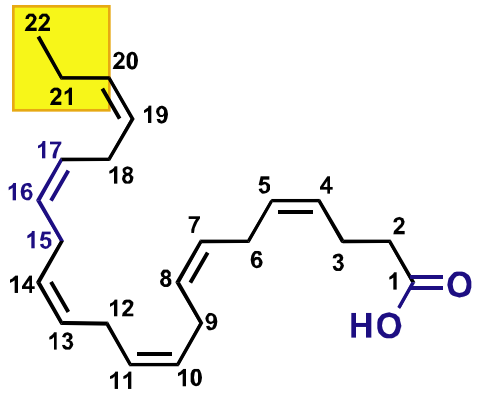


Belayev, et.al., Stroke (2005)

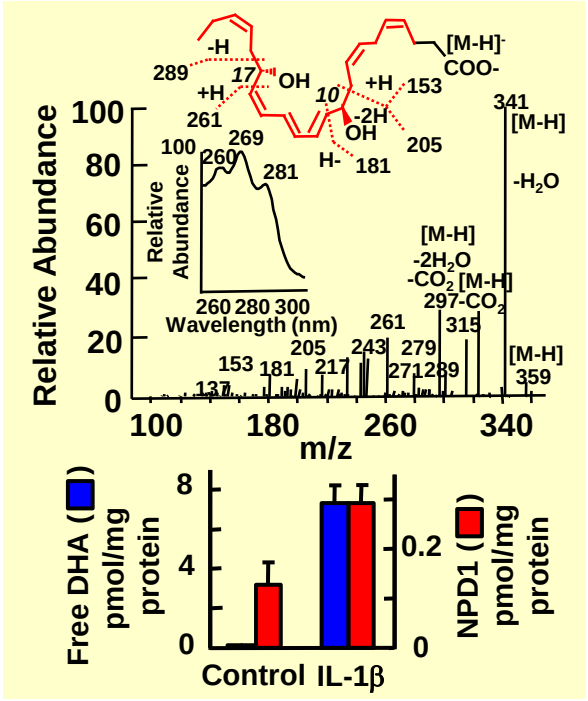


Phospholipase A 2

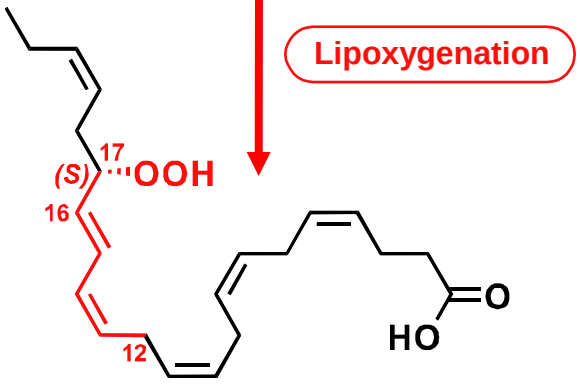
Omega-3 Tail



Docosahexaenoic acid (DHA)

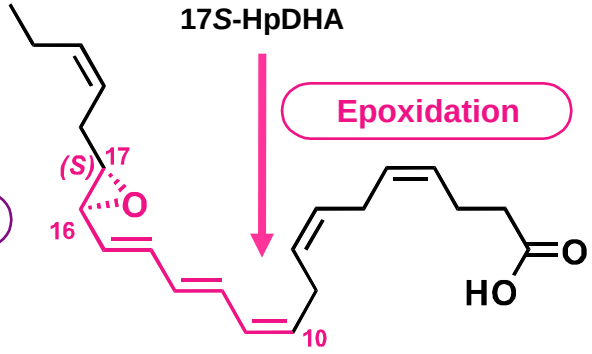


Lipoxygenation



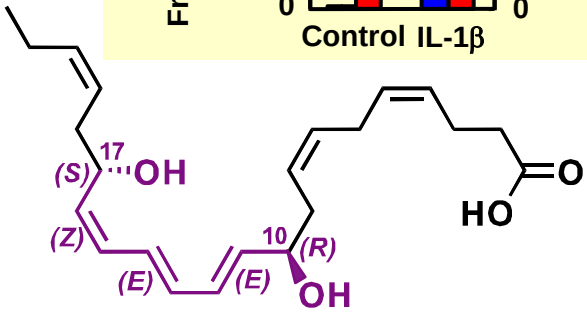
17S-HpDHA

Epoxidation



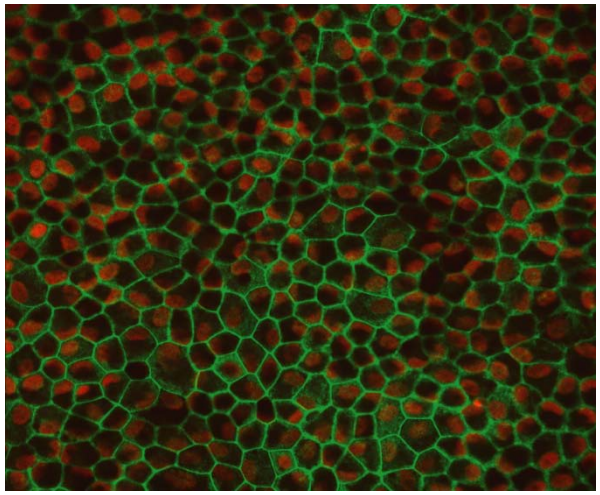
16, 17S-DHA Epoxide

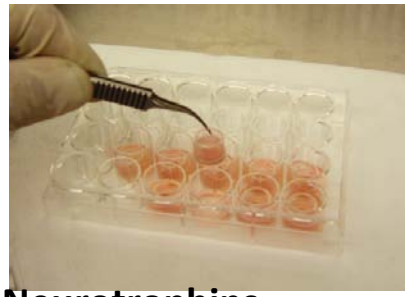
Hydrolysis



Neuroprotectin D1 (NPD1)

Neurotrophins Induce NPD1 Synthesis in Human RPE Cells



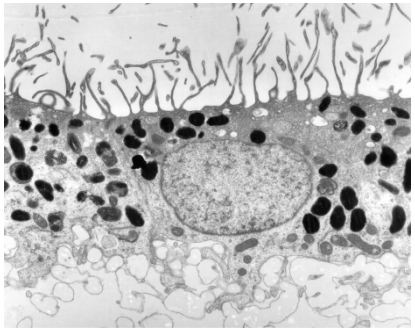


Neurotrophins
+ 50 nM DHA

Sampled

0 1 2 3

Days



Growth Factor Added

Apical

Basal

Fold NPD1 Synthesis by PEDF

2
1
0

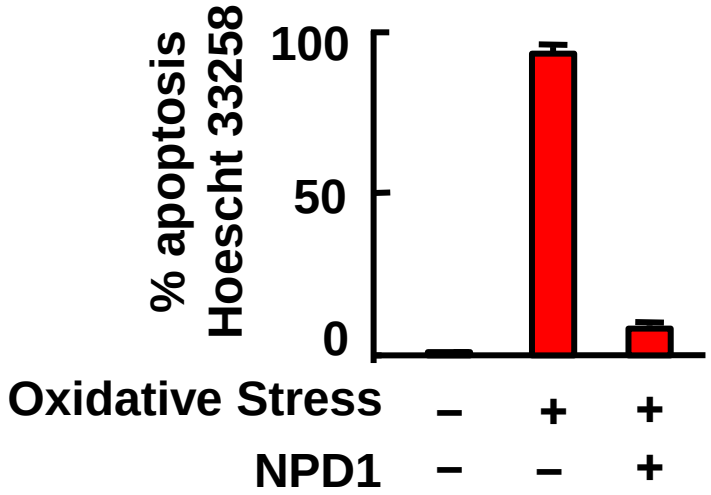
Cell Medium

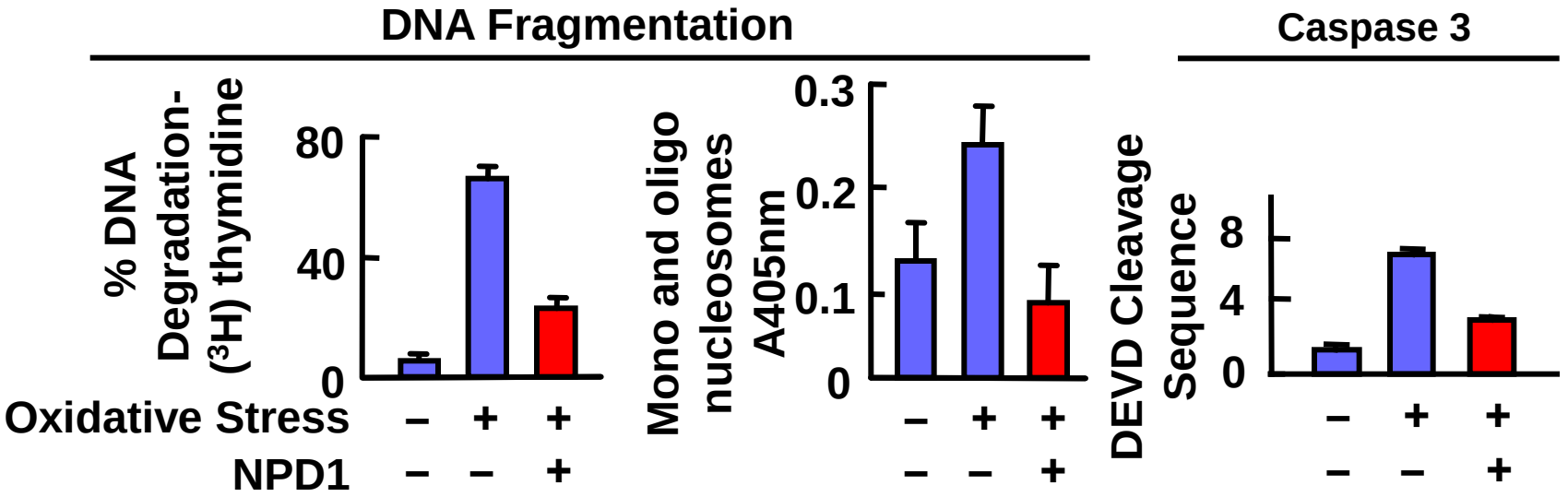
NPD1 (pmol/medium)

120
80
40
0

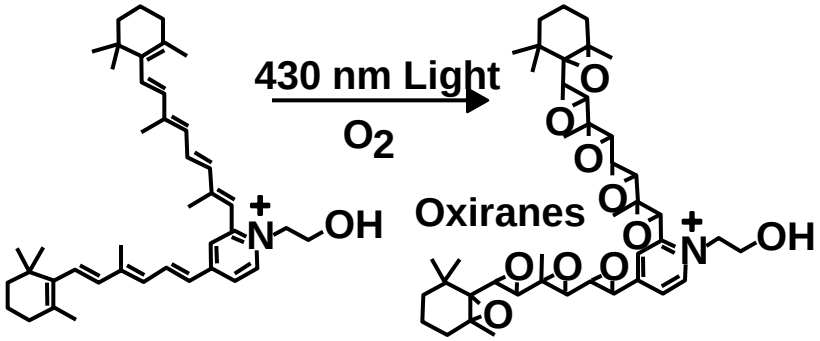
Control GDNF LIF NT3 CTNF NGF FGF BDNF Cardiotrophin Persepin PEDF

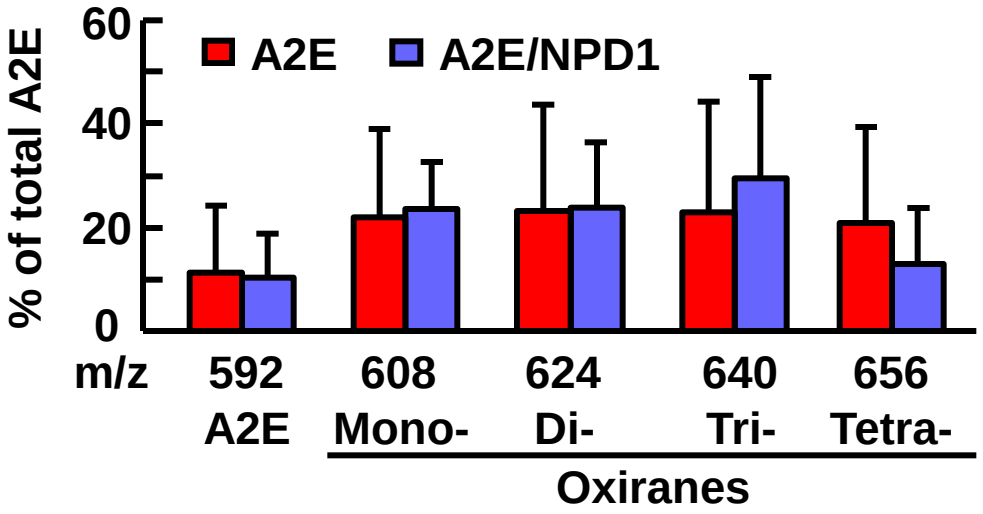
NPD1 (50nM) Attenuates Oxidative Stress-Induced Apoptosis of Retinal Pigment Epithelial Cells



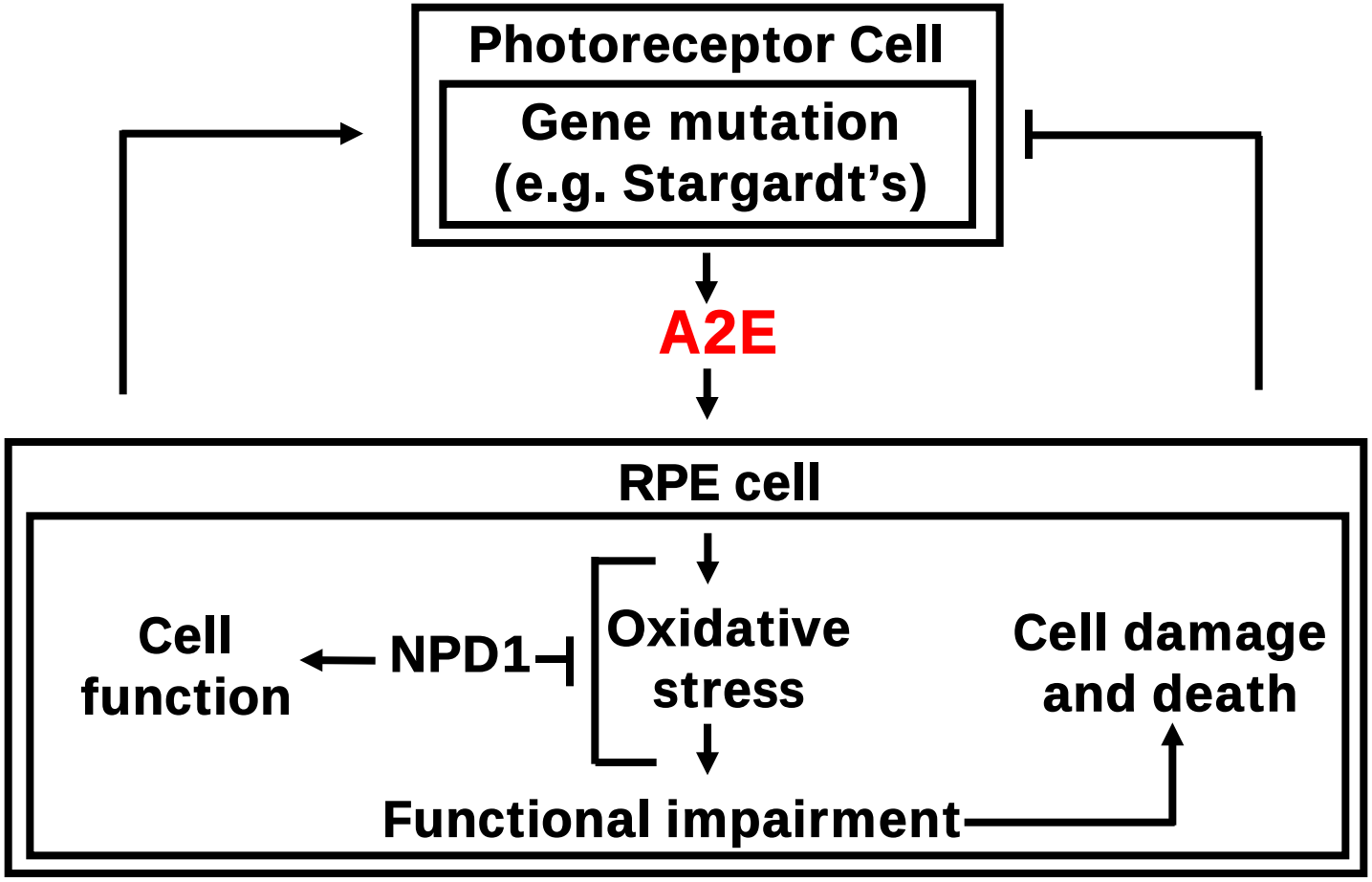


NPD1 Does Not Block Oxiranes Formation From A2E that Accumulates in Stargart Macular Degeneration

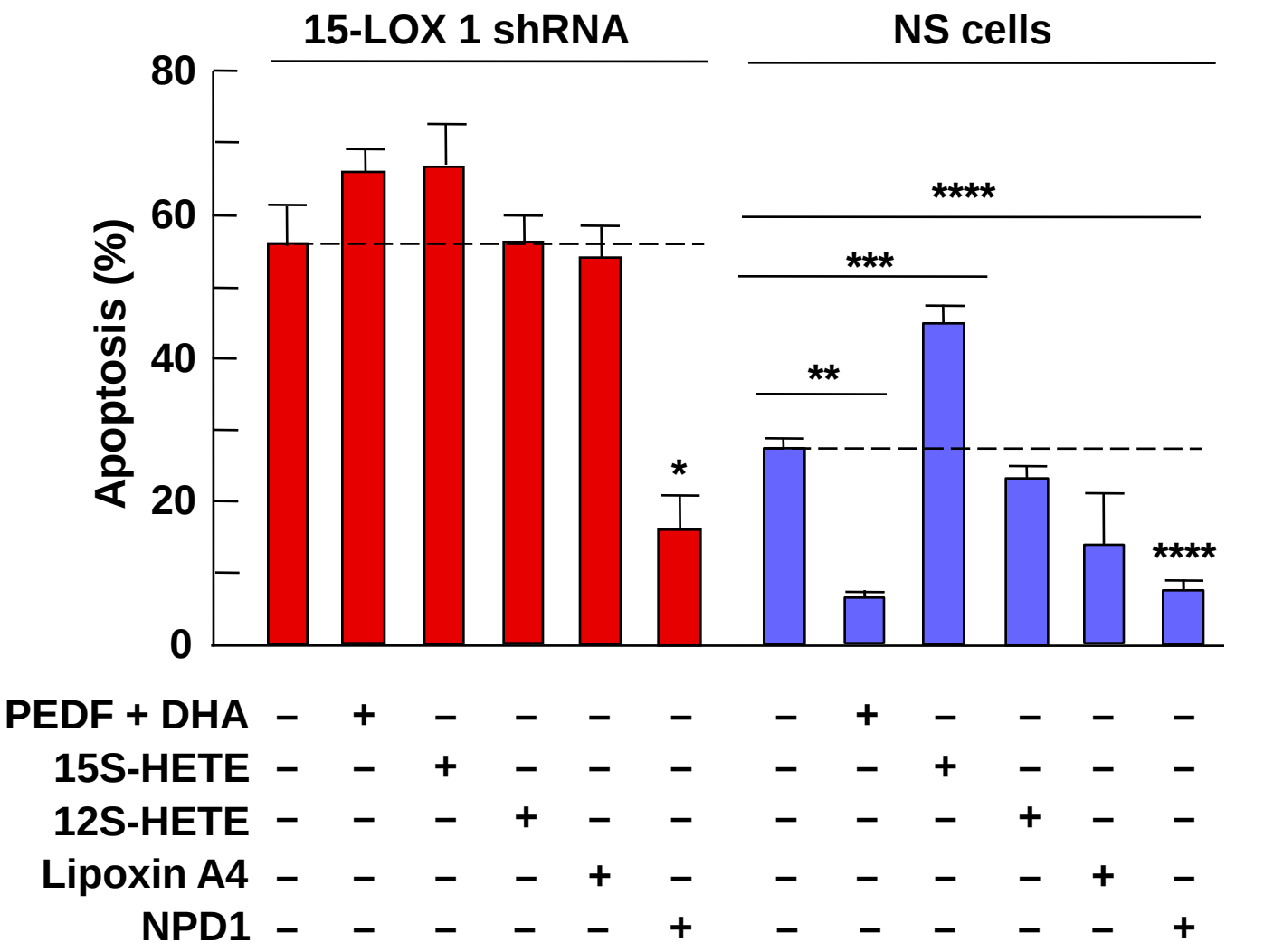




Mukherjee, P.K *et al.*, PNAS, 104:13152-13157, 2007

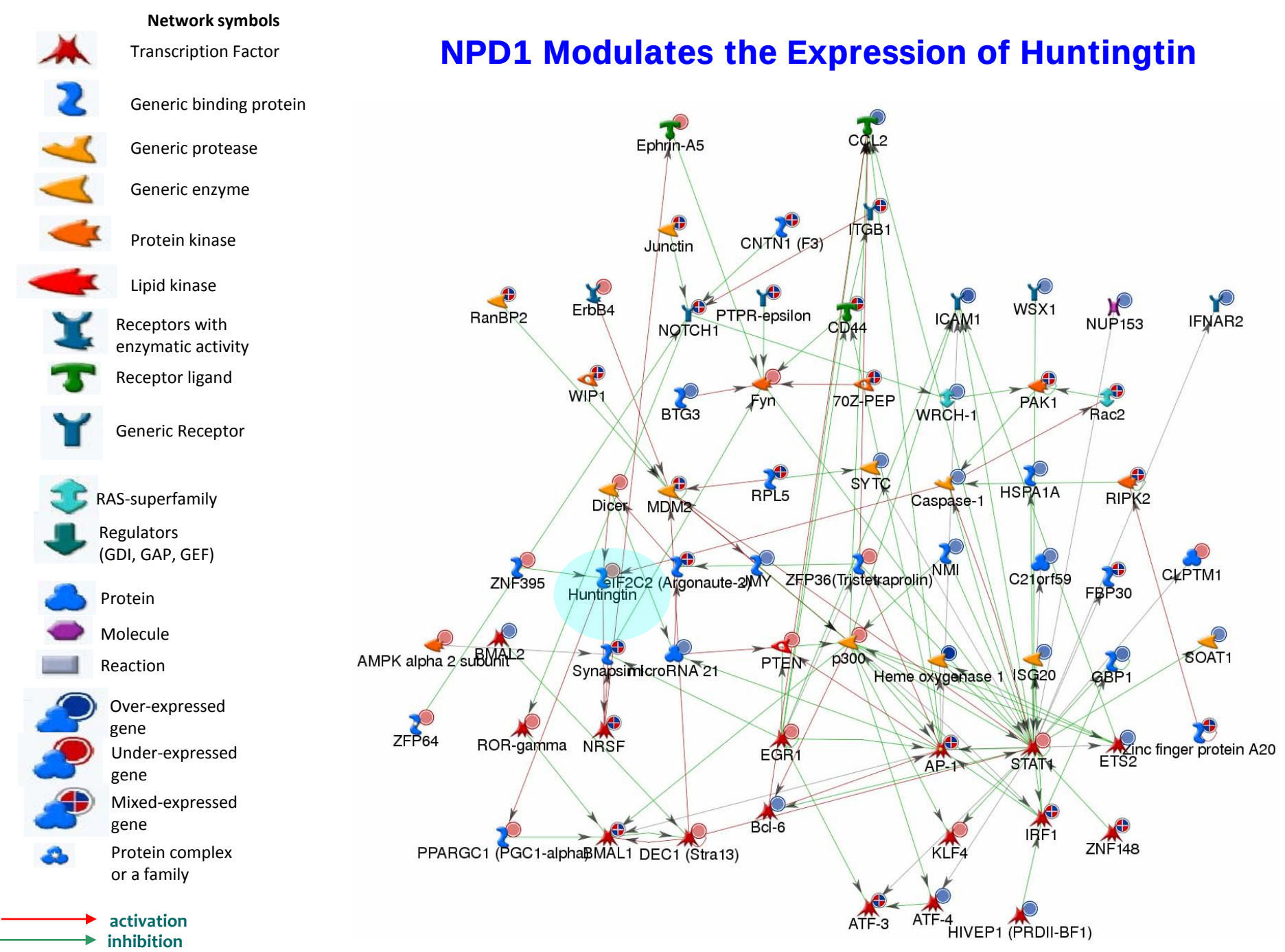

Photoreceptor Cell
Gene mutation
(e.g. Stargardt's)
A2E
RPE cell
Cell
function
NPD1
Oxidative
stress
Cell damage
and death
Functional impairment

Selective Survival Rescue By NPD1 in 15-Lipoxygenase-1 Deficient Cells



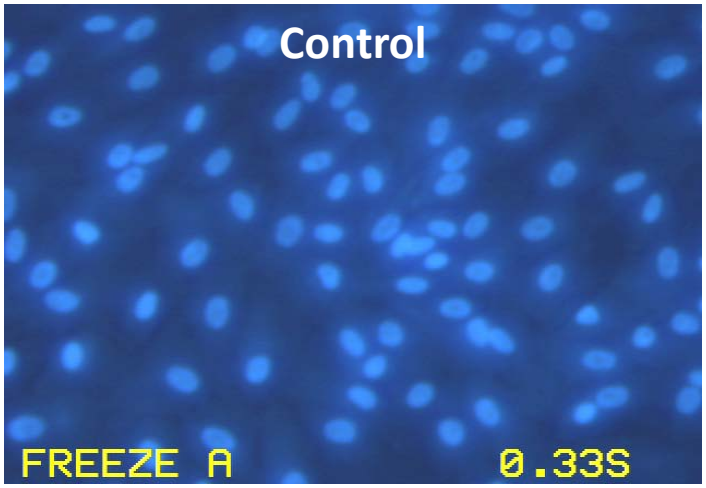
J. Calandria *et al*, JBC (in press)

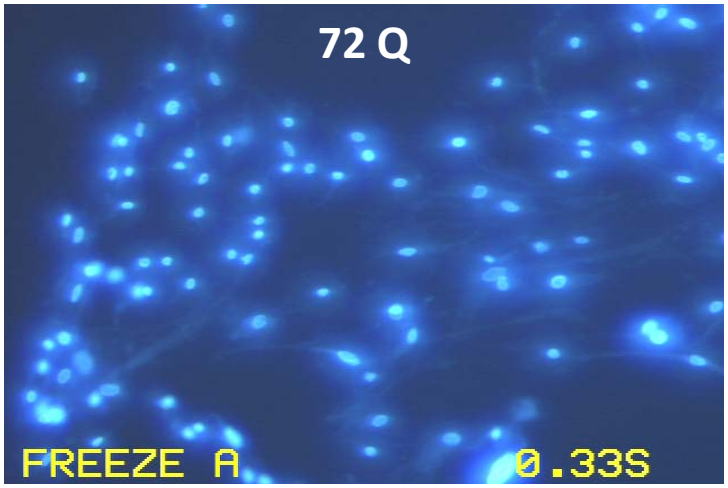
NPD1 Modulates the Expression of Huntingtin

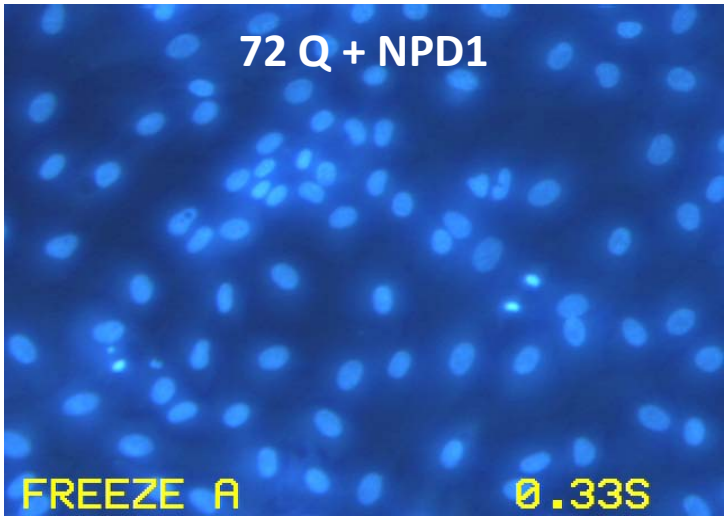


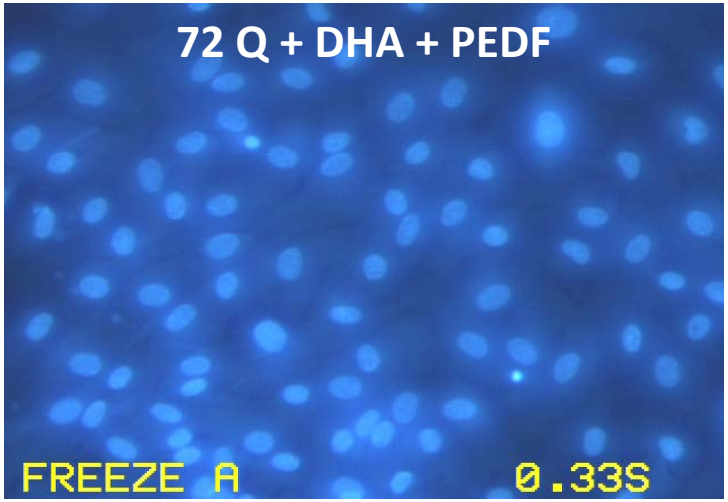
htt-72Q Expression induces Apoptosis in h-RPE:

NPD1 or DHA+PEDF Exert Protection (3 days)

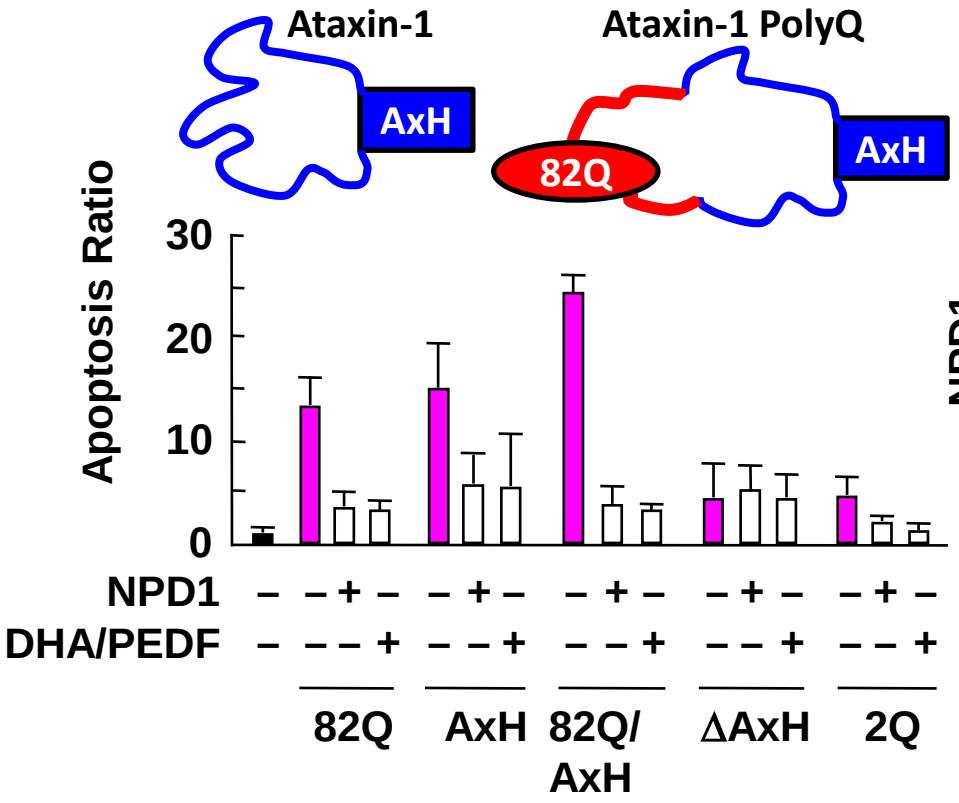


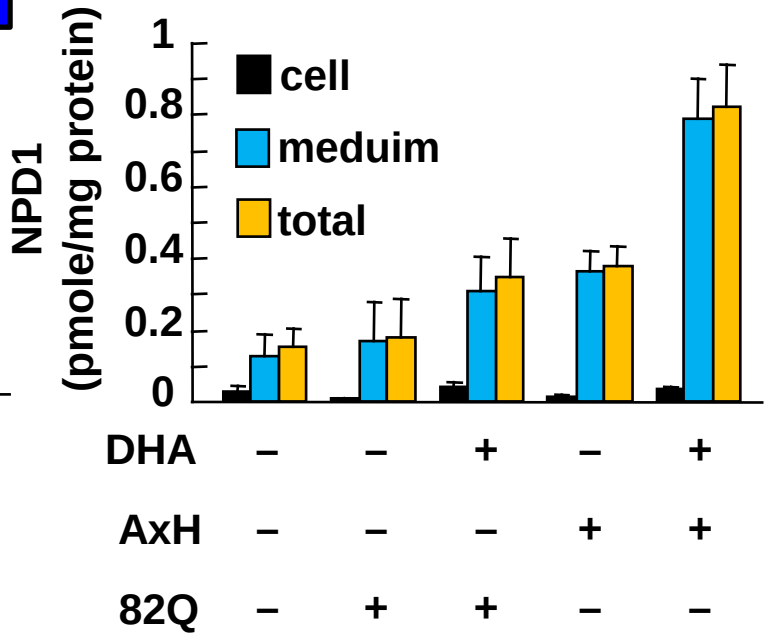


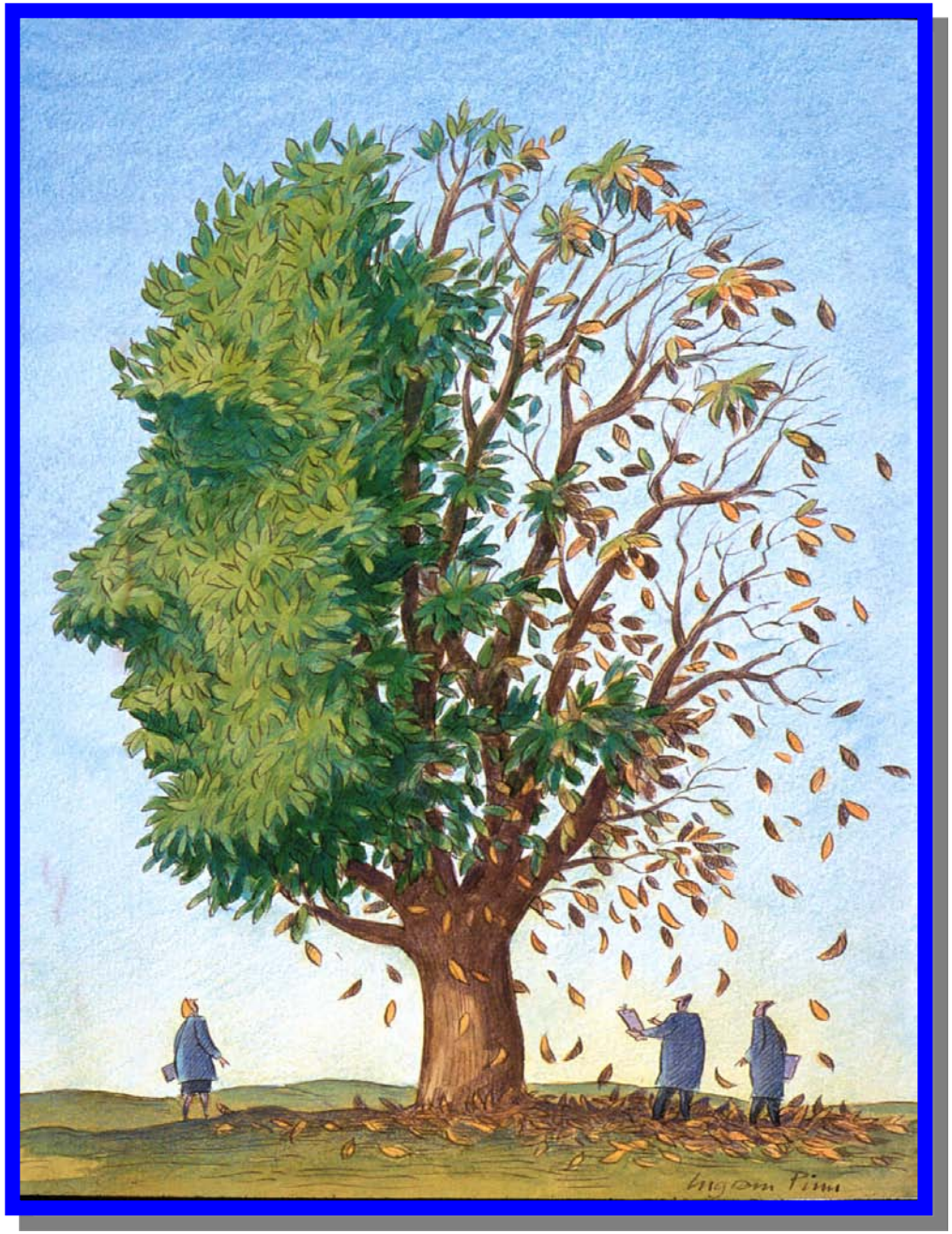




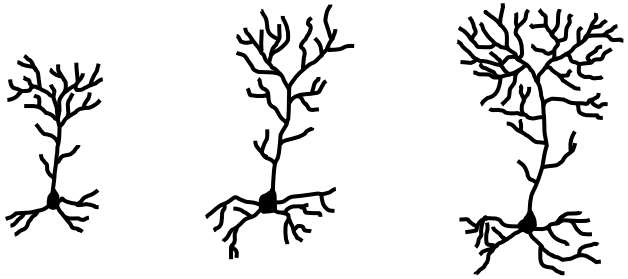
AxH Domain Contributes to Cytotoxicity by Ataxin-1 and Induces NPD1 Synthesis in Human RPE Cells



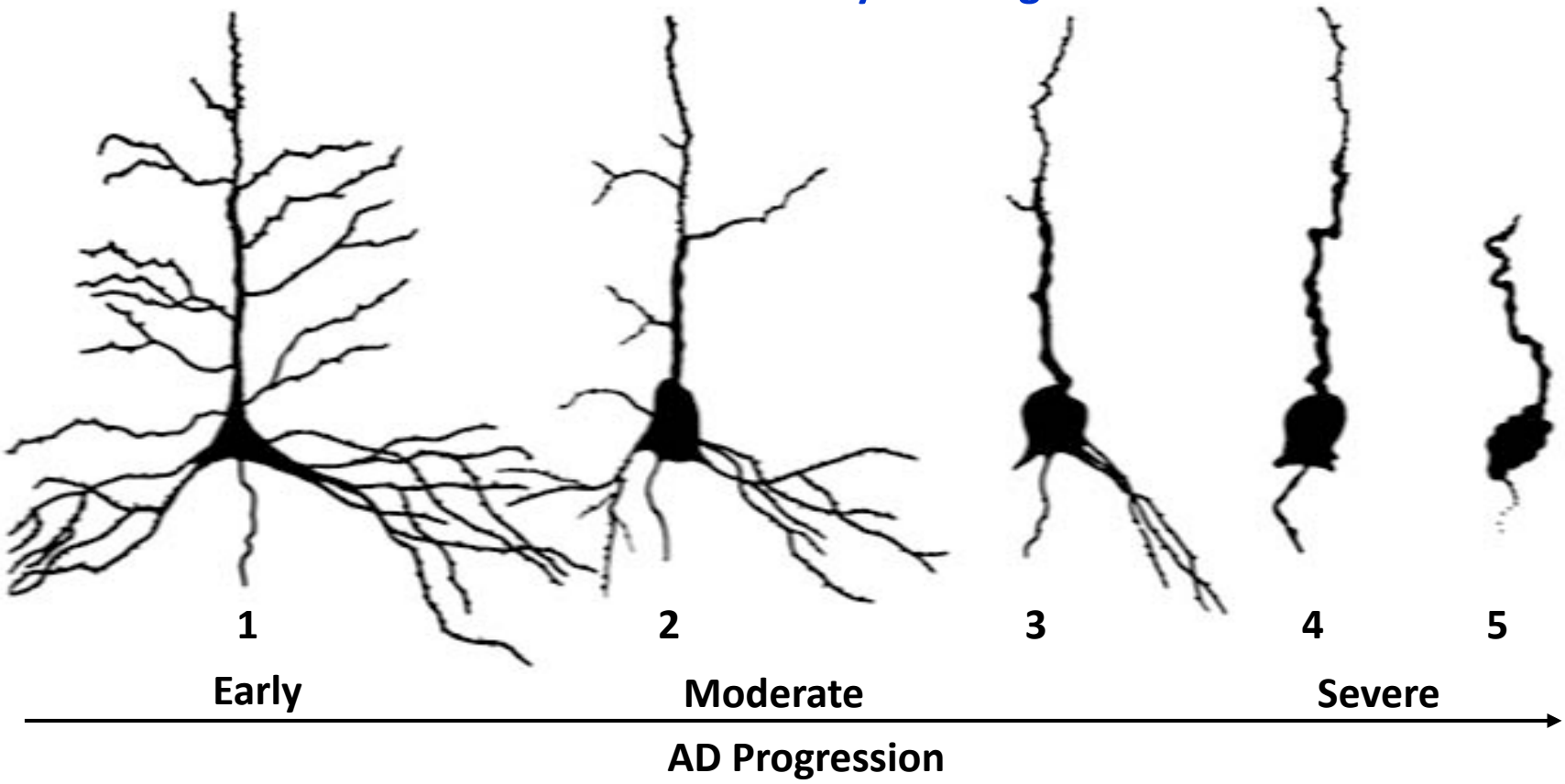




Normal Development



Neuroinflammation , Deposition of Plaques and Neurofibrillary Tangles, Synaptic Loss and Decline of Memory and Cognition



DHA, Neuroprotectin D1, Cognitive Decline and Alzheimer's.

In AD transgenic mice, dietary DHA restores cerebral blood volume, reduces Aβ deposition, and ameliorates Aβ pathology.

F Calon, …. and Greg M. Cole (2004); *Neuron;*

Green, K., LaFerla, F. (2007) *J. Neurosci.*

Eleven observational studies and four clinical trials favor a role for DHA in slowing cognitive decline in elderly individuals without dementia but not for the prevention or treatment of dementia, including AD". Fotuhi, M., Mohassel, P., and Yaffe, K., (2009) *Nature Clin. Pract. Neurol.*

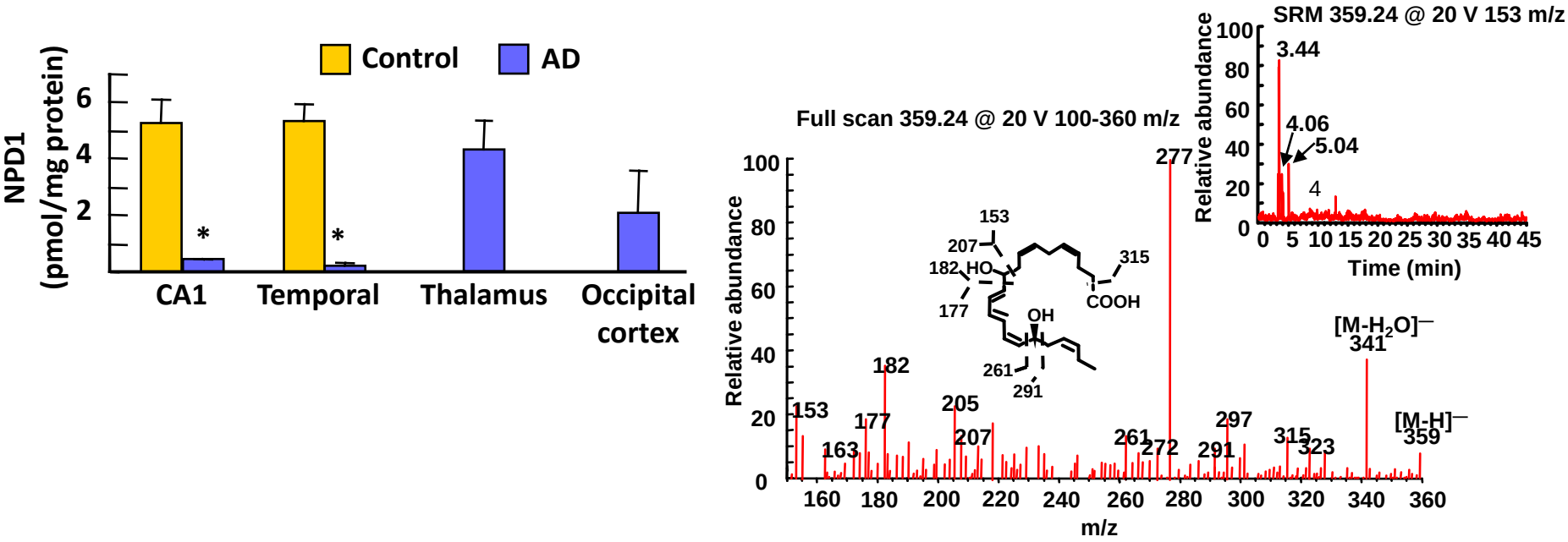
Mediterranean diet…"associated with a trend for reduced risk for MCI and with reduced risk for MCI conversion to AD" Scarmeas, N. *et al* (2009). *Arch Neurol.*

NPD1 downregulates Aβ release and is anti-apoptotic.

Lukiw, W., Cui, N.,…. and Bazan, N. (2005) *J. Clin. Invest.*

NPD1 downregulates neuroinflammation, is anti- apoptotic, and promotes cell survival. Marcheselli, V.L., *et al.* JBC (2003) ; Mukherjee, P., *et al* (2004) *Proc. Natl. Acad. Sci.;* Lukiw, W. *et al* (2005) *JCI*

NPD1 is Reduced in CA1 Region of AD Brain



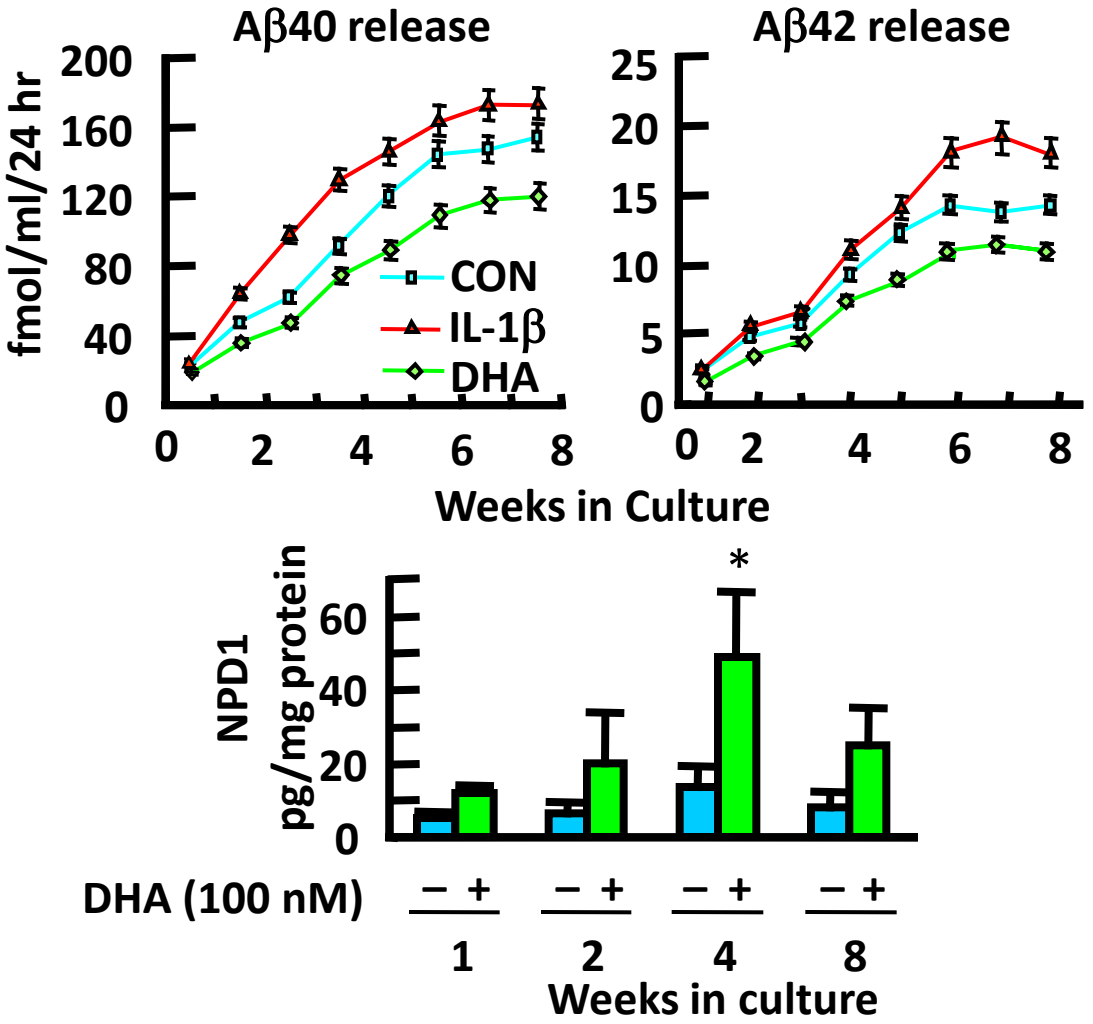
Hippocampal CA1 and Other Brain Samples

Case	Age/ Sex	PMT (hrs)	Plaque/Tangle (average lesion density/mm^2)	RNA (260 nm/ 280 nm)
Control				
1	70/M	1.3	0/5	2.0
2	69/M	3.0	0/2	2.1
3	68/F	2.0	1/2	1.9
4	71/F	1.5	0/4	2.1
5	66/F	2.4	0/5	2.0
6	70/M	2.5	1/2	1.9

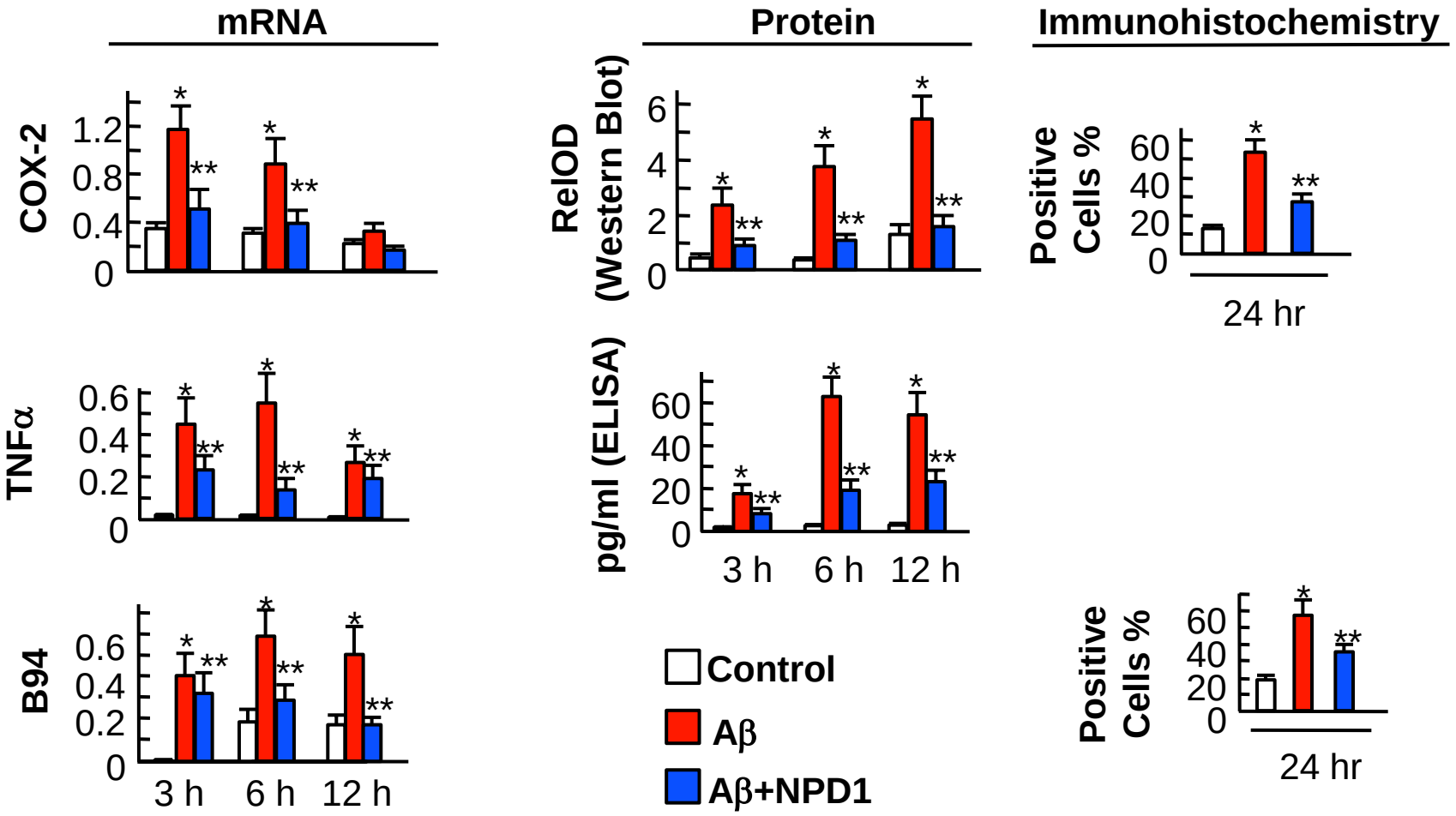
Case	Age/ Sex	PMT (hrs)	Plaque/Tangle (average lesion density/mm^2)	RNA (260 nm/ 280 nm)
Alzheimer's				
1	68/F	1.5	8/15	2.0
2	72/M	2.3	6/13	2.0
3	70/F	1.3	7/12	2.0
4	67/M	2.1	6/14	2.1
5	69/F	1.6	8/10	2.0
6	76/M	3.0	Severe	1.9

W. Lukiw, J. Cui, V.L. Marcheselli, M. Bodker, K. Gotlinger, C.N. Serhan, and N.G. Bazan; A Role for DHA–Derived Neuroprotectin D1 in Neural Cell Survival and Alzheimer's Disease; *J. Clin. Invest.*, 2005; 115: 2774 – 2783

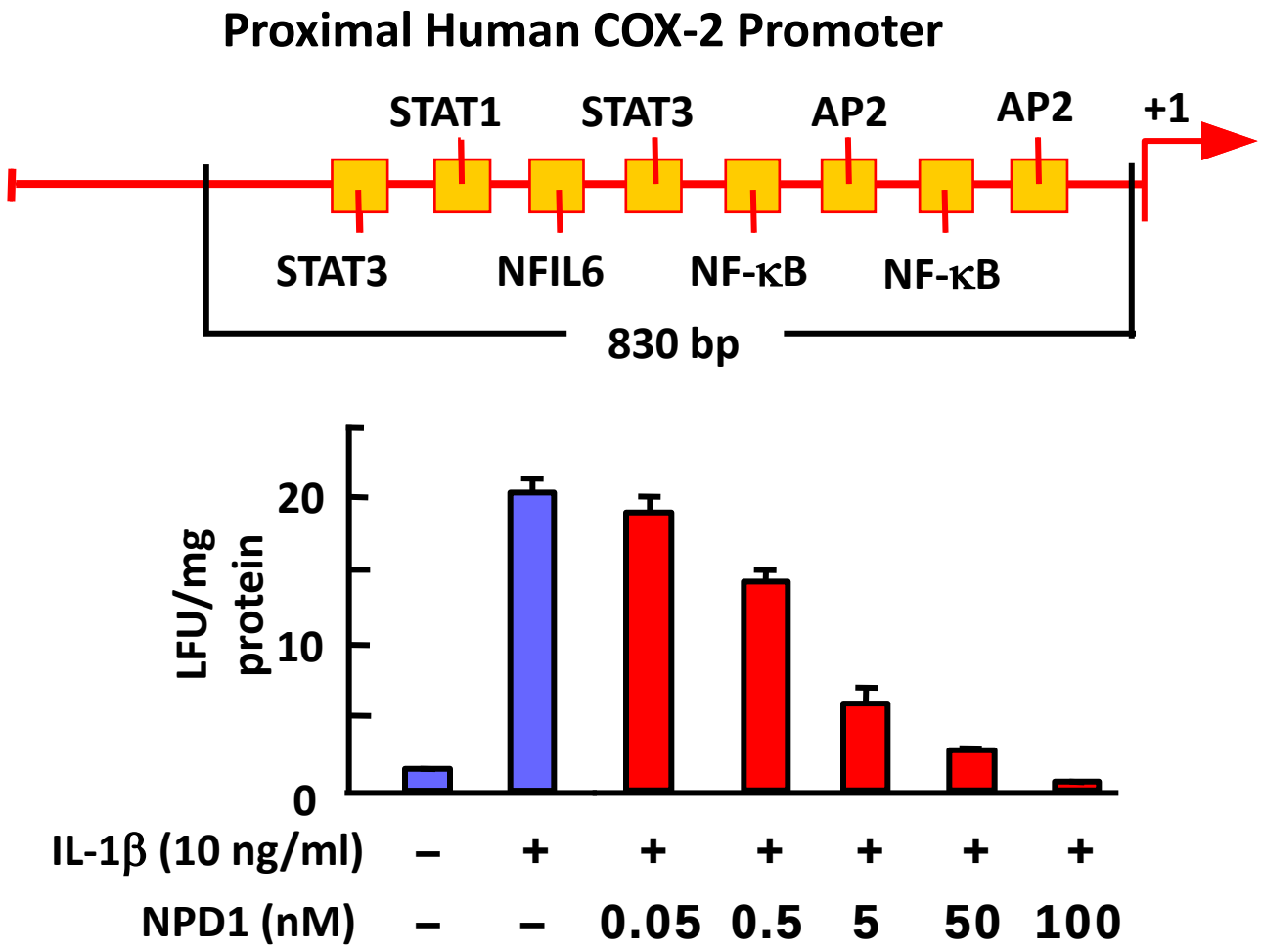
DHA Attenuates Aβ Peptide Secretion and Serves as the Precursor for NPD1 Biosynthesis.



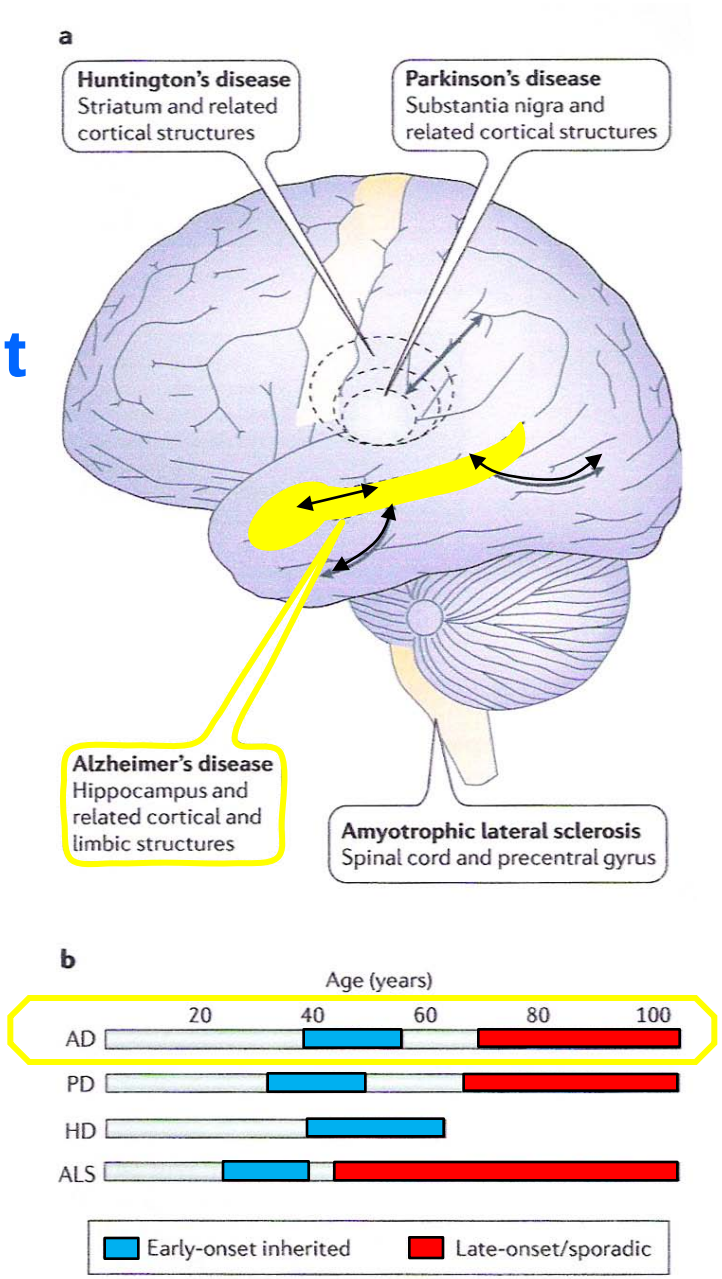
NPD1 Down-Regulates Aβ-Induced Expression of Pro-Inflammatory Genes



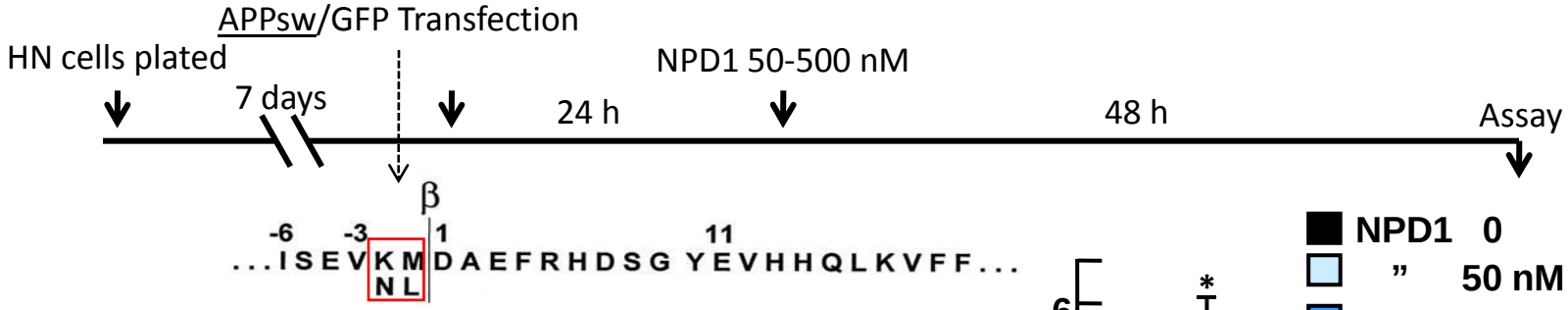
NPD1 Inhibits IL-1β-Induced COX-2 Expression in Retinal Pigment Epithelial Cells

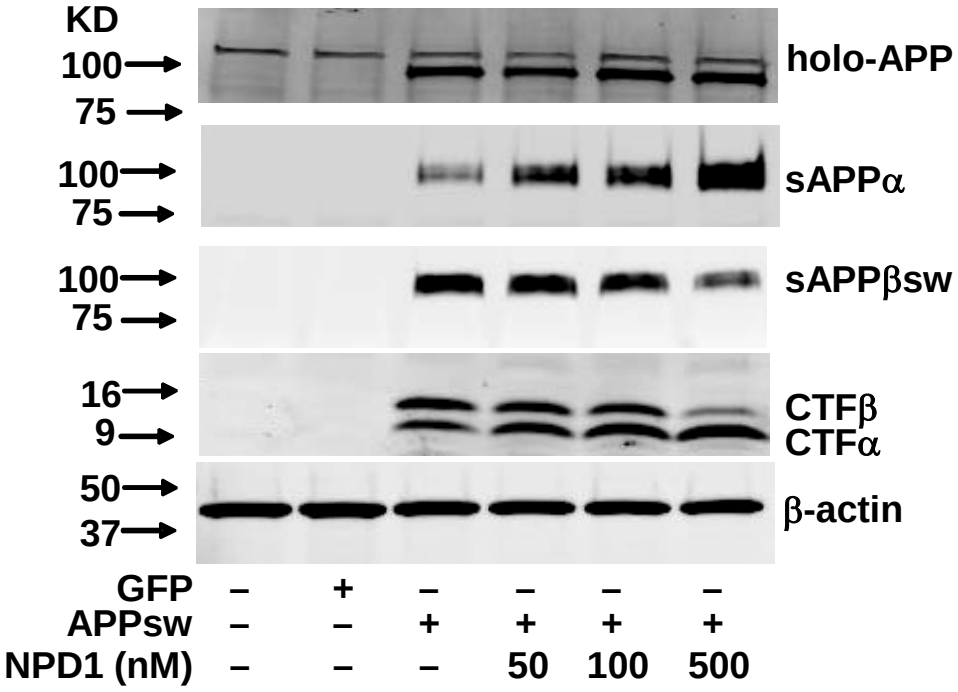


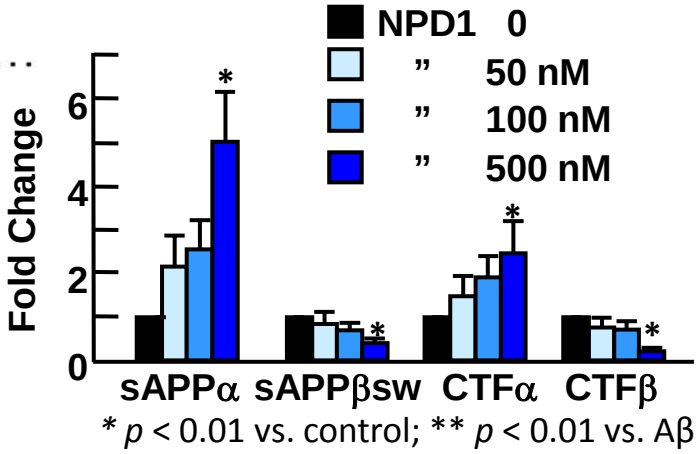
Swedish double mutation of Amyloid Precursor Protein is associated with early-onset familial Alzheimer's Disease

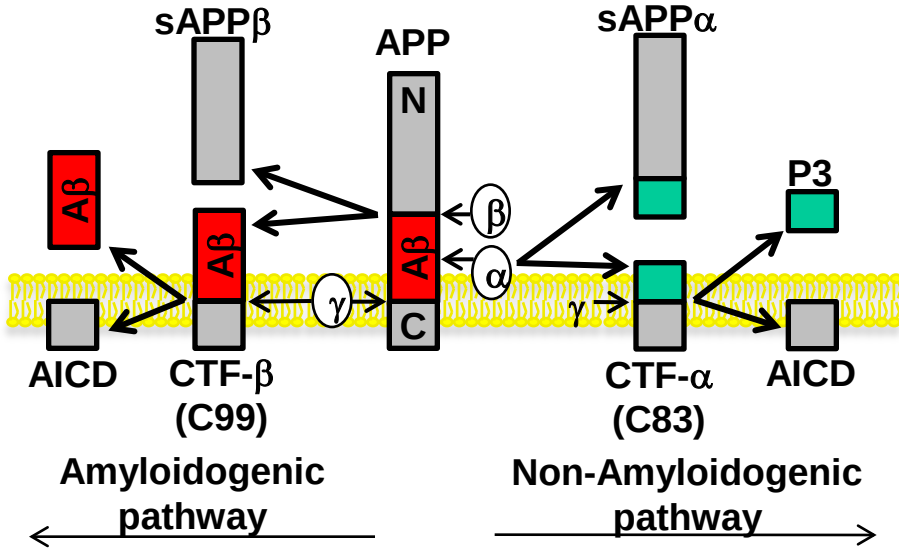


NPD1 Shifts APP Processing To Non-Amyloidogenic Pathway in Human Neural Progenitor Cells

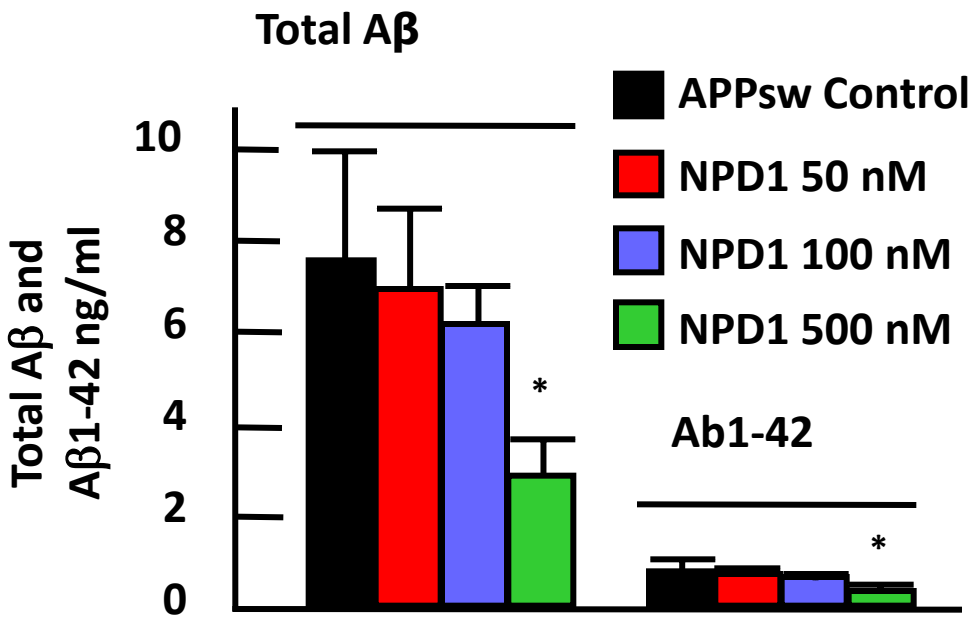






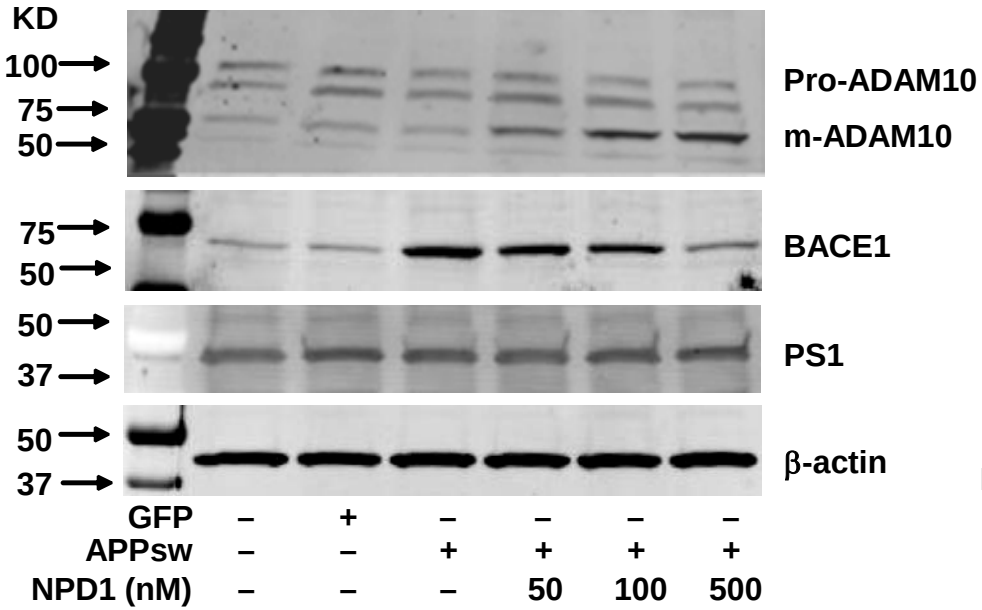


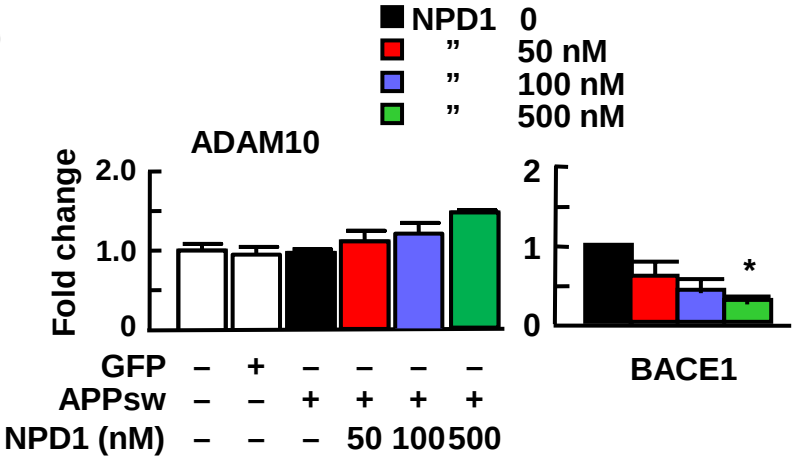
NPD1 Reduced Levels of Aβ Released From HN Cells Overexpressing APPsw

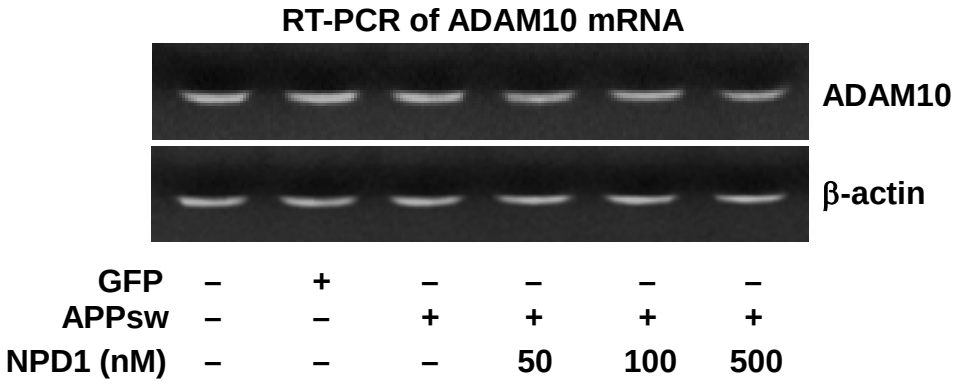


* $p < 0.01$ vs. control; ** $p < 0.01$ vs. Aβ

NPD1 Decreases BACE1 Levels While Simultaneously Activating ADAM10

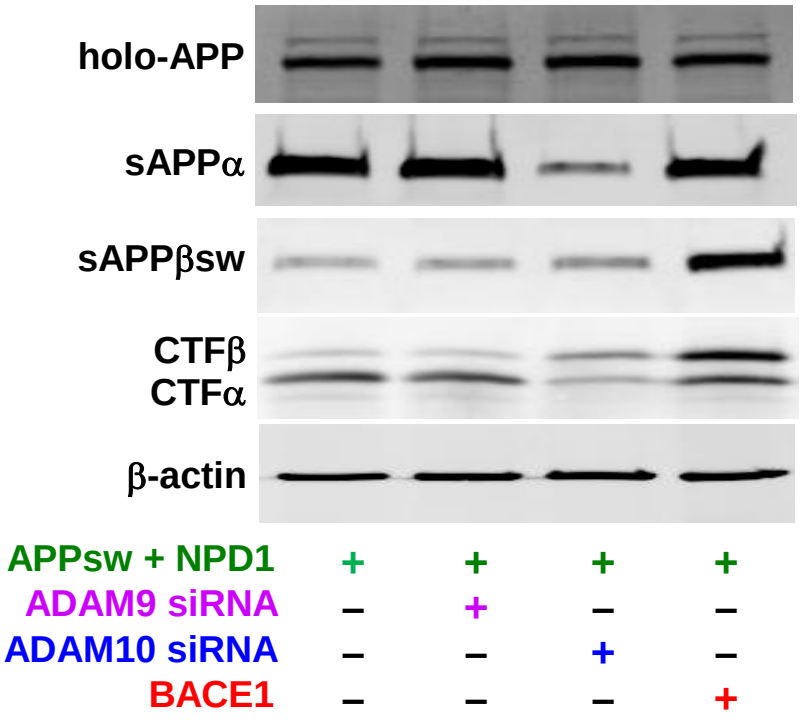


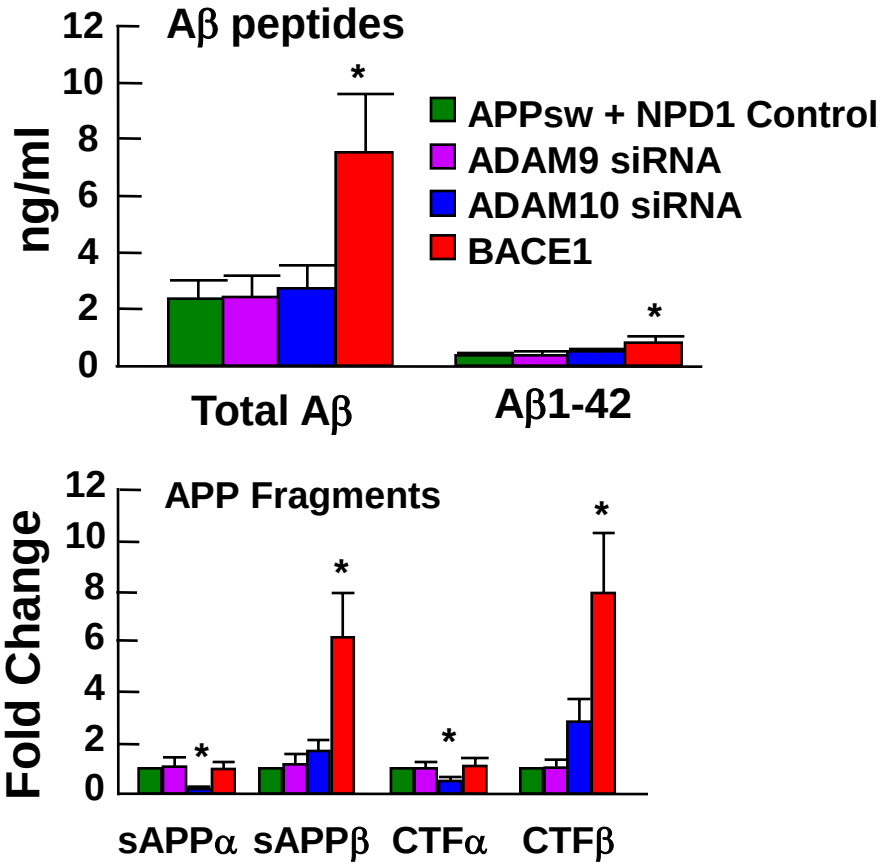




* $p < 0.01$ vs. control; ** $p < 0.01$ vs. Aβ

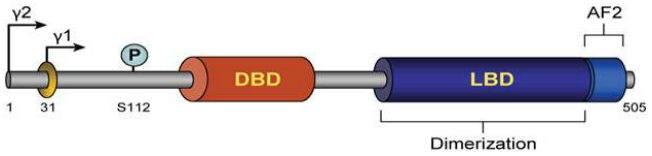
BACE1 and ADAM10 are Required for NPD1 Regulation of APP Processing

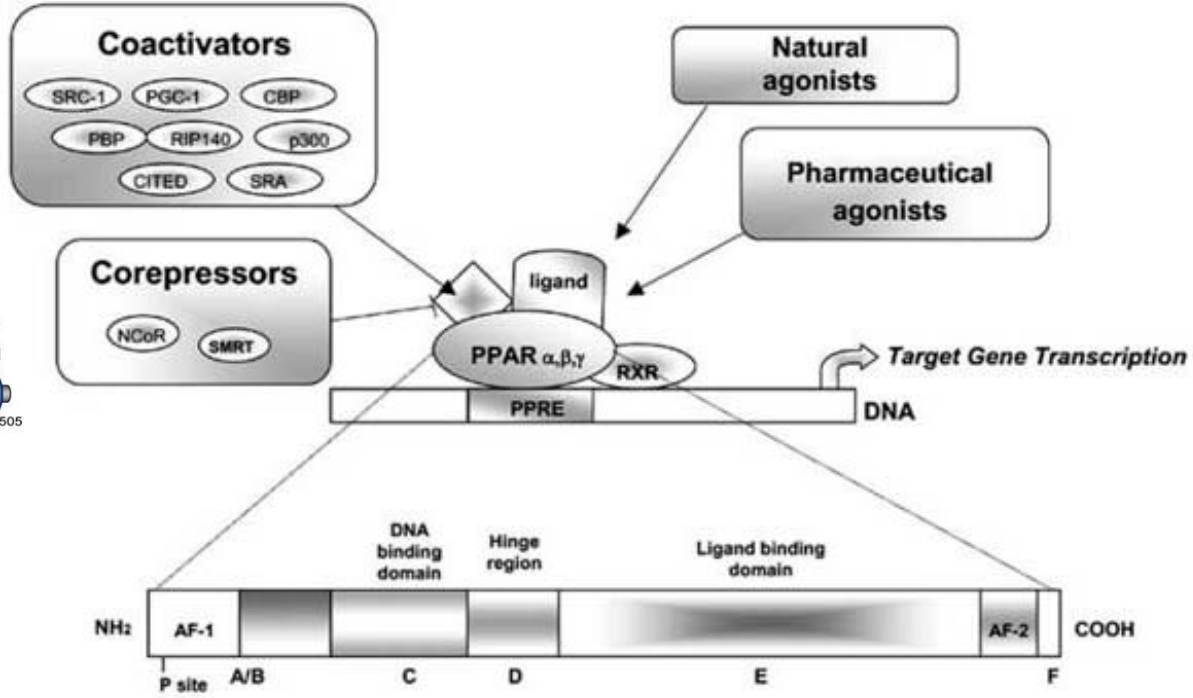




* $p < 0.01$ vs. control; ** $p < 0.01$ vs. Aβ

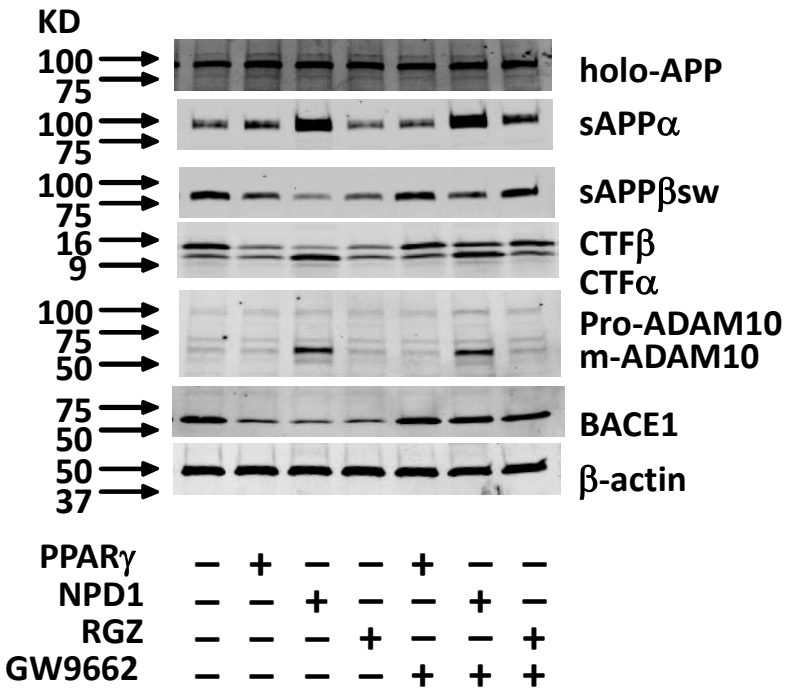
PPARγ is a DNA-Binding Transcription Factor Turned On After Agonist Binding

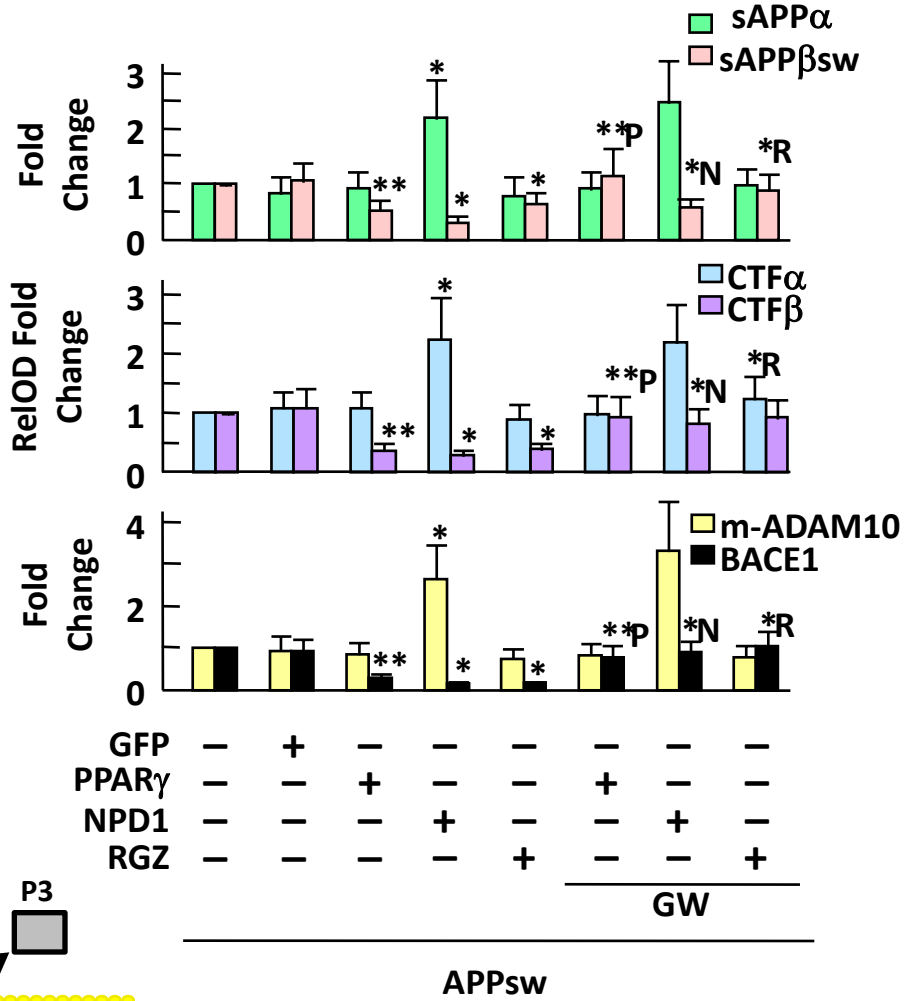


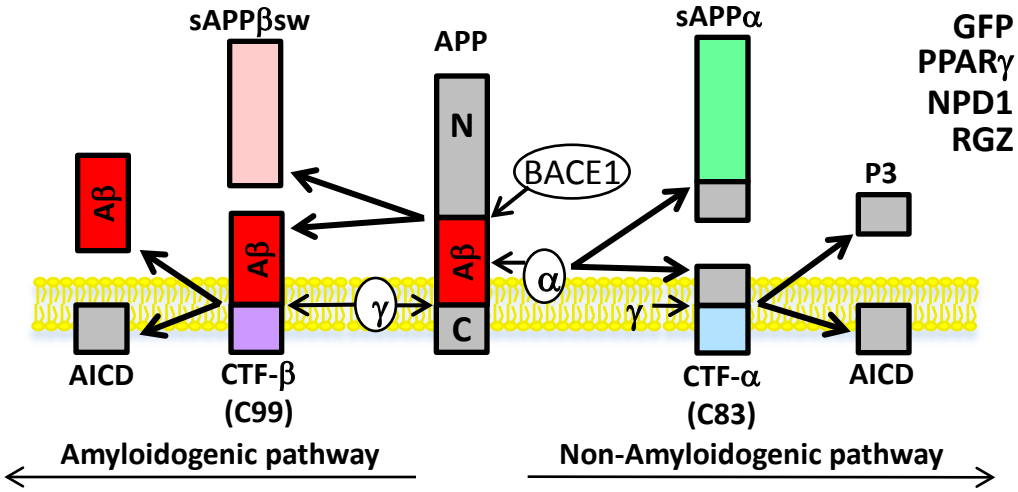


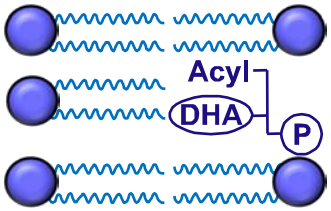
PPARγ Has a Versatile Fatty-Acid Binding Pocket

PPARγ Activation Required for NPD1 Suppression of BACE1 But Not for Activation of ADAM10



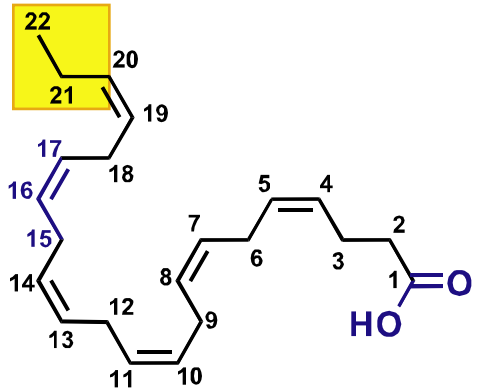






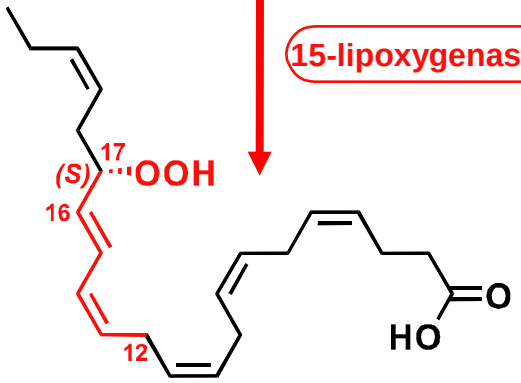
Phospholipase A 2

Omega-3 Tail



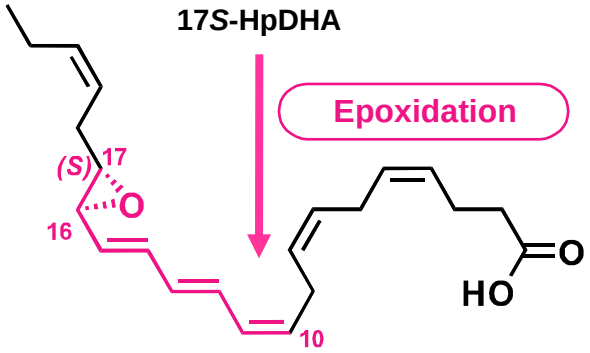
Docosahexaenoic acid (DHA)

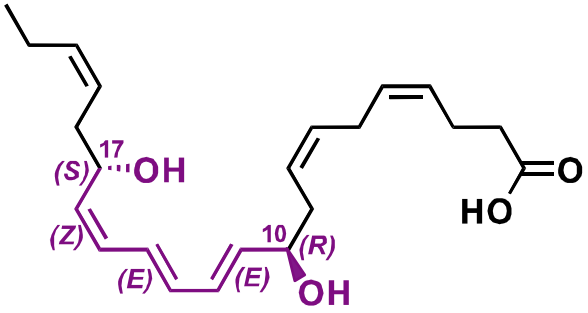
15-lipoxygenase-1



17S-HpDHA

Epoxidation





Neuroprotectin D1 (NPD1)

Hydrolysis

Bioactivity

- Nerve regeneration
- Leukocyte infiltration
- Anti-Apoptotic Bcl-2 proteins
- Shifts APP Processing to Non-Amyloidogenic Pathway
- BACE1 Levels While Simultaneously Activating ADAM10
- Anti-Apoptotic Bioactivity vs Aβ42
- Proinflammatory Gene expression

N. Bazan, 2009

Neuroprotectin D1 is a Sentinel Ready to be Deployed during the Initiation of CNS injury and /or Neurodegenerations.

- Interplay of NPD1–mediated signaling aims to counteract evolving pro-inflammatory, synaptic-damaging events triggered by converging cytokine and other factors.

- Bcl-2 pro- and anti-apoptotic gene families, Akt/m-TOR, pro-inflammatory signaling and neurotrophins lie, with NPD1, along a cell fate-regulatory pathway/s whose components are highly interactive, and have potential to function cooperatively in the maintenance of cellular homeostasis, neural cell plasticity and cell survival.

- Regulation of NPD1 synthesis may redirect cellular fate towards successful cell aging and survival upon injury/neurodegeneration.

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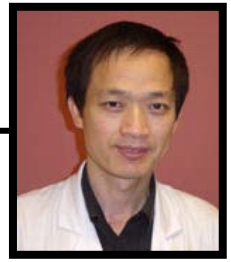

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