Nicolas G Bazan, MD, PhD

Neuroscience Center of Excellence

School of Medicine ,LSU Health New Orleans

nbazan@lsuhsc.edu

Accomplishments of Neuroscience Center of Excellence Faculty LSU Health New Orleans—School of Medicine

Dr. H. E. P. Bazan has revealed the human cornea nerve architecture and discovered therapeutic approaches to sustain cornea integrity. She has found a new Resolvin D6 isomer produced in the cornea and uncovered a transcriptomic link with the trigeminal ganglia for **cornea nerve regeneration**.

Dr. L. Belayev discovered that blocking pro-inflammatory receptors and docosanoid administration led to recovery and brain protection in **ischemic stroke and traumatic brain injury**.

Dr. J. Calandria uncovered that PLA2G6 releases messengers that determine dopaminergic neurons fate by converting astrocytes and microglia to protective phenotypes. She also found that Maresin 1 protects dopaminergic neurons in **Parkinson's** models.

Dr. J. Erickson discovered activity-regulated glutamine transport in hippocampal neurons and novel compounds that prevent brain injury in a model of temporal lobe **epilepsy**. He currently is investigating if these compounds are effective in a model of **Alzheimer's** disease.

Dr. H. Farris's research is focused on the limits of **visual and auditory processing**, including how hormones and reproductive cycle modulate the retina's sensitivity to light.

Dr. S. Gasparini studies how the dendrites, the smallest compartments of neurons, receive and combine electrical impulses in regions responsible for learning and memory. In one of these studies, she has discovered how the malfunction of a common ion channel can make neurons hyperexcitable and prone to **epilepsy**.

Dr. W. C. Gordon uncovered pathways of dietary-derived fatty acids needed for rods in retinal disease (**age-related macular degeneration**) and critical events for retention in retina.

https://www.medschool.lsuhsc.edu/neuroscience/faculty.aspx

Accomplishments of Neuroscience Center of Excellence Faculty LSU Health New Orleans—School of Medicine

Dr. S. Hong uncovered inflammation-resolving lipid mediators in **diabetes** and **aging-impaired wound healing**. Also, how western diet affects wound healing and neurodegeneration.

Dr. M. Jin discovered that FATP4 Is a promising therapeutic target that can prevent **retinal degeneration** and vision loss in patients with mutations in the RPE65 gene involved in the visual cycle.

Dr. J. J. Lentz discovered mechanisms of **Usher syndrome**, a genetic cause of deafness, imbalance, and blindness. She also created a mouse model of Acadian Usher to develop new therapies relevant in Louisiana and throughout the world.

Dr. X.C. Li uncovered language development events related to **autism spectrum disorders** using songbirds as a model, and found miRNAs regulating the FOXP2 gene, mutations in the FOXP2 gene lead to **language impairment** in humans.

Dr. W. J. Lukiw discovered critical events in the molecular genetics, epigenetics, proteomics and microbiomics of the aging brain and of **sporadic Alzheimer's disease**, and of **viral-and-prion**-mediated brain and retinal disorders.

Dr. X. Tian uncovered molecular events of aging and dopaminergic neurons. Her studies have significant impact on our understanding of **aging** and **neurodegenerative diseases**.

Dr. C. Wu uncovered Mask-mediated enhancement of autophagy to protect against neurodegenerations linked to **Alzheimer's and ALS**, and presynaptic Ubiquitin pathway and dephosphorylation pathway to control synaptic structural plasticity governing neural development and cognition/learning and memory.

https://www.medschool.lsuhsc.edu/neuroscience/faculty.aspx

Redundancy and Resiliency Signaling for Neuronal Longevity Counteracts Alzheimer's Onset.

Nicolas G Bazan, MD, PhD

Neuroscience Center of Excellence

School of Medicine ,LSU Health New Orleans

nbazan@lsuhsc.edu

www.awarenessties.us/nicolasbazan

Disclosure

Founder of startup companies that have exclusively licensed technologies from LSUHSC involving elovanoids and related lipids for clinical applications:

-NeuResto Therapeutics, LLC

-CurVirBiotech, LLC.

and also

-SouthRampartPharma,LLC

Failures of Effective Alzheimer's Disease Therapies

Over 300 compounds tested (2000 – 2020) were unsuccessful to achieve primary endpoints.

The N-methyl-D-aspartate-receptor antagonist memantine (Namenda), approved for moderate to severe AD.

Acetylcholinesterase inhibitors are used for mild to moderate AD (symptomatic)

-Donepezil (Aricept)
-Galantamine (Reminyl)
-Rivastigmine (Exelon)

Is There a Molecular Logic that Sustains Neuronal Survival When Confronted to Adversities including the Onset of Neurodegenerative Diseases?

- **Why don't diseases manifest during latency in inheritable neuro-degenerative diseases**(familial Alzheimer's, Retinitis Pigmentosa,)**?**

- **Do cell-specific responses based on defined molecular principles counteract the consequences of mutation expression, gene susceptibility, homeostasis disruptions and/or the onset of uncompensated oxidative stress?**

- The brain under imminent homeostasis disturbance does not surrender easily, it activates the production of molecular guardians of cellular integrity and function

Exploring if the brain under imminent homeostasis disturbance activates the production of molecular guardians of cellular integrity and function

1-Ischemic Stroke and short postmortem brains from early stages of Alzheimer's disease donors

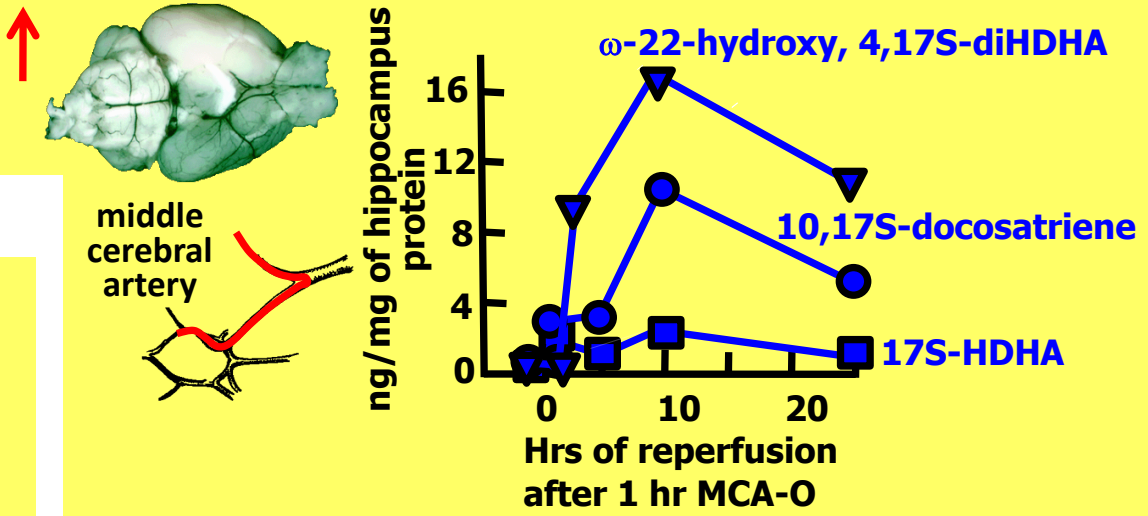
2- Can we identify additional specific molecules using our model of the genetic ablation of Adiponectin Receptor 1?

3-How the new molecules elicit their neuroprotective bioactivity?

4-How do they work in Alzheimer's disease models ?

5-How do they correlate with Alzheimer's onset?

Discovery of Endogenous Formation and Bioactivity of 10,17S-docosatriene in Ischemia-Reperfusion (MCA-O)

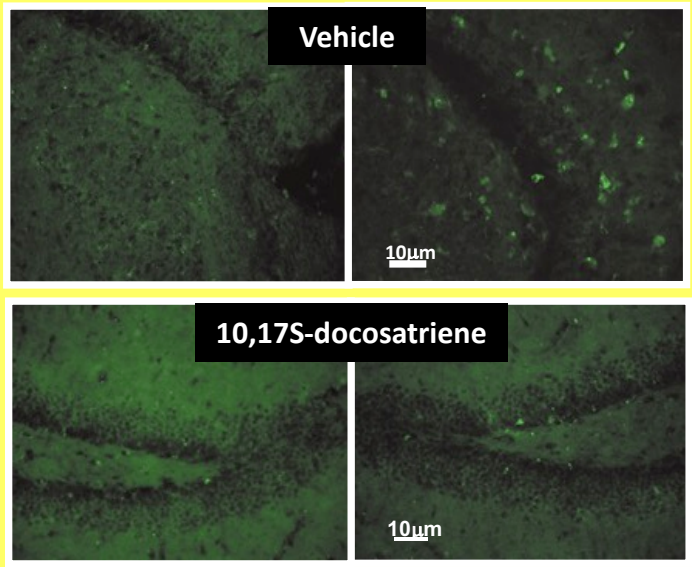


i.c.v. (400 ng/2days)

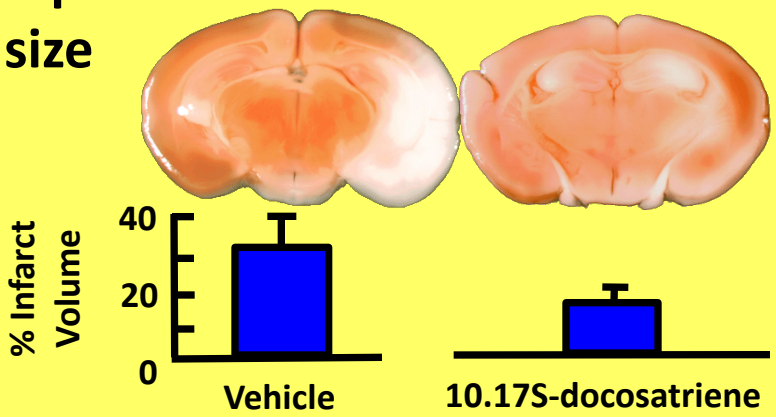
↓PMN infiltration

Myeloperoxidase

Contralateral Ipsilateral (MCA-O)



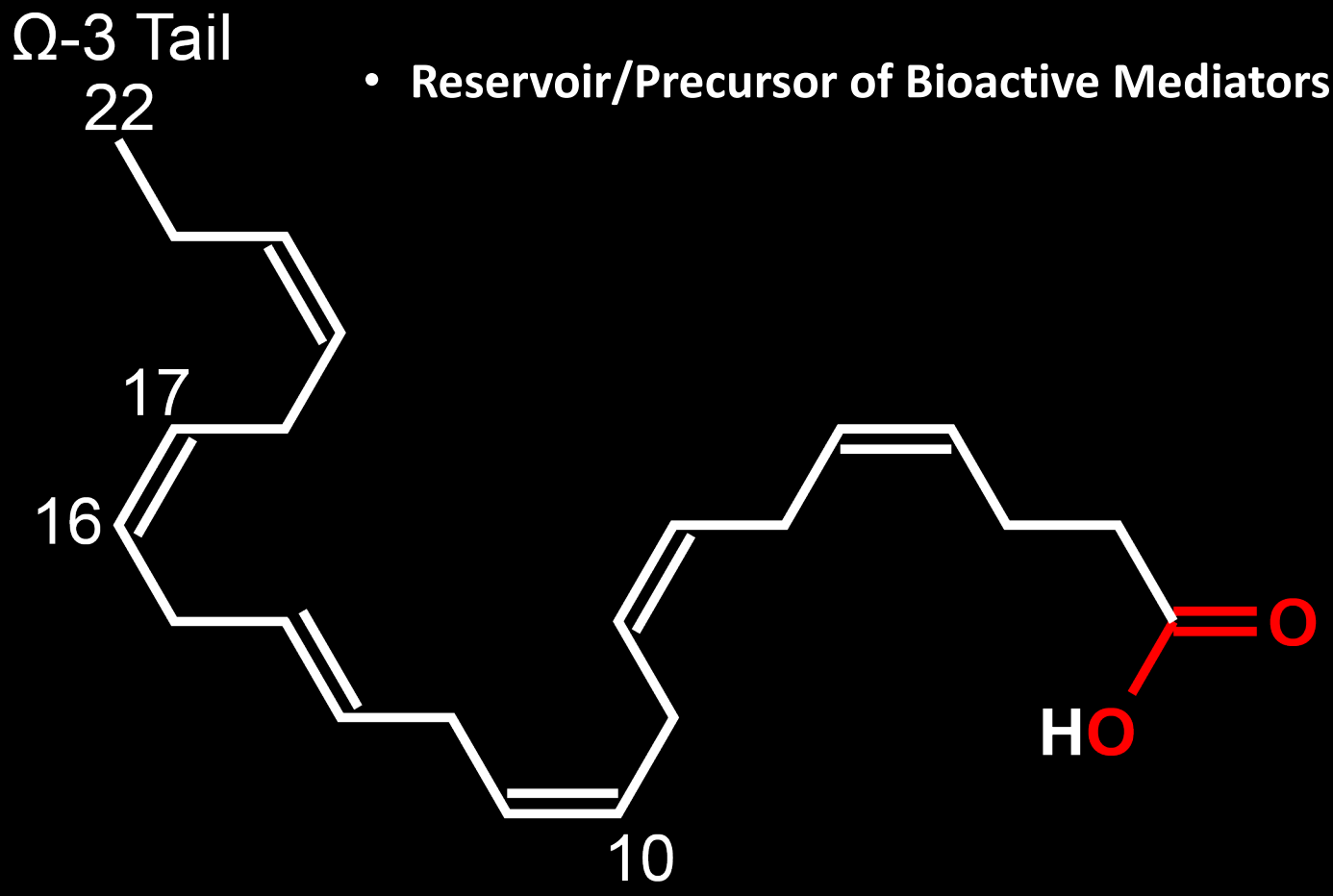
- ↓ NFκB induction
- ↓COX-2 expression
- ↓Stroke size



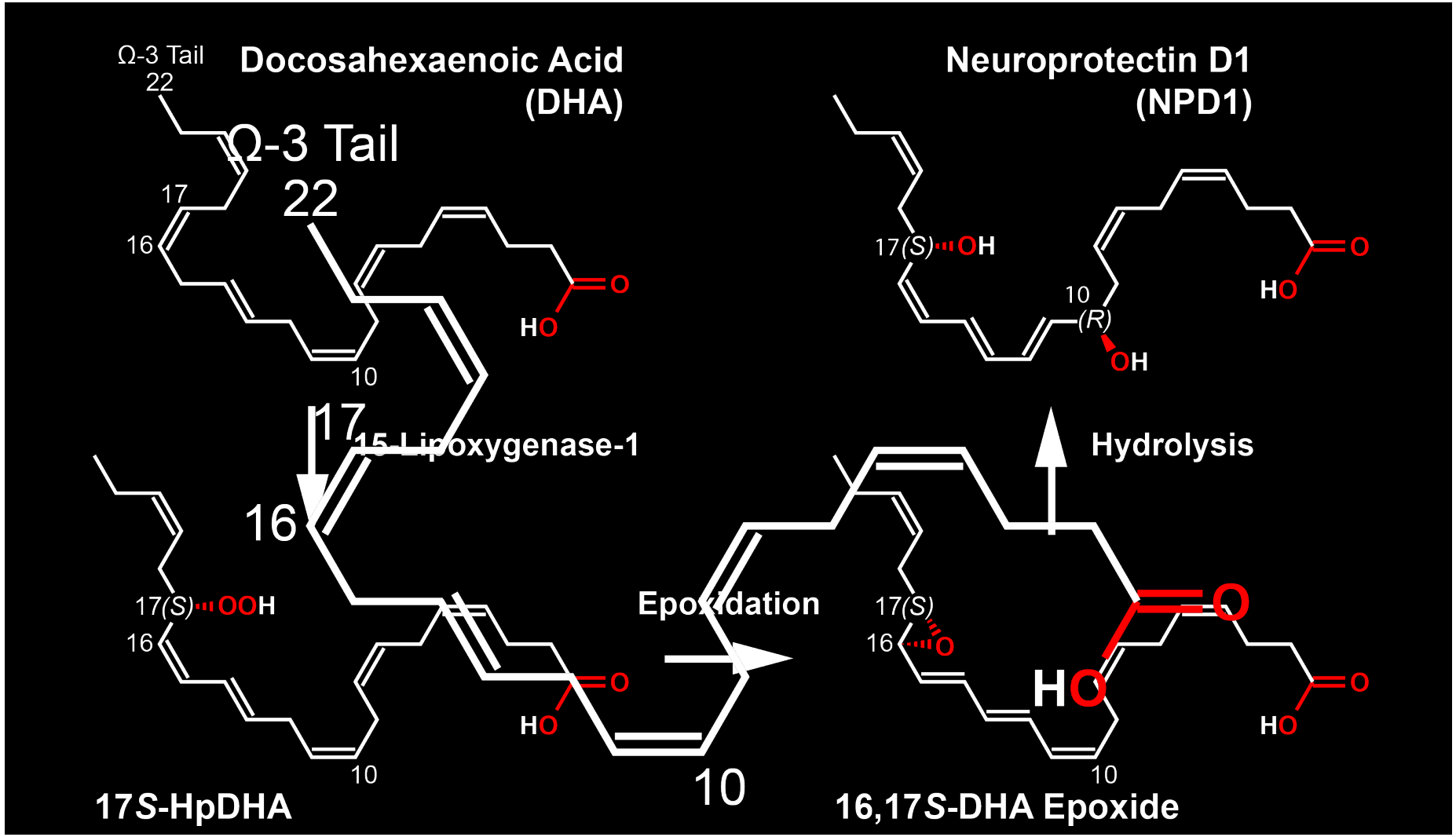
V. Marcheselli,et al. *JBC*, 2003

Docosahexaenoic Acid (Omega-3)

- **Enriched and Retained in Photoreceptors and other parts of the CNS**
- **Reservoir/Precursor of Bioactive Mediators**



Neuroprotectin D1: Stereoselective Lipid Mediator Made on Demand that contributes to RPE Cell Survival



P. Mukherjee, V. Marcheselli, C. Serhan, and N. Bazan,
"Neuroprotectin D1: A docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress" *Proc. Nat. Acad. Sci., U.S.A.*, 101:8491-8496, 2004

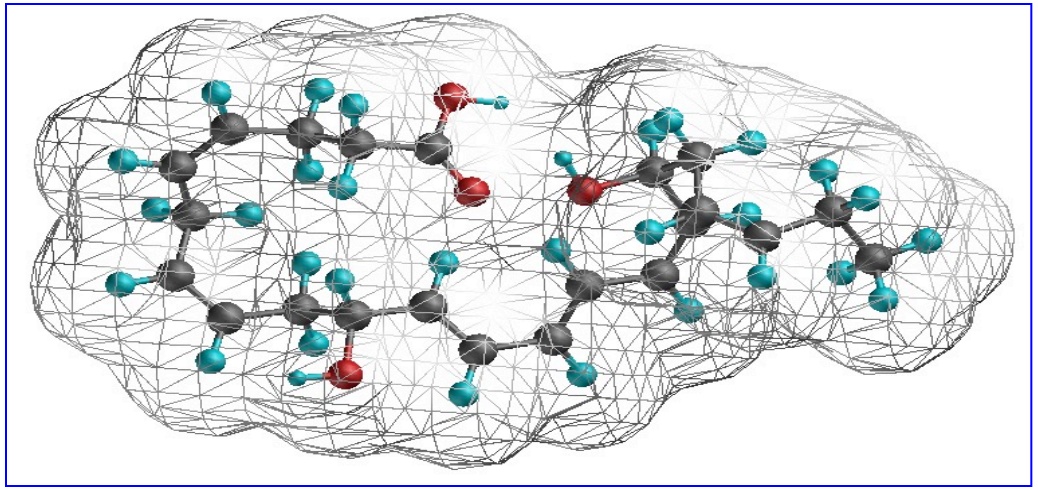
Neuroprotectin D1

A Stereoselective Mediator made on Demand with Modulatory Bioactivity on Inflammatory Signaling, Proteostasis, Nerve Regeneration, Neuroprotection and Cell Survival

Neuroprotective bioactivity during RPE oxidative stress

- **Potent ability to inactivate pro-apoptotic and pro-inflammatory signaling**

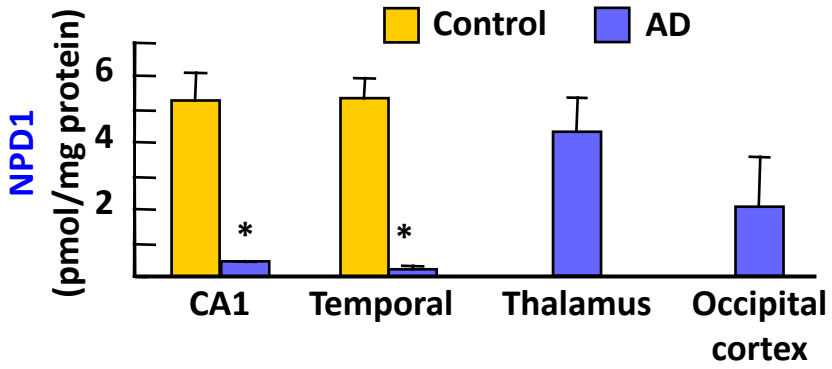
Because it is the first identified neuroprotective messenger of DHA



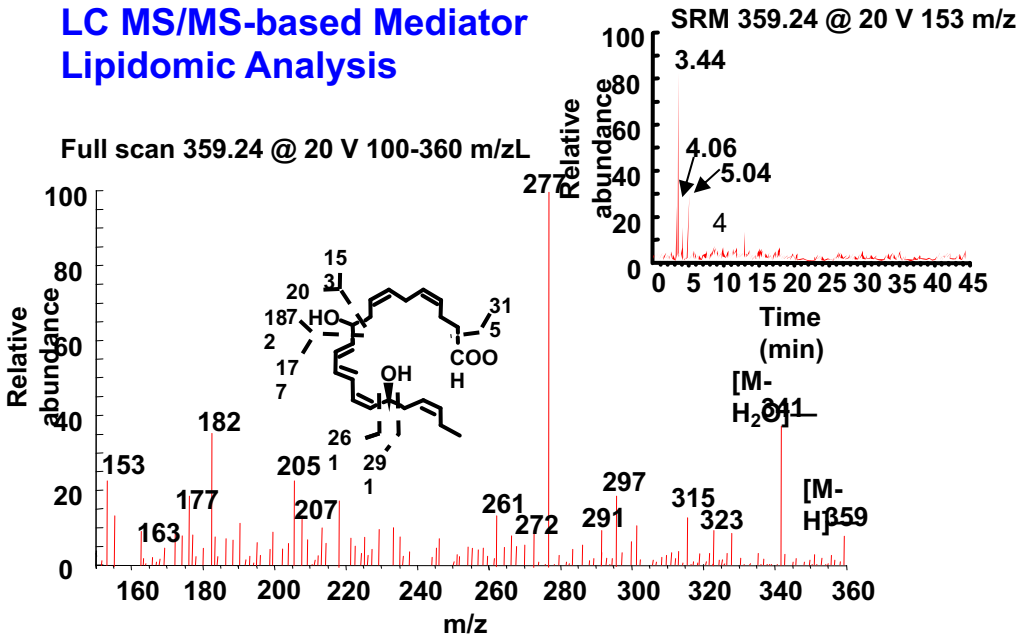
P.Mukherjee, V. Marcheselli, C. Serhan, and N. Bazan,

"Neuroprotectin D1: A docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress"
Proc. Nat. Acad. Sci., U.S.A., 101:8491-8496, 2004

Neuroprotectin D1 is Reduced in CA1 region of AD Brain



LC MS/MS-based Mediator Lipidomic Analysis



Post Mortem Time and Pathology of Human Brain Samples

Case	Age/ Sex	PMT (hrs)	Plaque/Tangle (average lesion density/mm2)	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

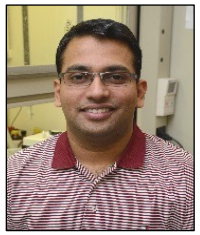
Case	Age/ Sex	PMT (hrs)	Plaque/Tangle (average lesion density/mm2)	RNA (260 nm/ 280 nm)
Alzheimer's				
1	68/F	1.5	8/15	2.0
2	72/M	2.3	6/13	2.0
3	70/F	1.3	7/12	2.0
4	67/M	2.1	6/14	2.1
5	69/F	1.6	8/10	2.0
6	76/M	3.0	Severe	1.9

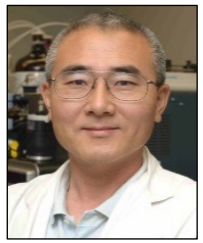
W. Lukiw, *et al*. A Role for DHA–Derived Neuroprotectin D1 in Neural Cell Survival and Alzheimer's Disease; *J. Clin. Invest.*, 2005; 115:2774 – 2783

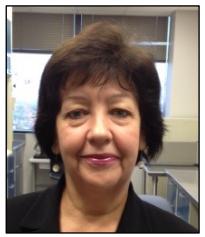
2- Can we identify additional specific molecules using our model of the genetic ablation of Adiponectin Receptor 1?
This model uncovered a molecular decision making to conserve DHA and a switch necessary
for membrane lipidome organization and gene regulation

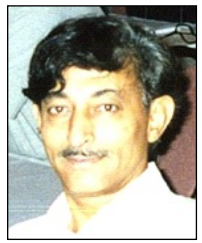
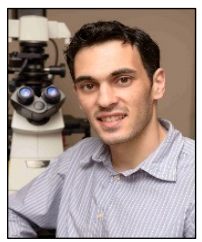
D. Rice et al, *Nature Comm.* 2015

3-How the new molecules elicit their neuroprotective bioactivity?
4-How do they work in Alzheimer's disease models ?
5-How do they correlate with Alzheimer's onset?




SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

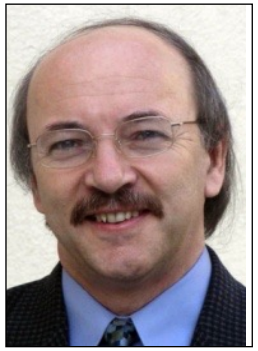
Elovanoids are a novel class of homeostatic lipid mediators that protect neural cell integrity upon injury

Surjyadipta Bhattacharjee,[1] Bokkyoo Jun,[1] Ludmila Belayev,[1] Jessica Heap,[1] Marie-Audrey Kautzmann,[1] Andre Obenaus,[2]* Hemant Menghani,[1,3] Shawn J. Marcell,[1] Larissa Khoutorova,[1] Rong Yang,[4] Nicos A. Petasis,[4] Nicolas G. Bazan[1†]

Sci. Adv. 2017;3: e1700735 27 September 2017

University of Southern California

Nicos A. Petasis



www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Elovanoids are novel cell-specific lipid mediators necessary for neuroprotective signaling for photoreceptor cell integrity

Bokkyoo Jun[1], Pranab K. Mukherjee[1], Aram Asatryan[1], Marie-Audrey Kautzmann[1], Jessica Heap[1], William C. Gordon[1], Surjyadipta Bhattacharjee[1], Rong Yang[2], Nicos A. Petasis[2] & Nicolas G. Bazan[1]

University of California, Irvine, CA

Andy Obenaus

Scientific Reports | 7: *5279* | 2017. DOI:10.1038/s41598-017-05433-7

Elovanoids (from Omega 3-Fatty Acids)

Neurons express

the fatty acid elongase ELOVL4 : ≥ C 28

(necessary enzyme to biosynthesize the precursors)

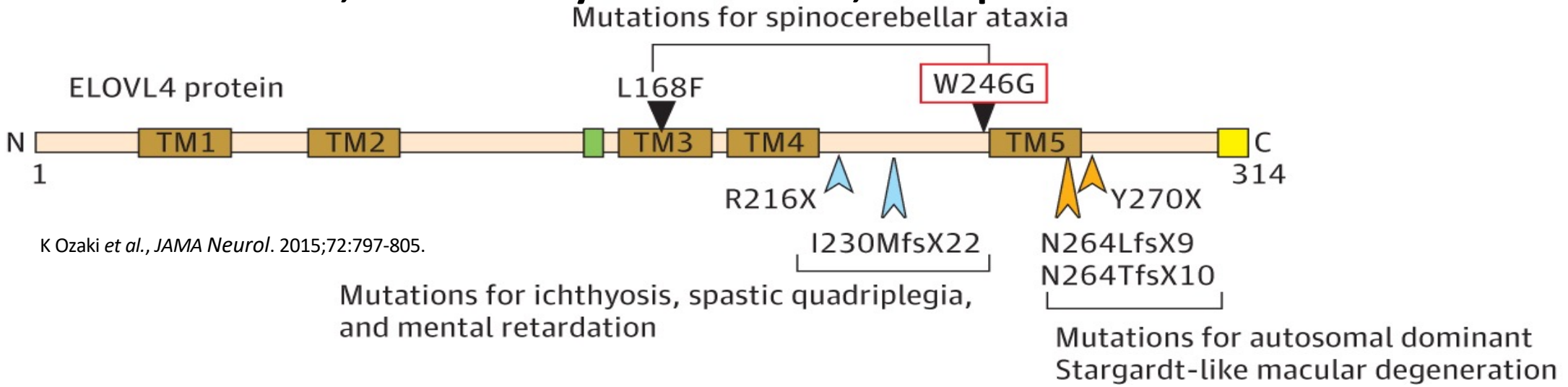
Stereoselective Mediators Made on Demand with Modulatory Bioactivity on Neuroinflammatory Signaling, Neuroprotection, Vision and Cell Survival

- **Counteract uncompensated oxidative stress**
- **Potent ability to inactivate pro-apoptotic and pro-inflammatory signaling**

Jun B et al, *Sci. Rep* (2017) ; Bhattacharjee S, et al *Sci. Adv*. (2017)

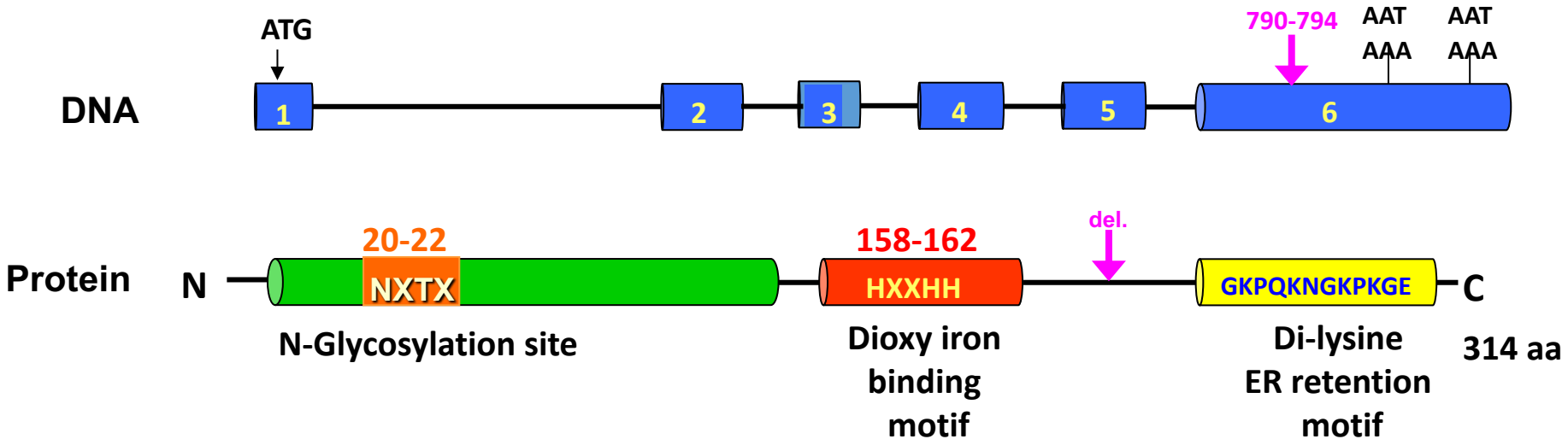
Mutations in *ELOVL4*

Impaired neural development, neuronal dysfunction, hyper-excitability and seizures, mental retardation, neuroichthyotic disorders, and spinocerebellar ataxia



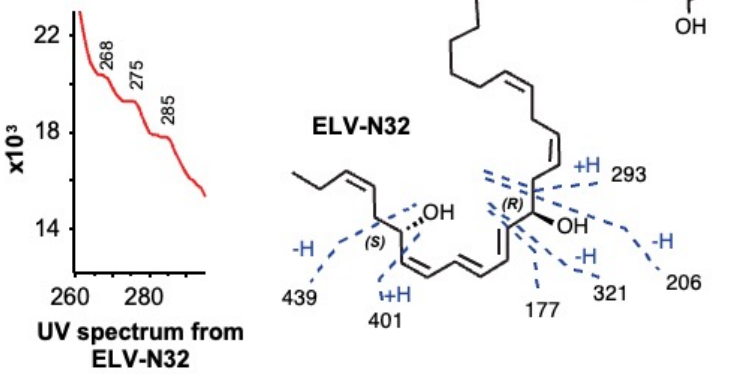
K Ozaki *et al.*, *JAMA Neurol*. 2015;72:797-805.

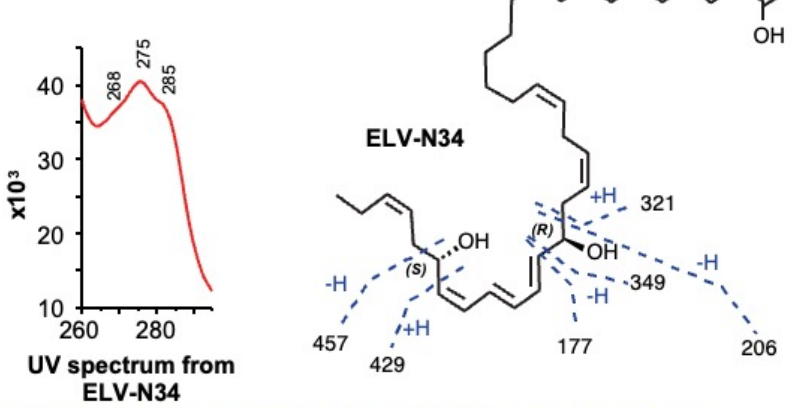
Logan et al., 2013 PNAS USA



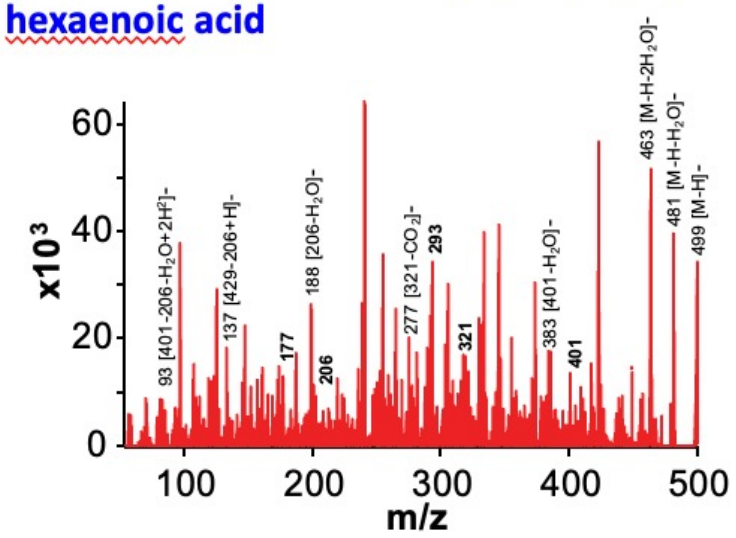
5 bp deletion, premature termination of the protein, loss of ER retention signal, mislocalized aggregation of a non-functional enzyme

Elovanoids are neuroprotective and pro-homeostatic in:

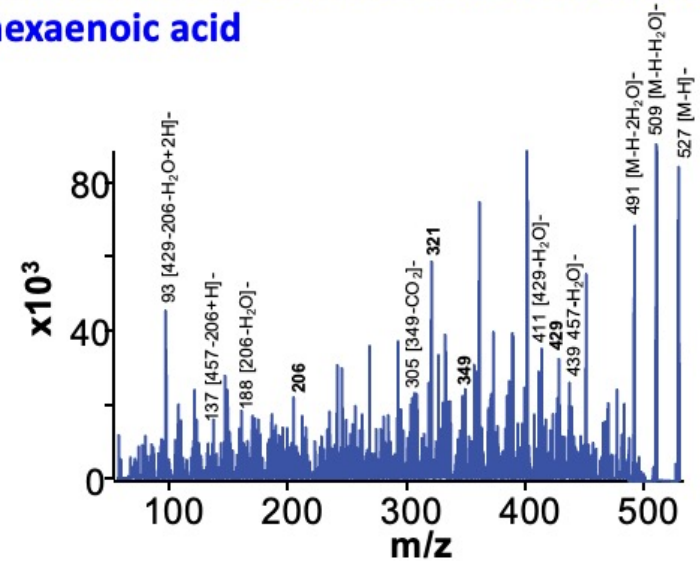




(14*Z*,17*Z*,20*R*,21*E*,23*E*,25*Z*,27*S*,29*Z*)-20,27-dihydroxydo-triaconta-14,17,21,23,25,29-hexaenoic acid



(16*Z*,19*Z*,22*R*,23*E*,25*E*,27*Z*, 29*S*,31*Z*)-22,29-dihydroxytetra-triaconta-16,19,23,25,27,31-hexaenoic acid



a) Oxygen/glucose deprivation or NMDA receptor-mediated excitotoxicity

b) Stroke: reduces volume, induces cell survival, and attenuates neurovascular unit disruption, injected 1h after 2 hrs of middle cerebral artery occlusion.

c) Upregulate anti-apoptotic and downregulate pro-apoptotic protein abundance

d) Retinal pigment epithelial cells, sustain photoreceptor cell integrity and function

-Bhattacharjee S, et al. Sci. Adv. 2017:3:e1700735

-Bazan N. Mol. Aspects Med. 2018;64:18-33.doi:10.1016/

-Jun, B. Et al. Sci. Rep. 2017;7:5279:doi:10.1038/

Exploring if the brain under imminent homeostasis disturbance activates the production of molecular guardians of cellular integrity and function

1-Ischemic Stroke and short postmortem brains from early stages of Alzheimer's disease donors

2- Can we identify additional specific molecules using our model of the genetic ablation of Adiponectin Receptor 1?

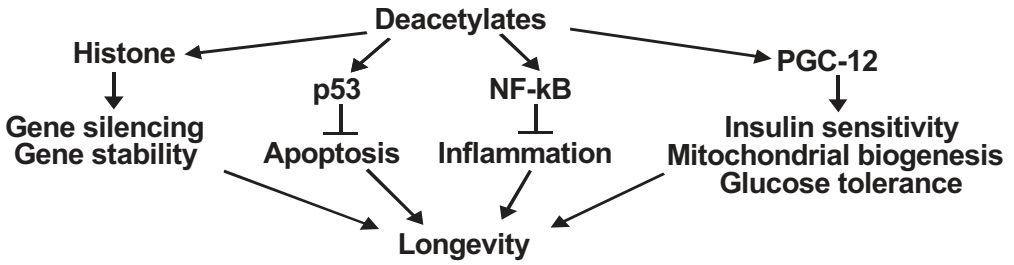
3-How the new molecules elicit their neuroprotective bioactivity?

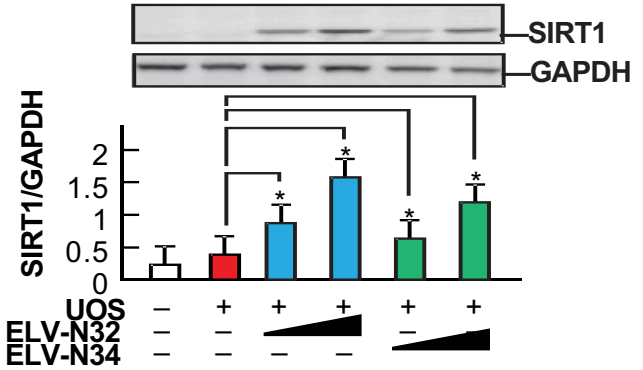
4-How do they work in Alzheimer's disease models ?

5-How do they correlate with Alzheimer's onset?

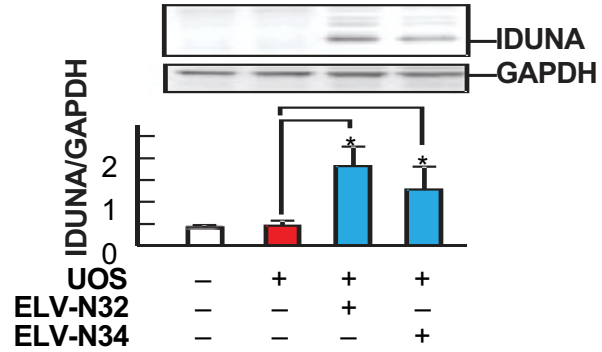
Proteins regulated by Elovanoids in human retinal cells undergoing uncompensated oxidative stress. (Jun B, et al *Sci. Rep* 7:5279 ,2017)

SIRTUIN 1



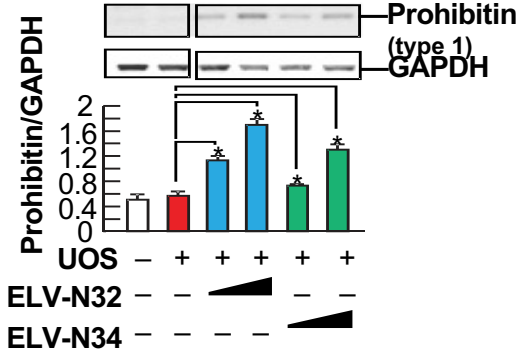


E3 Ubiquitin Ligase RNF146 (IDUNA)

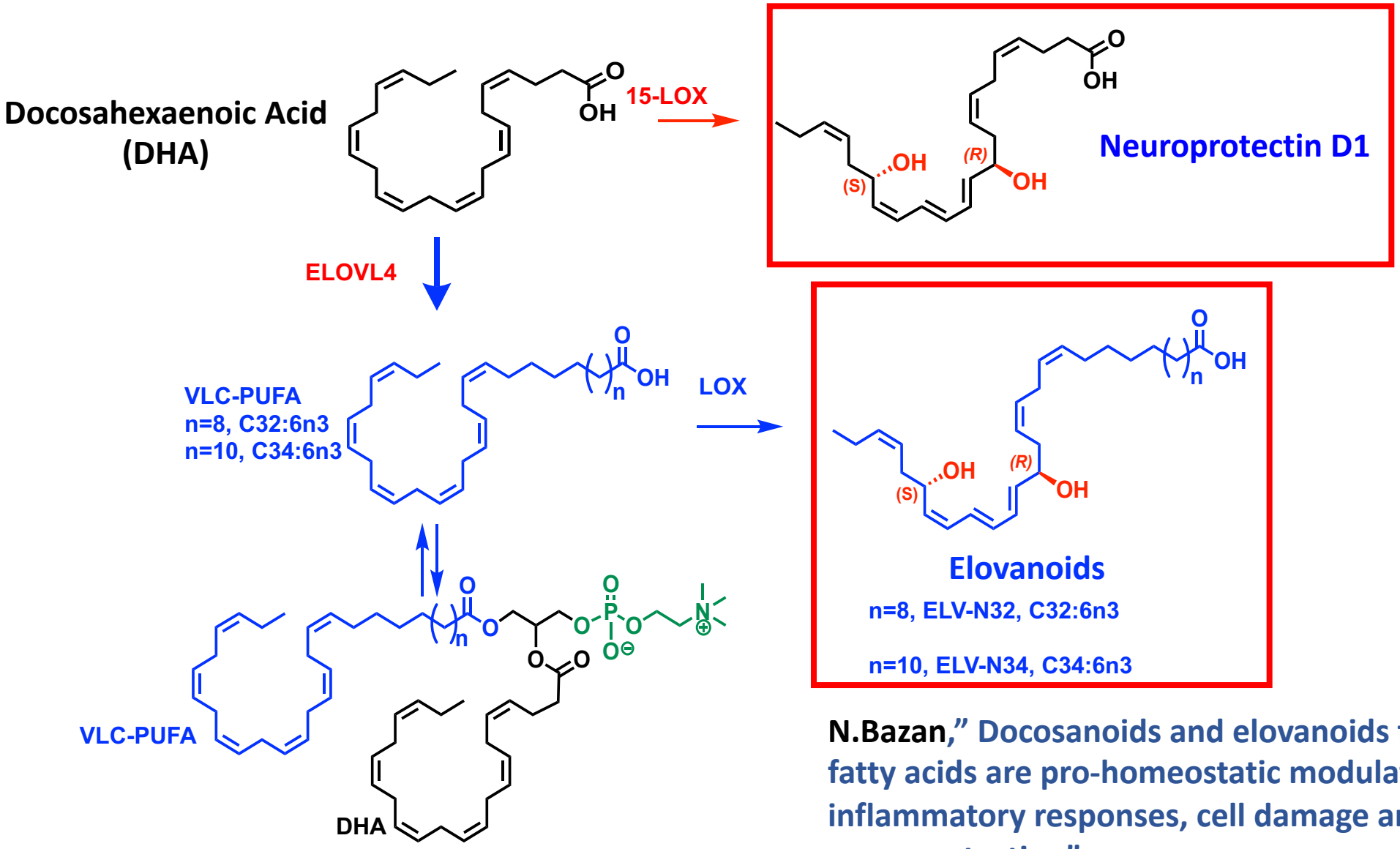


Prohibitin (Type 1)

- Scaffolding protein in mitochondria
- Adaptor molecule in membrane signaling
- Transcriptional co-regulator
- Neuroprotection



Biosynthesis of NPD1 and Elovanoids

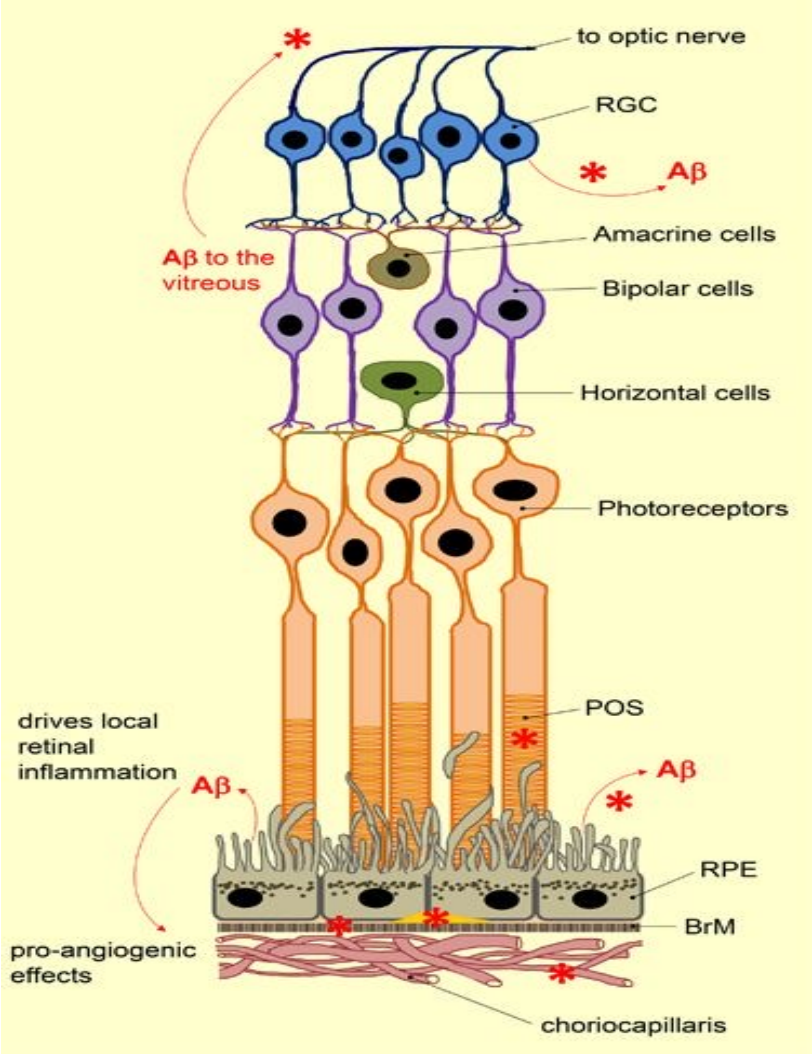


N.Bazan," Docosanoids and elovanoids from omega-3 fatty acids are pro-homeostatic modulators of inflammatory responses, cell damage and neuroprotection"
In Molecular Aspects of Medicine, 2018

- Oligomeric A-β peptide triggers retina damage leading to photoreceptor cell death

-Do Elovanoids (ELV) blocks the Oligomeric A-β peptide retina damage?

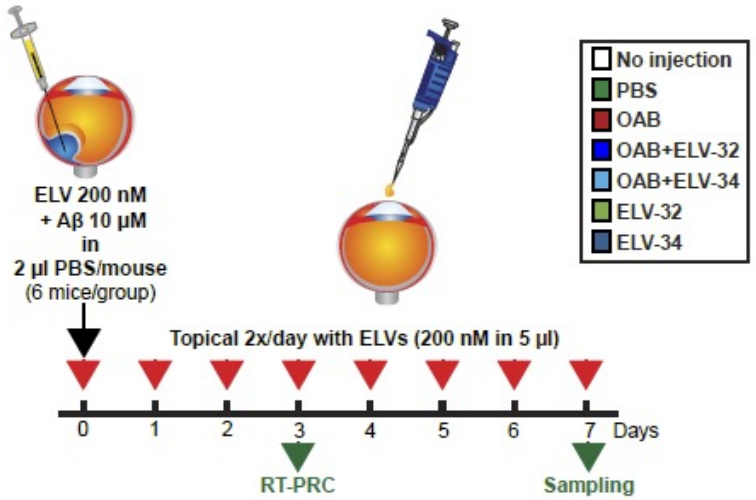
-Which mechanisms are involved?
-Induction of senescence gene programs?
- Mice (in vivo) as well as in human RPE cells in culture.



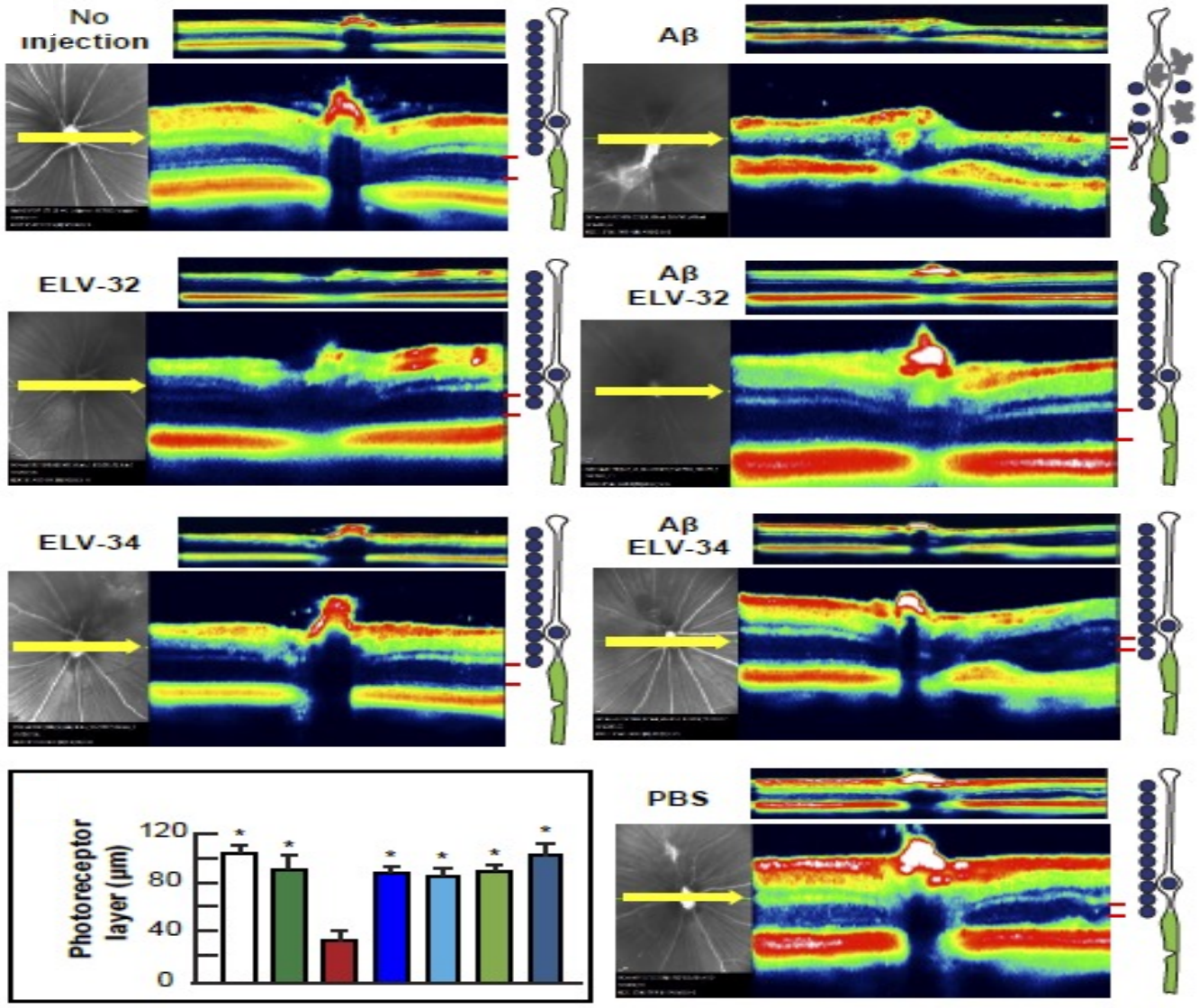
Ratnayaka JA, et al .
Eye Lond Engl. 2015;29:1013.
doi:10.1038/eye.2015.100

ELVs protects photoreceptors after subretinal injection of Oligomeric A-β peptide

Experimental Design



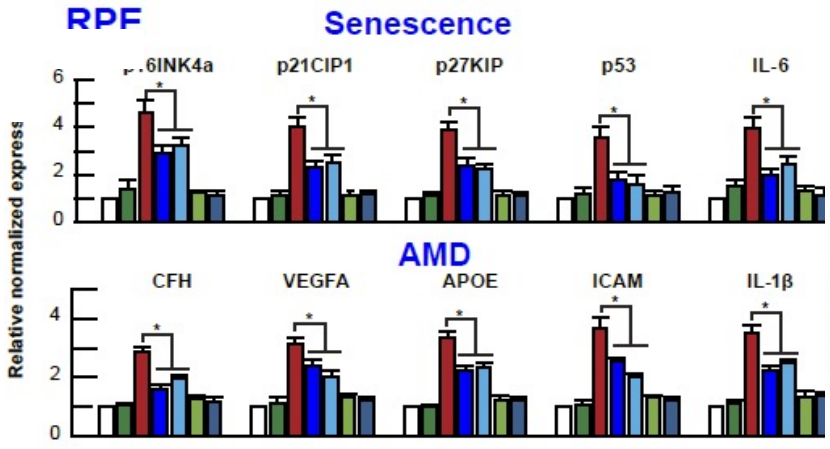
OAβ effects on retina and RPE by OCT

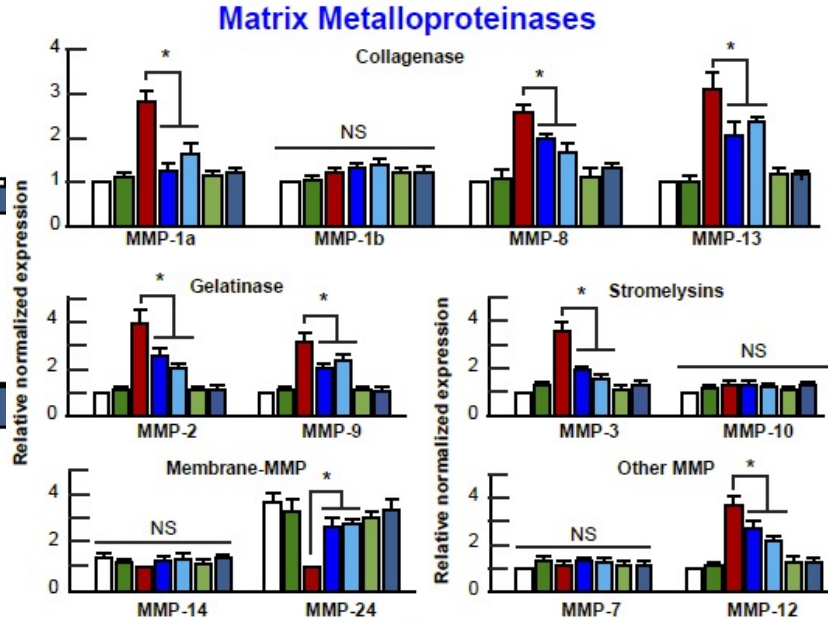


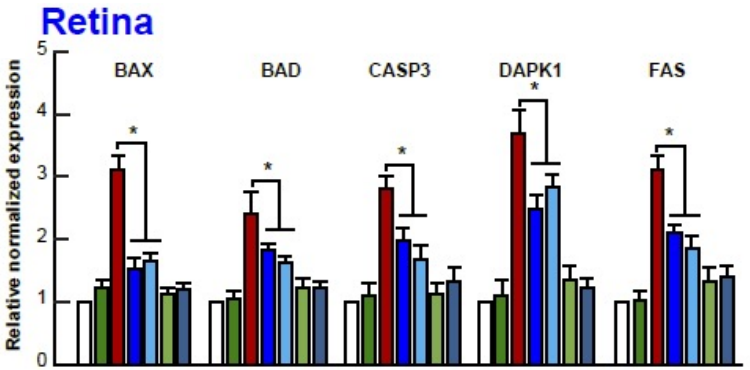
K. Do et al, PNAS 2019

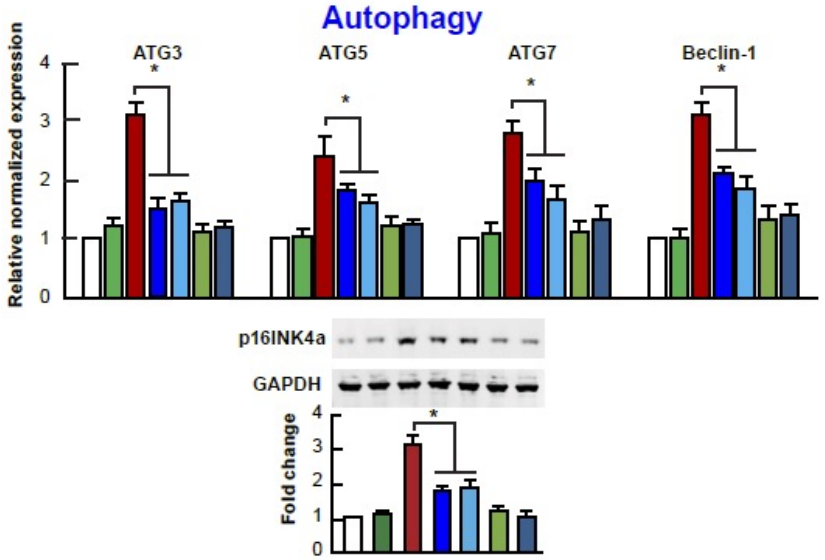
ELVs restores the expression of genes modified by OAβ in mice

Retinal Pigment Epithelium









-Senescent cells express p16 , a cell cycle inhibitor- that targets cyclin-dependent kinases - wound-healing and tumor suppression.

-Removal of p16 senescent cells extends health span and reverses senescence associated pathologies.

-Overexpression of p16 decreases cell proliferation and tissue regeneration , as an aged mouse.

K. Do et al, PNAS 2019

Loss of intercellular matrix integrity is a hallmark of aging .

-Matrix molecules exhibit long half-lives

-Drive phenotypes that increase cell integrity early in life but become detrimental in an aged organism.

-Placing senescent cells into a ‘young’ matrix can rejuvenate them, highlighting how the cellular microenvironment feeds into cell ageing.

Cellular Senescence : A homeostatic response to prevent propagation of damaged cells and neoplastic transformation.

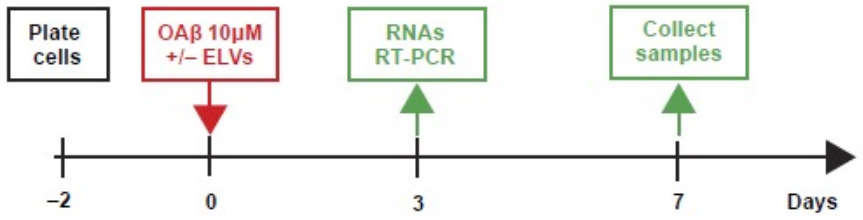
Stress-induced premature senescence due to uncompensated oxidative stress, impaired autophagy, mitochondrial dysfunction

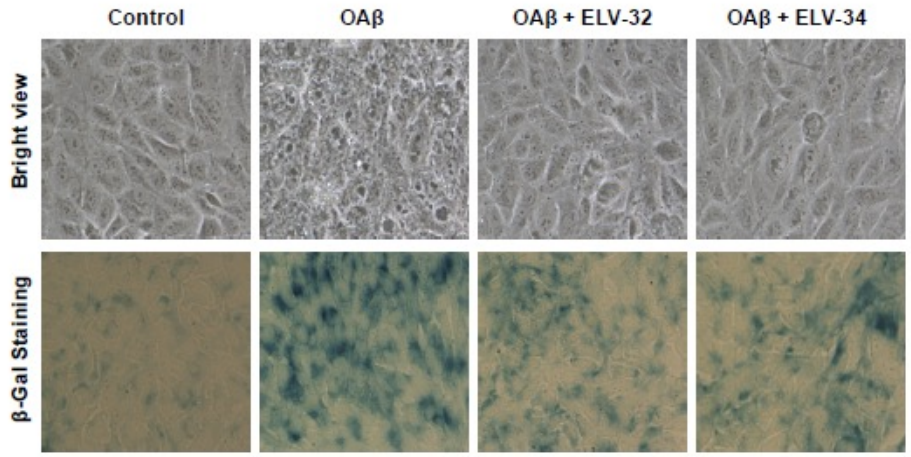
Unlike apoptosis, senescent cells remain viable and metabolically active.

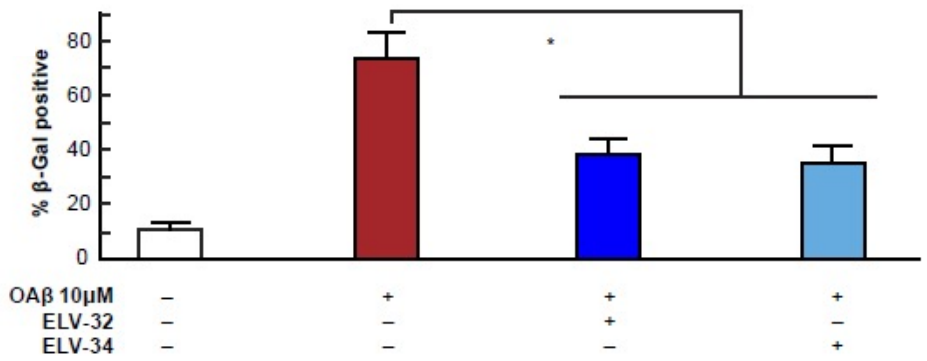
Detrimental effects in age- associated neurodegenerations.

Senescence-Associated secretory phenotype (SASP) induced by OA-β is counteracted by ELVs in primary human RPE cells

Cells were treated with 10µM OAβ +/- ELVs

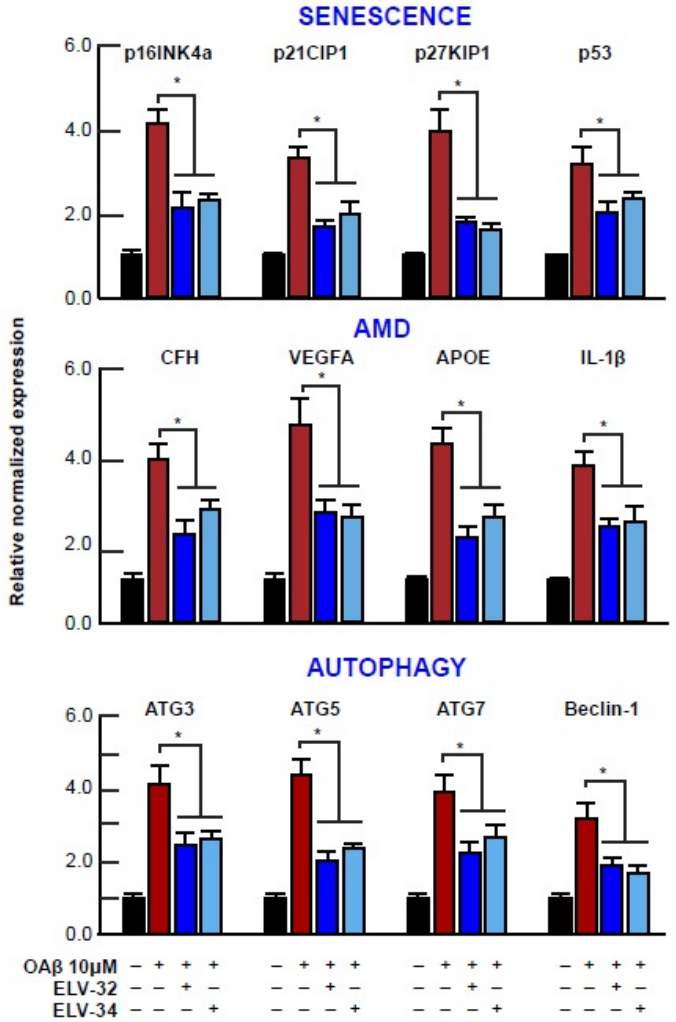






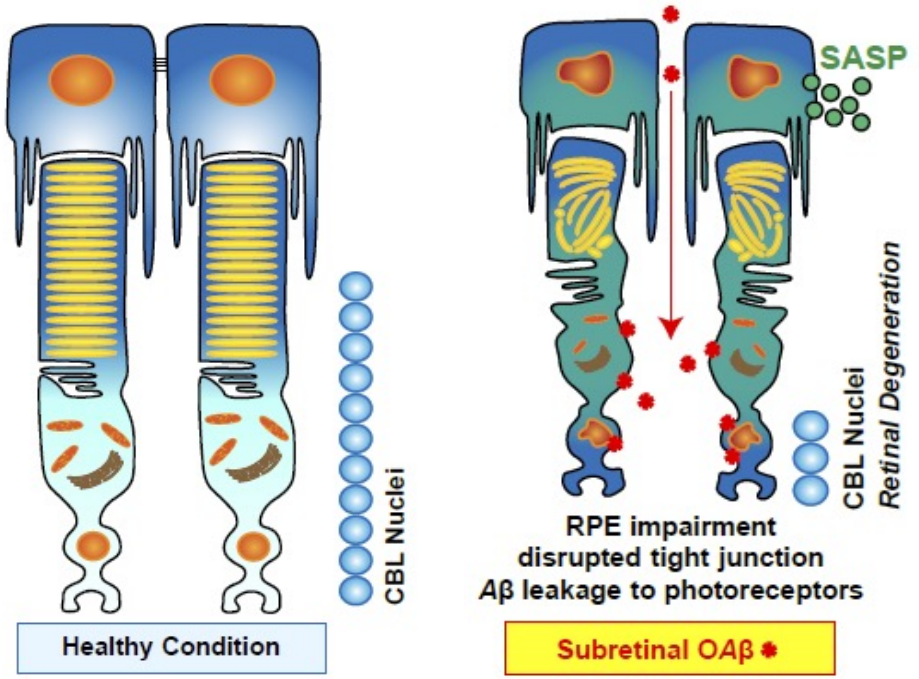
Live cell images of primary hRPE under bright field microscope imaging after 7 days

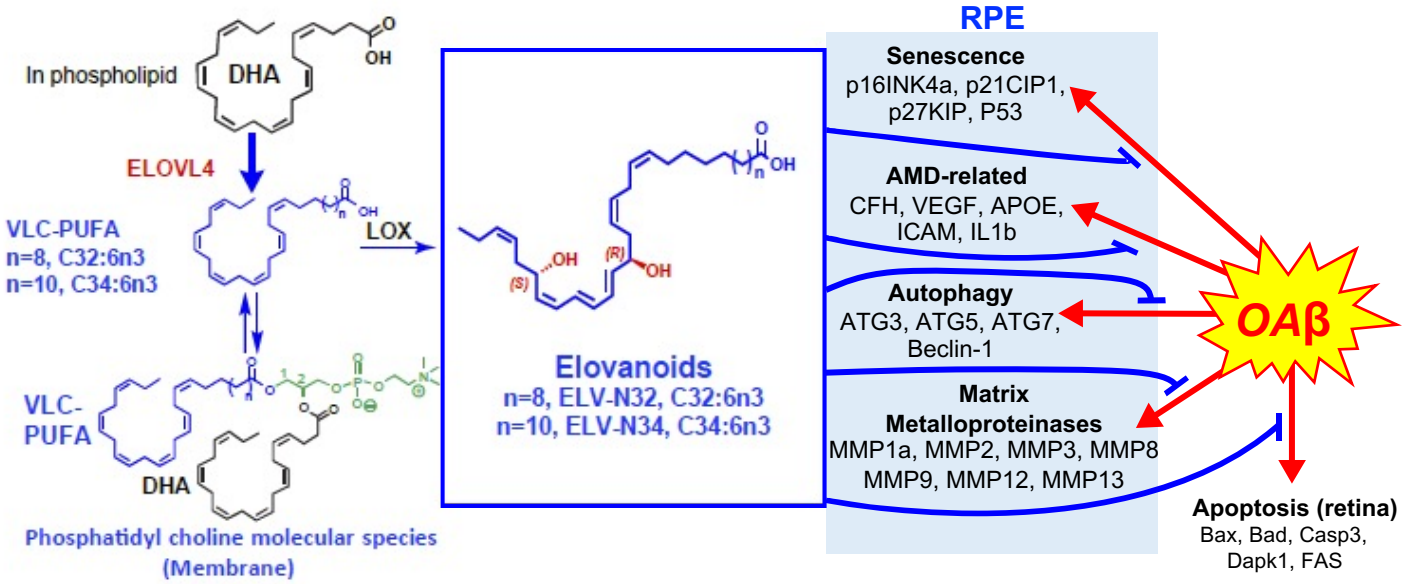
Transcription of senescence genes, AMD-related genes and autophagy genes

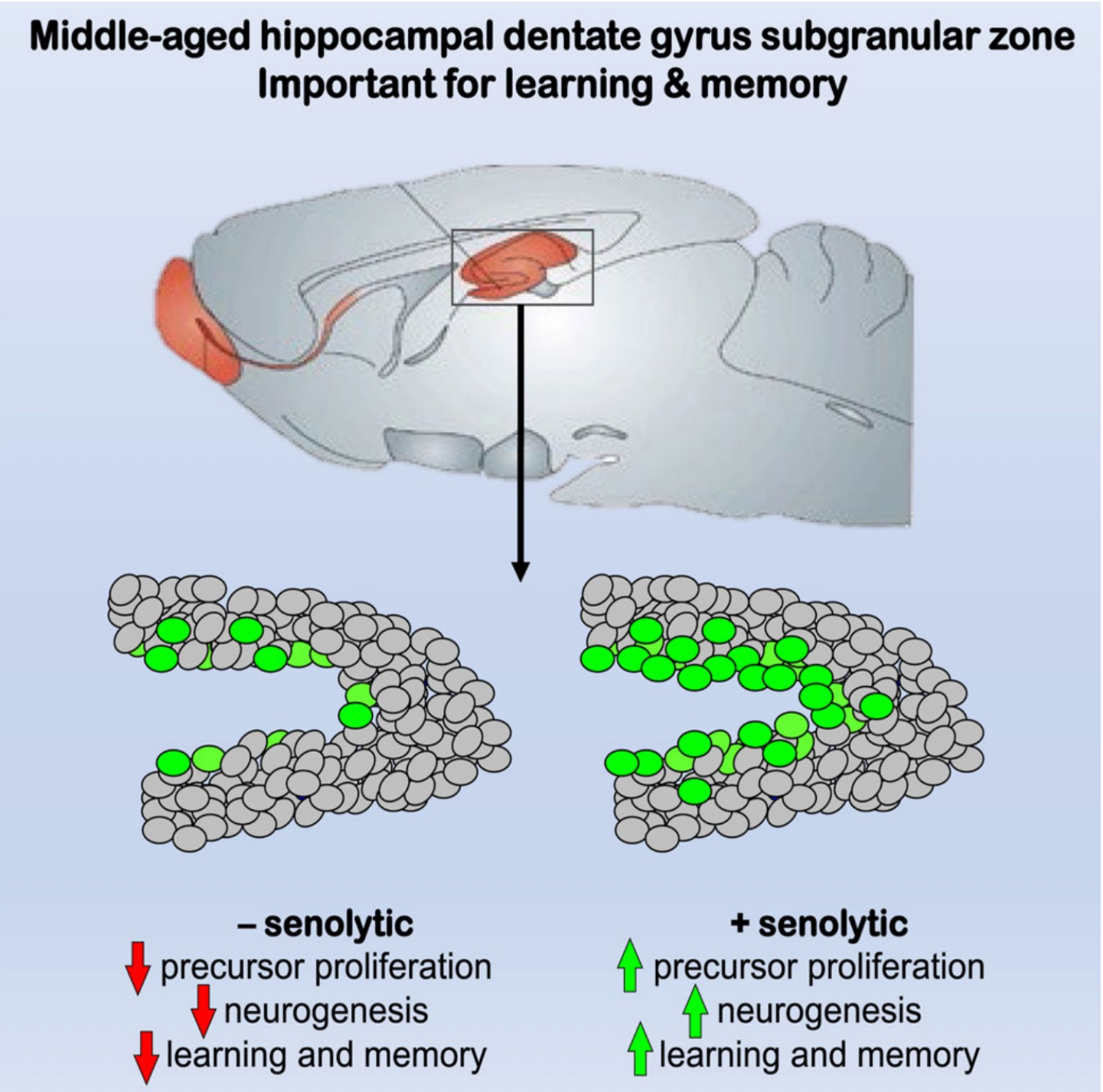


ELVs in OAβ-induced RPE and PRC damage

OAβ disrupts the tight junction of RPE







-Senescent neural precursor cells accumulate in the hippocampus with age , coincident with declining adult neurogenesis

-Ablating senescent precursors increases precursor proliferation and neurogenesis and improves hippocampus-dependent spatial memory

ABT-263 (Navitoclax) **experimental orally active anti-cancer drug,**
Bcl-2 inhibitor similar in action to obatoclax.

Exploring if the brain under imminent homeostasis disturbance activates the production of molecular guardians of cellular integrity and function

4-How do they work in Alzheimer's disease models ?

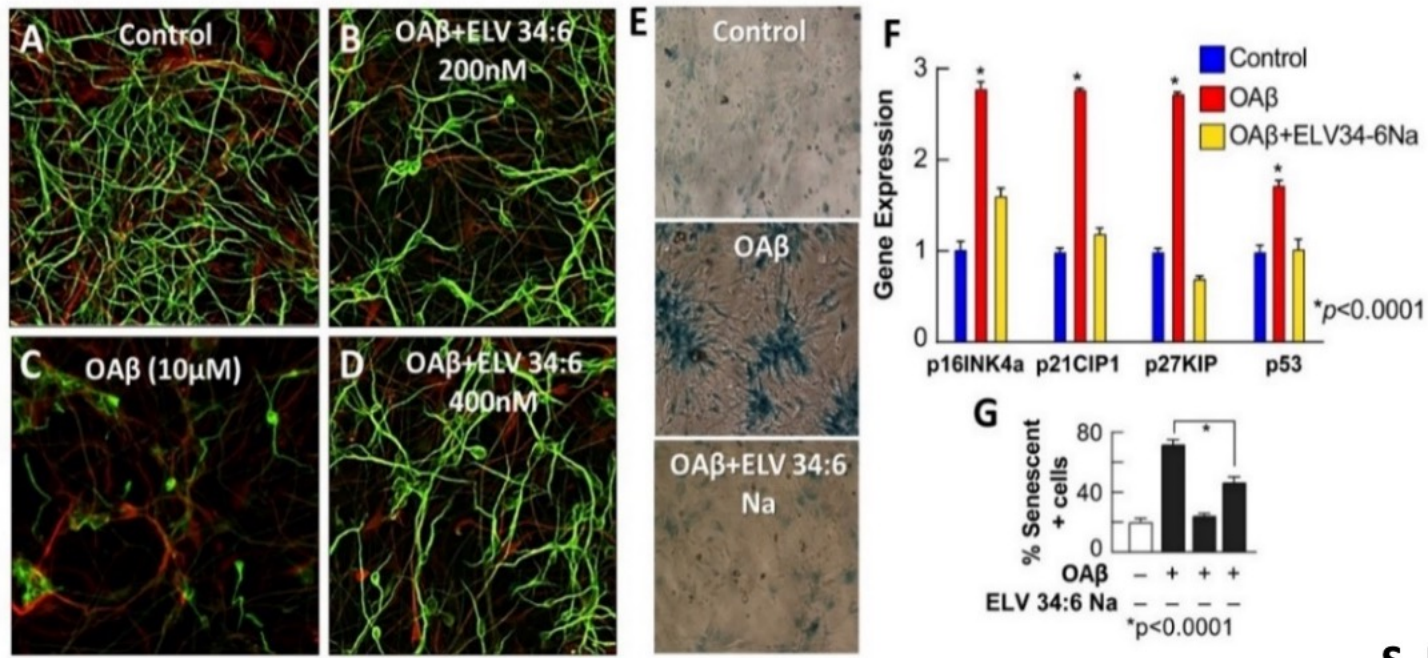
5-How do they correlate with Alzheimer’s onset?

-Since the App-Ki display memory deficits, will intranasally delivered LM attenuate those deficits?

-How is the abundance of LM in the CSF of SCI individuals?

-And in MCI and AD patients?

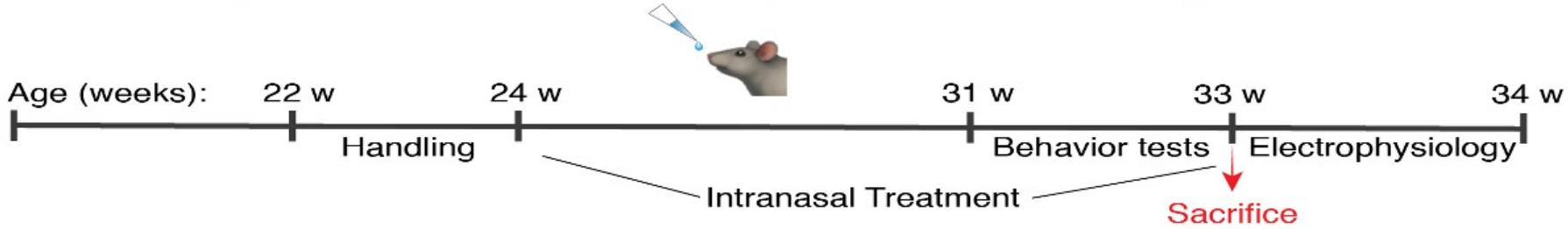
ELVS 34:6 counteracts Senescent Associated Secretory Phenotype and senescence gene expression induced by O-amyloid-β peptide



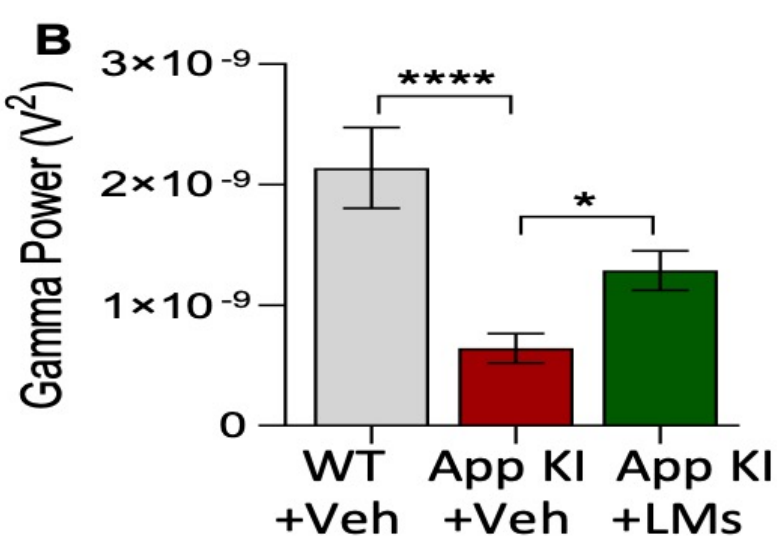
Human neuronal-glial cells (red: GFAP; green: β-III tubulin).
Senescence-associated β-galactosidase
SA-β-Gal⁺ cells were scored in 3 random fields of at least 150 cells.
Graphpad Prism software 8.3. Results compared with one-way ANOVA, followed by Holm's Sidak post hoc tests and p<0.05.

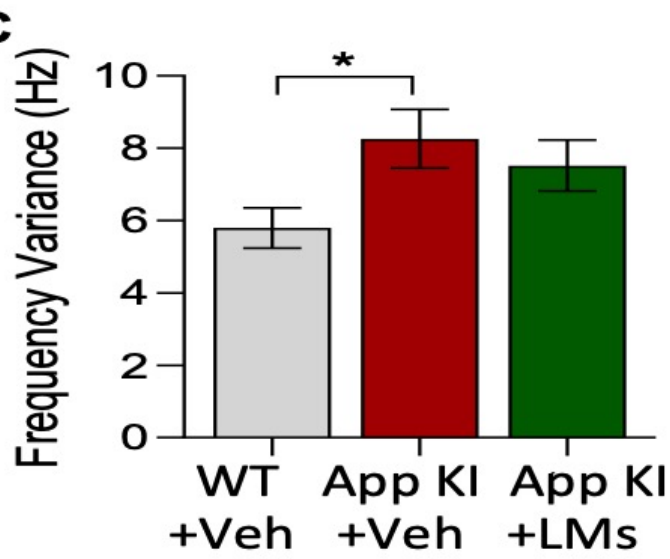
S .Bhattacharjee and N Bazan unpublished

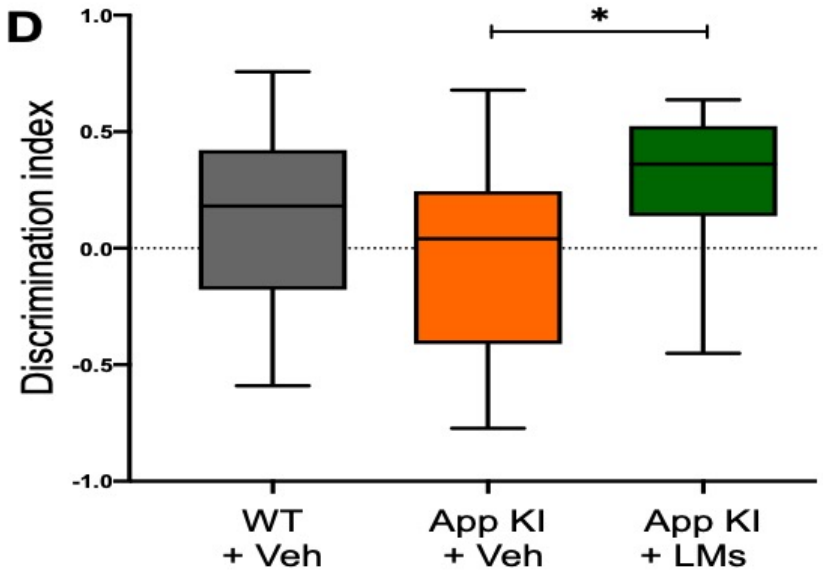
Intranasal lipid mediators improve memory functions in App KI mice



App KI n=10 ,
Vehicle (0.9% saline) n=10,
WT n=10.



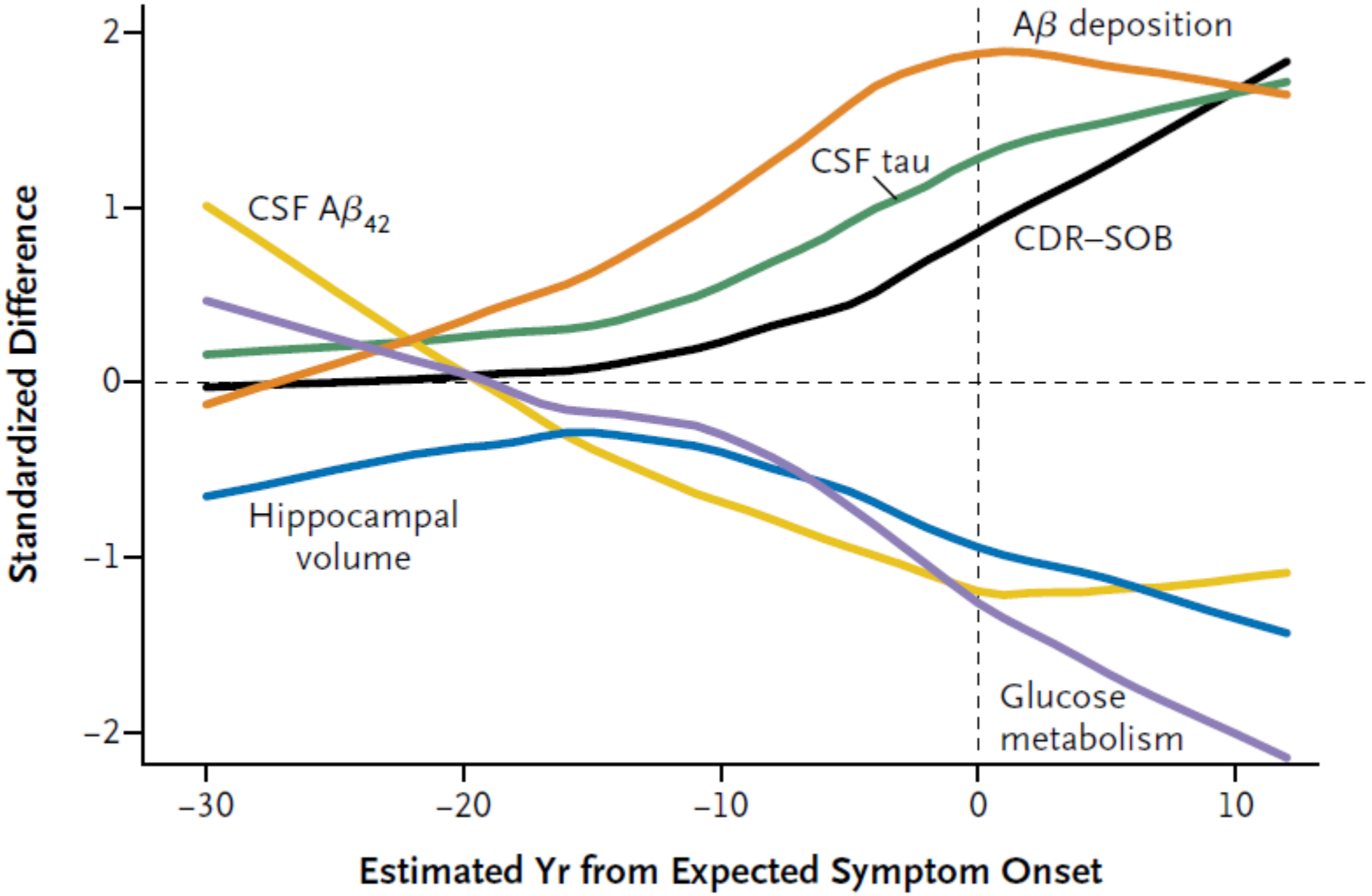




10 µl ,200 ng LM/ nostril , 10 µl pipette , 9 wks, 3 X/wk .

C Emre et al. Intranasal delivery of pro-resolving lipid mediators rescue memory and gamma oscillation impairment in *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice. Nature *Communications Biology*[in press] (2022).

Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset

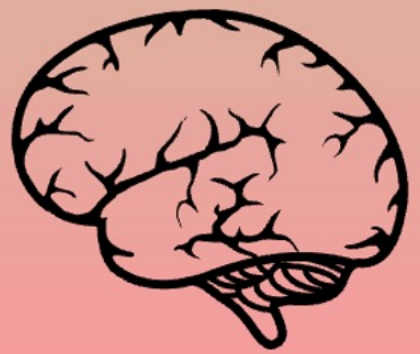


R.J. Bateman *et al.*,Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease N Engl J Med 1-10, 2012

Homeostasis

Disease progression characterized by increased Aβ and inflammation, while beneficial factors controlling these pathologies, such as pro-resolving lipid mediators (LMs), are decreased.

Prodromal stages (*i.e. SCI*, MCI)



Resolving LMs ↓

Aβ ↑ ⇨ Plaques ↑

p-tau ↑ ⇨ NFTs ↑ t-tau ↑

Inflammatory proteins and LMs ↑

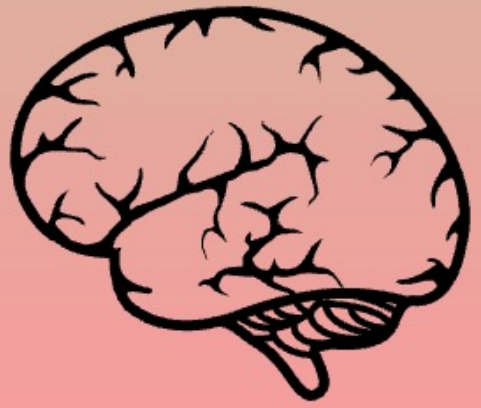
Neurodegeneration

Alzheimer's disease

Homeostasis

Disease progression characterized by increased Aβ and inflammation, while beneficial factors controlling these pathologies, such as pro-resolving lipid mediators (LMs), are decreased.

Prodromal stages (*i.e. SCI*, MCI)



Alzheimer's disease

Resolving LMs ↓

Aβ ↑ ⇨ Plaques ↑

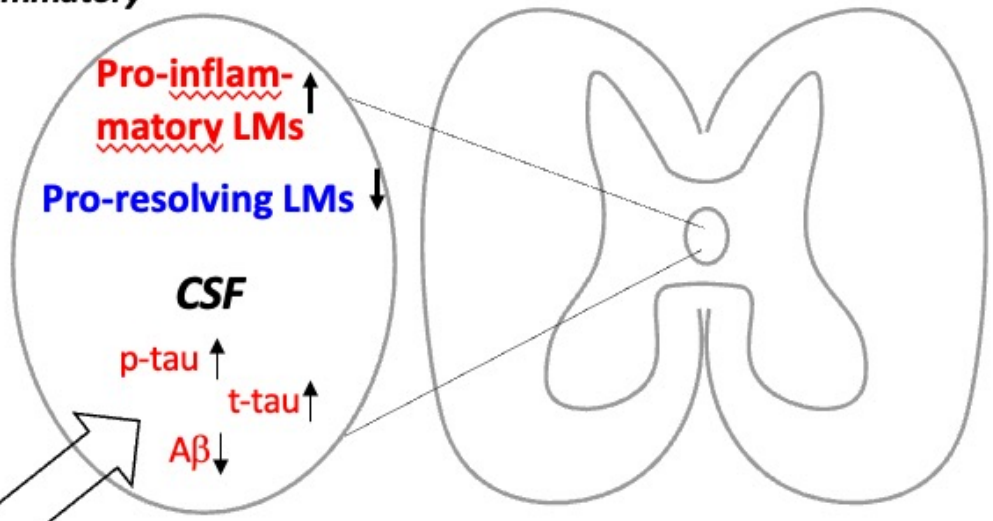
p-tau ↑ ⇨ NFTs ↑ t-tau ↑

Inflammatory proteins and LMs ↑

Neurodegeneration

Hypothesis

Impaired resolution in AD brain is indicated by a shift in the balance of LMs in CSF from pro-resolving to pro-inflammatory



Memory impairments and general cognitive dysfunction (*e.g.* as measured by MMSE score)

Findings

CSF levels of pro-resolving LMs MaR1, NPD1 RvD4, and RvE4 were decreased in AD patients or prodromal stages.

Impairment in the beneficial effects of LMs on phagocytosis, neuroprotection and control of inflammation may contribute to disease progression.

Potential biomarkers and treatment targets.

KV Do et al. Cerebrospinal fluid profile of lipid mediators in Alzheimer's disease. *(submitted)*.

ELOVANOIDS

Novel lipid mediators.

1- Induces neuronal and retinal cell survival in culture:

2- Counteracts Amyloid β Peptide-induced cell damage (AMD and Alzheimer's Disease)

3- In other disease experimental models:

-Neuroprotective in experimental ischemic stroke and after traumatic Brain Injury

4- How do they work?:

-Modulate transcriptome architecture to induce neuronal cell survival

-Enhances abundance of pro-homeostatic proteins and decreases abundance of proteins engaged in cell damage

-Downregulate senescence gene programming, autophagy, extracellular matrix remodeling, inflammaging,

Is there a Molecular Logic for Neurons Long Life? YES

- Why don't diseases manifest during latency in inheritable neurodegenerations (e.g., Familial Alzheimer's, Retinitis Pigmentosa)? Because the guardians are overwhelmed.

Neurons upon homeostasis disturbance does not surrender easily, they activate production of molecular guardians: Docosanoids :NPD1, Elovanoids

How do they sustain cell integrity and function ?

-Target pro-homeostatic regulation,

-Counteract senescence gene programing,

-Protect intercellular matrix

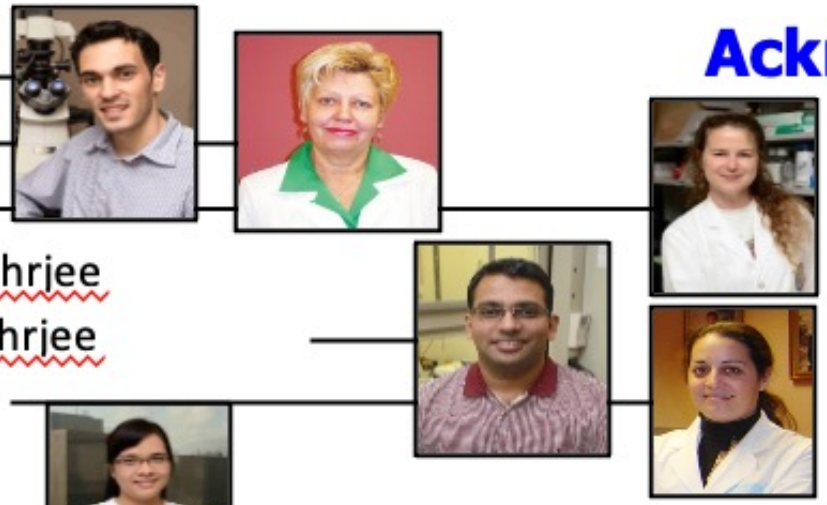
-Regulate Telomerase

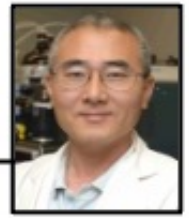
-Modulate Tau-P and missorting

-Regulate Netosis

Acknowledgements

- Aram Asatryan
- Ludmila Belayev
- Veronica Bender
- Sayantani (Misty) Bhattachrjee
- Surijadipta (Bibo) Bhattachrjee
- Jorgelina Calandria
- Brenda Chiappinelli
- John Cefalu
- Khanh Do
- Jessica Heap
- William Gordon
- Song Hong
- Bokkyoo Jun
- Marie-Audrey Kautzmann
- Larissa Khoutorova
- Walter Lukiw
- Eric Knott
- Miriam Kolko
- Shawn Marcell
- Pranab Mukherjee
- Ifeanyi (Obi) Iwuchukwu
- Madigan Reid





University of
Southern California

- Nicos A. Petasis

Department of Pediatrics
University
of California, Irvine, CA

- Andy Obenaus

nbazan@lsuhsc.edu

Acknowledgments

-R01 EY005121-33A1
PI: N. Bazan NIH, NEI
03/01/1984-03/31/2025
RPE Messengers, Transcription and Photoreceptor Renewal

-R01 NS104117
PI: N. Bazan, L. Belayev NIH, NINDS
05/01/18-01/31/23
Novel combinatory therapy for experimental ischemic stroke

-R01 NS109221
PI: N. Bazan NIH, NINDS
05/01/19-01/31/24
Docosanoids modulate homeostasis and cell survival after ischemic stroke

-1R42-12995283
PI: N.Bazan ,H. Bazan NIH, STTR
07/01/20-12/31/23
Novel non-narcotic analgesic for acute and chronic pain

-EENT Foundation of New Orleans (2019-2025)

-Ernest C. and Yvette C. Villere Endowed Chair
1981- LSUHSC