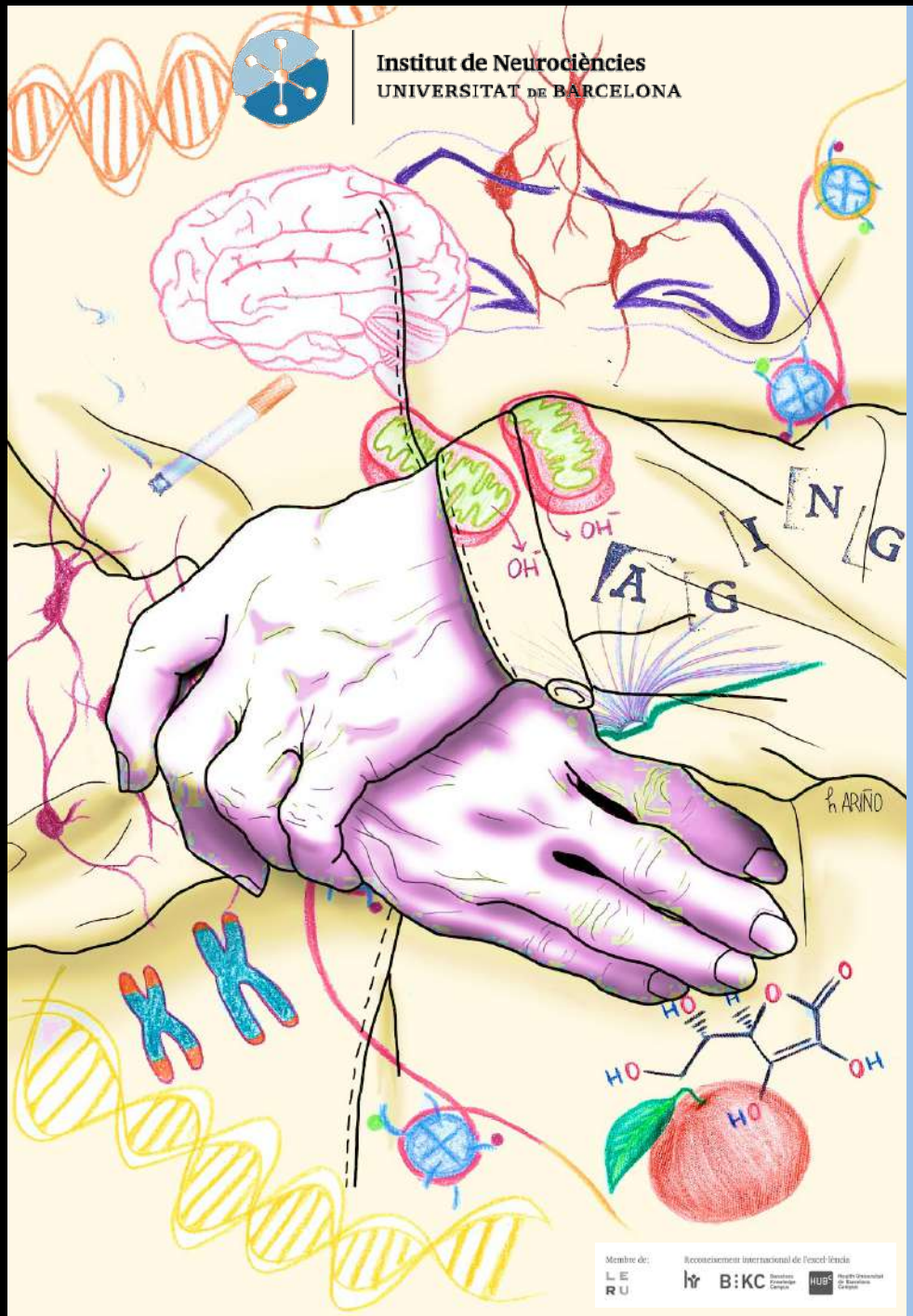


UNIVERSITAT DE BARCELONA

Facultat de Farmàcia
i Ciències de l'Alimentació

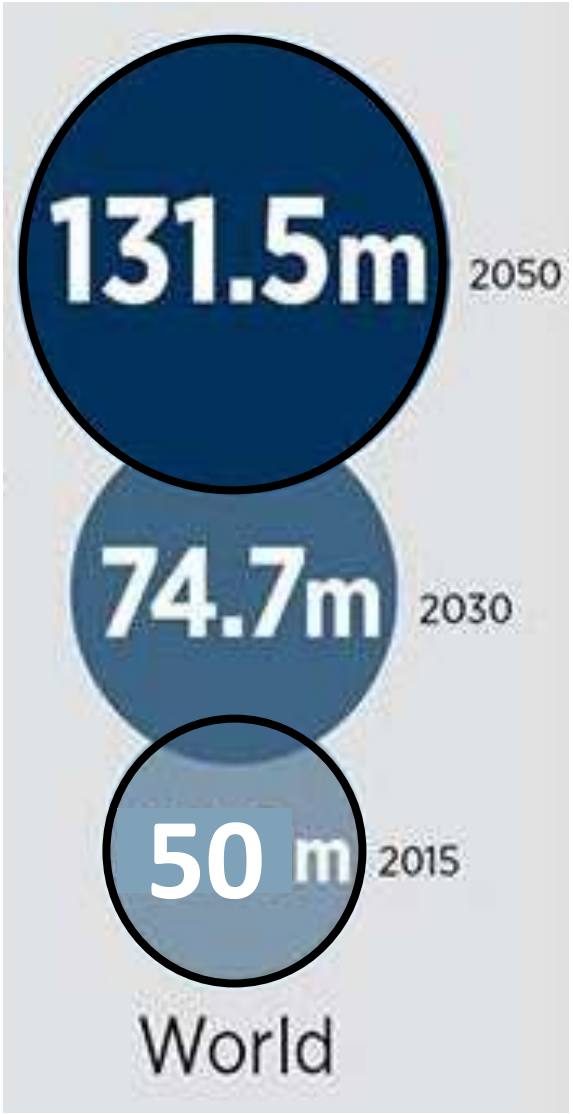
Epigenetic mechanisms in cognitive impairment linked to aging and Alzheimer's disease

SEMINARIS DE RECERCA 2019 SEMINARIS TECNOLÒGICS

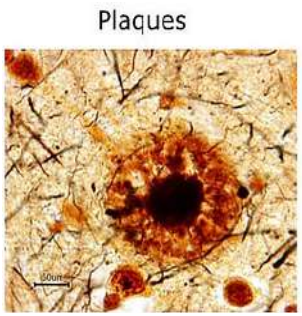
2n Seminari de Recerca 2019

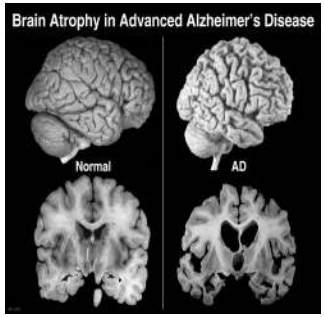
Dr Christian Griñán-Ferré
Neuropharmacology in Aging and Neurodegeneration
Faculty of Pharmacy and Food Sciences
May 14th, 2019

Alzheimer's Disease



- The most common cause of dementia
- Neurodegenerative disease
- Progessive and Irreversible
- Cognitive Impairment and behavioural abnormalities
- Neuropathological alterations: β-amyloid, Tau hyperphosphoryation, neurotransmitter deficits and cell death.



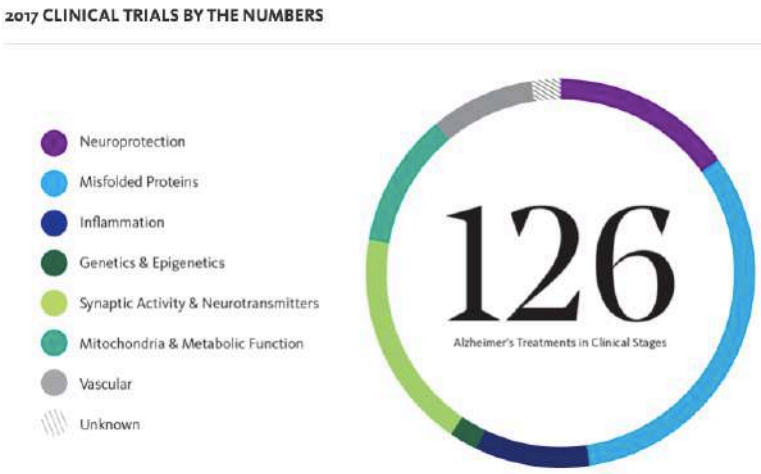


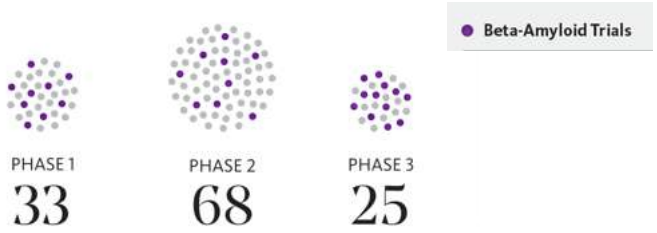
Current Available Therapy for AD

Characteristics	DONEPEZIL	RIVASTIGMINE	GALANTAMINE	MEMANTINE
Chemical class	piperidine	carbamate	phenanthrenea lkaloid	Similar to amantadine
Primary mechanism	AchE inh	AchE inh	AchE inh	NMDA antagonist
Other mechanism	None	None	Nicotine modulator	HT3 receptor antagonist
Half life	70 h	90 min	7 h	70 h

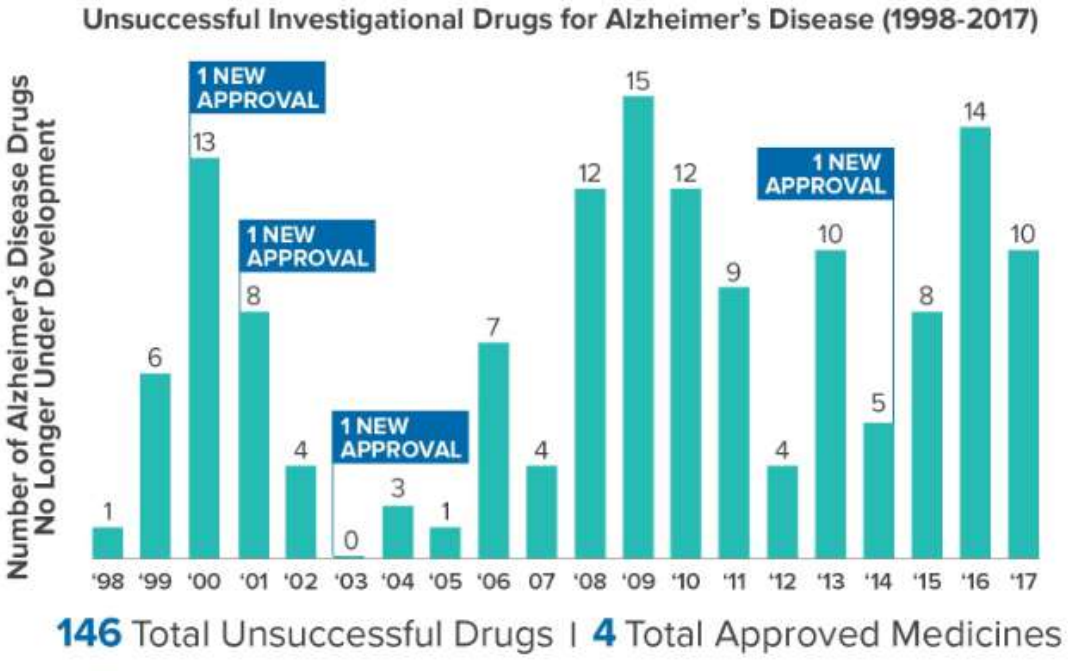
CURRENT PHARMACOLOGICAL THERAPIES DO NOT STOP THE PROGRESSION OF DEMENTIA

Clinical Trials for AD





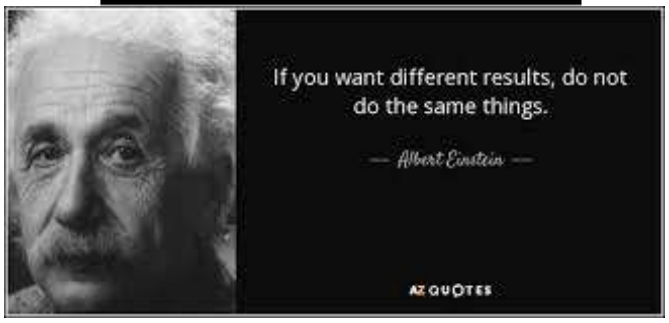
Beta-amyloid remains a major target in all phases of clinical trials, despite high-profile failures in the past few years.



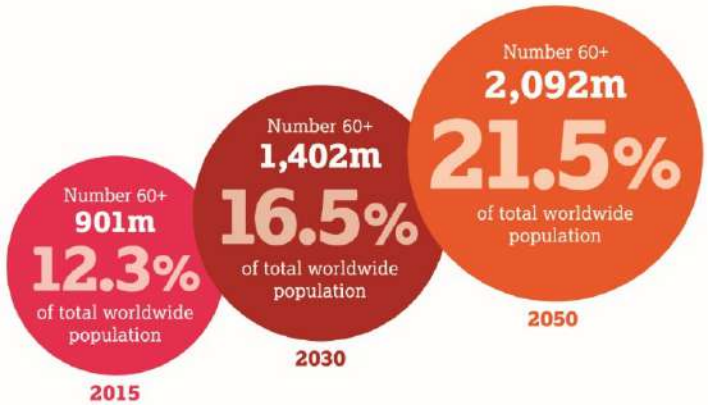
BIOPHARMA

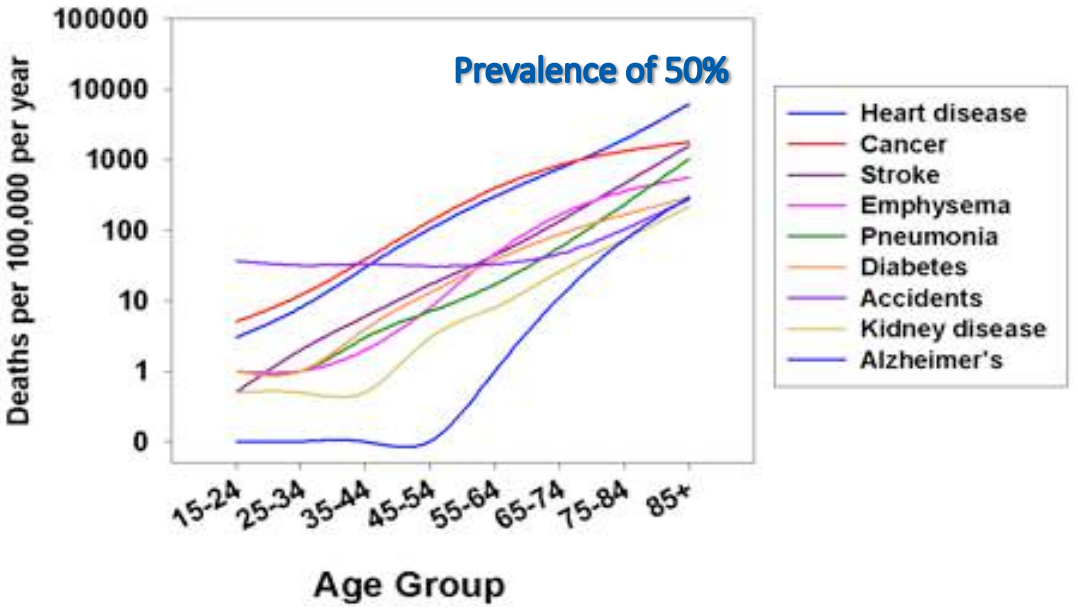
Failure of once-promising Alzheimer's drug reinforces doubts about amyloid beta

Biogen halting its Phase III trial of aducanumab last month had many proclaiming the amyloid beta hypothesis' demise. But many doctors soldier on, while others see potential alternative uses for Abeta-targeting drugs.



The greatest risk factor for AD is advanced age





Aging and Development. United Nations Development Programme. 2015 Nov

The hallmarks of aging

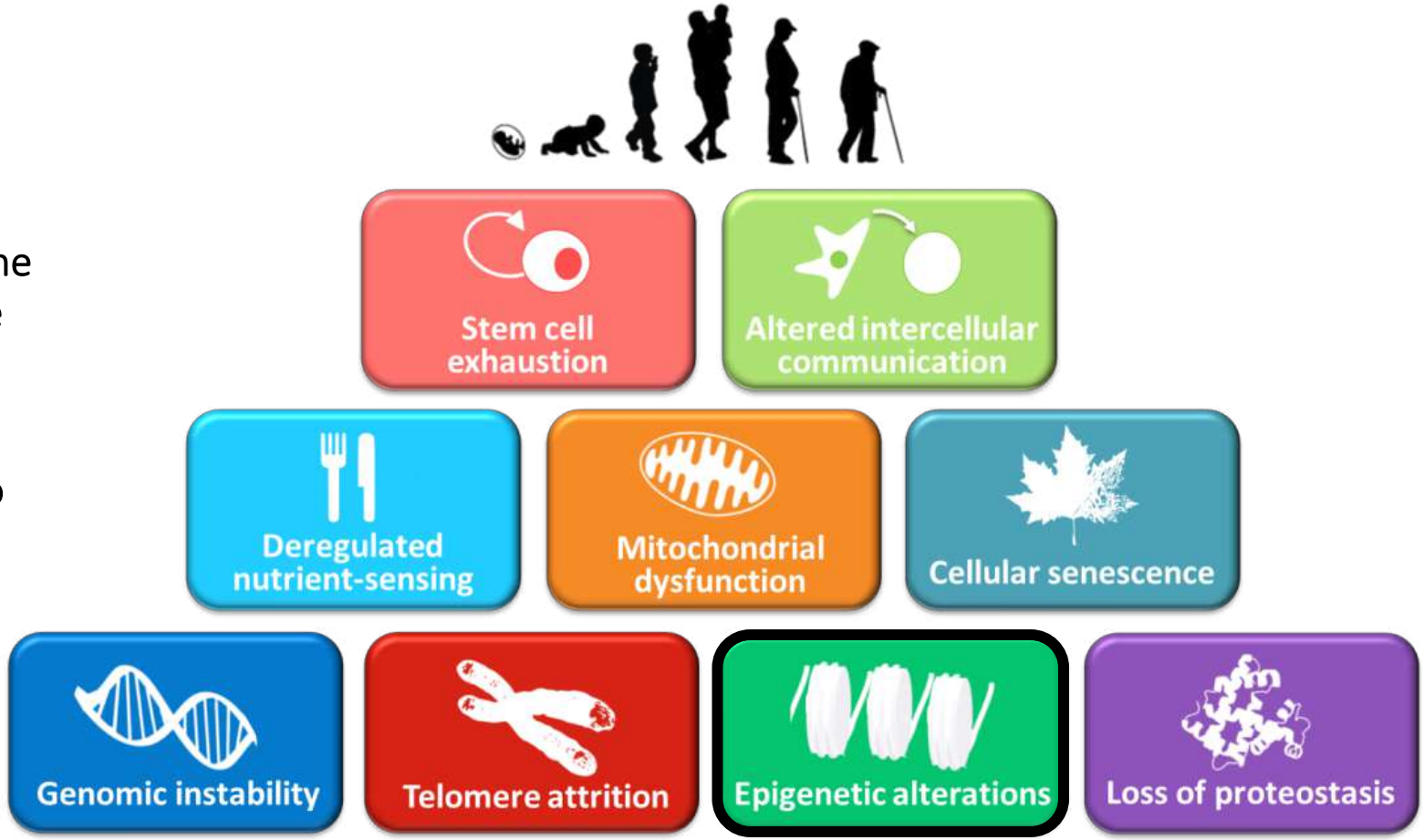
Culprits of the phenotype

↑

Response to damage

↑

Causes of damage

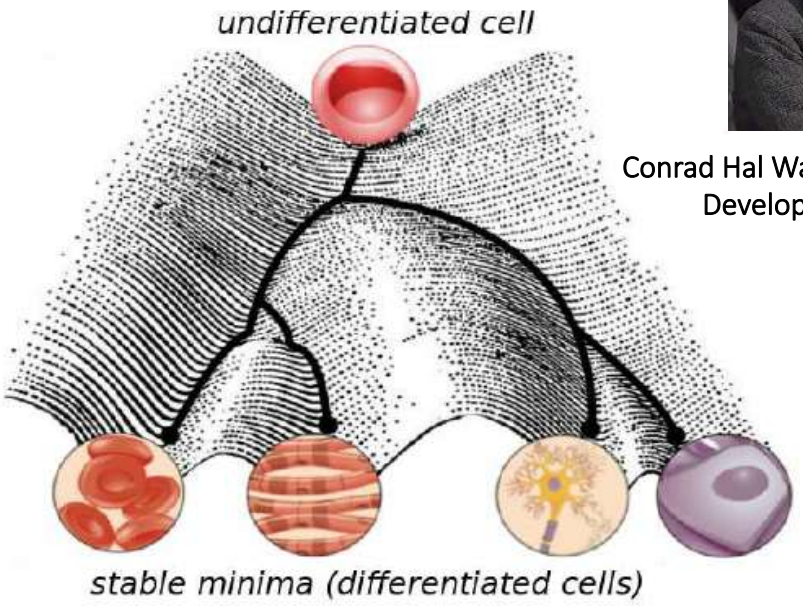


The hallmarks of aging, López-Otín et al., Cell 2013

What is epigenetics?

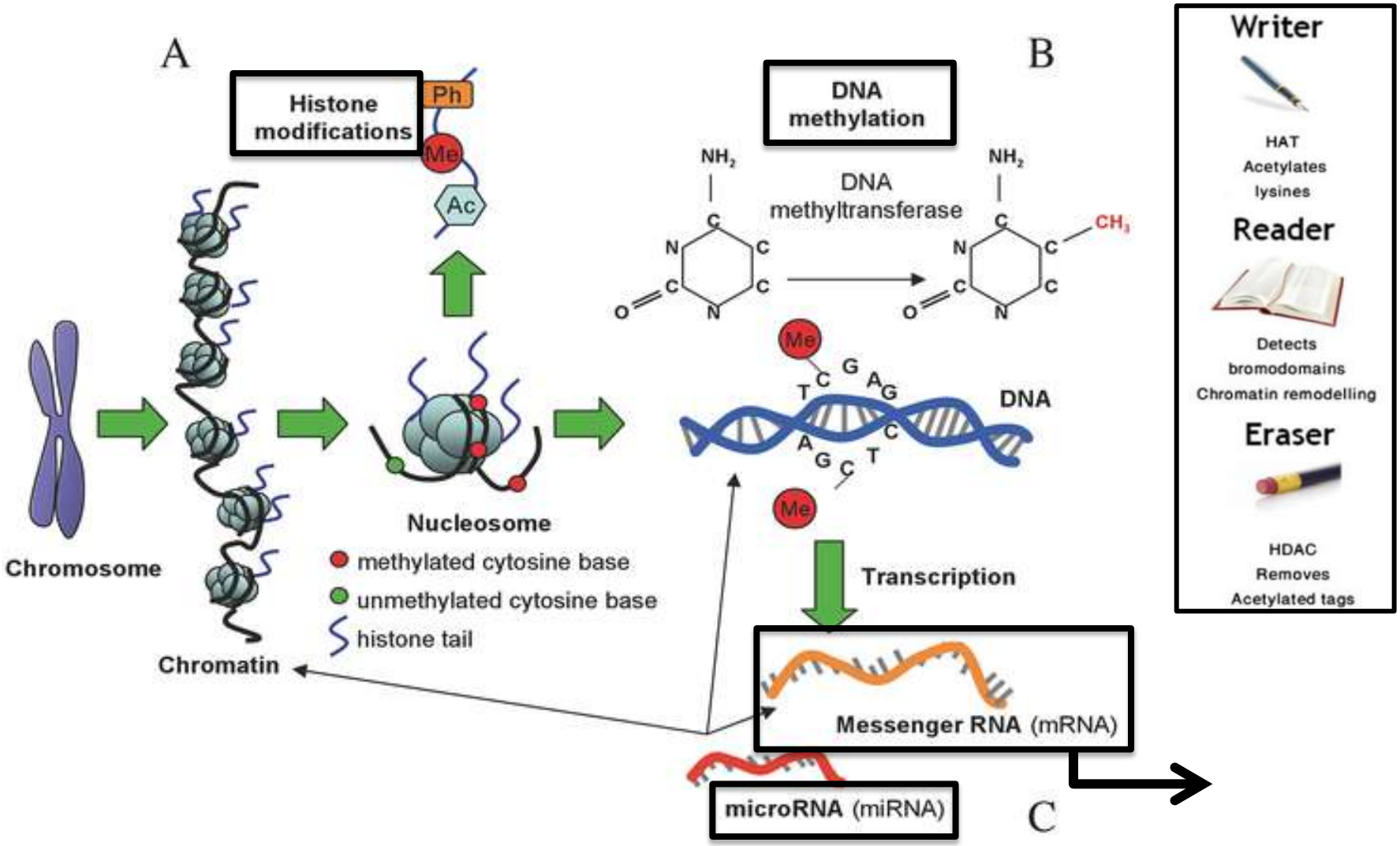
- Changes in gene expression or phenotype that don't involve changes to the DNA sequence
- Its defined as heritable changes in gene activity and expression that occur without alteration in DNA sequence

Conrad Hal Waddington (1905-1975)
Developmental biologist



Epigenetic landscape 1940

The three pillars of epigenetic regulations

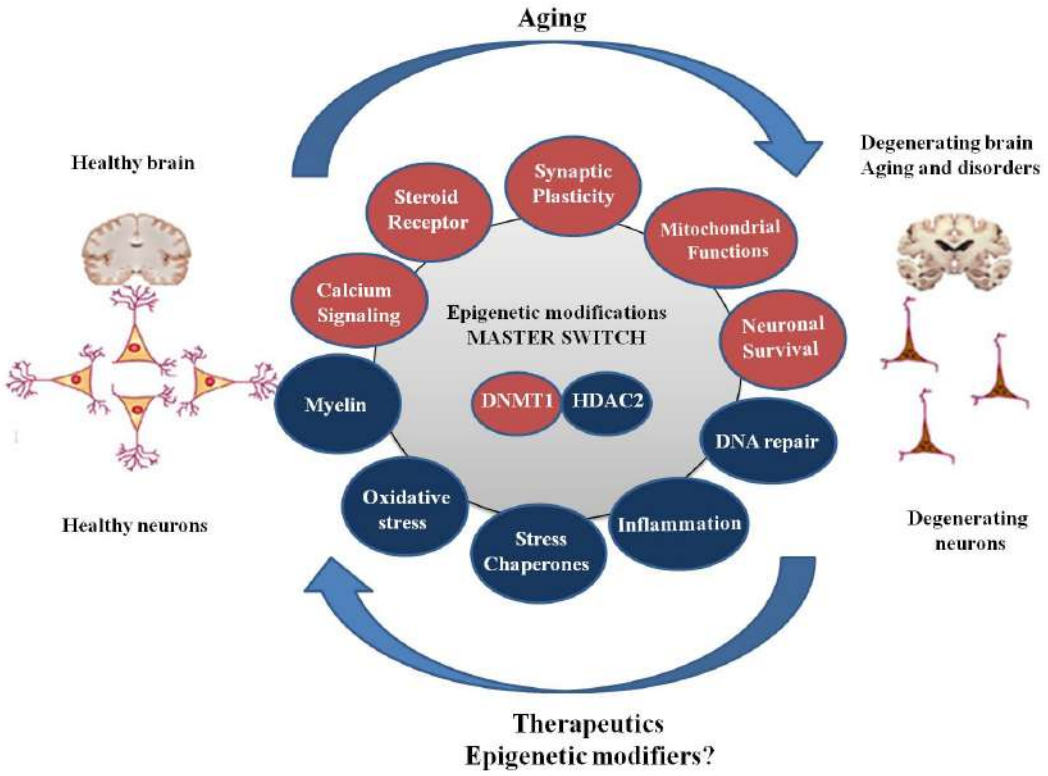


Gómez-Díaz E, Jordà M, Peinado MA, Rivero A (2012) Epigenetics of Host–Pathogen Interactions: The Road Ahead and the Road Behind. PLOS Pathogens 8(11): e1003007. https://doi.org/10.1371/journal.ppat.1003007
http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003007

Alterations of these epigenetic mechanisms

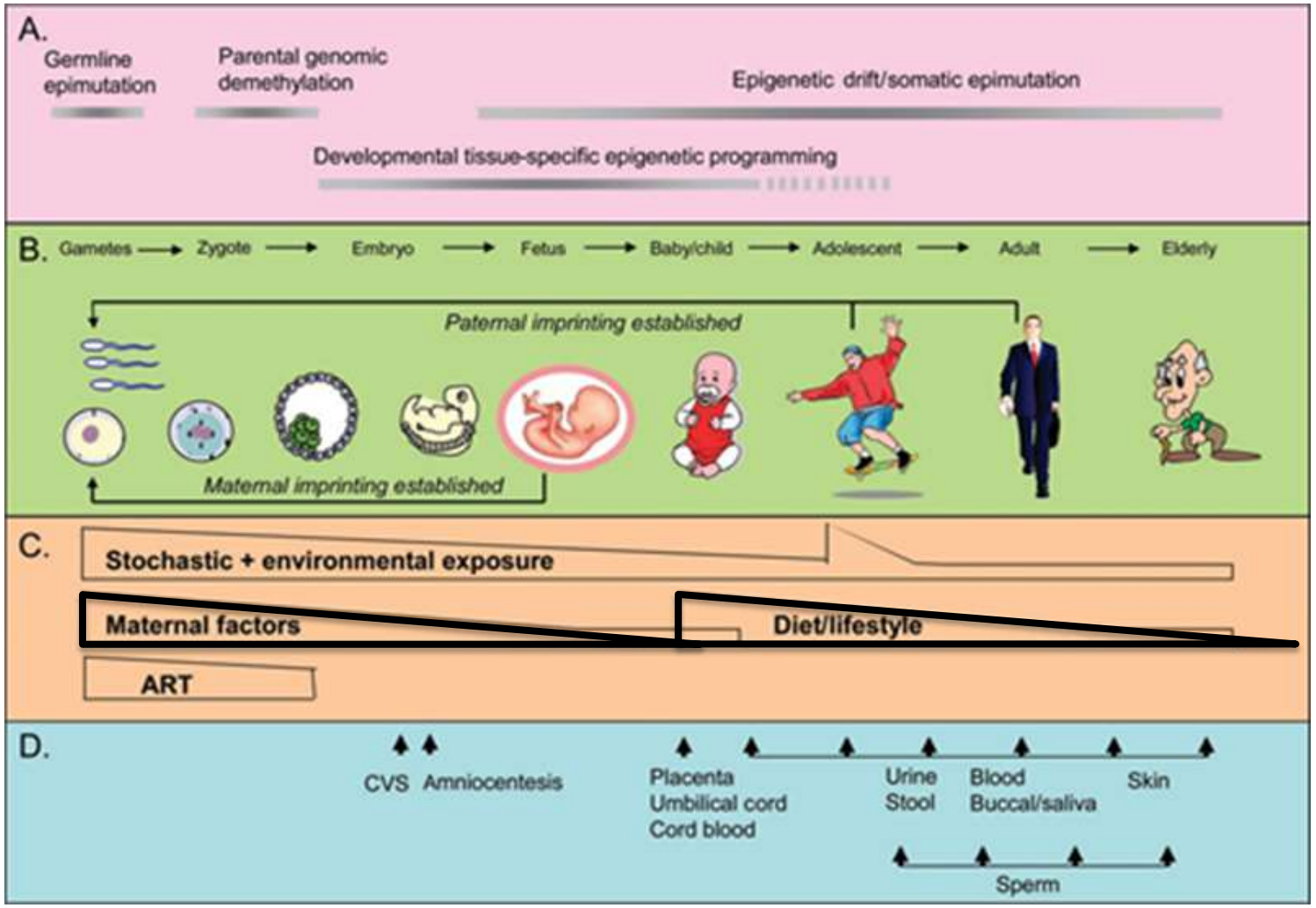
Alterations of these epigenetic mechanisms affect the vast majority of nuclear process, including:

- Gene transcription and silencing
- DNA replication and repair
- Cell cycle progression
- Telomere structure and function
- Mitochondrial function
- Inflammation
- Oxidative Stress
- Cell survival

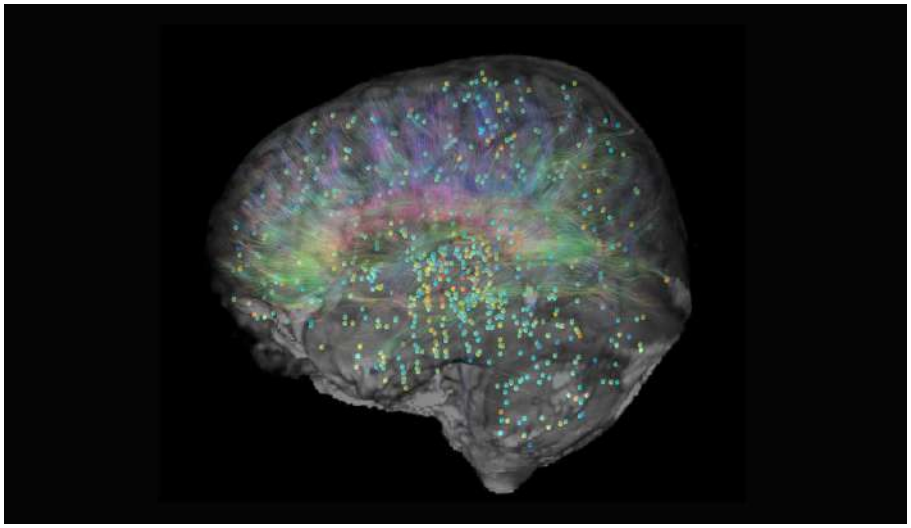


Konar A, Singh P, Thakur MK. Age-associated Cognitive Decline: Insights into Molecular Switches and Recovery Avenues. *Aging and Disease*. 2016;7(2):121-129. doi:10.14336/AD.2015.1004.

Epigenetic and life



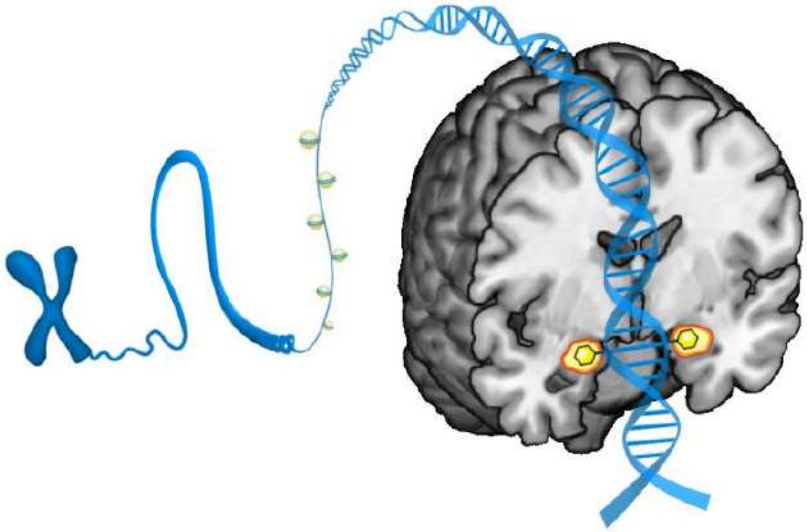
Epigenetic and brain



The human brain expresses numerous genes; approximately 80–95%

Bae B, Jayaraman D, Walsh CA. Genetic Changes Shaping the Human Brain. *Developmental cell.* 2015;32(4):423-434.
Levenson J. M., Sweatt J. D. (2005). Epigenetic mechanisms in memory formation. *Nat. Rev. Neurosci.* 6 108–118.

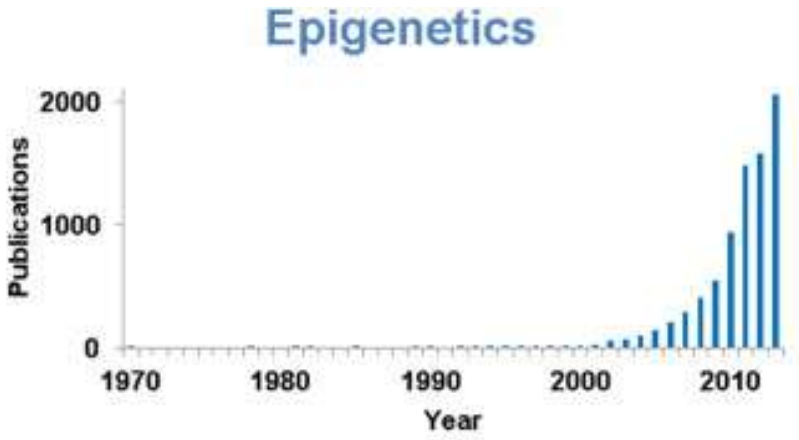
Epigenetic and brain



Neuronal activity *per se* modifies DNA methylation and histone modifications patterns, and further, that learning and memory depend on these epigenetic changes.

Bae B, Jayaraman D, Walsh CA. Genetic Changes Shaping the Human Brain. *Developmental cell.* 2015;32(4):423-434.
Levenson J. M., Sweatt J. D. (2005). Epigenetic mechanisms in memory formation. *Nat. Rev. Neurosci.* 6 108–118.

Epigenetic mechanisms in aged brain and AD



Epigenetic mechanisms in aged brain and AD

Contents lists available at ScienceDirect
Ageing Research Reviews
journal homepage: www.elsevier.com/locate/arr

Review

Epigenetic mechanisms in Alzheimer's disease: Implications for pathogenesis and therapy

Jun Wang[a], Jin-Tai Yu[a,b,c,**], Meng-Shan Tan[b], Teng Jiang[c], Lan Tan[a,b,c,*]

Contents lists available at ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry
journal homepage: www.elsevier.com/locate/pnp

Epigenetics in neurodegeneration: A new layer of complexity

Sueli C.F. Marques[a,b,c], Catarina R. Oliveira[c,d], Claudia M.F. Pereira[c,d], Tiago F. Outeiro[b,e,*]

Contents lists available at ScienceDirect
Progress in Neurobiology
journal homepage: www.elsevier.com/locate/pneurobio

Epigenetic regulation in the pathophysiology of Alzheimer's disease

Leonidas Chouliaras[a,1], Bart P.F. Rutten[a,1,*], Gunter Kenis[a], Odette Peerbooms[a], Pieter Jelle Visser[a,b], Frans Verhey[a], Jim van Os[a,c], Harry W.M. Steinbusch[a], Daniel L.A. van den Hove[a,d]

Contents lists available at ScienceDirect
Neurobiology of Aging
journal homepage: www.elsevier.com/locate/neuaging

Review

Epigenetically regulated microRNAs in Alzheimer's disease

Daniel L. Van den Hove[a,b,*], Konstantinos Kompotis[a], Roy Lardenoije[a], Gunter Kenis[a], Jonathan Mill[c,d], Harry W. Steinbusch[a], Klaus-Peter Lesch[a,b], Carlos P. Fitzsimons[e], Bart De Strooper[f,g], Bart P.F. Rutten[a]

frontiers in Behavioral Neuroscience
REVIEW
published: 17 December 2015
doi: 10.3389/fnbeh.2015.00347

Epigenetic Alterations in Alzheimer's Disease

*Jose V. Sanchez-Mut and Johannes Gräff**

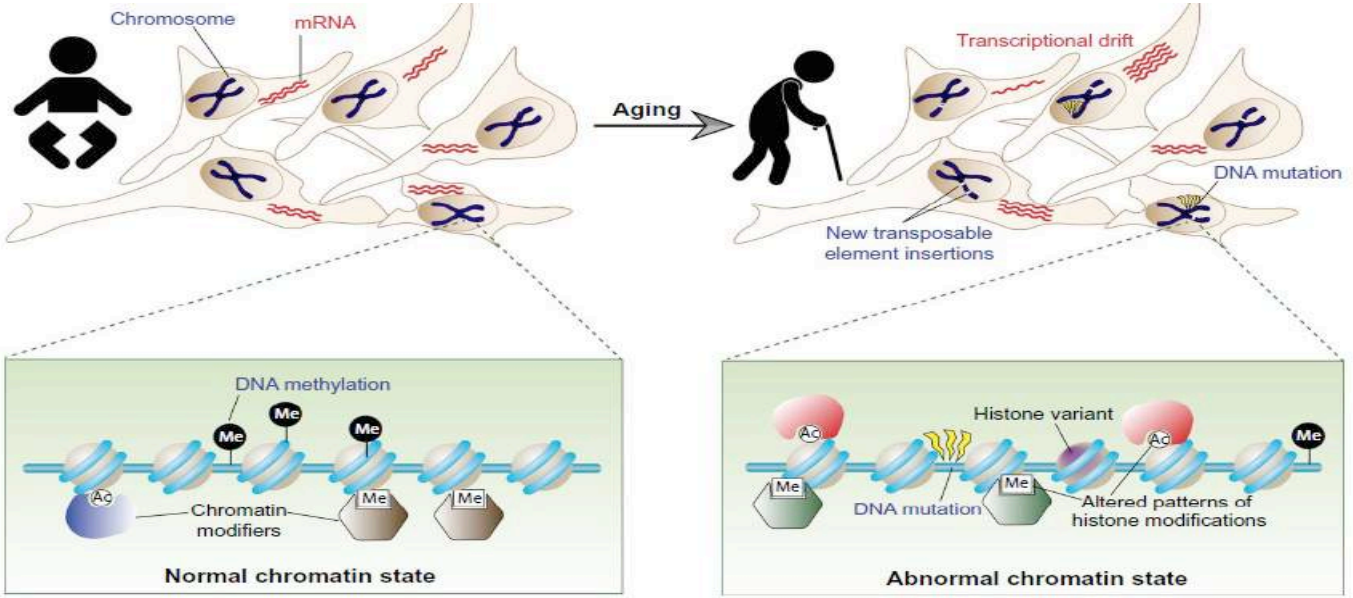
Neuroepigenetics Laboratory – UPGRADE, Brain Mind Institute, School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Mol Neurobiol (2018) 55:3021–3032
DOI 10.1007/s12035-017-0533-3

Synaptic Dysfunction in Alzheimer's Disease: Aβ, Tau, and Epigenetic Alterations

Ke Li[1] · Qing Wei[1] · Fang-Fang Liu[2] · Fan Hu[3] · Ao-ji Xie[3] · Ling-Qiang Zhu[3] · Dan Liu[4]

Epigenetic mechanisms in aged brain and AD



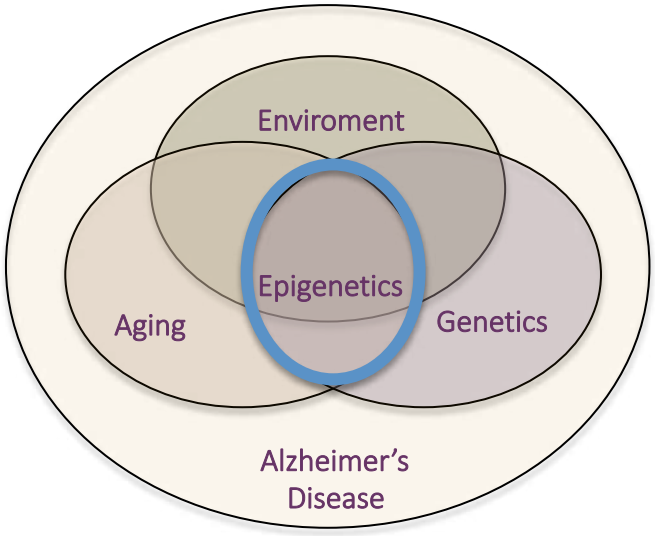
Related Aberrant Epigenetic Mark and Regulators	Epigenetic Alteration	References
DNA methylation	Global levels of 5-mC and 5-hmC ↓	[233]
Histone modifications	H3K24, H3K27, H3K36, H3K79, H3R128, H4K20 and H2AR89 ↓ Global acetylation levels of H3 and H4 ↑	[242]
miRNAs	miR-16, miR-9 and miR-139 ↓	[246, 247, 249]
DNTMs and HDACs	Dnmt3b ↑ Sirt1, Hdac5 and Hdac6 ↓	[233, 25]

Griñán-Ferré et al. J Alzheimer Dis. 2018

What causes AD?

The aetiology of Alzheimer's disease is multifactorial.

It is produced by a combination of genetic susceptibility factors added to exposure to environmental factors, where risk factors and protective factors interact, in a prolonged temporary sale that includes the aging process and with a different effect on each individual.



New Clinical Trial in Phase I for AD

0 Clinical Trials
for Epigenetic therapies

More than 5 Clinical Trials
for Epigenetic therapies

Collaboration

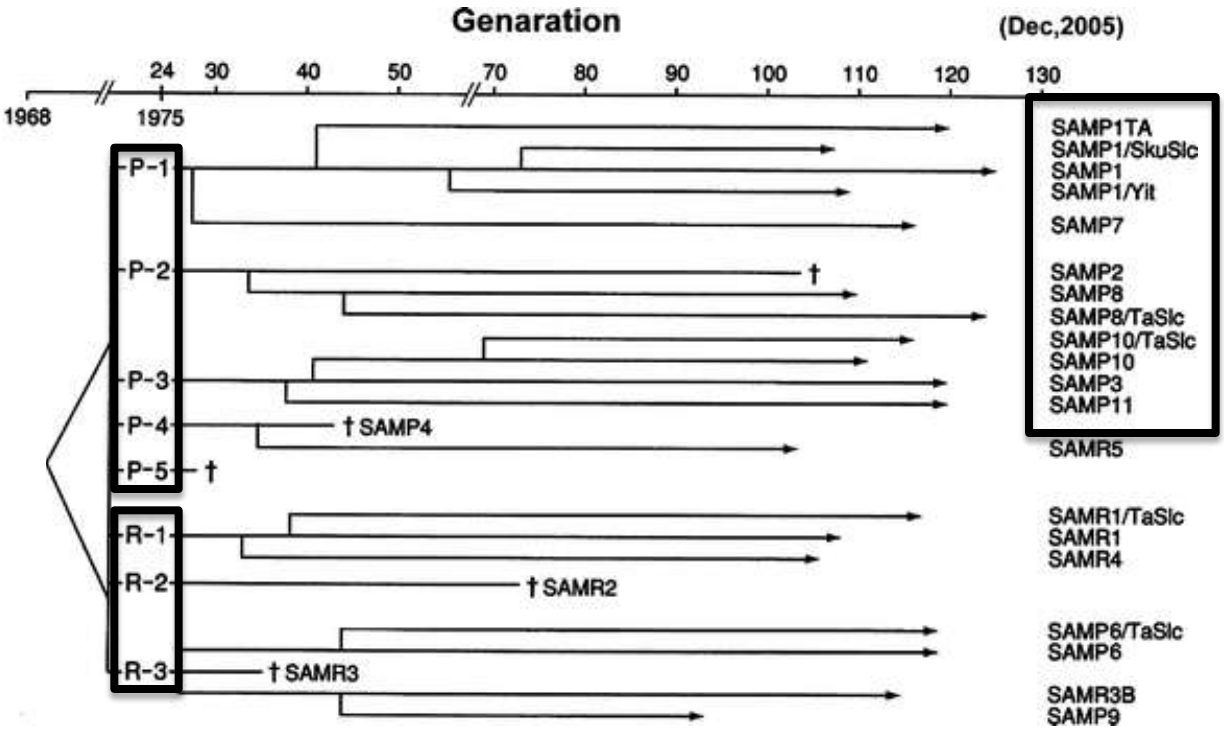
ORYZON

Vafidemstat
(ORY-2001)
Phase IIa
SATEEN (EM)
ETHERAL (AD)
REIMAGINE (AB)

The SAMP8 Mouse Model

Dr. Takeda 1968

AKR/J strain



SAM resistant (SAMR) mice

Median survival 16.3 months

SAM prone (SAMP) mice

Median survival 9.7 months

The SAMP8 Mouse Model

TABLE 1 Pathobiological phenotypes

Strains	Phenotypes
SAMP	
SAMP1	Senile amyloidosis, contracted kidney, impaired immune response, hyperinflation of lungs, hearing im ment
SAMP1TA	Deficits in learning and memory
SAMP2	Senile and secondary amyloidosis, contracted kidney, impaired immune response
SAMP3	Degenerative temporomandibular joint disease
SAMP6	Senile osteoporosis, secondary amyloidosis
SAMP6/Ta	Senile osteoporosis
SAMP7	Thymic lymphoblastic lymphoma, senile amyloidosis
SAMP8	Deficits in learning and memory, impaired immune response
SAMP8/Ta	Deficits in learning and memory, emotional disorder (reduced anxiety-like behavior)
SAMP9	Cataract, thymic lymphoblastic lymphoma, senile amyloidosis
SAMP10	Brain atrophy, deficits in learning and memory
SAMP10//Ta	Deficits in learning and memory, emotional disorder (depressive behavior)
SAMP11	Contracted kidney, senile amyloidosis.
SAMR	
SAMR1	Nonthymic lymphoma*, histiocytic sarcoma, ovarian cyst
SAMR1TA	
SAMR4	Nonthymic lymphoma*, histiocytic sarcoma
SAMR5	Colitis

Table 3: Molecular and cellular pathways altered in SAMP8.

Pathway/protein target	Modification	Reference
Sirtuin 1	Decreased	[20, 58, 97]
Autophagic process	Reduced	[117–119]
Cathepsin system	Inactivated	[117]
AMPK	Not determined	
mTOR	Not determined	
mtDNA damage	Increased	[125]
Mitochondrial electron chain	Diminished efficiency	[20, 21, 29, 126, 127]
Fusion/fission proteins	Not determined	
Mitochondrial fatty acid oxidation	Altered	[128]

Table 2: Histopathological and cellular markers of AD and aging found in SAMP8.

Target	Modification	References
Tau protein	Increased levels and phosphorylation	[22, 55, 56]
Tau kinases	Increased levels or activity in Cdk5/p25 and GSK3β	[22, 58, 59]
Receptor for advanced glycation end product (RAGE)	Increased	[75]
APP protein	Increased	[63–65, 80, 85, 86]
B-amyloid	Amyloid content increased and aggregates	[26, 61, 62, 69, 70, 74, 87]
Secretases	ADAM-10 and PS1	[65, 80, 88]
BBH	Disrupted	[72, 73, 89]

The SAMP8 Mouse Model

CHARACTERISTICS OF AGE-RELATED BEHAVIORAL CHANGES IN SENESCENCE-ACCELERATED MOUSE SAMP8 AND SAMP10

MASAOMI MIYAMOTO

Pharmaceutical Research Laboratories 1, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 2-17-85, Jusohonmachi, Yodogawa-ku, Osaka 532, Japan

Molecular Genetic Characterization of the Senescence-Accelerated Mouse (SAM) Strains

Haruo Kitado, Keiichi Higuchi, Toshio Takeda

Journal of Gerontology, Volume 49, Issue 6, 1 November 1994, Pages B247–B254,
https://doi-org.sire.ub.edu/10.1093/geronj/49.6.B247
Published: 01 November 1994 **Article history ▾**

GENETIC CHARACTERIZATION OF SENESCENCE-ACCELERATED MOUSE (SAM)

KEIICHI HIGUCHI

Department of Senescence Biology, Chest Disease Research Institute, Kyoto University, Sakyo-ku, Kyoto 606 Japan

RESEARCH ARTICLE Open Access

Exome sequencing of senescence-accelerated mice (SAM) reveals deleterious mutations in degenerative disease-causing genes

Kumpei Tanisawa[1,2], Eri Mikami[1,2,3], Noriyuki Fuku[1], Yoko Honda[1], Shuji Honda[1], Ikuro Ohsawa[4], Masafumi Ito[5], Shogo Endo[6], Kunio Ihara[7], Kinji Ohno[8], Yuki Kishimoto[9], Akihito Ishigami[9], Naoki Maruyama[9], Motoji Sawabe[10], Hiroyoshi Iseki[11], Yasushi Okazaki[11], Sanae Hasegawa-Ishii[12], Shiro Takei[12], Atsuyoshi Shimada[12], Masanori Hosokawa[12], Masayuki Mori[13], Keiichi Higuchi[13], Toshio Takeda[14], Mitsuru Higuchi[15] and Masashi Tanaka[1*]

Research

Open Access

Mechanisms of aging in senescence-accelerated mice

Todd A Carter[¤*], Jennifer A Greenhall[¤*], Shigeo Yoshida[†], Sebastian Fuchs[*], Robert Helton[*], Anand Swaroop[‡‡], David J Lockhart[§] and Carrolee Barlow[*¶]

Addresses: [*]The Salk Institute for Biological Studies, La Jolla, CA 92037, USA. [†]Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, MI 48105, USA. [‡]Department of Human Genetics, University of Michigan, Ann Arbor, MI 48105, USA. [§]Ambit Biosciences, San Diego CA 92121, USA. [¶]Current address: BrainCells Inc., 10835 Road to the Cure, San Diego, CA 92121, USA.

ELSEVIER

Available online at www.sciencedirect.com
SCIENCE DIRECT

Experimental Gerontology 40 (2005) 774–783

Experimental Gerontology
www.elsevier.com/locate/expgero

Mini review

The senescence-accelerated prone mouse (SAMP8): A model of age-related cognitive decline with relevance to alterations of the gene expression and protein abnormalities in Alzheimer's disease

D. Allan Butterfield*, H. Fai Poon

Review Article

Senescence-Accelerated Mice P8: A Tool to Study Brain Aging and Alzheimer's Disease in a Mouse Model

Mercè Pallàs

NEUROPATHOLOGY

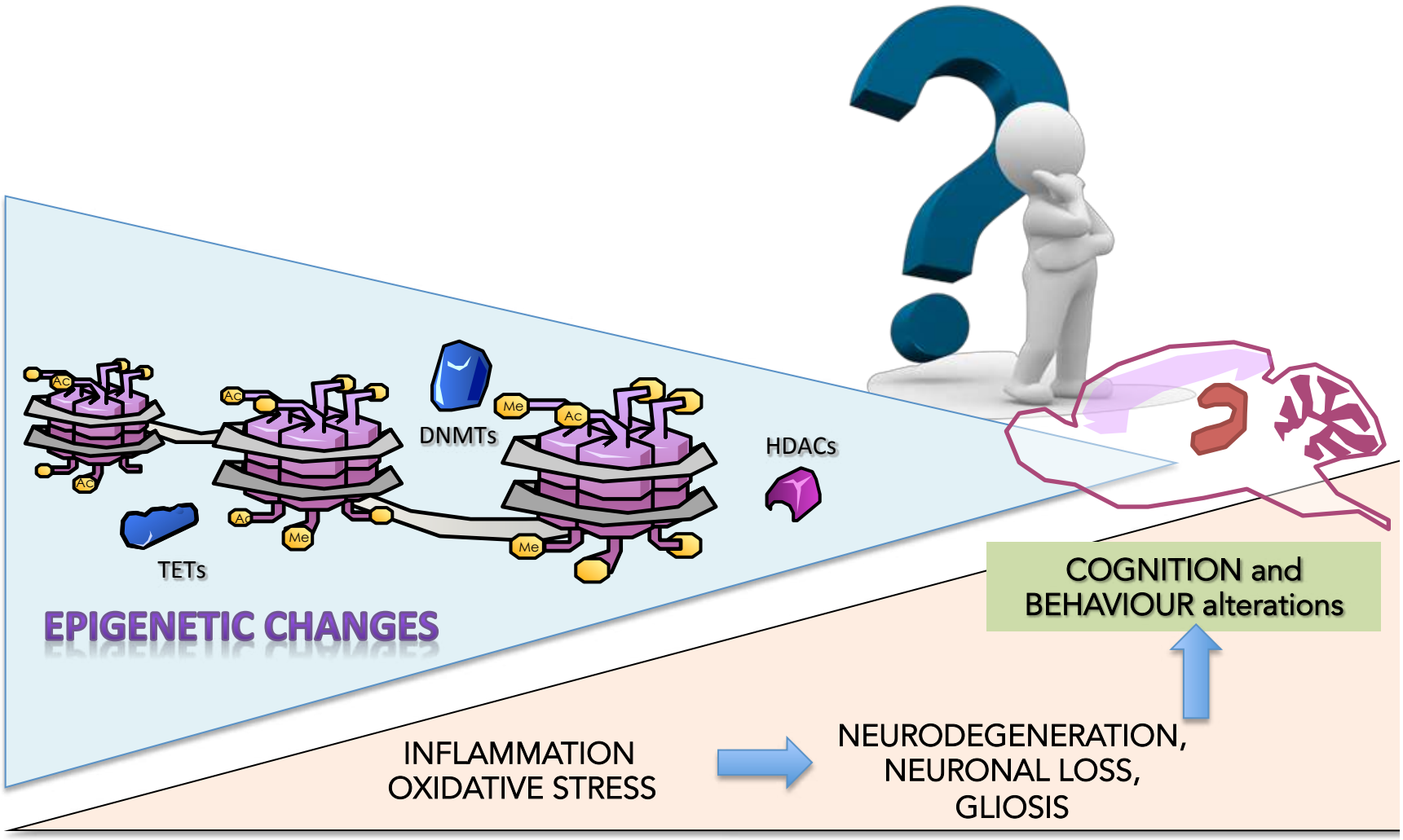
Neuropathology 2017; **37**, 293–305 doi:10.1111/neup.12373

Occasional Review

SAMP8 mice as a neuropathological model of accelerated brain aging and dementia: Toshio Takeda's legacy and future directions

Ichiro Akiguchi,[1,2] Mercè Pallàs,[10] Herbert Budka,[11] Haruhiko Akiyama,[4] Masaki Ueno,[5] Jingxian Han,[12] Hideo Yagi,[1] Tomohumi Nishikawa,[2] Yoichi Chiba,[5] Hiroshi Sugiyama,[3] Ryoya Takahashi,[6] Keiko Unno,[7] Keiichi Higuchi[8] and Masanori Hosokawa[9]

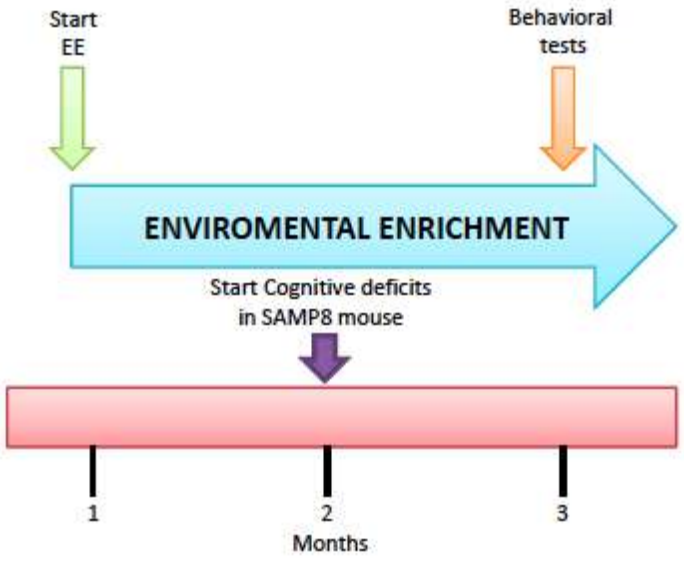
Accelerated senescence and epigenetics



Effect of Environment enrichment (EE) in SAMP8

SAMP8 Ct

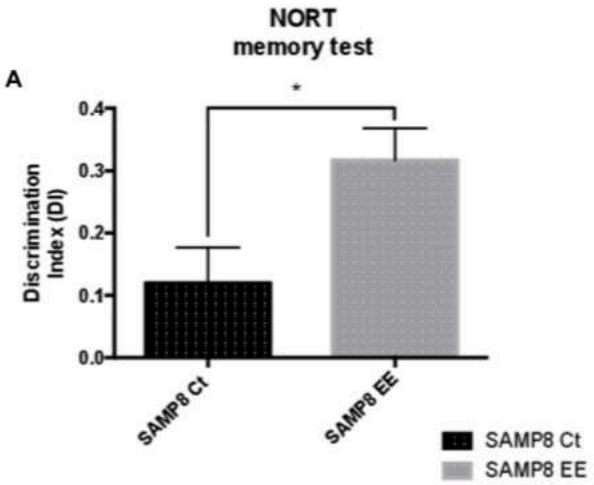
SAMP8 EE

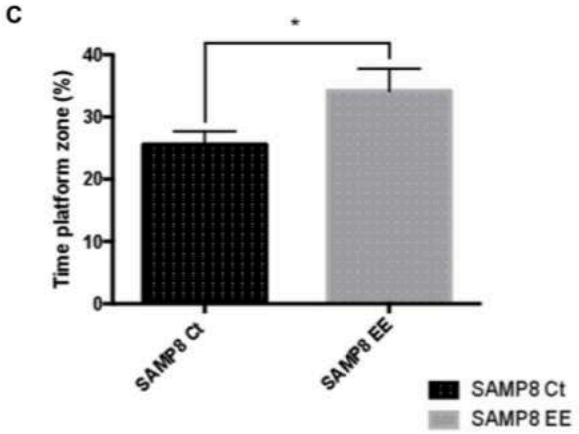


Griñán-Ferré et al. Molecular Neurobiology, 2015
Griñán-Ferré et al. Frontiers Aging Neurosci. 2016

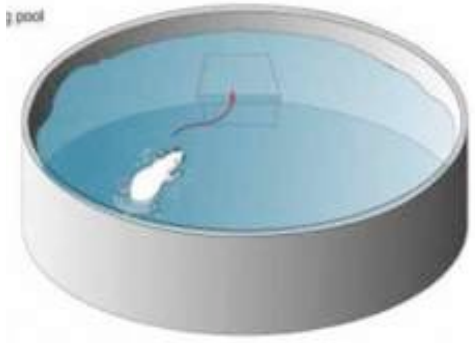
Beneficial effects of EE in cognition

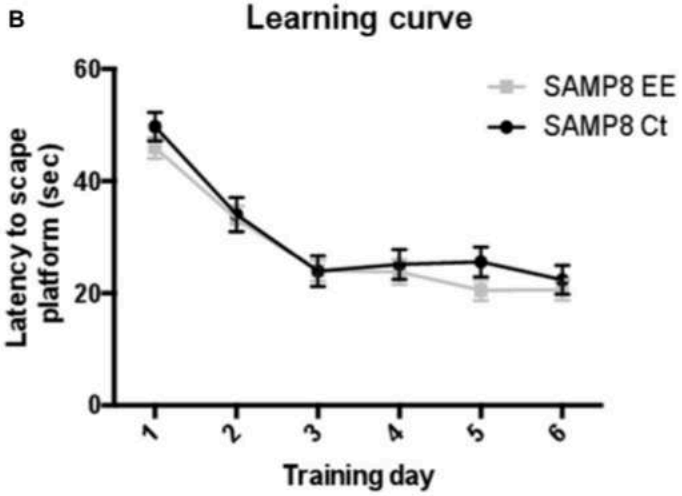
Novel Object Recognition

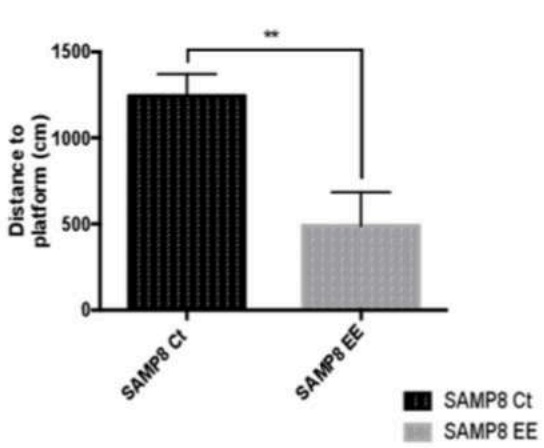




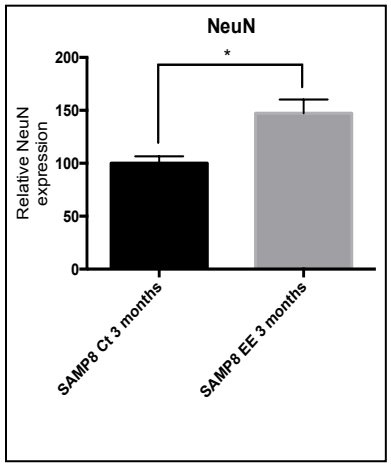
Morris Water Maze



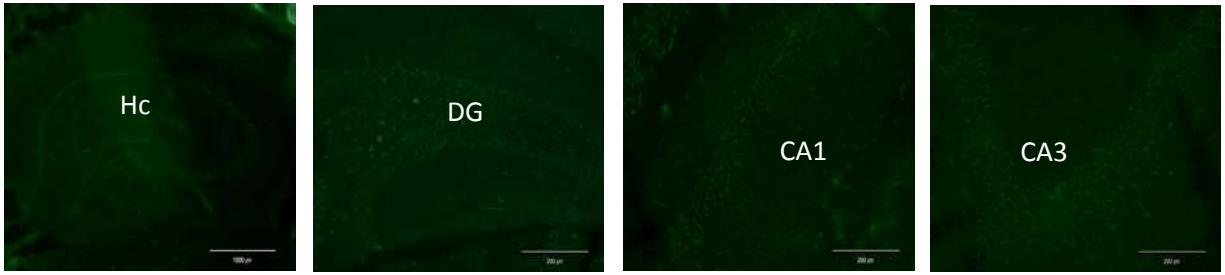




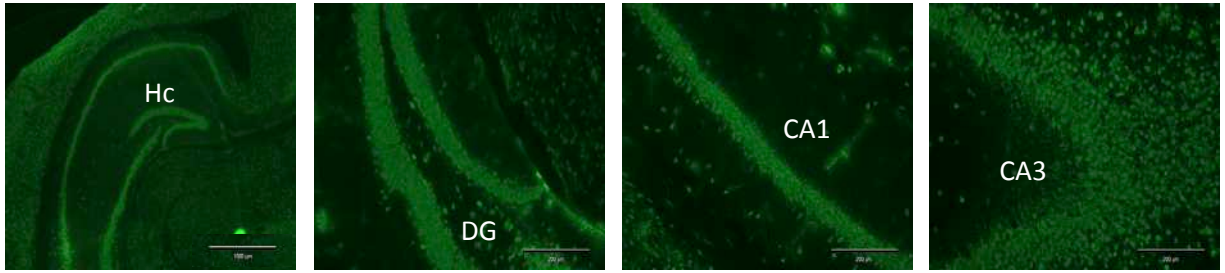
Neuroprotective effects of EE in SAMP8

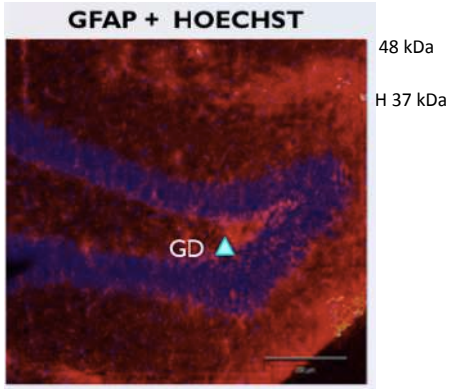


SAMP8 CT



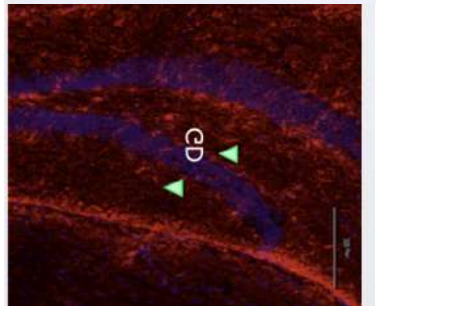
SAMP8 EE

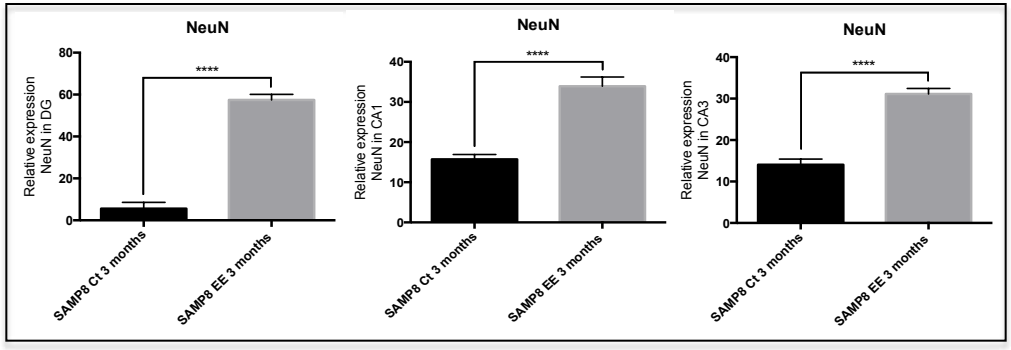




SAMP8 CT

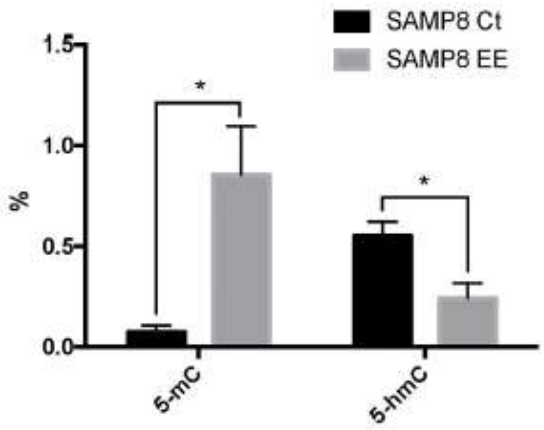
SAMP8 EE

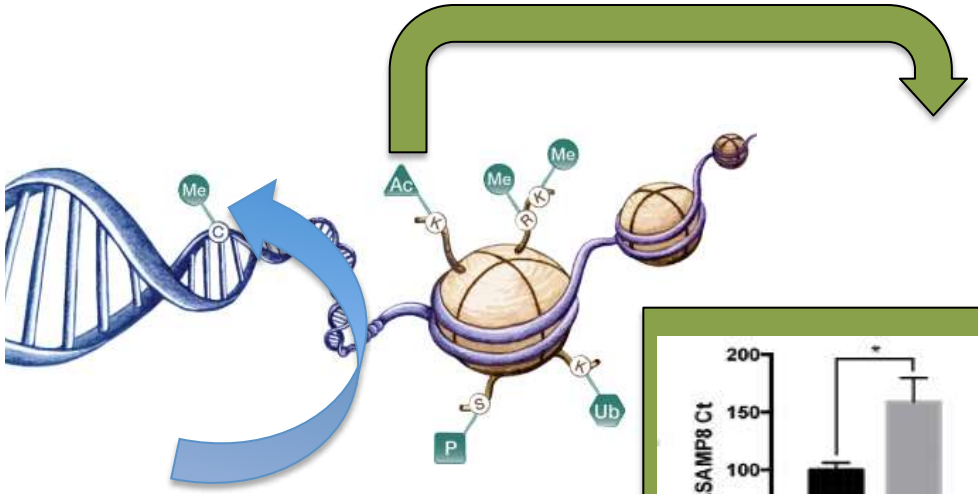


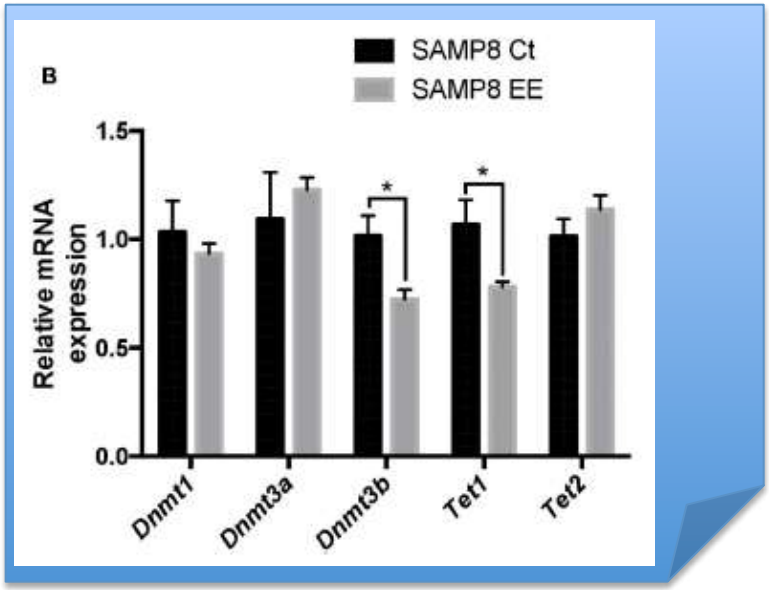


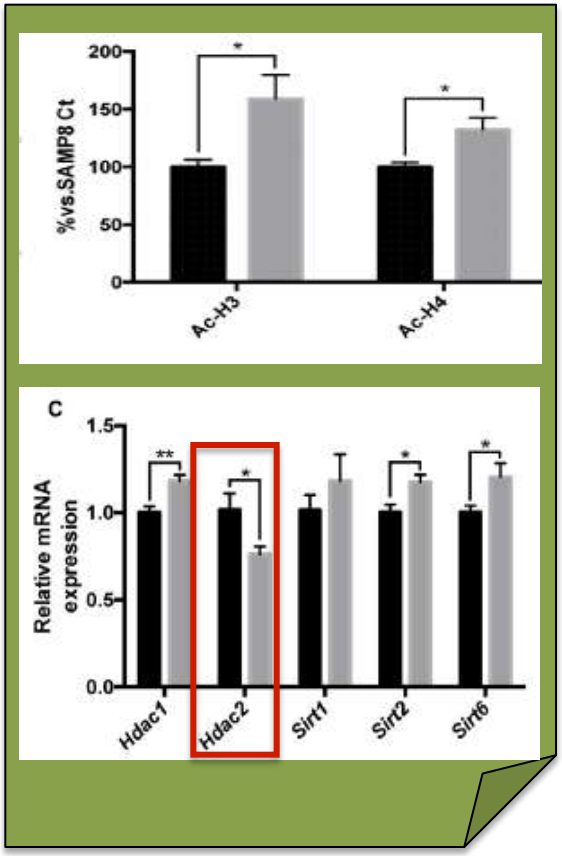
Griñán-Ferré et al. Molecular Neurobiology, 2015

Effects of EE on Epigenetics in SAMP8



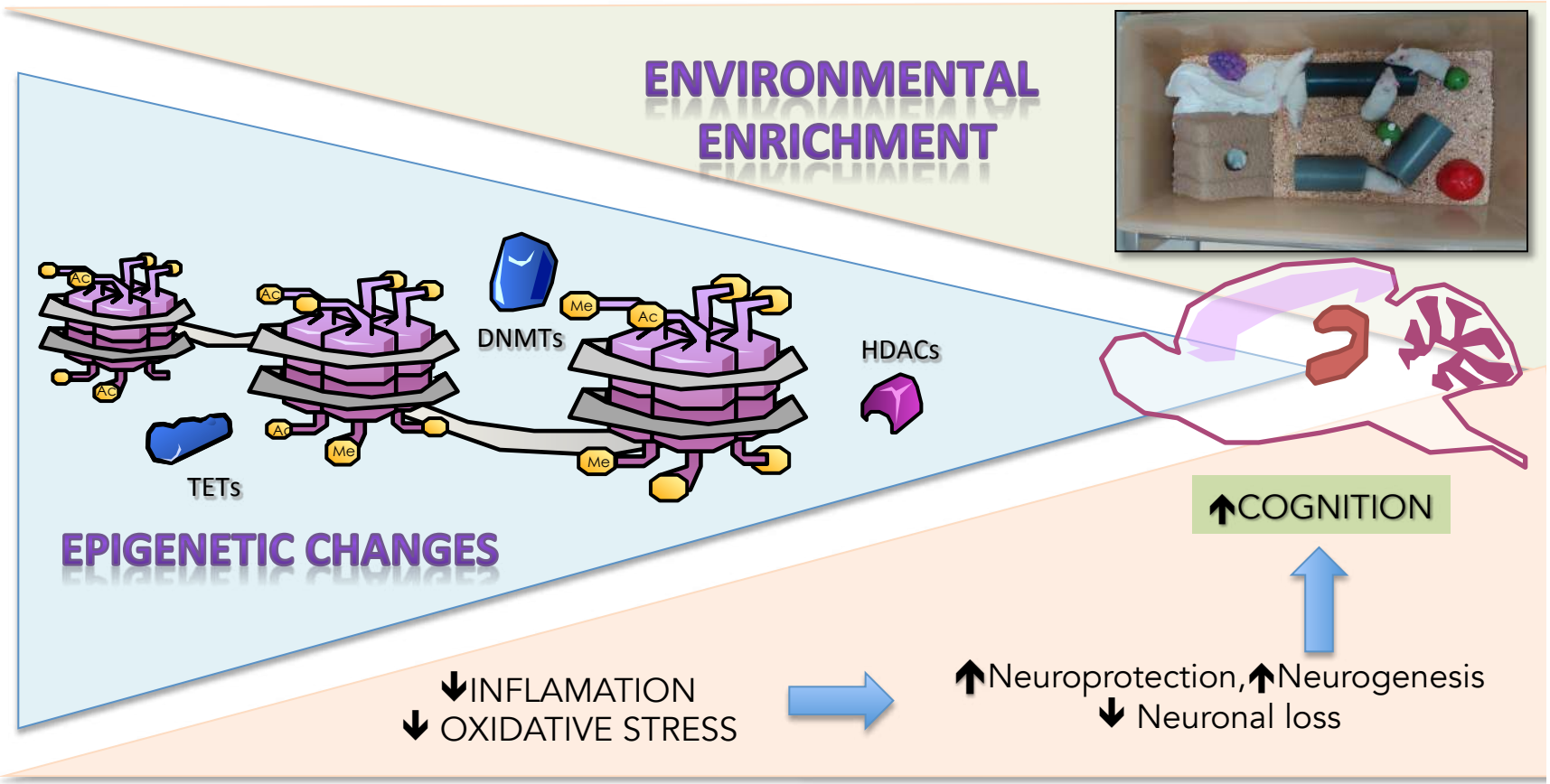






Griñán-Ferré et al. Frontiers Aging Neurosci. 2016

Accelerated senescence and epigenetics



frontiers in Cellular Neuroscience

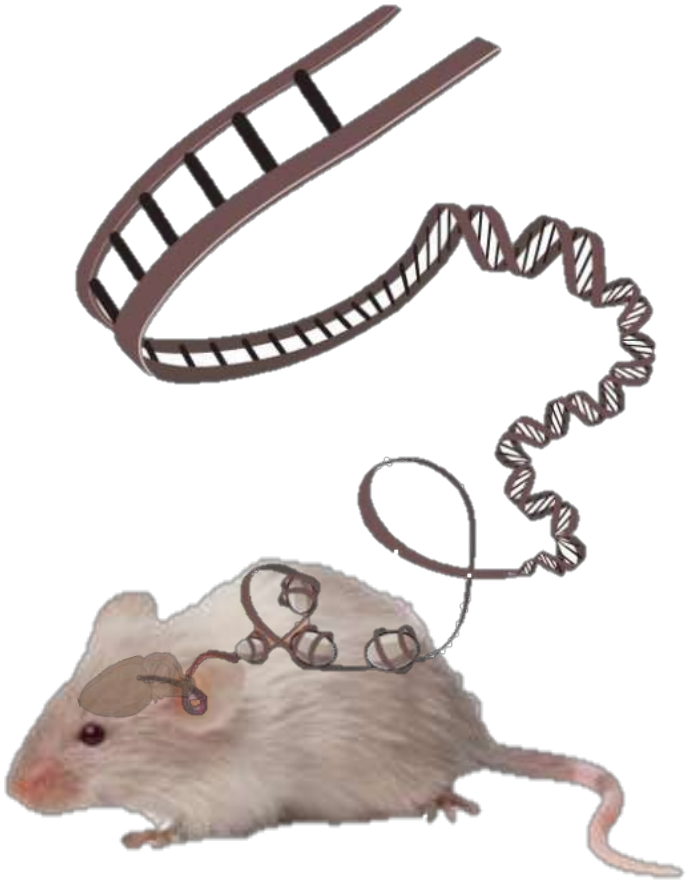
ORIGINAL RESEARCH
published: 15 August 2018
doi: 10.3389/fncel.2018.00224

Environmental Enrichment Improves Cognitive Deficits, AD Hallmarks and Epigenetic Alterations Presented in 5xFAD Mouse Model

*Christian Griñán-Ferré[1], Vanesa Izquierdo[1], Eduard Otero[1], Dolors Puigoriol-Illamola[1], Rubén Corpas[2], Coral Sanfeliu[2], Daniel Ortuño-Sahagún[3] and Mercè Pallàs[1]**

The SAMP8 Mouse Model

Epigenetics can explain in part the senescent phenotype that characterizes SAMP8



frontiers in AGING NEUROSCIENCE
ORIGINAL RESEARCH ARTICLE
published: 20 March 2014
doi: 10.3389/fnagi.2014.00051

Epigenetic alterations in hippocampus of SAMP8 senescent mice and modulation by voluntary physical exercise

*Marta Cosín-Tomás[1,2†], María J. Alvarez-López[1,2†], Sandra Sanchez-Roige[3], Jaume F. Lalanza[3], Sergi Bayod[1], Coral Sanfeliu[2], Merce Pallàs[1], Rosa M. Escorihuela[3] and Perla Kaliman[2]**

[1] Unitat de Farmacologia, Facultat de Farmàcia Institut de Biomedicina Universitat de Barcelona (IBUB), Nucli Universitari de Pedralbes, Barcelona, Spain
[2] Department of Brain Ischemia and Neurodegeneration, Institut d'Investigacions Biomèdiques de Barcelona (IIBB)-Consejo Superior de Investigaciones Científicas (CSIC), Barcelona, Spain
[3] Departamento de Psiquiatría y Medicina Legal, Facultad de Medicina, Instituto de Neurociencias, Universitat Autònoma de Barcelona, Barcelona, Spain

frontiers in Aging Neuroscience
ORIGINAL RESEARCH
published: 18 October 2016
doi: 10.3389/fnagi.2016.00241

Environmental Enrichment Modified Epigenetic Mechanisms in SAMP8 Mouse Hippocampus by Reducing Oxidative Stress and Inflammaging and Achieving Neuroprotection

*Christian Griñan-Ferré[1], Dolors Puigoriol-Illamola[1], Verónica Palomera-Ávalos[1], David Pérez-Cáceres[2], Júlia Companys-Alemany[1], Antonio Camins[1], Daniel Ortuño-Sahagún[3], M. Teresa Rodrigo[2] and Mercè Pallàs[1]**

Journal of Alzheimer's Disease 62 (2018) 943–963
DOI 10.3233/JAD-170664
IOS Press

Review

Understanding Epigenetics in the Neurodegeneration of Alzheimer's Disease: SAMP8 Mouse Model

Christian Griñán-Ferré[a], Rubén Corpas[b], Dolors Puigoriol-Illamola[a], Verónica Palomera-Ávalos[a], Coral Sanfeliu[b] and Mercè Pallàs[a,*]
[a]*Department of Pharmacology, Toxicology and Therapeutic Chemistry (Pharmacology Section) and Institute of Neuroscience, University of Barcelona and CIBERNED, Barcelona, Spain*
[b]*Institut d'Investigacions Biomèdiques de Barcelona (IIBB), CSIC, IDIBAPS and CIBERESP, Barcelona, Spain*

Accepted 11 January 2018

Epigenetic study in SAMP8

frontiers in Genetics

ORIGINAL RESEARCH
published: 11 December 2018
doi: 10.3389/fgene.2018.00596

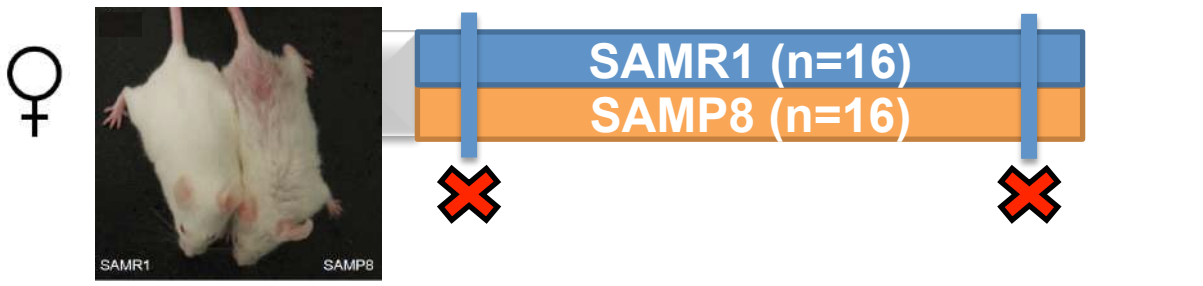
Temporal Integrative Analysis of mRNA and microRNAs Expression Profiles and Epigenetic Alterations in Female SAMP8, a Model of Age-Related Cognitive Decline

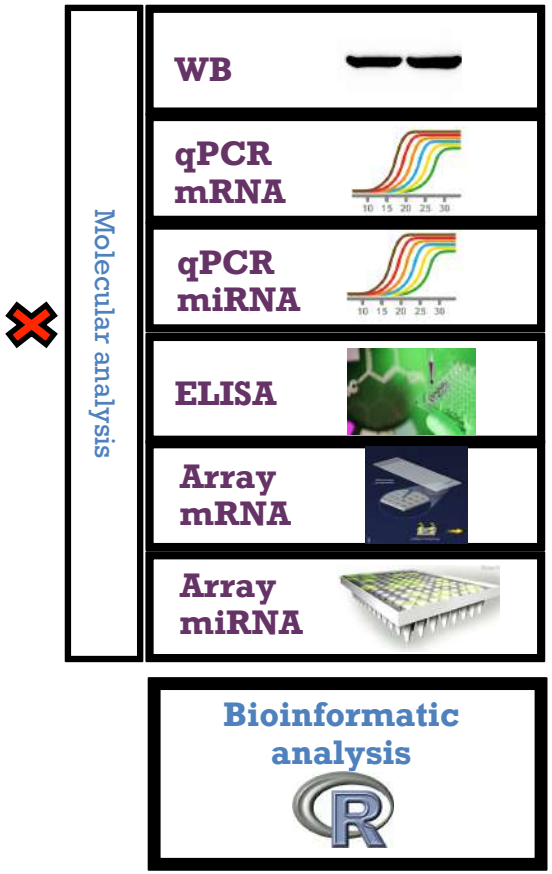
OPEN ACCESS

Edited by:
Ruth Luthi-Carter,
University of Leicester,

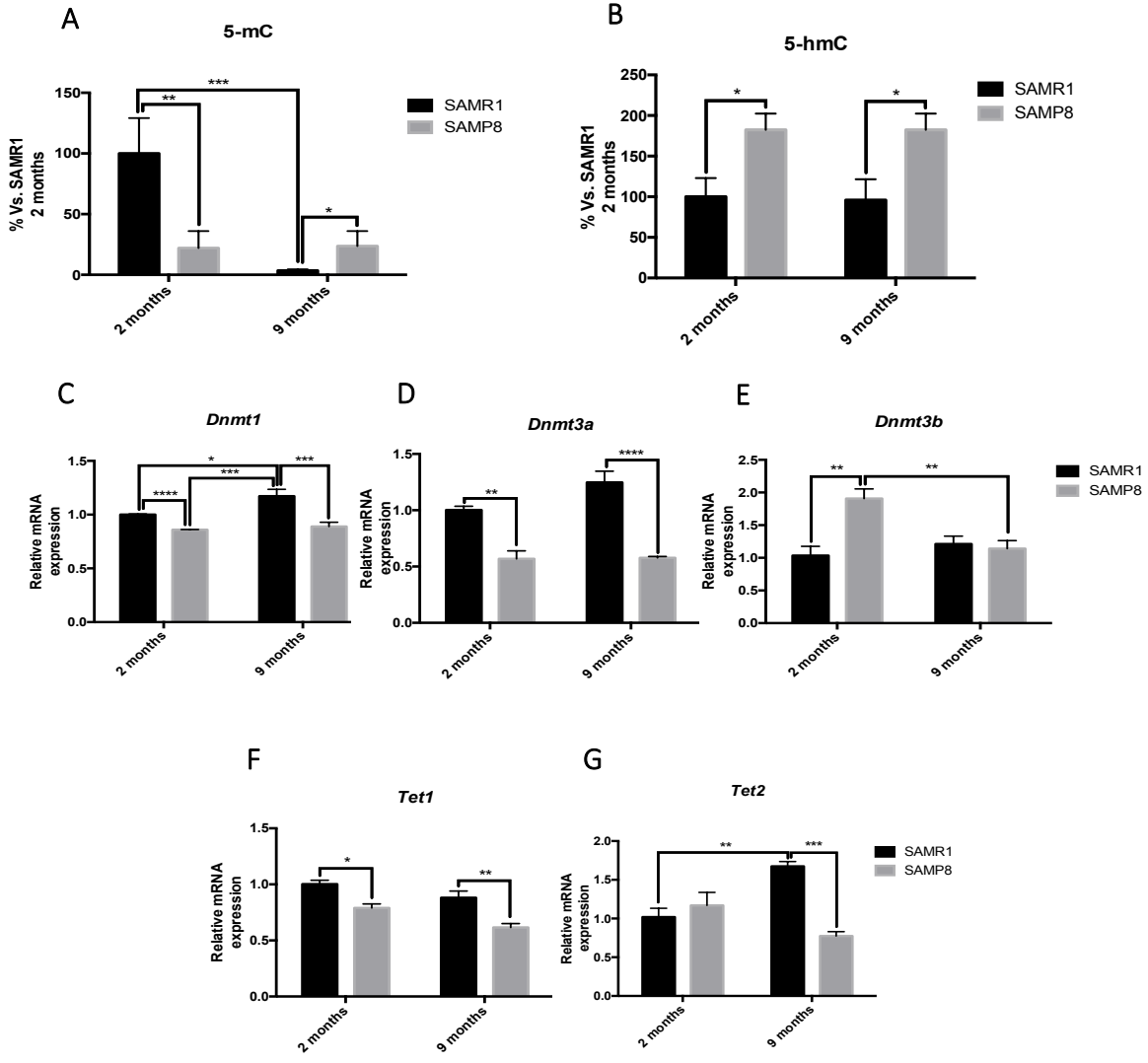
Marta Cosín-Tomás[1,2], María Jesús Álvarez-López[1], Júlia Companys-Alemany[1], Perla Kaliman[1,3], Celia González-Castillo[4], Daniel Ortuño-Sahagún[5], Mercè Pallàs[1] and Christian Griñán-Ferré[1]*

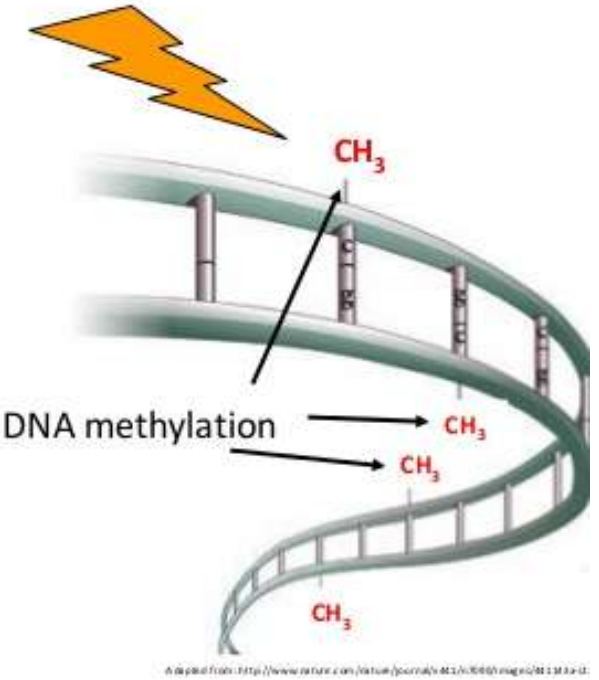
[1] Department of Pharmacology and Therapeutic Chemistry, Institute of Neuroscience, University of Barcelona, Barcelona,



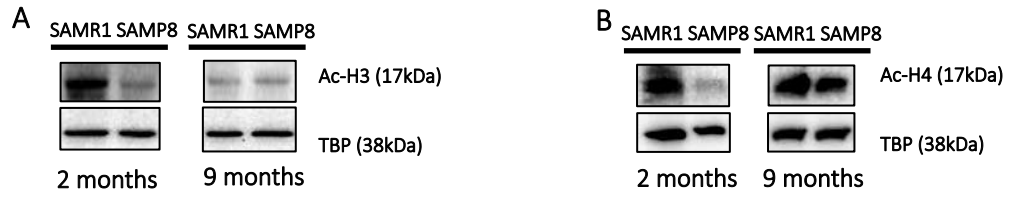


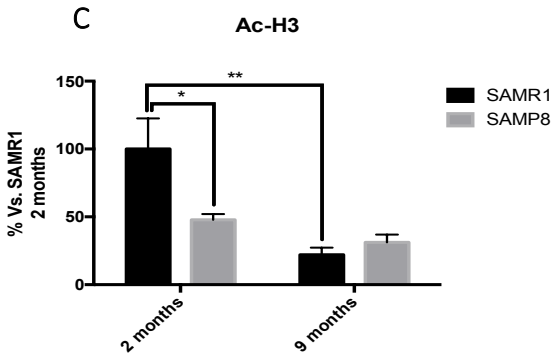
Epigenetic Landscape

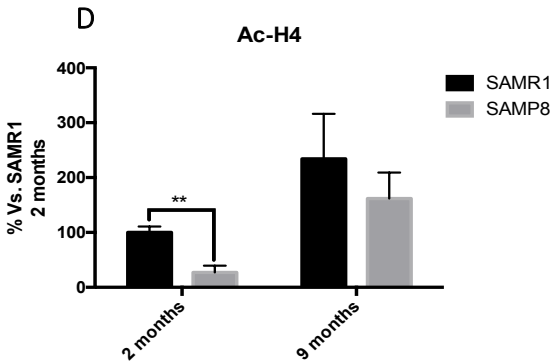


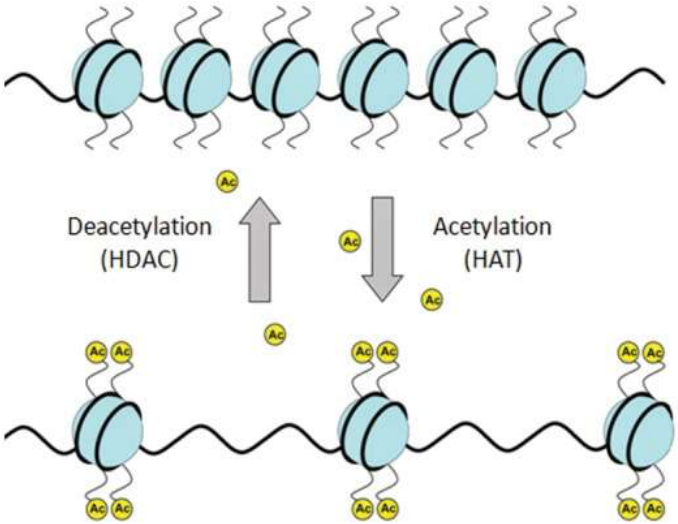


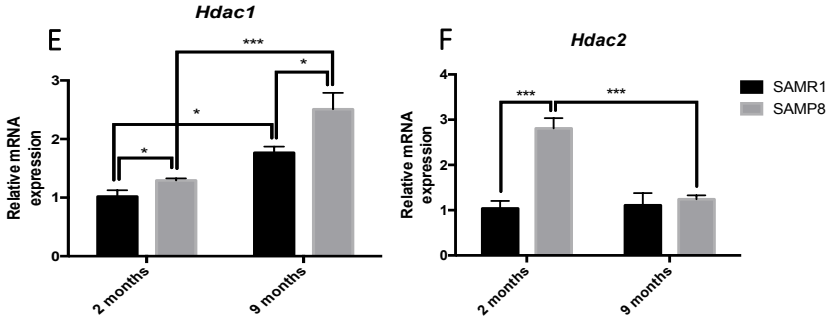
Epigenetic Landscape

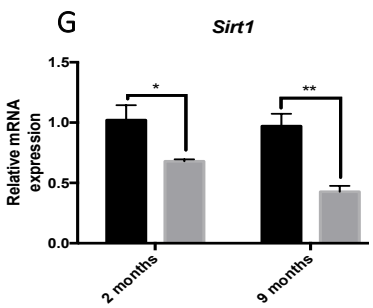


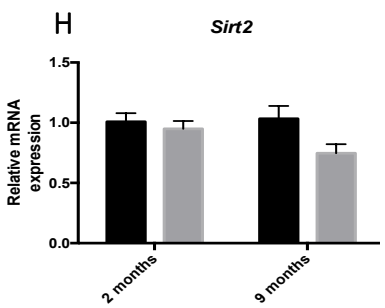


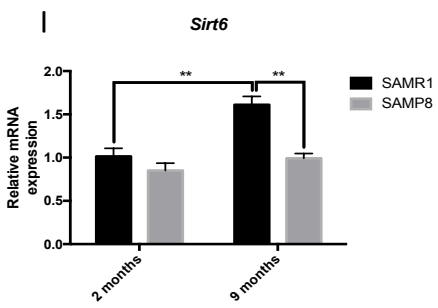










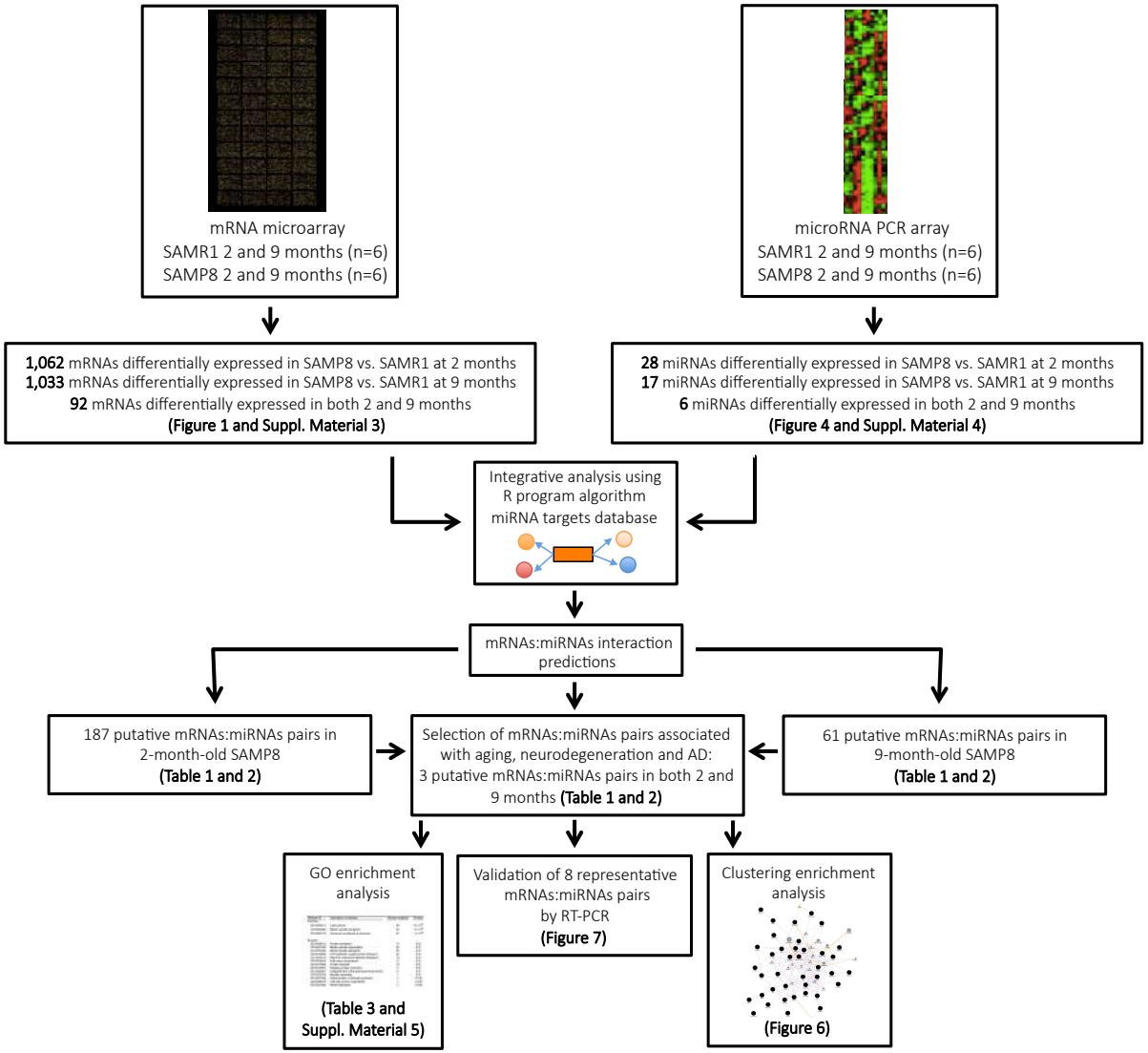


Epigenetics in Alzheimers Disease

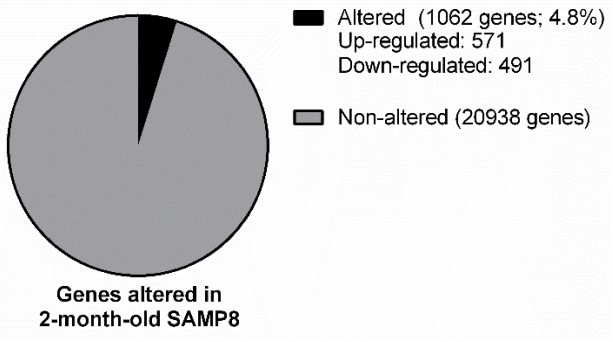
- Animal post-mortem studies show:

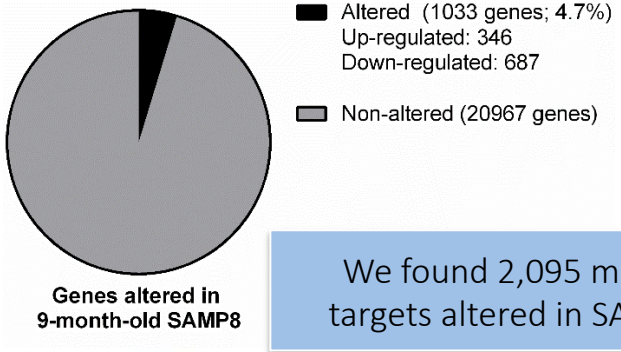
Pathology	Effect
Decreased global levels of 5'-mC in brain	Increased Tau phosphorylation
Decreased level of H3 acetylation in Temporal lobe	Decreased synaptic plasticity leading to decreased learning and memory

mRNA:miRNA integrative analysis



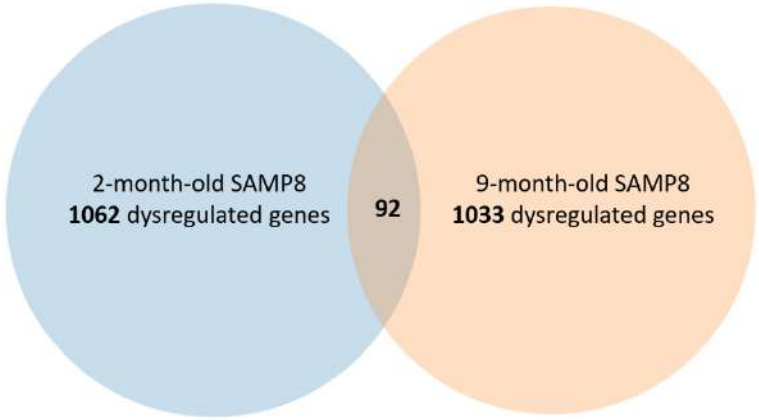
mRNA and miRNA expression profile

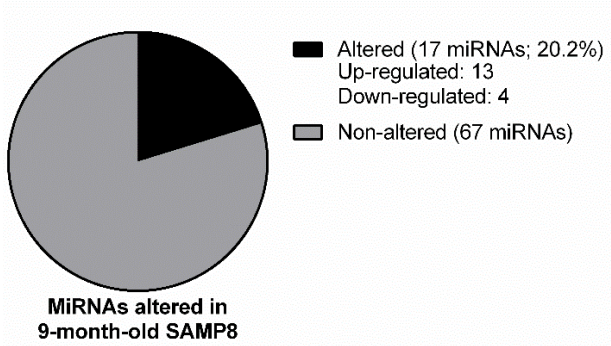


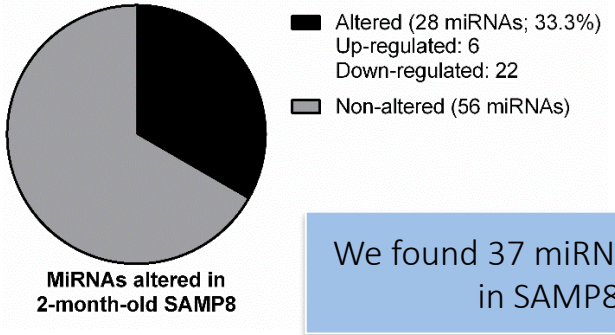


5%

We found 2,095 mRNA targets altered in SAMP8

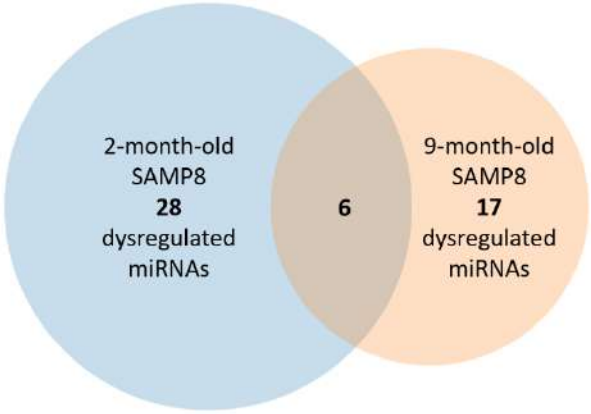






30%

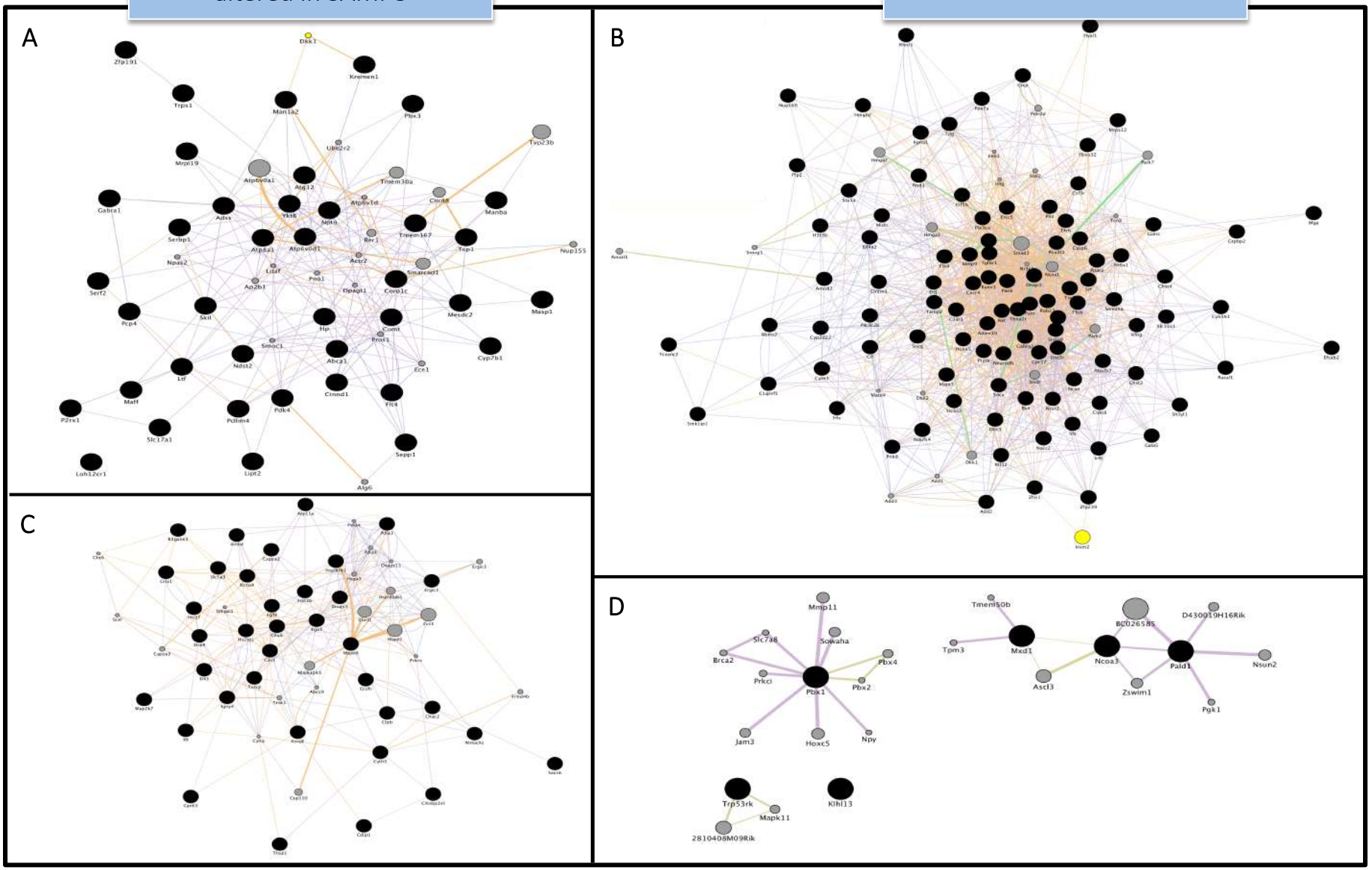
We found 37 miRNAs altered in SAMP8



Integrated mRNA:miRNA regulatory networks

We found 174 mRNA targets altered in SAMP8

We found 37 miRNAs altered in SAMP8



Integrated mRNA:miRNA regulatory networks

		MicroRNAS	Target mRNAs	Top 10 GO Biological process	p-value	Z-score	Combined score
2-month-old SAMP8	miRNAs up:mRNAs down	*mmu-miR-298-5-p* *mmu-miR-151-3p* *mmu-miR148b-3p* *mmu-let-7b-5p* *mmu-let-7e-5p*	*Adss,Ctnnd1, Comt1,Cyp7b1, Flt4, Ltf,Masp1, P2rx1, Pcp4, Nptn, Sepp1, Slc17a1, Atp8a1, Gabra1, Maff, Man1a2, Ndst2, Serf2, Skil, Coro1c, Abca1, Atp6v0d1, Tcp, Pdk4, Pbx3, Hp, Pdlim4, Ykt6, Kox17, Mesdc2, Tmem167, Serbp1, Lipt2, Atg12, Loh12cr1, Mrpl19, Manba, Trps1, Kremen1.*	Regulation of membrane lipid distribution (GO: 0097035)	0.002603	-2.53	4.08
				Cellular response to extracellular stimulus (GO: 0031668)	0.002990	-2.26	3.66
				Regulation of extrinsic apoptotic signaling pathway via death domain receptors (GO: 1902041)	0.005549	-2.37	3.33
				Wnt signaling pathway (GO: 0016055)	0.01844	-2.26	3.17
				Brain development (GO: 0007420)	0.01021	-2.25	3.16
				Neuron-neuron synaptic transmission (GO: 0007270)	0.008912	-2.05	2.88
				Insulin receptor signaling pathway (GO: 0008286)	0.04929	-1.97	2.77
				Cellular ion homeostasis (GO: 0006873)	0.07075	-1.96	2.76
				Positive regulation of neuron projection development (GO: 0010976)	0.04696	-1.89	2.65
				Locomotor behavior (GO: 0007626)	0.07133	-1.83	2.57
	miRNAs down:mRNAs up	*mmu-miR-92a-3p* *mmu-miR-24-3p* *mmu-miR-27a-3p* *mmu-miR-30e-5p* *mmu-miR-107-3p* *mmu-miR-26b-5p* *mmu-miR-7a-5p* *mmu-miR-181a-5p* *mmu-miR-181d-5p* *mmu-miR-132-3p* *mmu-miR-146a-5p* *mmu-miR-134-5p* *mmu-miR-29a-3p*	*Adam10, Bsn, Crcp, Csf3r, Ncan, Cyb561, Elk4, Gabrg2, Gata5, Gif, Slc6a9, H3f3b, Hlx, Hmg20b, Hyal1, Kif5b, Kpna1, Zfp239, Nsd1, Pde7a, Pik3ca, Pml, Pou3f2, Rab23, Ret, Rfng, Sema5a, Snca, Tarpb2, Tbx2r, Tgfbr1, Thrb, Unc5c, Nrsn1, Zhx1, Neurod6, Atp2b2, C3ar1, Casp6, Runx1, Cxcr4, En1, Esr2, Nr6a1, Gpr37, Hoxa5, Ids, Klf12, Matn3, Ndufs4, Pik3c2a, Ppara, Cyth3, Ptpre, Sncg, Tfeb, Tdg, Ercc5, Mrps12, Chst4, Add2, Crem, Eif4a2, Mmp9, Pam, Pax6, Sh3yl1, Mga, Rasal1, Slc33a1, Dkk3, Galns, Dnajc5, Irf6, Slc5a3, Chst2, Cldn8, Grpbp2, Rbms2, Plp2, Amotl2, Cyp2d22, Stx5a, C1qtnf1, Pnkd, Insm2, Srf, Nup160, Rhot1, Midn, Tsc1, Cmtm3, Tceanc2, Srek1ip1, Fbxo32, Nacc2, Efcab2.*	Embryonic morphogenesis (GO: 0048598)	0.0007922	-2.40	6.34
				Brain development (GO: 0007420)	0.05911	-2.13	4.16
				Synapse organization (GO: 0050808)	0.005018	-2.06	4.07
				Neuron migration (GO: 0001764)	0.00583	-2.05	4.01
				Neuron development (GO: 0048666)	0.006725	-2.06	3.97
				Behavior (GO: 0007610)	0.01035	-2.18	3.60
				Regulation of synaptic transmission (GO: 0050804)	0.01713	-2.04	3.16
				Response to oxygen levels (GO: 0070482)	0.02114	-2.09	3.11
				Cellular senescence (GO: 0090398)	0.01385	-1.90	2.98
				Inflammatory response (GO: 0006954)	0.02707	-1.91	2.65

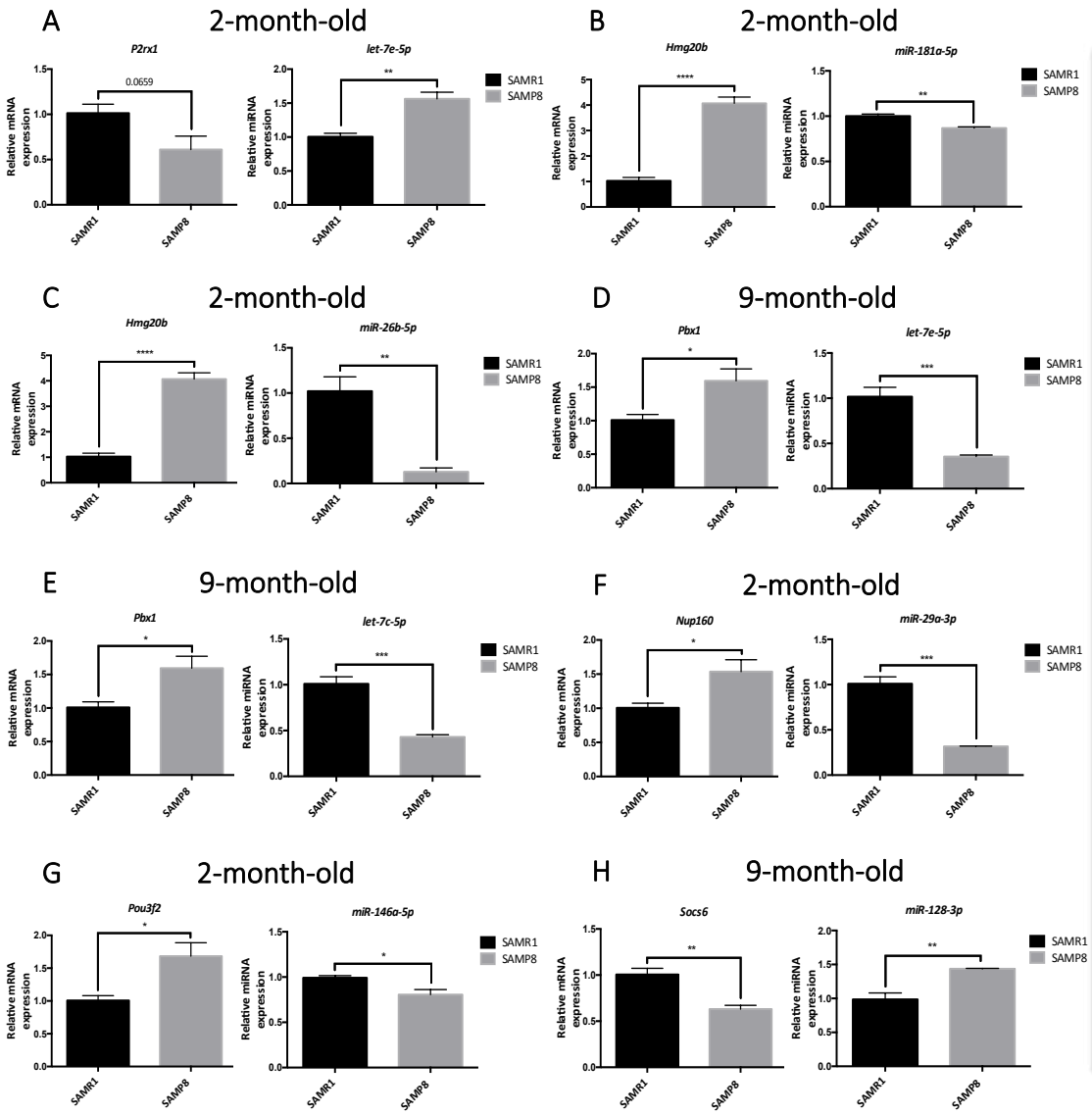
Integrated mRNA:miRNA regulatory networks

		MicroRNAS	Target mRNAs	Top 10 GO Biological process	p-value	Z-score	Combined score
9-month-old SAMP8	miRNAs up:mRNAs down	*mmu-miR-128-3p* *mmu-miR-140-5p* *mmu-miR-148b-3p* *mmu-miR-342-3p* *mmu-miR-98-5p* *mmu-miR-107-3p*	*Capza2, Cav1, Chuk, Dll3, Drd4, Pdia3, Gcdh, Gria1, H3f3b, Htr1f, Kcnj8, Dnajc3, Clpb, Itga5, Itk, Cyth3, Hsp90b1, Hs2st1, Spry4, Map2k7, Fgf9, Atp11a, Mapk6, Slc5a3, Socs6, Thsd1, B3galtn1, Kcna4, Txnip, Vps50, Arl4d, Cdip1, Mmachc, Ergic1, Chac2, Cttnbp2nl, Gpr63.*	Memory (GO: 0007613)	0.001378	-2.23	4.11
				Response to tumor necrosis factor (GO: 0034612)	0.002467	-2.31	3.96
				Synaptic transmission (GO: 0007268)	0.003559	-2.32	3.88
				Activation of innate immune response (GO: 0002218)	0.005741	-2.21	3.70
				Learning or memory (GO:0007611)	0.01189	-2.20	3.63
				Cognition (GO: 0050890)	0.01703	-2.16	3.57
				Positive regulation of canonical Wnt signaling pathway (GO: 0090263)	0.009200	-2.11	3.49
				Cellular response to unfolded protein (GO: 0034620)	0.01849	-2.01	3.32
				Neuron-neuron synaptic transmission (GO: 0007270)	0.008912	-2.01	3.32
				Response to carbohydrate (GO: 0009743)	0.04411	-1.89	3.11
	miRNAs down:mRNAs up	*mmu-let-7b-5p* *mmu-let-7c-5p* *mmu-let-7d-5p* *mmu-let-7e-5p*	*Ncoa3, Pbx1, Mxd1, Pald1, Trp53rk, Klhl13.*	Positive regulation of cell cycle G2/M phase transition (GO:1902751)	0.004199	-2.74	9.30
				Positive regulation of G2/M transition of mitotic cell cycle (GO:0010971)	0.004199	-2.74	9.29
				Positive regulation of mitotic cell cycle (GO:0045931)	0.02884	-2.15	6.24
				Intracellular steroid hormone receptor signaling pathway (GO:0030518)	0.02059	-2.07	6.09
				Negative regulation of sequence-specific DNA binding Transcription factor activity (GO:0043433)	0.03514	-2.10	5.95
				Histone acetylation (GO:0016573)	0.02829	-2.05	5.93
				Developmental growth (GO:0048589)	0.04520	-2.16	5.83
				Negative regulation of neuron differentiation (GO:0045665)	0.04085	-2.15	5.83
				Positive regulation of cell cycle process (GO:0090068)	0.06054	-2.29	5.74
				Negative regulation of neurogenesis (GO:0050768)	0.05032	-2.14	5.56

Validation of mRNA:miRNA pairs

The selected mRNA:miRNA pairs are involved in brain aging and neurodegeneration.

miRNAs upregulated/mRNAs blocked

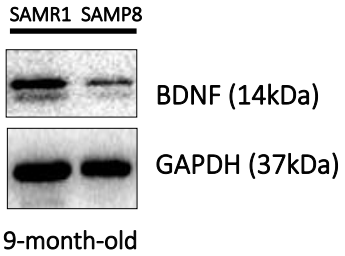


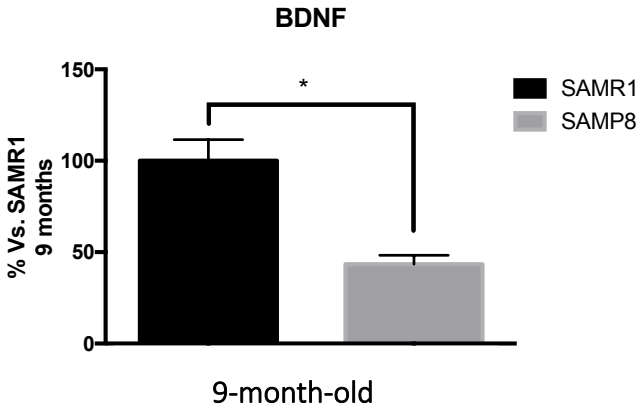
miRNAs downregulated/mRNAs enhanced

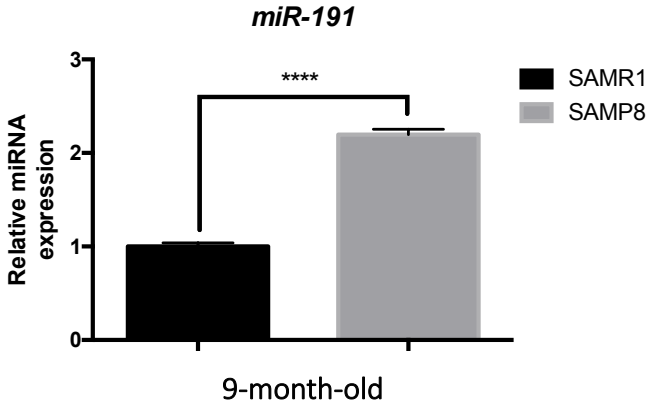
Abnormal pathways

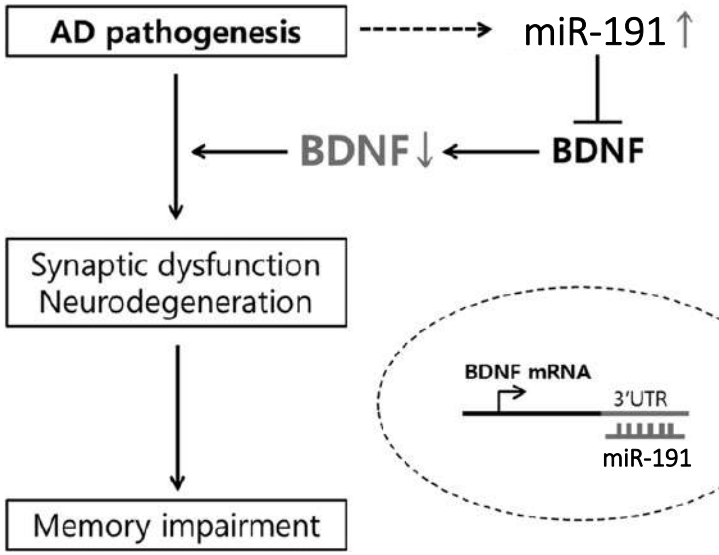
- Purinergic signaling *P2rx1*
- Inflammatory process *Socs6*
- Neuron differentiation *Pou3f2, Hmg20b*
- Neurogenesis *Pbx1*
- Protein trafficking *Nup160*

Validation of mRNA:miRNA pairs

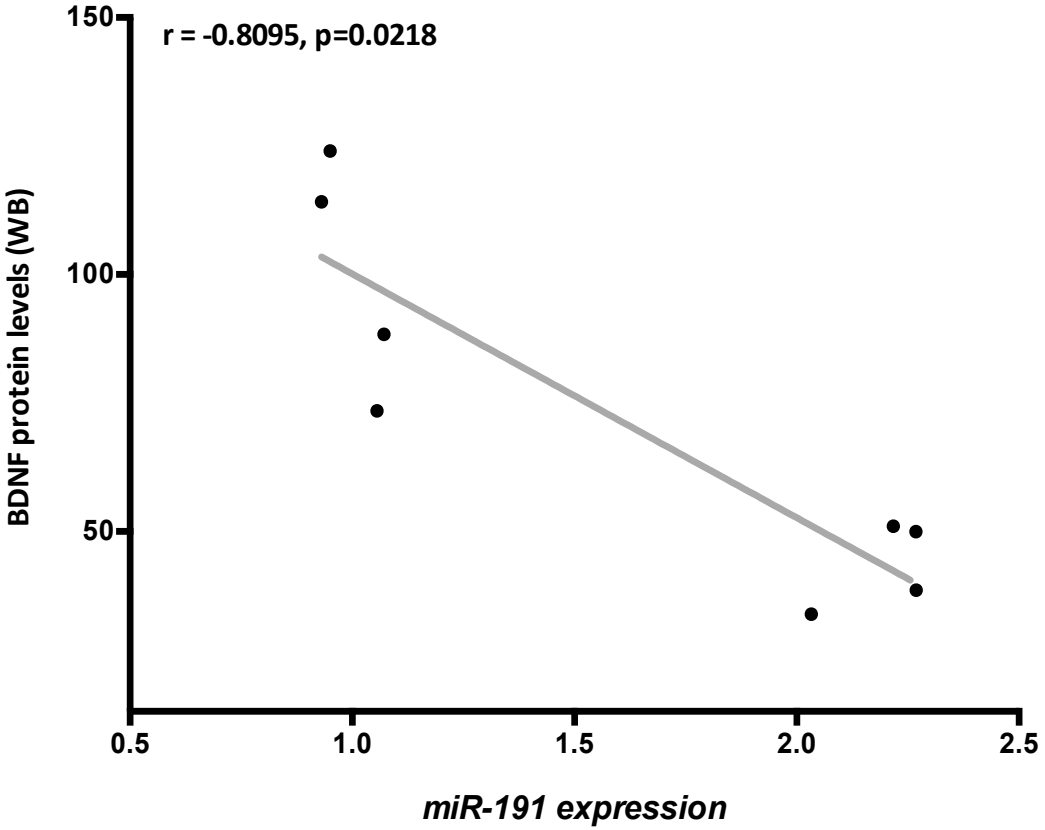


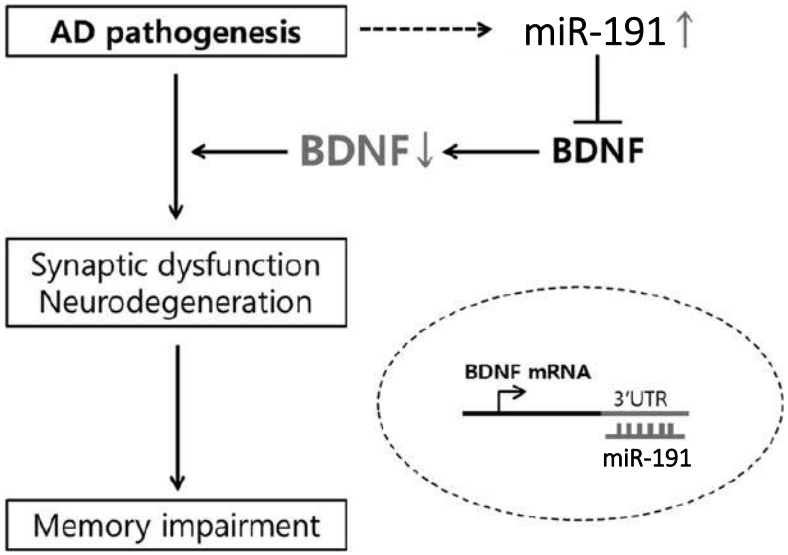






Validation of mRNA:miRNA pairs





5XFAD epigenetic characterization

www.impactaging.com AGING, April 2016, Vol 8 No 4

Research Paper

Epigenetic mechanisms underlying cognitive impairment and Alzheimer disease hallmarks in 5XFAD mice

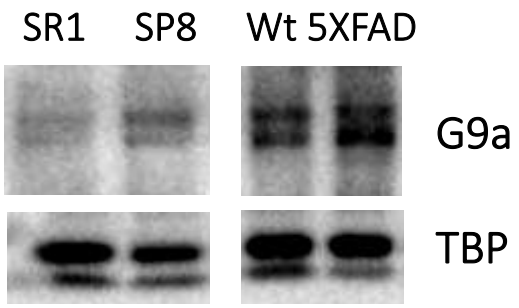
Christian Griñán-Ferré[1], Sara Sarroca[3], Aleksandra Ivanova[1], Dolors Puigoriol-Illamola[1], Fernando Aguado[2], Antoni Camins[1], Coral Sanfeliu[3], and Mercè Pallàs[1]

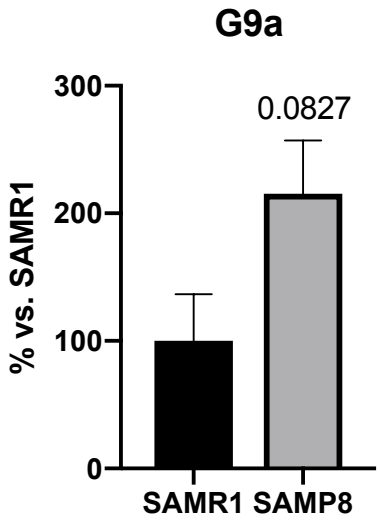
[1]*Department of Pharmacology and Therapeutic Chemistry (Pharmacology Section) and Institute of Neuroscience, University of Barcelona, 08028 Barcelona, Spain*
[2]*Department of Cellular Biology, University of Barcelona, 08028 Barcelona, Spain*
[3]*Institut d'Investigacions Biomèdiques de Barcelona (IIBB), CSIC, and IDIBAPS, 08036 Barcelona, Spain*

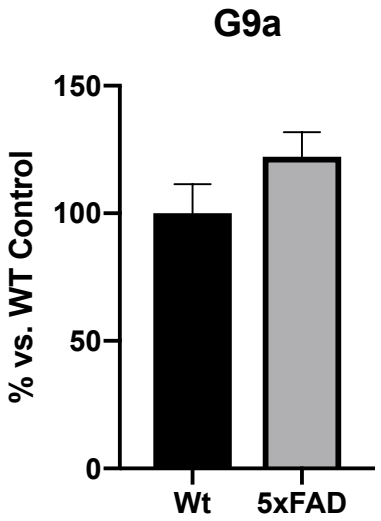
Key words: *Alzheimer disease, neurodegeneration, behavior, cognition, deacetylase, methyltransferase*
Received: *12/16/15; Accepted: 01/23/16; Published: 03/21/16*
Correspondence to: *Mercè Pallàs, PhD;* ***E-mail:*** *pallas@ub.edu*

Tg6799 (5xFAD) mice

New Challenges: G9a inhibition for AD





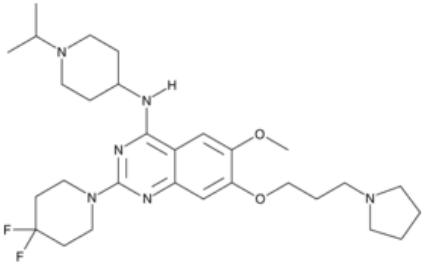


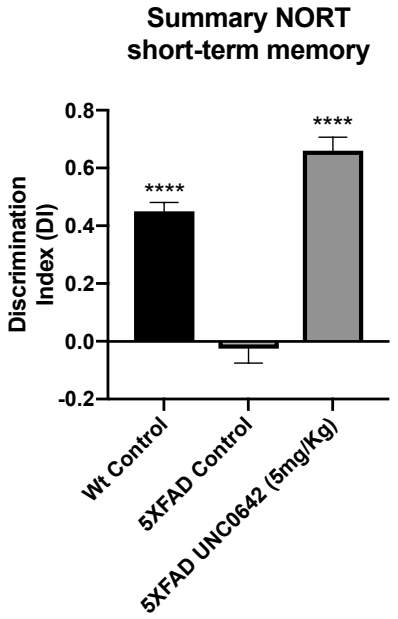
Unpublished results

Treatment with G9a inhibition for AD

Proof-of-Concept (PoC)

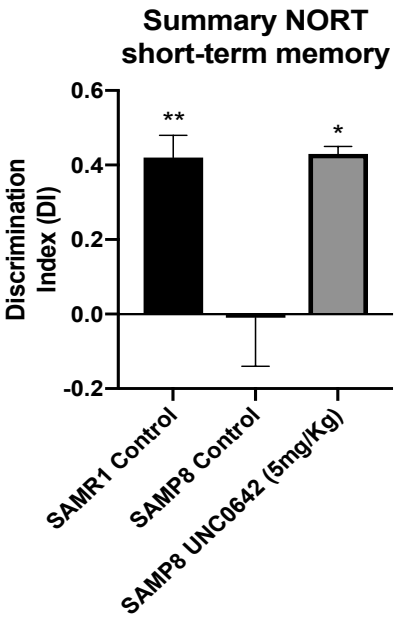
UNC0642 an *in vivo*
BBB penetrant
G9a inhibitor
IC_{50} < 2.5 nM





Inhibition of EHMT1/2 rescues synaptic and cognitive functions for Alzheimer's disease

Yan Zheng,[1,2,*] Aiyi Liu,[1,3,*] Zi-Jun Wang,[1,4,*] Qing Cao,[1] Wei Wang,[1] Lin Lin,[1] Kaijie Ma,[1,4] Freddy Zhang,[1] Jing Wei,[1,4] Emmanuel Matas,[1] Jia Cheng,[1] Guo-Jun Chen,[3] Xiaomin Wang[2] and Zhen Yan[1,4]



Unpublished results

Conclusions

1. SAMP8 and 5XFAD are a suitable model to study ageing processes, including AD.

2. EE, as a tool to unveil epigenetic influence in senescence process, supported the hypothesis of epigenetic control in ageing in SAMP8.

3. Our data indicate the reciprocal interaction between non-genetic factors and epigenetic mechanisms that can explain the senescence process in the SAMP8.

4. miRNA have a pivotal role in gene regulation in SAMP8.

5. The different pathological process that suffer SAMP8 and 5XFAD, will allow to use them an *in vivo* model for drug discovery in neurosciences, by using a broad number of different targets related with inflammation, oxidative stress, AD hallmarks and epigenetic mechanisms.

Our lifestyle choices affect our risk of developing dementia

Chemistry and Pharmacology of drugs against neurogenererative diseases (CHEMPHARNEURO)

SEMINARIS DE RECERCA 2019 SEMINARIS TECNOLÒGICS
2n Seminari de Recerca 2019

UNIVERSITAT DE BARCELONA

Dr Carmen Escolano
Sònia Abás
Sergio Rodríguez

Dr Santi Vázquez
Dr Rosana Leiva
Dr Carles Galdeano

Institut de Neurociències
UNIVERSITAT DE BARCELONA

IBUB Institut de Biomedicina de la Universitat de Barcelona

Dr Mercè Pallàs
Dr Christian Griñán-Ferré
Dolors Puigoriol-Illamola, Julia Companys and Fotini Vasilopoulou

Dr. Diego Muñoz-Torrero

Acknowledgments

THANK YOU!

Dra Perla Kaliman
Dra Marta Cosín-Tomás
Dra Maria Jesús Álvarez-López

Dra Mercè Pallàs
Dra Anna M. Canudas
Dra Verónica Palomera
Dr Christian Griñán
Fotini Vasilopoulou
Vanessa Izquierdo
Júlia Companys
Dolors Puigoriol

Dr Daniel Ortuño-Sahagún
Dra Celia González-Castillo

UNIVERSITAT DE BARCELONA

Institut de Neurociències
UNIVERSITAT DE BARCELONA

GOBIERNO DE ESPAÑA · MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD · Unión Europea
Fondo Europeo de Desarrollo Regional

CTQ2015-66030/R
SAF2016-77703-C-R

Universidad de Guadalajara
Mexico