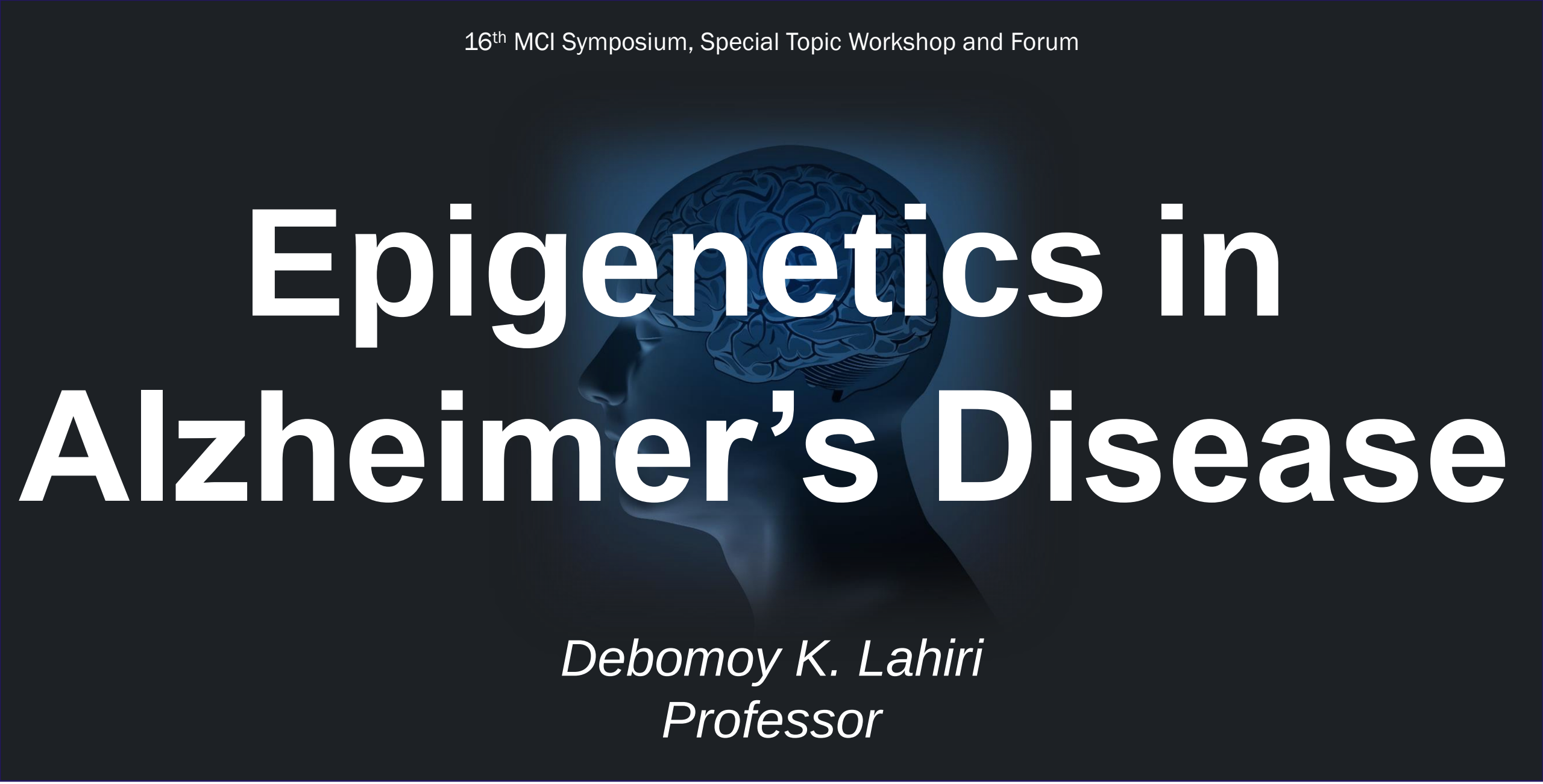


Epigenetics in Alzheimer's Disease

Debomoy K. Lahiri
Professor

DISCLOSURES

- Acknowledgment of Research Support:
  - National Institute on Aging (NIA) R01, R21 and P30 grants
  - Indiana Clinical & Translational Sciences Institute and ISDH Spinal Cord and Brain Injury Board
  - Alzheimer's Association
- Consultant/Advisory Boards :
  - Entia Biosciences, Inc., Sherwood, OR, USA
  - QR Pharma, Inc., West Chester, PA, USA
  - Yuma Therapeutics, Boston, MA, USA
  - Drug Discovery and Therapy World Congress, Boston, MA

Alzheimer's disease

Alzheimer's disease (AD), the most common cause of dementia, is a progressive degenerative disorder of the brain that destroys cognitive functions and ultimately lead to death.

5.5M

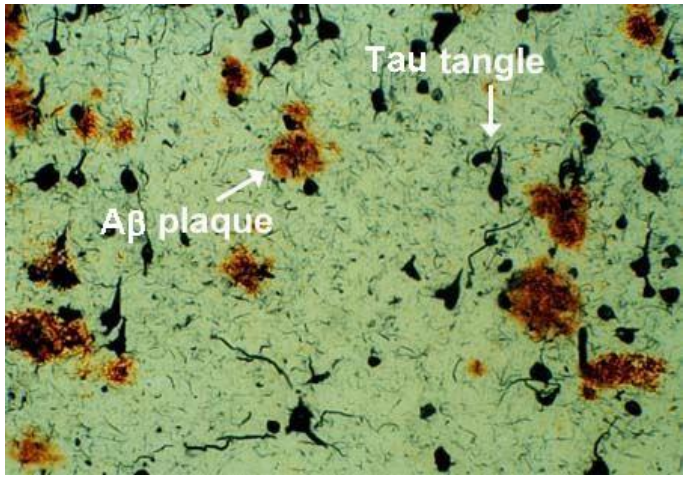
Cumulative prevalence of AD in people 65 years of age and older (5.3M) and 0.2M in individuals <65 years [1,4]

6th

AD is the 6th leading cause of death in older (65+) Americans. The only disease in top 10 that cannot be prevented or cured[1].

1.1 T

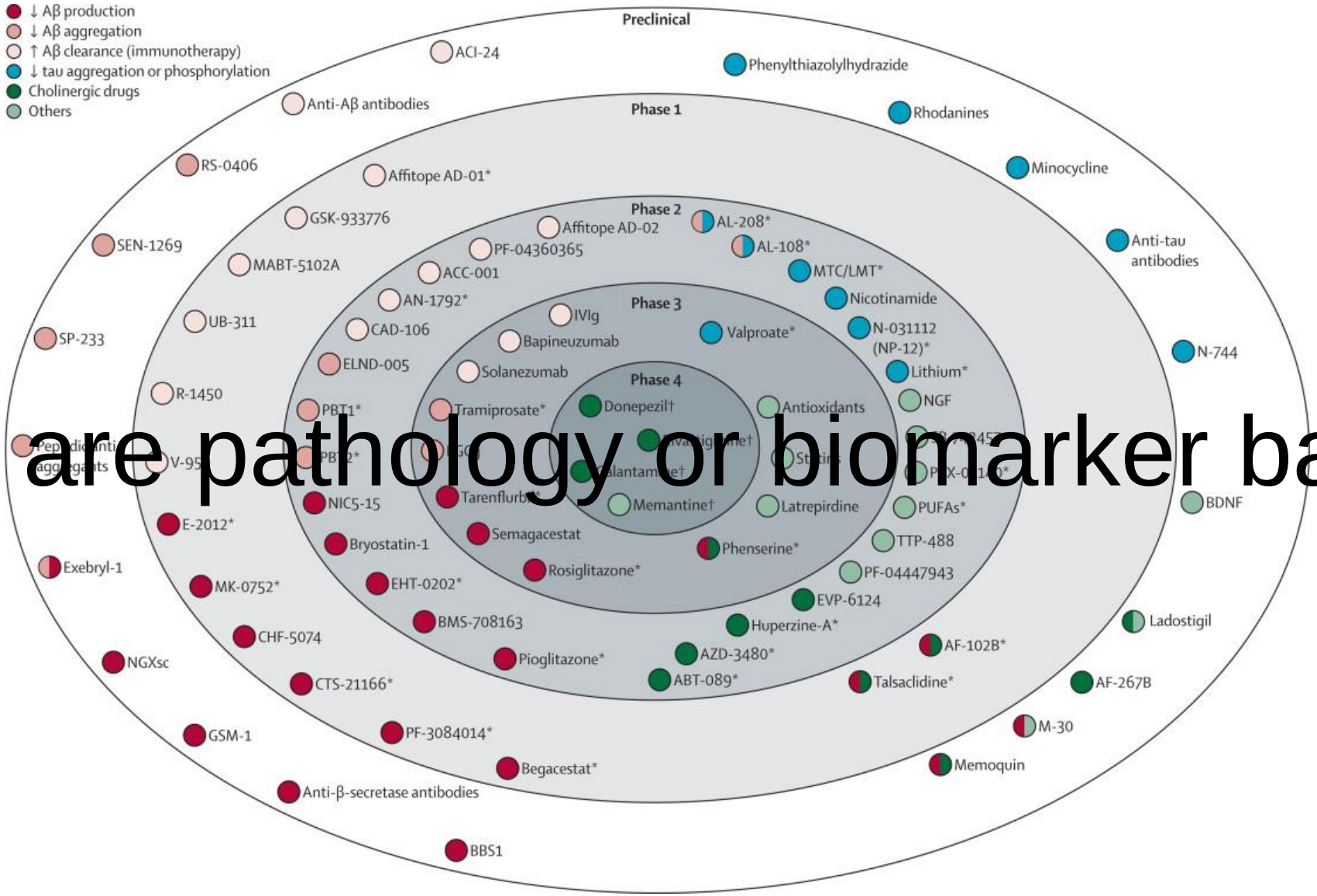
Projected cost to the nation in 2050, from the current 250 billion for AD and other dementia[1].



Sources: 1. Alzheimer's Association. 2017 Alzheimer's Disease Facts and Figures. Alzheimer's Dement 2017;13:325-373.

2. Global data: Pharma point. : Alzheimer's disease–Global drug forecast and market analysis to 2023.
3. Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 367-384
4. World Alzheimer Report 2016: Alzheimer's Disease International, the global voice on dementia.

AD drugs in development



Most are pathology or biomarker based.

Drug Development is not developing.

FierceBiotech

BIOTECH RESEARCH IT CRO MEDICAL DEVICES

Biotech

Alzheimer's hopes dashed as Lilly gives up on amyloid drug solanezumab

by *Phil Taylor* | Nov 23, 2016 8:08am

Lilly presents detailed results from failed late-stage study of solanezumab in people with mild Alzheimer's-related dementia

Dec. 9, 2016 6:55 AM ET | By: Douglas W. House, SA News Editor

HEALTH

Eli Lilly's Experimental Alzheimer's Drug Fails in Large Trial

By PAM BELLUCK NOV. 23, 2016

Health

Hopes for new Alzheimer's drug dashed

Fergus Walsh
Medical correspondent

23 November 2016 | Health

Share

Maybe, maybe, nope! Still got nuthin’

September 26, 2017

Axovant Alzheimer’s drug fails in clinical trials

New York- based biotech company shares plummet as dementia treatment hopes dashed

Axovant Sciences said its Alzheimer’s medicine had failed a late-stage clinical trial, extending a 14-year losing streak for companies trying to develop new drugs for the devastating form of dementia. The New York-based company said there was “essentially no difference” between its drug, known as intepirdine, and the placebo in the study of 1,150 patients on tests that measured a person’s ability to carry out daily activities like dressing or bathing. Nor did the drug have a significant effect on brain power.

By David Crow in New York

Pathology and biomarkers: Only *part* of the picture

"While participating in the study, both Marge and another subject, 'Mary', took annual tests of their cognition. *Although the two women had similar levels of [post-mortem] pathology, Marge's scores remained high and 'Mary's' steadily declined... ['Mary'] actually had less beta-amyloid and fewer tangles than Marge did."*

The "pathology" was wrong.
Is the problem one of process?

Try a different direction?

Revisiting AD Pathogenesis Pathway(s)?

♦ *Prior to Amyloid β-peptide formation*

Prusiner SB. **Cell biology. A unifying role for prions in neurodegenerative diseases.** Science 336(6088):1511-3.

♦ *Post-Amyloid β-peptide?*

Lahiri DK. **Prions: a piece of the puzzle?** Science. 7;337(6099):1172.

Try a different direction?

1)“Protein-only” school focuses on processing of APP to Aβ peptide and the mode of its aggregation. But even prion models are still just protein-only.

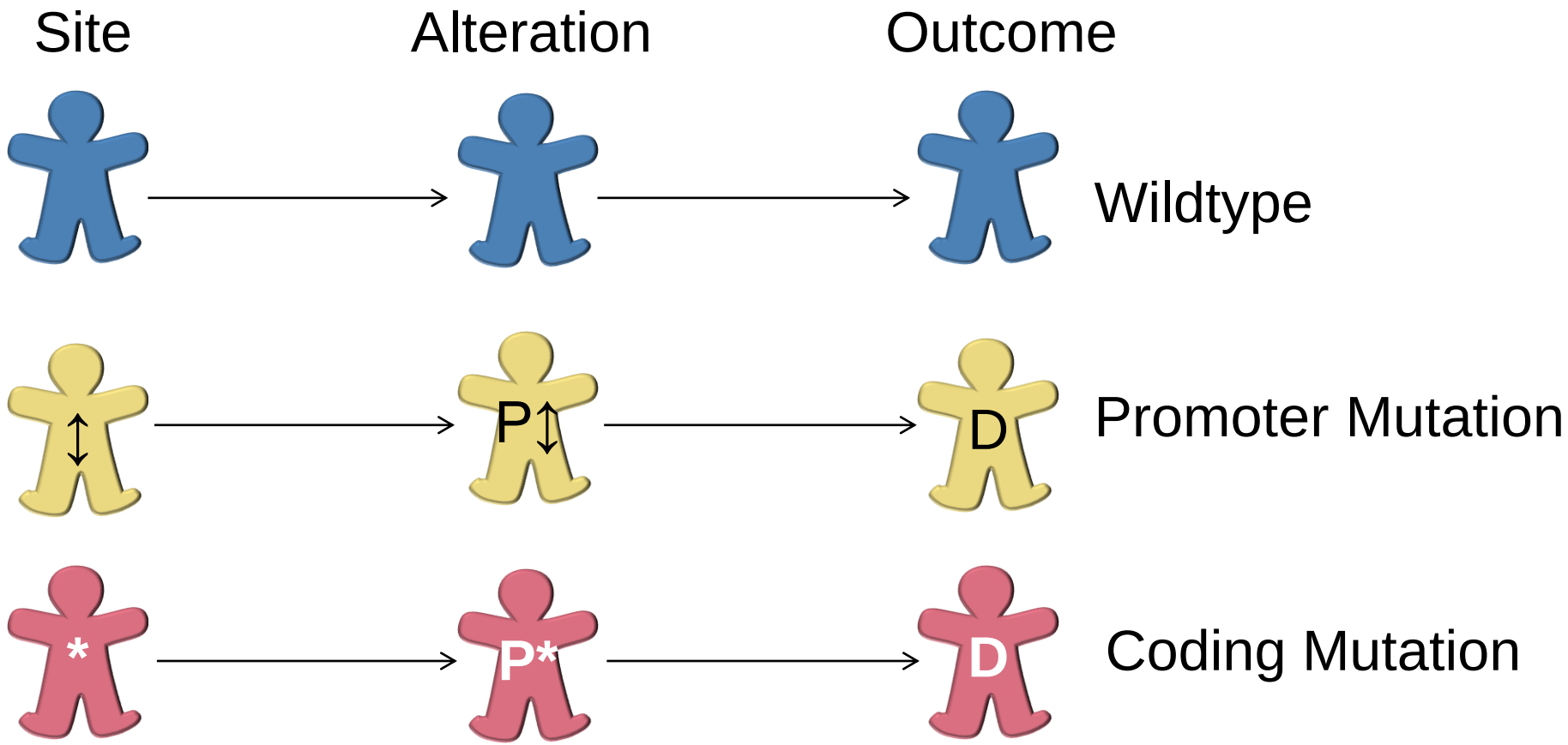
2) The “Latent Early–life Associated Regulation” (LEARn) model: environmental agents (metals), intrinsic factors (cytokines) and dietary factors (folate) affect *long–term* from early-life.

3) Nature & Nurture

(Basha et al, *J. Neurosci.* (2005); Lahiri & Maloney, *Nature Neurosci. Rev.* (2006); Lahiri et al. *Mol. Psychiatry* (2009); Maloney & Lahiri, *Lancet Neurol.* (20016)

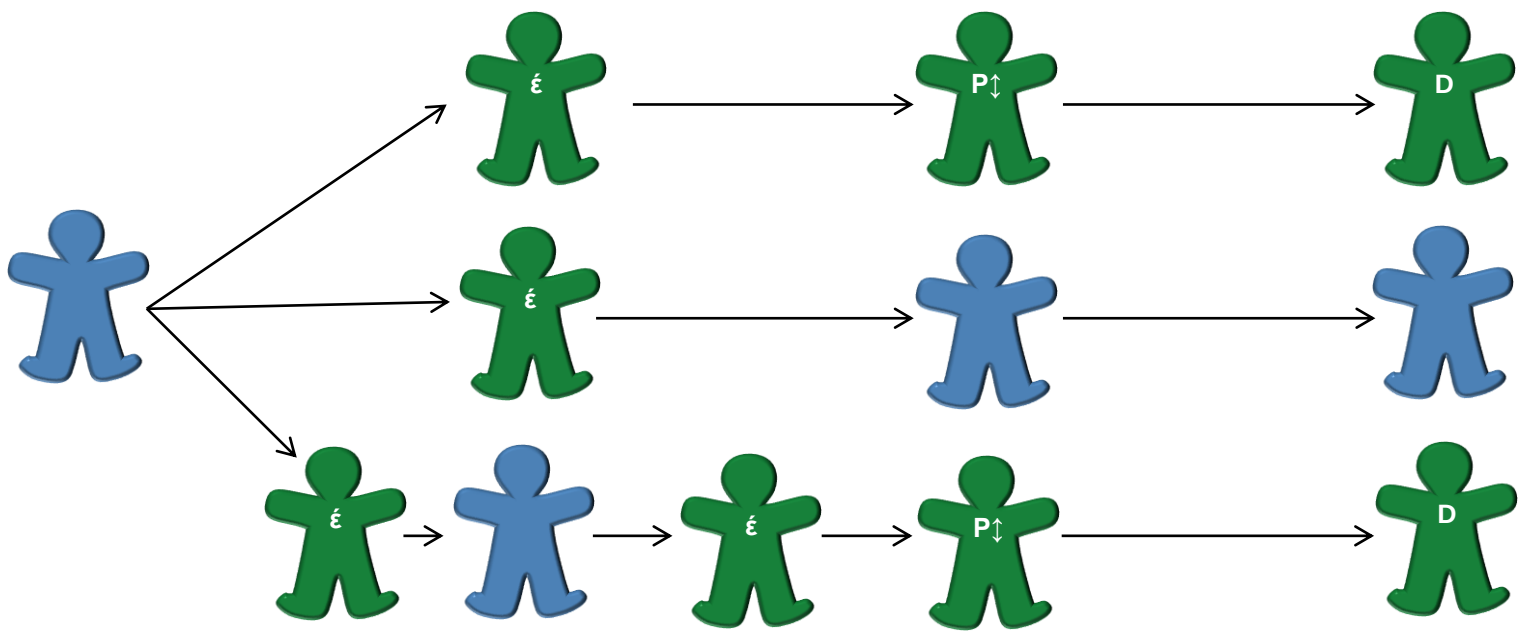
Where do accumulations come from?

The Good Old-Fashioned Way: Genetic Mutation



Where do accumulations come from (2)?

Epigenetic Markers



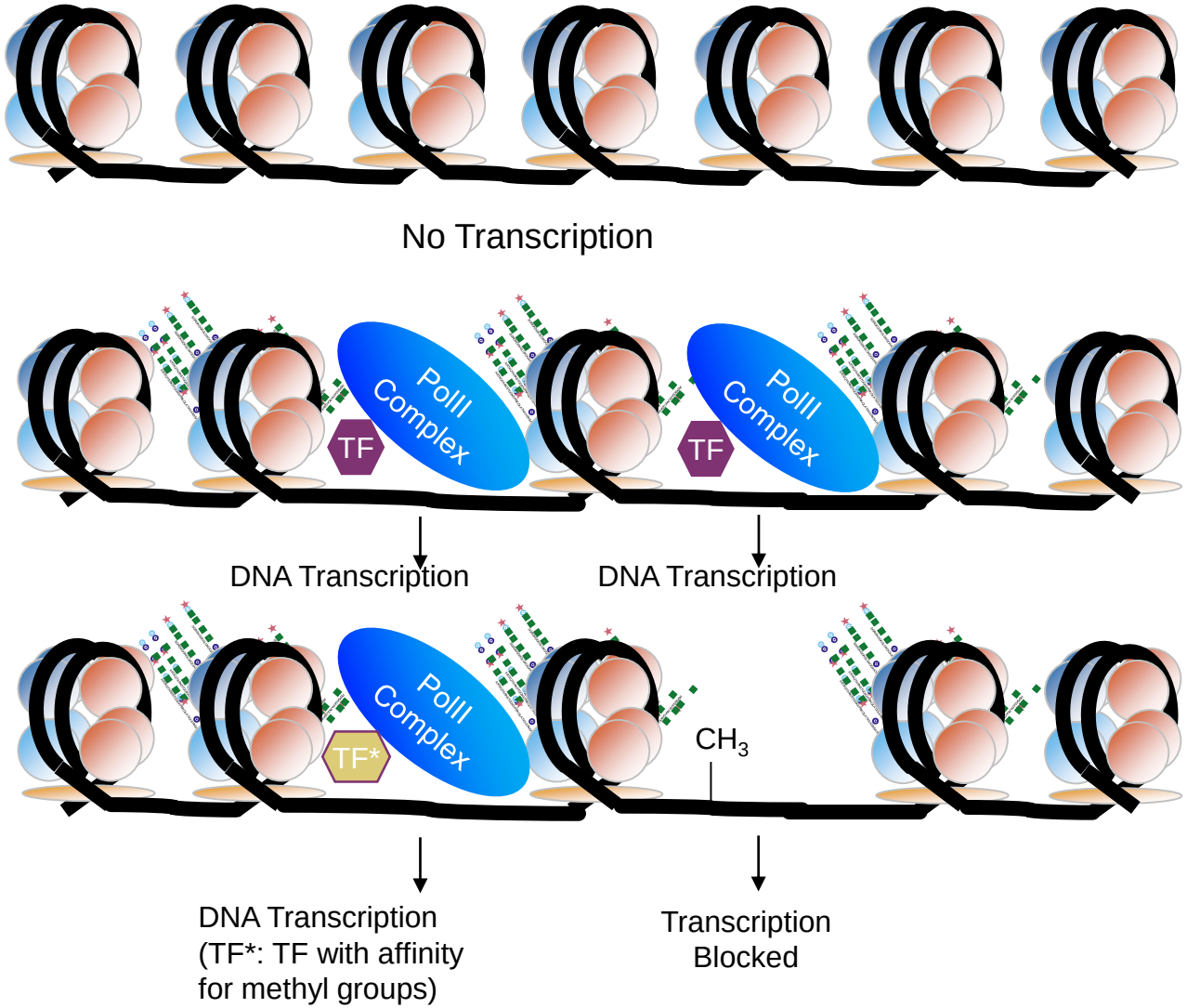
Pathogenic Epigenetic Acquisition

Protective Reversion

Pathogenic “Double” Reversion

Molecular Basics of Epigenetic Regulation

[Maloney B & Lahiri DK. Lancet Neurol 15:760-74]

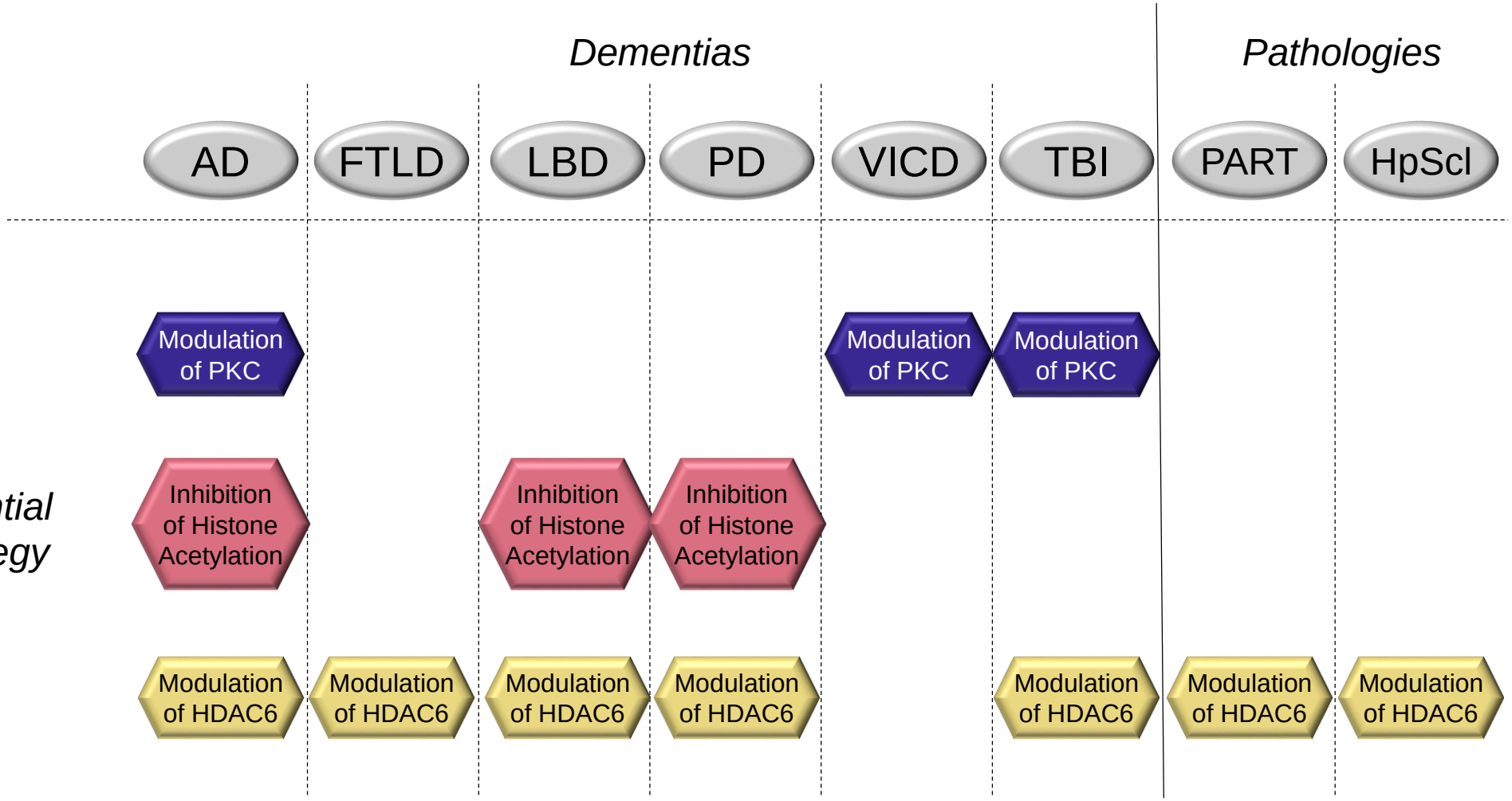


Condensed Chromatin
(influenced by epigenetic
modification of histones

Relaxed Chromatin
(influenced by epigenetic
modification of histones)

DNA Methylation
(can either facilitate
or block transcription)

Chromatin modification strategies under study:



The LEARn model is a unifying viewpoint.

Molecular Psychiatry (2009) 14, 992–1003

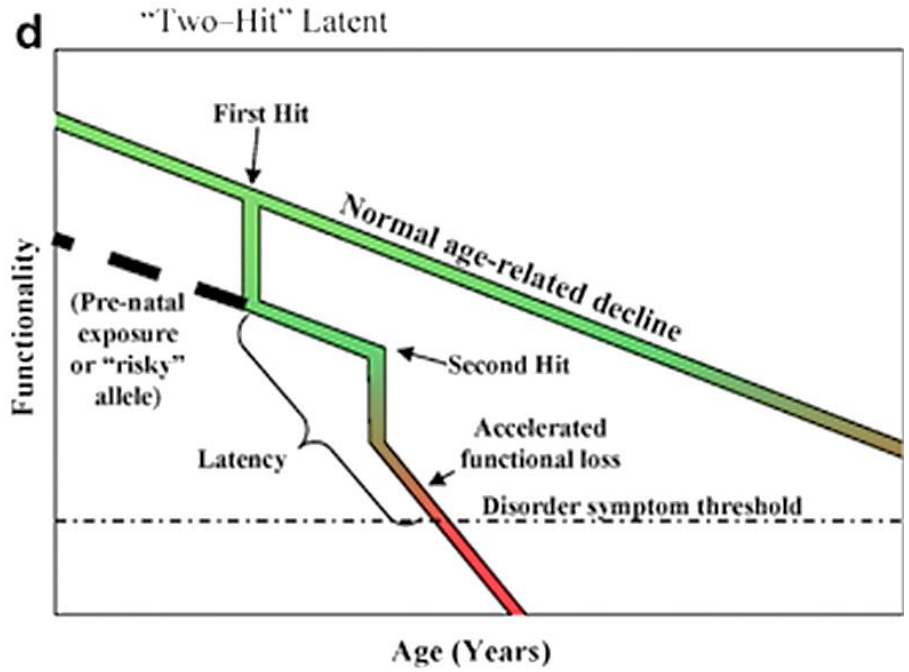
www.nature.com/mp

PERSPECTIVE

The LEARn model: an epigenetic explanation for idiopathic neurobiological diseases

DK Lahiri[1,2], B Maloney[1] and NH Zawia[3]

[1]Laboratory of Molecular Neurogenetics, Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA and [3]Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, USA



Special Report

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Epigenomics

Transgenerational latent early-life associated regulation unites environment and genetics across generations

The origin of idiopathic diseases is still poorly understood. The latent early-life associated regulation (LEARn) model unites environmental exposures and gene expression while providing a mechanistic underpinning for later-occurring disorders. We propose that this process can occur across generations via transgenerational LEARn (tLEARn). In tLEARn, each person is a 'unit' accumulating preclinical or subclinical 'hits' as in the original LEARn model. These changes can then be epigenomically passed along to offspring. Transgenerational accumulation of 'hits' determines a sporadic disease state. Few significant transgenerational hits would accompany conception or gestation of most people, but these may suffice to 'prime' someone to respond to later-life hits. Hits need not produce symptoms or microphenotypes to have a transgenerational effect. Testing tLEARn requires longitudinal approaches. A recently proposed longitudinal epigenome/envirome-wide association study would unite genetic sequence, epigenomic markers, environmental exposures, patient personal history taken at multiple time points and family history.

First draft submitted: 6 October 2015; Accepted for publication: 11 December 2015; Published online: 7 March 2016

Debomoy K Lahiri*[,1,2], Bryan Maloney[1], Baindu L Bayon[2], Nipun Chopra[1], Fletcher A White[3], Nigel H Greig[4] & John I Nurnberger[1,2]

[1]Department of Psychiatry, Stark Neurosciences Research Institute, Indiana University School of Medicine, 320 West 15th Street, Indianapolis, IN 46202, USA
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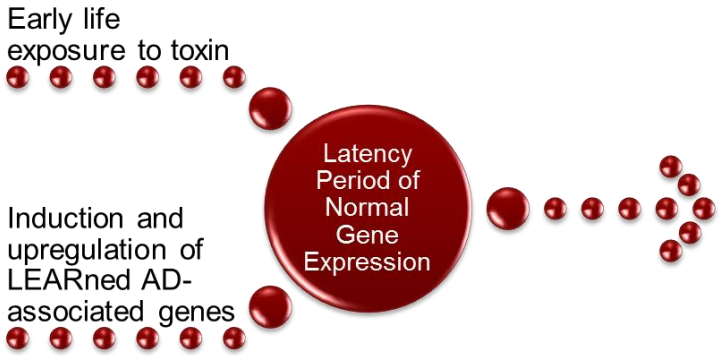
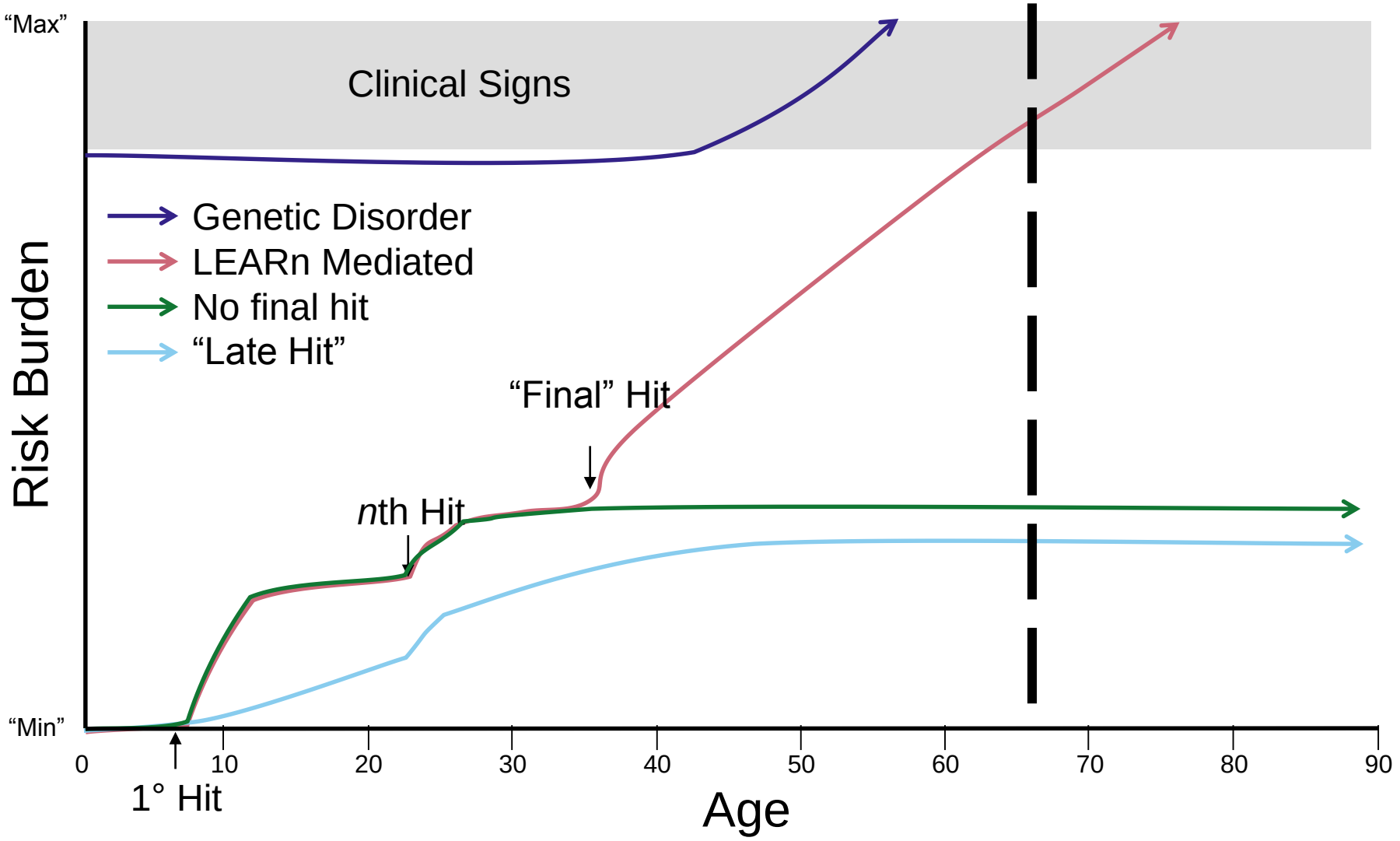
[4]Translational Gerontology Branch, National Institute on Aging, NIH, Baltimore, MD 21224, USA



disease-associated expression later in life

The LEARn model is a unifying viewpoint.



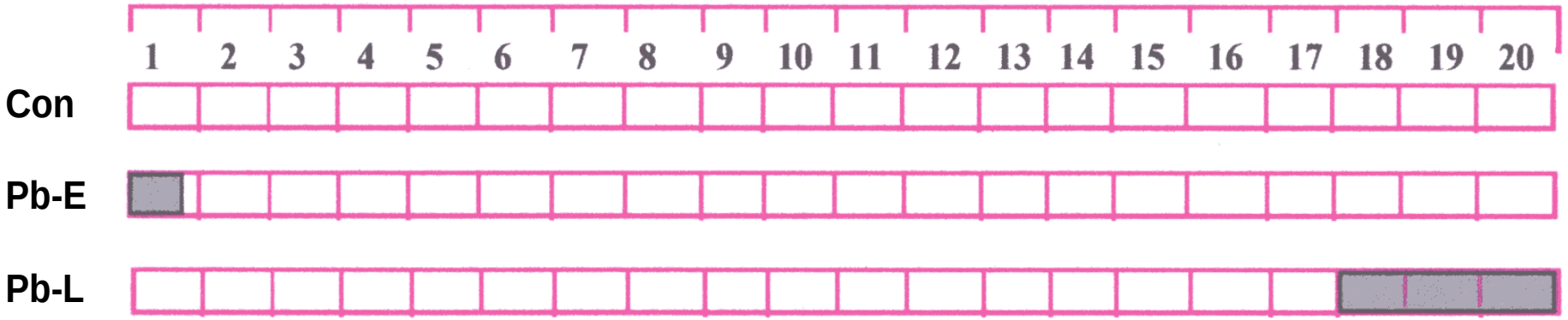
Jack, Knopman, Jagust, et al. 2013. *Lancet Neurol*. 12:207-216
Maloney & Lahiri. 2016. *Lancet Neurol*. 15:760-774

Where is the evidence?

-Animal studies-Rodents
-Non Human Primate (NHP) studies
-Human studies

Evidence: Pb can play a role

1) Rat pups were pooled into three groups, Control (C), Pb–E(arly), and Pb–L(ate)
2) Pb–E pups exposed to 200ppm Pb–acetate via dams' milk.
3) Pb–L rats exposed to 200ppm Pb–acetate at 18–20 months.
4) mRNA of APP and transcription factors were profiled.
5) APP protein and mRNA, Aβ levels, and SP1 binding were profiled.

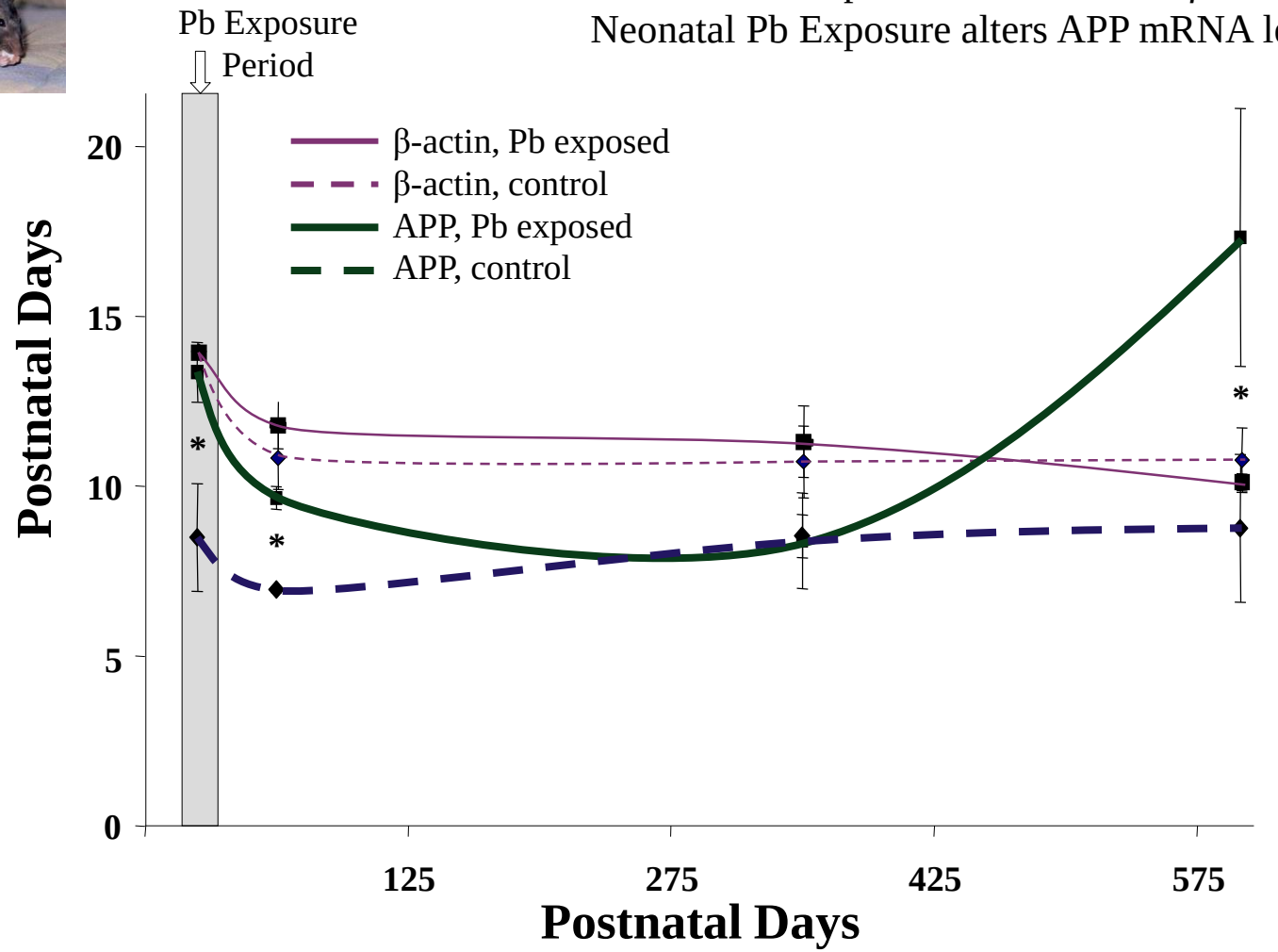


Windows of Pb Exposure

Basha…Lahiri, Zawia , *J. Neurosci*. 25:823-829

Pb contribution: Evidence

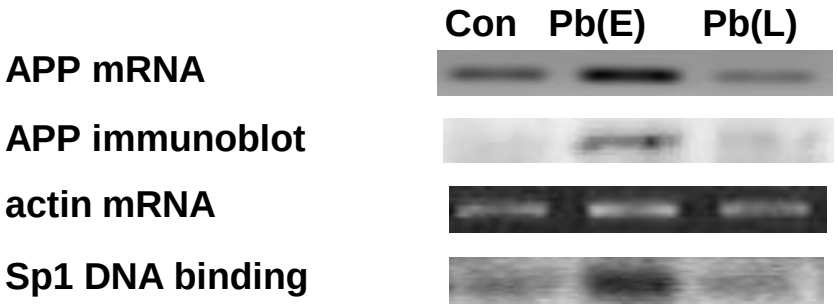
Neonatal Pb Exposure does not alter β-actin mRNA levels.
Neonatal Pb Exposure alters APP mRNA levels



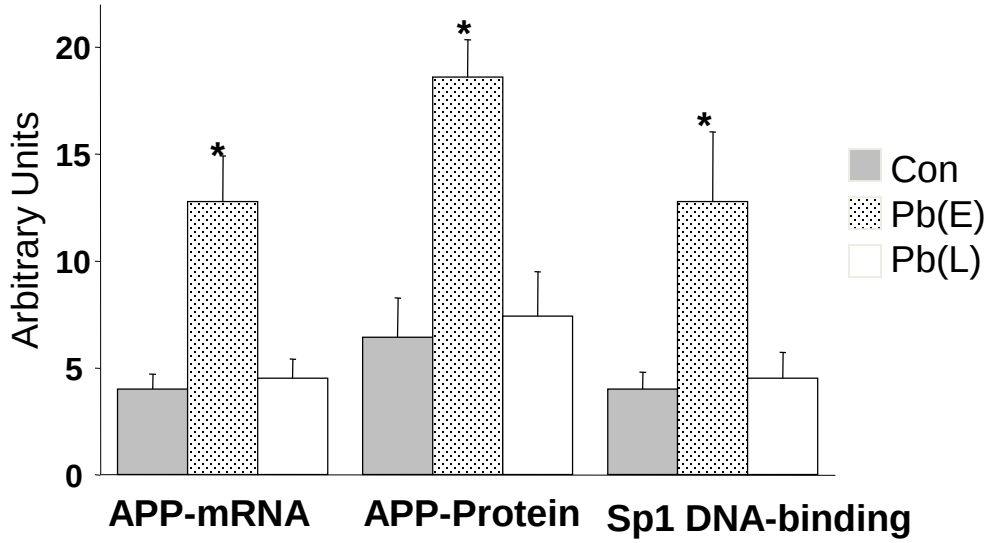
* Control and exposed results different at $p < 0.05$

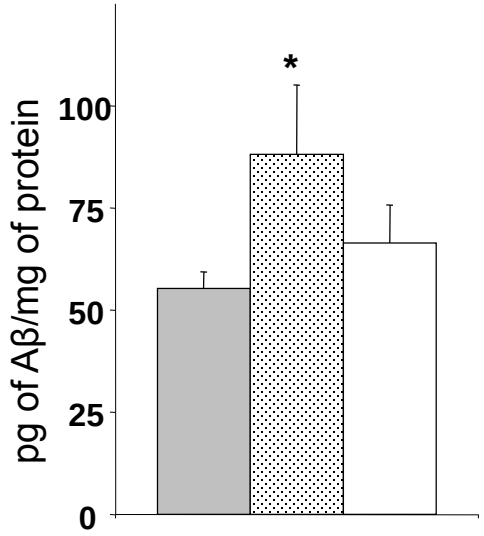
Basha, Wei, Bakheet, Benitez, Siddiqi, Ge, Lahiri, and Zawia. 2005, *J. Neurosci*. 25:823-829

Late-life exposure to Pb does not elevate AD-related markers.



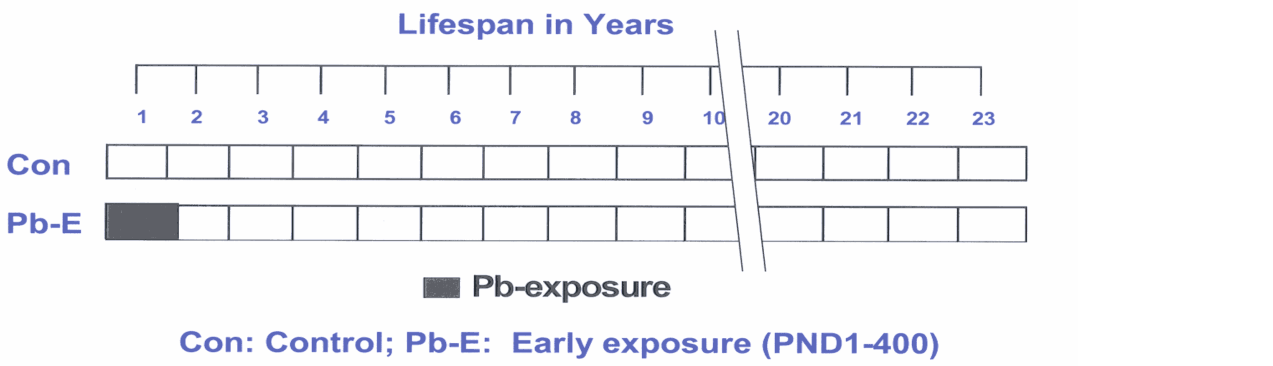
Sample	Blood µg/dL	Cortex µg/g wet wt. of tissue
Control (PND 20)	<2.0	<0.2
Pb (PND 20)	46.43±1.95*	0.41±0.04*
Control (20 month)	<2.0	<0.2
Pb-E (20 month)	<2.0	<0.2
Pb-L (20 month)	60.1±15.01*	0.32±0.03*





Basha…Lahiri, Zawia , *J. Neurosci*. 25:823-829

Cynamolgus Monkey: Pb Exposure



Con: Control; Pb-E: Early exposure (PND1-400)

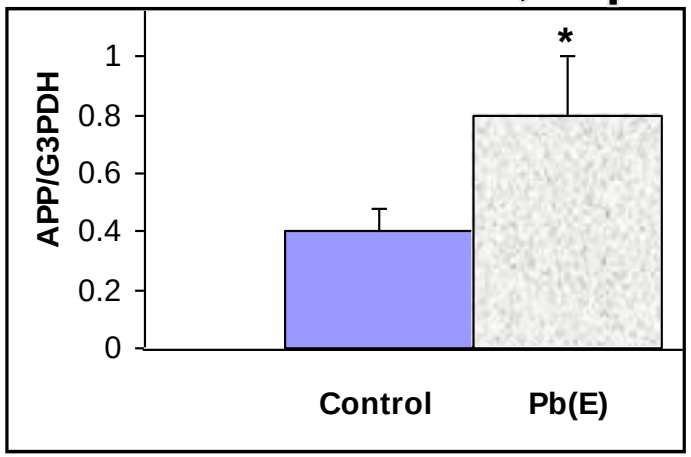
Sample	Frontal Association Cortex ng/g wet wt. of tissue
Control (23 Years)	<0.1
Pb-E (23 Years)	<0.1

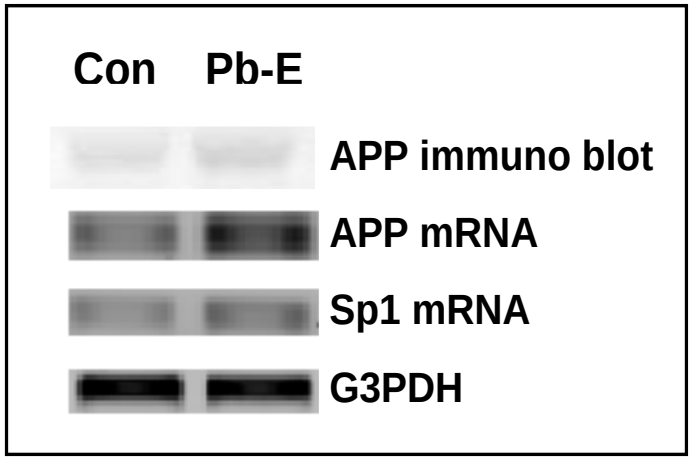
Exposure was done in 1980, animals sacrificed in 2003 at NIH.

Wu, Basha, Brock, Cox, Cardozo-Pelaez, McPherson, Harry, Rice, Maloney, Chen, Lahiri, Zawia. ***J Neurosci*****. 28:3-9**

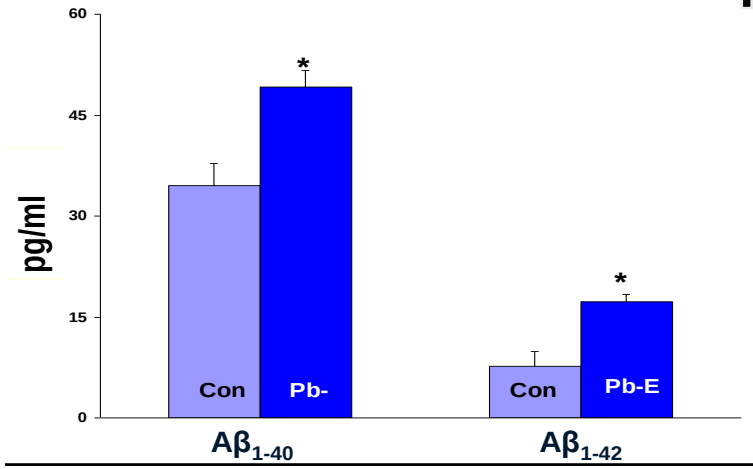
Cynamolgus Monkey: Pb Exposure

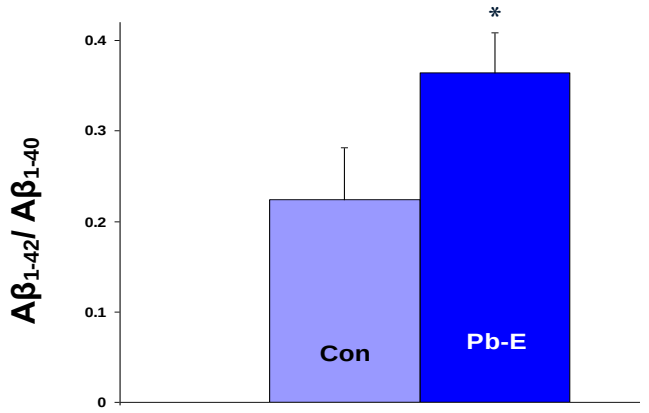
APP, Sp1 & G3PDH





Aβ





Wu et al., *J. Neurosci*. 28:3-9

Human DNA methylation can change.

- Over 100 individuals were sampled at intervals averaging 11 years apart.
- Disease status was not measured in this sample.
- Changes were found in global DNA methylation over time within many individual subjects' genomes.

(Bjornsson et al. 2008. *JAMA*)

Specific epigenetic associations exist in dementias

[Maloney B & Lahiri DK. Lancet Neurol. 2016;15:760-74].

Study Type	Subjects	Dementia Type	Target Genes (if specified)	Epigenetic Marker	Conclusion
Case Study	Monoz. Twins	AD		DNA methylation DNA hydroxymethylation	DNA methylation and hydroxymethylation reduced in twin with AD.
Cohort	AD: 10 Cont:10	AD		DNA methylation DNA hydroxymethylation	DNA methylation and hydroxymethylation reduced in AD, negative correlations between quantified methylation & hydroxymethylation vs. amyloid plaque and τ tangle.
Cohort	AD: 13 Cont:8	AD		DNA hydroxymethylation	DNA hydroxymethylation decreased in AD samples in both brain regions.
Cohort	AD: 429 Cont:279	AD	ANK1; CDH23; DIP2A; KIAA0145; RHBDF2; RPL13; SERPINF1; SERPINF2	DNA methylation	Methylation of specific CpG dinucleotides was associated with histopathologic diagnosed AD.
Cohort	AD: 447 Cont:293	AD	SORL1; ABCA7; HLA-DRB5; SL24A4; BIN1	DNA methylation	Methylation of specific CpG dinucleotides associated w/histopath. diagnosed AD and ↑Aβ.
Cohort	Cont:5 Braak I-II: 5 Braak III-IV: 5 Braak V-VI: 5	AD	DUSP22	DNA methylation	Hypermethylation of specific CpG dinucleotides in DUSP22 sequence and DUSP22 expression associated with AD Braak stages.
Cohort	ALS/FTD: 9 c9ALS/FTD: 10 Cont:8	FTD (ALS)	C9orf72	DNA methylation	DNA hypermethylation associated with ALS developing into dementia for C9orf72 carrier. C9orf72 ALS without hypermethylation did not show dementia.
Cohort	ALS/FTD: 9 c9ALS/FTD: 10 Cont:8	FTD (ALS)	C9orf72	Histone methylation	Trimethylation of Histone H3 linked to FTD and ALS in C9orf72 carriers. Carriers without trimethylation did not have ALS/FTD
Cohort	PD: 12 Cont:14	PD	SNCA	DNA methylation	PD patient samples were hypermethylated at specific sits of SNCA intron 1 vs. controls.
Cohort	2 cohorts: Leukocyte PD: 358 Cont:1084 Brain PD: 28 Cont:12	PD	MAPT	DNA methylation	Higher levels of leukocyte MAPT methylation associated with later age of onset for PD. Global PD cerebellum DNA hypermethylated and putamen DNA hypomethylated vs. controls.

Epigenetic drugs in Clinical Trials

Polyphenols
(DNMT inhibitor, HDAC inhibitor)

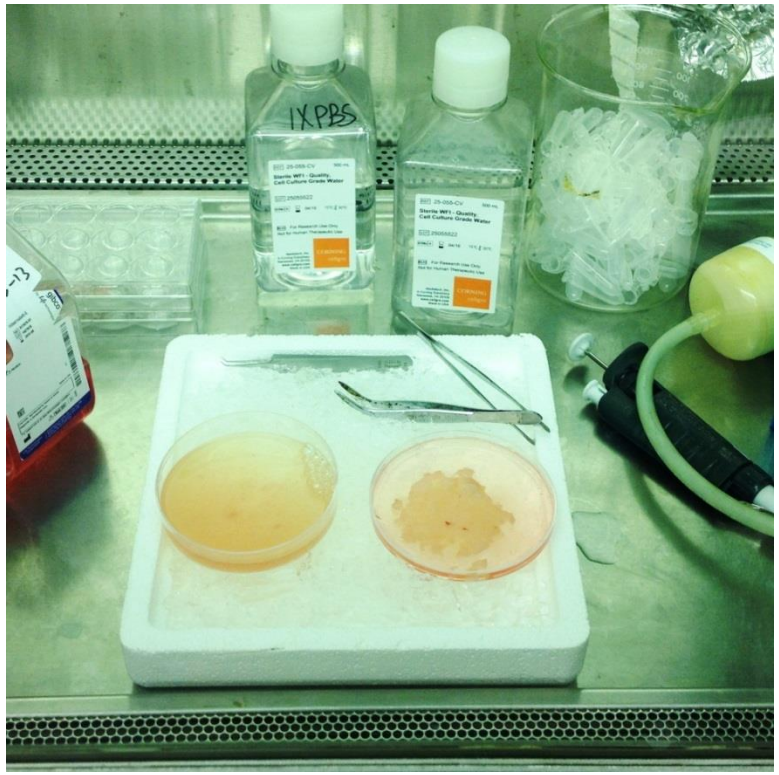
Category	Treatment	Activity	Condition	NCT #
Polyphenols	Epigallocatechin gallate	DNMTi, HDACi	Multiple System Atrophy	NCT02008721
	Flavenol		Cognitive Performance., Mood., Cardiometabolic Risk Markers	NCT02243956
	Grape Extract		Cardiovascular Diseases	NCT01449110
	Phenolic		Cardiovascular Disease, Endothelial Function	NCT01983943
			Cardiovascular Diseases	NCT02520739
	Polyphenols		Parkinson's Disease	NCT00461942
			Cardiovascular Risk Factors, Metabolic Syndrome, Lifestyle Modification, Coronary Artery Disease, Stroke	NCT00486993
			Cardiovascular Disease	NCT00795834
			Cardiovascular Disease	NCT02295878
			Cardiovascular Risk Factors	NCT01596309
			Cardiovascular Disease, Oxidative Stress	NCT01541826
			Cerebral Blood Flow	NCT01540123
			Cardiovascular Risk Factors	NCT02005939
			Neurodegenerative Disorders	NCT01589809
			Cardiovascular Function, Gene Expression	NCT01681394
			Cardiovascular Diseases	NCT01662232
			Vascular Diseases, Impaired Glucose Tolerance	NCT02158481
			Cardiovascular Diseases	NCT02292329
			Vascular Function	NCT02328339
			Stroke	NCT02442804
			Vascular Stiffness, Inflammation	NCT02459756
	Grape Juice		Cognition	NCT01411631
	Grape Seed		Mild Cognitive Impairment, Alzheimer's Disease	NCT02502253
			Mild Cognitive Impairment, Alzheimer's Disease	NCT02502253
	Red Grape Juice		Memory, Gene Expression	NCT00972972
	Resveratrol		Alzheimer's Disease	NCT00678431
			Alzheimer Disease	NCT00743743
			Memory	NCT01126229
			Alzheimer's Disease	NCT01716637
			Alzheimer's Disease	NCT01716637
			Mild Cognitive Impairment	NCT01219244
			Sports Concussion	NCT01321151
			Cardiovascular Disease	NCT01564381
			Alzheimer's Disease	NCT01504854
			Vascular System Injuries, Lipid Metabolism Disorders, Endothelial Dysfunction	NCT01668836
			Memory Impairment	NCT01766180
			Vascular Resistance, Aging, Hypertension, Antioxidants, Aerobic Capacity	NCT01842399
			Mild Cognitive Impairment, Alzheimer's Disease	NCT02502253
			Aging	NCT02523274
	Trans-Resveratrol		Cognitive and Cerebral Blood Flow Effects of Resveratrol	NCT01010009
			Cognitive Performance, Mood	NCT01794351
	Cranberry Juice		Cardiovascular Disease	NCT01295684

ω3 Fatty Acids, Curcuminols, Current Drugs, Other Fruit-derived, B Vitamins, Caloric Restriction, etc.
(DNMT inhibitors, HDAC inhibitors, TET stimulants, Hcyr, HMT inhibitors, Methyl Donors, other)

Category	Treatment	Activity	Condition	NCT #
Currently-Used Drug	Levetiracetam	HDACi	Parkinson's Disease	NCT00461942
	Lithium	DNMTi, HDACi	Dementia	NCT00197834
	Quetiapine	DNMTi, TETs	Alzheimer Disease	NCT00071721
			Agitation, Dementia	NCT00315900
	Valproate	HDACi	Autism	NCT00211757
			Alzheimer Disease	NCT00071721
			Dementia	NCT00197834
			Alzheimer Disease	NCT00088387
			Autism	NCT00211796
			Agitation, Dementia	NCT00315900
			Alzheimer's Disease, Dementia, Behavioral Symptoms	NCT00375557
			Traumatic Brain Injury (TBI), Alcoholism	NCT01760785
			TBI, Alcoholism, Irritable Mood	NCT01326663
			Autism, Autism Spectrum Disorders	NCT01170325
			Alzheimer's Disease	NCT01729598
			Traumatic Brain Injury	NCT02027987
			Autism	NCT02094651
			Autism	NCT00065884
Omega-3 Fatty Acids	EPA	Hcyr	Mild Cognitive Impairment	NCT01219244
	Omega-3		Parkinson Disease, Idiopathic Parkinson Disease	NCT02445651
Curcuminoids	Curcumin	DNMTi, HMTi, HDACi	Alzheimer's Disease	NCT00164749
			Mild Cognitive Impairment	NCT00595582
			Alzheimer's Disease	NCT01716637
			Alzheimer's Disease	NCT01716637
			Age-associated Cognitive Impairment, Mild Cognitive Impairment (MCI)	NCT01383161
			Vascular Aging	NCT01968564
			Mild Cognitive Impairment	NCT01811381
			Mild Cognitive Impairment	NCT01811381
			Parkinson Disease, Idiopathic Parkinson Disease	NCT02445651
			Vascular Stiffness	NCT02281981
	Curcumin C3		Alzheimer's Disease	NCT00099710
Apple	Apple Extract	Methyl Donor	Cardiovascular Disease	NCT01585519
	Apple pomace		Cardiovascular Diseases	NCT01141803
B Vitamins	Nicotinamide	Methyl Donor	Neurodegenerative Disorders	NCT01589809
	Vitamins B6, B9, B12		Cardiovascular Risk Factors	NCT00706888
Caloric restriction	Caloric Restriction	HDACs, DNMTs	Mild Cognitive Impairment	NCT01219244
Umbilical Cord Blood	Umbilical Cord Blood	Multiple supposed activities	Aging	NCT02418013

Novel Approaches

Neurosphere (NSP) Isolation to Single Layer

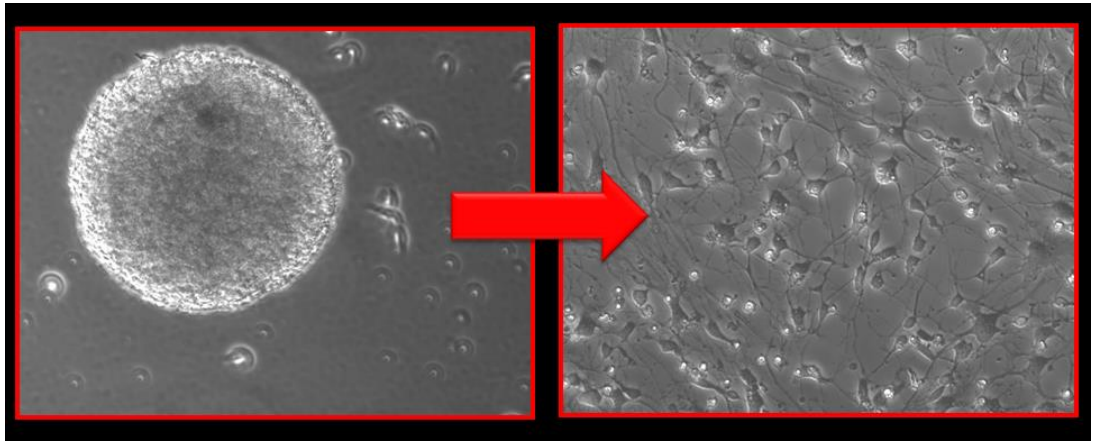


HFN to NSP

- Neural Stem Cells (NSC) derived from human fetal brain
- Neurospheres subcultured in proliferation media

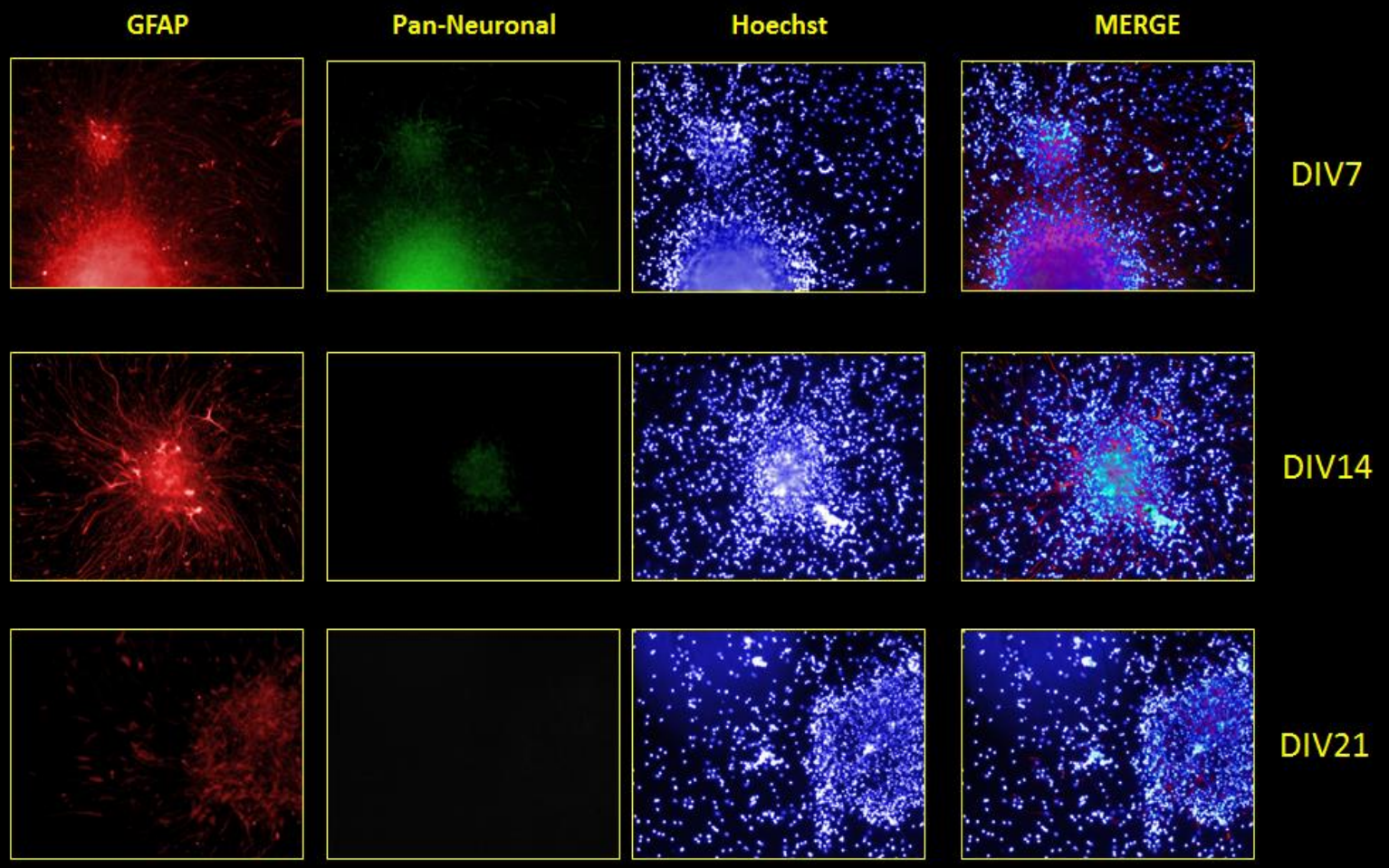
Spheres to Differentiated CNS cells

- Spheres collected, cells counted, and plated in differentiation media on plates absent of growth factors and with adhesive properties (PDL)
- Incubate at 37°C



Bayon, B.L. and Lahiri, D.K. unpublished

NSP characterization



Astrocytic population seen through Day 21; Pan-Neuronal (somatic, nuclear, dendritic, axonal protein marker cocktail) decreases by Day 14

Unexpected epigenetic drugs

Mithramycin
(MTM/plicamycin)

Antineoplastic antibiotic

- Treatment of Testicular Cancer
- Treatment of Paget's Disease of Bone
- Possible metastasis inhibitor
- Inhibits SP1
- **Interacts with core histones***

Tolfenamic Acid
(TA/clotam)

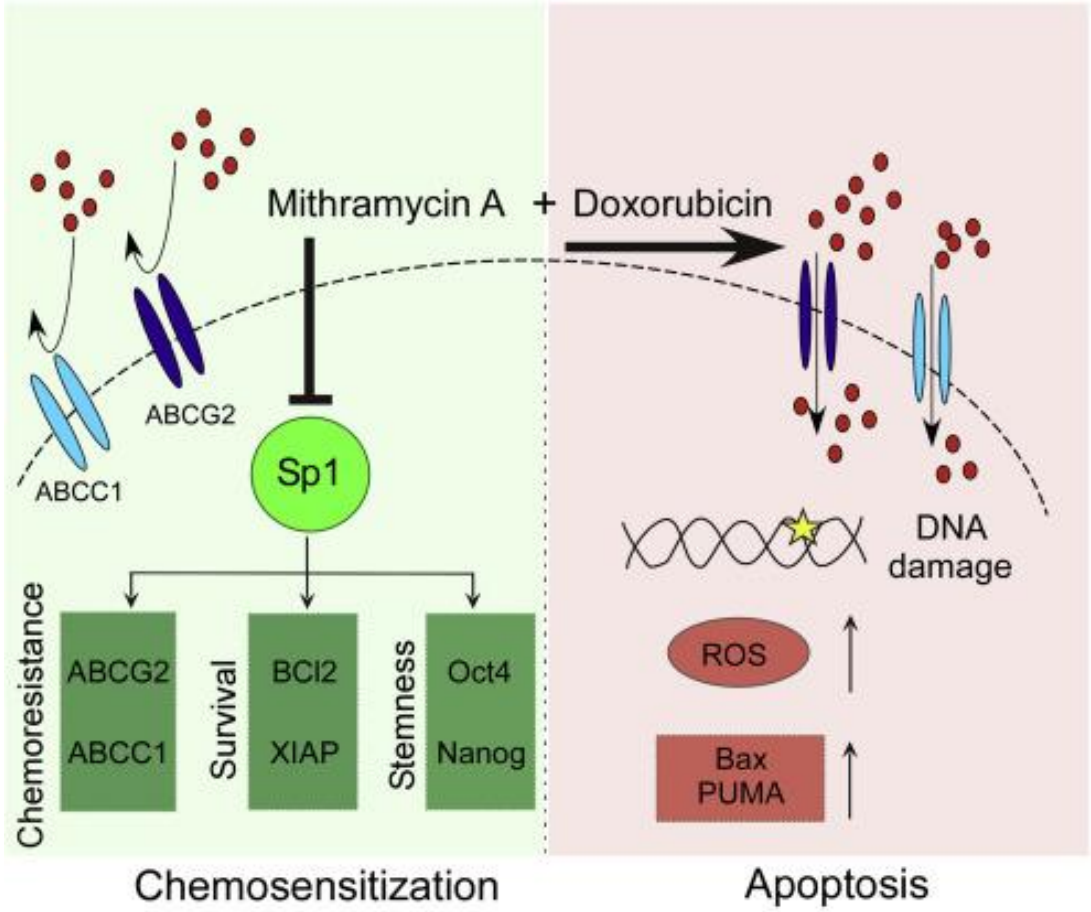
NSAID

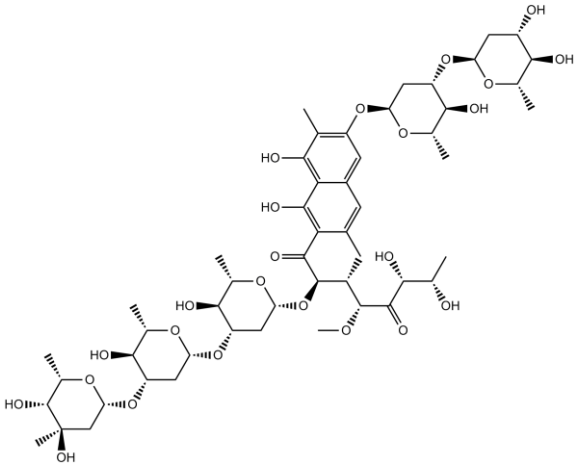
- Cox inhibitor
- Treatment of Migraine (not in USA)
- Inhibits SP1 and SP3

SP1 regulates DNA methyltransferase 1, which participates in epigenetic modification of DNA.

*Banerjee et al. 2014. *FEBS Open Bio.* 16:987-995

Novel Approaches



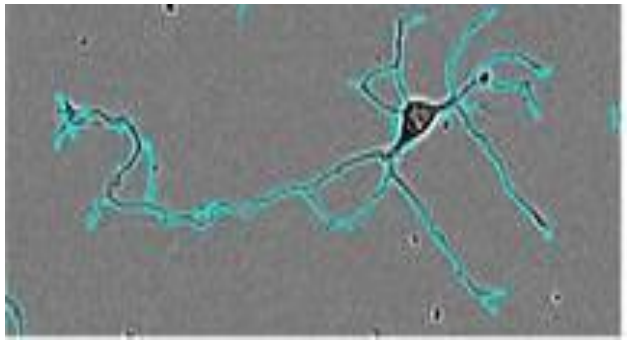


TA and MTM alter human neuronal cells

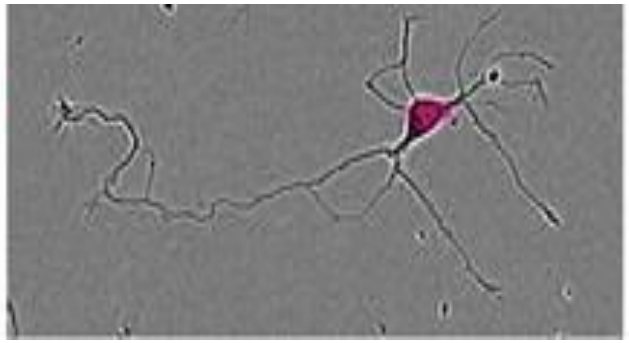
- Neurite Length
- Neurite Branch Points
- Cell bodies

Bayon B, Chopra N, Maloney B, Nho K, Saykin A & Lahiri DK. Regulation of APP and BACE1 expression by transcription factor modulating compounds Mithramycin A and Tolfenamic acid. SfN Presentation-2016

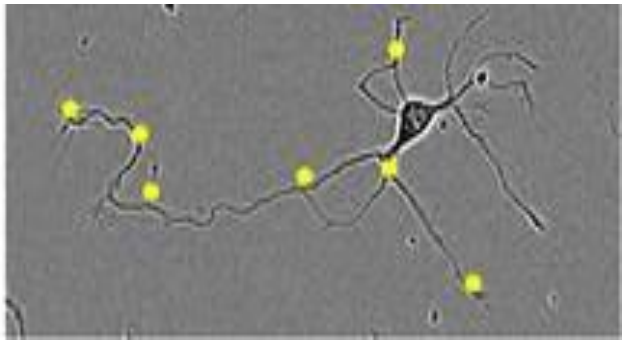
IncuCyte Visualization of Live Cultures



Neurite Length



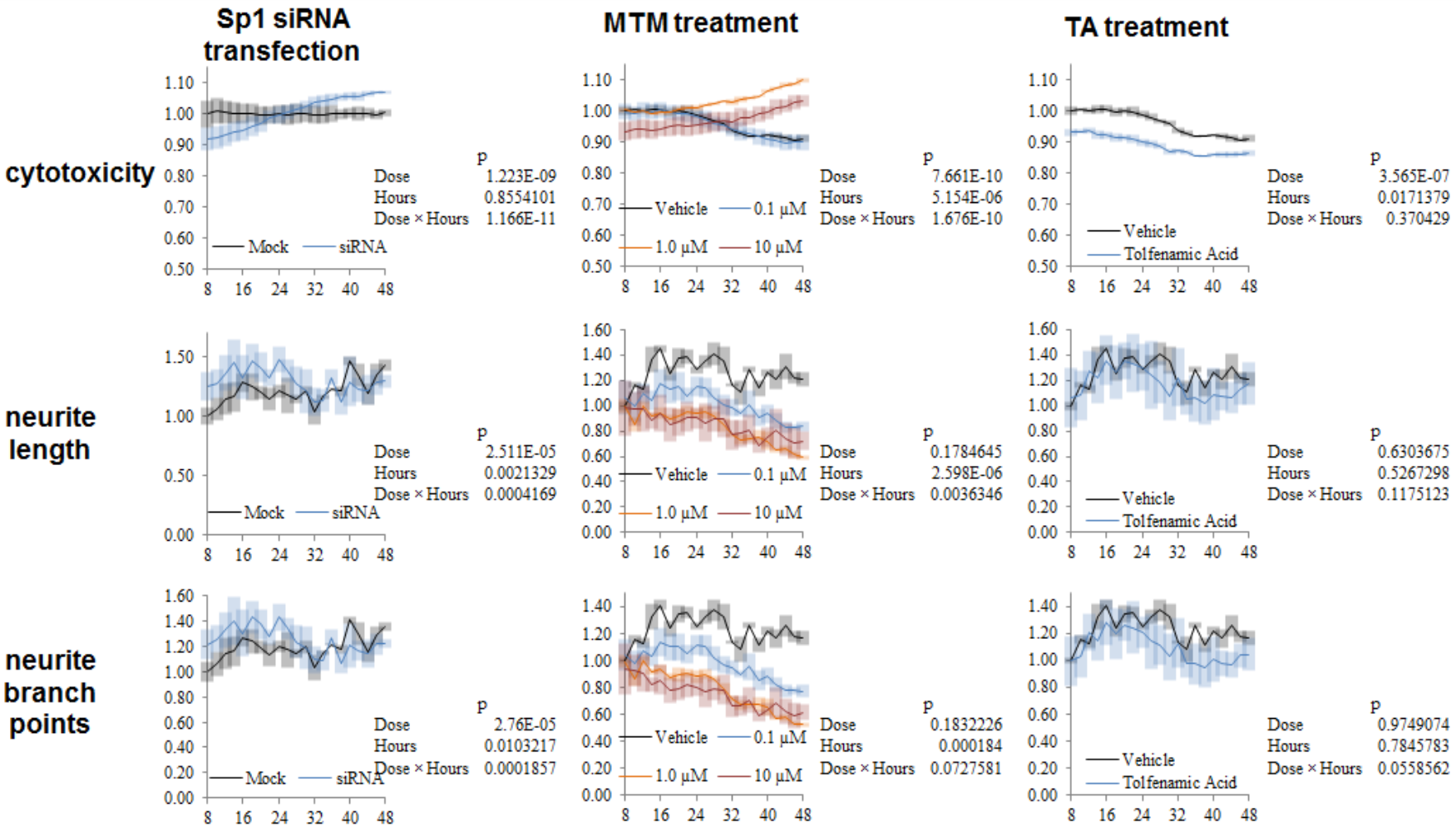
Cell bodies



Neurite Branch Points

Image Source: Essen BioScience

MTM & TA Effects on Cytotoxicity, Neurite Length, & Neurite Branch Points



Try an ounce first

Science
AAAS

DISEASE PREVENTION
www.sciencemag.org/special/prevention

PERSPECTIVE

Preventing Alzheimer's Disease

Dennis J. Selkoe

Despite intensive laboratory and clinical research over three decades, an effective treatment to delay the onset and progression of Alzheimer's disease is not at hand. Recent clinical trial failures suggest that we must treat the disease earlier than in its mild to moderate stages, and major progress in validating presymptomatic biomarkers now makes secondary prevention trials possible. We will learn more about the natural history of the disease and any partial therapeutic responses from detailed analyses of recent trial results. This process will likely position the field for success, but only with much greater investment in all aspects of Alzheimer research and with careful design of future trials.

Try an ounce first

Good E4:

Environment, Enrichment, Exercise, Exposure & Experience- Lifestyle

Transcultural Studies

Lancet. 2012 Jul 7;380(9836):50-8.
Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study.
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Ann N Y Acad Sci. 1999;893:331-6.
Effect of oxidative stress on DNA damage and beta-amyloid precursor proteins in lymphoblastoid cell lines from a Nigerian population.
Lahiri DK, Xu Y, Klaunig J, Baiyewu O, Ogunniyi A, Hall K, Hendrie H, Sahota A.

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J Neurochem. 2011;117(3):388-402.
Oxidative insults to neurons and synapse are prevented by aged garlic extract and S-allyl-L-cysteine treatment in the neuronal culture and APP-Tg mouse model.
Ray B, Chauhan NB, Lahiri DK.

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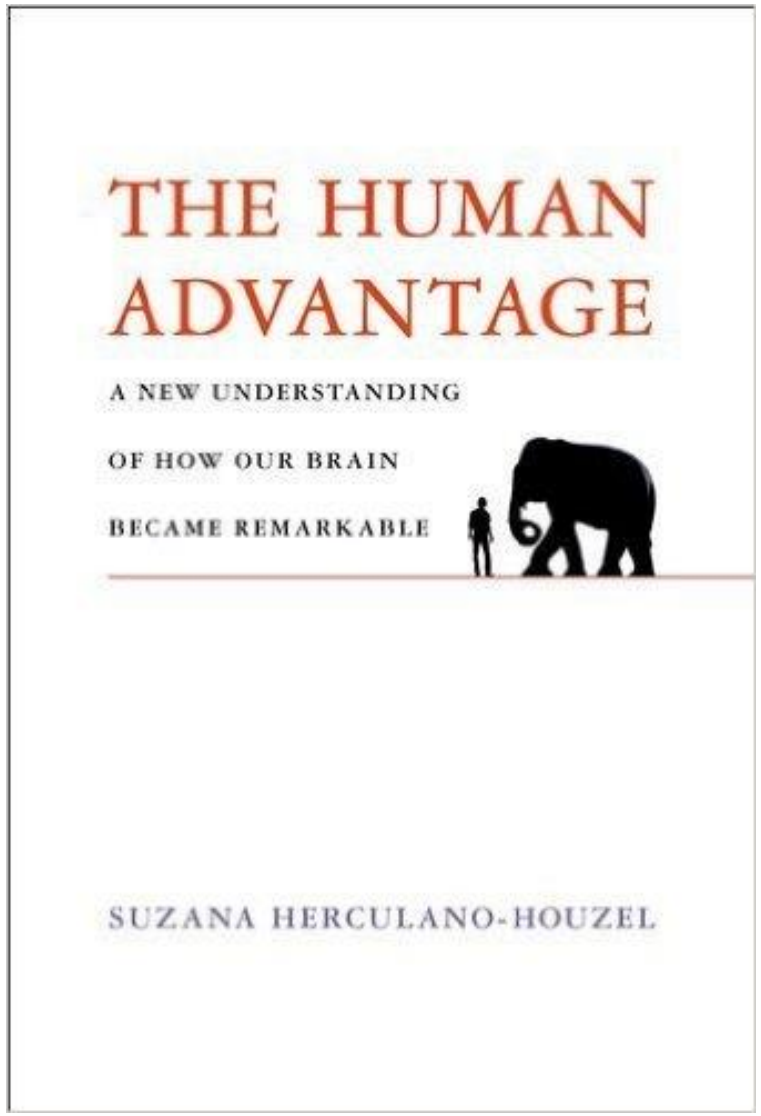
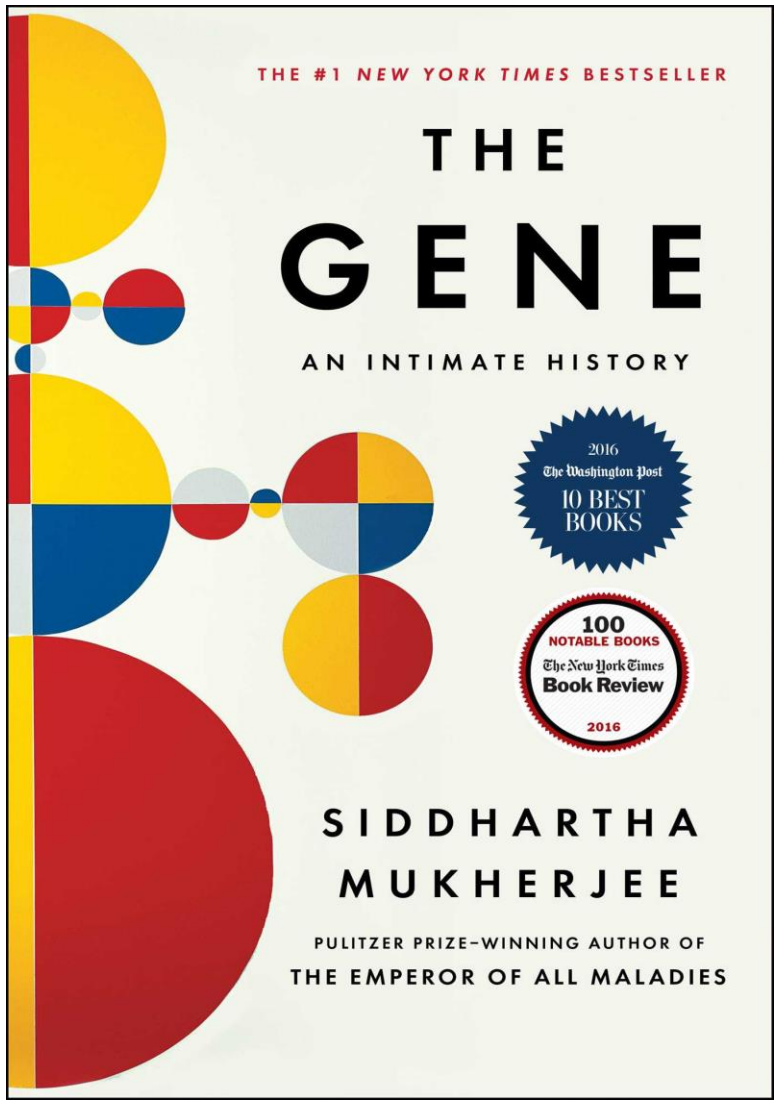
Ray B, Bisht S, Maitra A, Maitra A, Lahiri DK.

Gerontologist. 2007 Jun;47(3):307-22.
Cognitive functioning in healthy aging: the role of reserve and lifestyle factors early in life.
Fritsch T, McClendon MJ, Smyth KA, Lerner AJ, Friedland RP, Larsen JD.

Public Education





CONCLUSIONS: Neuroconvergence

- Adopt and integrate knowledge of epigenetics
- Apply via drugs and environmental modification.
- Environment *includes* diet, activity, lifestyle, *anything not within the organism.*
- Integrate therapy and diagnostics into “theranostics”
- Move beyond epigenomics to metabolomics, miRnomics, ultimately to *Pantonomics.*

And coming full circle...

THE LANCET Neurology

Epigenetics of dementia: understanding the disease as a transformation rather than a state

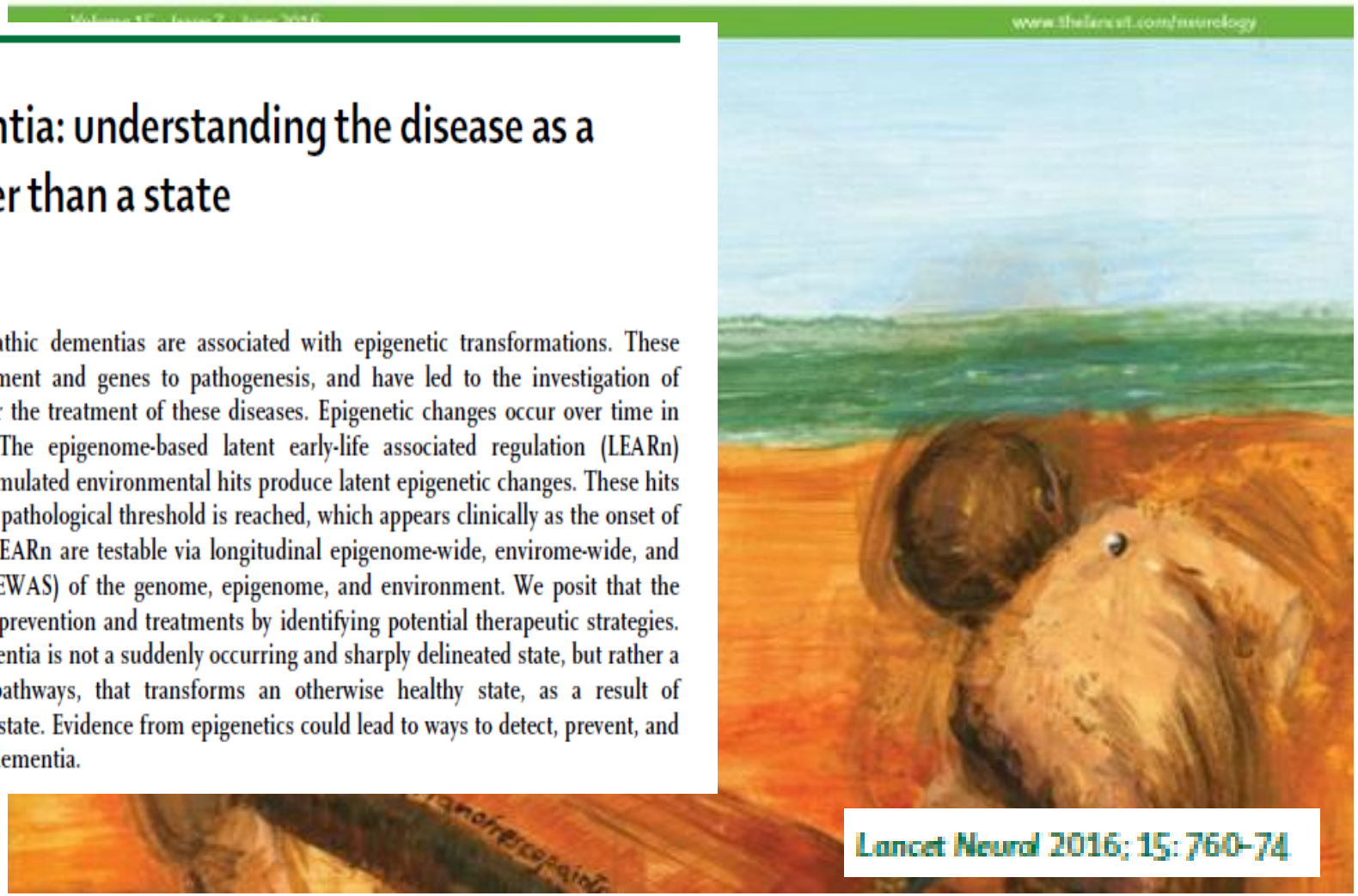
Bryan Maloney, Debomoy K Lahiri

Lancet Neurol 2016; 15: 760–74

Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Neuroscience Research Center, Indianapolis, IN, USA (B Maloney BA, Prof D K Lahiri PhD); and Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA (Prof D K Lahiri)

Correspondence to: Prof Debomoy K Lahiri,

Alzheimer's disease and other idiopathic dementias are associated with epigenetic transformations. These transformations connect the environment and genes to pathogenesis, and have led to the investigation of epigenetic-based therapeutic targes for the treatment of these diseases. Epigenetic changes occur over time in response to environmental effects. The epigenome-based latent early-life associated regulation (LEARn) hypothetical model indicates that accumulated environmental hits produce latent epigenetic changes. These hits can alter biochemical pathways until a pathological threshold is reached, which appears clinically as the onset of dementia. The hypotheses posed by LEARn are testable via longitudinal epigenome-wide, envirome-wide, and exposome-wide association studies (LEWAS) of the genome, epigenome, and environment. We posit that the LEWAS design could lead to effective prevention and treatments by identifying potential therapeutic strategies. Epigenetic evidence suggests that dementia is not a suddenly occurring and sharply delineated state, but rather a gradual change in crucial cellular pathways, that transforms an otherwise healthy state, as a result of neurodegeneration, to a dysfunctional state. Evidence from epigenetics could lead to ways to detect, prevent, and reverse such processes before clinical dementia.



CONCLUSIONS: Neuroconvergence

- Panto (Παντα): “All”
- nomos (νόμος): “Law”

Everything can make a difference

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University of Rhode Island, Kingston, RI: Nasser Zawia

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