Early-life Environment and Exposures at the crossroads of Epigenetics

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Indiana University School of Medicine, Indianapolis, USA

Editor-in-Chief: ‘Current Alzheimer Research’
EiC: ‘Current Aging Science’
Disclosures

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  - National Institute on Aging (NIA) R01 (R01AG18379, R01AG18884), R21 and P30 grants
  - Indiana Clinical & Translational Sciences Institute and ISDH Spinal Cord and Brain Injury Board
  - Alzheimer’s Association Zenith Award
  - Forest Labs
  - Novartis
  - Baxter

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  - QR Pharma, Inc., West Chester, PA, USA
  - Yuma Therapeutics, Boston, MA, USA
  - Drug Discovery and Therapy World Congress, Boston, MA
Most are pathology or biomarker based.
Drug Development is not Developing.
“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?
Revisiting AD Pathogenesis Pathway(s)?

♦ *Prior to Amyloid β-peptide formation*


♦ *Post-Amyloid β-peptide?*

Lahiri DK. Prions: a piece of the puzzle? Science. 7;337(6099):1172
The *APOE* ε4 allele is the most influential known genetic risk factor for sporadic AD.¹

In an African-American population, ε4 frequency was over twice as prevalent for AD patients as for age-matched non-AD controls.²

However, in African populations, the ε4/AD association was absent, very weak, or depended on cholesterol levels.³⁻⁵

Cell lines derived from both populations appear to show less mitochondrial DNA damage following oxidative challenge than do cell lines derived from caucasians.⁶

1. [https://www.alz.org/alzheimers-dementia/facts-figures](https://www.alz.org/alzheimers-dementia/facts-figures)
It is tempting to call this a “disparity” effect.

Not every difference is a disparity.
Air pollution can alter to DNA methylation.\(^1\)

Combustion-derived nanoparticles found in human brains, including in children.\(^2\)

Air pollution contributes to AD incidence and aggravation.\(^3\text{-}^5\)

Exposure to air pollution in the USA differs by race, with African Americans suffering greatest exposure.\textsuperscript{6}

Prevalence of AD differs by race, with African Americans having greatest prevalence.\textsuperscript{7}

Exposures can pathogenically alter Epigenetics.

Social disparity can determine Exposures.

When chromatin is condensed, DNA is usually not transcribed. When chromatin is relaxed, transcription factors and PolII complex have access to DNA and DNA can be transcribed.

Histone Modifications: can “tighten” or “loosen” chromatin.

DNA methylation physically interferes with binding of many transcription factors. But other transcription factors preferentially bind methylated DNA.
Newfangled Complications: Epigenetic Markers

Epigenetic markers can start with a "wildtype"

Environmental exposure can alter epigenetic markers

Epigenetic changes result in changes in protein levels, producing a "soft" loss/gain of function, which leads to disease

Epigenetic change is not like DNA mutation. It can be reverted (hypothetically).

Once it occurs...
And, thus, disease averted.

But the matter is more complicated.
Reversion does not prevent reimposition.
And we can still end up with epigenetic disease.

which leads to disease
Correspondence: Genes are not our destiny: the somatic epitype bridges between the genotype and the phenotype

Debomoy K. Lahiri & Bryan Maloney

Published online: 08 November 2006
10.1038/nrn2022-c1
“E4” drives neural proteins in later-life disorders

Via the

LEARn pathway

(Latent Early-life Associated Regulation)

So let us LEARn?
The LEARn model is a unifying viewpoint.

- **Genetic Disorder**
- **LEARn Mediated**
- **No final hit**
- **“Late Hit”**

Risk Burden vs. Age

- **“Min”**
- **“Max”**

Clinical Signs

- **“Final” Hit**

The LEARn model is a unifying viewpoint.

**Perspective**

The LEARn model: an epigenetic explanation for idiopathic neurobiological diseases

DK Lahrin, B Maloney, and NH Zevia

1 Department of Molecular Neurogenetics, Indiana University School of Medicine, Indianapolis, IN, USA
2 Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA

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 LEARns (LEARns). In LEARn, each person is a "unit" accumulating preclinical or subclinical "hits" as in the original LEARn model. These changes can then be epigenetically passed along to offspring. Transgenerational accumulation of "hits" determines a sporadic disease state. Few significant transgenerational hits would accompany conception or gestation of such 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 LEARn requires longitudinal approaches. A recently proposed longitudinal epigenome-wideneighborhood 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

**Early life exposure to toxin**

Induction and upregulation of LEARned AD-associated genes

Latency Period of Normal Gene Expression

disease-associated expression later in life
The concept of ‘Somatic Epitype’
Where is the evidence for the LEARn Model?

- 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(early), and Pb–L(ate).
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.

Basha…Lahiri, Zawia, J. Neurosci. 25:823-829
Neonatal Pb Exposure does not alter β-actin mRNA levels. Neonatal Pb Exposure alters APP mRNA levels.

Neonatal exposure to Pb changes APP expression late in life.


* Control and exposed results different at p < 0.05
Neonatal exposure to Pb selectively upregulates SP1 Early…
Neonatal exposure to Pb selectively upregulates SP1... and Late

* Control and exposed results different at p < 0.05
But it’s not lead poisoning.

Lifespan in months (1–20)

<table>
<thead>
<tr>
<th>Pb Exposure Period</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Pb (early)</td>
</tr>
<tr>
<td>Pb (late)</td>
</tr>
</tbody>
</table>

APP mRNA
APP immunoblot
actin mRNA
Sp1 DNA binding

Con Pb(E) Pb(L)

Control
Pb (early)
Pb (late)

Pb Exposure Period

Actin-adj. Densitometry

<table>
<thead>
<tr>
<th></th>
<th>APP mRNA</th>
<th>APP Protein</th>
<th>Sp1 DNA binding</th>
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</thead>
<tbody>
<tr>
<td>Con</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pb (early)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pb (late)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

pg of Aβ/mg of protein

<table>
<thead>
<tr>
<th></th>
<th>Aβ Levels</th>
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<tbody>
<tr>
<td>Con</td>
<td></td>
</tr>
<tr>
<td>Pb (early)</td>
<td></td>
</tr>
<tr>
<td>Pb (late)</td>
<td></td>
</tr>
</tbody>
</table>

* Control and early exposed results different at p < 0.05

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

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

<table>
<thead>
<tr>
<th>Sample</th>
<th>Blood µg/dL</th>
<th>Cortex µg/g wet wt. of tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (PND 20)</td>
<td>&lt;2.0</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>Pb (PND 20)</td>
<td>46.43±1.95*</td>
<td>0.41±0.04*</td>
</tr>
<tr>
<td>Control (20 month)</td>
<td>&lt;2.0</td>
<td>&lt;0.2</td>
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<tr>
<td>Pb-E (20 month)</td>
<td>&lt;2.0</td>
<td>&lt;0.2</td>
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<tr>
<td>Pb-L (20 month)</td>
<td>&lt;2.0</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>Control (20 month)</td>
<td>0.41±0.04*</td>
<td>0.32±0.03*</td>
</tr>
</tbody>
</table>

Cortex µg/g wet wt. of tissue

Blood µg/dL

APP mRNA

APP immunoblot

actin mRNA

Sp1 DNA binding

<table>
<thead>
<tr>
<th>Sample</th>
<th>APP mRNA</th>
<th>APP Protein</th>
<th>Sp1 DNA-binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con</td>
<td></td>
<td></td>
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<tr>
<td>Pb(E)</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<tr>
<td>Pb(L)</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Actin-adj. Densitometry

APP-mRNA

APP-Protein

Sp1 DNA-binding

pg of Aβ/mg of protein

Basha...Lahiri, Zawia, Zawia, J. Neurosci. 25:823-829
Where is the evidence for the LEARn model?

- Animal studies - Rodents
- Non Human Primate (NHP) studies
- Human studies
Cynamolgus Monkey: Pb Exposure

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
Cynnamolgus Monkey: Pb Exposure

**APP, Sp1 & G3PDH**

- **APP mRNA levels**
  - APP/G3PDH
  - Control     Pb(E)
  - *APP mRNA*  Con    Pb-E

- **APP immuno blot**
  - APP
  - Sp1 mRNA
  - G3PDH

**Aβ**

- **pg/ml**
  - Aβ1-40
    - Con  Pb-
  - Aβ1-42
    - Con  Pb-E

- **Aβ1-42/Aβ1-40**
  - Con  Pb-E

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

PERSPECTIVE
The LEARn model

ORIGINAL ARTICLE
IL33 and Alzheimer's disease

ORIGINAL ARTICLE
Markers of ioperidone QT prolongation

ORIGINAL ARTICLE
First Incidence of Substance Use, Mood and Anxiety Disorders

- About the cover
- Free online issue

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8/219 Neuroscience
9/276 Biochemistry & Molecular Biology

Editor:
Julio Licinio, MD

* 2008 Journal Citation Report (Thomson Reuters, 2009)

- Current issue table of contents
- Advance online publication in full
“LEARned” vs. “un-LEARned” Genes
“LEARned” vs. “unLEARned” Genes: CpG or GG density

Lahiri, Maloney, & Zawia, *Molecular Psychiatry*
<table>
<thead>
<tr>
<th>Non-Responding</th>
<th>Responding</th>
<th>Downregulated</th>
<th>Upregulated</th>
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<td>OGG1</td>
<td>AP2M1</td>
<td>IQGAP1</td>
<td>APP</td>
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<td>NR4A3</td>
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<td>PSEN1</td>
<td>ARHGDIA</td>
<td>KCNJ4</td>
<td>BACE1*</td>
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<td>PLA2G2A</td>
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<td>OPRD1</td>
<td>CALM1</td>
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<td>OPRM1</td>
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<td>GNB1</td>
<td>ADAM17#</td>
<td>MECP2</td>
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<td></td>
<td>HTR1B</td>
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</tr>
</tbody>
</table>

*β-secretase  #α-secretase
Why bother to care about Pb, anymore?
Lead does still matter!

**Then**

**THE INDIANAPOLIS STAR**

Lead poisoning fears send families to clinics

**Later**

**THE INDIANAPOLIS STAR**

‘A POTENTIAL CATASTROPHE’
Commentary

Latent consequences of early-life lead (Pb) exposure and the future: Addressing the Pb crisis

Bryan Maloney\textsuperscript{a,c}, Baiydu L. Bayon\textsuperscript{b,c}, Nasser H. Zawia\textsuperscript{d}, Debomoy K. Lahiri\textsuperscript{a,b,c,*}
Evidence for the LEARn Model?

- Animal studies - Rodents
- Non Human Primate (NHP) studies
- Human studies
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*]
Epigenetics and AD: A case study

- Both twins developed AD by age 60.
- Both became chemical engineers.
- Marked differences in methylation of histone H3 (K9) found in AD twin.
- Each had different employment and exposure experiences.
- A pair of monozygotic twins reared together.
- Had identical educational attainments.
- This provides interesting evidence pointing towards epigenetic factors in AD.

[Ryu et al. 2009. Alz & Dementia]
Specific epigenetic associations exist in dementias

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Subjects</th>
<th>Dementia Type</th>
<th>Target Genes (if specified)</th>
<th>Epigenetic Marker</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Case Study</td>
<td>Monoz. Twins</td>
<td>AD</td>
<td>DNA methylation, DNA hydroxymethylation</td>
<td>DNA methylation and hydroxymethylation reduced in twin with AD.</td>
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<tr>
<td>Cohort</td>
<td>AD: 10 Cont:10</td>
<td>AD</td>
<td>DNA methylation, DNA hydroxymethylation</td>
<td>DNA methylation and hydroxymethylation reduced in AD, negative correlations between quantified methylation &amp; hydroxymethylation vs. amyloid plaque and tangle.</td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>AD: 13 Cont:8</td>
<td>AD</td>
<td>DNA hydroxymethylation</td>
<td>DNA hydroxymethylation decreased in AD samples in both brain regions.</td>
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<tr>
<td>Cohort</td>
<td>AD: 429 Cont:279</td>
<td>AD</td>
<td>ANK1; CDH23; DIP2A; KIAA0145; RHBD2; RPL13; SERPINF1; SERPINF2</td>
<td>DNA methylation</td>
<td>Methylation of specific CpG dinucleotides was associated with histopathologic diagnosed AD.</td>
</tr>
<tr>
<td>Cohort</td>
<td>AD: 447 Cont:293</td>
<td>AD</td>
<td>SORL1; ABCA7; HLA-DRB5; SL24A4; BIN1</td>
<td>DNA methylation</td>
<td>Methylation of specific CpG dinucleotides associated with histopath. diagnosed AD and 1A8.</td>
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<tr>
<td>Cohort</td>
<td>Cont:5 Braak I-II: 5 Braak III-IV: 5 Braak V-VI: 5</td>
<td>AD</td>
<td></td>
<td>DNA methylation</td>
<td>Hypermethylation of specific CpG dinucleotides in DUSP22 sequence and DUSP22 expression associated with AD Braak stages.</td>
</tr>
<tr>
<td>Cohort</td>
<td>ALS/FTD: 9 c9ALS/FTD: 10 Cont:8</td>
<td>FTD (ALS)</td>
<td>C9orf72</td>
<td>DNA methylation</td>
<td>DNA hypermethylation associated with ALS developing into dementia for C9orf72 carriers. C9orf72 ALS without hypermethylation did not show dementia.</td>
</tr>
<tr>
<td>Cohort</td>
<td>ALS/FTD: 9 c9ALS/FTD: 10 Cont:8</td>
<td>FTD (ALS)</td>
<td>C9orf72</td>
<td>Histone methylation</td>
<td>Trimethylation of Histone H3 linked to FTD and ALS in C9orf72 carriers. Carriers without trimethylation did not have ALS/FTD</td>
</tr>
<tr>
<td>Cohort</td>
<td>PD: 12 Cont:14</td>
<td>PD</td>
<td>SNCA</td>
<td>DNA methylation</td>
<td>PD patient samples were hypermethylated at specific sites of SNCA intron 1 vs. controls.</td>
</tr>
<tr>
<td>Cohort</td>
<td>2 cohorts: Leukocyte PD: 358 Cont:1064 Brain PD: 28 Cont:12</td>
<td>PD</td>
<td>MAPT</td>
<td>DNA methylation</td>
<td>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.</td>
</tr>
</tbody>
</table>
### Epigenetic drugs in Clinical Trials

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment</th>
<th>Activity</th>
<th>Condition</th>
<th>NCT #</th>
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</thead>
<tbody>
<tr>
<td>Polyphenols</td>
<td>Epigallocatechin gallate</td>
<td>DNMTi, HDACi</td>
<td>Multiple System Atrophy</td>
<td>NCT02008721</td>
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<tr>
<td>Flavenol</td>
<td>Cognitive Performance., Mood., Cardiometabolic Risk Markers</td>
<td>NCT02243956</td>
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<td>Grape Extract</td>
<td>Cardiovascular Diseases</td>
<td>NCT01449110</td>
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<tr>
<td>Phenolic</td>
<td>Cardiovascular Disease, Endothelial Function</td>
<td>NCT01983943</td>
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<td>Grape Juice</td>
<td>Cognition</td>
<td>NCT01411631</td>
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<tr>
<td>Red Grape Juice</td>
<td>Memory, Gene Expression</td>
<td>NCT00972972</td>
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<td>Alzheimer's Disease</td>
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<td>Omega-3 Fatty Acids</td>
<td>EPA</td>
<td>Hcyr</td>
<td>Mild Cognitive Impairment</td>
<td>NCT01219244</td>
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<td>Curcuminoids</td>
<td>Curcumin</td>
<td>DNMTi, HMTi, HDACi</td>
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<td>Umbilical Cord Blood</td>
<td>Umbilical Cord Blood</td>
<td>Multiple supposed activities</td>
<td>Aging</td>
<td>NCT02418013</td>
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<td>Apple Extract</td>
<td>Methyl Donor</td>
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<td>Nicotinamide</td>
<td>Methyl Donor</td>
<td>Neurodegenerative Disorders</td>
<td>NCT01589809</td>
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<td>Caloric restriction</td>
<td>Caloric Restriction</td>
<td>HDACs, DNMTs</td>
<td>Mild Cognitive Impairment</td>
<td>NCT01219244</td>
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<tr>
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<td>Aging</td>
<td>NCT01219244</td>
</tr>
</tbody>
</table>

**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, etc.)

### Polyphenols
(DNMT inhibitor, HDAC inhibitor)
Using high-speed robots and the secrets of the human genome, scientists are changing forever the way they discover new medicines.
# 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*
• Neurite Length
• Neurite Branch Points
• Cell bodies
IncuCyte Visualization of Live Cultures

Neurite Length

Cell bodies

Neurite Branch Points

Image Source: Essen BioScience
Neurosphere (NSP) Isolation to Single Layer

- 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
MTM & TA Effects on Cytotoxicity, Neurite Length, & Neurite Branch Points
Alzheimer’s From A New Angle

A RADICAL NEW APPROACH TO TREATING THE FEARFUL DISEASE IS SHOWING PROMISE BY ALICE PARK
Try an ounce first

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.
Hacking your Genes through Epigenetics
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.

Effect of oxidative stress on DNA damage and beta-amyloid precursor proteins in lymphoblastoid cell lines from a Nigerian population.

Prayer at Midlife is Associated with Reduced Risk of Cognitive Decline in Arabic Women.
Dietary Factors

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.*

**Alzheimer Dis Assoc Disord.** 2004;18(2):57-64.
Exercise level and cognitive decline: the MoVIES project.
*Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M.*

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Cognitive functioning in healthy aging: the role of reserve and lifestyle factors early in life.
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Epigenetics of dementia: understanding the disease as a transformation rather than a state

Bryan Maloney, 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 targets 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

• Adopt and integrate knowledge of epigenetics
• Apply via drugs and environmental modification.
• Environment includes diet, activity, lifestyle, social conditions, anything not within the organism.
• Integrate therapy and diagnostics into “theranostics”
• Move beyond epigenomics to metabolomics, miRnomics, ultimately to Pantonomics.
--Prevention is better than cure!

LEARN to LEAN Lifestyle, Environment, Attitude & Nutrition to combat AD?
NeuroConverging approach

- Genomic level: Epigenomics (methylation+acetylation+chromatin modifi.)
- LEARn to LEAN
- Theranostics (Therapeutics + Diagnostic): Metabolomics+MiRonomics

(Adapted from Lahiri DK. An integrated approach to genome studies. Science 14;331(6014):147.)
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