Using *in vitro* and *in vivo* models to inform understanding of developmental neurotoxicity

PAMELA J. LEIN

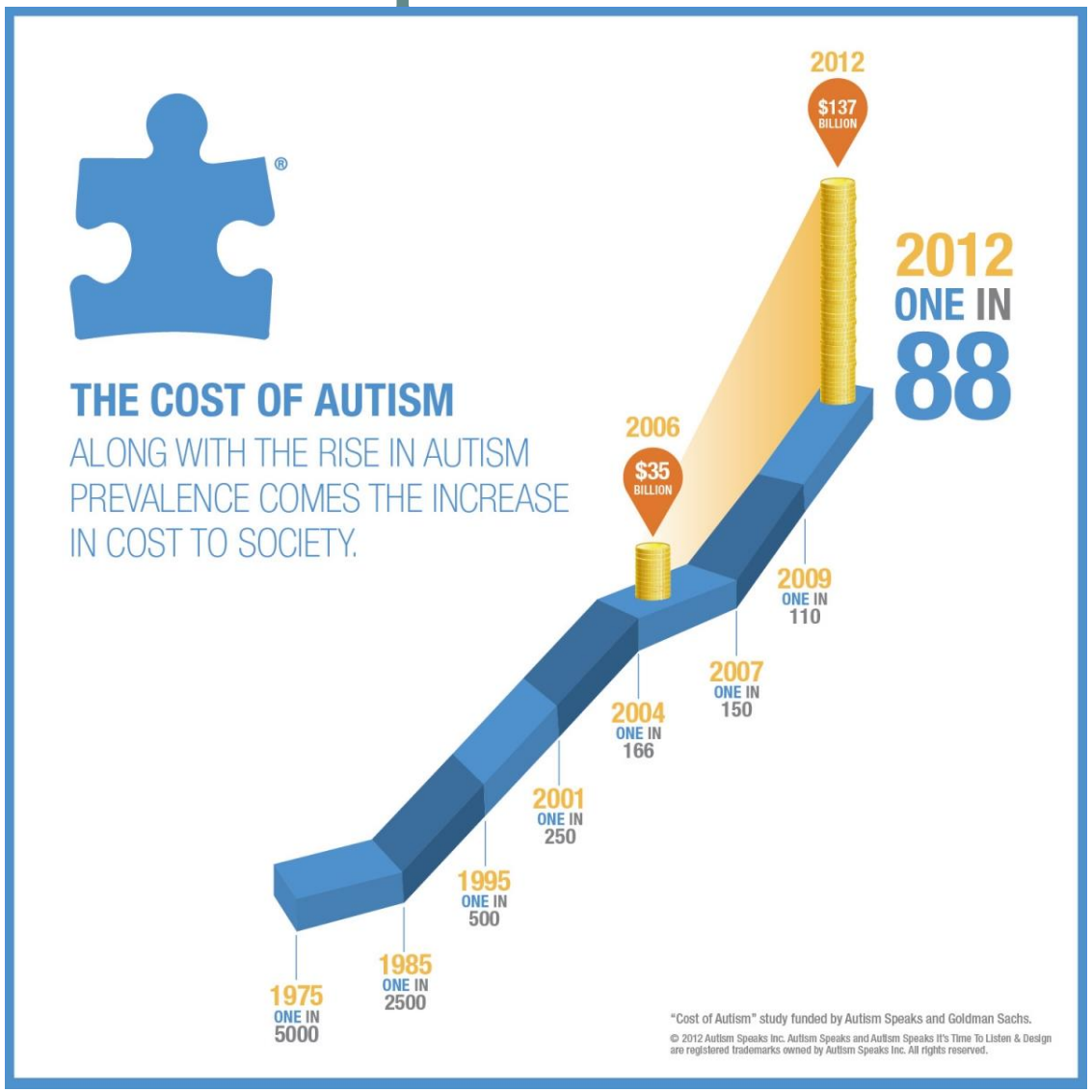
UNIVERSITY OF CALIFORNIA-DAVIS

Molecular Biosciences, School of Veterinary Medicine

Center for Children's Environmental Health

MIND Institute

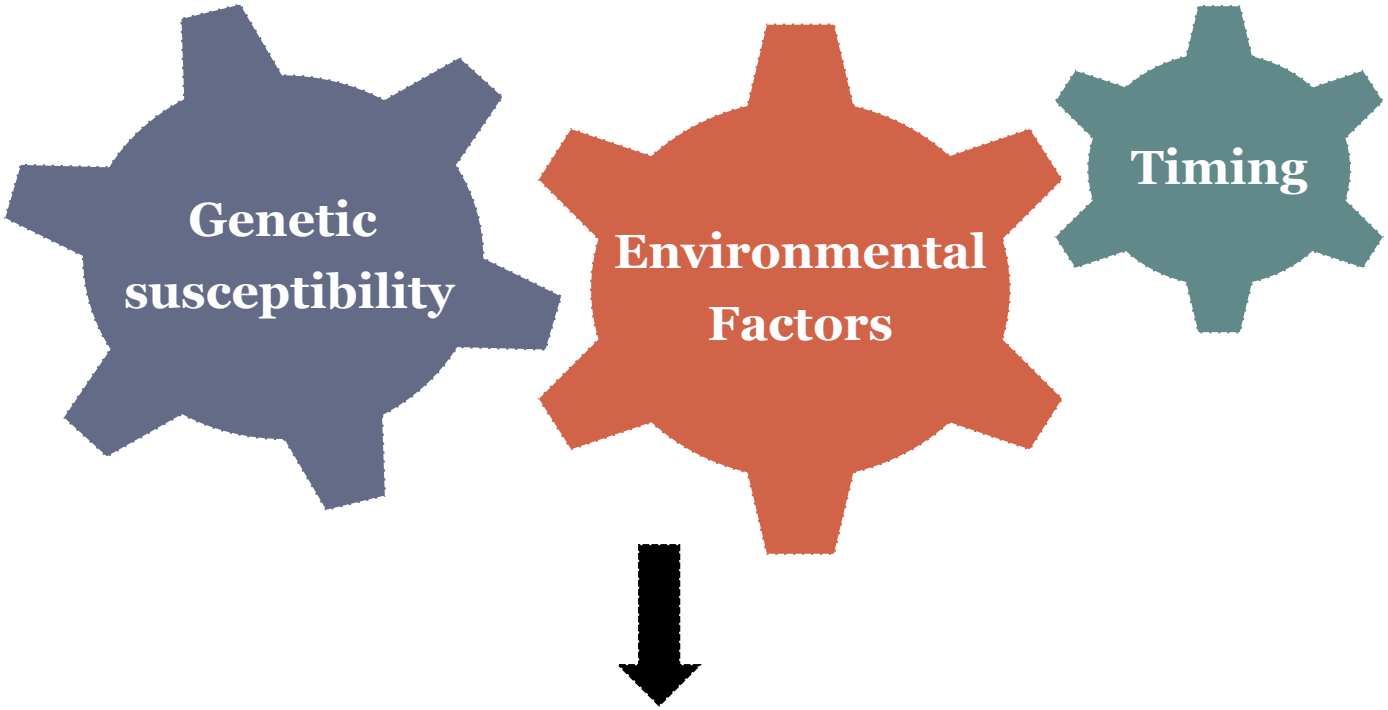
Need to screen environmental chemicals for developmental neurotoxicity (DNT)



2014

1 in 68 (USA)

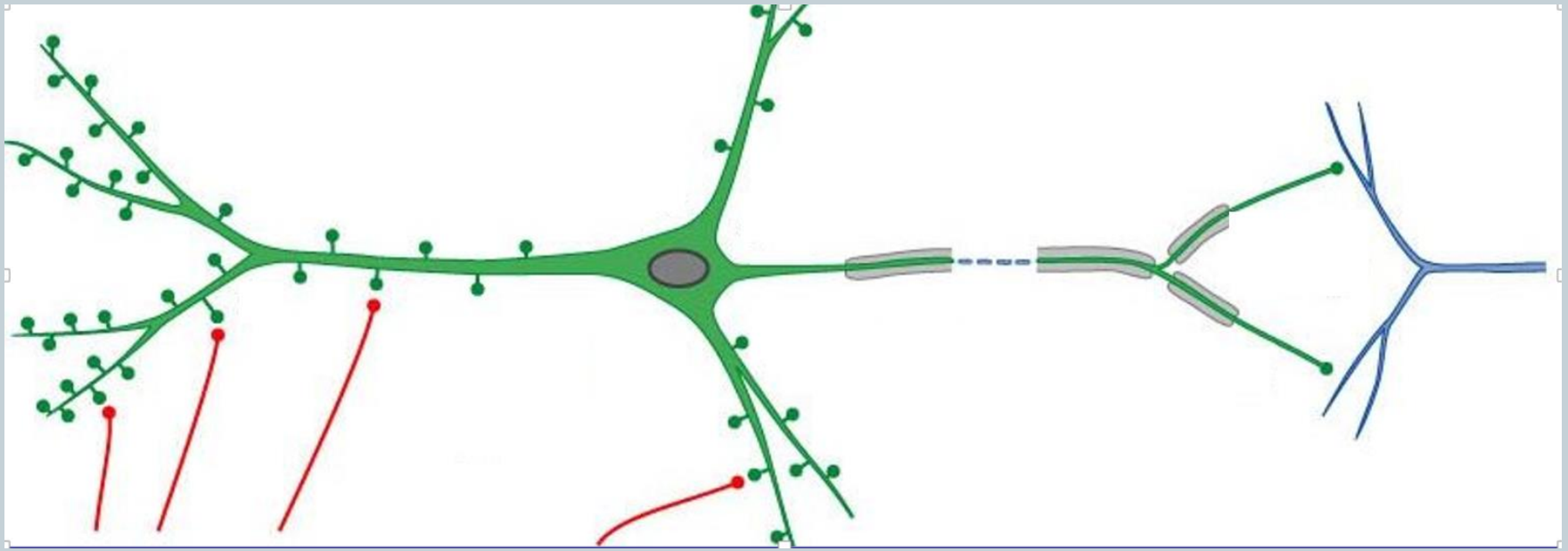
Screening for Gene-Environment Interactions for DNT Potential



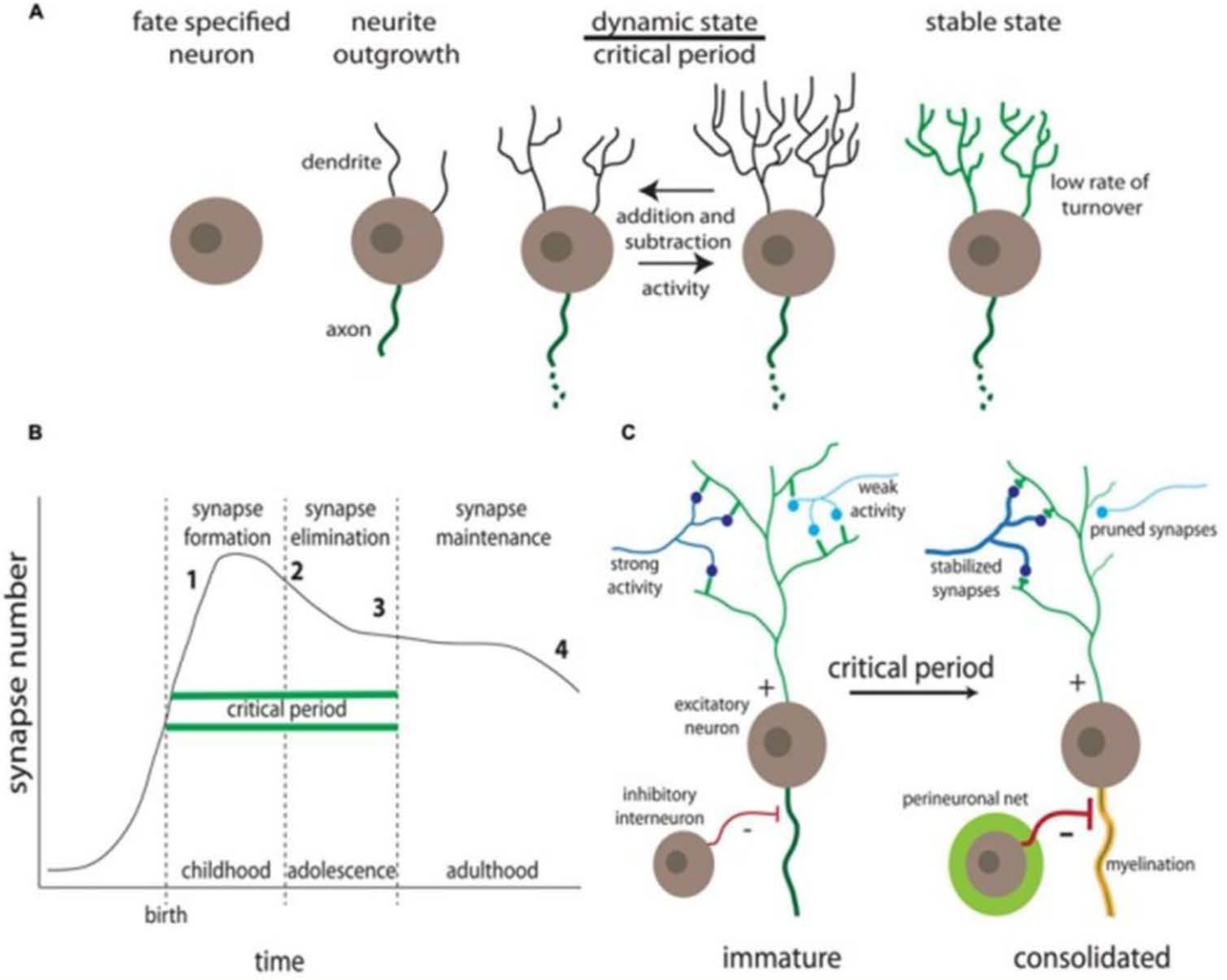
NDD risk, severity and treatment outcome

Focus on neuronal connectivity

Axonal, dendritic and synaptic structure are critical determinants of neuronal connectivity, which in turn determines brain function



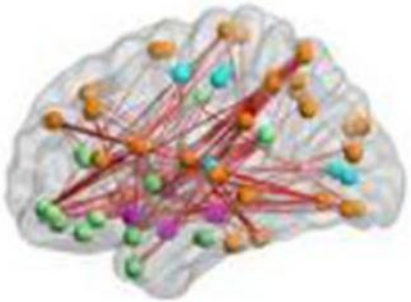
Common Pathways for Neurodevelopmental Disorders (NDDs):
Altered Neuronal Connectivity and Structural Plasticity



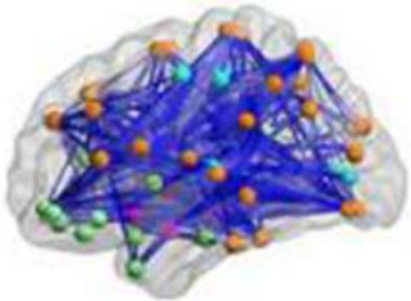
Neuronal Connectivity as a Relevant Endpoint for Studying Environmentally-Induced NDDs

Genetic, histological, electrophysiological and functional imaging studies identify altered synaptic connectivity in autism and other neurodevelopmental disorders (NDD)

- Many of the genes implicated as risk factors for ASD influence dendritic morphogenesis and/or synapse formation and stabilization
- Abnormalities in dendritic morphology are the most consistent pathologic correlate of behavioral deficits in ASD



Neurotypical children



Children with autism

Mechanistic approach for identifying environmental factors that influence NDD risk

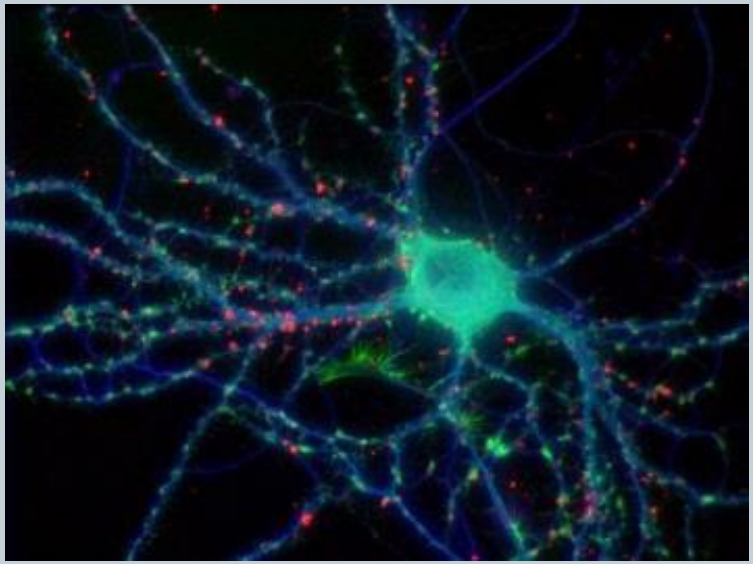
Heritable genetic vulnerabilities amplify adverse effects triggered by environmental exposures *if* genes and environment converge to dysregulate the same signaling system at critical times of neural development resulting in altered patterns of connectivity in the developing brain.

Pessah and Lein (2008) In: *Autism: Current Theories and Evidence* (Edited by Zimmerman) Humana Press, pp. 409-428

Example of applying this strategy

Calcium Signaling Defects: A point of convergence in G x E interactions in DNT

UC Davis Center for Children's Environmental Health
Project 4 (Pessah and Lein, Co-Leaders)



Hypothesis

CGG trinucleotide repeats in the FMR1 gene (Fragile X premutation) influence susceptibility to non-dioxin-like (NDL) persistent organic pollutants (POPs) identified in plasma of women during pregnancy who are at high risk for having a child with ASD.

We predict that these gene-environment interactions will converge on signaling pathways that regulate patterning of neuronal connections set down in the developing brain.

Why focus on NDL POPs?

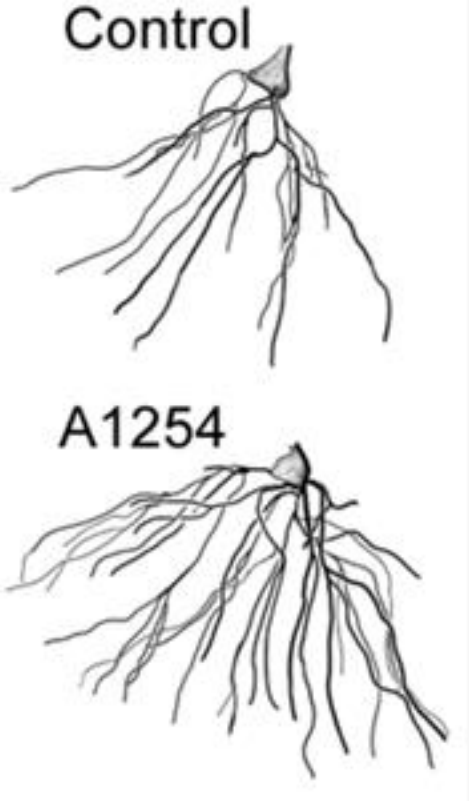
NDL PCBs remain a significant concern as NDD risk factors

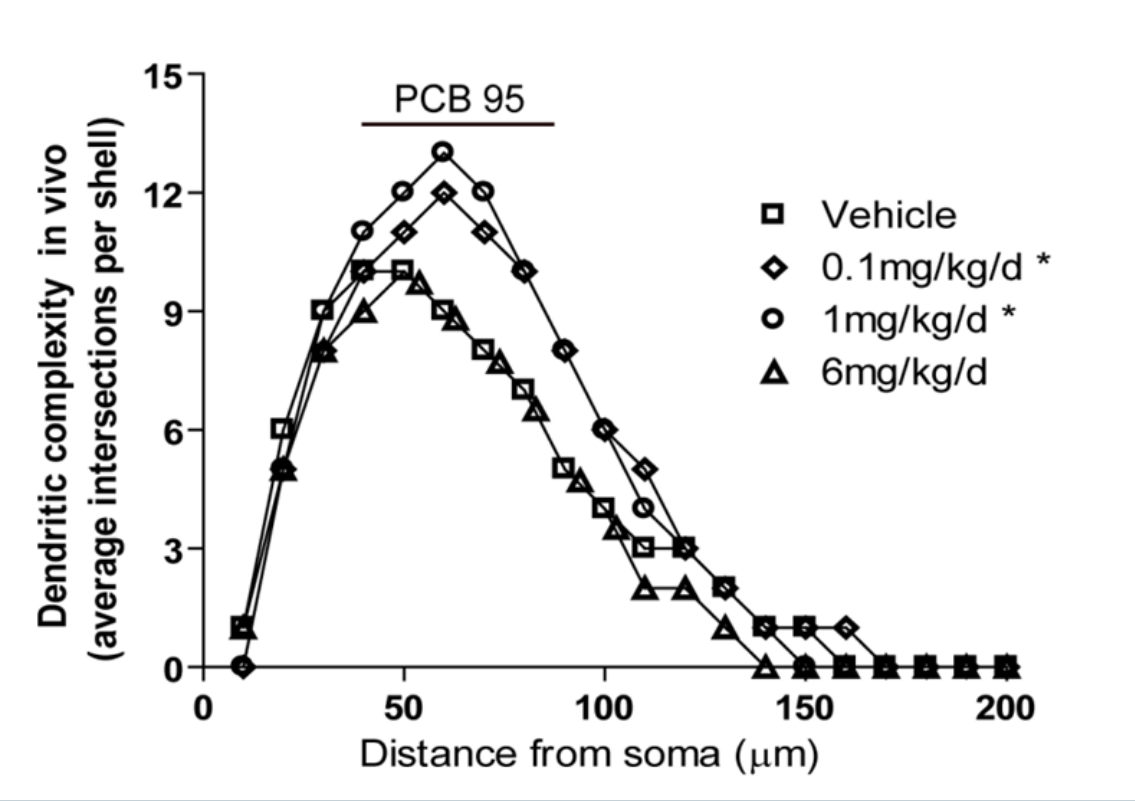
- ***ortho*-substituted NDL PCBs predominate over DL PCBs in environmental samples and human tissues**
  - ❖ Air in public schools
- **Contemporary unintentional sources of NDL PCBs have been identified, most notably commercial paint pigments**
- **The latest NHANES study confirmed widespread exposure to PCBs among women of childbearing age in the USA**
  - ❖ NDL PCBs detected routinely in the plasma of women enrolled in the MARBLES (Puschner, unpublished data)
- **Analyses of PCB and PBDE levels in brain tissue reveal that individuals with genetic risk factors for NDDs have higher NDL PCB levels in brain tissue compared to neurotypical controls**

Why focus on NDL POPs?

NDL PCBs alter endpoints relevant to NDD

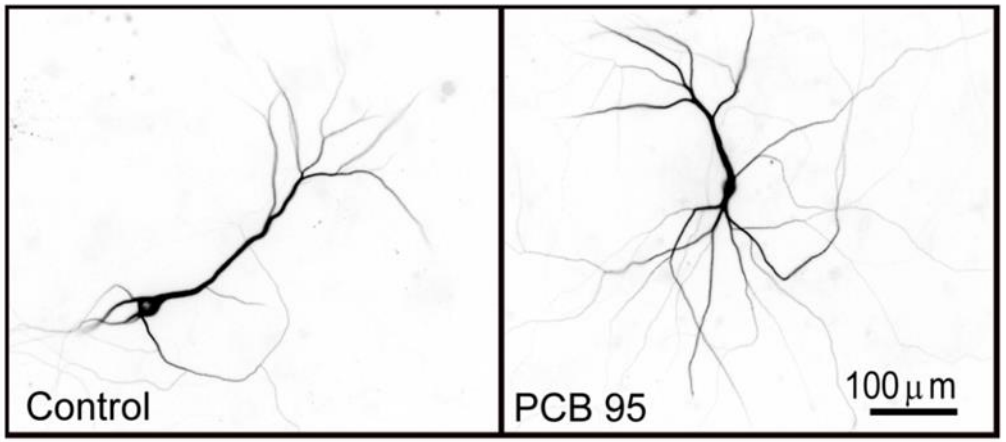
Developmental exposure to PCB 95 in the maternal diet throughout gestation and lactation alters dendritic arborization in the brain of weanling rats

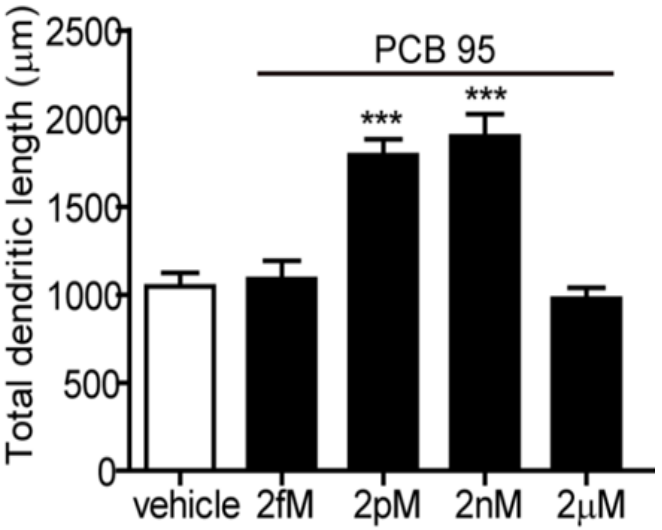


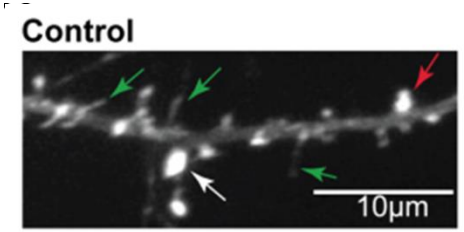


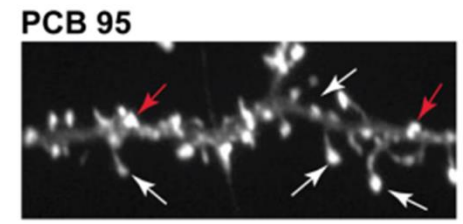
Wayman et al. (2012) *Environmental Health Perspectives* 120:997-1002.

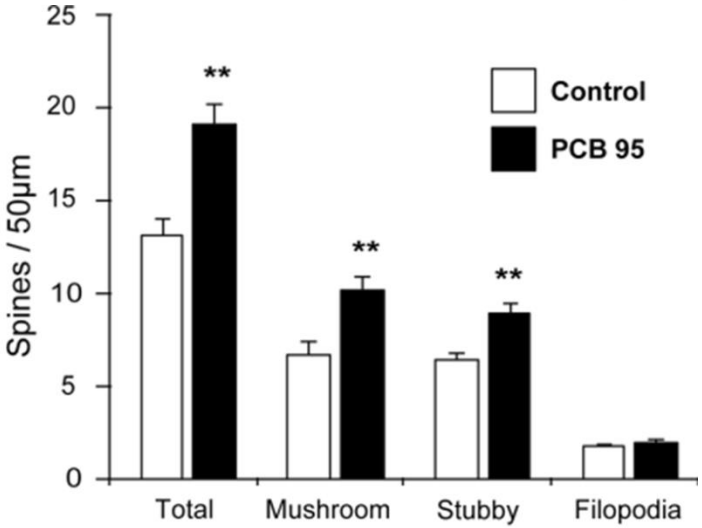
PCB 95 alters dendritic growth in primary cultures of hippocampal neurons





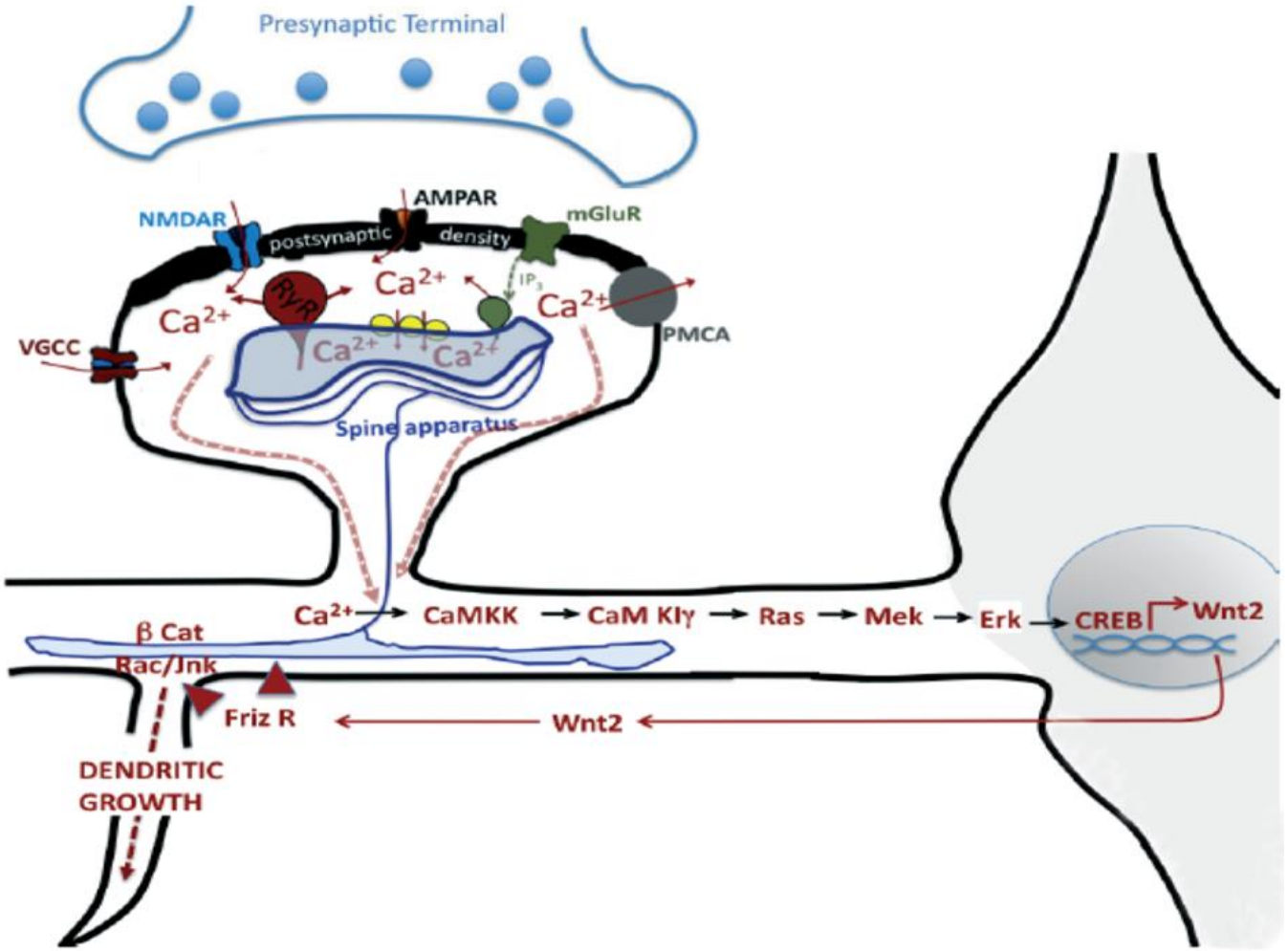






Wayman et al. (2012) *Environmental Health Perspectives* 120:997-1002.

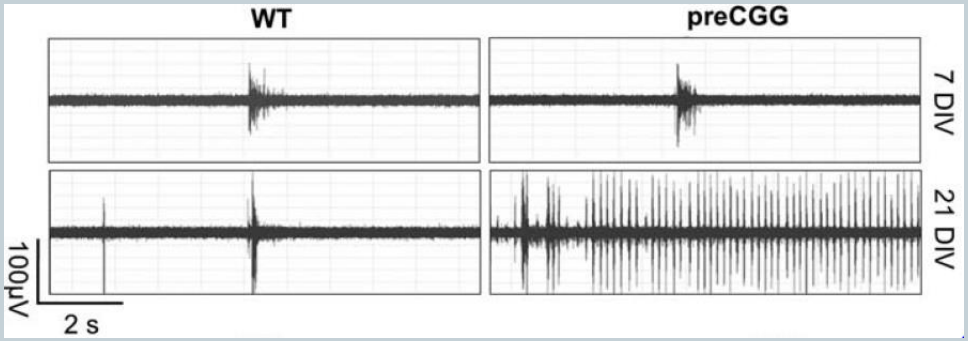
NDL PCBs alter dendritic growth by modulating the Ca^{2+}-CaMK-CREB-Wnt2 signaling pathway



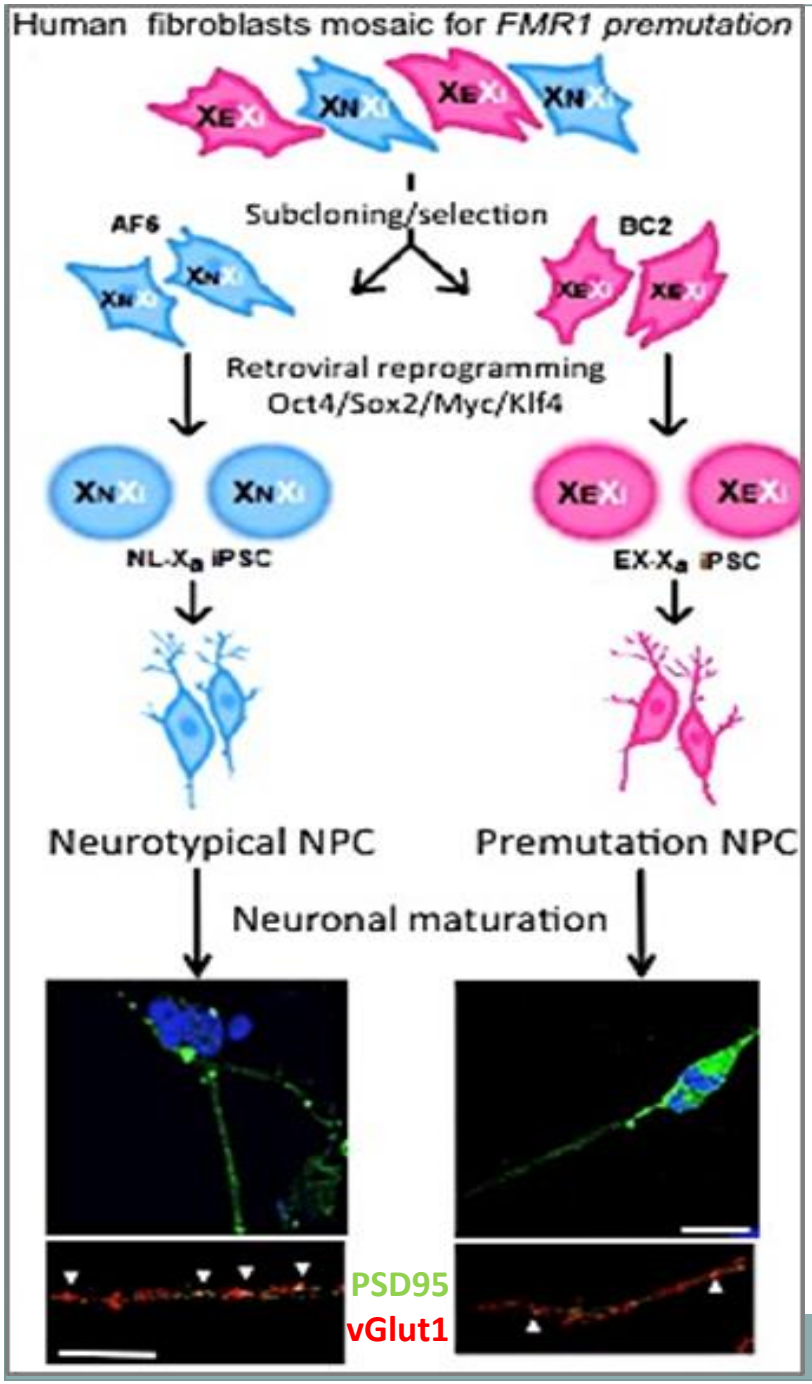
Wayman et al. (2012) *Environmental Health Perspectives* 120:1003-1009.

Why focus on FMR1 premutation?

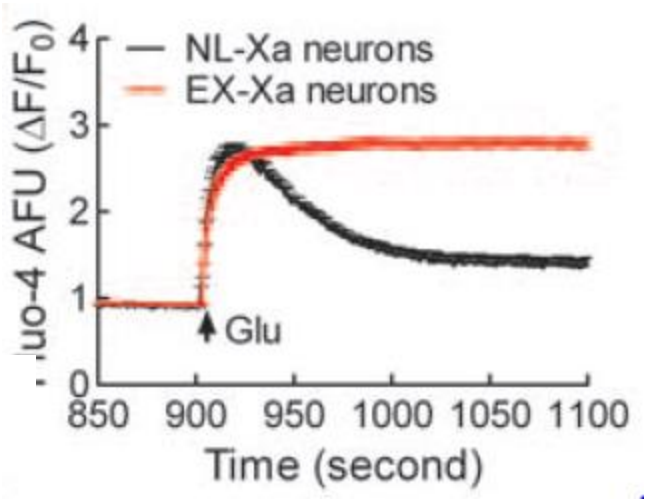
- **CGG trinucleotide repeats (expansion mutations) in the FMR1 gene are the most prevalent single gene disorder associated with ASD**
  - CGG-repeat expansions within the 5' non-coding portion of FMR1 in the premutation range (55-200 CGG repeats) give rise to fragile X-associated tremor/ataxia syndrome (FXTAS) and increase the risk of NDD
  - FMR1 expansions >200 CGG repeats give rise to Fragile X syndrome
- **FMR1 premutation KI mouse model identified impairments in neurodevelopment long before neuropathology evident***
  - Altered neuronal migration
  - Altered dendritic arborization
  - Aberrant Ca^{2+} oscillations
  - Altered electrical activity

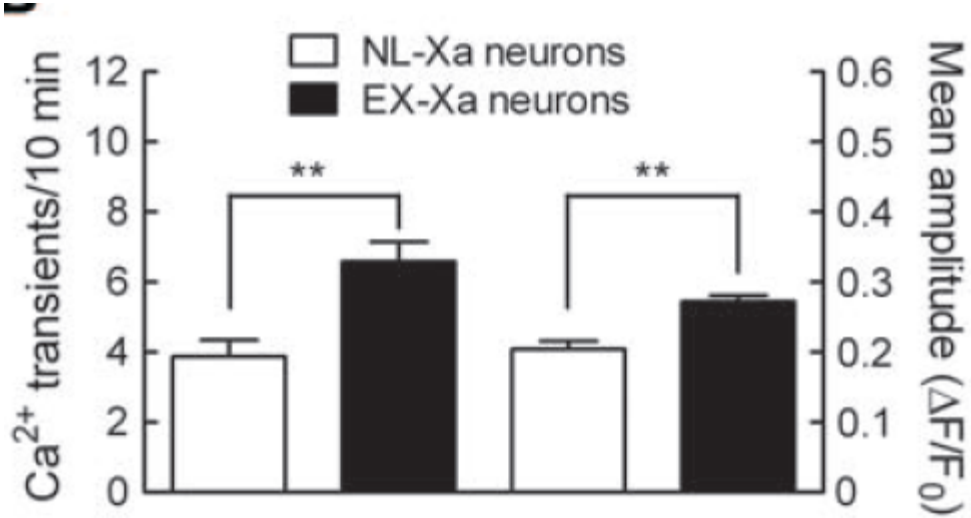


Cao et al. 2012 Hum Mol Genet 21:2923-35.



Human iPSC-derived neurons with NDD relevant genotypes





Acknowledgements

Collaborators

Isaac Pessah, University of California, Davis

Gary Wayman, Washington State University

Lein Laboratory

Christopher Barnhart

Donald Bruun

Hao Chen

Dongren Yang

Kim Keil

Funding Sources

NIEHS

USEPA

MIND Institute