Update: Center for Children’s Environmental Health and Disease Prevention

UNIVERSITY OF CALIFORNIA, DAVIS
UC Davis M.I.N.D. Institute
Isaac N. Pessah, Ph.D.
UC Davis Center for Children’s Environmental Health and Disease Prevention

Isaac N. Pessah, Ph.D. - Director
Irva Hertz-Picciotto, Ph.D. - Associate Director

- Established in 2001
- Competitive NIH/EPA Peer review
- Competitive renewal granted 2006

Funded by NIEHS P01ES011269 & EPA R833292/R829388
UC Davis M.I.N.D. Institute
Goal:

To advance scientific knowledge in the field of Autism

- evaluate environmental factors contributing to autism risk

- evaluate gene x environment factors contributing to autism susceptibility

- identify xenobiotic mechanisms of developmental neurotoxicity relevant to ASD
Integrated multidisciplinary approach

- **Epidemiology**  
  (Project 1/COTC: CHARGE, CHARGE-BACK, MARBLES)

- **Clinical and cellular immunology**  
  (Project 2: autoantibodies, cytokines, PBDEs)

- **Cellular & mechanism ➔ mouse models**  
  (Project 3: autoantibodies, mercury, PCBs, PBDEs)

- **Analytical chemistry**  
  (Core 3: Mercury, PBDEs, pesticides, oxylipids, vitamin D)

- **Molecular genomics**  
  (Core 4: transcription arrays, CNV, epigenetics)

- **Statistics Core**

- **Administrative Core**
EXTRAPOLATION OF EXPOSURE RISK

RISK ASSESSMENT
(susceptible groups)
(÷ 10)

EPIDEMIOLOGY
(human populations)

IN VITRO
(molecules)

IN VIVO
(animal models)

Identify associations
Chemical exposures vs. Health Outcome

High throughput screening
Mechanism of thimerosal immunotoxicity

Project 3; Core 4

*Environmental Health Perspectives* 114(7), 1083-91 (2006)

**Uncoupling of ATP-Mediated Ca$^{2+}$ Signaling and Dysregulated IL-6 Secretion in Dendritic Cells by Nanomolar Thimerosal**

Samuel Goth, Ruth Chu, Jeffery Gregg, Gennady Cherednichenko, Isaac N. Pessah

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Project 3

*Journal of Immunological Methods* 308, 179-191 (2006)

**Oxygen tension regulates the in vitro maturation of GM-CSF expanded murine bone marrow dendritic cells by modulating class II MHC expression**

Samuel Goth, Ruth Chu, Isaac N. Pessah
Low-Level Neonatal Thimerosal Exposure: Further Evaluation of Altered Neurotoxic Potential in SJL Mice

Robert F. Berman, Isaac N. Pessah, Peter R. Mouton, Deepak Mav, Jean Harry
Mercury and autism susceptibility

Projects 1,3; Cores 1,2,3

Environmental Health Perspectives 118(1), 161-166 (2010)

Blood Mercury Concentrations in CHARGE Study Children with and without Autism
Irva Hertz-Picciotto, Peter G. Green, Lora Delwiche, Robin Hansen, Cheryl Walker, Isaac N. Pessah

Projects 1,2,3; Cores 1,2,3,4

Neurotoxicology Research in press (2010)

Correlations of Gene Expression and Mercury Levels in Blood of Boys with Autism Compared to Typically Developing Controls
Boryana Stamova, Peter G Green, Yingfang Tian, Irva Hertz-Picciotto, Isaac N Pessah, Robin Hansen, Xiaowei Yang, Jennifer Teng, Jeffrey P Gregg, Paul Ashwood, Judy Van de Water, Frank R Sharp
Immunological Factors and Autism Risk

**Projects 1,2,3; Cores 1,2,4**  

**Altered gene expression and function of peripheral Blood natural killer cells in children with autism**

Amanda Enstrome, Lisa Lit, Charity Onore, Jeff Gregg, Robin Hansen, Isaac Pessah, Irva Hertz-Picciotto, Judy Van de Water, Frank Sharp, Paul Ashwood

**Projects 1,2,3; Cores 1,2**  
*NeuroToxicology* 118(1), 161-166 (2010)

**Autism: Maternally derived antibodies specific for fetal brain proteins**

Daniel Braunschweig, Paul Ashwood, Paula Krakowiak, Irva Hertz-Picciotto, Hansen, Lisa Croen, Isaac Pessah, Judy Van Judy Van de Water

**Autism: Maternal IgG from mothers at risk can affect brain development and produce behavioral syndrome in a mouse model (Projects 2,3; Cores 1,2,5)**
Non-dioxin-Like Compounds
Under the regulatory radar screen?

Dioxin
2,3,7,8-tetrachlorodibenzo-p-dioxin

Dioxin-like
Polychlorinated biphenyls

PCB 77
3,3’,4,4’-tetrachlorobiphenyl

PCB 126
3,3’,4,4’,5-pentachlorobiphenyl

Non-Dioxin-like
Polychlorinated biphenyls

PCB 95
2,2’,3,5’,6-pentachlorobiphenyl

PCB 153
2,2’,4,4’,5,5’-hexachlorobiphenyl
Project 3; Core 3


Excitatory and inhibitory synaptic transmission is differentially influenced by two ortho-substituted polychlorinated biphenyls in the hippocampal slice preparation

Kyung Ho Kim \(^a\), Salim Yalcin Inan \(^b,1\), Robert F. Berman \(^b\), Isaac N. Pessah \(^a,\ast\)

Project 3 and new investigator (Lein)

**Environmental Health Perspectives** 117(3):426-35 (2009)

Developmental Exposure to Polychlorinated Biphenyls Interferes with Experience-Dependent Dendritic Plasticity and Ryanodine Receptor Expression in Weanling Rats

Dongren Yang,\(^1\ast\) Kyung Ho Kim,\(^2\ast\) Andrew Phimister,\(^2\) Adam D. Bachstetter,\(^3\) Thomas R. Ward,\(^4\) Robert W. Stackman,\(^5\) Ronald F. Mervis,\(^3\) Amy B. Wisniewski,\(^6\) Sabra L. Klein,\(^7\) Prasada Rao S. Kodavanti,\(^4\) Kim A. Anderson,\(^8\) Gary Wayman,\(^9\) Isaac N. Pessah,\(^2\) and Pamela J. Lein\(^1,2,10\)
Common pesticide exposures could further influence already abnormal ratios of excitatory/inhibitory neurons and impact the networks they form.

Ca$^{2+}$: A Common Currency of Cell Signaling

All cells utilize spatially and temporally discrete changes in [Ca$^{2+}$]$_i$ to regulate ongoing functions:

- signal transduction
- metabolism
- gene transcription
- growth
- migration
- apoptosis

Pessah Lab, Unpublished
Nanomolar non-coplanar PCB 95 enhances hippocampal excitability *in vitro*

PCBs alters activity dependent dendritic growth

In vivo

• Do PCB-like effects extend to other nondioxin-like compounds of concern to human health?
Living in a Non-Planar World

Bisphenol-A

Triclosan

BDE-47
PBDEs and Autism susceptibility?


PBDEs in 2—5 Year-Old Children from California and Associations with Diet and Indoor Environment

MELISSA ROSE,†
DEBORAH H. BENNETT,†,*
ÅKE BERGMAN,§ BRITTA FÄNGSTRÖM,§
ISAAC N. PESSAH,‡ AND
IRVA HERTZ-PICCIOTTO†
PCBs, PBDEs and non-dioxin-like environmental contaminants

Role in autism risk?

Projects 2,3

Preliminary evidence of the in vitro effects of BDE-47 on innate immune responses in children with autism spectrum disorders

Paul Ashwood a,d,e, Joseph Schauer b,d,e, Isaac N. Pessah c,d,e, Judy Van de Water b,d,e,*
Impairments of mitochondrial bioenergetics in autism?

Scheme of the mitochondrial electron transport chain and its complexes