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NIEHS Investments in Autism Research

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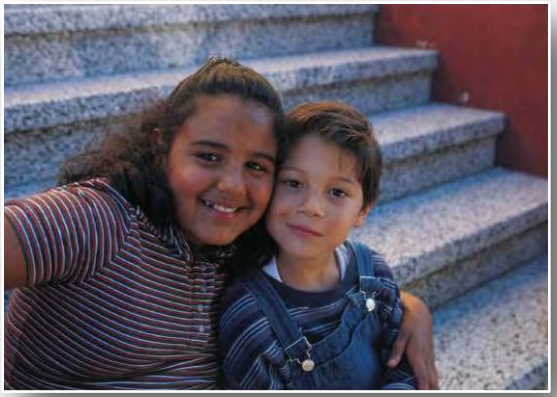

Interagency Autism Coordinating Committee
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Principles Guiding Investments

Autism has both an environmental and genetic component—understanding gene environment interplay is a priority

- Autism research is an integral part of a larger program that supports children's environmental health research
- A mix of research approaches are needed—from population-based studies to laboratory investigations of relevant cellular and molecular mechanisms
- Strong partnerships, with other federal entities and public stakeholders are essential to speed discovery and ensure rapid translation to public health
- Fundamental investments in exposure science and toxicology will benefit autism research

Children's Environmental Health and Disease Prevention Centers (NIEHS/EPA Partnership)

Program Description:

- Created to enhance communication, innovation and research excellence in Children's Environmental Health, using integrate multidisciplinary approaches
- UC Davis Children's Center is focused on autism etiology and supports research projects and service and facility Cores
  - Epidemiology of autism risk (Project 1)
  - Clinical and cellular immunology (Project 2)
  - Mouse Models (Project 3)
  - Analytical Chemistry, Molecular Genomics, Statistics Cores (Service Cores)
  - Community Outreach and Translation

CHARGE Epidemiology Study Design

- ***CH***ildhood ***A***utism ***R***isks from ***G***enetics and the ***E***nvironment
- Case control study with 3 groups: ASD; Developmental Delay (DD); children with Typical Development (TD), ages 24-60 months
- Goal: To identify causes and contributing risk & protective factors for childhood autism, understand etiologic heterogeneity
- Population based recruitment: 1300 families
- Clinical confirmation of diagnosis
- Extensive collection of environmental, medical, lifestyle, sociodemographic, & phenotypic information
- Linkage to state-of the art laboratories through Center Core resources

Recent study results from CHARGE

- Blood mercury (Hg) concentrations are similar for children with ASD vs. Typical Development (TD) (*Hertz-Picciotto et al. Env Health Persp 2009)*
- Gene expression differs in ASD vs. TD children, particularly in NK cells (*Gregg et al. Genomics 2008)*
- Epigenetic markers near Methyl-CpG-binding protein-2 (MECP2) promoter in ASD vs. TD children (*Nagarajan et al. Autism Res 2008)*
- Numerous immune markers distinguish children with ASD vs. TD
  - Maternal auto-antibodies to fetal brain (*Braunschweig et al. Neurotox 2008)*
  - Child's total IgG levels are reduced (*Heuer et al. Autism Res 2008)*
  - Child's IgG4 levels are increased (*Enstrom et al. Brain Behav Immun 2009)*
  - Child's TGF-beta levels are reduced (*Ashwood et al. J Neuroimmunol 2008)*
- Regression found to be as high as 44% when both language and social skills are taken into account (*Hansen et al. Ambul Ped 2008)*
- Sleep patterns differ for ASD vs. TD controls (*Krakowiak et al. J Sleep Res 2008)*
- Docosahexaenoic acid (DHA) is significantly lower in certain lipid subclasses among children with ASD as compared with TD controls (*Wiest et al. Prostaglandins, Leukot, Essent Fatty Acids 2009)*

EARLI: Early Autism Risk Longitudinal Investigation

- NIH Autism Centers of Excellence (ACE) Network R01
- Lead institute: NIEHS, cofunding by NIMH, NICHD, NINDS
- Four site study enrolling mothers with at least one child with autism who are planning to become pregnant or in the early stages of a subsequent pregnancy
- Enriched risk cohort design offers advantages for detecting autism risk and g x e interplay
- Prospective, real time data collection during critical periods of early development avoids disadvantages of retrospective methods of exposure assessment
- Enrollment began Spring 2009; enrollment target is 1200 mothers

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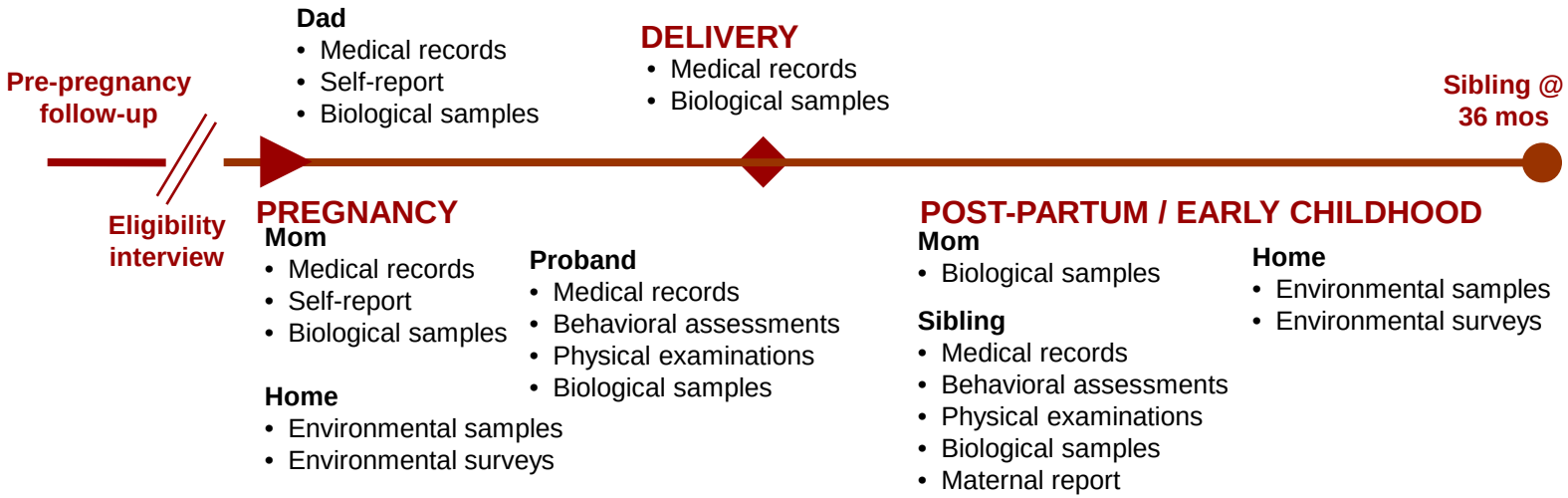
Data collection for an EARLI Study participant

- A wide array of data and biologic specimens are being collected throughout pregnancy and during the first three years of the new baby's life.
  - Mother—blood, hair, urine, saliva, placenta, cord blood, breast milk
  - Father—blood, semen
  - Baby—blood, hair, meconium, urine
  - Older sibling —blood



Hypotheses being pursued in EARLI Study

- The EARLI study is based on a ten year timetable
- A small number of 'exemplary aims' were chosen for the first five years of the project. These aims:
  - can be accomplished with small sample size and limited follow-up
  - are designed to demonstrate analytic feasibility
  - are focused on association between autism risk and maternal autoimmune biomarkers, prenatal environmental exposures, epigenetic vulnerability, and gene-environment interaction
- EARLI infrastructure and data collected under the auspices of Autism Center of Excellence (ACE) funding will provide ample opportunities for ancillary studies and pursuit of additional etiologic hypotheses
  - EARLI collaboration with Infant Brain Imaging Study (funded by Autism Speaks)
  - Environment, the Perinatal Epigenome and Risk for Autism and Related Disorders (Funded by NIEHS and NIH Epigenetics Roadmap)

American Recovery and Reinvestment Act (ARRA)

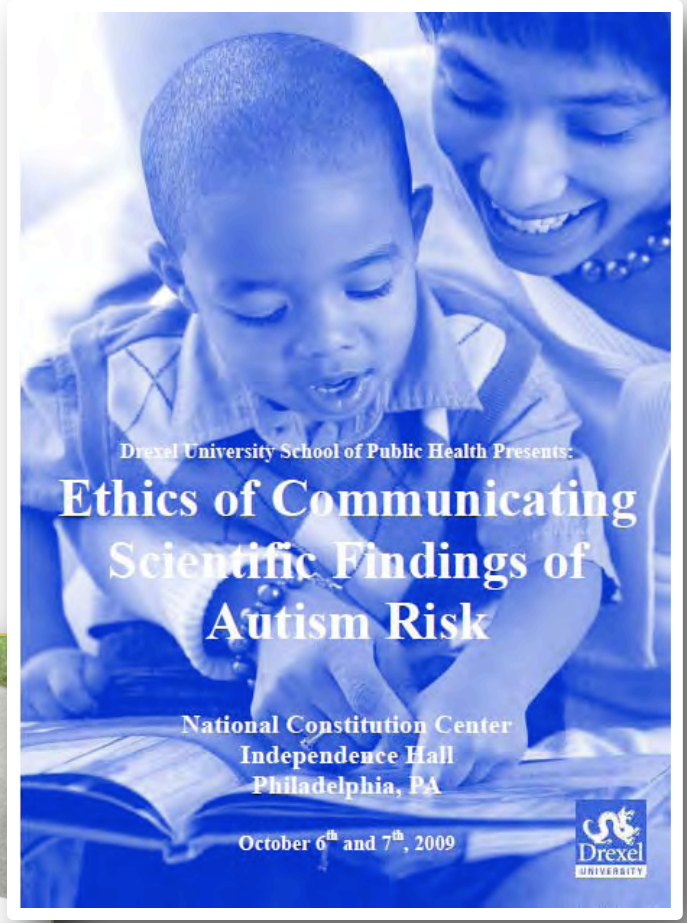
- Provided funding for four new NIEHS projects solicited through Heterogeneity of ASD initiatives
- These projects expand the range of exposures being investigated for association with autism risk and leverage existing resources being supported through other agencies
  - Genome-wide Environment Interaction Study for Autism: The Study to Explore Early Development (SEED) study
    Danielle Fallin, Johns Hopkins University
  - Prenatal Exposure to Polyfluoroalkyl Compounds in the Early Markers of Autism (EMA) Study
    Lisa Croen, Kasier Permanente Northern California
  - Investigating Gene-Environment Interaction in Autism: Air Pollution
    Rob McConnell, University of Southern California
  - Prenatal factors and risk of autism in a Finnish national birth cohort
    Alan Brown, Columbia University

American Recovery and Reinvestment Act (ARRA)

- NIEHS ARRA funding provided supplements to existing grants to:
  - Hire additional outreach coordinators for EARLI study to speed pace of enrollment
  - Support hiring of new personnel to speed analysis and dissemination of findings from CHARGE study
  - Support home visits for dust collection to measure additional environmental exposures in CHARGE study

Partnerships in Environmental Public Health

- Supplemental funding provided to UC-Davis Children's Center to facilitate interaction with diverse communities and support dissemination of findings in English and Spanish
- Support for Autism Risk Communication conference to bring together stakeholders (including parents, educators, community clinicians, scientists, media, policy-makers) all concerned with ethical issues surrounding how information on autism risk factors is communicated



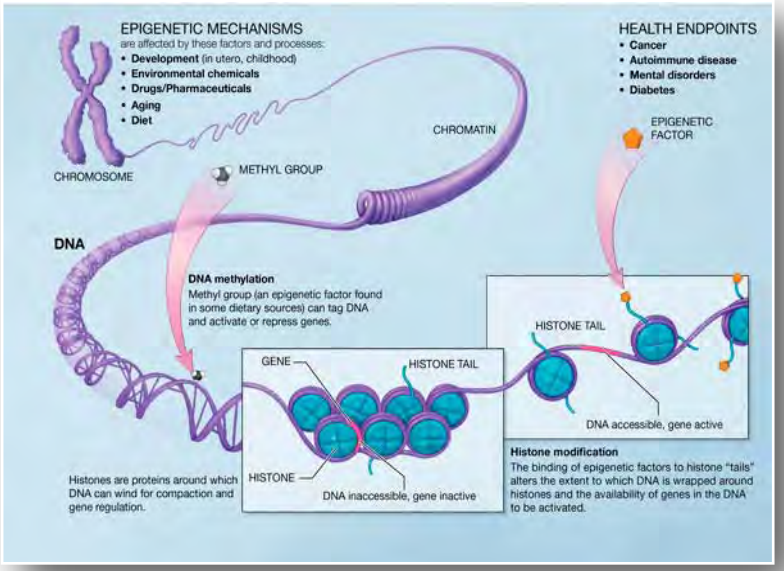
Epigenetics/Epigenomics Programs

Environmental Epigenetics Program: To examine the impact of gene-environment interactions on diseases by studying alterations in gene expression as influenced by environmental exposures

- Epigenetic Interaction of MECP2 and Organic Pollutants in Neurodevelopment
  Janine LaSalle, UC-Davis

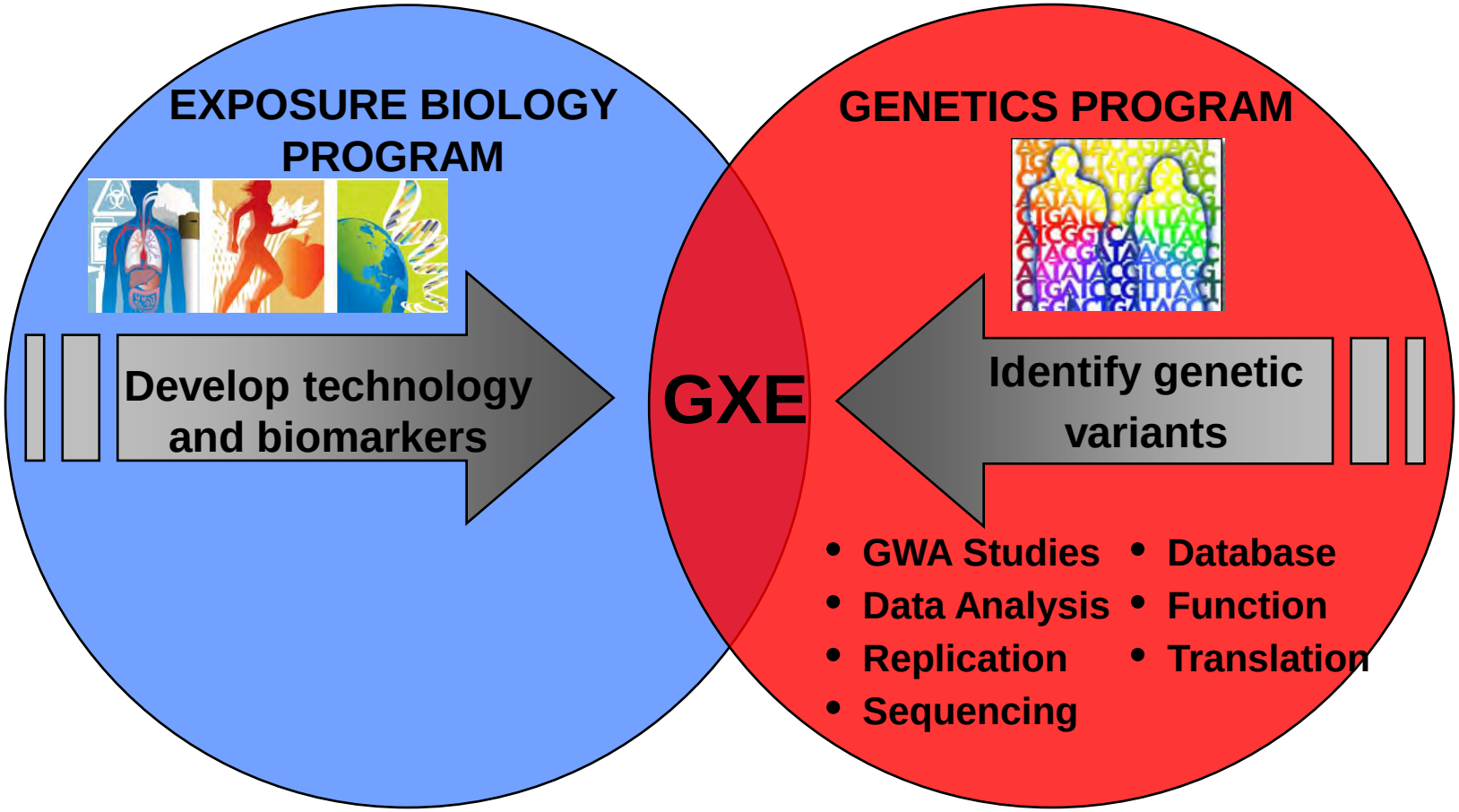
Epigenetics Roadmap Program: NIEHS co-leads trans-NIH Roadmap efforts in epigenomics to understand the importance of epigenetic marks and how environmental exposures may alter them

- Environment, the Perinatal Epigenome and Risk for Autism and Related Disorders
  Danielle Fallin/Andy Feinberg, Johns Hopkins University



Genes Environment and Health Initiative

- Will provide new tools for autism researchers to measure exposures and identify interactions of exposures with genetic variation

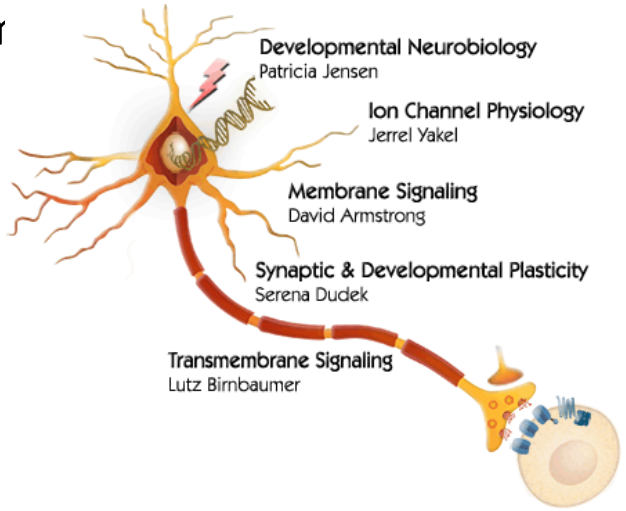


NIEHS Intramural Research in Neurobiology

- The Laboratory of Neurobiology (LN) investigates the cellular and molecular processes in the developing and aging nervous system that increase its vulnerability to environmental toxicants
- The Synaptic and Developmental Plasticity Group, led by intramural investigator Serena Dudek, studies the regulation of synaptic effectiveness and how synaptic changes early in development are consolidated to last a lifetime
- These studies can help inform ideas about the role of brain connectivity and synaptic development and plasticity in autism

Major areas of research in Synaptic and Developmental Plasticity Group:

- Transcriptional regulation by neuronal activity to consolidate synaptic plasticity
- Synapse elimination during brain development
- Critical periods of synaptic plasticity during development



NIEHS Intramural Epidemiology Research

- The Epidemiology Branch investigators study a wide range of health effects linked to environmental exposures
- The Pediatric Epidemiology Group, led by Walter Rogan, studies the effects of environmental chemicals on childhood growth/development
- The Biomarker-based Epidemiology Group, led by Matt Longnecker, is focused on health effects of early exposure to background levels of environmental contaminants
  - NIEHS is supporting the collection of additional biologic specimens from pregnant women in the Norwegian Mother & Child study (MoBa) , an ongoing long–term prospective cohort study of 100,000 pregnant women and their babies
    - These samples can be used for investigation of autism gene environment interplay in the Autism Birth Cohort (ABC) study nested within MoBa (funded by NINDS)

- Toxicity testing has relied traditionally on cancer endpoints
- Increased interest in neurodevelopmental outcomes
- NTP is currently exploring an Integrated Testing Protocol for Examining the Effects of Developmental Exposure on the Nervous, Reproductive, and Immune Systems which includes:
  - Expansion of Nervous System Endpoints to assess Sensory, Motor, and Cognitive Endpoints

Summary

- NIEHS funding for autism research has grown considerably over the past 10 years
- NIEHS investment in autism research in fiscal year 2009 was approximately 9.3 million dollars (including 4.9 million dollars in ARRA funding)
- NIEHS supported studies span from human epidemiology to mechanistic laboratory investigations
- Infrastructure for large scale human studies (CHARGE, EARLI) is in place to enable identification of environmental risk factors and gene environment interplay
- Biologic markers for subtypes of autism with possible etiologic relevance (e.g., immune alterations) have been identified
- NIEHS support for basic research in neurotoxicology and exposure science will be essential for understanding and informing human studies in autism

Future NIEHS autism activities will emphasize:
opportunities identified in IACC Strategic Plan
coordination with other federal agencies
meaningful involvement of affected communities
translation of findings to public health & prevention

Thanks

NIEHS Intramural Scientists & Extramural Staff

- David Armstrong
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- Matt Longnecker

NIEHS Extramural Investigators

- Alan Brown (Columbia)
- Lisa Croen (Kaiser Permanente)
- Danielle Fallin (Johns Hopkins)
- Irva Hertz-Picciotto (UC Davis)
- Rob McConnell (USC)
- Rebecca Morrison (UC-Davis)
- Craig Newschaffer (Drexel)
- Isaac Pessah (UC Davis)