



National Institute of Environmental Health Sciences
Your Environment. Your Health.

Autoimmune Research Supported by the Division of Extramural Research and Training, NIEHS

NASEM

Committee for the Assessment of NIH
Research on Autoimmune Diseases

March 4, 2021

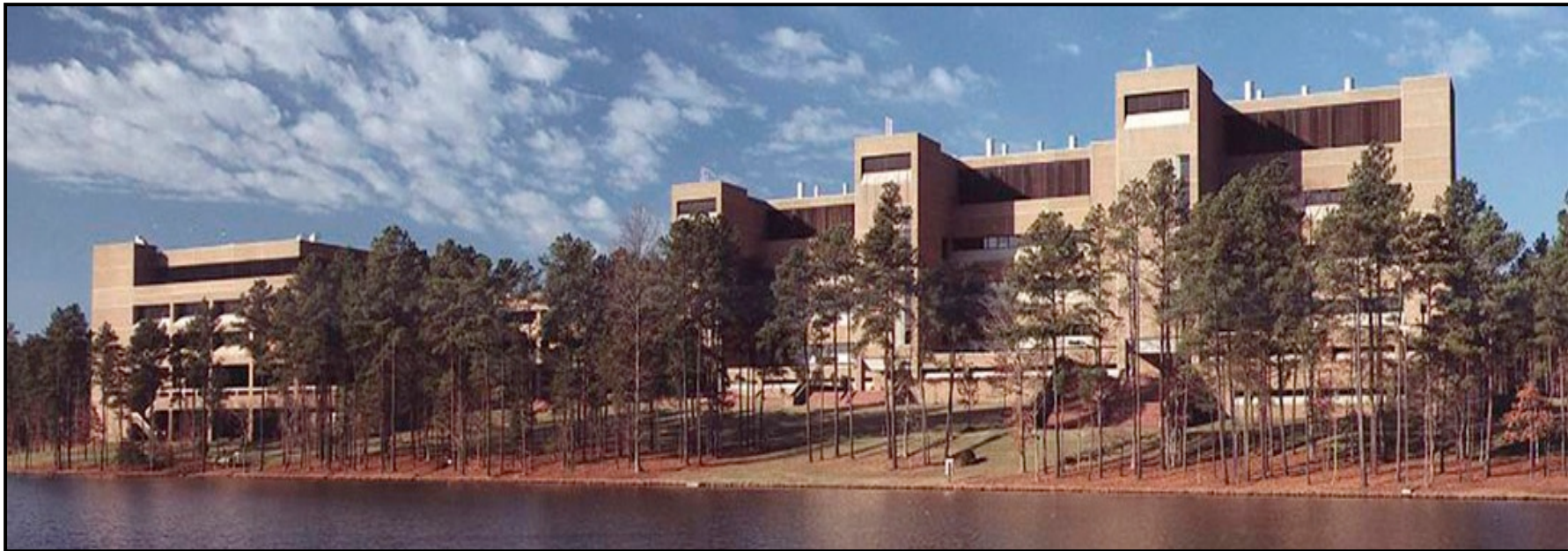
Dr. Michael Humble

Program Administrator

Genes Environment and Health Branch,
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
National Institutes of Health

The National Institute of Environmental Health Sciences

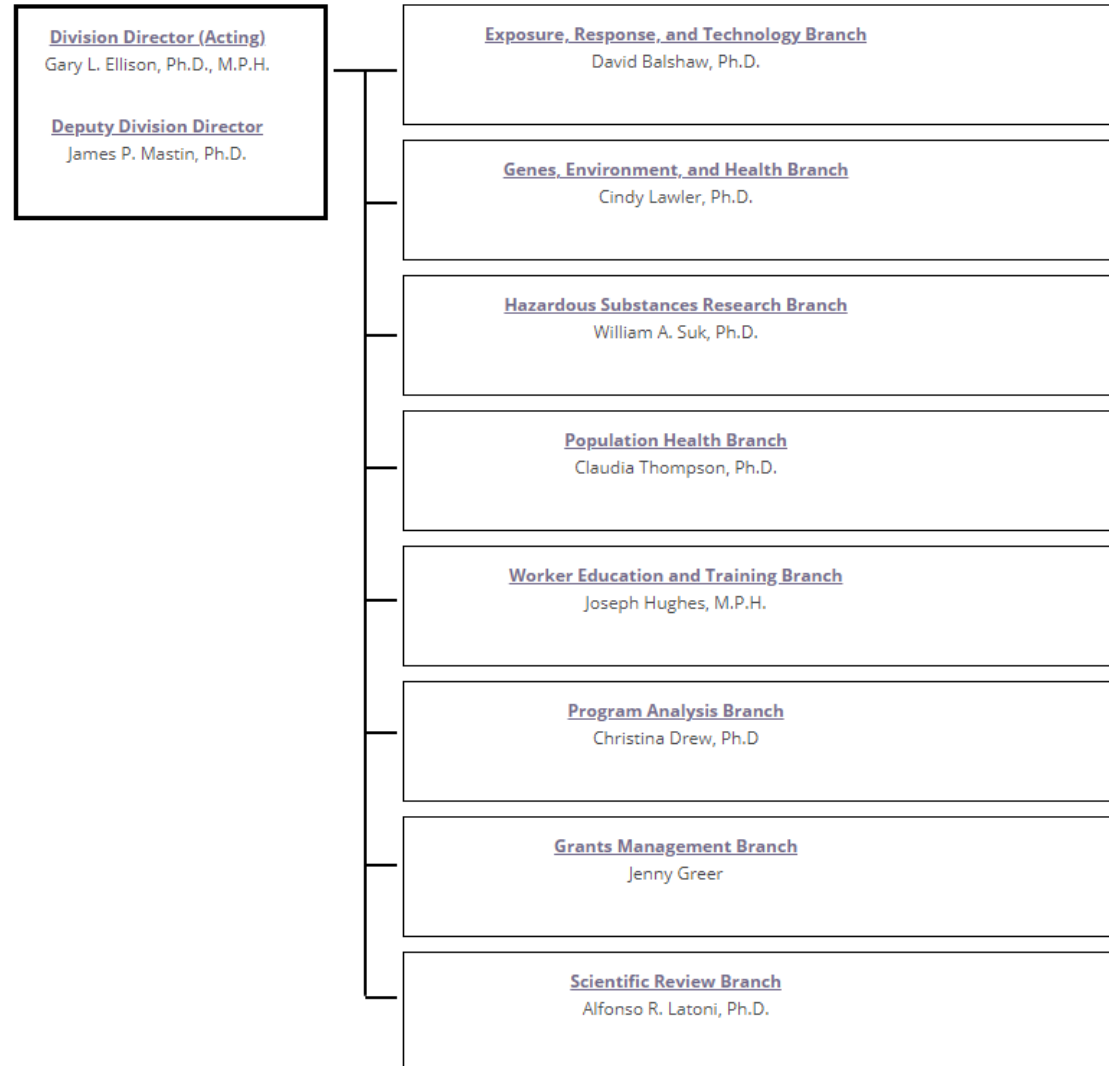
- Our **mission** is to discover how the environment affects people in order to promote healthier lives.



NIEHS Division of Extramural Research and Training (DERT)

- The Division of Extramural Research and Training plans, directs and evaluates the institute's grant program which supports research and research training in environmental health.
- It develops program priorities and recommends funding levels to assure maximum utilization of available resources in attainment of institute objectives.

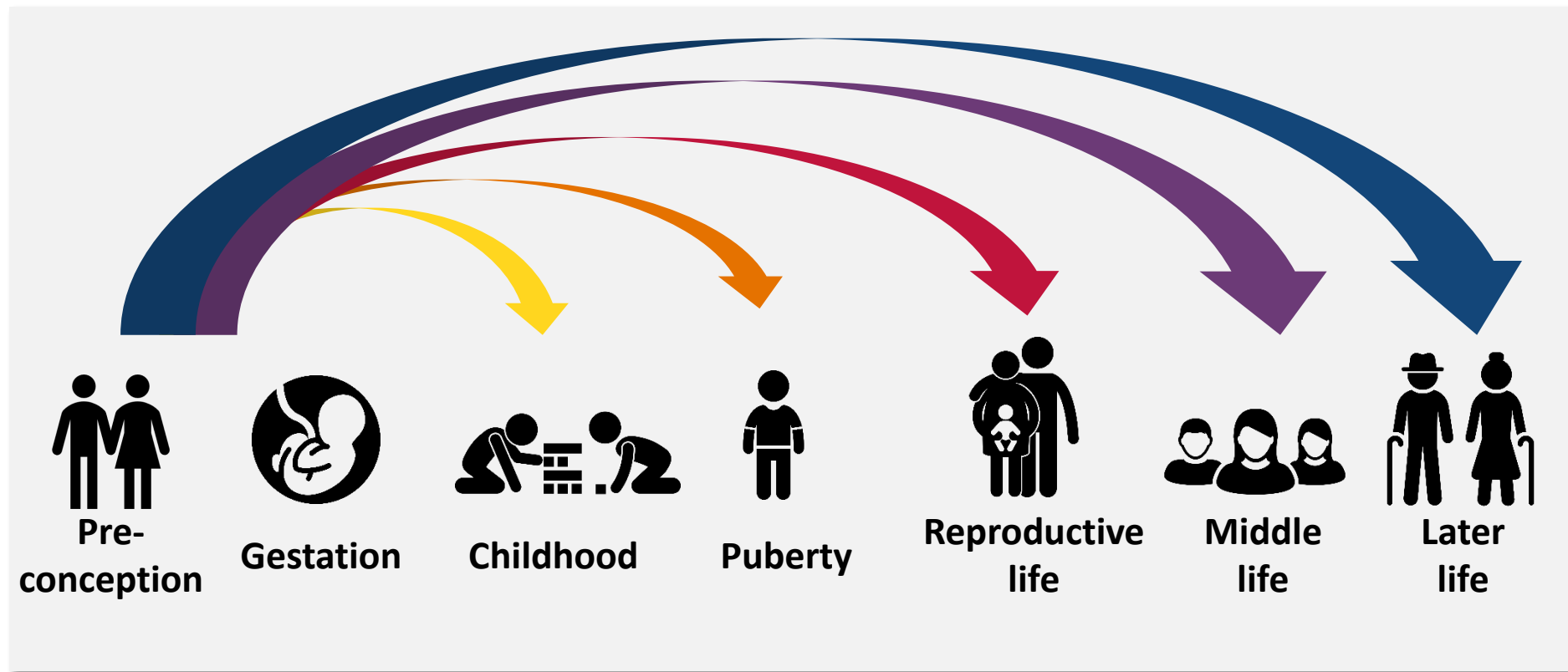
<https://www.niehs.nih.gov/research/supported/dert/index.cfm>



What is Our “Environment?”



Exposures Across the Lifespan Impact Life-long Health



Who We Fund: The NIEHS Extramural Research Portfolio

Basic Cellular And Molecular Research	Grants *
Basic Cellular or Molecular processes	9
Carcinogenesis	22
Cell Transformation	
Circadian Rhythms	4
Epigenetics	64
Gene Polymorphism	1
Genome Integrity	79
Human Genetics	14
Gene X Environment Interaction	
Metabolism	9
Signal Transduction	22
Stem Cell Biology and Cellular Differentiation	7
Structure-Function	1
Superfund Basic Research (non- P42 center grants)	34

Exposure Research	Grants *
Counter-Terrorism	14
Exposure Assessment	31
Exposome	
Fracking	4
Mixtures	19
Nanotoxicology	27

Center And Center-Like Programs	Grants *
Breast Cancer Centers	7
Children's Centers	9
Environmental Health Sciences Centers	26
Oceans and Human Health	17
Superfund Research Program Centers	27

Application Of Technology To Disease	Grants *
Alternative Model Development	3
Bioinformatics	3
BISTI Related	
Biosensors	19
Biomarkers	
Computational Biology	12
Computational Methods for Exposure Assessment	
Imaging	2
Metabolomics Technology	7
Predictive Toxicology	24
Assay Development	
Small Business (SBIR, STTR)	100
Statistics	11
Statistical Methods	
Development	
Systems Biology	1
Tissue Engineering	17
Toxicogenomics Technology	1

Translational Research	Grants *
Communication Research	13
Environmental Health Literacy	
Cookstoves Research - technology and health effects	6
Environmental Justice	16
Environmental Health Disparities	
Ethical Legal and Social Implications of Research	1
Global Health	9
Climate Change	
Partnerships for Environmental Public Health	16
Community Research	
Social Environment	5
Built Environment	

Organ Systems Or Disease Processes Research	Grants *
Aging	1
Autoimmunity	13
Bone and Cartilage	3
Cardiovascular System	32
Circulatory	2
Blood (Bone Marrow)	
Developmental Biology	35
Teratogenesis	
Developmental Origins of Health and Disease	3
Diabetes	16
Metabolic Syndrome	
Endocrine System	13
Female Reproduction	23
Immunology	15
Immunotoxicology	
Kidney and Bladder	14
Liver	9
Male Reproduction	11
Microbiome	22
Mitochondrial Disorders	18
Nervous System Research	15
Neurodegenerative	53
Neurodevelopmental	83
Obesity	12
Puberty	1
Reproductive System - non-gender specific	2
Respiratory	89
Skin	17

Training And Career Development	Grants *
AREA (Secondary only)	31
Institutional Training	67
Institutional Career Development Grants	
ONES (Secondary only)	32
Worker Education (U45)	34

<https://tools.niehs.nih.gov/portfolio/index.cfm/portfolio/topic>

Autoimmune Disease and Immunotoxicology

There is growing evidence for an environmental component in the development of autoimmunity and autoimmune diseases.

NIEHS-funded researchers examine the role environmental exposures play in the development and progression of autoimmune diseases, and the biological mechanisms involved.



Mike Humble, PhD
Program Administrator
Genes, Environment and Health Branch



Bonnie Joubert, PhD
Program Administrator
Population Health Branch

Who We Fund: Autoimmunity

Exposures: mercury, silica,
TCE, virus (as a co-exposure)

Targets: B cells, T cells,
macrophage, AhR, ER

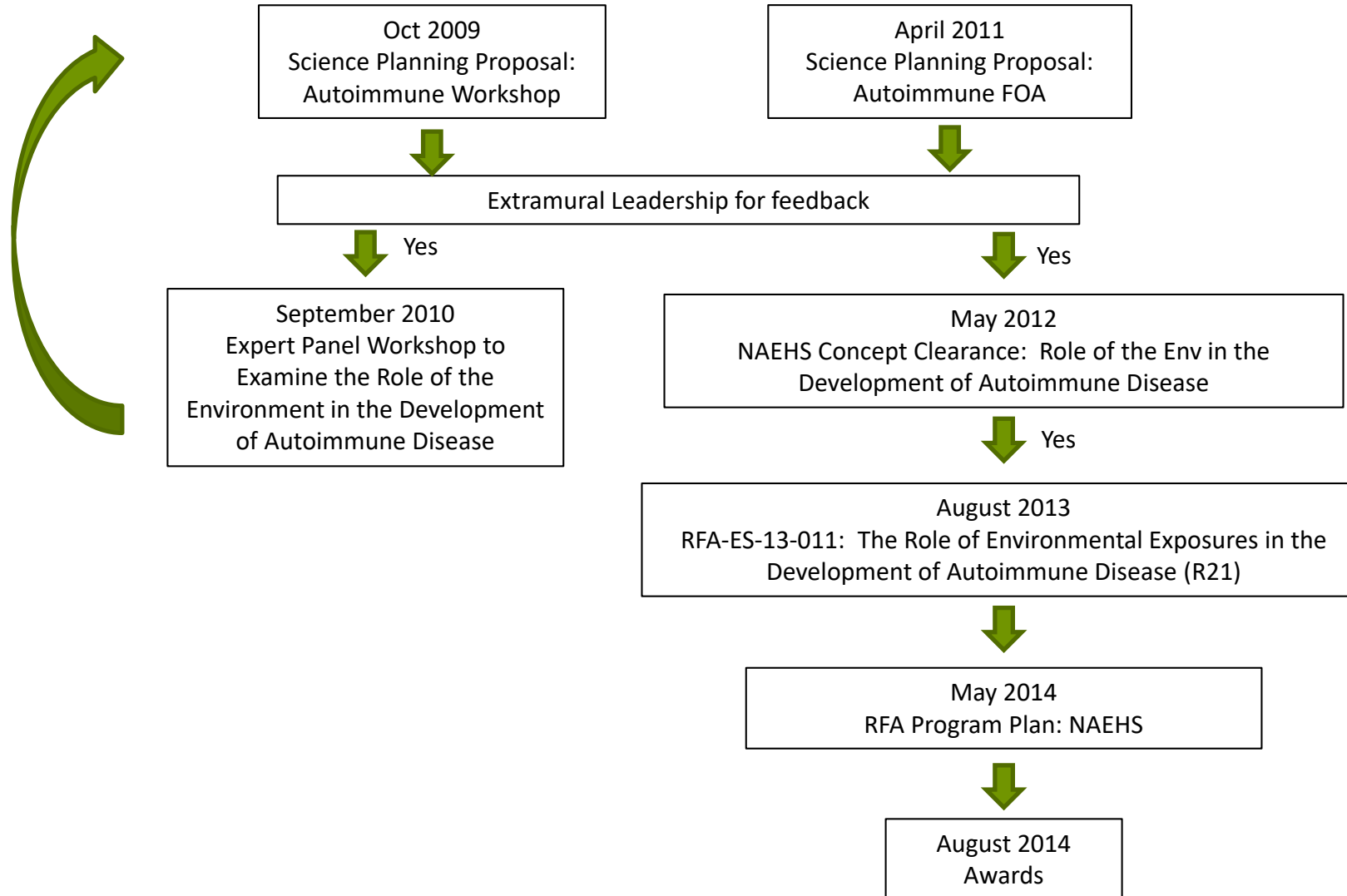
Disease Endpoints: MS, SLE,
autoimmune hepatitis,
systemic autoimmunity,
interventions

Applications are:

- Investigator Initiated
- Solicited

Title	Principal Investigator	Institution	Grant Number
AHR AND REGULATORY T CELLS	Mckarns, Susan C	University Of Missouri-Columbia	R01ES022966
DIETARY LIPIDS AND SILICA-TRIGGERED AUTOIMMUNITY.	Pestka, James J	Michigan State University	R01ES027353
DO XENOBIOTICS EXACERBATE IDIOPATHIC AUTOIMMUNITY?	Pollard, Kenneth Michael	Scripps Research Institute	R21ES029263
GENE-ENVIRONMENT COLLABORATION IN AUTOIMMUNE DISEASE	Foster, Mary H.	Duke University	R01ES027873
MODELING XENOBIOTIC-INDUCED AUTOIMMUNITY USING COLLABORATIVE CROSS STRAINS.	Pollard, Kenneth Michael	Scripps Research Institute	R21ES031454
MOLECULAR AND CLINICAL ENDOCRINE IMPACTS OF ARSENIC EXPOSURE IN CHILDREN	Argos, Maria	University Of Illinois At Chicago	R01ES024423
OMEGA-3 FATTY ACID SUPPRESSION OF SILICA-INDUCED INFLAMMASOME ACTIVATION IN A NOVEL ALVEOLAR MACROPHAGE MODEL	Wierenga, Kathryn Alexandria	Michigan State University	F31ES030593
OXIDATIVE STRESS AND AUTOIMMUNITY	Khan, M. Firoze	University Of Texas Med Br Galveston	R01ES016302
SYNERGISTIC EFFECTS OF SILICA EXPOSURE, VIRUS INFECTION AND GENETIC PREDISPOSITION IN SYSTEMIC AUTOIMMUNITY	Baccala, Roberto G	Scripps Research Institute	R01ES031082
THE EFFECT OF AGE ON XENOBIOTIC-INDUCED AUTOIMMUNITY	Pollard, Kenneth Michael	Scripps Research Institute	UH3ES027679
THE GENETICS OF SILICA-INDUCED AUTOIMMUNITY	Pollard, Kenneth Michael	Scripps Research Institute	R01ES029581
TRICHLOROETHENE EXPOSURE AND AUTOIMMUNE HEPATITIS	Khan, M. Firoze	University Of Texas Med Br Galveston	R01ES026887
UNDERSTANDING THE CONNECTION BETWEEN EXPOSURE TO MERCURY, AUTO-IMMUNITY AND TOLERANCE IN B CELLS.	Rosenspire, Allen J	Wayne State University	R01ES029484

Developing Extramural FOAs: Autoimmune RFA-ES-13-011



Expert Panel Workshop to Examine the Role of the Environment in the Development of Autoimmune Disease

Sept 2010

With support from the American Autoimmune Related Diseases Association, Inc. (AARDA)

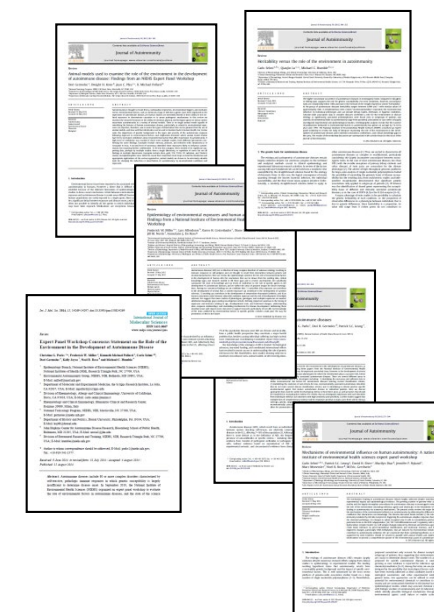
The goal of the workshop was to bring together experts from the environmental health science and autoimmune research communities to:

- review the findings from their diverse research disciplines concerning the role of the environment and the development of autoimmune disease
- identify conclusions that can be drawn with confidence from existing data:
 - “Based on existing evidence we are confident of the following....”
 - “We consider the following to be likely but require confirmation....”
- identify knowledge gaps and areas of uncertainty

Expert Panel Workshop to Examine the Role of the Environment in the Development of Autoimmune Disease

Autoimmune Expert Panel Workshop Publications:

- Selmi C, Lu Q, Humble MC. Heritability versus the role of the environment in autoimmunity.. J Autoimmun. 2012 Dec;39(4):249-52.
- Miller FW, Pollard KM, Parks CG, Germolec DR, Leung PS, Selmi C, Humble MC, Rose NR Criteria for environmentally associated autoimmune diseases. . J Autoimmun. 2012 Dec;39(4):253-8
- Miller FW, Alfredsson L, Costenbader KH, Kamen DL, Nelson LM, Norris JM, De Roos AJ. Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. J Autoimmun. 2012 Dec;39(4):259-71.
- Selmi C, Leung PS, Sherr DH, Diaz M, Nyland JF, Monestier M, Rose NR, Gershwin ME. Mechanisms of environmental influence on human autoimmunity: a National Institute of Environmental Health Sciences expert panel workshop. J Autoimmun. 2012 Dec;39(4):272-84.
- Germolec D, Kono DH, Pfau JC, Pollard KM. Animal models used to examine the role of the environment in the development of autoimmune disease: findings from an NIEHS Expert Panel Workshop. J Autoimmun. 2012 Dec;39(4):285-93
- Parks CG, Miller FW, Pollard KM, Selmi C, Germolec D, Joyce K, Rose NR, Humble MC. Expert panel workshop consensus statement on the role of the environment in the development of autoimmune disease. Int J Mol Sci. 2014 Aug 15;15(8):14269-97.



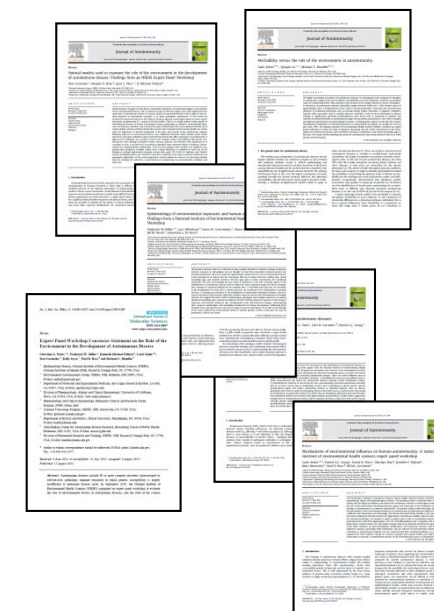
Expert Panel Workshop to Examine the Role of the Environment in the Development of Autoimmune Disease

Based on existing evidence we are confident of the following....

- Epi: Crystalline silica exposure contributes to development of RA, SScl, SLE and ANCA-related diseases including vasculitis and glomerulonephritis
- Epi: Solvent exposure contributes to development of SScl
- Animals: Autoimmune responses to chemical factors are influenced by species and strain of animal selected for study
- Animals: Forms of inorganic mercury (HgCl_2 , vapor, amalgam) induce systemic autoimmune disease in rats (transient) and mice
- Animals: The mineral oil component 2,6,10,14-tetramethylpentadecane (TMPD or pristane) can induce chronic lupus-like disease and inflammatory arthritis in several strains of mice

We consider the following to be likely but require confirmation....

- Epi: Solvent exposure contributes to development of MS
- Animals: There is some indication that TCDD can promote autoimmunity when exposure occurs during fetal or early neonatal development
- Animals: Organochlorine pesticides have been reported to enhance lupus-like disease in a predisposed mouse strain



RFA-ES13-011: The Role of Environmental Exposures in the Development of Autoimmune Disease (R21)

Purpose:

- The funding announcement encouraged exploratory research applications aimed at investigating the role environmental exposures play in the development and/or the exacerbation of autoimmune disease.
- Applicants could propose to use *in vitro* studies or animal models to explore possible mechanisms in which environmental exposures associated with human autoimmune endpoints are involved in the induction of an autoimmune response or an autoimmune disease.
- Of particular interest were:
 - projects that could identify and characterize critical windows of exposure susceptibility
 - projects that explore mechanisms responsible for sex differences
 - studies that could produce potential biomarkers for use in subsequent human studies.
- NIEHS committed \$2.4 million to fund 10 awards

Awarded Applications

Exposures: bisphenol A,
genistein, mercury,
silica, PCB, TCDD, TCE,
UV, along with
microbiome

Disease Endpoints:
Lupus, myocarditis, RA,
type 1 diabetes, hepatic
autoimmunity

Project	PI Name(s) All	Title	Institution
R21ES024437-01	ELKON, KEITH B	Mechanisms of Ultraviolet Inflammation in Lupus	UNIVERSITY OF WASHINGTON
R21ES024414-01	FAIRWEATHER, DELISA	Endocrine disruptors effect on inflammatory heart disease	JOHNS HOPKINS UNIVERSITY
R21ES024451-01	FOSTER, MARY H	Mechanism of Silica-induced Autoimmunity	DUKE UNIVERSITY
R21ES024487-01	GUO, TAI L	Exacerbation of type 1 diabetes in mice by bisphenol A and genistein	UNIVERSITY OF GEORGIA
R21ES024428-01	HOLOSHITZ, JOSEPH	A novel mechanism of gene-environment interaction in autoimmune arthritis	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R21ES024470-01	LUYENDYK, JAMES P	Mechanisms of fibrosis exacerbation by trichloroethylene in hepatic autoimmunity	MICHIGAN STATE UNIVERSITY
R21ES024485-01	POLLARD, KENNETH MICHAEL	The Diversity Outbred Mouse as a Model of Silica-induced Autoimmunity	SCRIPPS RESEARCH INSTITUTE
R21ES024476-01	ROSENSPIRE, ALLEN J	The Role of Mercury Exposures in Disrupting Central Tolerance	WAYNE STATE UNIVERSITY
R21ES024425-01	SANCAR, AZIZ	UV Light and Autoimmunity: A Role for Small Excised DNA Oligonucleotides	UNIV OF NORTH CAROLINA CHAPEL HILL
R21ES024413-01	STOLL, MATTHEW L; WEAVER, CASEY T	Interactions between AHR ligands and the gut microbiota in murine arthritis	UNIVERSITY OF ALABAMA AT BIRMINGHAM



NIEHS Extramural Activities in Autoimmune Disease

- 1998: NIH Autoimmune Diseases Coordinating Committee (ADCC)
- 1999: RFA ES-99-003: Environment/Infection/Gene Interactions in Autoimmune Disease
(Participants: NIAID, NIDDK, NIAMS, NICHD, NIDCD, NEI, NHLBI, NINDS, NIMH, NIDCR, ORWH)
- 2003: NIEHS Workshop “Environmental Factors in Autoimmune Disease”
(cosponsored by ORD, ORWH, NIAID, NIAMS, NEERL/EPA, and the AARDA)
- 2005: NIEHS “Workshop on Lupus & the Environment: Disease Development, Progression and Flares,”
(cosponsored by DHHS OWH)
- 2010: NIEHS Expert Panel Workshop to Examine the Role of the Environment in the Development of Autoimmune Disease
(with support from the AARDA)
- 2012: AAI Symposium: The Role of Environmental Exposures in the Development of Autoimmune Disease
- 2012: NIEHS Strategic Plan Trans-Divisional Inflammation Faculty (with a subcommittee on autoimmunity)
- 2013: RFA-ES-13-011: The Role of Environmental Exposures in the Development of Autoimmune Disease (R21)
- 2016: AAI Symposium: Environmental Triggers of Autoimmunity
- 2017: AAI Symposium: B Cell Responses to Environmental Exposures

Going Forward: Gaps and Recommendations

- Epidemiological studies linking specific exposures to autoimmunity and [specific] autoimmune disease
 - Mixtures/multiple exposures
- Multisite collaborations with standardized protocols for collection of environmental exposure data, establishing a nationwide surveillance network and population-based registries for autoimmune diseases
- Support basic and clinical research on mechanistic relationships between environmental factors and autoimmunity (genetic polymorphisms, gender, hormones, animal models)
- Facilitate interactions between specialties and the use of multidisciplinary approaches to improve overall knowledge of the mechanism of action and human health consequences associated with environmental agents and autoimmune disease
- Defining critical windows in the timing of exposures and their health outcomes
- Develop useful biomarkers of effect linking environmental agents to autoimmune disease

Resources

- NIEHS <https://www.niehs.nih.gov/>
- 2018-2023 NIEHS Strategic Plan
<https://www.niehs.nih.gov/about/strategicplan/index.cfm>
- Division of Extramural Research and Training
<https://www.niehs.nih.gov/research/supported/index.cfm>
- Who We fund <https://tools.niehs.nih.gov/portfolio/>
- NIEHS DERT Autoimmune Disease and Immunotoxicology
<https://www.niehs.nih.gov/research/supported/health/autoimmune/index.cfm>



National Institute of Environmental Health Sciences
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Thank You!

Michael Humble, PhD

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