Framing Our Birth Defects Questions with Systems Biology: Learning from Our Mentors

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SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON

Disclosure

The authors of this research have no financial or other interests which pose a conflict of interest.

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Outline

- Summers in Seattle
- Role of environment in the etiology of birth defects (E)
- Role of Genetics and Environment (G x E)
- Role of Context both Risk Assessment and Systems Biology
- Unique aspects of our Societies and our Mentors

Dr. Josef Warkany

Founders in the late 1950s. Left to right: James Wilson, F. Clarke Fraser, and Josef Warkany.

University Center for Excellence in Developmental Disabilities

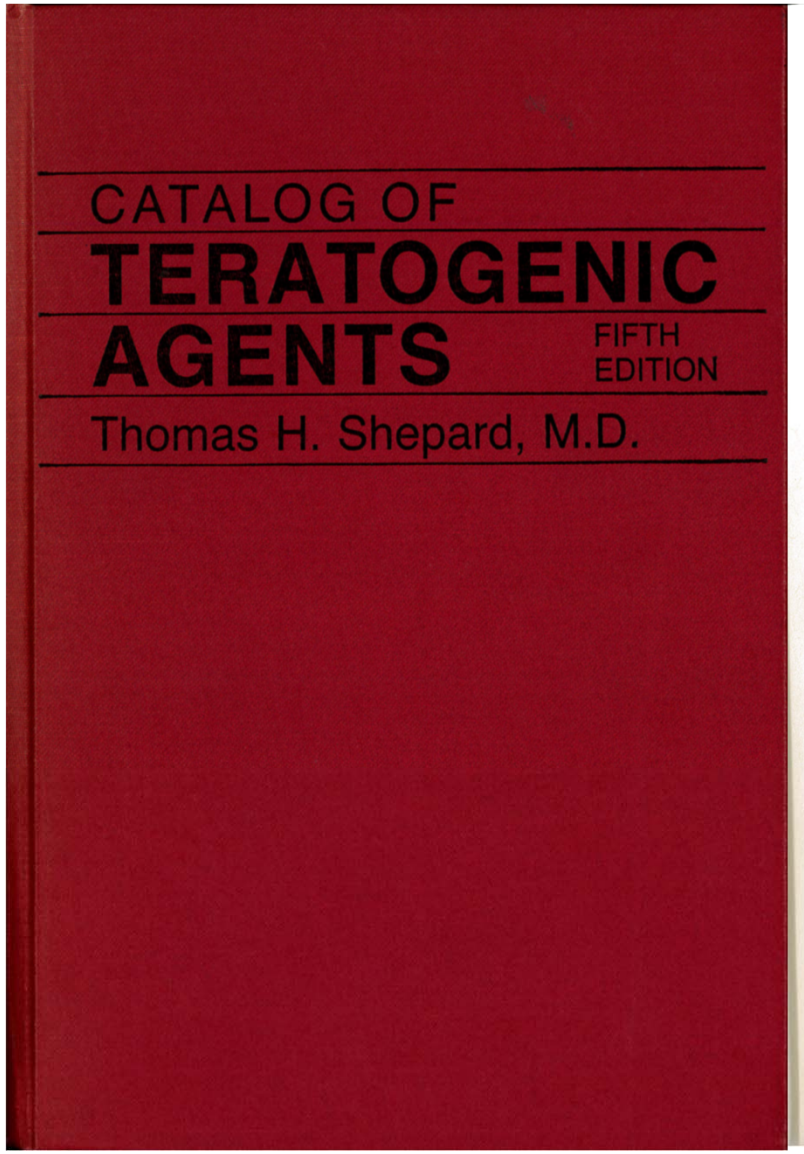
This view of the the UW campus shows the newly completed Center.

Center Director Emauel (left) meets with Senator Henry (Scoop) Jackson in the CD150 auditorium in 1973.

Seattle Teratology Club-- Best science but suffers no ties (or formality)

Central Laboratory for Human Embryology

University of Washington



CATALOG OF TERATOGENIC AGENTS

Fifth Edition

Thomas H. Shepard, M.D.

Central Laboratory for Human Embryology
Department of Pediatrics
School of Medicine
University of Washington

THE JOHNS HOPKINS UNIVERSITY PRESS
Baltimore and London

1980 Interview of Dr. J. Warkany Part 4

Role of the Environment in Birth Defects

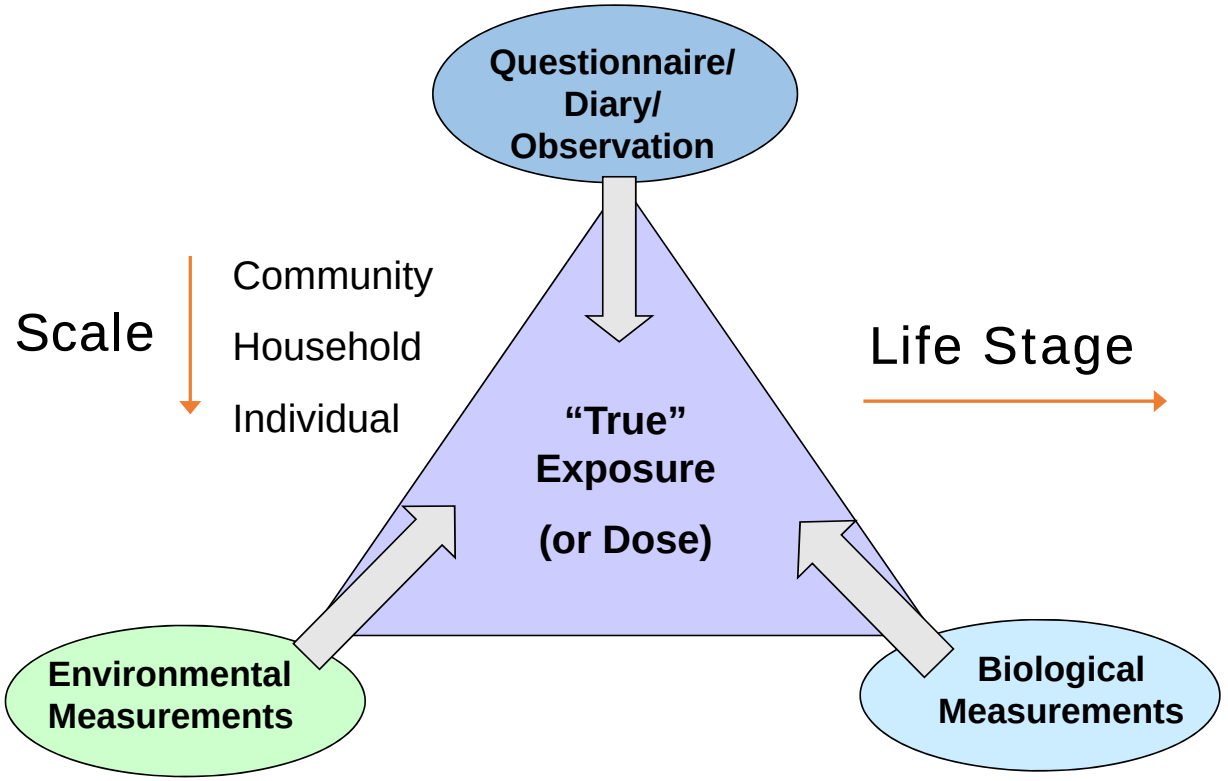
Role of environmental agents in the overall etiology of birth defects is largely unknown, with estimates of 3-25% of all birth defects due to some type of environmental interaction.

NAS, 2010

"Environment" Broadly Defined in Longitudinal Studies

- **Physical** environment:
  - housing, neighborhoods and communities, climate, radiation…
- **Chemical** exposures:
  - air, water, soil, food, dust, industrial products, pharmaceuticals…
- **Biological** environment:
  - womb, infection, nutrition; inflammatory and metabolic response…
- **Genetics**:
  - influence of genetics on disease; relationships between genes and the environment
- **Psychosocial**:
  - influence of family, socio-economics, community, culture, stress…

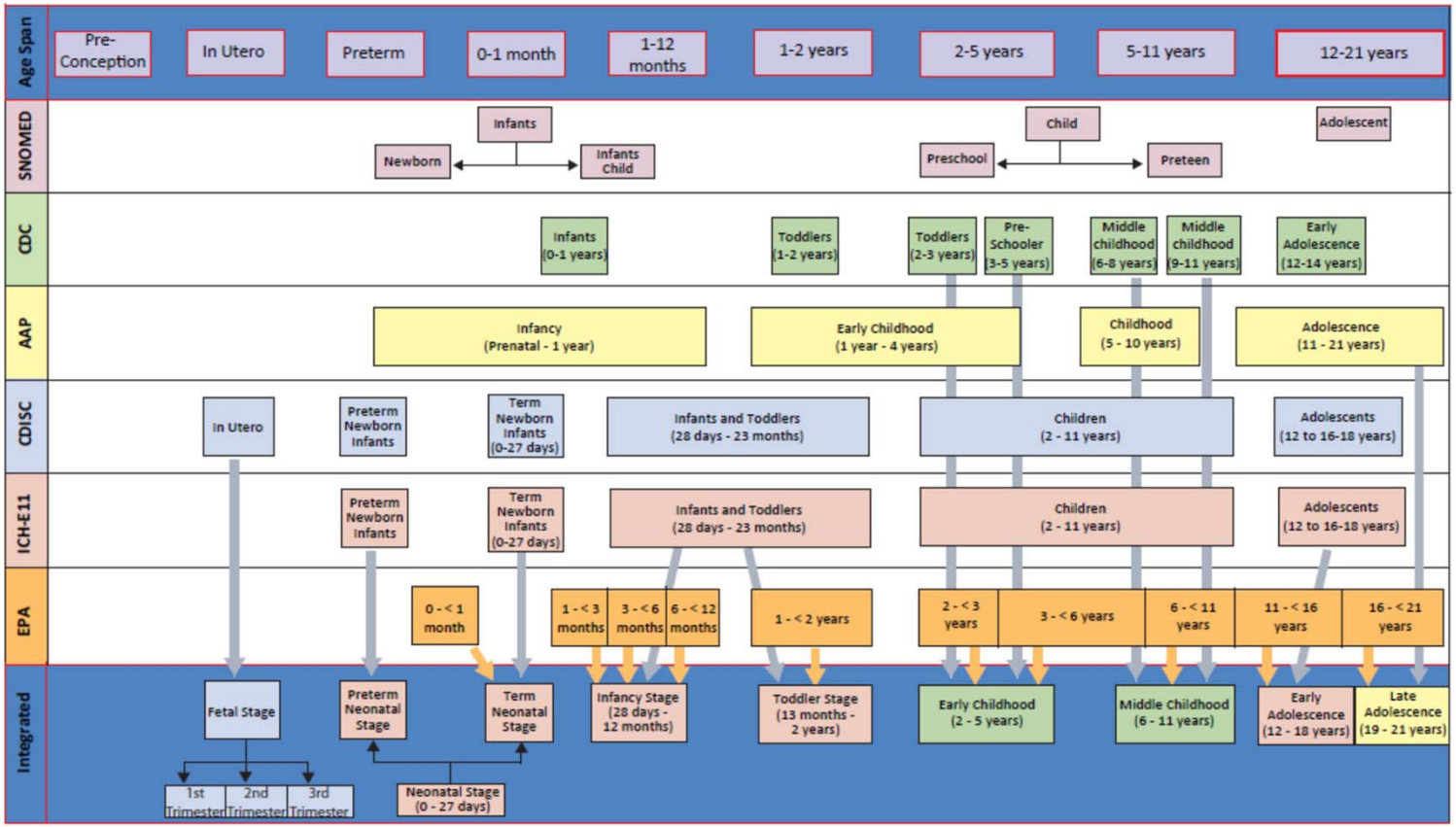
Combined Approaches Needed for Children's Exposure Assessment



NCS 2010

Figure 1

Integrated child-life stages for NICHD Pediatric Terminology as mapped to existing medical terminologies



AAP: American Academy of Pediatrics
CDC: Centers for Disease Control and Prevention
CDISC: Clinical Data Interchange Standards Consortium
EPA: Environmental Protection Agency
ICH-E11: International Conference on Harmonisation
SNOMED: Systemized Nomenclature of Medicine

Figure 4

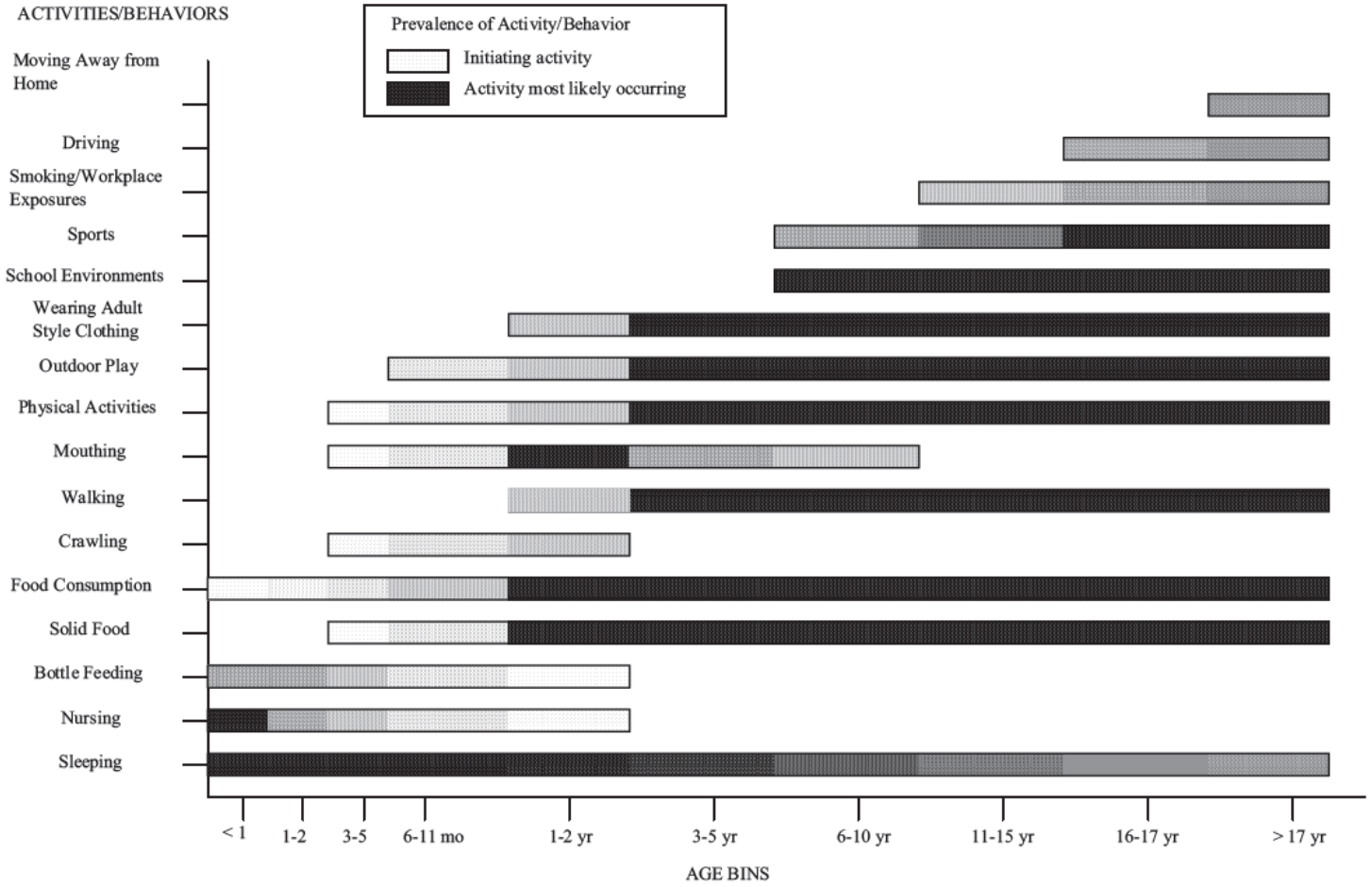


Fig. 14. Children's activities that impact exposure as a function of developmental age (from USEPA, 2003b)

WHO (2006) Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals, Environmental Health Criteria, 237

@theNAMedicine

"Health and development each builds on themselves; **each period of development lays the foundation for the next.** This is important when it comes to understanding the drivers of health within a population. Even though the impacts of early exposures may not be evident for years or decades, **they have consequences.**"

Why the United States Needs a National Birth Cohort Study
An NAM Perspective

www.nam.edu/LifelongHealth

@theNAMedicine

"A national birth cohort study is essential for developing evidence-based policies that are capable of improving the United States' international health standing and ensuring that **every member** of the U.S. population has an **equal opportunity to thrive**."

Why the United States Needs a National Birth Cohort Study
An NAM Perspective

www.nam.edu/LifelongHealth

Discussion Paper

Why the United States Needs a National Birth Cohort Study

Anne Riley, Ezekiel Dixon-Román, Barbara Entwisle, Ruth Etzel, Ann Masten, Kerry Anne McGeary, Hirokazu Yoshikawa

May 31, 2016

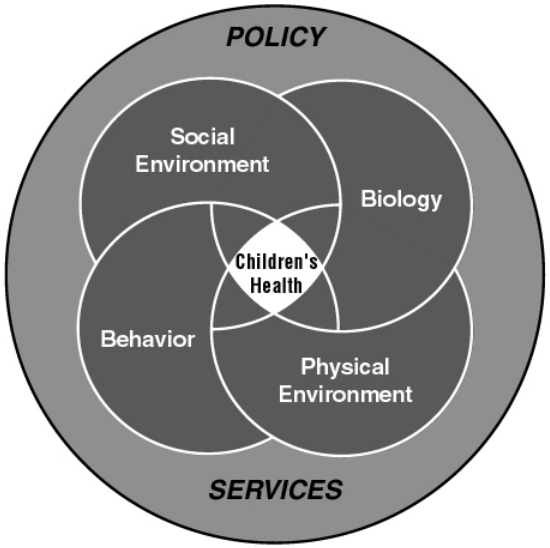
Discussion Paper

Methods for a National Birth Cohort Study

Greg Duncan, Virginia Lesser, Barbara Entwisle, Graham Kalton, Andy Shih, Elaine Faustman, Rosalind Wright, Kerry Anne McGeary, Richard Gershon, Steven Wysmuller, Shelley Merritt, and Charlee Alexander

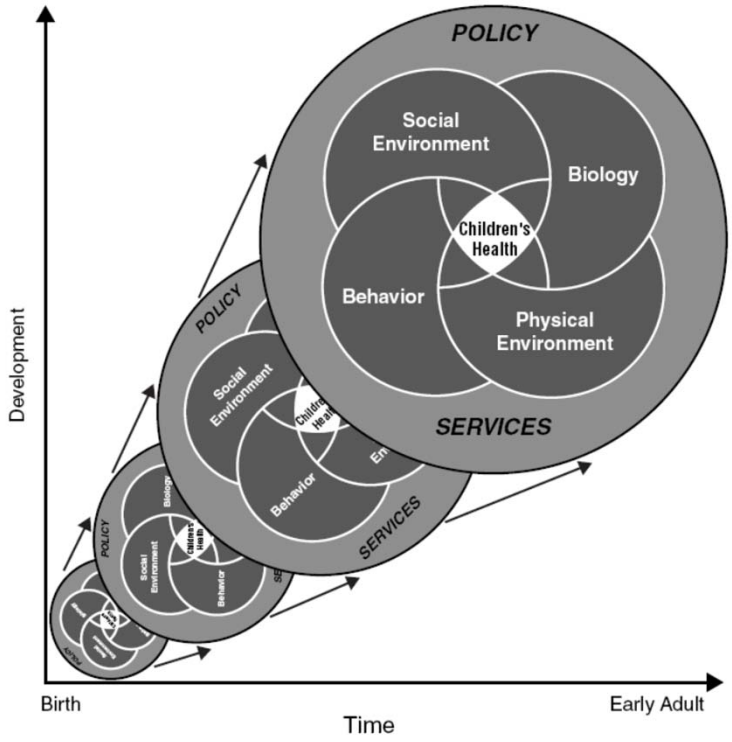
May 31, 2016

Multiple, Interacting Influences Affect Children's health including Chemical and Non Chemical Stressors



IOM, 2004

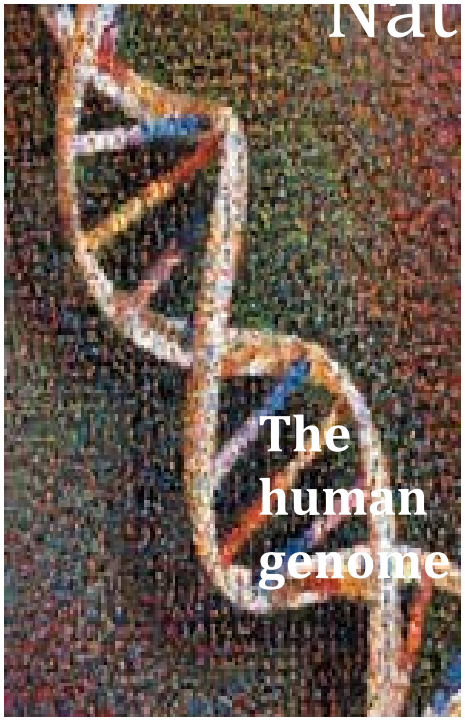
Life Course Based Model of Children's Health and its Influences:

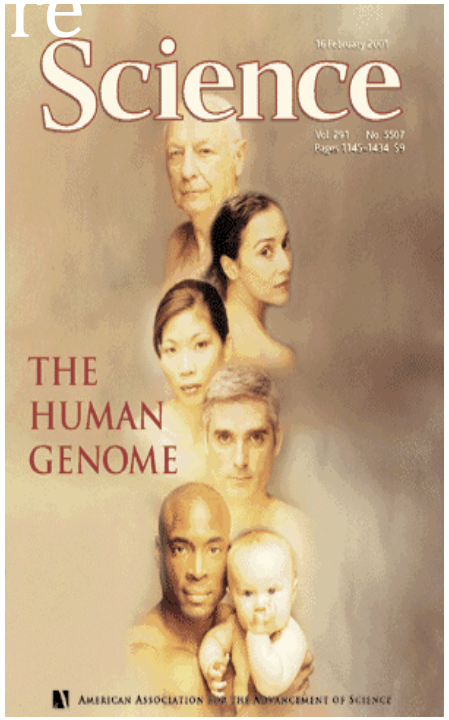


Source: Children's Health, Nation's Health, IOM report, 2004

“A Child of Non-disjunction.”
Dr. Josef Warkany

February 2001: Completion of the Draft Human Genome





- Identified 25,000 genes in human DNA
- Identified over 3 billion base pairs
- Provided new avenues for advances in medicine and biotechonology
- Allowed for discovery and annotation of new genes

To date, 46 animal genomes have been sequenced and annotated to some degree.
(http://genome.ucsc.edu/cgi-bin/hgGateway)

Adapted from Faustman, 2006

Genomics Feasibility Study for National Children's Study

Our goal: To build on our team

Elaine Faustman
UW

Jim Swanson
UC Irvine

Bonny Specker
South Dakota State

Jeff Murray
U Iowa

Genomics Feasibility Study for National Children's Study

- **The Trios Project:** A Feasibility Study of Human Whole Genome Sequencing in the National Children's Study
    - Goal to better characterize the full spectrum of variation in the human genome (nucleotide as well as structural variation) and to provide some details about two sources of this variation (the inherited as well as the non-inherited *de novo* components)

Genomics Feasibility Study for National Children's Study

Identify a genomics laboratory for whole genome sequence

Debbie Nickerson

Jay Shendure

Mike Bamshad

Evan Eichler

Holly Tabor

30 Trios - Genome Variation

Per Genome:

~ 3.8 - 4.4 million single nucleotide substitutions

~ 250,000 small indels

~ 24,000 variants in coding (exome)

- 12,000 non-synonymous (change aa)
- 12,000 synonymous (don't change aa)
- 145 nonsense (truncate)
- 70 splice

Approximately ~ 6,000 genes carry missense per individual

Building Capacity: Application

REPORT

Mutations in *ECEL1* Cause Distal Arthrogryposis Type 5D

Margaret J. McMillin,[1,2] Jennifer E. Below,[3] Kathryn M. Shively,[1] Anita E. Beck,[1,2] Heidi I. Gildersleeve,[1] Jason Pinner,[4] Gloria R. Gogola,[5] Jacqueline T. Hecht,[6] Dorothy K. Grange,[7] David J. Harris,[8] Dawn L. Earl,[2] Sujatha Jagadeesh,[9] Sarju G. Mehta,[10] Stephen P. Robertson,[11] James M. Swanson,[12] Elaine M. Faustman,[13] Heather C. Mefford,[1,2] Jay Shendure,[3] Deborah A. Nickerson,[3] Michael J. Bamshad,[1,2,3,*] and the University of Washington Center for Mendelian Genomics

The American Journal of Human Genetics 92, 150–156, January 10, 2013

Distal arthrogryposis (DA): group of at least ten disorders characterized by nonprogressive, congenital contractures that typically affect the hands, feet, wrists, and ankles. ECEL1 is endothelial converting enzyme like 1 (Endopeptidase)

Used linkage analysis and whole-genome sequencing (WGS) of a consanguineous trio to discover that mutations in ECEL1 cause DA5D and explain ~70% of cases in our
cohort

Built Capacity: Application

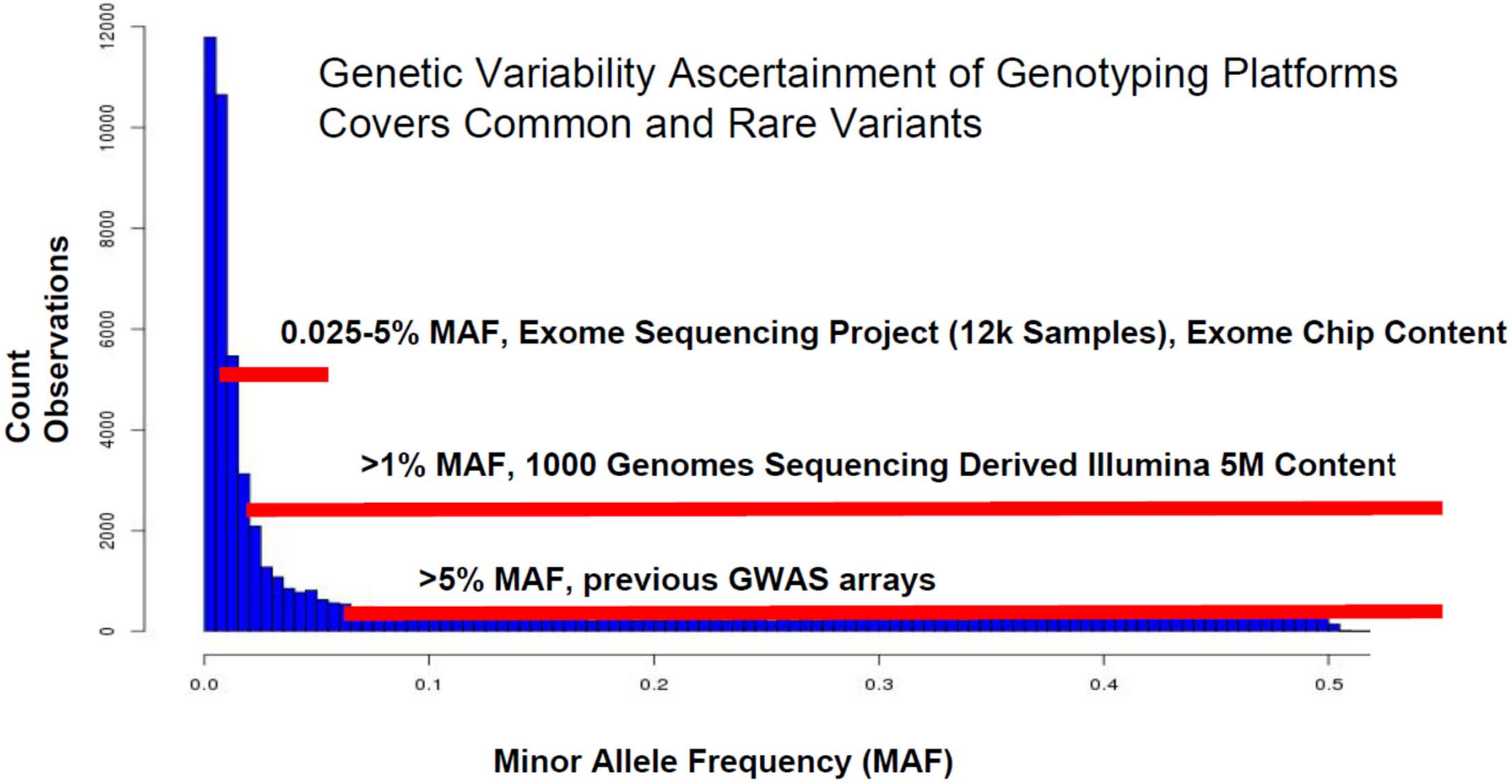
REPORT

Whole-Genome Analysis Reveals that Mutations in Inositol Polyphosphate Phosphatase-like 1 Cause Opsismodysplasia

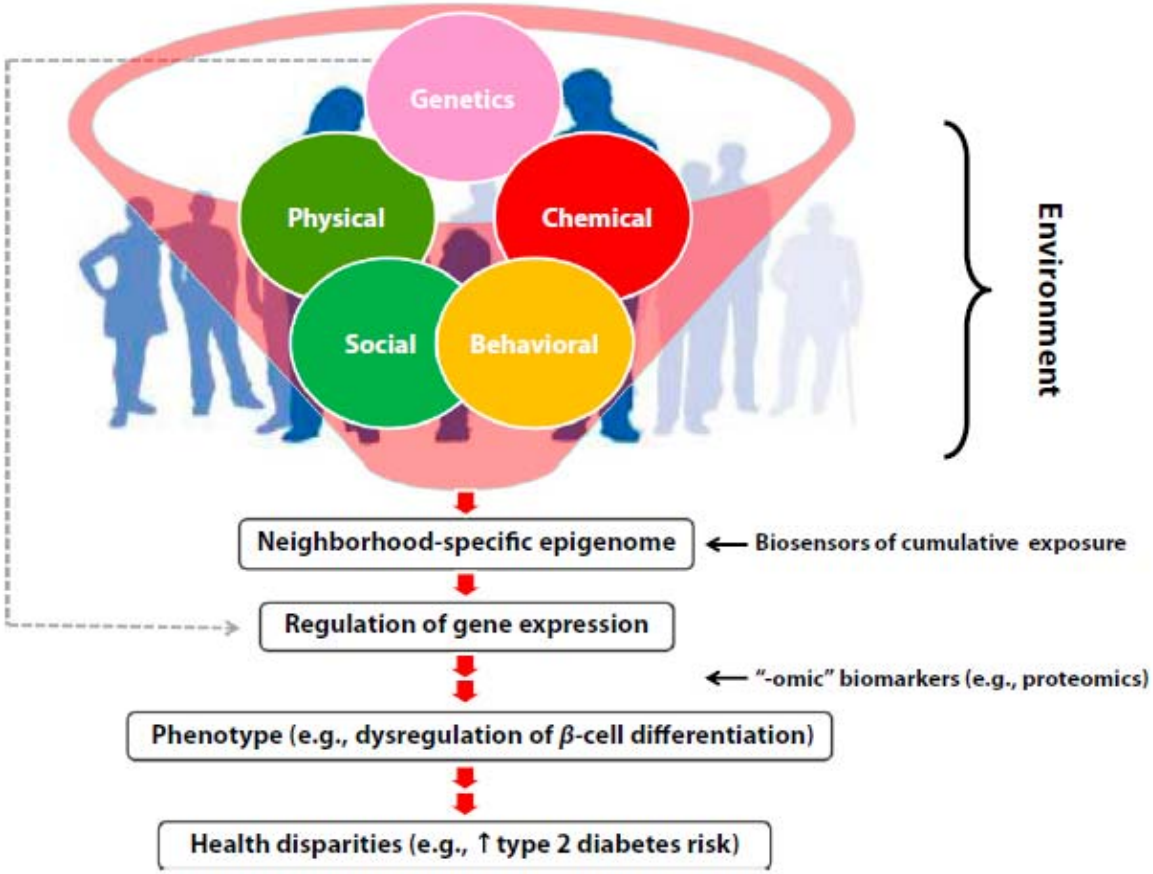
Jennifer E. Below,[1] Dawn L. Earl,[2,3] Kathryn M. Shively,[3] Margaret J. McMillin,[3] Joshua D. Smith,[1] Emily H. Turner,[1] Mark J. Stephan,[4] Lihadh I. Al-Gazali,[5] Jozef L. Hertecant,[5] David Chitayat,[6] Sheila Unger,[7] Daniel H. Cohn,[8,9] Deborah Krakow,[9,10] James M. Swanson,[11] Elaine M. Faustman,[12] Jay Shendure,[1] Deborah A. Nickerson,[1] Michael J. Bamshad,[1,2,3,*] and University of Washington Center for Mendelian Genomics

The American Journal of Human Genetics 92, 137–143, January 10, 2013

- Opsismodysplasia: rare, autosomal-recessive skeletal dysplasia characterized by short stature, characteristic facial features, and in some cases severe renal phosphate wasting.
- Linkage analysis and whole-genome sequencing of a consanguineous trio to discover mutations in inositol polyphosphate phosphatase-like 1 (INPPL1)
- Evaluation of 12 families with opsismodysplasia revealed that INPPL1 mutations explain ~60% of cases overall, including both of the families in our cohort with more than one affected child and 50% of the simplex cases.


Genetic Variability Ascertainment of Genotyping Platforms
Covers Common and Rare Variants
0.025-5% MAF, Exome Sequencing Project (12k Samples), Exome Chip Content
>1% MAF, 1000 Genomes Sequencing Derived Illumina 5M Content
>5% MAF, previous GWAS arrays
Count
Observations
0
2000
4000
6000
8000
10000
12000
0.0
0.1
0.2
0.3
0.4
0.5
Minor Allele Frequency (MAF)

Epigenome: Biosensor of Cumulative Exposure to Chemical and Nonchemical Stressors Related to Environmental Justice



K. Olden et al, American Journal of Public Health | October 2014, Vol 104, No. 10

Why is social stress relevant to children's environmental health?

- Both physical toxicants and social stress exposure during development can have life-long impacts
- Social stress can be an effect modifier of physical toxicant exposure and disease pathway
- Social stress and environmental toxicants often have overlapping exposure profiles, potentially impacting low income and minority populations most heavily

From Wright, *Curr Opin Pediatr*. 2009 April ; 21(2): 222–229

Epigenomic Factors that Effect our Risk Assessment Approaches

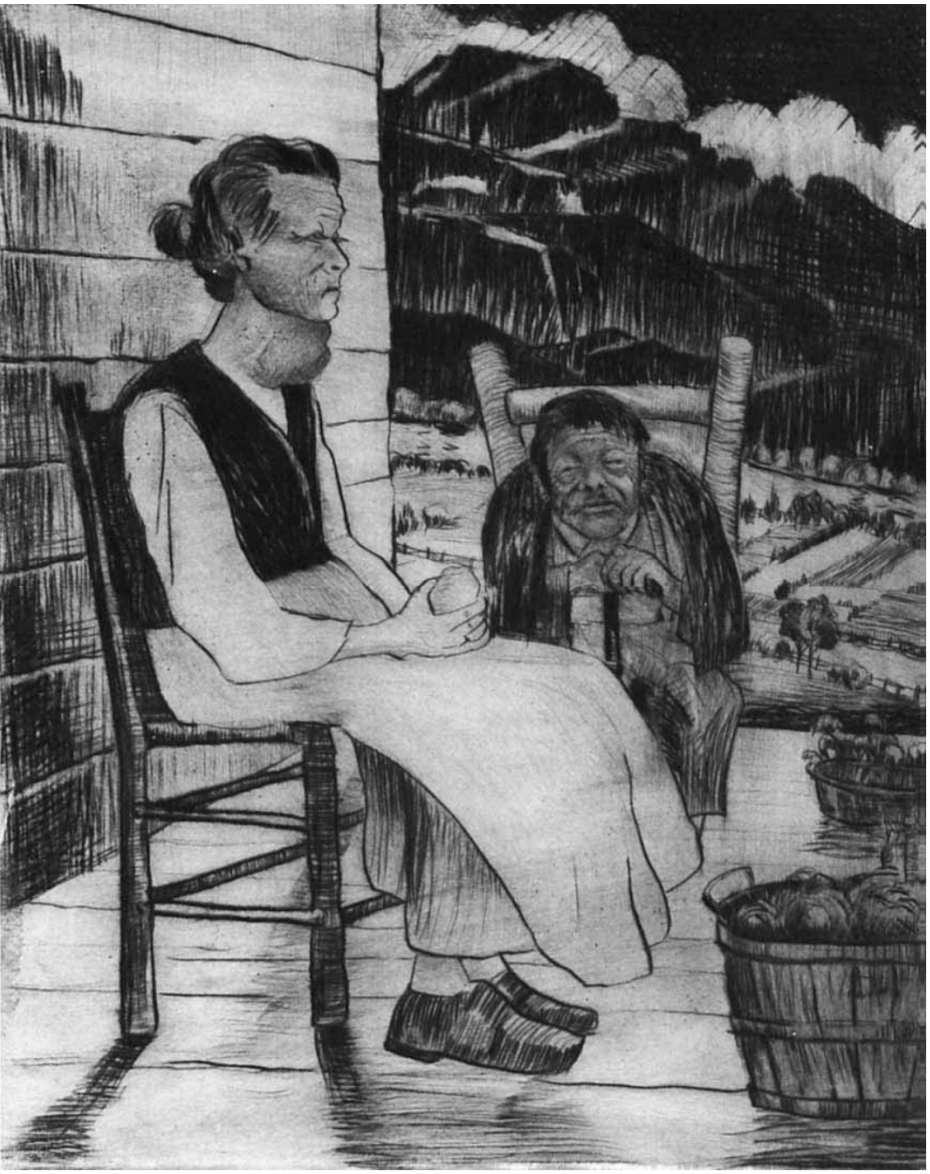
- Epigenomic changes are known to be affected by both chemical and non-chemical stressors
- Epigenomic changes occur after exposure to many chemicals, not related by structure
- Epigenomic or stress changes can be inherited and affect multiple generations.
- Epigenomic changes after chemical and non-chemical stressors can affect the same pathways.
- There are many different types of epigenomic pathways that can be changed by stressor exposure and these occur differentially across time (lifestage) in various biological tissues and can be species, organic and organism specific.
- There are known genetic polymorphisms that affect epigenomic responses

Small Magnitude Effect Sizes in Epigenetic Endpoints are Important in Children's Environmental Health Studies

The Children's Environmental Health and Disease Prevention Research Center's Epigenetics Working Group

Carrie V. Breton, Carmen J. Marsit, Elaine Faustman, Kari Nadeau, Jaclyn M. Goodrich, Dana C. Dolinoy, Julie Herbstman, Nina Holland, Janine M. LaSalle, Rebecca Schmidt, Paul Yosefi, Frederica Perera, Bonnie R. Joubert, Joseph Wiemels, Michele Taylor, Ivana V.Yang, Rui Chen, Kinjal M. Hew, Deborah M. Hussey Freeland, Rachel Miller, and Susan K. Murphy

Under Review, 2016

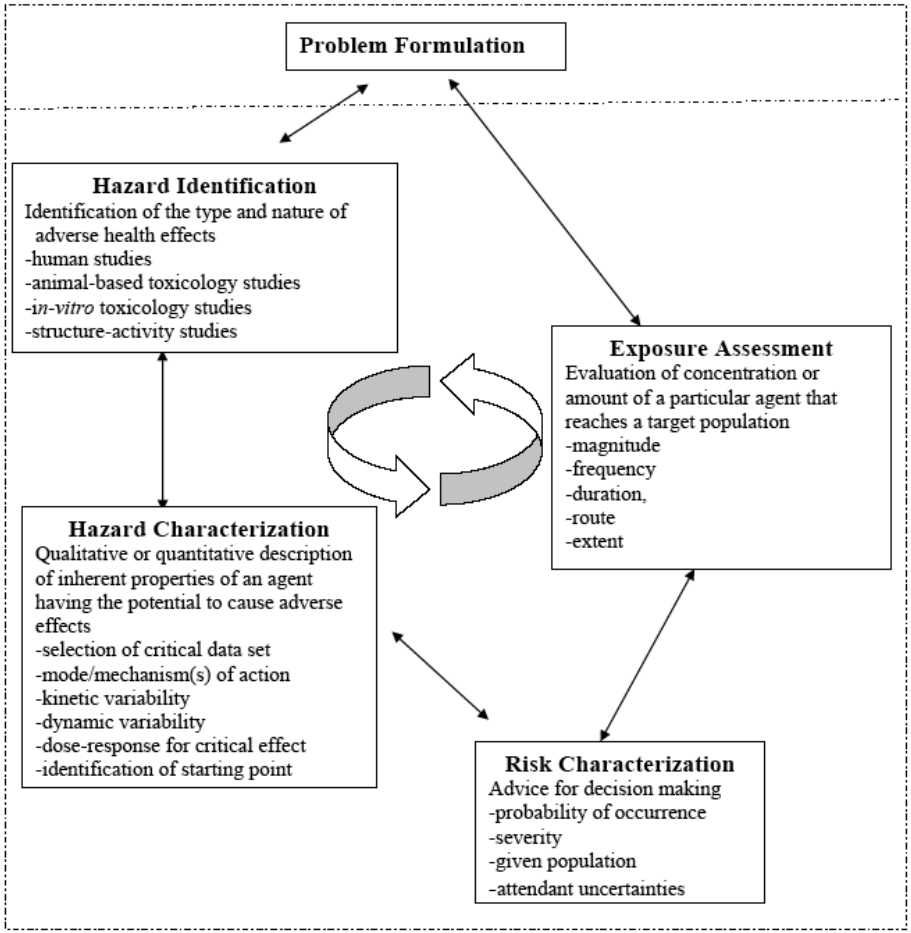


Untitled

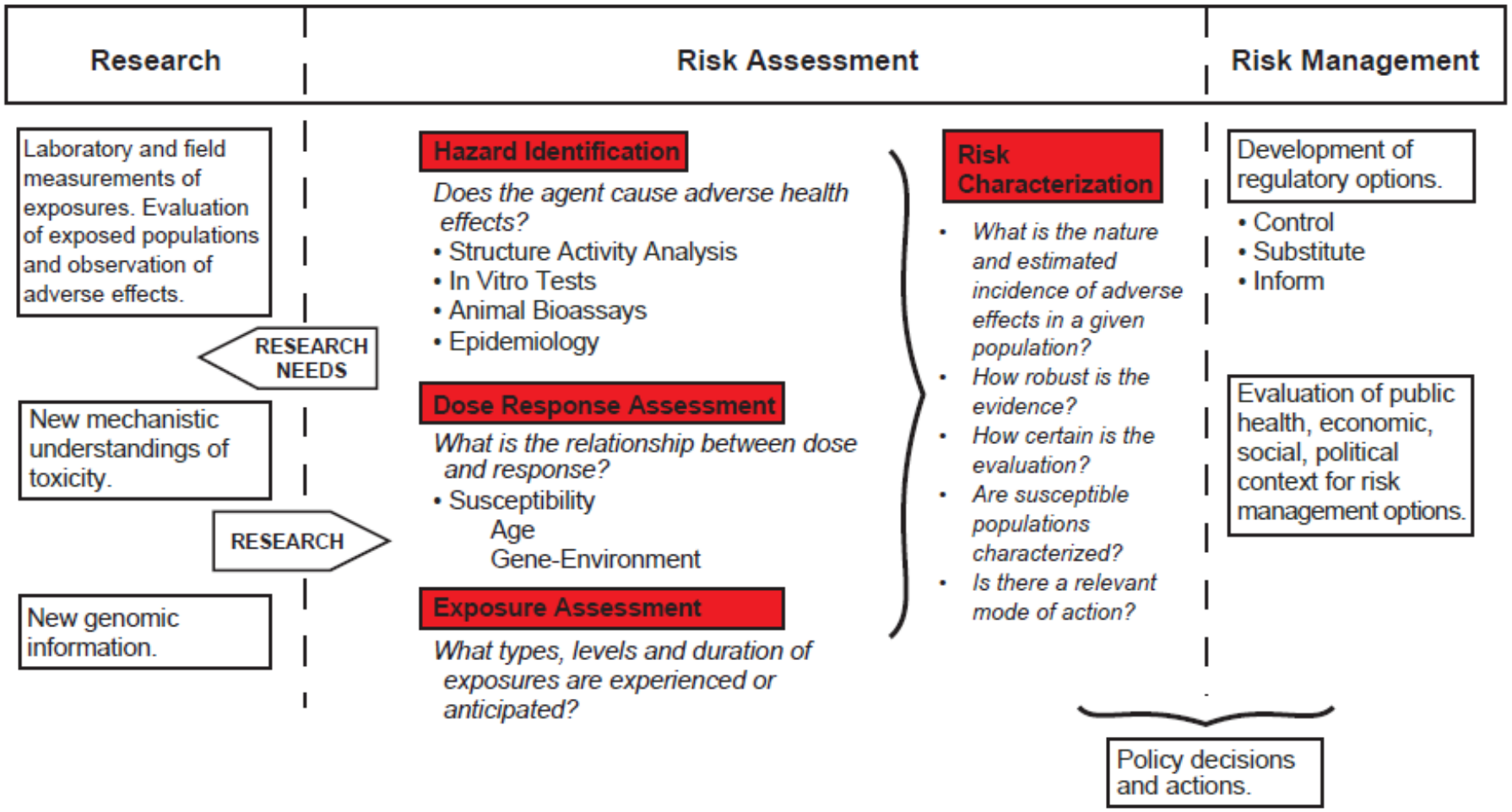
Warkany recognized both in his science and in his art a broad definition of environment and in this drawing in particular emphasized under exposure to iodine in underserved populations as a critical missing component for health and development.

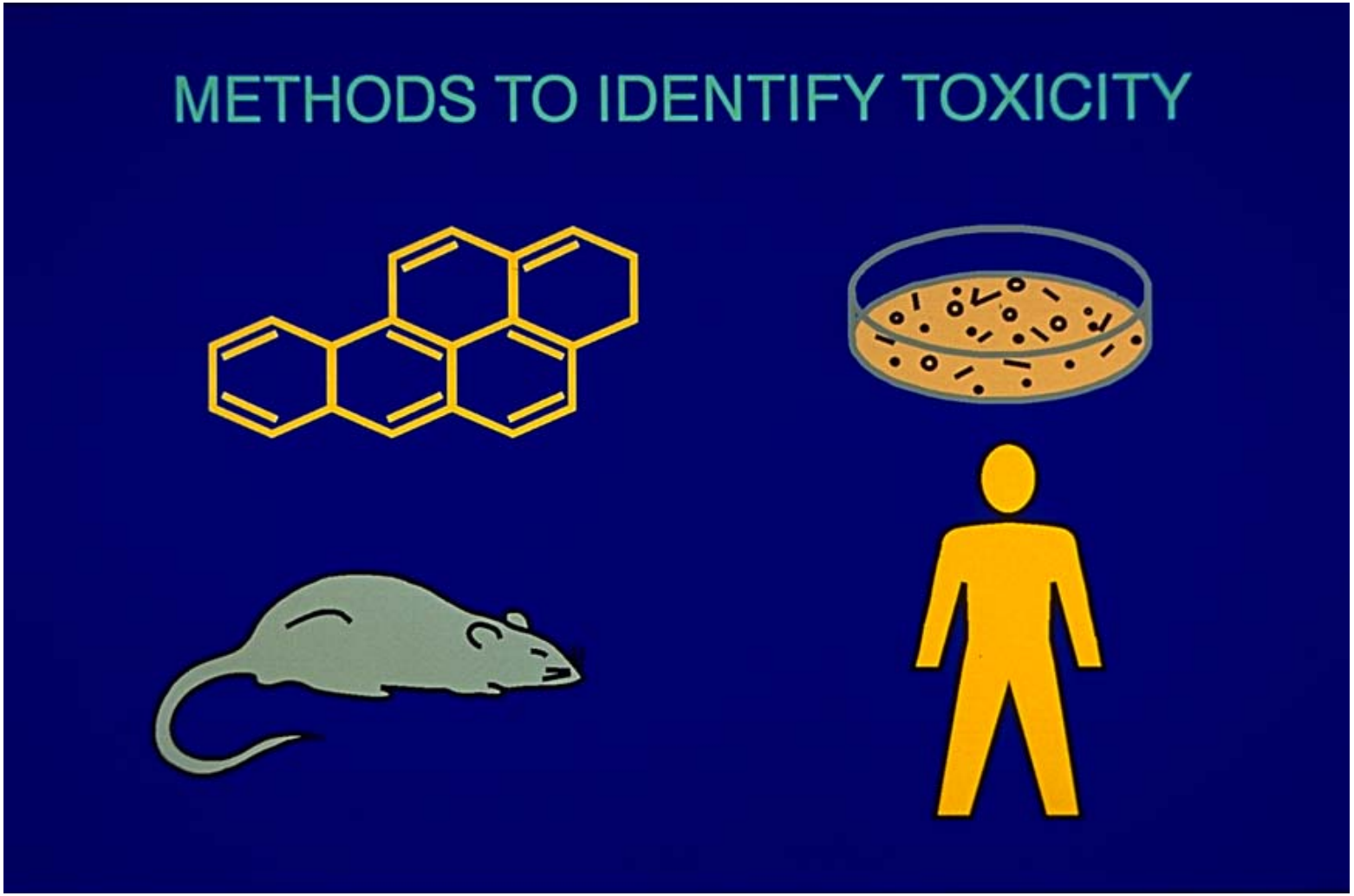
Past Presidents Luncheon, 2009 Annual Meeting, Rio Mar, Puerto Rico. Presidents in attendance (standing, left to right): Richard K. Miller, J.F. Cordero, T.H. Shepard, J.M. Friedman, Lewis B. Holmes, G.P. Daston, M.S. Tassinari, T.B. Knudsen, J.M. Rogers, C.D. Chambers, R.L. Brent, R.W. Tyl, B.F. Hales, J.M. DeSesso, E.M. Faustman, R.J. Kavlock, C.A. Kimmel, K.L. Jones. Standing far right is Louise Winn, Chair of the Education committee, and seated are students and postdoctoral fellows (Photograph by Dr. Robert Parker).

Risk Assessment



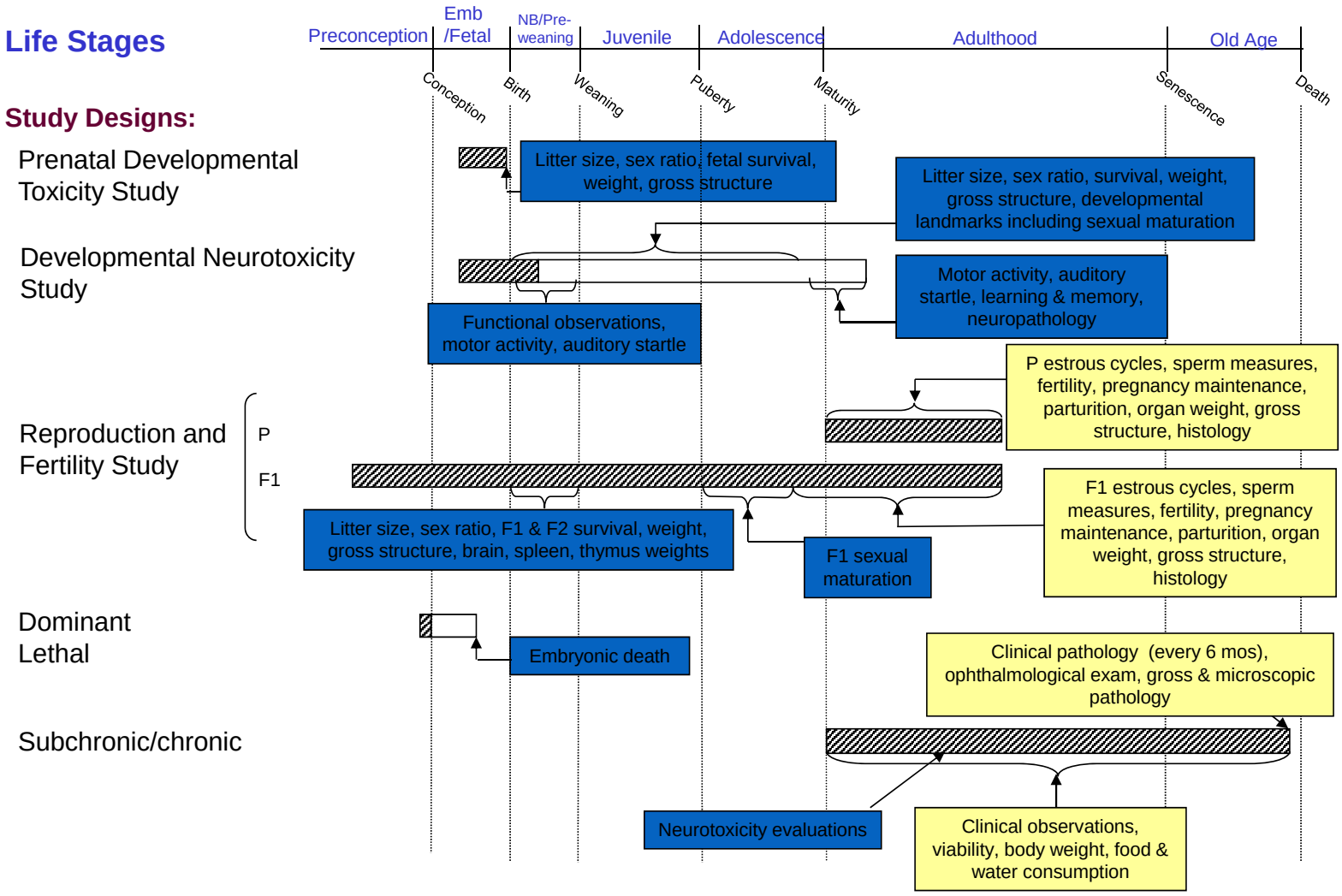
WHO, 2006


Research
Risk Assessment
Risk Management
Laboratory and field measurements of exposures. Evaluation of exposed populations and observation of adverse effects.
RESEARCH NEEDS
New mechanistic understandings of toxicity.
RESEARCH
New genomic information.
Hazard Identification
Does the agent cause adverse health effects?
• Structure Activity Analysis
• In Vitro Tests
• Animal Bioassays
• Epidemiology
Dose Response Assessment
What is the relationship between dose and response?
• Susceptibility
Age
Gene-Environment
Exposure Assessment
What types, levels and duration of exposures are experienced or anticipated?
Risk Characterization
• What is the nature and estimated incidence of adverse effects in a given population?
• How robust is the evidence?
• How certain is the evaluation?
• Are susceptible populations characterized?
• Is there a relevant mode of action?
Development of regulatory options.
• Control
• Substitute
• Inform
Evaluation of public health, economic, social, political context for risk management options.
Policy decisions and actions.

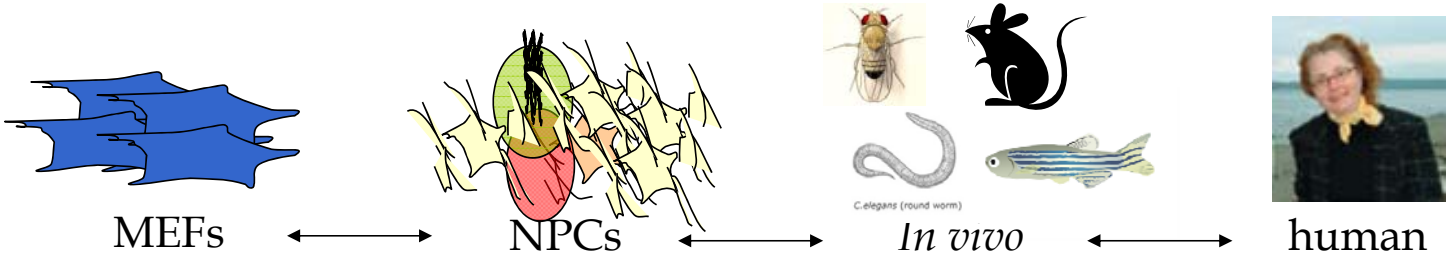


Faustman et al, 2010

Spectrum of Reproductive Toxicity Evaluations



Ability of experimental systems to assess and predict neurodevelopmental toxicity across multiple levels of biological complexity



MEFs ⟷ NPCs ⟷ *In vivo* ⟷ human

- Signaling pathways
- Cell cycle kinetics
- Viability including mechanism of cell death

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- Viability including mechanism of cell death
- Differentiation
- Neuronal phenotype

- Signaling pathways
- Cell cycle kinetics
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- Neuronal phenotype
- Migration
- Brain structure and morphology
- Function
- Behavior

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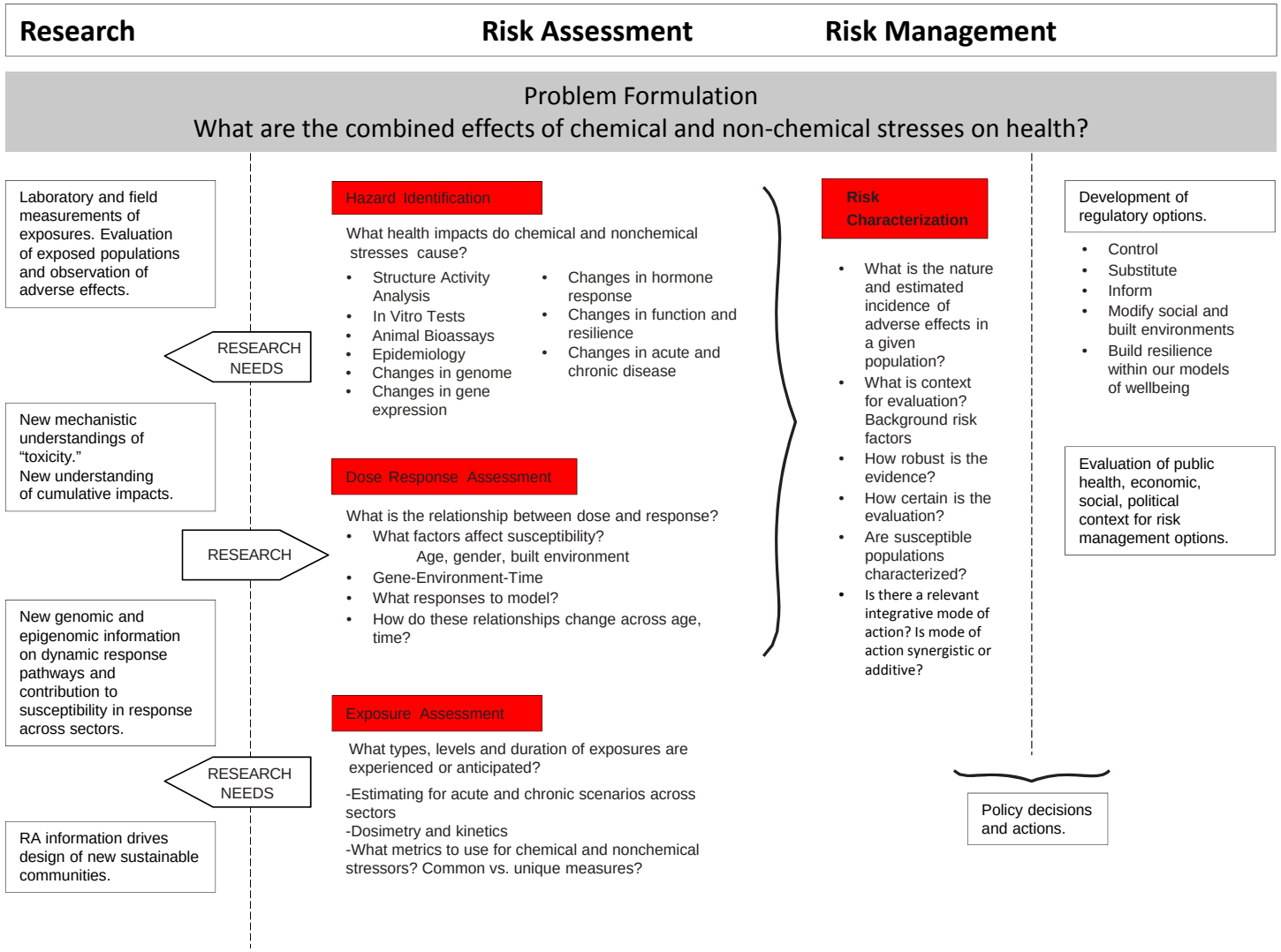
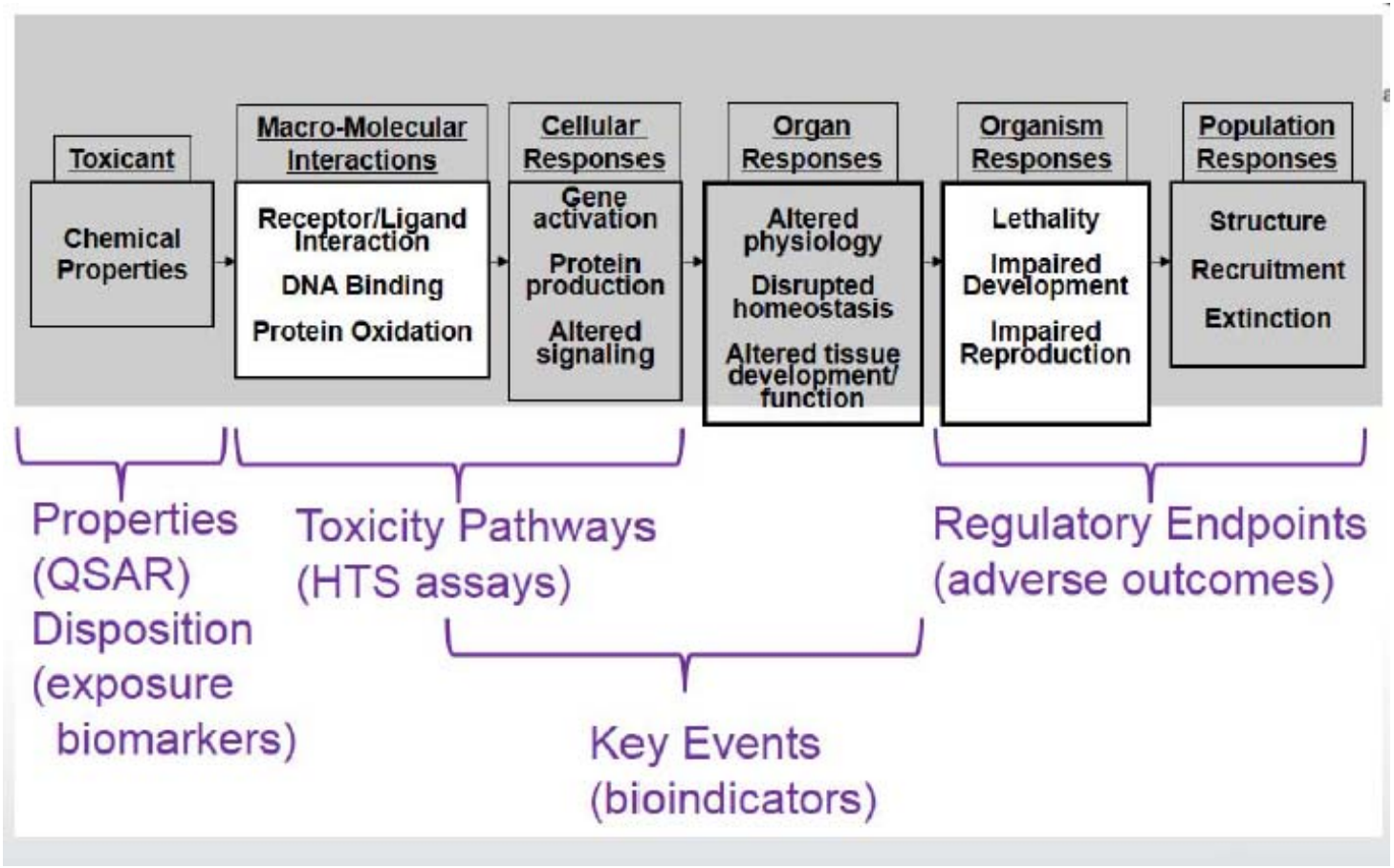
Stem Cell Now, CH Scott, 2005

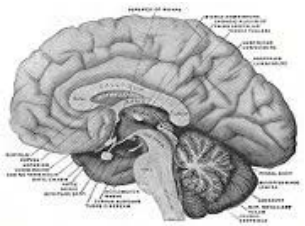

Research
Risk Assessment
Risk Management
Problem Formulation
What are the combined effects of chemical and non-chemical stresses on health?
Laboratory and field measurements of exposures. Evaluation of exposed populations and observation of adverse effects.
RESEARCH NEEDS
New mechanistic understandings of "toxicity."
New understanding of cumulative impacts.
RESEARCH
New genomic and epigenomic information on dynamic response pathways and contribution to susceptibility in response across sectors.
RESEARCH NEEDS
RA information drives design of new sustainable communities.
Hazard Identification
What health impacts do chemical and nonchemical stresses cause?
Structure Activity Analysis
In Vitro Tests
Animal Bioassays
Epidemiology
Changes in genome
Changes in gene expression
Changes in hormone response
Changes in function and resilience
Changes in acute and chronic disease
Dose Response Assessment
What is the relationship between dose and response?
What factors affect susceptibility?
Age, gender, built environment
Gene-Environment-Time
What responses to model?
How do these relationships change across age, time?
Exposure Assessment
What types, levels and duration of exposures are experienced or anticipated?
-Estimating for acute and chronic scenarios across sectors
-Dosimetry and kinetics
-What metrics to use for chemical and nonchemical stressors? Common vs. unique measures?
Risk Characterization
What is the nature and estimated incidence of adverse effects in a given population?
What is context for evaluation? Background risk factors
How robust is the evidence?
How certain is the evaluation?
Are susceptible populations characterized?
Is there a relevant integrative mode of action? Is mode of action synergistic or additive?
Development of regulatory options.
Control
Substitute
Inform
Modify social and built environments
Build resilience within our models of wellbeing
Evaluation of public health, economic, social, political context for risk management options.
Policy decisions and actions.

AOP and biomarkers serve to link elements and describe disease pathogenesis



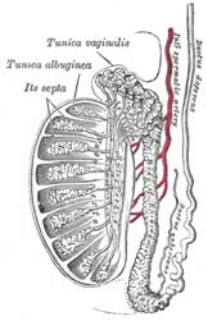
John Vandenberg, Annie M. Jarabek 2014

In Vitro Brain



Human neural progenitors cells (hNPCs)
Commercially available line derived from male human embryonic stem cells

In Vitro Testis



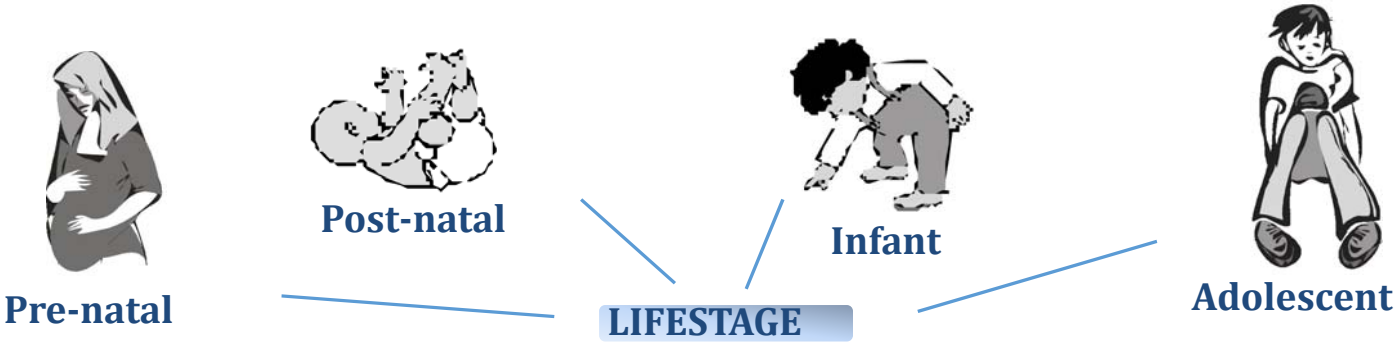
3D testicular co-culture
Primary co-culture derived from postnatal day 5 rat testis and cultured with a Matrigel overlay

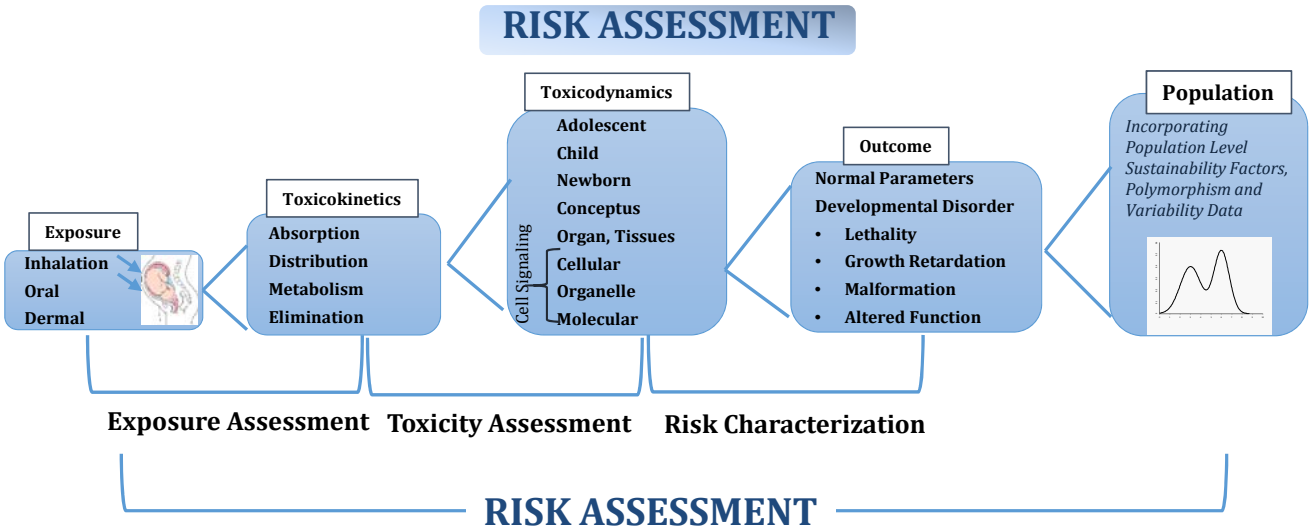
Common Pathways of Response

- Proliferation
- Differentiation
- Apoptosis
- Stress response
- Hormonal regulation
- Epigenetic regulation

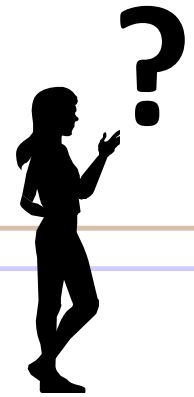
Common Approaches

- Expression of key protein markers of specific cell types and developmental stages
- Quantification of normal pathway dynamics through time in culture (general assessment as well as targeted assessment of pathways of interest)
- Anchoring to *In Vivo* developmental pathway dynamics


Pre-natal
Post-natal
Infant
Adolescent
LIFESTAGE


RISK ASSESSMENT
Exposure
Inhalation
Oral
Dermal
Toxicokinetics
Absorption
Distribution
Metabolism
Elimination
Toxicodynamics
Adolescent
Child
Newborn
Conceptus
Organ, Tissues
Cellular
Organelle
Molecular
Cell Signaling
Outcome
Normal Parameters
Developmental Disorder
Lethality
Growth Retardation
Malformation
Altered Function
Population
Incorporating Population Level Sustainability Factors, Polymorphism and Variability Data
Exposure Assessment
Toxicity Assessment
Risk Characterization
RISK ASSESSMENT

How can we use new genomic information to inform our risk assessments?

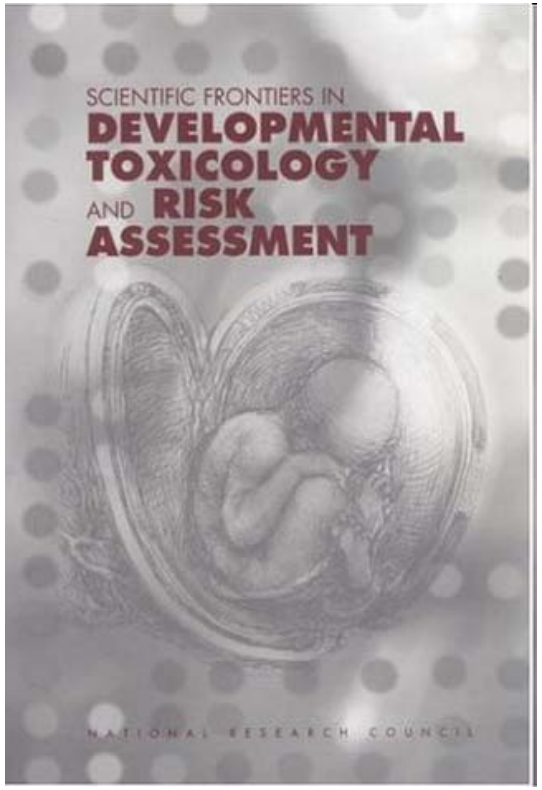


Scientific Frontiers in Developmental Toxicology and Risk Assessment

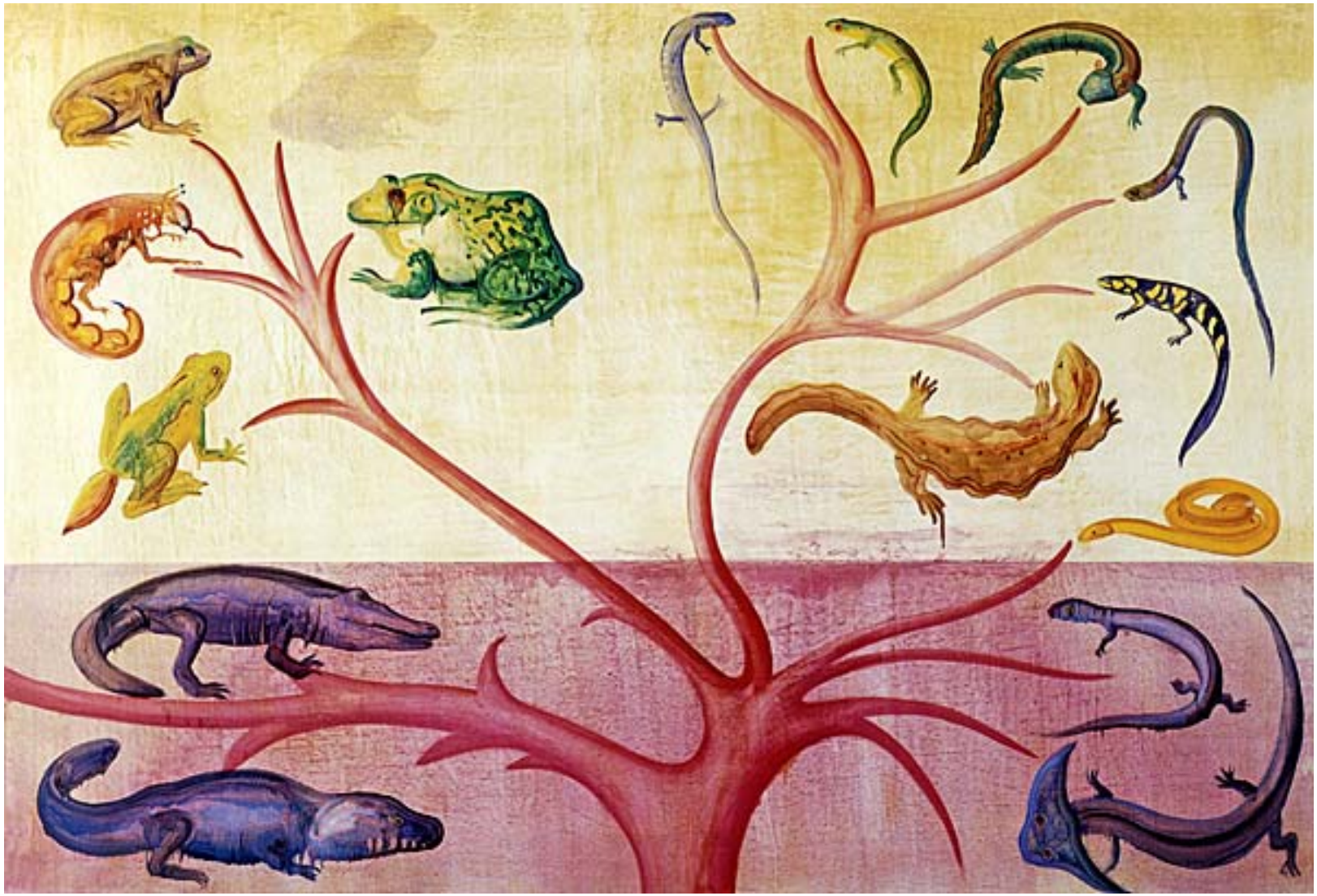
National Research Council

Chair: Elaine M. Faustman

Co-Chair: John C. Gerhart



www.books.nap.edu/catalog/9871.html



Alexis Rockman - *Amphibian Evolution*, 1987, oil & acrylic on canvas

Gene Ontology: Tool for the unification of biology. The Gene Ontology Consortium

Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, Davis AP, Dolinski K, Dwight SS, Eppig JT, Harris MA, Hill DP, Issel-Tarver L, Kasarskis A, Lewis S, Matese JC, Richardson JE, Ringwald M, Rubin GM, Sherlock G.

Nat Genet. 2000 May;25(1):25-9.

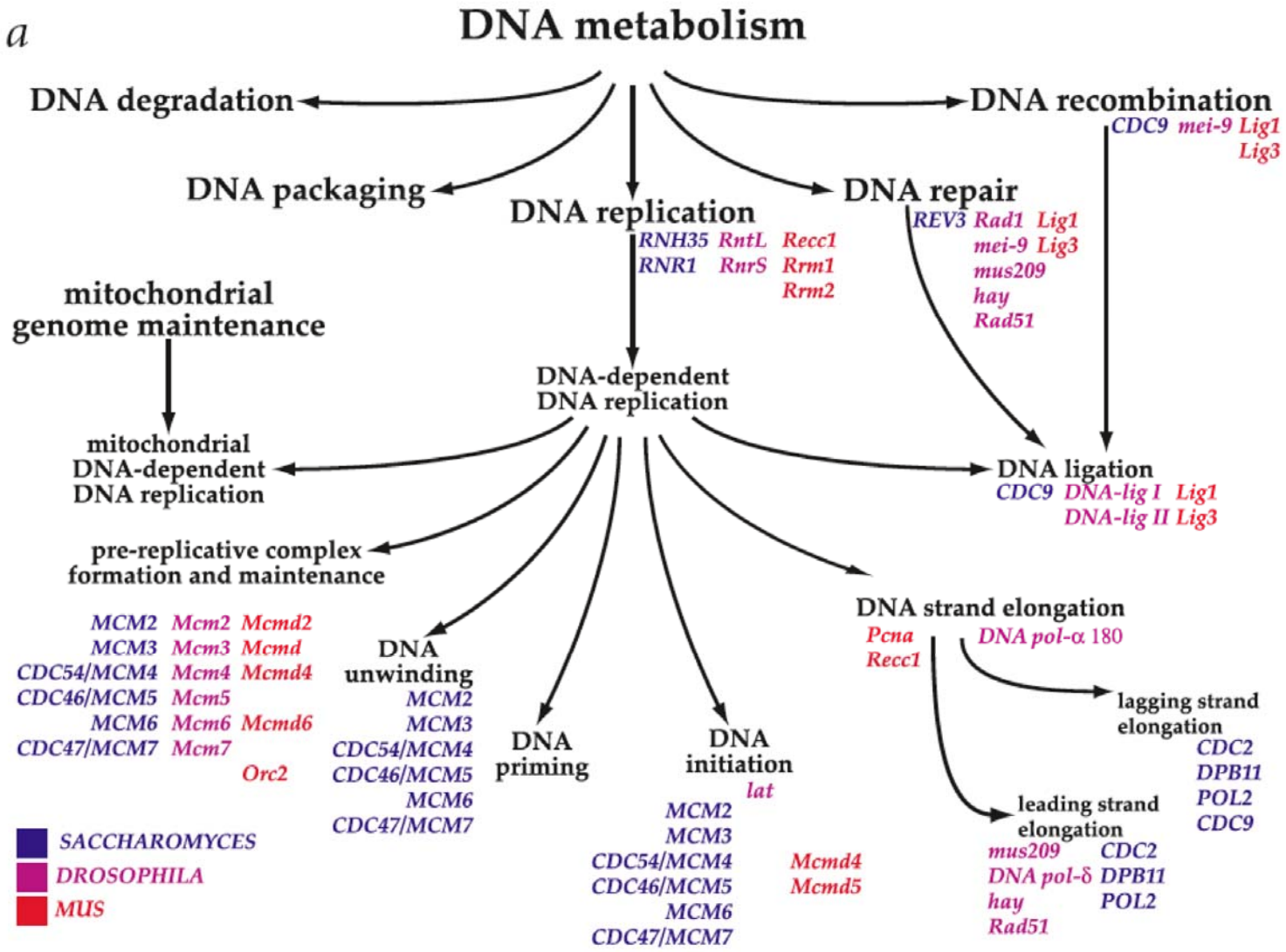
Gene Ontology Hierarchy: Based on the AmiGO, the GO Consortium's annotation and ontology toolkit

Carbon S, Ireland A, Mungall CJ, Shu S, Marshall B, Lewis S, AmiGO Hub, Web Presence Working Group. AmiGO: online access to ontology and annotation data.

Bioinformatics. Jan 2009;25(2):288-9

http://www.geneontology.org/

Examples of Cross-Species Extrapolation within Gene Ontology Framework



Ashburner et al., 2000

Generalizations about cell-cell signaling in development

- Signaling is used in almost every developmental event, probably in all metazoa.

  (E.g., in axis specification, morphogenesis, organogenesis, tissue renewal, cytodifferentiation…)

- There are approximately 17 pathways of cell-cell signaling.

  (Perhaps a few more will be discovered.)

- The 17 pathways are highly conserved among metazoa. They were probably present in the last common ancestor of all modern bilateral animals.

The 17 Intercellular Signaling Pathways

Period During Development When Signaling Pathway Used

(The mammalian fetus uses all 17)

Early (axis specification, germ layer specification, left-right asymmetry) and continued in all later stages.

1. Wnt pathway
2. Hedgehog pathway
3. TGFB receptor (ser/thr kinase) pathway
4. Receptor tyrosine kinase (small G protein)pathway
5. Notch/Delta pathway
6. Cytokine receptor (cytoplasmic tyrosine kinases; JAK/STAT pathway

Middle (during organogenesis and cytodifferentiation) and continued in all later stages.

7. IL1/Toll NFkB pathway
8. Nuclear hormone receptor pathway
9. Apoptosis pathway
10. Integrin pathway
11. Receptor phosphotyrosine phosphatase pathway

Late (after cell types have differentiated). Used in Fetal/ Larval/Adult Physiology.

12. Receptor guanylate cyclase pathway
13. Nitric oxide receptor pathway
14. G-protein coupled receptor (large G protein) pathway
15. Cadherin pathway
16. Gap junction pathway
17. Ligand-gated cation channel pathway

The 17 Intercellular Signaling Pathways

We now have new common languages and genomically conserved response pathways identified.
We are using our newly gained knowledge about genomic conservation to:

- Identify common pathways that are impacted across species and platforms?
- How and what toxicants impact these conserved pathways?
- At what levels and times of exposure are impacts observed?

Toxicology and Applied Pharmacology 257 (2011) 111–121

Contents lists available at SciVerse ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

Identifying developmental toxicity pathways for a subset of ToxCast chemicals using human embryonic stem cells and metabolomics ☆

N.C. Kleinstreuer [b,*], A.M. Smith [a], P.R. West [a], K.R. Conard [a], B.R. Fontaine [a], A.M. Weir-Hauptman [d], J.A. Palmer [a], T.B. Knudsen [b], D.J. Dix [b], E.L.R. Donley [a], G.G. Cezar [a,c]

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Genomic Conservation

Challenges for *in vitro* to *in vivo* extrapolation.

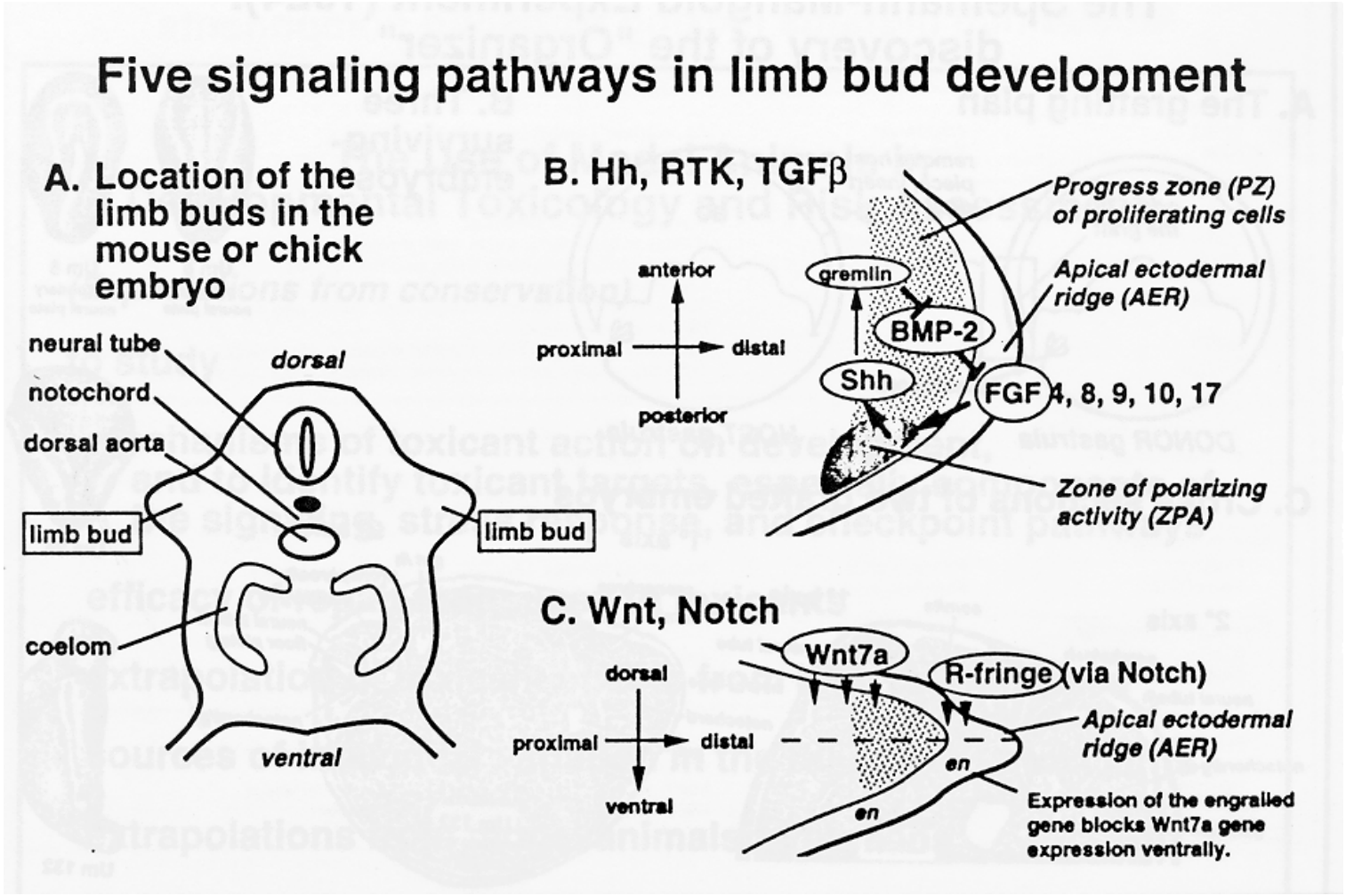
- Cellular pathways information is used in a 3-D context at organ level.

Challenges for cross-species specific information.

- Although cellular pathway conservation occurs, organ specific context is organism specific.

Challenges for cross-compound extrapolations.

- Generation of toxicogenomic examples for toxicants are at the earliest stages.


Five signaling pathways in limb bud development
A. Location of the limb buds in the mouse or chick embryo
neural tube
dorsal
notochord
dorsal aorta
limb bud
limb bud
coelom
ventral
B. Hh, RTK, TGFβ
anterior
proximal
distal
posterior
gremlin
BMP-2
Shh
FGF 4, 8, 9, 10, 17
Progress zone (PZ) of proliferating cells
Apical ectodermal ridge (AER)
Zone of polarizing activity (ZPA)
C. Wnt, Notch
dorsal
proximal
distal
ventral
Wnt7a
R-fringe (via Notch)
Apical ectodermal ridge (AER)
en
en
Expression of the engrailed gene blocks Wnt7a gene expression ventrally.

NAS, 2000

Roles of the Hedgehog Signaling Pathway

In vertebrate development:

- Induction of the floorplate of the neural tube by notochord
- Induction of the brain floorplate by prechordal mesoderm
- Induction of the sclerotome (from somite) by notochord left-right asymmetry
- Anteroposterior development of the fin/limb (via ZPA)
- Gut development, interactions with the visceral mesoderm
- Hair follicle development
- Break development
- Spermatogenesis

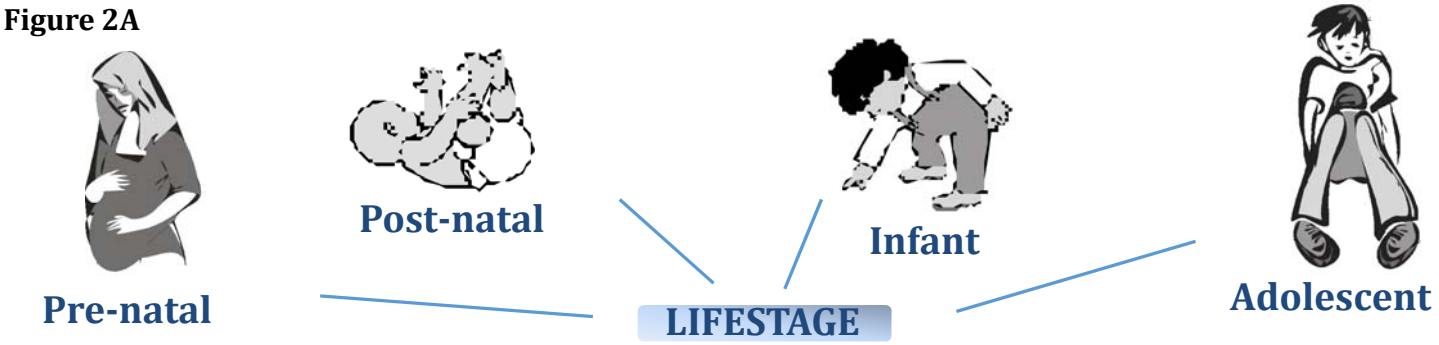
In Drosophila development:

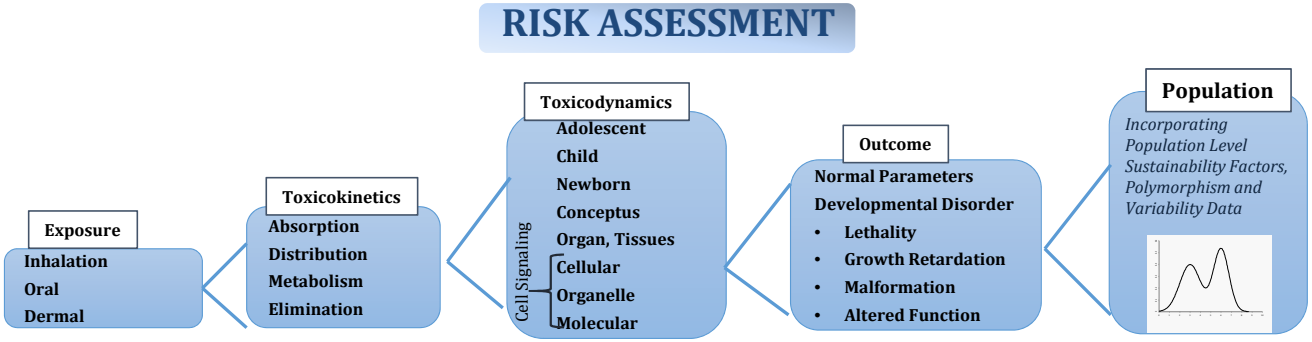
- Segment formation, posterior compartment
- Appendage development
- Gut development, interactions with visceral mesoderm
- Eye/brain development
- Oogenesis

Challenges and Opportunities
for using systems biology information and approaches for understanding mechanisms of toxicity and dose-response

- Intra- and cross-species extrapolation
- Facilitate use of model systems
- Characterize low dose and early temporal response
- Facilitate in vitro to in vivo extrapolation
- Extrapolation across levels of biological complexity
- Identify actual pathways of disease

Figure 2A





Faustman et al

Cerebral Cortex October 2007;17:2433–2442
doi:10.1093/cercor/bhl151
Advance Access publication January 4, 2007

Computational Models of Neocortical Neuronogenesis and Programmed Cell Death in the Developing Mouse, Monkey, and Human

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Assessing the Health Benefits of Air Pollution Reduction for Children

Eva Y. Wong,[1] Julia Gohlke,[1] William C. Griffith,[1] Scott Farrow,[2,3] and Elaine M. Faustman[1,2]

A Computational Model for Neocortical Neuronogenesis Predicts Ethanol-Induced Neocortical Neuron Number Deficits

J.M. Gohlke[a] W.C. Griffith[a] S.M. Bartell[b] T.A. Lewandowski[c] E.M. Faustman[a]

Research report

The role of cell death during neocortical neurogenesis and synaptogenesis: implications from a computational model for the rat and mouse

Julia M. Gohlke, William C. Griffith, Elaine M. Faustman*

A SYSTEMS-BASED COMPUTATIONAL MODEL OF ALCOHOL'S TOXIC EFFECTS ON BRAIN DEVELOPMENT

Julia M. Gohlke, Ph.D.; Susanne Hiller-Sturmhöfel, Ph.D.; and Elaine M. Faustman, Ph.D, DABT

Modeling developmental processes in animals: applications in neurodevelopmental toxicology

Elaine M. Faustman[a,b,c,*], Julia Gohlke[a,b,c], Nancy L. Judd[a,b,c], Thomas A. Lewandowski[a,b,c,d], Scott M. Bartell[a,b,c,e], William C. Griffith[a,b,c]

Wiley-Liss, Inc.

Birth Defects Research (Part B) 83:1–11 (2008)

Original Article

Computational Models of Ethanol-induced Neurodevelopmental Toxicity Across Species: Implications for Risk Assessment

Julia M. Gohlke, William C. Griffith, and Elaine M. Faustman*

TOXICOLOGICAL SCIENCES 86(2), 470–484 (2005)
doi:10.1093/toxsci/kfi209
Advance Access publication May 25, 2005

A Systems-Based Computational Model for Dose-Response Comparisons of Two Mode of Action Hypotheses for Ethanol-Induced Neurodevelopmental Toxicity

J. M. Gohlke,[1] W. C. Griffith, and E. M. Faustman[2]

Summary Points

To extrapolate across organisms and biological levels of complexity (cell-free, *in vitro* to *in vivo*, rodent and human) risk assessors need…

- **KINETIC** and **DYNAMIC** information
- Framework to link information across biological systems/assay conditions
- Qualitative and quantitative information
- Systems biology allows for such considerations and provides a platorm for examining mechanisms of action as well as extrapolation of results

Dr. Josef Warkany.


Mari Katayama


CALL THE MIDWIFE

Acknowledgements

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