

# Venter Symposium

# Environmental Genomics: A Key to

# Understanding Human Disease

December 06, 2005

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Director  
National Institute of Environmental  
Health Sciences





**NIEHS**

National Institute of  
Environmental Health Sciences

# Environmental Genetics and Genomics



- **Scientific Opportunities**
- **Infrastructure Needs**
- **Priorities for Program Development**



U.S. Department of Health and Human Services  
National Institute of Health  
National Institute of Environmental Health Sciences

# Environmental Genetics and Genomics

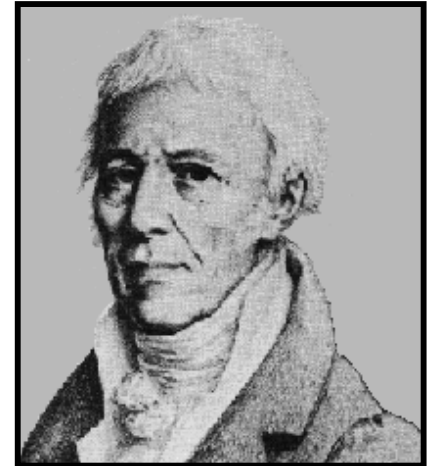


# Environmental Epigenetics

*Lamarckism Revisited*



**Inheritance of  
Acquired Traits**



**1744-1829**

**Environmental  
Stress**



**Gene  
Expression**

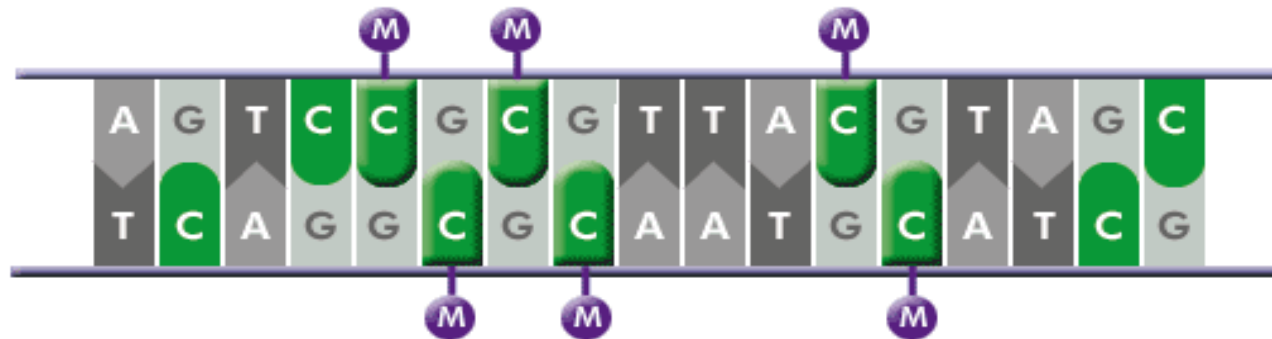


**Inherited Adverse  
Health Outcome**

# Mechanisms of Epigenetic Inheritance

*Inheritance not dependent on DNA sequence*

- **DNA Methylation** – silences gene by methylating the cytosine of a CpG motif



# Mechanisms of Epigenetic Inheritance

*Inheritance not dependent on DNA sequence*

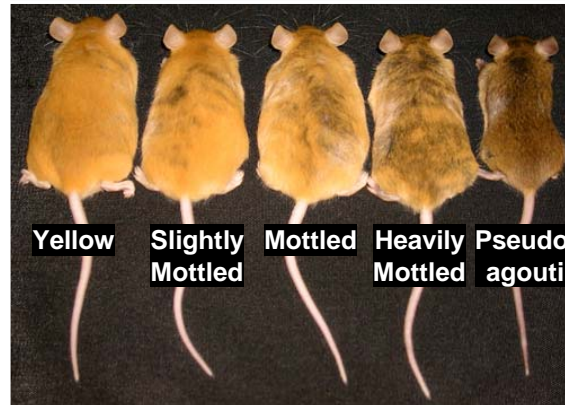
- **DNA Methylation** – silences gene by methylating the cytosine of a CpG motif
- **Genomic Imprinting** – differential methylation results in preferential silencing of maternal or paternal allele
- **Histone Modification** – methylation, acetylation, or phosphorylation of histone can regulate transcription of genes

# **Proof of Concept: Agouti Mice**

# Proof of Concept: Agouti Mice

Coat color in Agouti mice varies from black to yellow due to stochastic methylation of CpG motifs

Unmethylated *agouti*  
(expressed)



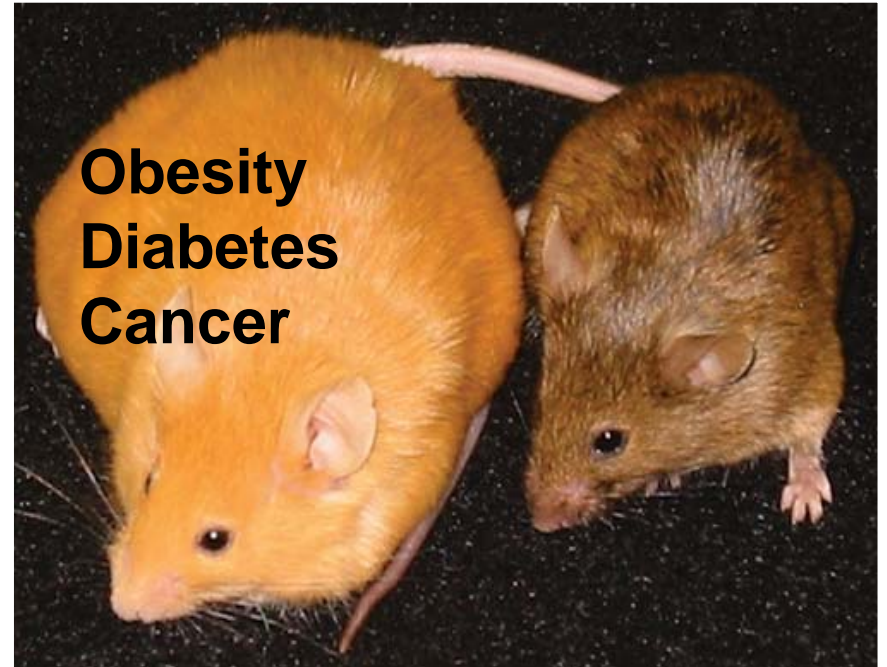
Methylated *agouti*  
(not expressed)

**Mol Cell Biol**  
**August, 2003**  
**Volume 23**



**Folate and B12 have  
transgenerational effect on  
decreased expression of the  
Agouti gene**

Bob Waterland and Randy Jirtle

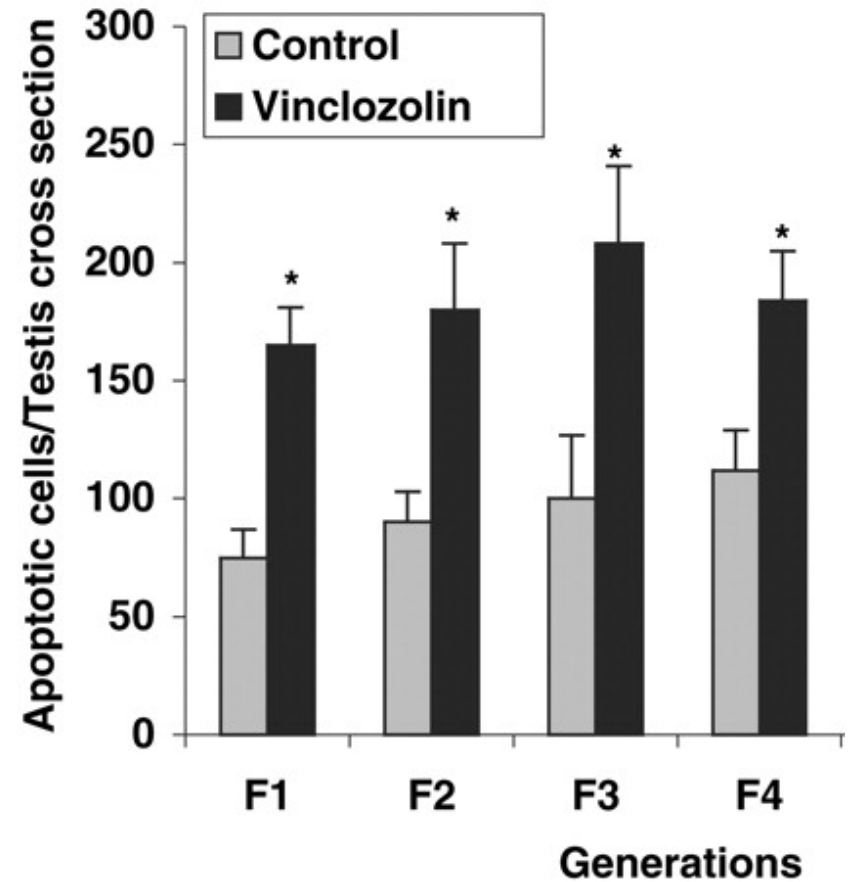


**Waterland. *Mol Cell Biol* 2003; 23:5293**



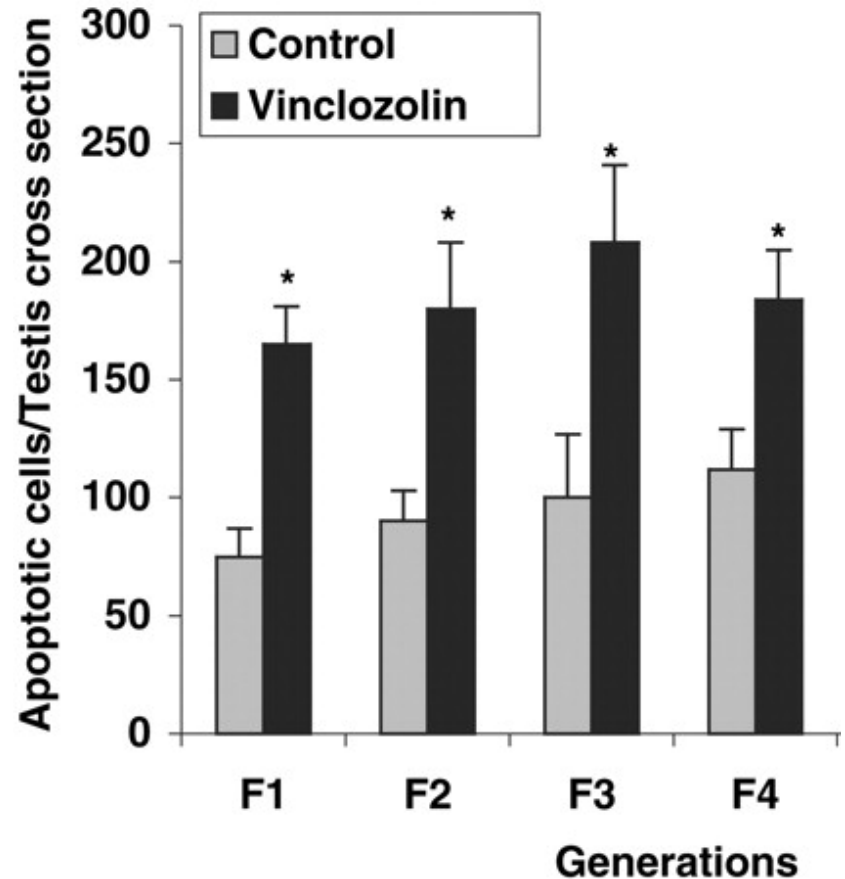
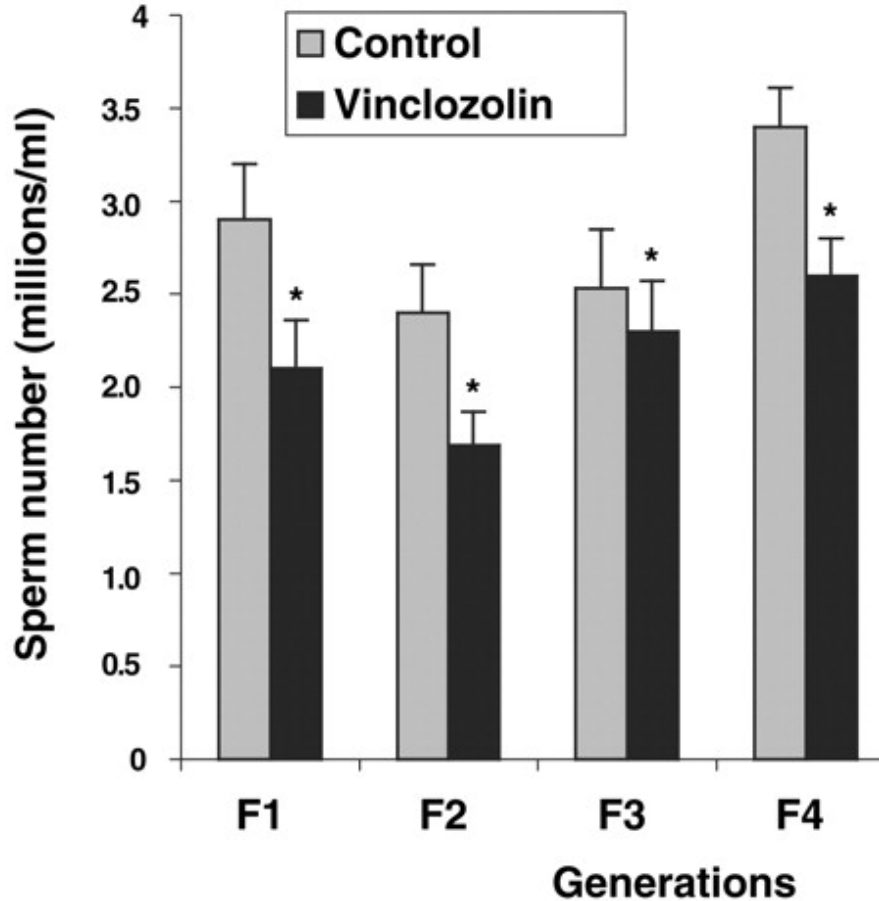
**Endocrine disruptors have transgenerational effect on male fertility**

Matt Anway et al.



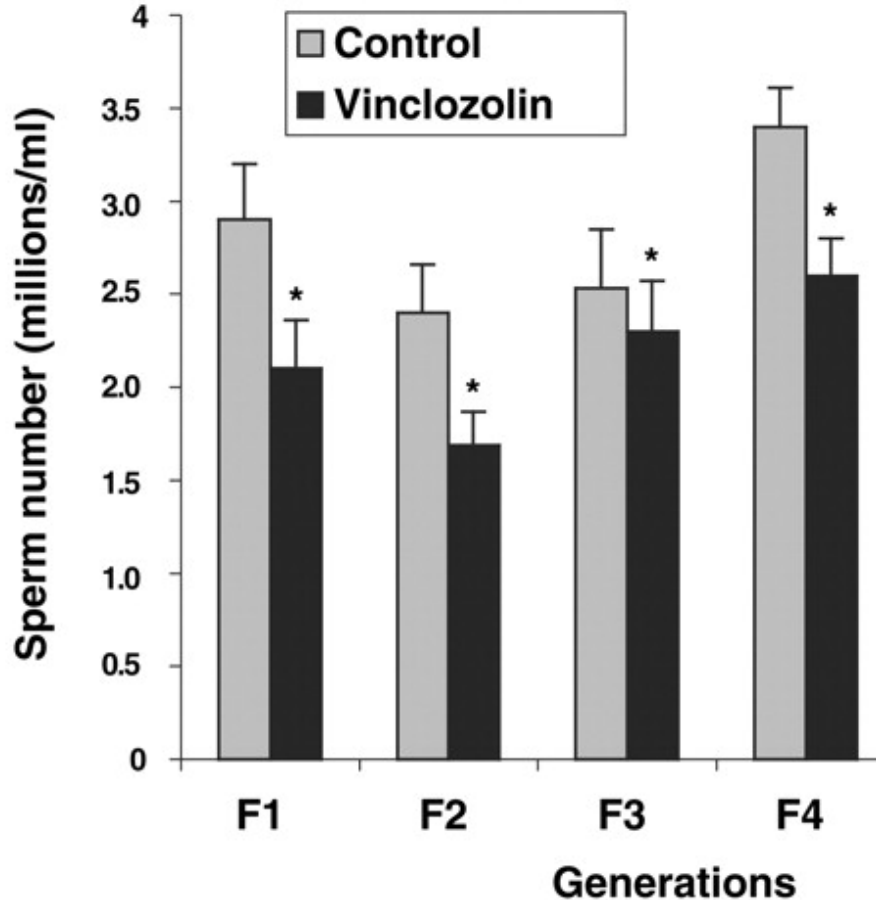
Anway. *Science* 2005; 308:1466

# Environmental Epigenetics



Anway. *Science* 2005; 308:1466

# Environmental Epigenetics



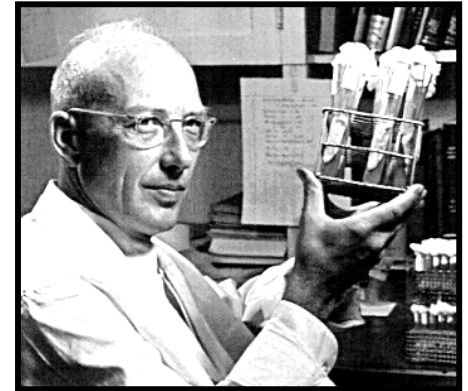
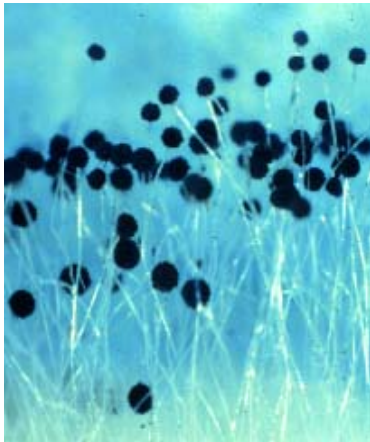
- Effects of vinclozolin (antiandrogenic fungicide) on reproduction correlated with DNA methylation patterns of specific genes
- Effects transferred through male germ line

# Environmental Genomics and Human Disease



# Environmental Genomics

*Beadle the first environmental geneticist  
(one gene – one enzyme)*



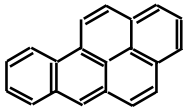
1903-1989



# Aryl Hydrocarbon Receptor (AHR)

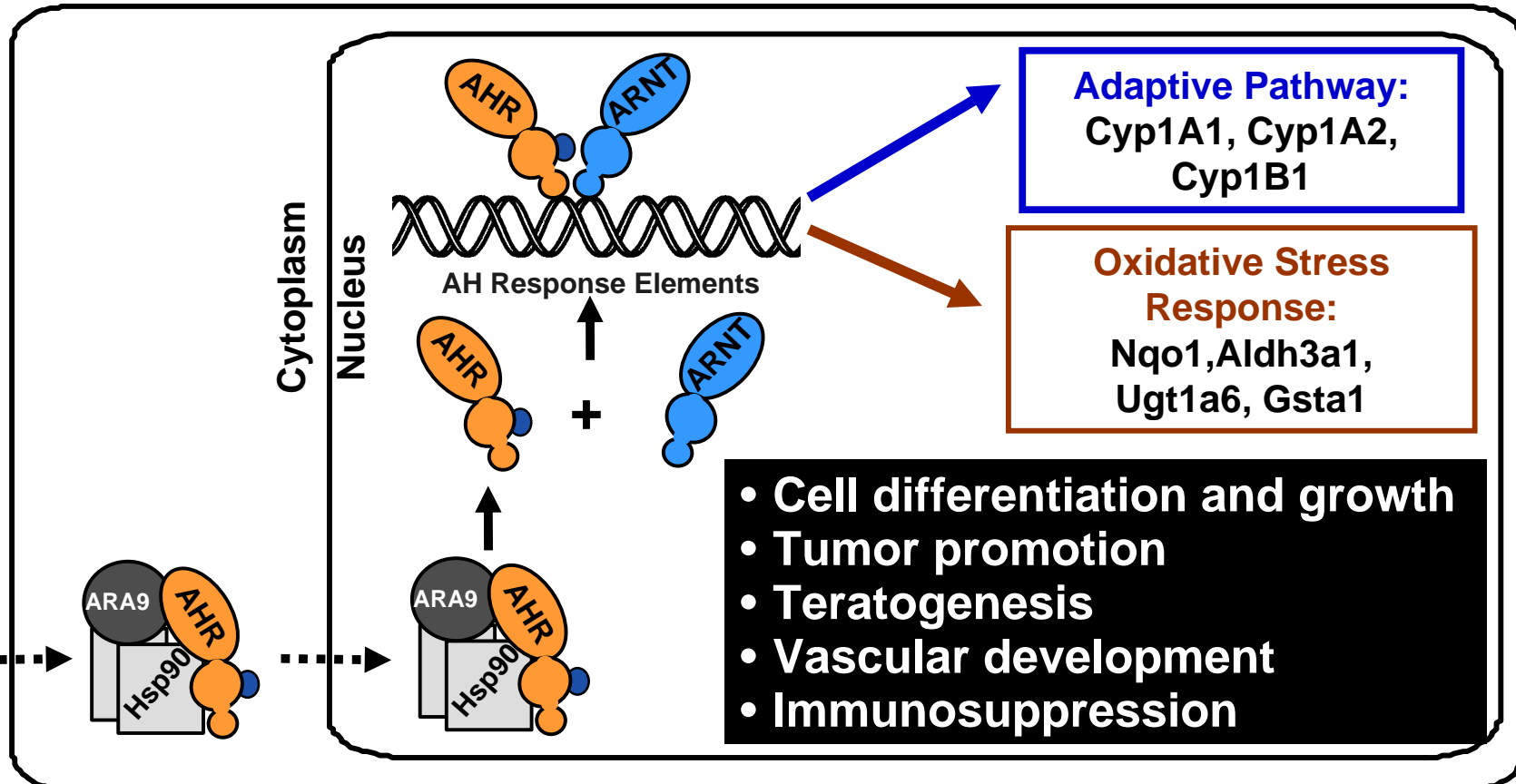
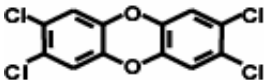
- Discovered due to the carcinogenicity of polyaromatic hydrocarbons
- One of the first receptors to mediate carcinogenesis (1st orphan receptor)
- Evolutionarily conserved (*C. elegans* to humans)

BaP



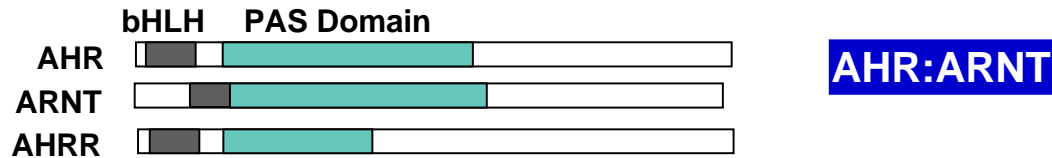
Coal tar pitch,  
tobacco smoke, and  
auto exhaust

Dioxin

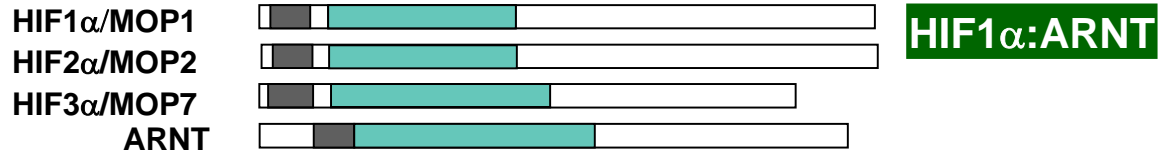


# PAS Superfamily: *Environmental Sensors*

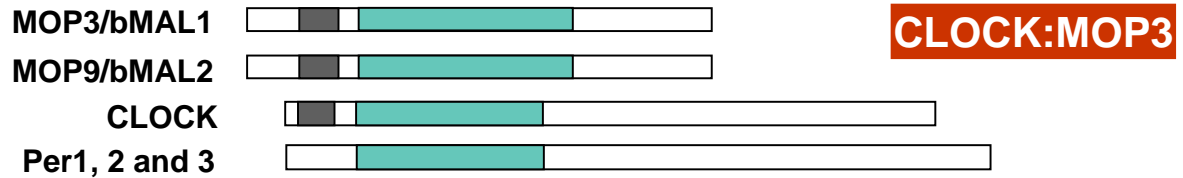
## Dioxin



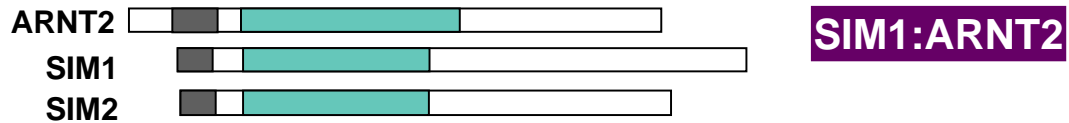
## Hypoxia



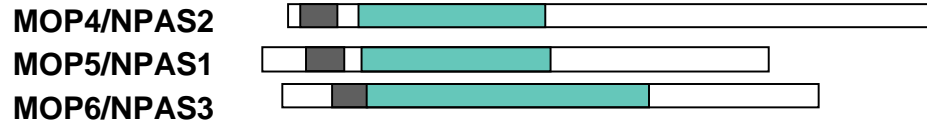
## Circadian



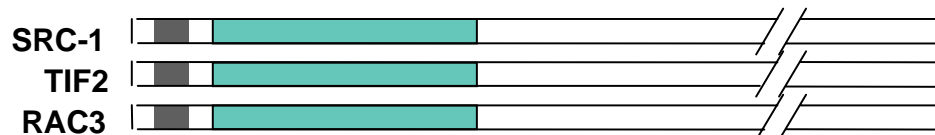
## Neurogenesis



## Orphans



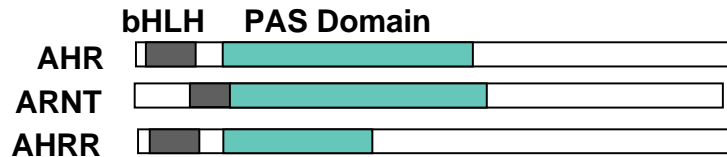
## Coactivators



100 aa

# PAS Superfamily: *Physiologic Sensors*

## Dioxin



**AHR:ARNT**

Vascular Development

Carcinogenesis

## Hypoxia



**HIF1 $\alpha$ :ARNT**

Vasculogenesis

Angiogenesis

## Circadian



**CLOCK:MOP3**

Circadian Rhythms

Joint Maintenance

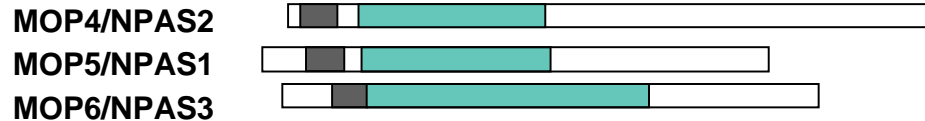
## Neurogenesis



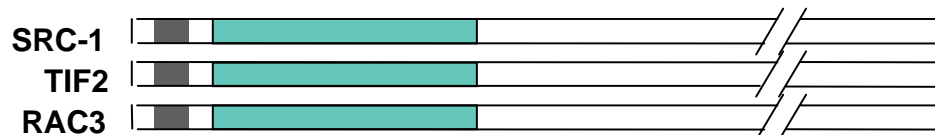
**SIM1:ARNT2**

Learning

## Orphans



## Coactivators

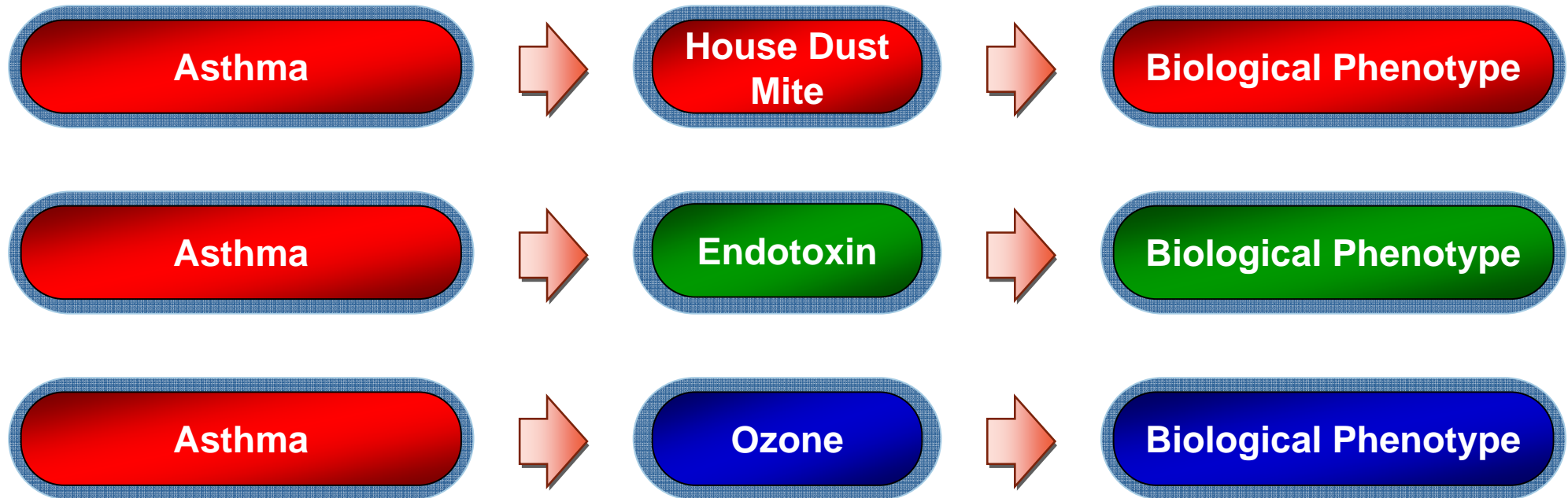


100 aa

# Exposures Can Simplify Complex Diseases



# Exposures Can Simplify Complex Diseases



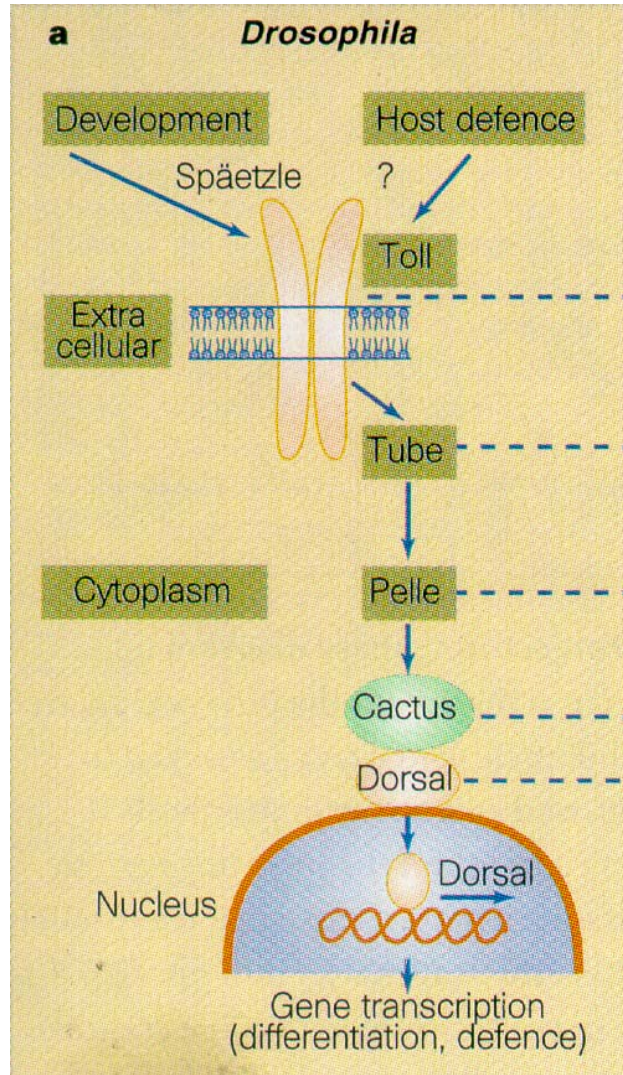
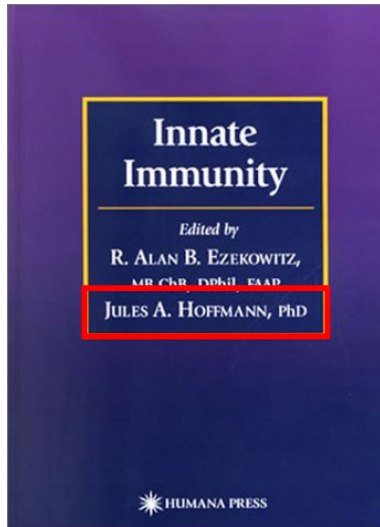
# Comparative Genomics

*Evolutionary Conservation of Biology*



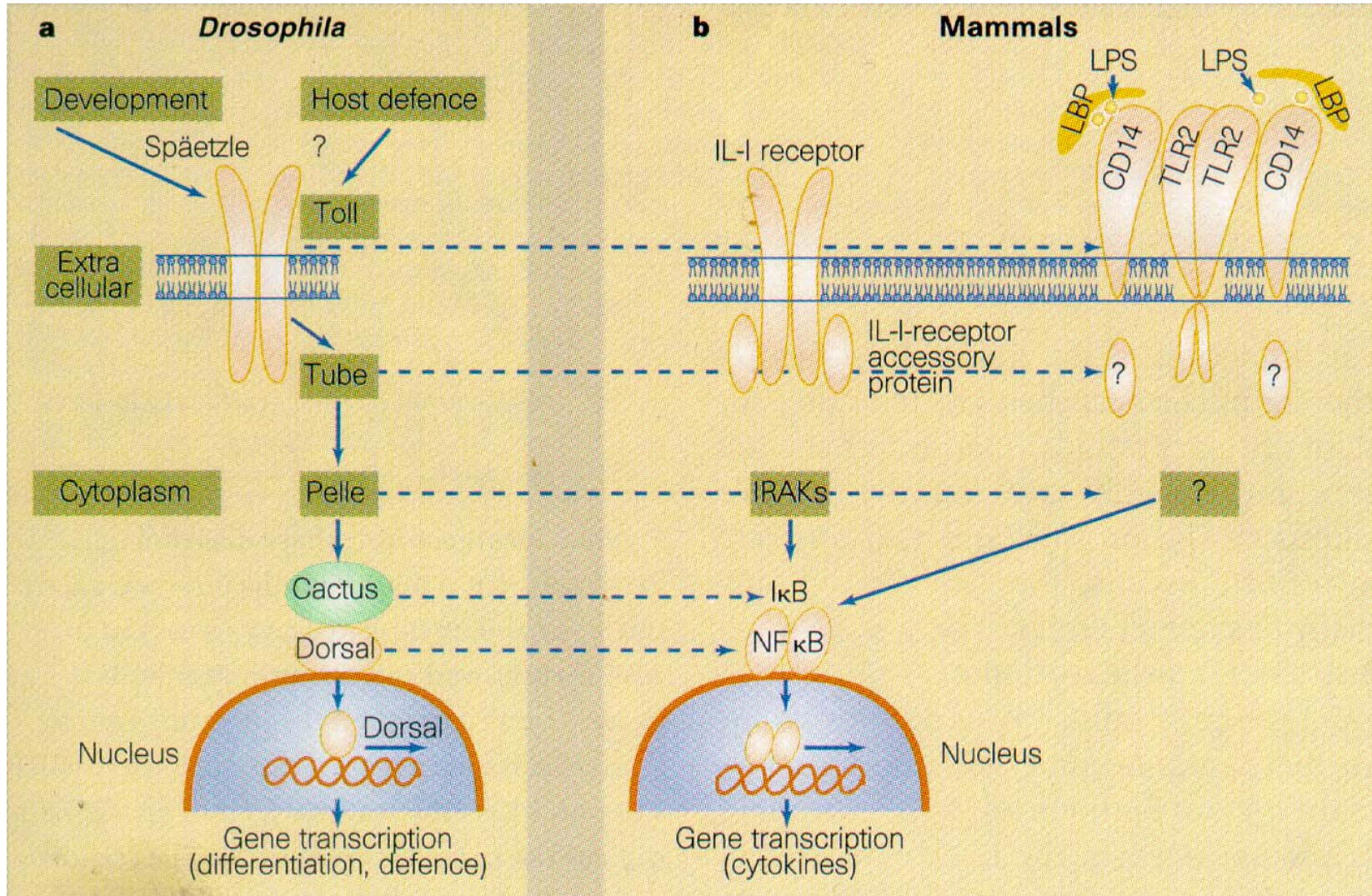
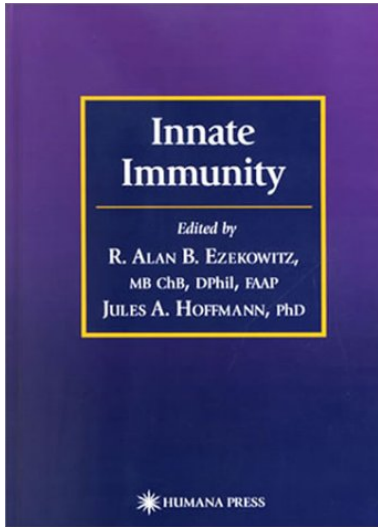
# Comparative Genomics

## *Evolutionary Conservation of Biology*



# Comparative Genomics

## Evolutionary Conservation of Biology



nature  
*genetics*

Volume 25  
June, 2000



**Polymorphisms in *TLR4*  
blunt the response to LPS in  
humans**

Brian Schutte et al.



The  
New England  
Journal of Medicine

Volume 347

July 18, 2002

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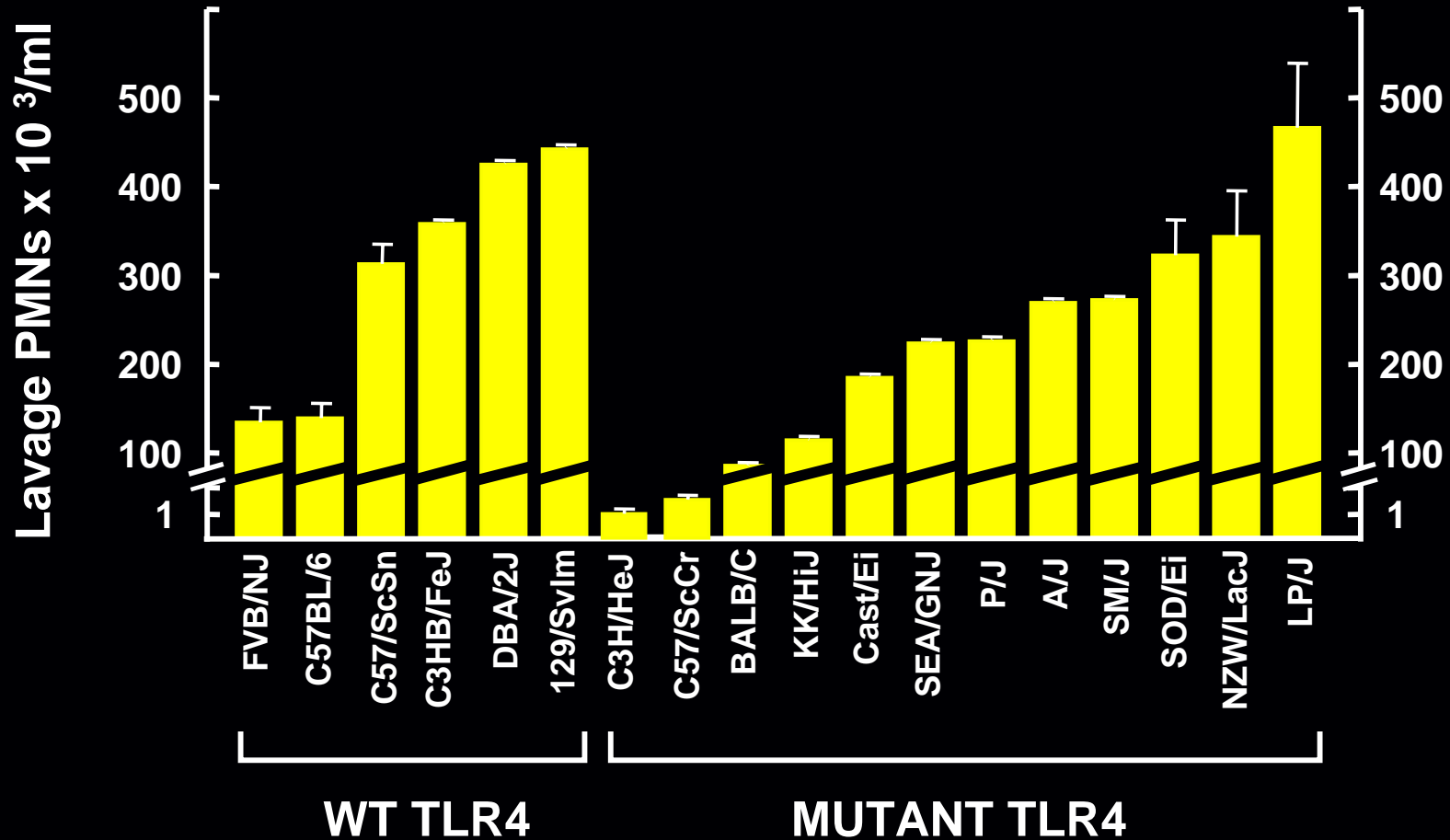
**CLINICAL IMPLICATIONS  
OF BASIC RESEARCH**

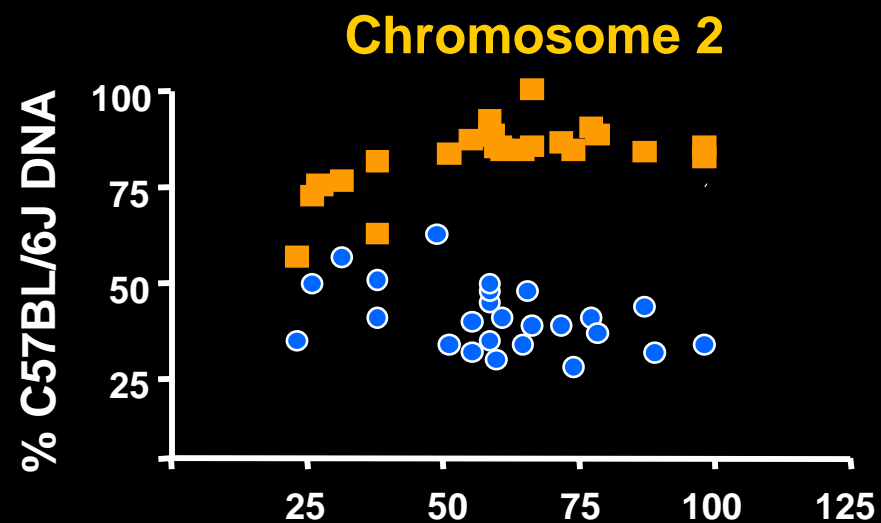
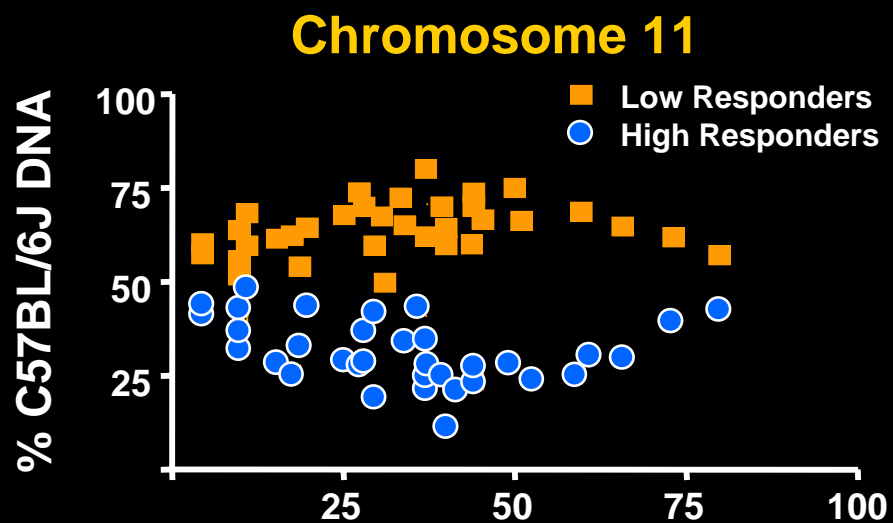
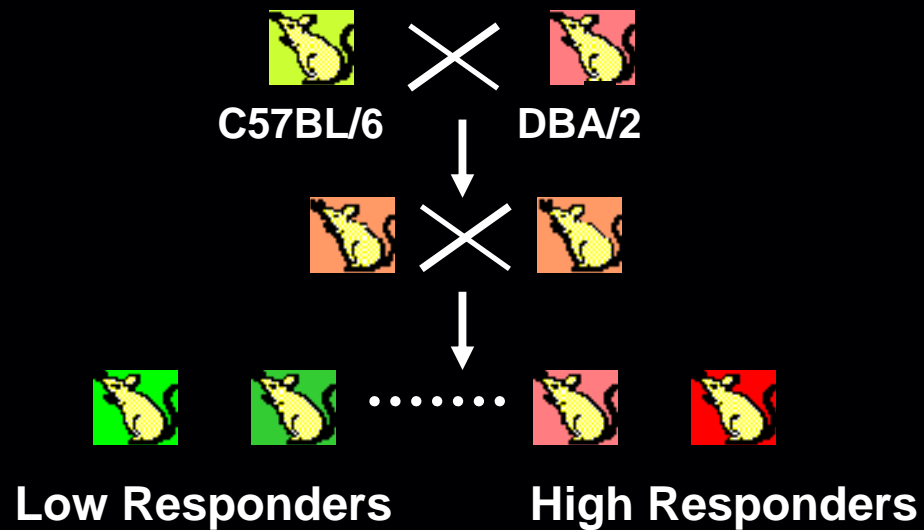
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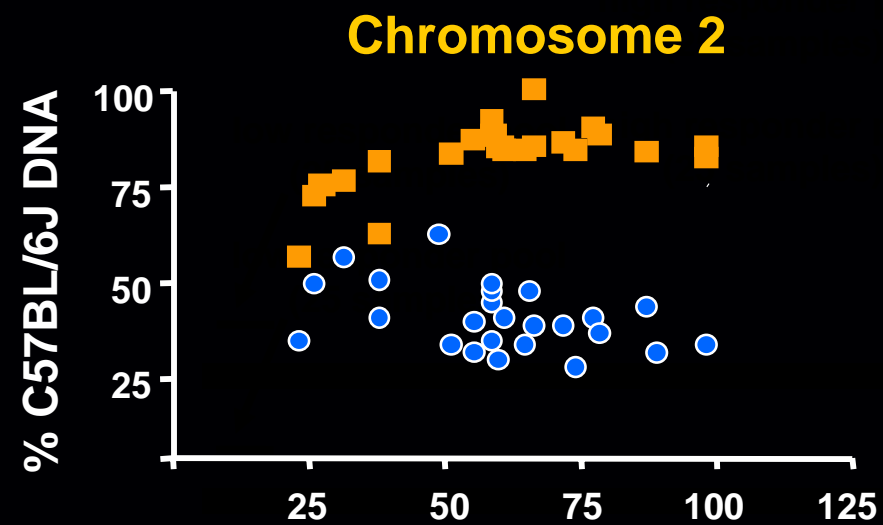
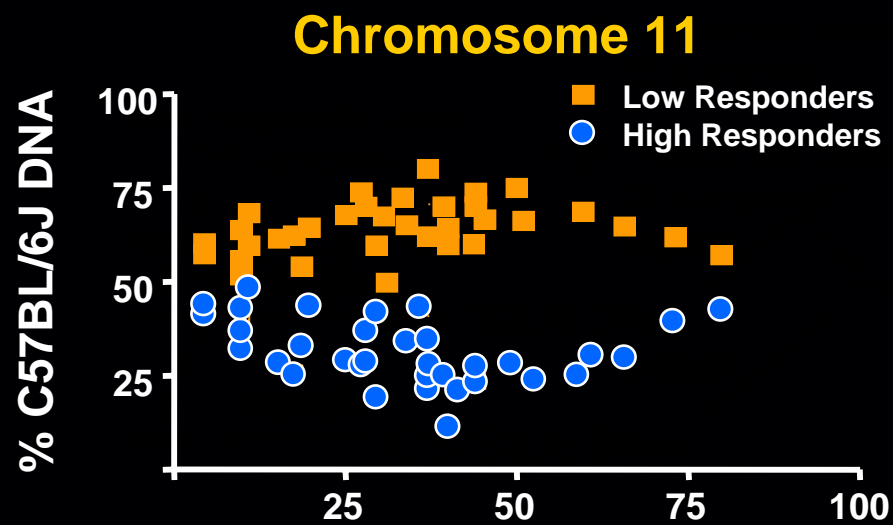
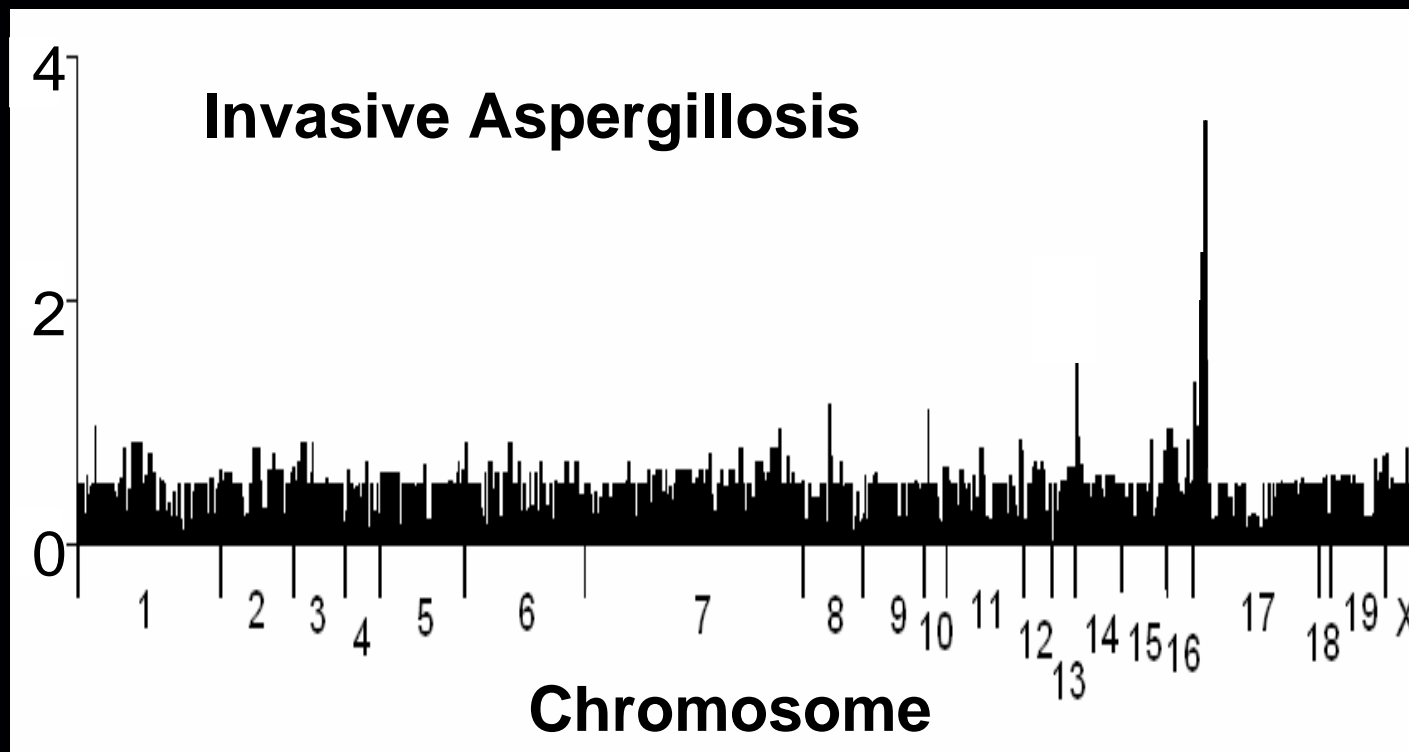
**Polymorphisms in *TLR4*  
protect humans from  
atherosclerosis**

Steven Kiechl et al.

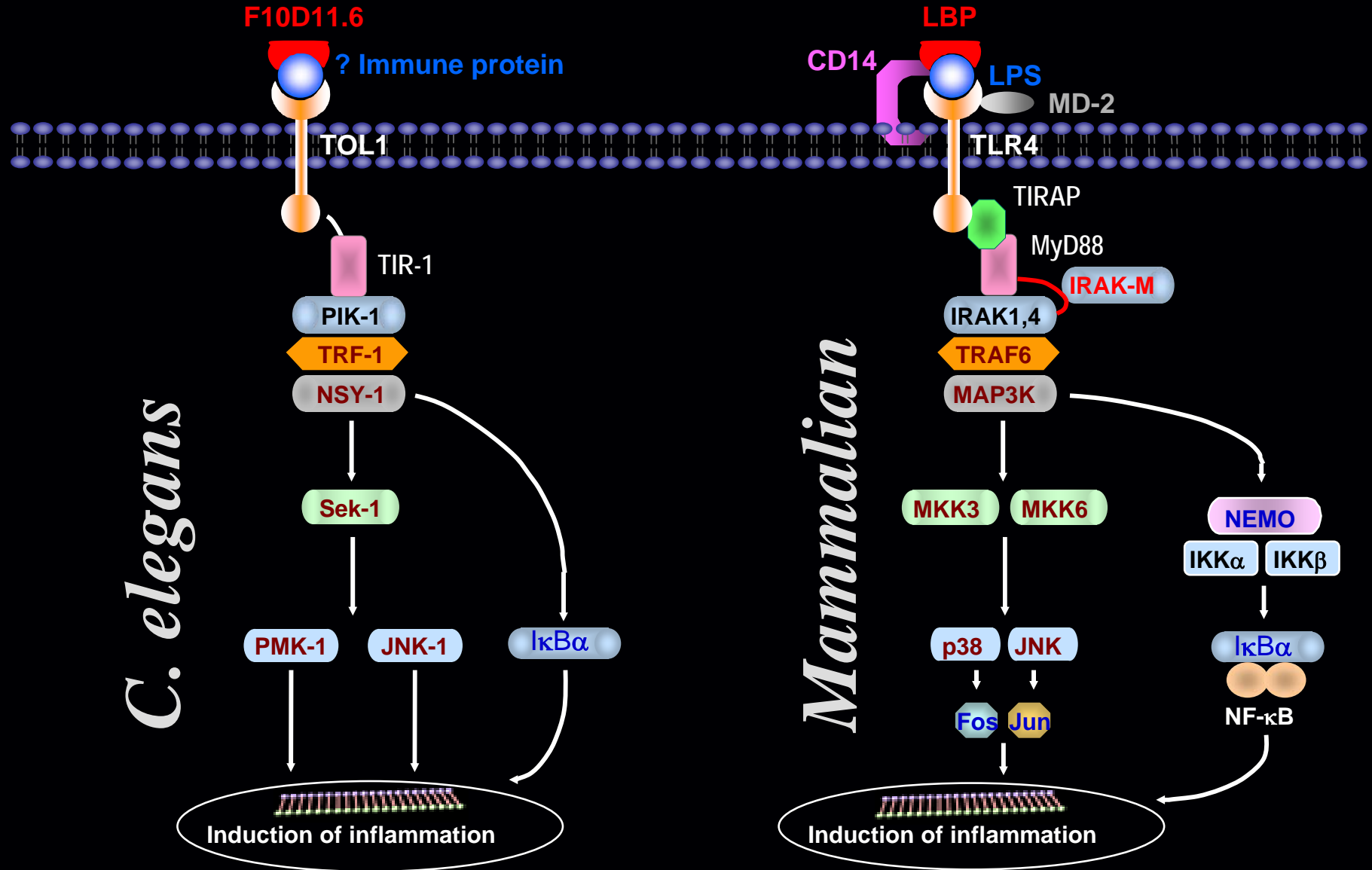
# LPS Responsiveness in Inbred Strains of Mice



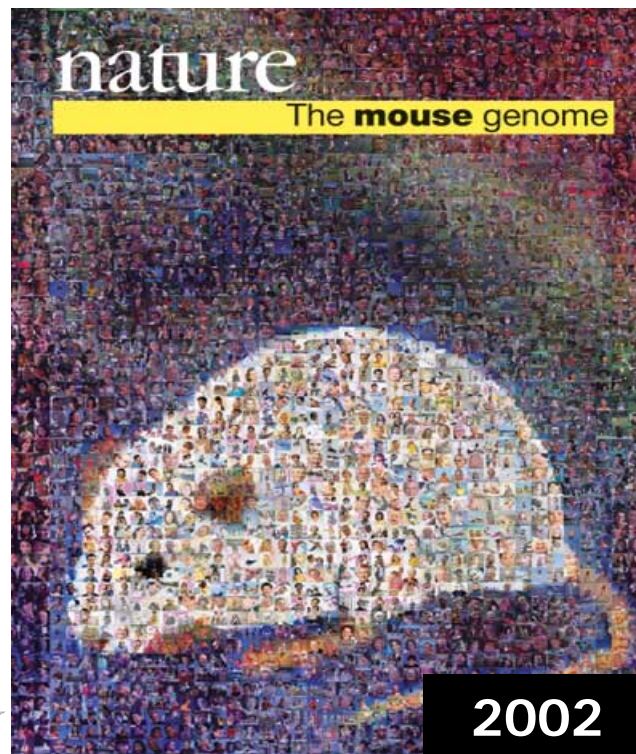




# Comparative Genomics in Innate Immunity



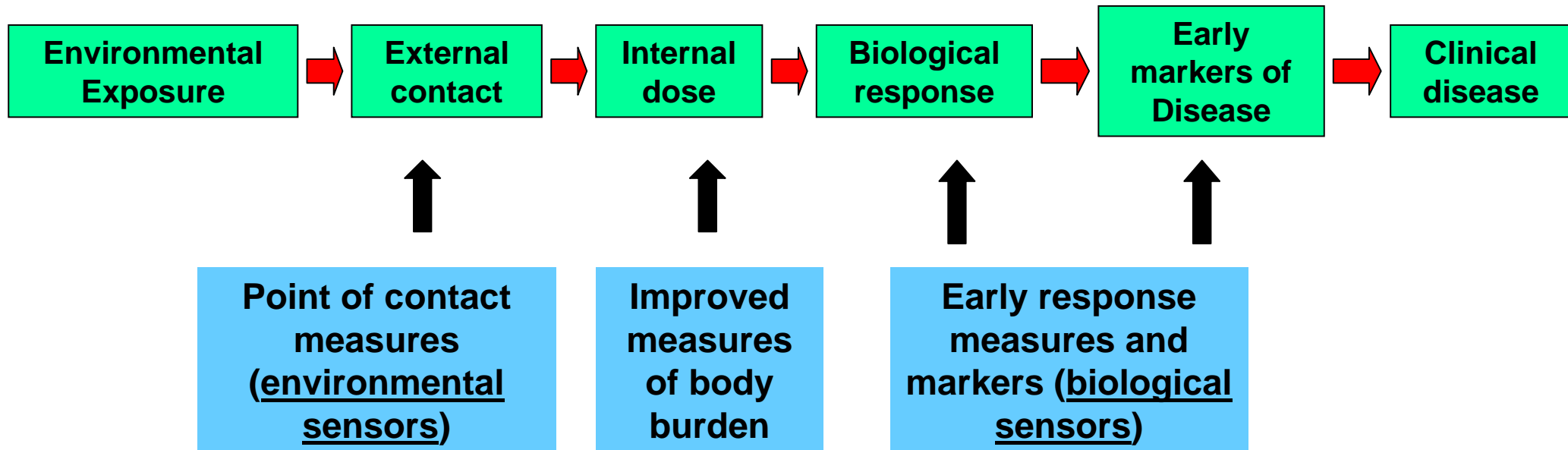
# Why Don't We Know More?



***Genes are only a small part of our make-up...  
the environment has a spectacular impact***

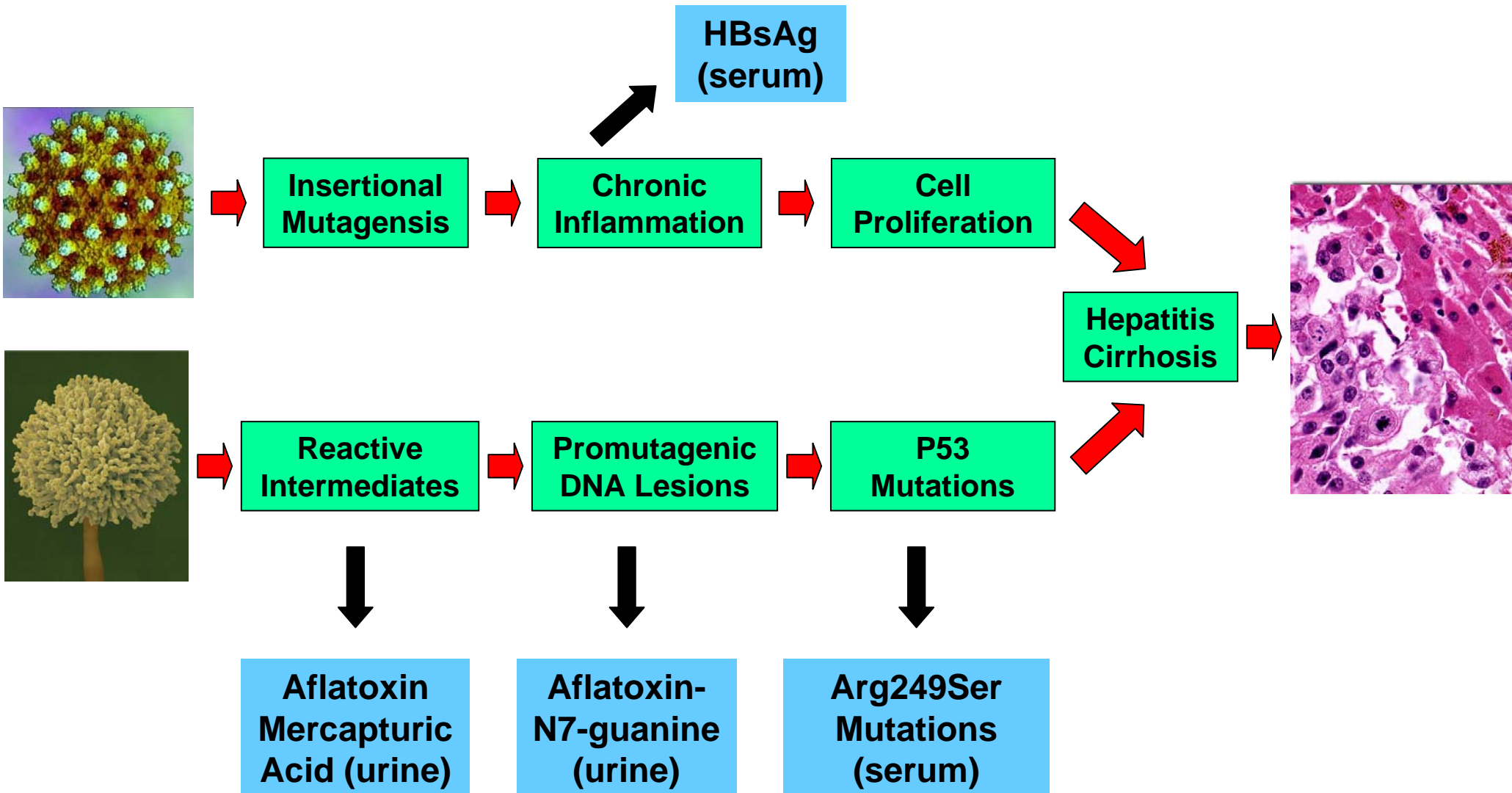
**Eric Lander**

# Infrastructure Needs: More Precise Markers of Exposure

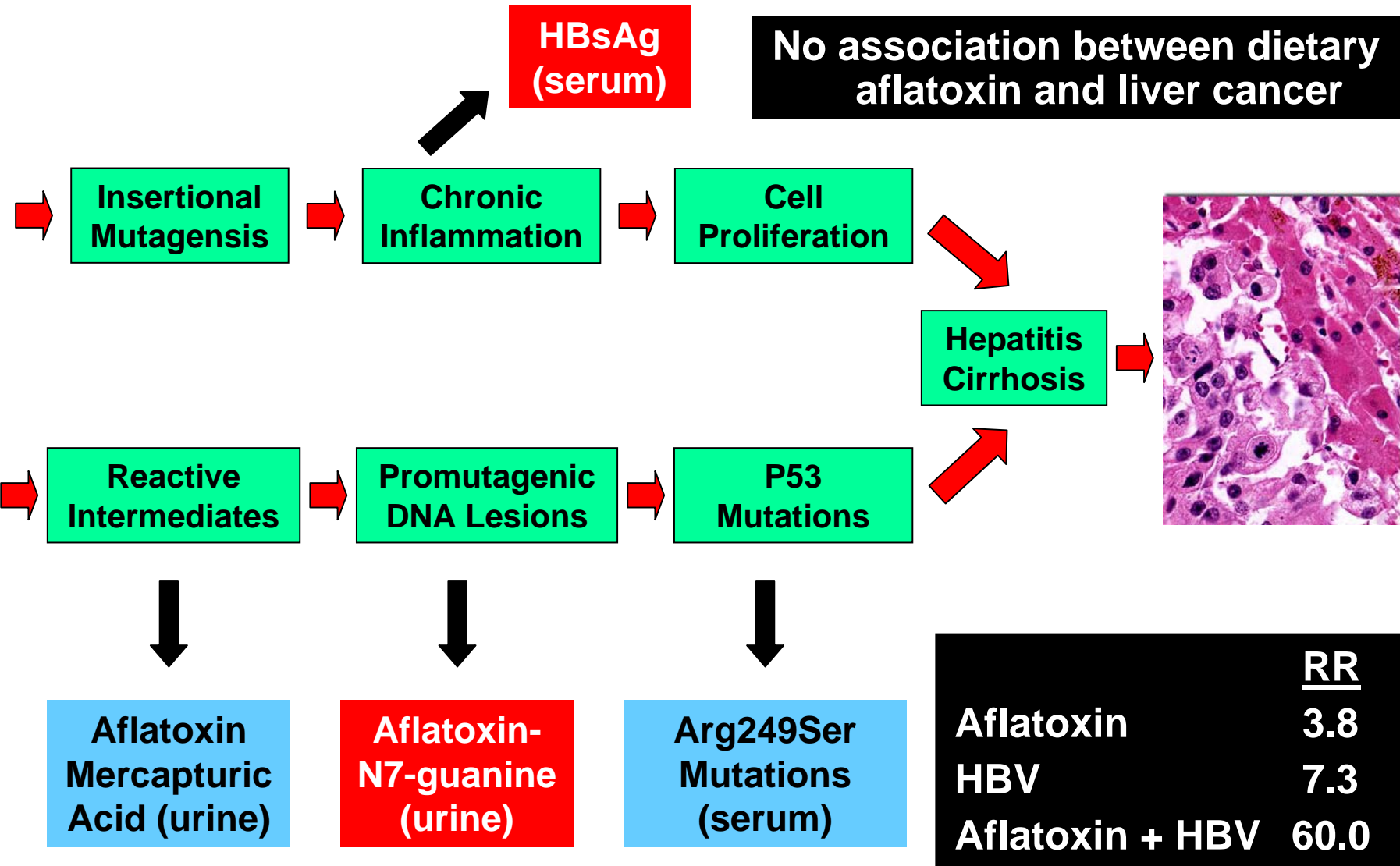
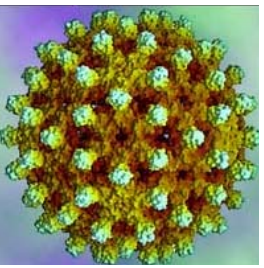


**Links personal exposures to biological response**

# Etiology of Hepatocellular Carcinoma



# Etiology of Hepatocellular Carcinoma



# Gene – Environment Prospective Cohort

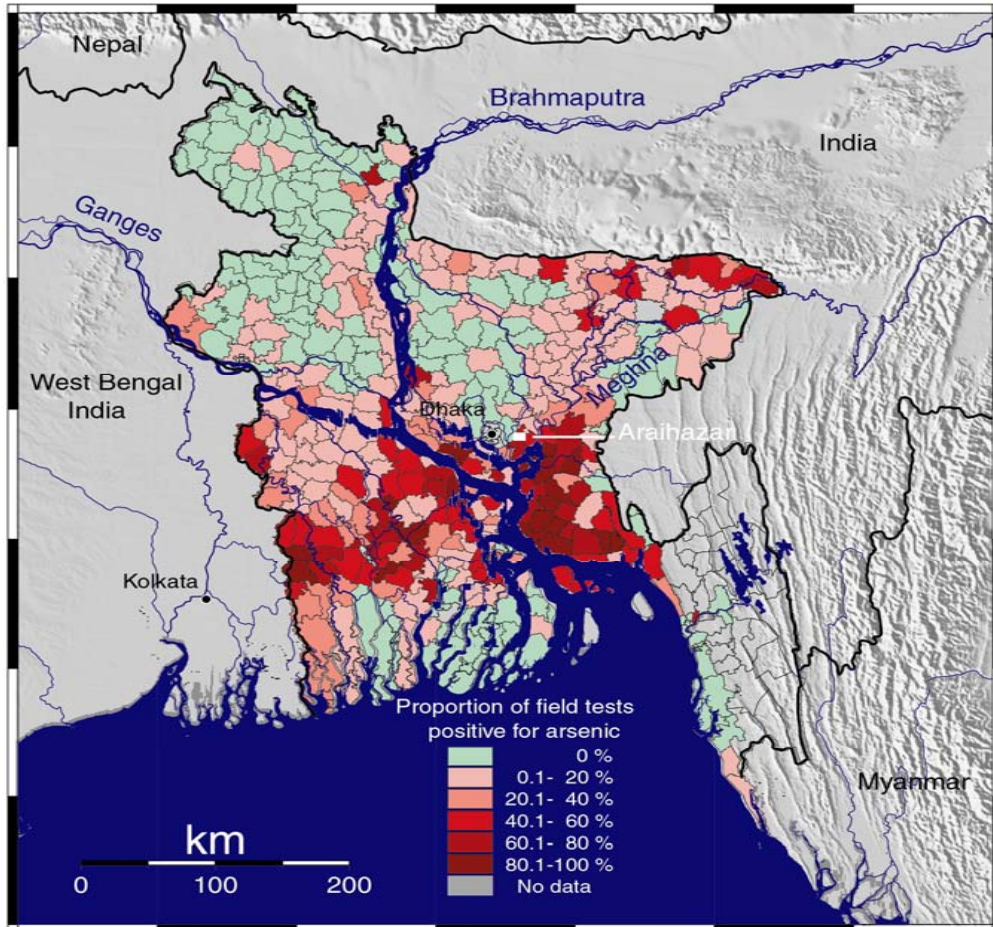
- **Large sample size – at least 500,000**
- **Demographics and environmental exposures to match U.S. population**
- **Personalized exposure assessment**
- **Precise phenotypes**

**Effective approach to identify the role of genes and environment on the development of disease**

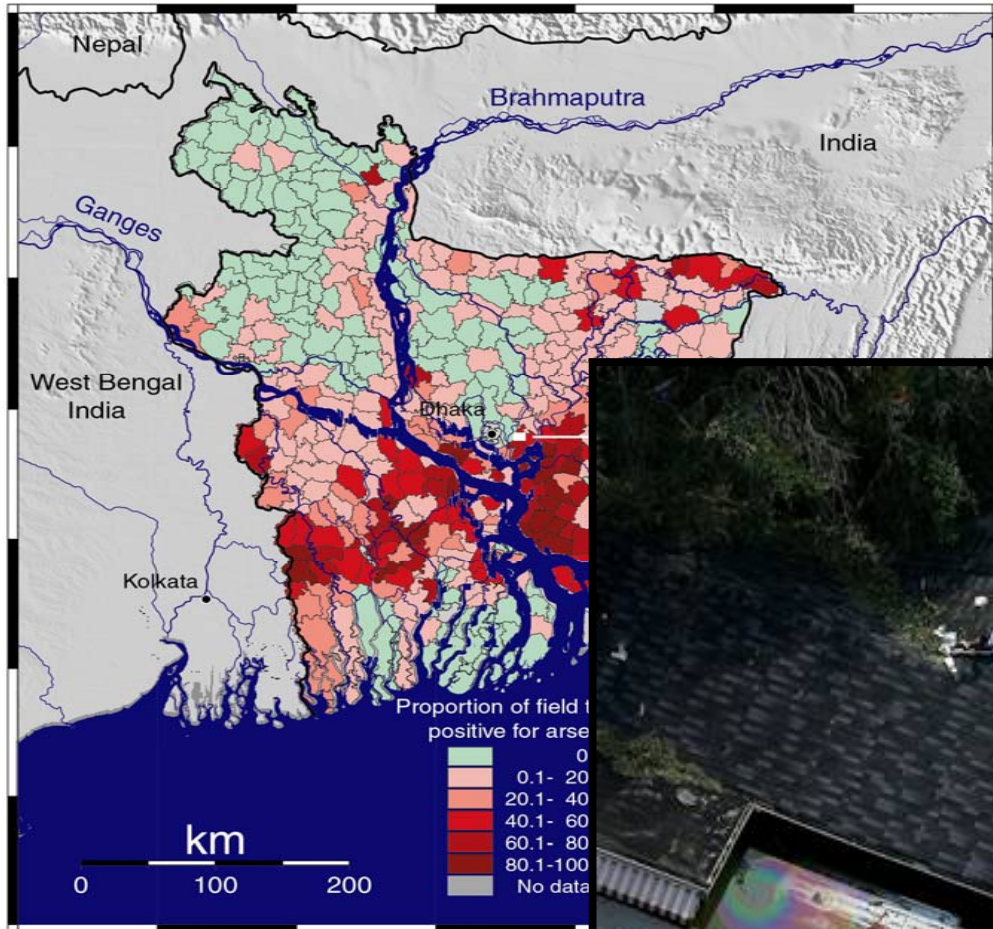
# Prioritize Diseases and Populations

- **International patterns of disease (rates, geographical distribution, and changes with migration)**
- **Familial and twin studies (genetic vs. environmental contribution to disease phenotype)**
- **Populations exposed to high concentrations of common toxins**

# Global Environmental Health



# Global Environmental Health



# Priorities for Program Development

- **Impact on Human Health and Disease**
  - Programmatic research focusing on complex human diseases
  - Enhance role of physician scientist
- **Environmental Genomics**
  - Epigenetics
  - Comparative biology/genomics
  - Training in environmental genomics
- **Exposure Biology Initiative**
- **Global Environmental Health**