NTP
National Toxicology Program

Update - NTP Host Susceptibility Initiative

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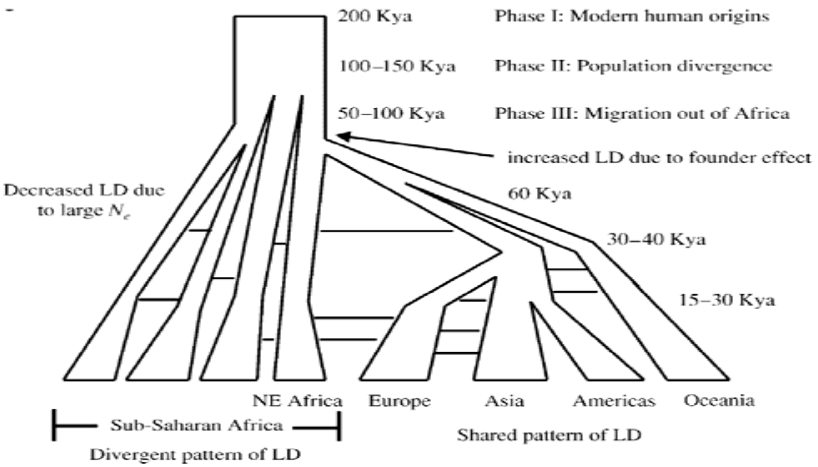
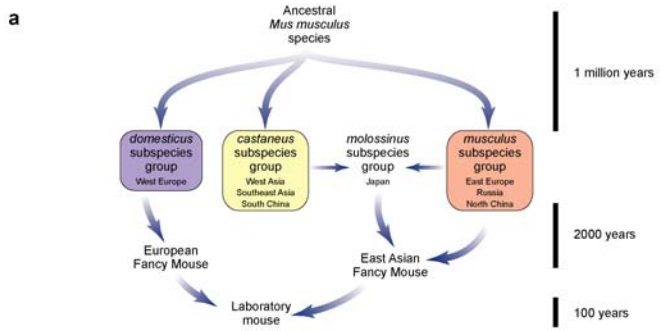
NIEHS
National Institute of Environmental Health Sciences

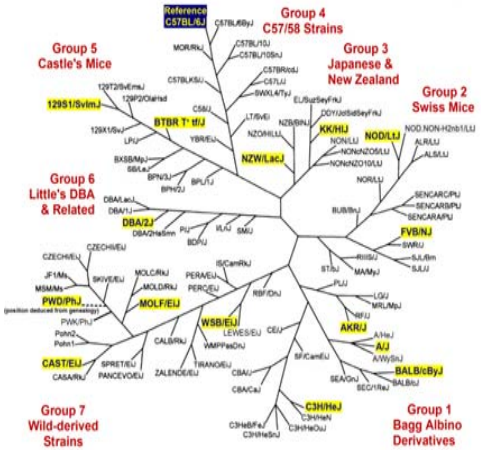
NATIONAL INSTITUTES OF HEALTH

Host (Individual) Susceptibility

- ***Host susceptibility*** to disease is definec by the interaction between multiple ***host*** (genetics, behavior,nutritional status, life stage, etc.) and ***environmental factors*** (cold, heat, diet, infectious agents, environmental toxicants, etc.).
- The elucidation of the role of ***genetic variation*** on environmental toxicant ***exposure*** in complex toxicity phenotypes and the ***range of biological response*** in genetically diverse animal models is our initial goal.







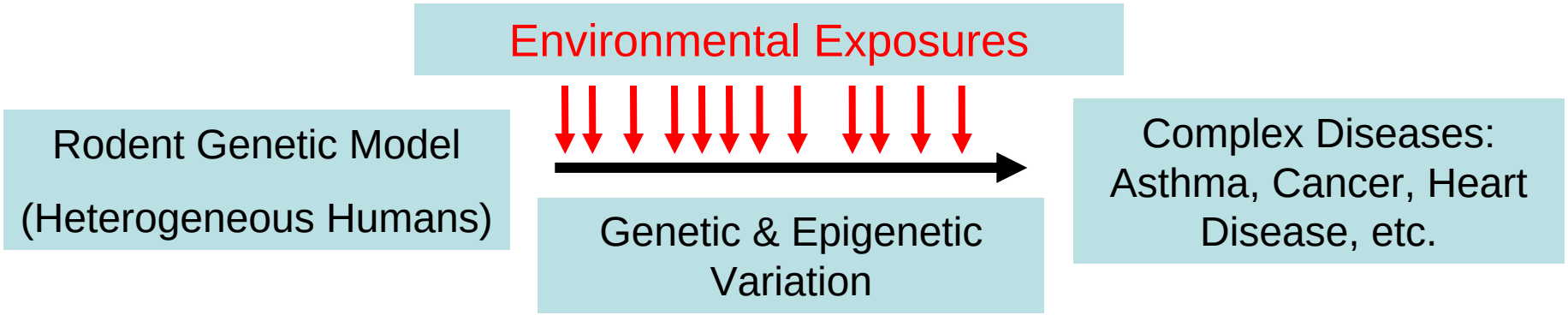
Development of the Host susceptibility Initiative

- **NTP/NIEHS Discussions**
  - Intramural Research Scientists (Series-Meetings)
  - NTP BSC 13 June 2006
  - NTP Retreat, RTP, 18-19 October 2006
  - NTP BSC Concept Review, 1 December 2006
- **Consultation with Extramural experts**
  - Extramural Experts (Mouse Genomics), NIEHS 21July2006
  - CTC, Braunschweig, Germany May 2007
  - ToxForum, Aspen, July 2007
- **Announcements and requests for input**
  - NIH Guide & Federal Register RFI, 14 October 2007
  - SOT Workshop, Seattle, 18 March 2008
- **Assessment of potential intramural-extramural collaboration models**
  - Models - NIH RAID; NCI RAID; R03/X01, R01, etc.
  - Joe Tomaszewski, NCI RAID, 30 November 2007

HSI-Request for Public Input

- **NIH Guide & Federal Register RFI (October 2007)**
- **25 informative of 27 unique responses from different 21 institutions**
  - STRONG SUPPORT
- **Survey highlights**
  - Genetic variation, a critical parameter; uncertain correlation between species
  - Select toxicants of public health and human importance
  - Systems approach necessary
  - Multidisciplinary collaborative research critical
  - Develop NTP resource centers
    - Bioinformatics, RNA & DNA microarrays; high dimensional data set analysis

Genetic Variation and Host Susceptibility to Environmental Toxicants



$$\text{Phenotype} = [G + E + (G \times E)] \times T$$

- To predict potential population-level ranges of biological response to aid across species extrapolation and risk characterization
- To identify and functional characterize allelic variants of genes that are associated with individual differences (mouse and human orthologs) in response to toxicant exposure
- To identify the genetic basis and MOA for toxicity and disease in animal models and to correlate with human disease genes to aid extrapolation and prediction between species

NTP Host Susceptibility Branch (HNV2E3; HSB)

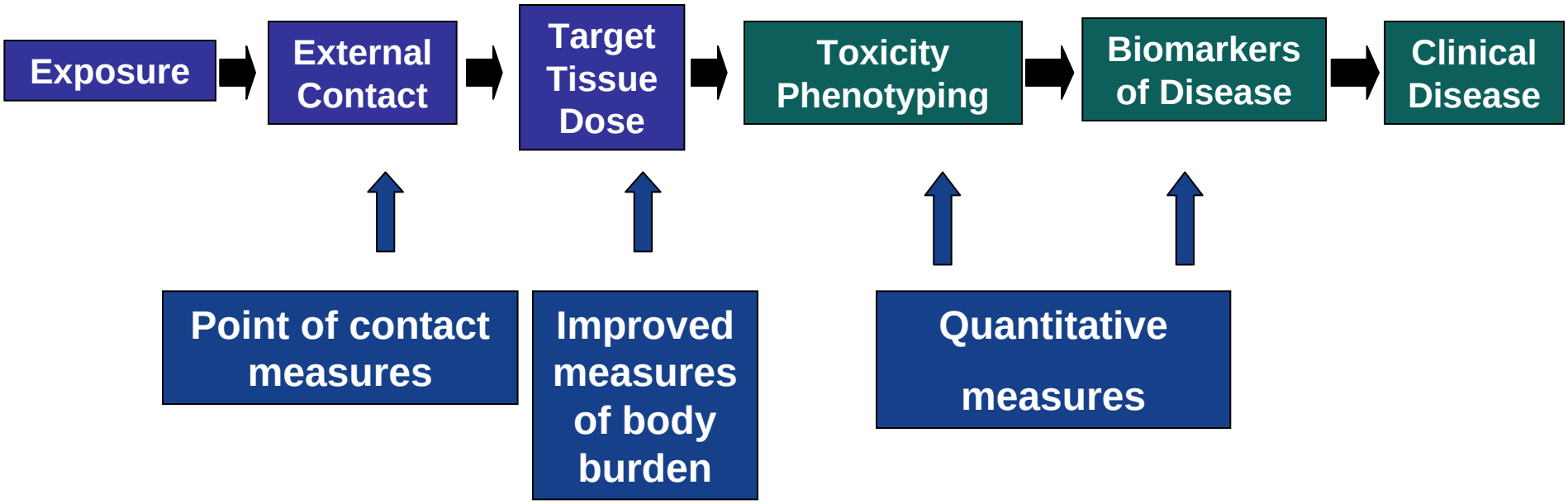
- **Created as part of the NTP Realignment (October 2007)**
- **Core HSB Staff**
  - Cunningham, M. (ADME; Carcinogenicity; Toxicology)
  - French, JE (Carcinogenicity; GMM, Molecular Genetics)
  - Irwin, R (Adjunct; Toxicology, Toxicogenomics)
  - Johnson, F (Genetics)
  - Hoehnerhoff, M. (Adjunct; molecular pathology/toxicology)
  - Stasiewicz, S (Program and Project Officer)
  - Geneticist (to be hired)
  - Environmental Genomicist (to be hired)
- **Adjunct NIEHS staff & collaborators**
  - Dunnick, J (Cardiotoxicity; Cancer; Toxicology)
  - Kissling, G. (Biostatistics)
  - Kamel, F (Epidemiology)
  - Bioinformaticist/Computation Biologist (Biostatistics; in progress)
  - Computational Biology Facility (Grovenstein, J; Reter, R; Tyson, M)

Environmental Toxicant Exposure

Dose & Dose Rate

ADME

Genetic and Epigenetic Basis for Susceptibility

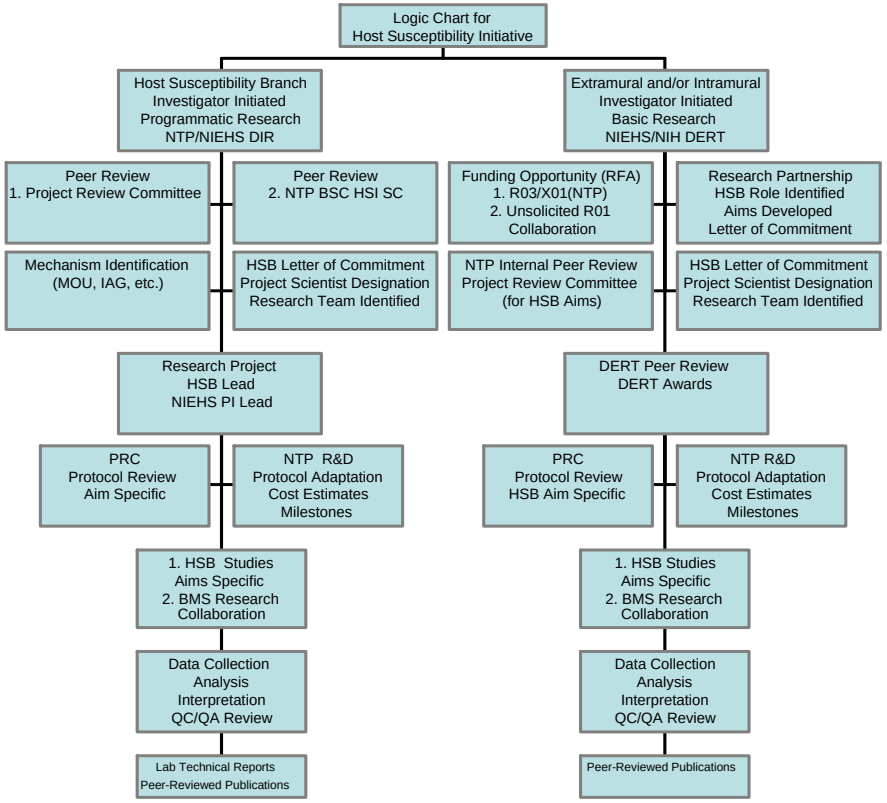


Link individual exposure to biology and to disease

(Adapted from National Research Council, 1987)

HSI Process

- **Intramural Research**
  - HSB Initiated Programmatic Research
- **Extramural Research Partnerships**
  - Capitalizing on new & novel gene x environment interaction research and new technologies
  - Support R03-X01 small grants and/or R01 research
    - Use NTP contract resources through X01 mechanisms
    - DERT oversight & management
- **Oversight**
  - Through Internal & External Peer Review
- **Communication**
  - Publish peer-reviewed technical and open literature of the highest level



Intramural Research Projects: Developing Tools

- **In Progress or in Planning (Lead Scientists)**
  - ADME: Benzene, BCEM (Cunningham)
  - Biomolecular Screening (French & Tice)
  - Cardiotoxicity, BCEM, Ephedra (Dunnick)
  - Collaborative Cross Heterogeneous Mouse Stock
  - Short-term Cancer Bioassays (*Trp53* & DNA repair models; French)

- **Nominations (In planning)**
  - Benzene (Smith & Rappaport, UC-Berkeley)
  - Cardiotoxins & Hepatotoxins (Jacobson-Kram, CDER, FDA)

Next steps - short term and long term goals

- **Complete creation of HSB**
  - Recruit Chief, Host Susceptibility Branch
  - Recruit Geneticist
  - Recruit Environmental Genomicist
- **Intramural Research:**
  - Develop portfolio on programmatic mission research to complement needs of participating NTP agencies
  - Identify and develop NIEHS intramural collaborative research partnerships
  - Encourage agent specific nominations from federal agencies, intramural and extramural scientists to use genetic models for toxicology
  - Evaluate pilot projects and development of requisite tools
- **Extramural partnerships**
  - Assist development and implementation of DERT peer reviewed R03/X01 and R01/X01 collaborations with the extramural research community
  - Develop peer reviewed partnerships with industry labs where appropriate
- **Oversight**
  - Create a Host Susceptibility NTP BSC Subcommittee (members plus ad hoc) to provide advice and oversight

Questions/Discussion