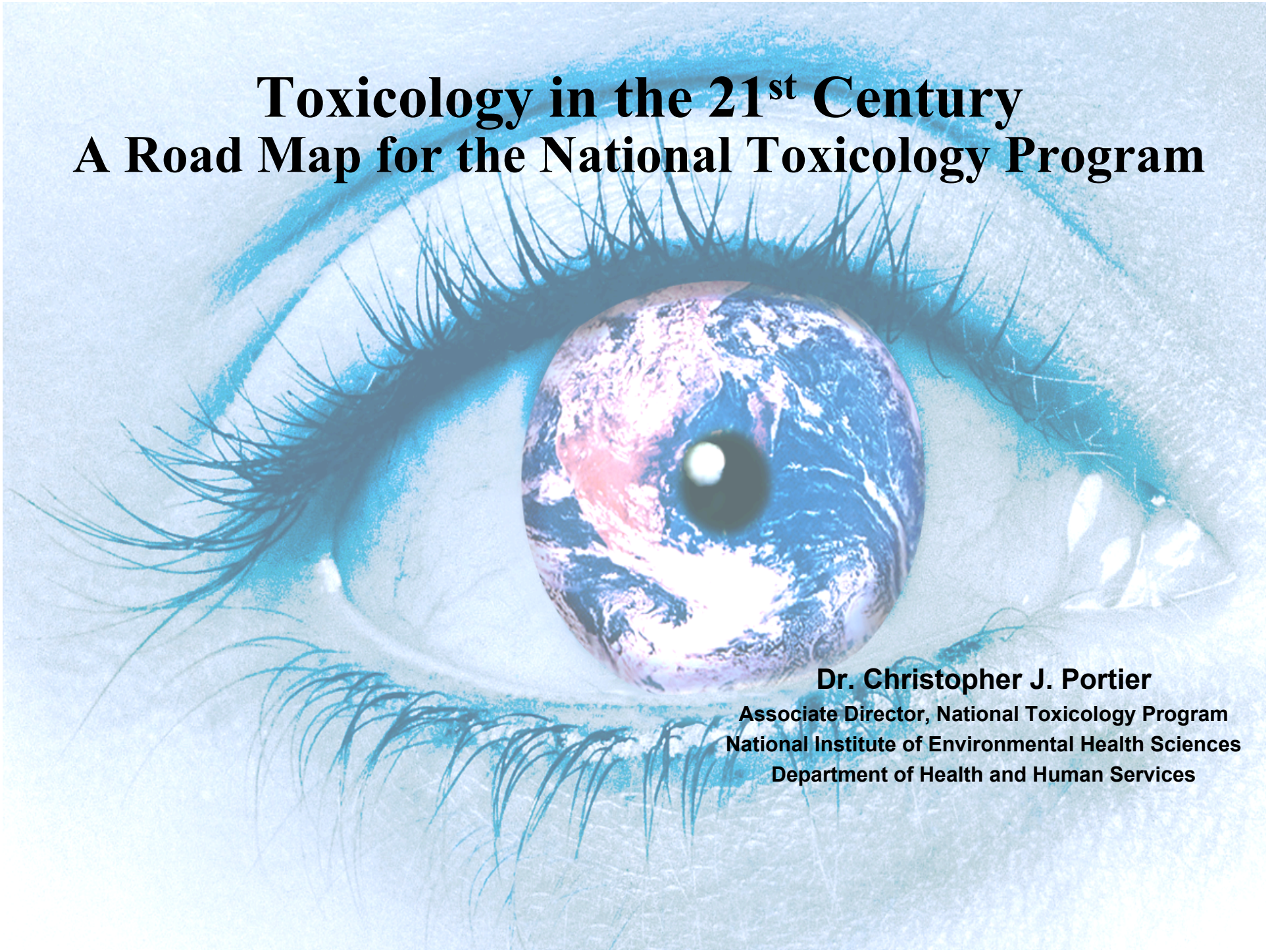
# Toxicology in the 21st Century
## A Road Map for the National Toxicology Program



**Dr. Christopher J. Portier**
**Associate Director, National Toxicology Program**
**National Institute of Environmental Health Sciences**
**Department of Health and Human Services**

# 25 Years of the NTP

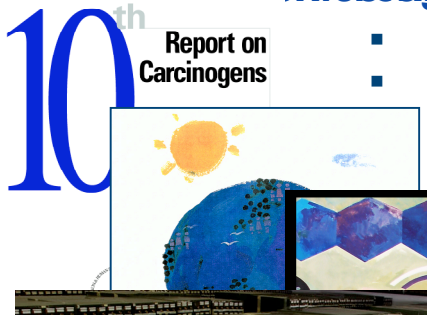
Basic Research

Public Health

Research In Toxicology

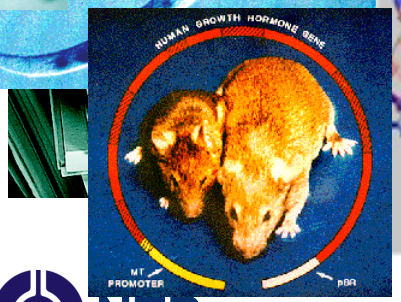
Testing And Evaluation

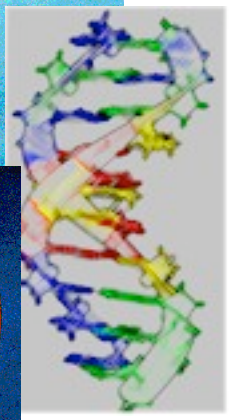
- Improved toxicology d
- Toxicology d
  - Cancer
  - Immunotoxi
  - Genetic tox
  - Tissue bloc









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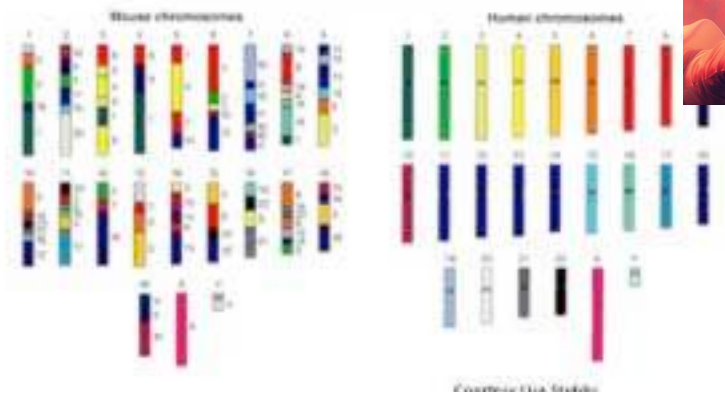
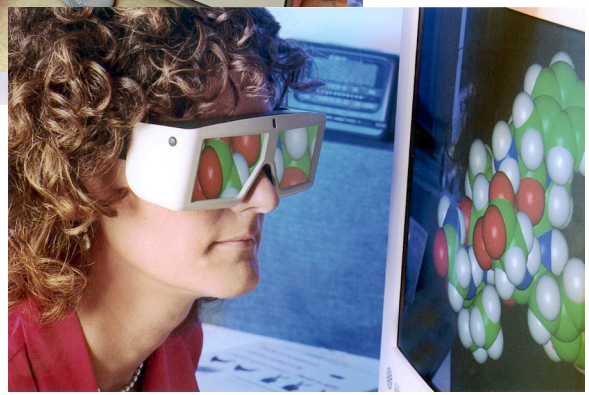
# The Challenge for the NTP

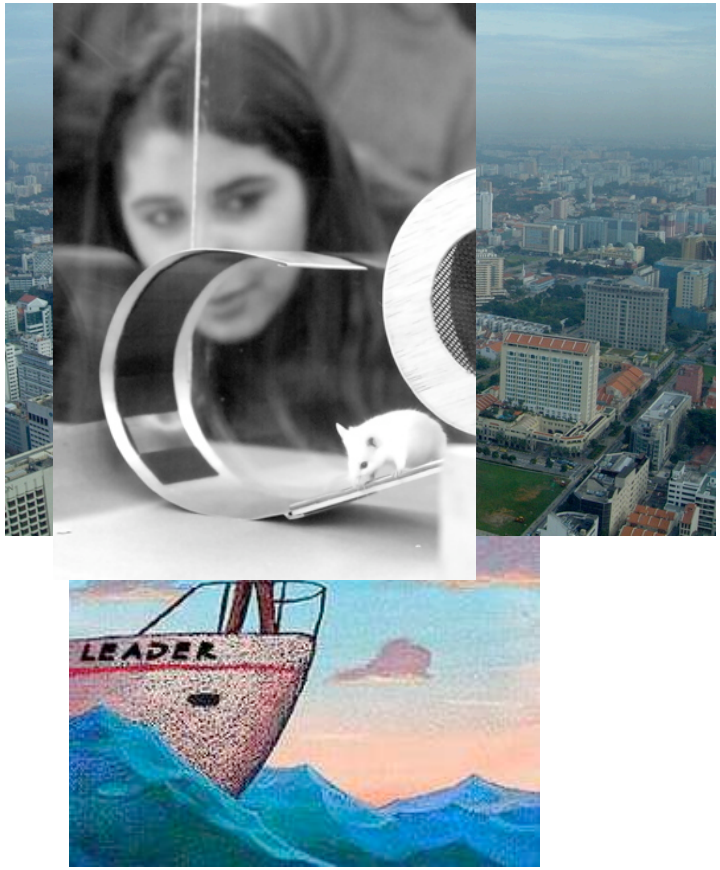
- **Our expanding concerns**
  - Chemicals
  - Pharmaceuticals
  - Physical and biological agents
  - Mixtures
- **Our expanding knowledge**
  - Genomics/Genetics/Mo. Bio.
  - Toxicity mechanisms



# The NTP for the Next 25 Years

- **Continue to lead**
  - Mechanism-based toxicology
  - Faster screening
  - Interpretation
- **Continue to build**
  - Databases and analysis tools
  - Scientific foundation for a transformation of toxicology
- **Continue to improve**
  - Standard toxicological assays
  - Public health decisions

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# What? How?

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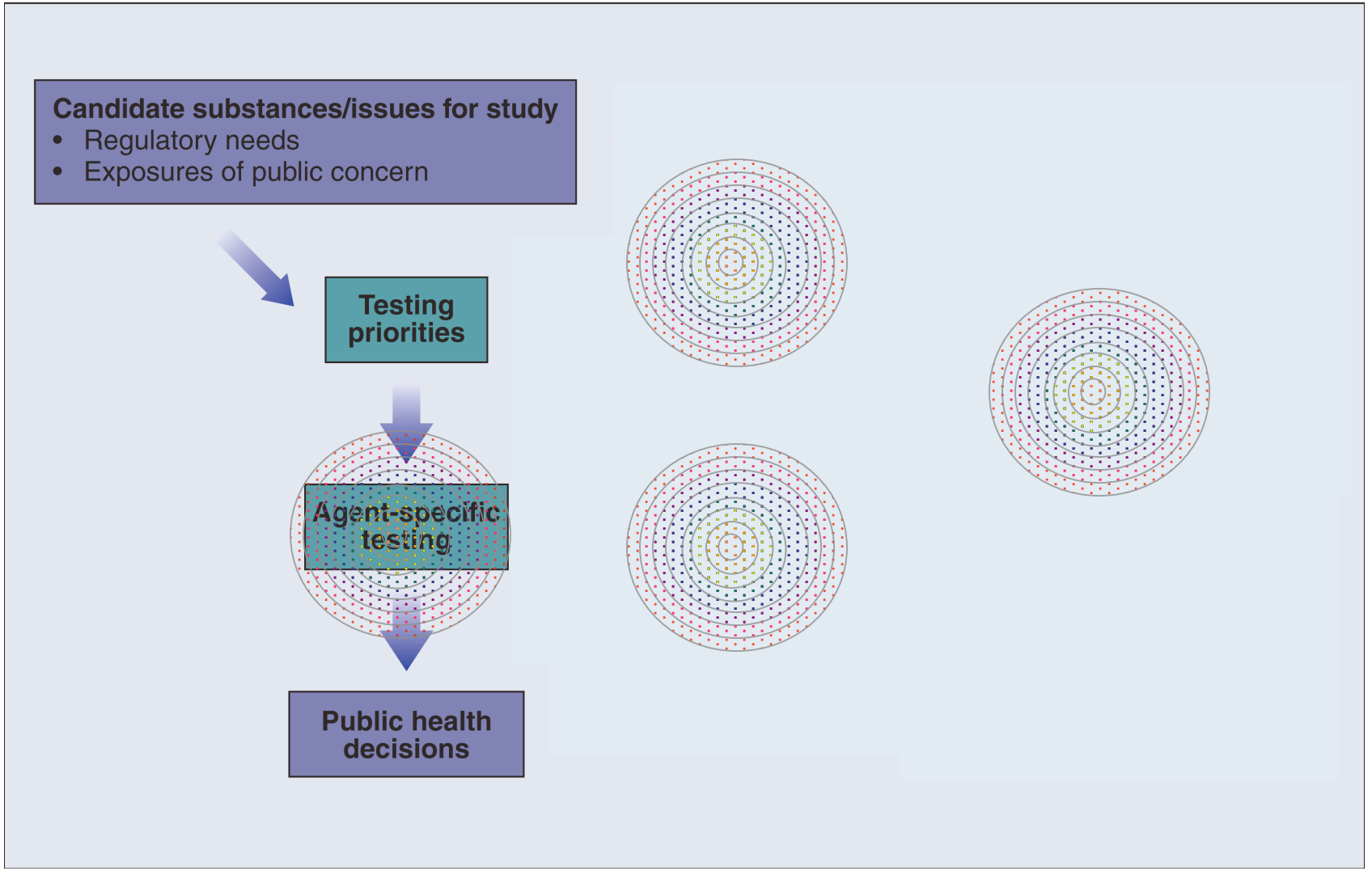
# Use of Mechanistic Toxicology Studies in Public Health Decision Making

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# Approaching Toxicology Today

- First level screen
  - High-Throughput
  - Fairly inexpensive
  - Lot's of possible mechanistic links
- Second Level Screen
  - Integrated living organism
  - Medium throughput
  - Complex inter-related mechanistic information
- Definitive Evaluation
  - Bioassay of the future

# The Bioassay of the Future

- Species/strain/genetics
- Dose spacing/timing/age of exposure
- Use of sub-chronic/pre-chronic/other
- Toxicokinetics
- Digital pathology and non-invasive methods
- Addition of mechanistic endpoints
- Presentation and interpretation

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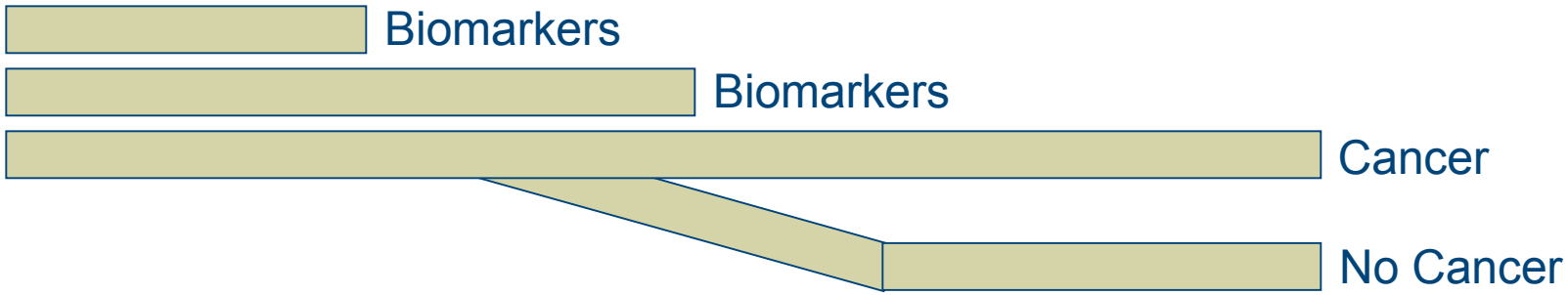
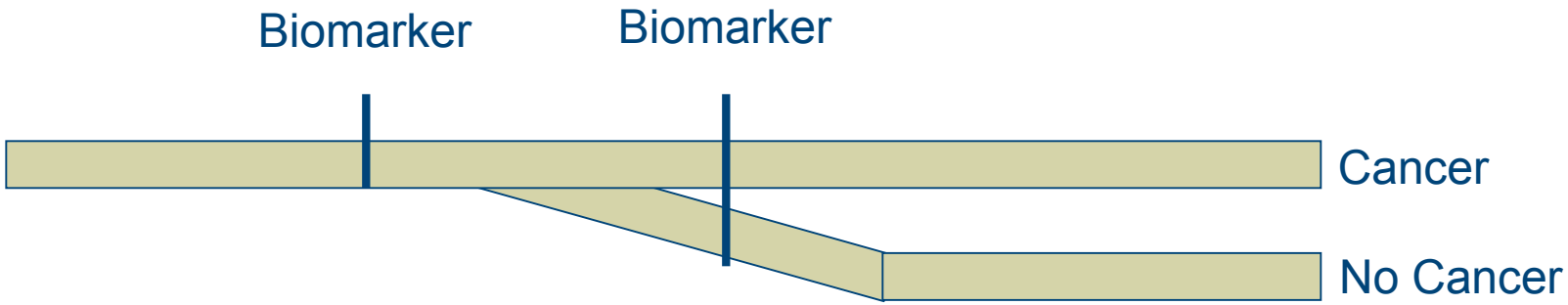
# Chronics, Cancer and Genomics

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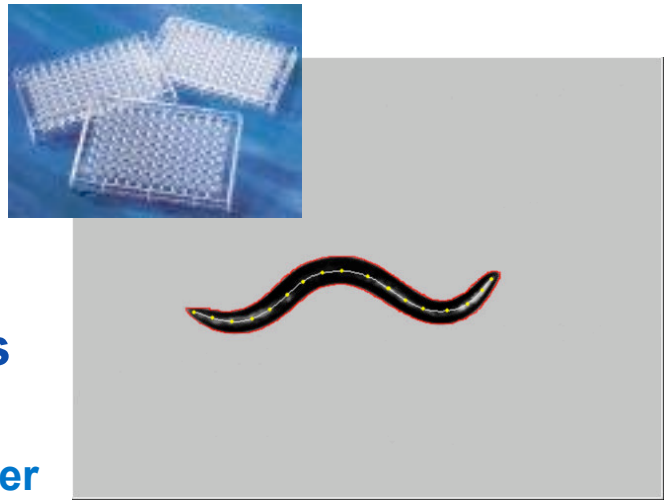
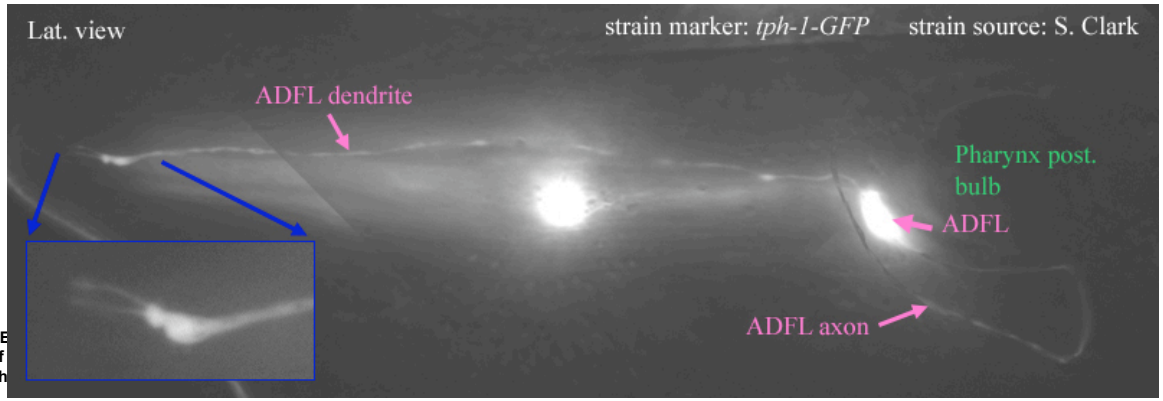
# Second Level Screens

- Shorter-term whole animal assays
  - C. elegans
  - Zebra fish
  - Transgenics and others
- Molecular screening assays
  - Gene chips with large numbers of genes
  - Proteomic screens
  - Metabolomic screens
- Combined assays
  - Reproductive/developmental/cancer/cardiotox/other

# *C. Elegans* and developmental neurotoxicity



- **Develop the screen**
  - 200 +/- agents
  - Reproduction, development, behaviour, movement
- **Expand the tool to expand endpoints**
  - Subtle changes in individual neurons
  - Alterations in egg sac function and number
- **Evaluate mechanism**
  - Knock down every gene for a few chemicals

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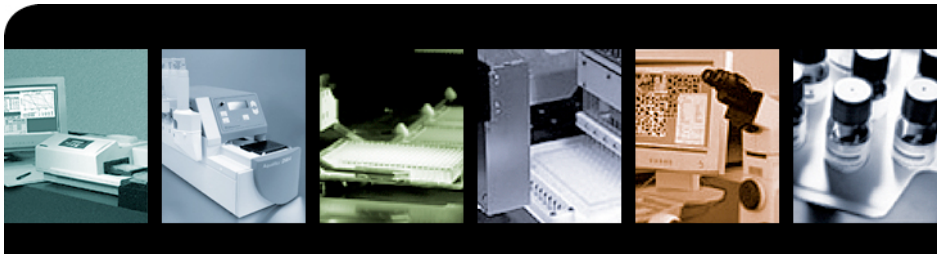
# High-Throughput Screening

- **Develop capacity**
  - One to two thousand agents initially
  - Obvious toxicity targets
  - Develop data handling tools
  - Build a validation data set
- **Expand as warranted**
  - Broader number of assays
  - Broader number of agents
  - Wider number of targeted toxicities



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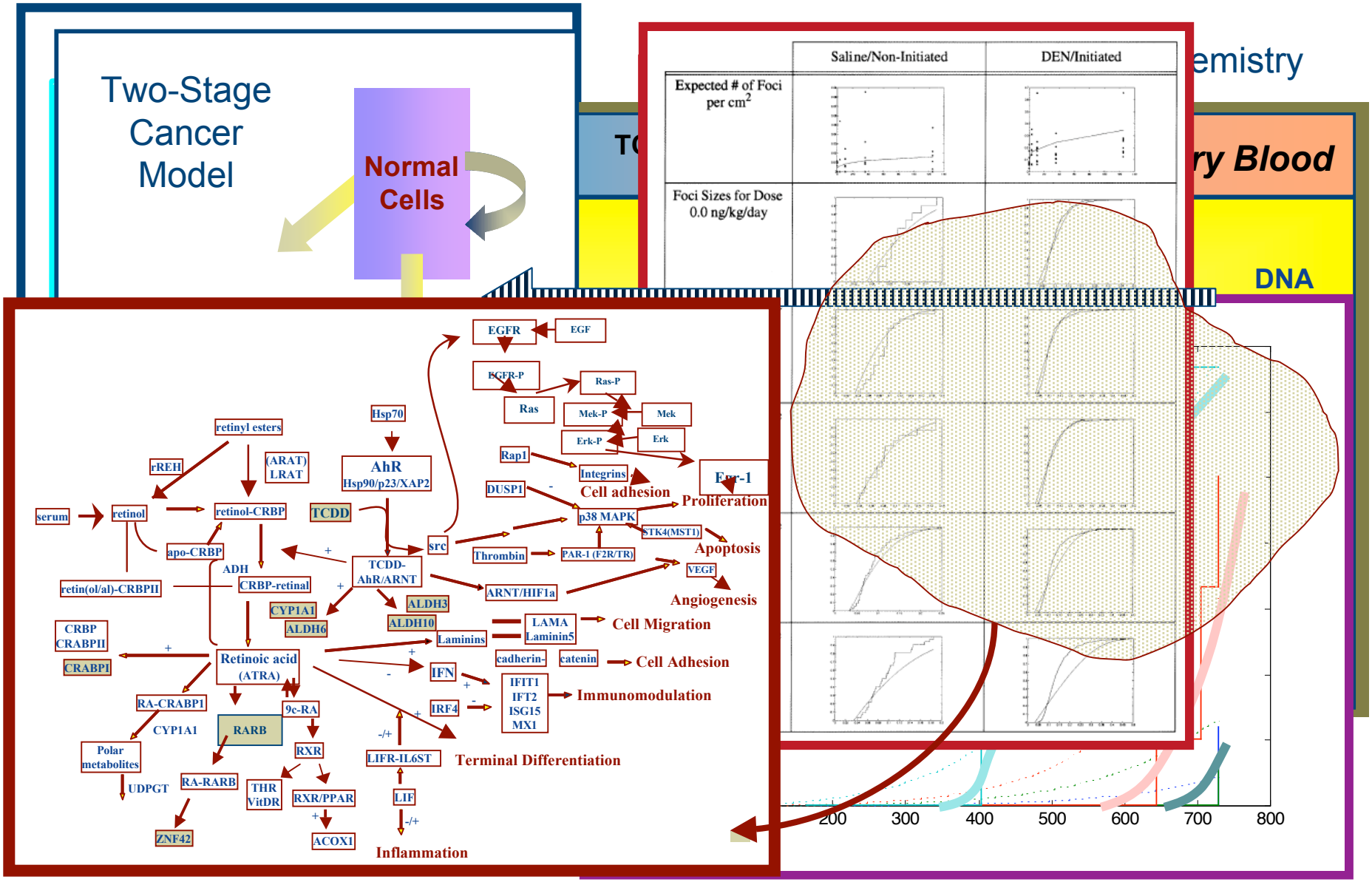
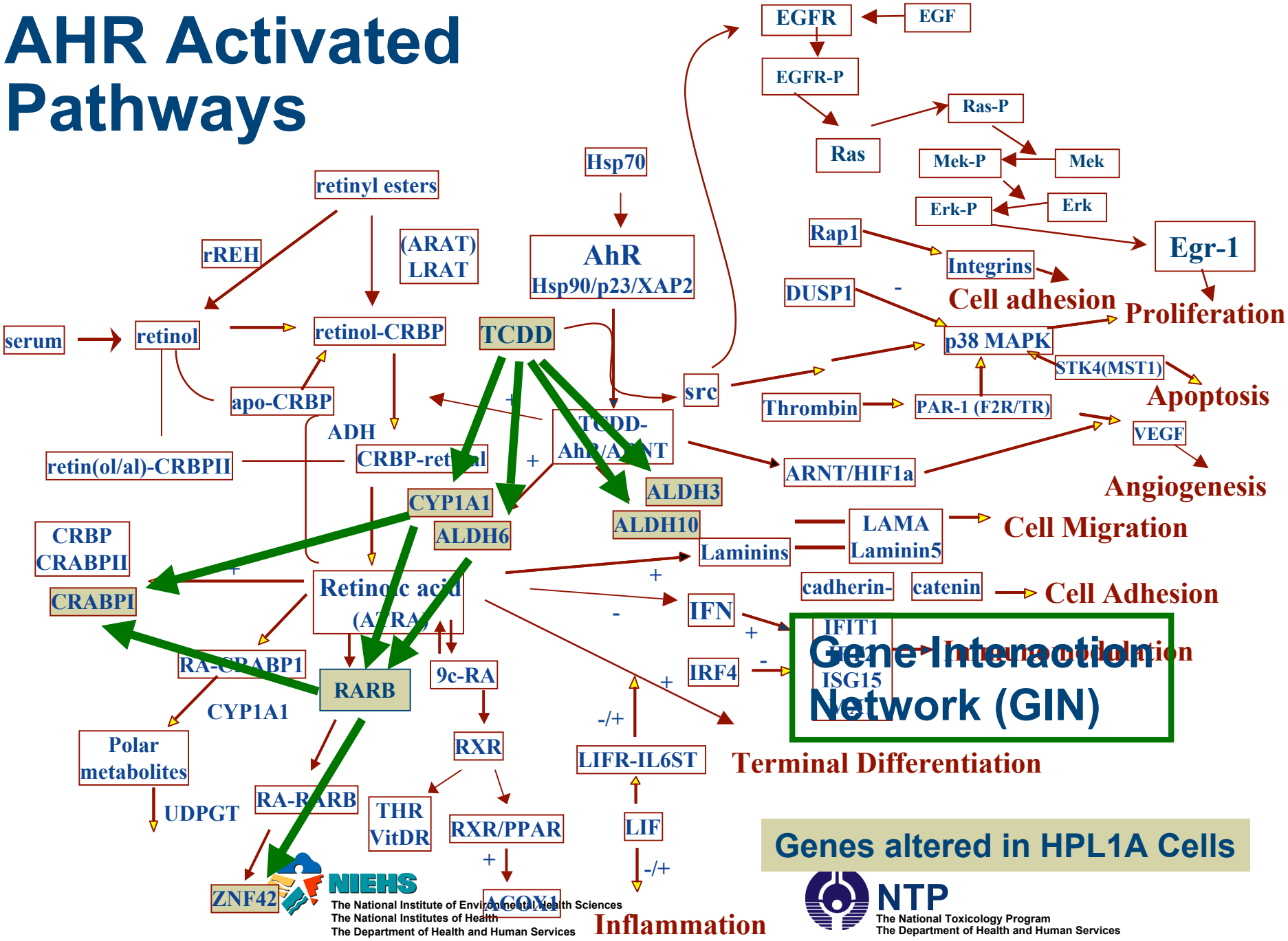
# Data Analysis and Interpretation

- Evaluate current and future information technology needs
- Methods for new assays and HTS
- Interaction with public health decision makers
  - How and when to use new results
  - Steps as we proceed
- Staffing and expansion of skills
  - NTP staff
  - Decision makers
  - International community

# Environmental Systems Biology



# AHR Activated Pathways

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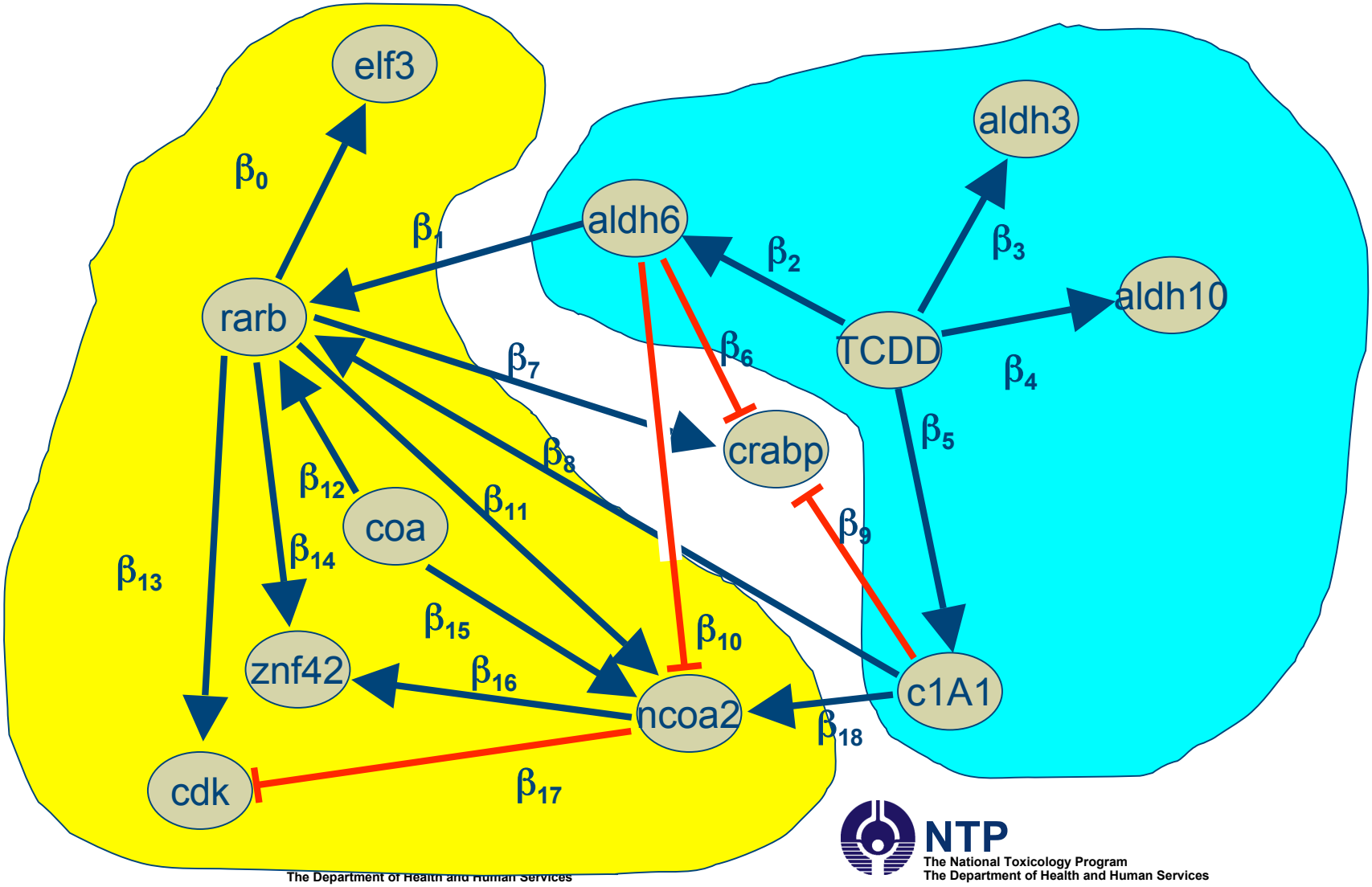
# Hypothetical Network



# The Next 25 Years of the NTP

- Expanding toxicology databases
  - New assays
  - High-Throughput Screening
  - Genetics/genomics and toxicology
  - Testing the “BIG” hypotheses
- Continuing innovative reviews
  - Traditional toxicology screens
  - Genetics/genomics/HTS/new assays and ROC/CERHR
  - Validation on a broader scale
- Improved toxicological sciences
  - Design
  - Implementation
  - Interpretation

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# 21st Century Toxicology

## *NTP Leading the Way*


## *Developing the Best Science to Achieve the Best Decisions*

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