National Toxicology Program
Roadmap Retreat

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”We don’t receive wisdom; we must discover it for ourselves after a journey that no one can take for us or spare us.”

Marcel Proust (1871-1922)
To move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.
Major Activities and Products of the NTP
Roadmap Target #1: High-Throughput Screening (HTS)

Target Date: Begin exploratory testing mid 2005

Example Activities:
- Target selection
- Compound Selection
- Experimental Design
- Funding Mechanism/Type of Activity
- Database Development
- Analysis Methods
- Effectiveness of Program
- Communication
Roadmap Target #2: Bioassay Review and Redesign

Target Dates: Begin review of bioassays immediately
Complete review of bioassays by mid-2006

Example Activities:
- Digital pathology
- Targets in the two-year chronic exposure bioassay
- Dose-selection
- Life stages and dosing patterns
- Choice of model
- Toxicokinetics
- Toxicogenomics
- Developmental toxicology screens
Roadmap Target #3: Medium-Throughput Screening (MTS)

Target Date: Analyze and report initial C. elegans results by mid-2005

Example Activities:
- Evaluate C. elegans study
- Other species and targets for MTS
- MTS design
- Select compounds
- MTS toxicogenomics target genes
- Cell line or species
- Analysis of results
Roadmap Target #4: Data Analysis and Interpretation

Example Activities:
- Existing analysis tools
- Web access
- Existing predictive toxicology tools
- Interpretation of HTS and MTS for NTP priority setting
- Assay usage in hazard identification
- Validation by ICCVAM of predictive models
A National Toxicology Program for the 21st Century - Roadmap to Achieve the NTP Vision

Introduction

Since its inception in 1978, the National Toxicology Program (NTP) has stood as a leader in toxicological testing and research within the United States and has contributed significantly to the scientific knowledge upon which public health decisions are based. Over the last two decades, the toxicology community has placed increasing emphasis on mechanism-based investigations. In the last few years, increasing knowledge of the human and rodent genomes have expanded the possibilities for fruitful mechanistic studies. This evolution has and will continue to lead to improvements in the interpretation of toxicology data and has already begun to influence the scientific basis for public health decisions. This change has not, however, reduced the need for the classical tests developed in the 1970s and 80s that are the basis for most decisions related to evaluation of environmental and occupational hazards and prioritization of chemicals for further testing. The …
## Roadmap Target #1: HTS Activity Matrix

<table>
<thead>
<tr>
<th>SEQUENCE</th>
<th>TIMELINE</th>
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<tbody>
<tr>
<td></td>
<td>Short-term</td>
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<td>Mid-term</td>
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<td>Long-term</td>
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### Sequence Details
- **Add New Mechanisms**
- **Expand Compounds to be Studied**
- **Identify Compounds for further NTP Testing**
- **Define Experimental Design**
- **Communicate Scientific Results**
- **Identify Mechanisms to Target**
- **Review Effectiveness of HTS**
- **Identify Initial Set of Compounds**
## Roadmap Target #1: HTS Screening Activity Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Target/Compound Selection</th>
<th>Experimental Design/HTS Facility/Database</th>
<th>Analysis/Effectiveness/Communication</th>
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<tr>
<td>2005</td>
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Roadmap Target #1: HTS Screening
Activity Descriptions

**BSC Review Compounds** A: The initial set of compounds to be used in the HTS program can probably be selected without much formal review. The NTP has studied several hundred compounds in the last few years and stored samples of these compounds for other uses. It should be possible to choose a number of compounds from this repository to be used in the initial HTS. The NTP is encouraged to choose compounds that have known toxicity (if any) and encouraged to use at least 500 compounds in the original screening.

**BSC Review Mechanisms** B: One of the most critical aspects of the HTS program will be the choice of assay to use; the list is endless. The NTP should initially choose assays that relate to mechanisms that are known to be related to toxicity such as genotoxicity, micronuclei, cellular replication and apoptosis. The choices should be reviewed by the BSC and discussed openly to develop a consensus of their future utility.
Mechanism-Based Toxicology

Agent-Specific Toxicity

“Top Down”

Studies to Elucidate Mechanism

Identify Key Targets

Screen Other Agents

“Bottom Up”

Evaluation and Analysis

Set Testing Priorities

“Top Down”

“Bottom Up”

NIEHS
The National Institute of Environmental Health Sciences
The National Institutes of Health
The Department of Health and Human Services

NTP
The National Toxicology Program
The Department of Health and Human Services
Advantages

- Strengthen prediction of hazards for humans
- Link to existing databases for “validation”
- Expand number of agents studied
- Turn sporadic mechanistic insights into broader knowledge base
- Improve extrapolations
- Test smarter
Challenges

- Avoid resource drains
- Avoid over-interpretation
- Include validation at the planning stage
  - How?
- Which mechanistic assays?
- Who will do this?
“The future is not some place we are going to, but one we are creating…. The paths are not to be found, but made, and the activity of making them changes both maker and the destination.”

John Schaar