Integrating Literature Analysis into the NTP Research Pipeline

Windy Boyd
NTP Board of Scientific Counselors Meeting
December 12, 2018
DNTP Translational Toxicology Pipeline Plan

Define Hypotheses & Design a Testing Strategy

Knowledge Integration

Data Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

 Longer-term in vivo Tests

Short-term in vivo Tests

Communication

Evidence Mapping

Literature Analysis

Inform Public Health Decisions

Systematic Review
Evidence Mapping
- Inform Research
  - Data pockets
  - Data gaps

Define Hypotheses & Design a Testing Strategy

Knowledge Integration
Longer-term in vivo Tests
Short-term in vivo Tests

Inform
Public Health Decisions

Communicate

DNTP Translational Toxicology Pipeline Plan

Literature Analysis
Parkinson’s disease (PD) due to progressive neurodegeneration

- Aggregation of $\alpha$-synuclein in Lewy bodies
- Loss of dopaminergic neurons in substantia nigra
- Signs include tremor, rigidity, and shuffling gait

Highly prevalent but etiology of most PD cases unknown

- Genetics only account for ~10% of cases
Exposures to pesticides linked to Parkinson’s in epidemiological studies

Need for better understanding of which environmental factors may be contributing and how they act

Neurodegeneration is not included in routine toxicological testing strategies

Lack of methods to rapidly identify environmental exposures
Strategy to identify potential chemical contributors

- Project team
  - Combined scientific expertise in neurotoxicology, *in vitro* screening, toxicoinformatics, and literature analysis

- Goals
  - Identify previously evaluated chemicals, genes and pathways, and model systems
  - Develop a battery of *in vitro* and alternate model organism assays to screen chemicals for potential effects
NTP Parkinson’s Disease Project

Strategy to identify potential chemical contributors

- Expert knowledge
- Published literature
- Tox21 HTS data
- Chemical and assay selection
- Toxicogenomic databases
Questions: Which chemicals, genetic targets, and models have been reported in the scientific literature?

PubMed search identified >90,000 records with mention of Parkinson’s disease

Screened studies for environmental chemical exposure and categorized by study characteristics
Exposures Associated with Parkinson’s Disease

Automated Tagging of All Environmental Exposures

- Metals (1734)
- Pesticides (2576)
- Drugs of Abuse (2654)
- Stress (4339)
- PAHs (35)
- Miscellaneous (172)
- Air Pollution (235)
- Occupational (142)
- Alcohol (778)
- Smoking (1163)
- Nutrition (2490)
Manual categorization of 1,840 studies revealed similar trend as automated tagging and allows researchers to explore published literature.
# Parkinson’s Disease Evidence Map

## Most-reported Environmental Chemicals

<table>
<thead>
<tr>
<th>Chemical</th>
<th></th>
<th>Human</th>
<th>In vivo</th>
<th>In vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manganese</strong></td>
<td>Exposure</td>
<td>115</td>
<td>106</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>Positive control</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Paraquat</strong></td>
<td>Exposure</td>
<td>22</td>
<td>135</td>
<td>97</td>
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<tr>
<td></td>
<td>Positive control</td>
<td>37</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td><strong>Rotenone</strong></td>
<td>Exposure</td>
<td>10</td>
<td>137</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>Positive control</td>
<td>204</td>
<td>274</td>
<td></td>
</tr>
<tr>
<td><strong>Nicotine</strong></td>
<td>Exposure</td>
<td>21</td>
<td>36</td>
<td>17</td>
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<tr>
<td></td>
<td>Treatment</td>
<td>16</td>
<td>61</td>
<td>18</td>
</tr>
</tbody>
</table>
### Parkinson’s Disease Evidence Map

#### Environmental Chemicals in >10 Studies

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Human</th>
<th>In vivo</th>
<th>In vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maneb</td>
<td>8</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>Aluminum</td>
<td>17</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Iron</td>
<td>17</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>10</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Mercury</td>
<td>19</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Copper</td>
<td>10</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Lead</td>
<td>20</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Cadmium</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>PCBs</td>
<td>9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Zinc</td>
<td>8</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Mancozeb</td>
<td>1</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

- Very few chemicals with multiple reports
- All metals and/or pesticides except PCBs
- Many chemicals with single study (not shown)
Candidate Chemical Library

- **Predicted actives**
  - Positive controls
    - MPTP, rotenone, paraquat
  - Metals and metal compounds
    - Manganese tricarbonyl (MMT), maneb, methyl mercury, ziram
  - Organochlorines
    - DDT, heptachlor, dieldrin, lindane, endosulfan, TCE, hexachlorobenzene
  - Organophosphates
    - Chlorpyrifos, diazinon
  - Other pesticides
    - Permethrin, benomyl, tributyltin methacrylate, quintozene

- **Unknowns**
  - Triphenyl phosphate
  - Isopropylated phenyl phosphate
  - Captan
  - Glyphosate
  - Pyridaben
  - Acetaminophen

- **Predicted Negatives**
  - Saccharin sodium
  - L-ascorbic acid
  - D-glucitol
  - Acetyl salicylic acid
Informing Assay Selection for Targeted Testing

Motor deficits

Related changes in gene expression

Neuroinflammation

Mamta Behl
Tox Branch

Motor deficits

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*Some studies may have characterized multiple health effects or species and therefore may be represented multiple times. Row and column grand totals represent counts of distinct references.*
- Majority of studies conducted in human and rat tumorigenic cell lines with fewer more relevant, complex models.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Category</th>
<th>Cell, tumor, subfraction type</th>
<th>Tissue origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH-SY5Y</td>
<td>tumor</td>
<td>neuroblastoma</td>
<td>brain, bone marrow metastasis</td>
</tr>
<tr>
<td>SK-N-SH</td>
<td>tumor</td>
<td>neuroblastoma</td>
<td>nerve, bone marrow metastasis</td>
</tr>
<tr>
<td>primary mesencephalic</td>
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<td>neurons</td>
<td>mesencephalon</td>
</tr>
<tr>
<td>primary cerebellar</td>
<td>primary</td>
<td>glia</td>
<td>cerebral cortex</td>
</tr>
<tr>
<td>cultures</td>
<td>primary</td>
<td>microglia</td>
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</tr>
<tr>
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<td>neurons</td>
<td>cerebral cortex</td>
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<tr>
<td>cultures</td>
<td>primary</td>
<td>neurons, glia</td>
<td>cerebral cortex</td>
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<tr>
<td>N27</td>
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<td>mesencephalon</td>
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<tr>
<td>PC12</td>
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<td>microglia</td>
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<td>ex vivo</td>
<td>mixed</td>
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</tr>
<tr>
<td>brain cultures</td>
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</tr>
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</table>
Toxicoinformatic Analysis

- Selected genes associated with Parkinson’s
  - Illumina’s NextBio datamining software
  - Comparative Toxicogenomics Database (CTD)

- Grouped 233 genes into 15 disease-relevant pathways

- Linked genes to studies included in literature analysis

- Gene expression reported in 47% of relevant studies
  - 57% of 233 genes evaluated in those studies
Identifying Chemical-Gene Combinations

Chemical Classes
- Pesticides
- Nicotine
- Metals
- Other

Biological Pathways
- Apoptosis
  - Adenosine Receptor
  - Axon guidance/synaptic
  - Dopamine
  - Dopamine Receptor
  - Immune System
- α-synuclein/Lewy body
  - Neuronal survival/activity
  - Other
  - Other receptors
- Mitochondria/ox phos
  - Transcription factor
  - Transporter
  - Ubiquitin

Nisha Sipes
BSB
Identifying Chemical-Assay Combinations

ToxCast and Tox21 Data

Legend
- Screened in Tox21
- Active in Tox21
- Published literature

Chemicals

Adenosine receptor
Apoptosis
Axon guidance/synaptic
Dopamine
Dopamine Receptor
α-synuclein/Lewy body
Neuronal survival/activity
Other
Other receptors
Mitochondrial/ox phos
Transcription factor
Transporter
Ubiquitin

Parkinson's Disease Pathways

Screened in Tox21
Active in Tox21
Published literature
NTP Parkinson’s Disease Project

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- Expert knowledge
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- Data Mining
- QSAR Profiling
- Bioactivity Screening
- In vitro Studies
- ADME/Chemistry
- Longer-term in vivo Tests
- Short-term in vivo Tests
- Knowledge Integration
- Communicate

Informed

Next

Future?

Evidence Map

Systematic Review

Inform Public Health Decisions

✓
NTP/NIEHS

- Nisha Sipes
- Mamta Behl
- Andy Rooney
- Vickie Walker
- Scott Auerbach

OHAT

- Brandy Beverly
- Kembra Howdeshell
- Kyla Taylor

External

- Kris Thayer, former project lead, US EPA
- Ana Antonic, University of Melbourne
- Courtney Skuce, Robyn Blain, Pamela Hartman, Kelly Shipkowski, Sophie Hearn, ICF
- Austin Wray and Aaron Niman, US EPA

Peer Review

- Chris McPherson, Paraquat Scoping Report
- Nisha Sipes, Paraquat Scoping Report
Thank you

Questions?

…on behalf of OHAT