The Path to Converging on Cancer

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• Problem identification
  – Cancer and environmental chemicals
  – The Halifax Project

• Problem formulation
  – Key features
  – Groups involved in problem formulation
    • The National Toxicology Program
    • University of California, Berkeley Working Group
    • Converging on Cancer Workshop

• Implementation
### Public Health Burden of Cancer

<table>
<thead>
<tr>
<th>Leading Sites of New Cases</th>
<th>U.S. Cancer Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% Breast</td>
<td>1,735,350 Estimated new cancer cases diagnosed in 2018</td>
</tr>
<tr>
<td>13% Lung &amp; bronchus</td>
<td>609,640 Estimated 2018 cancer deaths</td>
</tr>
<tr>
<td>7% Colon &amp; rectum</td>
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<tr>
<td>7% Uterine corpus</td>
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<tr>
<td>19% Prostate</td>
<td>38.4 Percentage of people that will be diagnosed during their lifetime</td>
</tr>
<tr>
<td>14% Lung &amp; bronchus</td>
<td>147 billion Estimated expenditures for cancer care in 2017</td>
</tr>
<tr>
<td>9% Colon &amp; rectum</td>
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<tr>
<td>7% Urinary bladder</td>
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</table>

From American Cancer Society

From National Cancer Institute
Intrinsic risk factors = random errors in DNA replication, aka ‘bad luck’ (unmodifiable)

Non-intrinsic risk factors

Endogenous risk factors (partially modifiable)
- Biologic aging
- Genetic susceptibility
- DNA repair machinery
- Hormones
- Growth factors
- Inflammation

Exogenous risk factors (modifiable)

“it is detrimental to prevention and cancer control measures if the risk, especially for clinically significant cancers, is over interpreted to be due solely to bad luck. This underestimates the potential impact of prevention and control measures aimed at reducing or delaying incidence and death due to cancer. Similarly, underestimating the fraction of preventable cancer risk impedes progress to identify modifiable exposures for cancer prevention and control measures when possible.”

Adapted from Wu et al. 2018
• 135 biomarkers measured in blood, serum, or urine
• 91 biomarkers detected on average (range of 60-108)
• Some biomarkers detected in 100% of women (phytoestrogens, PCBs, hexachlorobenzene, perchlorate, PFAS, metals, and PAHs)
• Brought together cancer biologists and environmental toxicologists

• Teams formed to review the Hanahan and Weinberg (2000, 2011) hallmarks of cancer ‘pathways’ and identify 1) biomarkers and assays associated with each pathway and 2) environmental chemicals likely to interact with each pathway

• Underlying hypothesis: Environmentally-relevant levels of noncarcinogenic chemicals interact with hallmark pathways to contribute cumulatively to the development of cancer
• Reviewed the key signaling pathways involved in angiogenesis
• Identified molecular markers associated with those signaling pathways
• Reviewed the pro-angiogenic action of environmental carcinogens (cigarette smoke, nicotine, and arsenic)
• Identified environmental chemicals predicted to act on the signaling pathways
  – Ubiquitous environmental chemicals
  – Shown to disrupt specific pathways
  – Not known to cause cancer
• Discussed cross-talk with other hallmarks
Key angiogenic pathways

**VEGF pathway**
- Growth factors (EGF, IGF-1)
- Environment (hypoxia, pH)
- Cancer genes (p53, src, ras)
- Increased VEGF
- VEGFR
- Pro-angiogenic signaling

**Tissue factor (TF) pathway**
- Release of negative regulatory control
- PAR-2 signaling
- Rac1
- MAPK/ERK
- PI3K/Akt
- VEGF, uPAR, etc.
- TSPs

**References**
- Bluff et al. 2008
- Hicklen and Ellis 2005
Kleinstreuer et al. 2013

Identification of genes, pathways, and hallmark processes linked to EPA ToxCast assays (672 high throughput assays), which correlated to animal cancer data.
Environmental chemicals

Hu et al. 2015

- HPTE
- Bisphenol AF
- Chlorothalonil
- Diniconazole
- Biphenyl
- Ziram
- Methylene bis(thiocyanate)
- Tributyltin chloride
- C.I. solvent yellow 14
- PFOS
Halifax project output

Nomination of the Halifax Project Hypothesis to NTP for testing
Low doses of environmental chemicals that target cancer pathways (but are not complete carcinogens) contribute cumulatively to the development of the disease and would not be accounted for in the current cancer risk assessment process.

- **Tame**: Single chemical risk assessment
- **Wicked**: Environmental mixtures and cancer
- **Wicked**: Stop the progression of climate change
Problem Identification

Problem Formulation

Implementation/Testing
<table>
<thead>
<tr>
<th>Process</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evaluate available information</td>
<td>• Is systematic and iterative</td>
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<tr>
<td>• Identify data needs</td>
<td>• Involves stakeholders (including relevant experts)</td>
</tr>
<tr>
<td>• Gain preliminary understanding of potential risks</td>
<td>• Incorporates experiential knowledge</td>
</tr>
<tr>
<td>• Develop hypotheses and conceptual models</td>
<td>• Includes logical and reasonable debate</td>
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Incorporate experiential knowledge

- Understanding the underlying biology of cancer: Dean Felsher (Stanford University) and David Beebe (University of Wisconsin - Madison)

- Research programs that incorporate knowledge of biological systems to understand mixtures
  - EuroMix projects: Johanna Zilliacus (Karolinska Institutet):
    - Liver steatosis
    - Endocrine disruption of estrogen/testosterone balance leading to disruption of reproductive function
    - Skeletal malformations
  - Research on mixtures that disrupt male reproductive tract development: Earl Gray (US EPA)
Male reproductive tract development

Androgen Receptor Antagonism → Reduced AR dependent mRNA/protein → Abnormal cell apoptosis/proliferation → Disruption of AR tissue development

Inhibition of steroidogenic enzymes → Reduced T synthesis → Reduced cholesterol synthesis

Inhibition of HMG-CoA reductase → Reduced cholesterol synthesis

Unknown → Decreased INSL3 synthesis → Abnormal cell apoptosis/proliferation → Suppressed development of gubernaculum cords

Decreased INSL3 synthesis → Malformations

Abnormal cell apoptosis/proliferation → Undescended testis

Disruption of AR tissue development → Impaired fertility

Suppressed development of gubernaculum cords transabdominal

Molecular Initiating Event → Key Event

Key Event → Key Event → Adverse Outcome → Adverse Outcome

Adapted with permission from Justin Conley (EPA)
Decrease testosterone
DBP
BBP
DEHP

AR antagonists
Vinclozolin
Procymidone

Mixed mechanism
Prochloraz
Linuron

Implication of this work: Chemicals that do not act independently but contribute to toxicity in a dose additive manner should be considered in cumulative risk assessment in order to be health protective.
Groups that have been working on the problem

- NTP Study Design Team
- UC Berkeley Working Group
- Converging on Cancer Workshop

Problem Formulation
The National Toxicology Program

Mission: To improve public health through the development of data and knowledge that are translatable, predictive and timely

- Interagency program
  - Headquartered at NIEHS
- Research on nominated test articles
  - Thousands of agents evaluated in comprehensive toxicology studies
  - GLP compliant testing through government contracts
- Analysis activities
  - Report on Carcinogens (RoC)
  - Office of Health Assessment and Translation (OHAT)
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
Environmental mixtures and cancer project

Mixtures toxicology

Cancer

*In vitro*/*in silico*/mechanistic

Operational
• Refine the key characteristics with knowledge of cancer biology in mind (hallmarks)

• Develop a list of recommended assays that map to characteristics and hallmark pathways

• Formulate hypotheses and testing approaches related to environmental mixtures and cancer
• Gather experts in cancer biology, *in vitro*/*in silico*, risk assessment, mixtures toxicology, methods development

• Present effort to date
  – Pre-meeting webinars
  – Presentations during meeting

• Further refine problem statement and develop a path forward for implementation
  – Identify key challenges
  – Get input on testing strategies

https://ntp.niehs.nih.gov/go/COC
Low dose
- Environmentally-relevant levels
- Below NOAEL
- Less concerned about low dose, more concerned about understanding the joint action of multiple chemicals that converge on pathways leading to cancer

Mixtures
- Focus on chemicals that have not been identified as carcinogens
- Only include non-genotoxic chemicals
- Identify chemicals based on pathways

Cancer
- De novo cancer
- Priming the conditions for cancer (e.g., decreased time to cancer with genetic predisposition, lower dose of carcinogen required)
- Cancer type-specific or generalizable to all cancers
Cancers are a complex set of related diseases with wide ranging etiologies, and humans are exposed to a milieu of chemicals that may contribute to disease development. Can current knowledge of cancer hallmarks and key characteristics of carcinogens inform a new approach for assessing the carcinogenic risk posed by chemicals and mixtures?
Questions

• What are the benefits and challenges to using mechanistic cancer data (e.g., key characteristics of carcinogens framework) in public health-based decision-making?

• Where along progression of cancer development would we be comfortable in predicting the eventual outcome of malignancy? What key events, individually or in combination, would be necessary/sufficient to indicate carcinogenicity?

• How might we detect those key events in an *in vivo* animal modeling system and *in vitro/in silico* modeling systems? Specifically, what are the existing technologies and platforms (*in vivo*, *in vitro*, and *in silico*) that should be applied to a human-relevant carcinogenicity evaluation strategy, and in what combinations?
• How would we go about building scientific confidence in new testing strategies? How can we better communicate the probabilistic nature of chemical carcinogenic risk?

• Should we be addressing the joint action of co-carcinogens below their individual cancer thresholds, or focusing on chemicals that are not carcinogens but target the Hallmarks/Key Characteristics and could contribute to cancer development jointly?

• Can mixtures hypotheses be generalizable across cancer types? When should they be specific to tumor types/incidence based on ADME principles and knowledge of key events for that cancer type?
Identifying data needs

• Use of data to identify cancer hazard
  – Organizations that synthesize bodies of evidence to determine the carcinogenic potential of substances
    • International Agency for Research on Cancer – Kate Guyton
    • NTP Report on Carcinogens – Amy Wang and Gloria Jahnke
  – Industries that use cancer data to inform product development
    • Syngenta – Doug Wolf

• Assessment of cancer risk from real-world exposures
  – Environmental Protection Agency – Glenn Rice
  – Food and Drug Administration - Tim McGovern
  – CalEPA Office of Environmental Health Hazard Assessment – Martha Sandy and Lauren Zeise
Problem Identification

Problem Formulation

Implementation/Testing
Requirements

• Tractable
  – Can be executed in a reasonable timeframe with a reasonable investment

• Interpretable
  – Upon completion of testing, knowledge is gained, regardless of outcome

• Impactful
  – Will either support current risk assessment paradigm as protective of human health or provide data to advance cancer risk assessment practice
12:00-12:30 pm
Carcinogenicity Health Effects Innovation: Modernizing the NTP Approach for Assessing Carcinogenic Risk from Environmental Exposures
Warren Casey (NIEHS/NTP)

12:30-1:00 pm
The Key Characteristics of Carcinogens: Integration with the Hallmarks of Cancer and Assays and Biomarkers to Measure Them
Mark Fielden (Amgen)
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NTP study design team

Workshop Steering Committee
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Bill Goodson (CPMCRI)
Olga Naidenko (EWG)
Johanna Congleton (EPA)
Danielle Carlin (NIEHS)
**Contribution to Cancer Development**
- Wu et al. 2018. Nature Communications 9, 3490

**Exposure to mixtures**

**Hallmarks of Cancer**
- Hanahan and Weinberg 2000. Cell 100, 57–70

**Halifax Project**
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- Casey et al. 2015. Carcinogenesis 36 (Supplement 1), S160–S183
- Engström et al. 2015. Carcinogenesis 36 (Supplement 1), S38–S60
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- Hu et al. 2015. Carcinogenesis 36 (Supplement 1), S184–S202
- Kravchenko et al. 2015. Carcinogenesis 36 (Supplement 1), S111–S127
- Langie et al. 2015. Carcinogenesis 36 (Supplement 1), S61–S88
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- Narayanan et al. 2015. Carcinogenesis 36 (Supplement 1), S89–S110
- Ochieng et al. 2015. Carcinogenesis 36 (Supplement 1), S128–S159
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- Thompson et al. 2015. Carcinogenesis 36 (Supplement 1), S232–S253
- Miller et al. 2017. Environmental Health Perspectives 125, 163-169

Angiogenesis


Problem Formulation


Mixtures

Thank you!
Questions?