

Converging on Cancer Workshop

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NTP Board of Scientific Counselors Meeting June 18, 2019





- Strong interest
 - 130 registered for in-person attendance
 - ~500 registered for webcast
- Location: Washington DC, EPA William Jefferson Clinton Building
- Format: Plenary talks and breakout session work
- Themes for breakout session groups:
 - Hazard and risk assessment
 - Tools and technologies
 - Mixtures





Report on Carcinogens Use of mechanistic data in monographs Health Effect Innovation Modernizing Cancer Testing at NTP

Testing Program Nomination of Low Dose Mixtures and Cancer

Engage experts and stakeholders in discussions to inform multiple NTP efforts

Converging on

Cancer Workshop



- Multiple agencies use mechanistic data in evaluation of carcinogenicity
 - They are at different stages of developing more structured frameworks (e.g., key characteristics of carcinogens)
 - There are multiple tools for extracting, organizing, and visualizing mechanistic data
- Early communication and collaboration among agencies and with stakeholders on this topic is beneficial to all









Why did we have the workshop?





 The Halifax Project hypothesis was nominated by the Environmental Working Group to NTP for testing

Halifax Hypothesis

Environmentally-relevant levels of noncarcinogenic chemicals interact with hallmark pathways to contribute cumulatively to the development of cancer

Hanahan and Weinberg, 2011. Cell 144: 646-674 Goodson et al., 2015. Carcinogenesis 36: S254-296





Groups engaged in problem formulation





- The Path to Converging on Cancer
 - Cynthia Rider (NIEHS/NTP)
- Cancer Risk Assessment for Chemical Mixtures at US EPA
 - Glenn Rice (US EPA)
- Carcinogenicity Health Effects Innovation: Modernizing the NTP Approach for Assessing Carcinogenic Risk from Environmental Exposures
 - Warren Casey (NIEHS/NTP)
- The Key Characteristics of Carcinogens: Integration with the Hallmarks of Cancer and Assays and Biomarkers to Measure Them
 - Mark Fielden (Amgen)



- What should we be studying (carcinogens or noncarcinogens)?
 - Should we be addressing the joint action of co-carcinogens below their individual cancer thresholds?
 - Should we focus on chemicals that are not carcinogens but target the Hallmarks/Key Characteristics and could contribute to cancer development jointly?
- How should we be studying them?
 - 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?



Presenting options



- Low dose
- Mixtures
- Cancer

• Co-carcinogen • Non-carcinogen

Combination

Approaches

- Disease
- Model
- Pathway



- Hypothesis: Certain combinations of carcinogens will produce dose additive or greater-than-dose additive (i.e., synergistic) interactions when present jointly by targeting cooperative pathways
- Research aim: Identifying which causal pathway combinations are sufficient to elicit cancer





- Review of co-carcinogen research
- Map substances from co-carcinogen literature to Hallmark/Key Characteristic pathways
 - Expert judgment
- Highlight examples of mixtures studies that include multiple cancer pathways (e.g., genetic instability + immunosuppression)
- Identify promising combinations for study (indications of potential for synergy of pathways)
- Design combination studies to advance the science:
 - Moving beyond binary combinations (including 3 or more pathways)
 - Quantitative evaluation of joint effects based on pathway combinations



- Hypothesis: Non-carcinogenic chemicals that target Hallmark/Key Characteristic pathways can contribute to the development of cancer by creating optimal conditions (aka the perfect storm)
- Moving forward
 - Prioritize pathways for inclusion
 - Preference for "upstream" and "critical" pathways
 - Deprioritize pathways activated at later stages of cancer development
 - Screen environmental (non-carcinogenic) chemicals for pathway activation in battery of *in vitro* assays mapped to pathways
 - Evaluate single chemicals and mixtures to explore pathway interactions in complex systems (e.g., 3D tissue and animal models)



Non-carcinogen research plan





- Select a cancer of interest (e.g., breast cancer)
 - Ideal candidate: we know something about etiology, widespread occurrence (important public health concern)
- Identify a model that reflects the cancer type
- Identify pathways that are early stage events in the cancer type
 - For example, receptor-based pathway
- Select chemicals that target those pathways and are implicated for association with the cancer of interest (e.g., known presence in tissue)



- Start with the model (e.g., *ras*H2 mice)
- Identify a tissue where cancer is likely to develop in that model (e.g., lung)
- Select pathways
 - Pathway 1: Sustained proliferation/evasion of cell death (human HRAS transgene)
 - Pathway 2: TBD
 - Pathway 3: TBD
- Select chemicals that hit those pathways and that will reach the tissue of interest



- 1. Frequency distribution of combinations of Key Characteristics exhibited by carcinogens
- 2. Select the most common combination set
- 3. Select chemicals that target those pathways
- 4. Select a model (and cancer type) appropriate for those pathways





Generating hypotheses via AOP networks





Building a carcinogenicity toolbox



- Expert-driven approach
 - Identify assays/biomarkers that map to key characteristics of carcinogens/hallmarks of cancer





- Semi-supervised systematic review
 - Broad keyword search for all relevant scientific literature, abstract screening and tagging
- Applying HTS data



- Prioritize environmental chemicals based on bioactivity against targets that map to KCs/HMs
- Construct QSAR models for key characteristics



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- Recommended cancer type(s) for study:
 - Most prevalent
 - Most deadly
 - Most well-understood
 - Availability of a good animal model
 - Existence of a significant database of known carcinogens
 - Discussion of cancer clusters to identify risk factors
- Answers from poll: breast, liver, colon, lung



Developing a mixtures research plan





What should our starting point be?





Path forward

- Outcomes from the workshop
 - Slides posted to website
 - Workshop report in progress
- Influence on NTP programs



- Successful dissemination of information on current relevant NTP activities (e.g., cancer HEI, development of RoC framework for incorporating mechanistic data) and engagement with stakeholders
- Clear feedback from experts on design of a research program on mixtures and cancer



- Focus on combining co-carcinogens as a first priority
 - Considered to be more tractable option
 - Support for pursuing non-carcinogen research in the future
- Use a disease-centered approach
- Recommended cancer types: breast, liver, colon
 - Identify appropriate animal model(s)
 - Build AOP-based hypotheses





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Workshop speakers

Poster presenters

Breakout session participants

Sincere thank you to all who responded to the RFI, submitted answers to our questions, and participated in the workshop via webcast or in person!