

Breakout Report back

Group 1: Hazard and Risk Evaluation



(1) Benefits to using mechanistic data

- Reduced time
- Reduced animal use
- Efficiency to address data gaps (integrate all data)
- KC framework provides directionality



(1) Challenges to using mechanistic data

- Establishing hazard without informing risk
- Cancer is a family of diseases, how to contextualize influence / relevance of KCs across all
- Mechanistic framework may imply that our knowledge of carcinogenesis is sufficient to be predictive



(2) Progression of cancer development

Tipping point to malignancy? Evidence?

- Genetic toxicity
- Hyperplasia, metaplasia, metastasis
- *Sustained* immune suppression



(3) Technologies and platforms

In vivo

- Genetically modified rodent models



(3) Technologies and platforms

In vitro

- High Content assays (gene expression, cell painting)
- Tissue chips/MPS developed specifically for assessing carcinogenicity



(3) Technologies and platforms

In silico

- Estimating human-relevant exposure (e.g., IVIVE)
- QSAR



(4) Building scientific confidence

- Human relevance from biomarker and biosampling would help build confidence. Clinical trials may be an opportunity to provide some of this data. FDA may have this data.
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- NIH-all of us program...complete genome...other metrics...may provide some helpful



(5) What should we be studying?

Carcinogens (pros and cons)

- Initiator and promoter
- Need a thorough systematic review and get some additional expert opinions.
- Not everything is necessarily cumulative due to repair and compensatory mechanisms



(6) How should we be studying joint action?

Disease-centered approach considerations

- Recommended cancer type(s) for study: Use from human cancer data to identify most relevant (i.e. increased incidence)