

Clinical Trials and Translational Research Advisory Committee
Translational Research Strategy Subcommittee

Chi V. Dang M.D., Ph.D.

Nancy E. Davidson, M.D.

TRSS Meeting - March 29, 2021

- Topic - Resistance to immunotherapy
- Research gaps and opportunities
 - Preclinical models
 - Combination immunotherapies
 - Molecular mechanisms, genetics, and cellular basis of response and resistance to immunotherapy
 - Identification and validation of biomarkers of response and resistance to immunotherapy
- TRSS members were asked to submit suggestions for immunotherapy research priorities

Suggestions for Immunotherapy Research Priorities

- Development of better in vivo and in vitro IO preclinical models
 - Immunocompetent murine models (e.g., GEMMs, syngeneic tumor models)
 - Human organoid models
- Other immunotherapy research priorities
 - Development of better IO predictive biomarkers
 - Use of imaging methods to develop biomarkers
 - Study of long-term responders
 - Microbiome and tumor microenvironment studies
 - Better understanding of cellular and molecular mechanisms

Today's Topic: Assessment of the Translational Potential of Organoid Cultures and Animal Tumor Models

- Introduction to Topic
 - TRSS member facilitator: Dr. Kevin Shannon
 - Preclinical models in relation to response and resistance, particularly for immunotherapies

Assessment of the Translational Potential of Organoid Cultures and Animal Tumor Models

Dr. Kevin Shannon

Practical Considerations with Any Cancer Model

- Ability to accurately model primary human cancer
- Reproducibility
- Throughput
- Cost
- Predictive track record (or lack thereof)
- Organ site-specific considerations

In the real world, there are many unknowns and trade-offs in using cancer models for drug testing, which is especially true in immuno-oncology

Types of Models For Testing Cancer Therapies and Combinations

In vitro

- “Traditional” cancer cell lines
- 3D culture systems for cancer cell lines
- Organoids +/- immune cells

In vivo mouse models

- Cancer cell line xenografts
- Syngeneic mouse cell lines
- Chemical carcinogenesis models
- Genetically engineered mouse (GEM) models
- PDX models
- “Humanized” mouse models using human CD34+ cells

Unique Considerations for Preclinical Testing of IO Agents

- **Challenges of modeling the key role of the tumor microenvironment (TME) in cancer maintenance and drug response/resistance in immunodeficient mice**
- **Many existing models that were evolved to rapidly measure direct anti-proliferative activity are not ideal for testing IO agents**
- **Species-specificity of some cytokine and chemokine signaling networks (i.e., molecules generated in the mouse TME do not activate/inhibit human cells and *vice versa*)**
- **IO drugs generated for treating human patients may not cross react with mouse cells**
- **“State A” (pretreatment) versus “State B” (relapsed/resistant) genomic analysis of tumor cells less straightforward/informative**

Ideas and Questions for Discussion

- Models are models and no existing model completely recapitulates the biology of primary human cancers
- Perhaps best to avoid “*one fits all*” prescription (e.g., PDAC versus lung adenoCA versus leukemia)
- Consider stepwise approaches in which drugs and drug combinations are “filtered” in high throughput models followed by careful validation in more complex models
- Proposals to benchmark preclinical models by testing existing drugs and regimens will never make it through an R01 study section

None of these general principles are unique to testing IO therapeutics but also apply to targeted agents and combinations

Discussion



**NATIONAL
CANCER
INSTITUTE**

www.cancer.gov

www.cancer.gov/espanol