DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
AD HOC TRANSLATIONAL RESEARCH STRATEGY SUBCOMMITTEE MEETING

Summary of Meeting
June 17, 2021

Webinar

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
AD HOC TRANSLATIONAL RESEARCH STRATEGY SUBCOMMITTEE
Summary of Meeting
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A meeting of the *ad hoc* Translational Research Strategy Subcommittee (TRSS) of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held by webinar on Thursday, June 17, 2021, at 11:00 a.m. The TRSS chairs, Drs. Davidson and Dang, presided.[1] The meeting was adjourned at 12:01 p.m.

Co-Chairs
Chi V. Dang
Nancy E. Davidson

***Ex Officio* Members**
James H. Doroshow, NCI

Executive Secretary
Peter Ujhazy, NCI

TRSS Members
Francis Ali-Osman
Walter J. Curran, Jr. (absent)
David A. Mankoff
Lynn M. Matrisian
Roman Perez-Soler
Kevin M. Shannon
David A. Tuveson
Kevin P. White (absent)
Max S. Wicha

Presenters
Chi V. Dang, MD, PhD, Scientific Director, Ludwig Institute for Cancer Research; Professor, The Wistar Institute
Nancy E. Davidson, MD, Senior Vice President, Director, and Full Member, Clinical Research Division, Fred Hutchinson Cancer Research Center
Kevin M. Shannon, MD, Professor, Department of Pediatrics, University of California, San Francisco, School of Medicine, San Francisco, California

[1]A roster of TRSS members and their affiliations is included as an appendix.

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I. Welcome and Opening Statement

Chi V. Dang, MD, PhD
Nancy E. Davidson, MD

Dr. Davidson reviewed the confidentiality and conflict-of-interest practices required of TRSS members during their deliberations. She invited members of the public to send written comments on issues discussed during the meeting to Dr. Ujhazy within 10 days of the meeting.

Dr. Dang summarized the key points discussed during the previous TRSS meeting held on March 29, 2021. During that meeting, the subcommittee discussed resistance to immunotherapy and research gaps and opportunities regarding preclinical models; combination immunotherapies; molecular mechanisms, genetics, and the cellular basis of response and resistance to immunotherapy; and identification and validation of biomarkers of response and resistance to immunotherapy. TRSS members were asked to submit suggestions for immunotherapy research priorities.

Expanding on the topic of preclinical models, Dr. Dang noted that the suggested immunotherapy research priorities included development of better *in vivo* and *in vitro* immuno-oncology (IO) models with a focus on immunocompetent murine models (e.g., genetically engineered mouse models [GEMMs], syngeneic tumor models) and human organoid models. Other immunotherapy research priorities were to develop better predictive IO biomarkers, use imaging methods to develop biomarkers, study long-term responders, conduct microbiome and tumor microenvironment studies, and better understand cellular and molecular mechanisms of response or resistance. These topics segued well into the theme of the current meeting, which was to assess the translational potential of organoid cultures and animal tumor models, related primarily to IO but also to any cancer therapy.

II. Discussion of Opportunities and Gaps in Translational Research

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

Kevin Shannon, MD

Several practical considerations need to be taken into account with any cancer model, including the ability to accurately model primary human cancer, reproducibility, throughput, cost, predictive track record (or lack thereof), and organ site-specific issues. In the real world, there are many unknowns and trade-offs in using cancer models for drug testing, which is especially true for IO, for which most models to date use immunodeficient mice.

Both *in vitro* and *in vivo* models for testing cancer therapies and combinations have been developed. *In vitro* models include traditional cancer cell lines that have led to the discovery of many anti-proliferative cancer drugs, 3D culture systems that enhance the value of cancer cell lines, and organoids with and without immune cells. *In vivo* mouse models include cancer cell line xenografts, syngeneic mouse cell lines and chemical carcinogenesis models that should be given a fresh look in the era of IO, GEMMs, patient-derived xenograft (PDX) models of human cancer, and "humanized" mouse models using human CD34+ cells engrafted into immunodeficient mice to replicate an immune microenvironment for injecting tumor cell lines and other reagents.

There are several unique considerations for preclinical testing of IO agents. Researchers face challenges in modeling the key role of the tumor microenvironment (TME) in cancer maintenance and drug response/resistance in immunodeficient mice. Although the focus is often on the immune cells in these microenvironments, the species specificity of some cytokine and chemokine signaling networks (i.e., molecules generated in the mouse TME) do not activate or inhibit human cells and *vice versa*; a good example is human and mouse GM-CSF, which does not cross-react between species. In addition,

many existing models that were evolved to rapidly measure direct anti-proliferative activity are not ideal for testing IO agents and may require an extended observation time and additional cycles to show a response compared to other agents. Another concern is that IO drugs generated for treating human patients may not cross-react with mouse cells; as a result, agents may need to be "murine-ized" to be tested in preclinical models. Finally, "State A" (pretreatment) versus "State B" (relapsed/resistant) genomic analysis of tumor cells is less straightforward and informative for IO agents than for other interventions.

Dr. Shannon noted that "models are models," and no existing model completely recapitulates the biology of primary human cancers. It might be best to avoid a "one-size-fits-all" prescription and instead consider stepwise approaches in which single drugs and drug combinations are "filtered" in high-throughput models followed by careful validation in more complex models before bringing drugs to clinical trials. He commented that proposals to benchmark preclinical models by testing existing drugs and regimens will never make it through an R01 study section, which tend to be more supportive of newer models and concepts. None of these general principles are unique to testing IO therapeutics; they also apply to targeted agents and combinations.

Discussion

Preclinical models: History and current questions. Dr. Tuveson opened the discussion by noting that NIH and NCI have been aware of and supported the preclinical model space for decades. A large collaborative, trans-disciplinary program known as the Mouse Models of Human Cancers Consortium (MMHCM) was established in 1998. The goals of the MMHCM were to derive and characterize mouse models, develop and use innovative approaches in preclinical and drug intervention studies, and accelerate the pace of the research through the collaborative process. At the time the consortium launched, many researchers were still using carcinogenic-induced models. The last version of the MMHCM started to focus on therapeutics.

Dr. Tuveson acknowledged that it is a good idea to do cause-and-effect mechanistic studies in these models. He noted, however, that the costs of testing therapeutics in a preclinical genetically engineered animal model are as high as assessing therapeutics in a phase I clinical trial. In addition, it takes considerable infrastructure and time to do such studies properly. The time and research required to do cause and effect mechanistic studies is substantial and can go beyond a postdoctoral fellowship career.

For the current discussion, the question is whether existing genetically engineered, patient-derived, or newer *in vitro* tissue/organoid models can be used to decide which are the best clinical trials to enroll patients in or which standard of care treatment might provide the greatest benefit. The breakdown appears to be in the clinical trials arena in that the individual patient is not being studied. Rather, outdated parameters are applied in monitoring patients and assessing whether a patient is responding to a therapy.

An alternative that addresses an individualized approach to treatment/management is to look directly at tissue from the patient. The goal of this strategy is to develop a "bacteriology test" for cancer and to be able to return results to the patient within hours or days—not weeks or months. It is not clear at this point whether a piece of tissue from the patient is sufficient to achieve this goal or whether the tissue would need to be cultured or placed in an immunosuppressed or a humanized mouse model. These are some of the unanswered questions as to why current cancer drugs are not more effective. These questions could be answered with better organization and funding. One of NCI's efforts in trying to address this issue on its own was through a "mouse hospital" program set up at NCI-Frederick more than a decade ago. Dr. Tuveson said this bench-to-bedside approach was an innovative idea, but it did not work out in the end.

Dr. Tuveson described other efforts that involve performing microfluidics on small pieces of tissue to ask if an IO agent can cause productive responses (e.g., T cell activation, release of proper cytokines) in patients. Dr. Tuveson relayed an early experience using an organoid developed from a patient's pancreatic cancer tissue to test chimeric antigen receptor (CAR) T cell therapy. The CAR T cells were created, and although the therapy did not work, it provided a relatively quick answer so that the patient could consider other options.

IO is promising and should be pursued, but it is not clear if or to what extent it will work in the clinical setting. Improved organization and increased government funding, along with funding from all sectors including foundations and industry can help answer these questions about IO, advance the field, lead to new discoveries, and support the research pipeline to attract new investigators.

Barriers. Dr. Dang asked what conceptual, technical, and administrative barriers exist that are preventing the advancement of preclinical models. Dr. Tuveson identified numerous barriers. One conceptual barrier is that not every cancer type can be modeled. Another conceptual barrier is the feasibility of creating individualized cancer models for each patient that will generate results quickly, since patients cannot wait long periods of time for results that will guide their care and management. For example, development of PDX models involves months, which does not serve patients who need rapid turnaround of test results. Another challenge involves species differences and whether results in animal models translate to humans. Technical barriers include access to tissues and animal facilities and an insufficient number of trained scientists currently in the field and in the pipeline. Administratively, the high cost of preclinical modeling is prohibitive. Dr. Tuveson noted that his organization and others raise funds for modelers to help subsidize the costs of their research. Prioritization of models also needs further consideration. One of the main barriers to prioritization of models is that their predictive value is often questioned. Models that stabilize tumor growth are often given priority often without sufficient consideration to tumor shrinkage and the durability of the drug effect; as a result, the relative importance of these outcomes need to be revisited.

Predictive models. Dr. Matrisian asked whether there is a predictive animal model in any cancer type that might serve as a model for other cancers (e.g., chemotherapy agents that block cell proliferation) or whether there are examples of models that show benefit in both animals and humans. If so, what statistical analyses have been done to demonstrate how sensitive and specific a model is for a certain disease? Dr. Dang noted that pharmaceutical companies often use results of predictive models when making "go or no go" decisions toward proceeding to clinical trials. However, it is unlikely that one model would be applicable to all or most cancer types. He suggested identifying models that can be used as pipeline checkpoints for proceeding to phase I trials.

Dr. Davidson pointed to translation of animal models of therapies for breast cancer, which have demonstrated, for example, the efficacy of agents such as tamoxifen, aromatase inhibitors, and other drugs. These models involve straightforward biochemistry by manipulating the endocrine system. Dr. Shannon pointed to cell line models for targeted agents (e.g., KRAS vs. BRAF mutant cell lines) and noted that BCR-ABL–transformed cells from both patients and mice can be modeled for resistance. One of the more elegant examples of a mouse model that helped resolve a problem in human cancer was the administration of arsenic with all-trans retinoic acid to treat acute promyelocytic leukemia (APL). The model not only clearly demonstrated synergistic efficacy of the two agents in treating APL, but it also showed that the combination was safe. Arsenic is now part of standard treatment for APL. The hematologic malignancy field appears to be further along than other cancer types, possibly because the hematologic models are more tractable. Dr. Shannon acknowledged that there are few or no translational models for other cancers (e.g., glioblastoma, pancreatic cancer) and advanced disease, which is frustrating given patient suffering.

Dr. Ali-Osman agreed that having one model to serve as a template to answer questions across cancer types and scenarios is not realistic. However, it may be helpful to distinguish between predictive and treatment preclinical models. The preclinical discovery phase might leverage unique models that allow the research to go forward in terms of mechanistic studies and targeted hits. Developing predictive models for treatment presents greater challenges and would likely involve a completely different set of models. Differentiating between models can be guided by the questions being asked through those models. For example, for brain tumors, cell lines are used in the early discovery phase, while more complex models (e.g., PDX) are used as the research progresses to the clinical setting.

Immunocompetent models. Dr. Wicha further distinguished models that directly target pathways and their effects on the immune system. An early problem in trying to target cancer stem cells was that researchers focused on the pathways that regulated tumor cells without understanding that those same pathways were exploited by the immune system (e.g., Notch and Wnt signaling).

Dr. Wicha noted the importance—and lack—of immunocompetent preclinical mouse models and organoids with immune systems, adding that models that do not address changes in the immune system are off track. He inquired about NCI's efforts in the development of immunocompetent humanized mouse models and whether there are any requests for applications to support creation of these models. Dr. Doroshow referred to the Cancer Moonshot℠ Immuno-oncology Translational Network program, which has both a pediatric and an adult program, and how investigators are thinking about these problems. NCI has been looking to find basic answers to questions involving PDX organoid models, and this has been one of the primary goals of the PDX network. One task has been to determine the level of data required to proceed to a clinical trial for a single agent or drug combination. The team found that until recently, the bar for data informing clinical trials has been very low—far less than the amount and quality of data that an Institutional Review Board would require for a phase II trial.

Dr. Doroshow also noted two outstanding questions to long-term problems in this field: What do *in vitro* data mean vis-à-vis *in vivo* models, and how often do data from xenografts map to the patient? A related question is how often do studies show a dose-response curve in a cell line or organoid that is predictive of an *in vivo* response in those organoids or with xenografts from the same cell line?

Dr. Doroshow cited an older paper that looked at clinical cancer drug development using NCI xenograft data from the 1980s and 1990s. The study authors performed a meta-analysis of all models of tested drugs that proceeded to a phase II trial. The findings were disappointing. There was no correlation between single agents that were active in preclinical models that were also active in phase II clinical trials. However, agents that were active in three or four xenografts (irrespective of histology) were subsequently tested in phase II trials. These findings show some predictive effect of established cell line xenografts and support having a diversity of approaches, which is not often seen in this field. Take-home messages from this analysis are to find better ways to correlate *in vitro* models with *in vivo* models and to ask how data from *in vivo* models inform patient response.

Dr. Shannon also questioned the value of a cytostatic tumor response as an endpoint of efficacy. His trials look at mortality (survival curves) and treat until all leukemia is relapsed, even in patients who otherwise have a good response, to better understand the course of treatment and disease.

Dr. Dang noted that the overall discussion shifted between personalized predictive models and models that inform general principles. Models for general principles (e.g., checkpoints, anti-metabolites) need to be distinguished as conceptually different from personalized models for individual patients. Preclinical models remain important for deriving general principles, finding new points of vulnerability in many cancers, and developing new drug pipelines.

Immuno-oncology Models. Dr. Perez-Soler said the field is open for the creation of predictive models of IO for both new IOs and mechanisms of resistance. A challenge to developing these models is how to transplant immune cells to whatever platform is being used. Double transplant of immune cells and tumor cells in PDX, as suggested by Dr. Wicha, is probably the ideal model from the clinical perspective. Dr. Perez-Soler recommended exploring the best ideas for developing predictive models of IO and then supporting research to create those models.

Dr. Mankoff inquired about differences in transplantable versus spontaneous mouse models within the context of angiogenesis. Specifically, he asked about the importance of development of a spontaneous versus transplanted vasculature on the immune response and for immunotherapy. He also asked about the impact of the microvasculature on the tumor microenvironment (TME). Dr. Shannon noted that tumor vasculature from xenografts differs considerably from spontaneous vasculature, and tumors that arise spontaneously are probably better models of actual tumors. He agreed this is an important area to pursue. Dr Tuveson noted that the TME is difficult to replicate and sustain *in vitro*, presenting a unique challenge to the development of these models. In addition, *in vitro* models of the TME do not enable a high-throughput approach for screening drugs. Dr. Tuveson referenced Dr. Calvin Kuo's team at Stanford University, which has developed an air-fluid interface culture model that simulates the tumor microenvironment and can be sustained for up to 2 months.

Dr. Ali-Osman inquired about the status and potential of organoids for IO and other immunotherapies. Dr. Tuveson said investigations are underway in which human cancer cells are mixed with PDLs and TILs from that person's tumor to determine if they have T cells specific to class I presented peptides. This approach is currently being tested primarily for melanoma, for which personalized tumor vaccines have been effective in some patients.

Dr. Shannon agreed that a clear plan for development of predictive models of IO is lacking but needed. He suggested giving further consideration to a plan for targeted therapies, where there is better understanding of how to proceed.

Potential Workshop. Dr. Davidson suggested that a workshop be recommended by the TRSS group on the topic of preclinical models, where there could be a more robust discussion by experts in the field over a longer period of time. Dr. Tuveson agreed that a workshop where the group can learn more from experts in this field would be beneficial.

Dr. Tuveson stressed the importance of keeping the patient at the forefront of this endeavor and investing scientific knowledge to succeed in the preclinical model space. Tissue, *in vitro* models, and organoids will facilitate the process. Animal models will probably be too slow to return relevant information to the patient in a timely manner but will inform general principles and resistance. The proposed workshop could explore this topic in detail with experts in the field.

Dr. Dang noted that precision oncology models test existing drugs to determine which agents work best for patients and are more aspirational than models for general principles.

Both areas—personalized predictive models and general principles for models—should be discussed at the workshop.

Next Steps. Dr. Dang asked each TRSS member to send workshop topics to Dr. Ujhazy for NCI to consider. The group will reconvene in September to further discuss the workshop. Subcommittee members interested in helping to plan the workshop should contact Dr. Dang and Dr. Davidson.

III. Wrap-Up

Peter Ujhazy, MD, PhD

Dr. Ujhazy thanked the TRSS members for their valuable input.

IV. Adjournment

There being no further business, the TRSS meeting was adjourned at 12:01 p.m.

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Date Chi V. Dang, MD, PhD, Co-Chair

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Date Nancy E. Davidson, MD, Co-Chair

_____

Date Peter Ujhazy, MD, PhD, Executive Secretary

Appendix

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee
***Ad Hoc* Translational Research Strategy Subcommittee**

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