WHITE PAPER

# Accelerating immuno-oncology therapeutic development: Choosing the best preclinical model

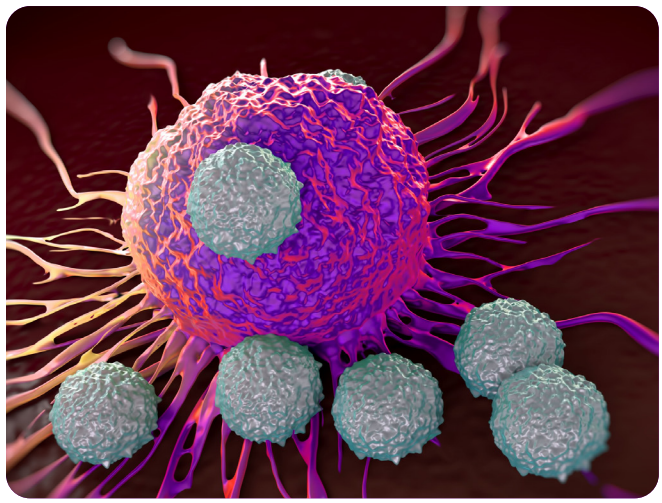
## Introduction

Oncology research remains a major focal point of the pharmaceutical and biopharmaceutical industry. Standalone historic approaches such as chemotherapy, albeit effective, pose tolerability issues that often coincide with unintended systemic side effects.

Current approaches to oncology treatment often involve a multi-faceted therapeutic approach. Researchers strive to incorporate various drug types with the intent of combating cancer on multiple fronts with the goal of remission and elimination. The delicate interplay between homeostatic control mechanisms and cancer cells offers evolving opportunities for both therapeutic targeting and the development of new drug candidates.

The immune system represents a major player in systemic anti-cancer activity. As research evolves, as does our understanding of the many ways in which cancer cells are able to evade surveillance and checkpoint measures facilitated by the immune system. Transitioning from theory to practical application takes significant time and financial investment, all without the promise of regulatory approval. Ethical checkpoints with the primary goal of evaluating safety are structured throughout the drug development life cycle to ensure that only drug candidates with data to support a robust safety profile are able to proceed to human testing.

Food and Drug Administration (FDA) review and approval of preclinical data is required prior to beginning clinical development through an Investigational New Drug (IND) application. Research companies therefore put forth substantial efforts into evaluating the safety and efficacy of drug candidates early on in animal studies.



Preclinical study assessments may include pharmacokinetics and pharmacodynamics, systemic and local toxicity, and immunogenicity. Studies involving at least two species are required for preclinical toxicological assessment of small molecule drugs. However, for biologics, toxicology studies often use a pharmacological relevance species such as nonhuman primates. Challenges in selecting an appropriate preclinical species include predictability and applicability surface when comparing preclinical to clinical results. Certain species models will offer higher predictability in certain body systems, yet lower in others making it very difficult to establish a best-fit model.

This difficulty is elevated further in immuno-oncology as small animal models lack the complex interplay of the immune system and cancer microenvironment as observed in humans. Large animal studies are becoming more commonplace, although still pose a degree of ethical concerns of which are weighed for every drug candidate investigation.

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## Preclinical model

Establishing a series of preclinical models to characterize safety, toxicity, and tolerability of a drug candidate requires a significant amount of planning and foresight. No matter the selection, animal models are unable to fully represent the complexity of the human body system in its entirety. Successful preclinical design for new small molecule drug candidates involves investigation using at least two animal species and a pharmacological relevance species for biologics.

Additionally, an acceptable preclinical assessment may not necessarily translate to a positive phase I human outcome. Tolerability issues and adverse events may surface during the initial phases of clinical development; however, a robust preclinical evaluation stands as a means of predicting potential problematic clinical observations.

## Intended purpose in immuno-oncology

Cancer as a series of diseases, has the ability to evolve to incorporate a series of hallmarks which allow for uncontrolled cell replication and metastases. Coined the 6 Hallmarks of Cancer, cancer cells may progress to exhibit certain capabilities including sustained proliferative signaling, evading growth suppressors, activation of invasion and metastatic pathways, enablement of replicative immortality, angiogenic induction, and apoptotic resistance (Hanahan, Wrinberg, 2011). Further investigation has uncovered two additional hallmarks, energy metabolism reprogramming and evasive immune destruction. Cancer therefore isn't necessarily a disease in itself, rather a series of alterations in normal cell functioning which if left unchallenged can lead to tumorigenesis and metastasis.

Three main phases of immunosurveillance failure promote carcinogenic progression including elimination, equilibrium, and escape. Each mechanism involves intricate innate and adaptive functions facilitated by varying immune cells (Overgaard et al., 2018). By investigating the key molecules that pay a role in immunosurveillance, researchers can develop a wide array of therapeutics on which to combat carcinogenesis. Immuno-oncology drug candidates including checkpoint inhibitors, monotherapies, replacement therapies, vaccines, small molecules, and cytokines offer varying risks and benefits to treating cancer at both local and systemic levels.

*In vitro* research of molecular targets offers an opportunity for investigation of potential drug candidates specific to a target expressed at high levels on certain types of cancer cells. Endothelial cells express an angiogenic inducer, vascular endothelial growth factor (VEGF), which functions in the generation of new blood vessels. One of the classic hallmarks of cancer is angiogenesis, therefore cancer cells that progress into tumors often have the capability of stimulating the generation of new vasculature (Fridman et al., 2012). Tumors harboring this capability are invasive in nature, and if able to progress toward proliferation has a higher probability of invading neighboring or systemic tissues.

Targeting the immune system as a means of stimulating anti-carcinogenesis also offers a mechanism of developing an immuno-oncology drug candidate. Immune checkpoint inhibitors including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and programmed death-ligand 1 (PD-L1) represent a major focus of the current immuno-oncology biologics market. Developing therapeutics which block inhibitory signaling allows the immune system to recognize tumor cells as foreign and elicit anti-carcinogenic effects enhancing anti-tumor immune responses by targeting immune cells.

Antigen presenting cells such as dendritic cells that display tumor specific antigen or tumor associated antigens can also be used as cancer vaccines to boost antitumor responses. Using the preclinical model to evaluate safety and tolerability combined with a deep understanding of potential immunological impact offers insight into results that may be observed in the clinic.

## Selecting a model

Preclinical model selection focuses on utilizing small and large animal data to predict the potential safety and efficacy parameters that may be observed in a clinical setting. Differences are observed between species, including human, therefore the selection of a preclinical model is highly dependent on drug candidate characteristics and underlying associated biologic mechanisms. Certain species exhibit higher predictability trends depending on the level of granularity of analysis. It is also estimated that the average rate of successful translation from rodent models to clinical cancer trials is less than 8T (Mak et al., 2014) and their utility in translational research is highly limited. Furthermore, while tumors in humans arose spontaneously, it is often induced in mice.

In *vivo* oncology murine models have been used for decades to categorize cellular mechanisms with a high level of granularity. Mouse models offer insight into genetic alterations and cancer, observed biomarkers as potential diagnostic molecules, and therapeutic drug targets. These data represent a piece in the larger puzzle comprising the current therapeutic landscape of the immuno-oncology area of focus (Gargiulo, 2018). Mouse models, although easily controlled, cost effective, and reproducible fall short of providing clinically relevant toxicology and immunogenicity data.

Rat and canine models are used most commonly to investigate immuno-oncology mechanisms within a living system. As companion animals, canines mimic human diets, and exhibit exposure to similar environmental factors that may, similarly to humans, contribute to a high prevalence of cancer in the elderly. Organ, tissue, and cell functioning is similar in humans and dogs, therefore immuno-oncology canine research continues to expand (Overgaard et al., 2018).

Porcine models offer promising investigation of the metabolic effects of drug candidates. Given their longer life cycle, disease characterization and progression can be monitored prior to clinical evaluation. Broadening the spectrum of animal model applicability and predictability can contribute to deepening the relevance of preclinical data, increase drug development efficiency, and elevate the experimental design parameters of clinical studies.

## Timeline

Preclinical study data represents one piece of a much larger puzzle in the drug development cycle. With timelines of lead and target discovery to market approval upward of twelve to fifteen years, efficiencies can have a substantial impact especially in the immuno-oncology market. Multiple studies contribute to preclinical development, which combined can take anywhere from one to five years. Acceleration based on market size, unmet medical need, and regulatory enhancement programs can help drug candidates for immuno-oncology progress in upward of four years.

Efficiency planning takes into account time required for regulatory review, and clinical study designs are formulated based on preclinical data. Early clinical phases focus primarily on safety, tolerability, and establishment of dosing parameters yet preclinical data is required for setting relevant clinical endpoints for later phase clinical studies.

## Clinical endpoints

Cancer as a degenerative change in genotype first at the tissue and organ level with the capability of spreading systemically poses challenges on multiple fronts. Clinical studies are structured to measure certain facets of safety and efficacy with later phase evaluations monitoring for specific measurements referred to as clinical outcome parameters. Common immuno-oncology outcome parameters are progression-free survival, disease-free survival, and overall survival. Certain types of cancers are considered highly aggressive in that the timeframe between initial progression and evasion of immunosurveillance mechanisms is very short (Fridman et al., 2012).

Specific types of cancer exhibiting aggressive progression often fail to provide data in support of disease-free or overall survival. In aggressive cancer types, supporting a singular clinical endpoint poses a challenge for regulatory approval unless the market exhibits an unmet medical need. Data investigating the immuno-oncology interaction can help to more effectively predict whether issues may surface in setting relevant and attainable secondary endpoints.

## Supporting data

For IND approved drug candidates that progress to perform early evaluations, some fail for toxicity or tolerability in the clinic. Observations in the failed clinical studies allow for further investigation using additional preclinical studies. Models to isolate body systems or tissues provide added granularity of cardiac, neurological, kidney, gastro-intestinal, or liver toxicology. These data can be applied in adjusting the dosing and recovery period cycle timeline.

Making alterations to the therapeutic window based on pharmacokinetic, pharmacodynamic and immunogenicity data can help to predict downstream clinical performance. Additional preclinical study data may allow for clinical studies to proceed with newly established parameters.

## Summary

The complexity of the immune system coupled with cancer's ability to evolve and evade homeostatic immunosurveillance measures makes compiling meaningful yet specific data increasingly difficult. A robust approach to developing the right preclinical model involves systems toxicology, immunogenicity, and 3D primary human tissue *in vitro* studies.

The best approach to preclinical testing involves balancing data generation in support of a positive safety profile that also incorporates clinical relevance with cost and market potential. Presenting regulatory authorities with data representative of these criteria helps to propel thoroughly investigated drug candidates toward IND approval, and future clinical evaluation.

**Dr. Seyoum Ayehunie**

Vice President of Immunological Systems, MatTek Corporation

Dr. Seyoum Ayehunie is currently, Vice President of Immunological Systems at MatTek Corporation, Ashland, MA, and is the lead scientist responsible for the incorporation of immune cells into MatTek's different organotypic tissue models. He has successfully generated dendritic cells and plasmacytoid dendritic cells from progenitor stem cells and applied the technology in cancer immunotherapy research and to screen chemical allergenicity.

He has developed MatTek's current commercial products such as, EpiGingival-FT, EpiOral-FT (full thickness gingival and Buccal tissues), and psoriasis (SOR-300-FT) tissue models. In the last 5 years, he has developed a new *in vitro* primary human cell-based organotypic small intestinal (SMI) microtissues for predicting intestinal drug absorption, metabolism, drug-drug interaction, and inflammation. The 3D-intestinal microtissues recapitulate the structural features and physiological barrier properties of the human small intestine. The microtissues also expressed drug transporters and metabolizing enzymes found on the intestinal wall. The developed Intestinal tissue model are widely used by major pharmaceutical drug companies involved in drug-induced gastrointestinal toxicity of cancer drugs, intestinal drug permeation, inflammation, wound healing, and microbial infection.

In the last couple of months, Dr Ayehunie developed a nasal tissue model for COVID-19 research and is being tested in different academic laboratories. In addition, he has received more than 15 Small Business Innovation Research (SBIR Phase I and Phase II) grant awards from the National Institute of Health (NIH) and the Department of Defense (DoD) which led to the development of commercial products. Dr. Ayehunie has also served as permanent member of NIH Study Sections.

Prior to joining MatTek, Dr. Ayehunie, who received his PhD from the Karolinska Institute (1992), Stockholm, Sweden, did his post-doctoral fellowship at Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA (1993-1997). At Harvard Dr. Ayehunie was involved in HIV vaccine research and received the Fogarty International and NIH fellowship awards and also worked as an instructor of Medicine.

Dr. Ayehunie has more than 40 publications in refereed journals to his credit and has made a number of presentations on his work involving cancer immunotherapy, drug permeation, and metabolism, and in the field of mucosal toxicology using *in vitro* tissue models.

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**Revvity, Inc.**
940 Winter Street
Waltham, MA 02451 USA

(800) 762-4000
www.revvity.com

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