7th Annual
PREDiCT: TUMOR MODELS BOSTON

July 16-18 | Boston, MA

SPEAKER INTERVIEW

AN EXCLUSIVE INTERVIEW WITH:

Davy Ouyang,
Executive Director,
Cancer Pharmacology
Crown Bioscience

Crown Bioscience is the leading preclinical CRO with expertise in the disease areas of oncology, inflammation, and metabolic disease. They are known for the breadth and quality of their *in vitro* and *in vivo* models. Ahead of the **PREDiCT: 7th Annual Tumor Models Boston** Summit in July, we have caught up with **Davy Ouyang**, Executive Director, Cancer Pharmacology, Crown Bioscience to hear his thoughts and insights in the fast evolving oncology space!

Davy, thanks so much for taking some time to speak to us. As a leader in cancer pharmacology, how would you describe the industry's shift in preclinical drug discovery – particularly the utilization of data-driven models to support preclinical assessment?

Historically, the success rate of oncology drugs in clinical trials is particularly low, suffering from the lack of translational preclinical models. Patient-derived or cell line-derived xenografts that recapitulate autonomous tumor growth driven by aberrant signaling through de-regulated pathways have shown great value in the evaluation of chemotherapies and targeted agents.

However, most of the preclinical research using PDX and CDX is conducted in subcutaneously engrafted tumors in immune deficient mice, completely devoid of the context of the tissue specific microenvironment and involvement of immune cells, which play significant roles in tumor onset and progression. Genetically engineered mouse models (GEMM), or other syngeneic tumor homograft models, serve as good surrogate models with a fully competent immune system. Still, it is mouse tumor and mouse immunity, which may not fully recapitulate the biology of human disease.

Since there are limitations with each model, more drug developers are using various model platforms and a data-driven approach to address different scientific objectives. Cancer pharmacologists and preclinical scientists are now seeking extensive characterization of various preclinical models on histopathology, genomics, immune profile, and responses to benchmark drugs in order to select the most appropriate model.

While pharma and biotechs certainly welcome more advanced preclinical oncology models, they are now facing a new set of challenges with targeted IO therapies, especially because there's a lack of animal models for preclinical evaluation. What is your advice?

There are certainly huge challenges in preclinical evaluation of IO therapeutics. As aforementioned, there is no one human avatar model that can provide you with all the answers. My advice is to define your specific questions upfront, and then choose the appropriate model to address each question.

> "Knock-in models expressing a human drug target on immune cells (HuGEMM™) and/or tumor cells (HuCELL™) can provide a platform to evaluate therapeutic antibodies which don't cross-react with mouse targets"

For example, hematopoietic stem cell humanized mice grafted with PDX offer a system to evaluate IO therapies with human tumors in a partially reconstituted human immunity. The results from these studies can reflect the tumor growth inhibition and pharmacodynamic (PD) responses observed in the clinic to some extent. However, these studies can produce highly variable results depending on the donor, thus complicate the identification of truly effective compounds. Moreover, the reconstituted human immune system is incomplete and non-autologous, so it can only partially reflect the mechanism of action (MOA) of the treatment. We must understand the advantages and challenges of each model in order to maximize their translatability.

Crown Bioscience is a leader in the tumor models, and we've seen how your teams have supported preclinical scientist to advance their drug development programs. Where do you see the opportunities lie in this area?

While the challenge is big, we are striving hard to meet the IO drug development needs. I believe opportunities lie in 3 areas:

1. GEMM models, which preserve clinically relevant oncogenic driver mutations and tumor architecture relevant to its original TME and can reflect key aspects of human disease, offering great value in IO drug MOA evaluation. However, these models are often difficult to access and not conducive to large pharmacology studies. During its collaborations with other industry leaders, CrownBio has developed many GEMM models. The GEMM-derived tumors are then passaged *in vivo* to set up tumor homograft models for pharmacology studies, making GEMM models more accessible to researchers.

> I foresee the organoid *ex vivo* system with autologous immune cells from patients become increasingly important

2. Knock-in models expressing a human drug target on immune cells (HuGEMM™) and/or tumor cells (HuCELL™) are also promising. These models provide a platform to evaluate therapeutic antibodies, which don't cross-react with mouse targets.

3. Organoids, which largely capture the histopathology of human cancer, especially those from our collection of autologous patient PBMC or TILs, can be used to set up *ex vivo* immuno assays to test various types of IO therapeutics.

Using human target knock-in mouse model for IO drug discovery is definitely a hot topic, could you give us a snippet of the talk?

Sure! Yes, HuGEMM and HuCELL are useful models for efficacy evaluation of human-specific therapeutic antibodies. Crown has developed over 20 HuGEMM models, including many double knock-in models, and some HuCELL models.

I will be sharing examples of these models, how they are being used to evaluate monotherapies, various combination therapies and bi-specifics. I'll also be giving examples of IO safety assessment as it's a critical part of preclinical study. However, since not all models behave as hypothesized due to the complex nature of biology, I will discuss a case example where a HuGEMM model failed to maintain signal transduction. This lesson learned is very important for researchers and scientists, as this helps us to anticipate risks and refine design of experiment.

We are very excited about our 7th annual summit in Boston. Ahead of the meeting, would you be able to share a top tip with our PREDiCT: Tumor Models community, particularly when selecting the right models during drug discovery?

When evaluating MOA and PD, I think mouse tumor models such as GEMM, tumor homografts, and syngeneic models are great options for surrogate proof of concept and target engagement studies.

GEMM and tumor homografts certainly offer higher translational value than traditional syngeneic models because they resemble human cancer histopathology, molecular pathology, and tumor microenvironment.

HuGEMM should be considered as a different type of syngeneic model since only the targets are humanized. Under pre-defined parameters, it can serve as an effective model system for efficacy and toxicology evaluation of human-specific therapeutic antibodies and various combinations.

Xenograft models (CDX & PDX) in a humanized setting are good at reflecting drug responses observed in the clinic to some extent, but still require a lot of work to be considered as robust preclinical tools.

Last but not least, I personally can foresee the organoid *ex vivo* system with autologous immune cells from patients becoming increasingly important – and would love to hear more about industry developments!

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Crown Bioscience is the **Lead Partner** at the **7th Annual PREDiCT: Tumor Models Boston Summit** (July 16 – 18).

Davy will be sharing an expertise talk on Developing Human Target Knock-In Mouse Models for Immuno-Oncology Drug Discovery and joining a panel discussion on the changing expectations of model requirements.

Find out more by accessing your full event guide.