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SPEAKER INTERVIEW

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Ludovic has over 10 years of research experience in oncology. Prior to joining CrownBio, he worked at Invectys (Paris, France) as head of the pharmacology department working on cancer vaccines and antibody immunotherapy from preclinical to early clinical phases. Ludovic holds a PhD in Pharmacology from Nantes University (France), and served as postdoctoral researcher in the UK and Ireland followed by positions in academia and preclinical CROs.

What do you think are the current challenges facing the preclinical oncology modelling industry?

Despite the incredible progress made in cancer treatment, oncology drug development still faces a very high attrition rate. Only 5% of new compounds in development reach final approval for patient use. This is most often due to lack of efficacy rather than safety issues, indicating that more advanced preclinical models that better predict patient response are urgently needed. The main challenge we are facing in preclinical modelling is to provide robust models that reflect the diversity of cancer and the complexity of the tumour microenvironment for the whole drug discovery workflow. We need models that take a candidate compound from early stage *in vitro* investigation to late stage of *in vivo* validation, as well as for translational studies to stratify patient populations and identify potential biomarkers or companion diagnostics.

Traditionally drug discovery has used *in vitro* cancer cell lines in a 2D format to provide indications on target identification and drug mechanism of action. These models though, fail at recapitulating the complex microenvironment of cancers *in vivo*. This has become increasingly relevant for immunotherapies where we need to evaluate the interaction between the tumour and the immune system to be able to take decisions on efficacy. Additionally, native tumour architecture, known to influence drug response, is lacking in 2D cell lines. We've therefore witnessed a shift in interest towards 3D models, including primary cells, which better preserve tumour architecture as well as original genomic makeup. Primary cells, however, are difficult to establish and don't offer sufficient scalability for large-scale repeat experiments.

Patient-derived *in vivo* models such as PDX are considered best-in-class to predict patient response, capturing heterogeneity, diversity and original genomic characteristics and are widely used in translational studies to mimic Phase II clinical trials. However, they require considerable effort to generate and maintain, they can be costly, and they can't be used to evaluate immunotherapies because they lack a functional immune system.

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Which models do you currently work with? How do they benefit the industry in improving drug discovery and candidate selection?

CrownBio provides a very diverse and comprehensive portfolio of *in vitro, in vivo* and *ex vivo* models to support the different stages of drug development and the diverse nature of therapeutics and combinations. We offer a customised solution depending on the type of compounds that need to be tested and the required endpoints. Our experience and expertise in preclinical and translational studies is accessible through our scientists as well as our databases.

PDX are among our most popular and well know offering, and the size and the level of characterisation of our collection is available through our online PDX database, HuBase™. PDX reflect the diversity of the patient population allowing clients to replicate Phase II-like clinical trials, providing invaluable information on the expected response in the patient population.

We also offer large panels of well-characterised cancer

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cell lines that can be run in large-scale screens for proof of concept studies on target engagement across several cancer types. These initial results can then be translated *in vivo* through associated cell line derived xenograft models. Again, we share our model characterisation through our human cell line and xenograft database XenoBase®.

For immunotherapy development we provide models to evaluate cross reactive or surrogate agents such as syngeneics and our unique tumour homografts (derived from GEMM tumours and better preserving the original tumour morphology and genetic make-up). Most of these models feature human disease-relevant mutations that can be lost in syngeneic models. If our clients are interested in evaluating human specific immunotherapies, we also provide humanized PDX and cell line derived xenografts, as well as human target knock-in models which are a robust and cost-effective alternative to more complex fully humanised systems.

Finally, we have recently launched what I consider our most ground-breaking offering yet, developed in partnership with Hubrecht Organoid Technology (HUB), our organoid platform. Organoids are a 3D *in vitro* system which has become increasingly popular following recent publications showing that patient-derived tumour organoids effectively predict clinical response. Due to our exclusive agreement with HUB we now provide preclinical drug discovery services using HUB organoids. Our offering includes PDX-derived organoids paired with their corresponding *in vivo* models, which together offer a unique drug development workflow featuring a continuum in *in vitro* to *in vivo* modelling with relevance to human patients. In addition to the lab-based activities we have extensive in silico expertise to support discovery and biomarker identification which can be easily integrated into any work package.

How are Crown Bioscience adapting their practices following the latest success of IO therapeutics in the preclinical oncology field?

CrownBio's immuno-oncology model panel is one of the most comprehensive available, including models recapitulating the human immune system as well as leveraging immunocompetent murine models. We have demonstrated expertise in running mouse clinical trials using humanised models and are continuously expanding our bioinformatic tools to better support study designs for complex models and therapeutic combinations. Additionally, we have developed a growing portfolio of human target knock in models that provide a cost effective and robust alternative to more complex humanised systems. This is one of our most popular offerings for I/O, suited to evaluation of human-specific agents targeting checkpoint molecules on the immune cells, tumour antigens on cancers, or both in the case of T cell engagers or some bispecific antibodies.

Syngeneics are still the workhorse of immuno-oncology models for target engagement and proof of concept efficacy studies, and our broad collection is one of the best characterised and annotated in the market. We recognize the pace at which immunotherapies and combinations need to be validated so we developed MuScreen™, our syngeneic model large scale screening platform that we have been successfully running for several years to achieve this in a cost-effective manner.

Our R&D team is also working on the development of co-cultures of PBMC or TILs with tumour organoids. Without a doubt this will represent a pioneering opportunity for bringing clinical relevance to *in vitro* assays for immuno-oncology, which is currently lacking.

What are you most looking forward to at the upcoming 8th PREDiCT: Tumour Models London Summit and what do you expect will be your key learnings?

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I think there is an increasing need for advanced preclinical models that allow us to answer very specific and increasingly more complex questions. I think this year we will have the chance to explore how humanised models can be improved a bit further, as well as what progress has been made in 3D modelling in the cancer stem cells and organoids field and finally the incorporation of machine learning/AI to enhance discovery even further.