Humanized avian xenograft models: advancing preclinical evaluation of immunotherapies and immune cell therapies with enhanced predictive accuracy

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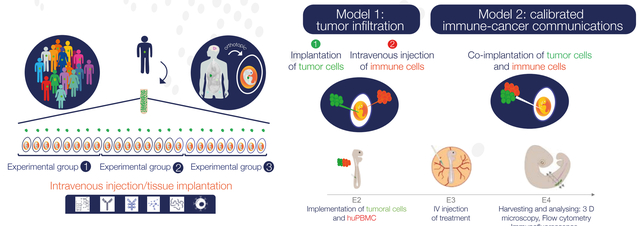
Abstract

Despite the success of immunotherapies and immune-cell therapies, clinical attrition remains high, in part due to the limited predictive value of current preclinical models. This highlights the need for innovative patient tumor-based technologies to enable rapid and reliable evaluation of immunotherapies. To address this need, we have built on our proprietary and patented AVI-PDX technology, which involves implanting human cancer cells into selected organs of the avian embryo for evaluation of therapeutic efficacy within a few days. We developed advanced humanized avian xenograft models for xenograft of cell lines and patient tumors, namely Humanized-AVI-PDX™ and Humanized-AVI-cellDX™, based on either (i) co-micro-implantation of human PBMCs and cancer cells or (ii) implantation of cancer cells followed by intravenous injection of human PBMCs. We performed a series of experimental steps combining whole embryo light-sheet microscopy, analyses of molecular markers by immunolabelling on cryosections and flow cytometry on microdissected tumors. We demonstrated highly efficient uptake and survival of hu-PBMCs, with preservation of T and B lymphocyte, monocyte and NK cell populations, minimal allogenicity, successfully established tumor-immune interaction, with enhanced infiltration and persistence of human immune cells within the tumors. We then validated our models with an anti-PD-1 immune checkpoint inhibitor, pembrolizumab. We found that intravenous administration of the anti-PD-1 mAb efficiently targets PD-1 receptors on T cells, resulting in their activation.
Next, we evaluated anti-PD-1 efficacy in a panel of humanized AVI-CellDX and AVI-PDX models for colorectal cancer (CRC), breast cancer and melanoma using whole embryo light sheet imaging and tumor volume quantification. We found that our models successfully reproduced the anti-PD-1 effects, demonstrating efficacy on known sensitive cell lines and not on known resistant cell lines. Interestingly, our CRC models were also effective in revealing the heterogeneity of patient tumor responses according to molecular features currently used to predict outcome in the clinic. Finally, using an ovarian IMMUNO-AVI-cellDX™ model, we demonstrated the efficacy of a co-implanted HERV-specific T cell clone (collaboration with ErVimmune), extending the application of our models to immune cell therapy. Our models thus provide new solutions for the study of immune-based therapeutic approaches and associated predictive biomarkers.

Method and Models

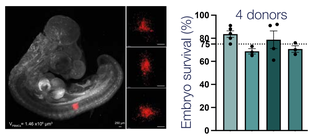
The HUMANIZED-AVI-PDX™ platform

ERBC-Oncofactory has pioneered the development and full characterization of avian patient-derived xenograft models, introducing New Approach Methodology (NAM) for assessing the efficacy of therapeutic compounds with unparalleled robustness and speed compared to traditional models. Here, we designed novel paradigms to engraft cancer cell lines or patient-derived samples with human immune cells.

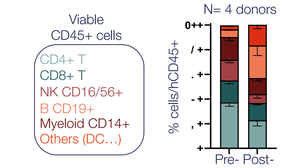


STEP 1 Do avian host and grafted hu-immune cells survive?

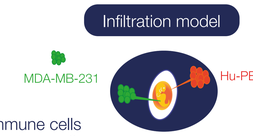
1 Do embryos survive ?



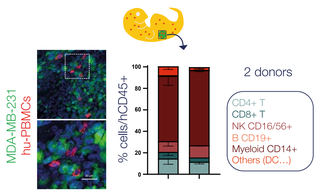
2 Do human immune cells survive ?



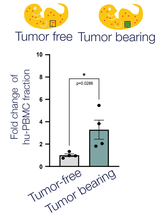
STEP 2 Do circulating hu-PBMCs infiltrate the tumor?



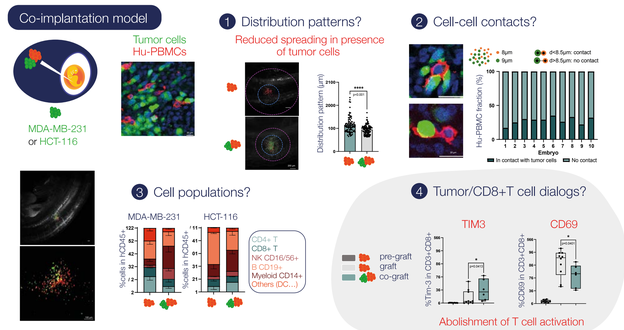
1 Are there immune cells infiltrating the tumors?



2 Do tumor cells attract injected immune cells?

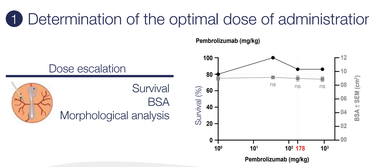


STEP 3 Do hu-PBMCs-cancer cells communicate?

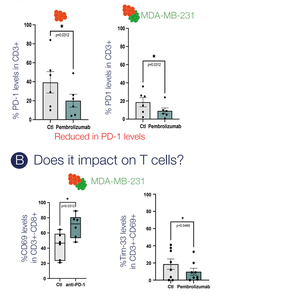


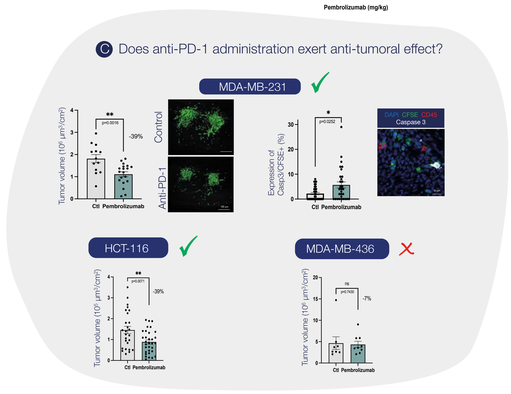
STEP 4 Do humanized avian models allow assessing efficacy of immunotherapy?

1 Determination of the optimal dose of administration

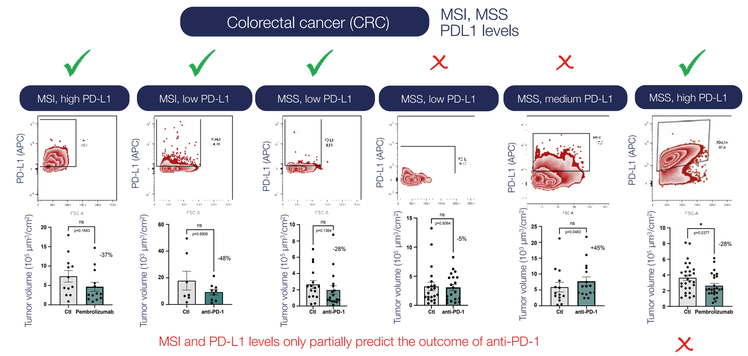


2 Validating the models with an immunotherapy

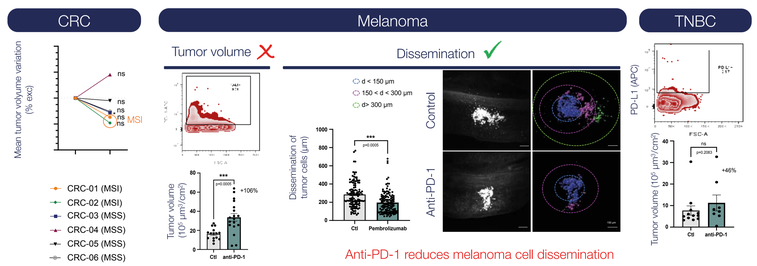




STEP 5 Can we recapitulate patient tumor heterogeneity with humanized patient-derived xenograft avian models?



MSI and PD-L1 levels only partially predict the outcome of anti-PD-1

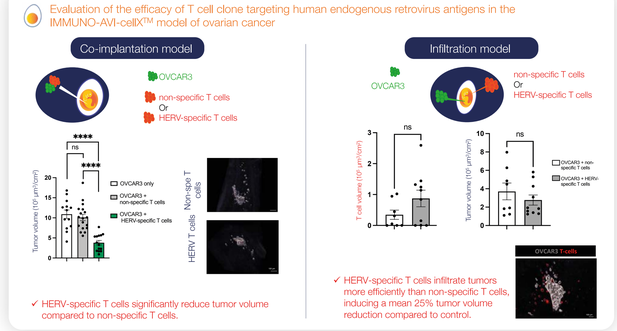


Anti-PD-1 reduces melanoma cell dissemination

In Partnership with ErVimmune

NEXT GENERATION CANCER IMMUNOTHERAPIES

Evaluation of the efficacy of T cell clone targeting human endogenous retrovirus antigens in the IMMUNO-AVI-cellX[TM] model of ovarian cancer



Conclusion

Humanized avian models recapitulate an immune microenvironment, allowing rapid screening of immune-based therapeutic approaches and stratification of patient responses for biomarker discovery

- In the humanized avian models, cell populations of Hu-PBMCs survive, infiltrate the tumors and establish communications with cancer cells
- Pembrolizumab efficiently targets PD-1 of effector T cells, triggers their activation.
- Pembrolizumab anti-tumoral effect is recapitulated in the humanized avian models
- Humanized AVI-PDX models reveal patient tumor heterogeneity of response to anti-PD-1
- Analyses using humanized AVI-PDX models show that clinical criteria for patient eligibility do not allow stratification of the entire patient population, highlighting the need to discover additional biomarkers
- Through our partnership with ErVimmune, we have demonstrated the relevance of the humanized avian models for the rapid evaluation of innovative therapies, particularly T-cell clones targeting HERV sequences in ovarian cancer, accelerating the path to precision medicine