RESEARCH AWARD: VAN FOREEST AWARD

CANINE TUMOR ORGANOIDS, THE NEXT STEP IN PERSONALIZED MEDICINE

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Each year in the Netherlands 180,000 companion animals die due to cancer. Although primary liver tumours are relatively rare in dogs, representing 0.6-1.5% of all tumours[1], the lack of therapy options make novel ways of studying primary liver tumours vital. Currently, the only available treatment is surgery, which is also only possible in a fraction of patients. A new promising investigational technique is the organoid culture system[2]. By creating a biobank of patient-derived tumour organoids, one can predict the clinical response to different targeted therapies for various patients and study malignancy in vitro. Therefore, the aim of this study is to create and characterise a tumour organoid culture system from primary liver tumours. In turn, this will allow preclinical drug screening and personalised medicine.

Three non-tumour organoid and tumour organoid cultures were derived from three patients with Hepatocellular Carcinoma (HCC). The genomic stability and background of these cultures were analysed by long-term culturing, RNA sequencing, metaphase spreads and mouse xenotransplantation.

Initial results showed that the non-tumour organoids and tumour organoids were comparable in both karyotype and RNA data. The gene expression heat map demonstrates that even the 2,000 most variable genes of the tumour and non-tumour organoids cluster together (Figure 1) and xenotransplantation of the tumour organoids confirmed these findings (Figure 2). None of the tumour organoids grew out as tumours in the xenograft model.

In conclusion, the current protocol does not allow the culture of tumour organoids as the non-neoplastic counterpart cells of the tumour overgrew the neoplastic organoids. The current approach is to handpick and characterise single tumour organoids by gauging their density, to circumvent contamination and thus creating a new tumour organoid culture system.

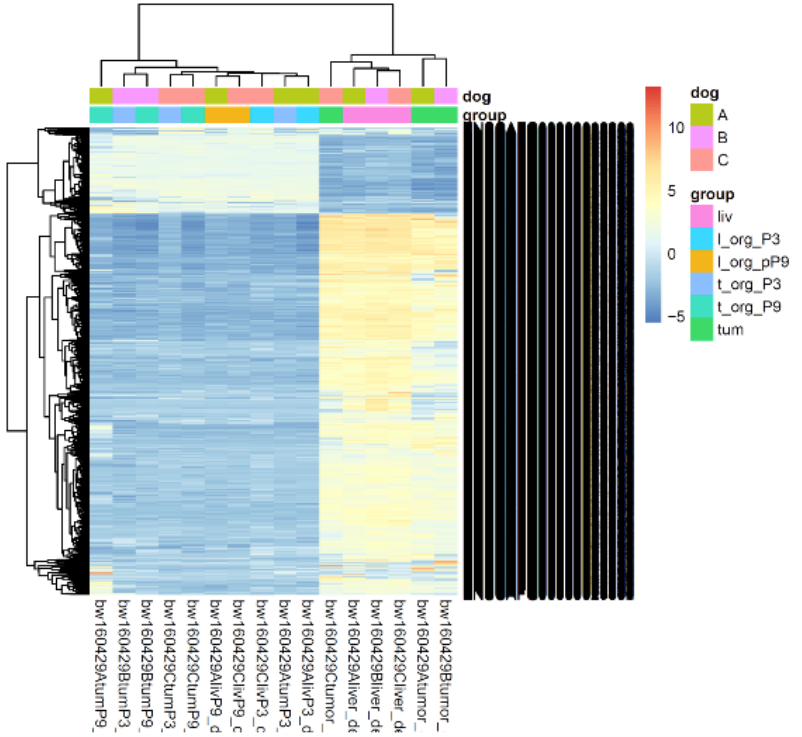

Fig.1 Clustering of samples based on the 2.000 most variable genes in organoids. Heat map with the differences in expression between the 2.000 most variable genes in the various organoids and tissues. Red is upregulation, blue is downregulation.

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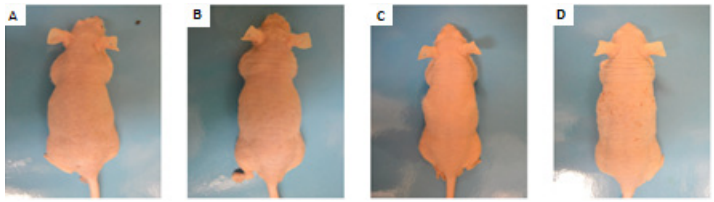

Fig.2 Xenotransplantation pilot of the patient derived tumor organoids and normal hepatic organoids. (A) Macroscopic view of a mouse injected with organoids from dog A (210814) (B) Macroscopic view of a mouse injected with organoids from dog B (200415) (C) Macroscopic view of a mouse injected with organoids from dog C (040615) (D) Macroscopic view of a mouse that was not injected.

References:

1 van Sprundel RGHM, van den Ingh TSGAM, Guscetti F, Kershaw O, Kanemoto H, van Gils HM, et al. Classification of primary hepatic tumours in the dog. The Veterinary Journal 2013 9;197(3):596-606.

2 Nantasanti S, Spee B, Kruitwagen HS, Chen C, Geijsen N, Oosterhoff LA, et al. Disease Modeling and Gene Therapy of Copper Storage Disease in Canine Hepatic Organoids. Stem Cell Reports 2015 Nov 10;5(5):895-907.