ESTRO Mobility Grant Report:

Targeting the Adaptive Resistome in TNBC Patient-derived Organoids

Host institute: *Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, The Netherlands*

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Breast cancer is the leading cancer type in women, with about two million newly diagnosed cases and more than 620000 deaths in 2018 worldwide [1]. Despite a good initial response to radio- and chemotherapy, triple-negative breast cancer (TNBC) remains the subtype with the worst overall prognosis and survival. One major challenge in TNBC treatment is the resistance to radio- and chemotherapy that is acquired by recurrent tumours. Resensitising the tumour cells by targeted inhibition of resistome-related factors seems to be a promising therapeutic approach.

My PhD research focuses therefore on the identification of new targets and strategies to improve the treatment of TNBC. To identify the factors involved in resistance mechanisms in a clinically relevant setting, we will use patient-derived organoids (PDOs) from TNBC tumour samples, since this method is becoming the new method of choice in cancer research. This pre-clinical setting also offers the possibility to analyse intrinsic TNBC resistance mechanisms directly on patient material.

However, it is not trivial to grow organoids from patient-derived samples. Therefore I spent three weeks at Professor Coppes's lab at the University Medical Center at Groningen. Professor Coppes has great expertise in the field of organoid technology.

During my stay I was able to learn how to establish and maintain organoid cultures efficiently from fresh mouse and human tissue samples. To improve my handling of organoids in different experimental settings, I chose to learn two further methods that were of interest for the characterisation of the organoid cultures.

An important point in my project will be the determination of radioresistant or radiosensitive PDOs. For that reason I analysed the survival of the organoids after proton radiation with 0, 2 and 8 Gy (Figure 1A). To analyse the effects on repair of damaged DNA, I embedded the organoids in paraffin, sectioned them and stained the DNA-damage markers yH2AX and 53BP1 after radiation with 3 Gy at different time points. I was able to detect the foci within the 3D structure of the organoids (Figure 1B). The next step will be to establish this staining in whole-mount organoids, as well as staining of further DNA-damage markers.

As well as the experimental methods, the discussions and scientific exchanges with everyone in Professor Coppes lab were very valuable and gave me further insight into different applications of the organoid technology.

Thanks to the mobility grant that was offered to me by the European SocieTy for Radiotherapy and Oncology (ESTRO) and the great expertise of Professor Coppes, I am now able to effectively establish organoid cultures from human tumour samples. It enables my whole home institute to work with this great technology and apply it to many ongoing projects. For my project, it will enhance the possibility to translate my results fast into the clinic and I hope in the end it will improve the outcome of treatment for TNBC patients.

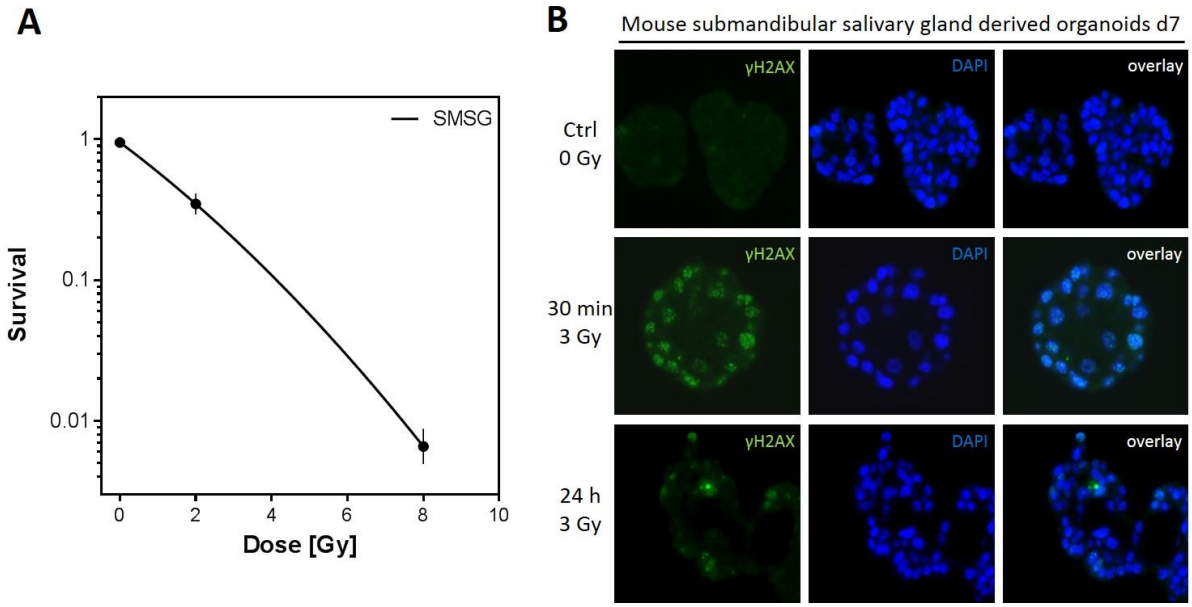

Figure 1: Analysis of the survival and DNA-damage by γH2XA foci after radiation of the isolated organoids
(A) Determination of the survival of mouse submandibular salivary gland (SMSG)-derived organoids after proton radiation with up to 8 Gy. The survival was analysed seven days after treatment. (B) Staining of γH2AX foci in mouse SMSG-derived organoids that were grown for seven days. The foci were stained at different time points post radiation with 3 Gy.

[1] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. and Jemal, A. (2018), Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68: 394-424. doi:10.3322/caac.21492

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