M2 Project: Examining tumour radio-sensitivity to FLASH-RT vs CONV-RT in a complex 3D ECM structure to determine possible predictive biological markers of tumour radio-sensitivity.

Radiotherapy and chemotherapy are customary implemented in cancer treatments with curative intent. It is very often accompanied with the development of moderate to high levels of treatment-related toxicity. The treatment-induced toxicities often interfere with the completion of the initial treatment plan. To enhance curing chances, it is crucial to alleviate treatment-related toxicities to improve post-treatment outcomes and advance patients' welfare. The phenomenon therapeutic index occurs during radiotherapy, describing the measurement of treatment safety expressed in normal tissue complication probability (NTCP) and tumour control probability (TCP). An increase in the therapeutic window, e.g. TCP is increased and the NTCP is still as low as possible, will result in better tumour control and equal or less normal tissue complications.

The recent development of FLASH radiotherapy could potentially impact this therapeutic window. FLASH radiotherapy (FLASH-RT) is characterised by the application of an ultra-high dose rate, almost instantaneously, within milliseconds. The concept first arose from preliminary research conducted in the 60s and was rediscovered by Favaudon et. al. [1] Various studies of FLASH-RT have revealed a tremendous diminishment of normal tissue toxicities while maintaining equal tumour control, compared to conventional radiotherapy (CONV-RT). [1–5] Translation was made to larger in vivo models applying FLASH-RT on mini-pigs and cats diagnosed with squamous cell carcinoma of the nasal planum. Post treatment a protection of the normal tissue was observed in both pig skin and tumour clearing with no acute toxicity in cats.[4] The promising outcomes in preclinical studies provided support to conduct FLASH-RT on human patients.[6] Despite the repeatable encouraging *in vivo* results displayed after FLASH-RT, the molecular and cellular mechanism are still poorly understood and fluctuations in FLASH-RT sensitivity or resistance of tumours are widely unexplored. To examine which tumours are more suitable for a specific radiotherapy procedure, to identify biomarkers and to potentially unravel the mechanism behind the FLASH-RT phenomenon, a complex *in vitro* model is needed.

Project outlay:

The initial step of the project will be the determination of radiation sensitivity of numerous cell lines in the complex 3D ECM model in response to FLASH vs CONV-RT with clonogenic endpoint.[7–11] Secondly, the most FLASH resistant and FLASH sensitive cell lines (and similarly CONV resistant and sensitive cells) will be further examined using phosphotyrosine kinase (PTK) or serine-threonine kinase (STK) arrays to identified activated pathway in response to FLASH or CONV irradiation. Identification of the main activated kinases will be further confirmed by western blot. The aim of this project is to get more insight into the possible mechanism of tumour resistance or sensitivity to FLASH-RT versus CONV irradiation

For this challenging but exciting project, we are looking for a motivated student with a natural interest in radiation oncology and furthermore is very comfortable with communicating and writing in English. Gratification will be provided for the duration of the project. If interested, please provide a CV and motivation letter to anouk.sesink@curie.fr and pierre-marie.girard@curie.fr

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