**POSTER 25: A clickable melphalan for monitoring DNA interstrand crosslink accumulation and detecting ICL repair defects in Fanconi anemia patient cells**

**Christophe Lachaud**

Centre de Recherche en Cancérologie de Marseille - Aix Marseille Université, Institut Paoli-Calmettes, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Centre National de la Recherche Scientifique : UMR7258, Institut National de la Santé et de la Recherche Médicale : U1068, Institut Paoli-Calmettes : UMR7258, Aix Marseille Université : UM105 - France

Fanconi anemia (FA) is a genetic disorder associated with developmental defects, bone marrow failure, and cancer. The FA pathway is crucial for the repair of DNA interstrand crosslinks (ICLs). In this study, we have developed and characterized a new tool to investigate ICL repair: a clickable version of the crosslinking agent melphalan which we name click-mephalan. Our results demonstrate that click-melphalan is as effective as its unmodified counterpart in generating ICLs and associated toxicity. The lesions induced by click-melphalan can be detected in cells by post-labelling with a fluorescent reporter and quantified using flow cytometry. Since click-melphalan induces both ICLs and monoadducts, we generated click-mono-melphalan, which only induces monoadducts, in order to distinguish between the two types of DNA repair. By using both molecules, we show that FANCD2 knock-out cells are deficient in removing click-melphalan-induced lesions. We also found that these cells display a delay in repairing click-mono-melphalan-induced monoadducts. Our data further revealed that the presence of unrepaired ICLs inhibits monoadduct repair. Finally, our study demonstrates that these clickable molecules can differentiate intrinsic DNA repair deficiencies in primary FA patient cells from those in primary xeroderma pigmentosum patient cells. As such, these molecules may have potential for developing diagnostic tests.