Molecular mechanisms of DNA crosslink recognition and repair

Fanconi Anemia (FA) is a hereditary syndrome caused by a defective ability to repair DNA inter-strand crosslinks (ICLs). This induces genome instability and leads to developmental defects and cancer predisposition. The products of at least 23 genes participate in a network for ICL repair, termed the FA pathway. A central step in the FA pathway is the monoubiquitination of FANCD2-FANCI (D2-I) by the FA core complex. Ubiquitinated D2-I (ubD2-I) is thought to serve as a molecular hub to recruit nucleases that will ‘unhook’ the lesion. We recently discovered that D2-I is a DNA clamp locked onto DNA by the FA core complex. However, it is still unknown how the DNA damage site is detected, and how ubD2-I marks its location and recruits repair factors. I will present our recent and ongoing work combining electron cryo-microscopy (cryoEM) with mass spectrometry, biochemistry and other molecular biology techniques, to dissect the molecular basis for the activation and regulation of this essential DNA repair pathway.

All welcome.