Inherited or acquired defects in detecting, signalling or repairing DNA damage are associated with various human pathologies, including immuno-deficiencies, neurodegenerative diseases and various forms of cancer\(^1\). Work in my laboratory aims to decipher the mechanisms by which cells detect DNA damage and signal its presence to the DNA-repair and cell-cycle machineries. In particular, much of our work focuses on DNA double-strand breaks (DSBs) that are generated by ionizing radiation and radiomimetic chemicals, and which can also arise when the DNA replication apparatus encounters other DNA lesions. In this talk, I will describe some of our recent work that has identified new proteins that mediate DSB responses, control DSB processing or modulate chromatin structure at DNA damage sites. If time permits, I will also explain how our increasing knowledge of such processes is providing opportunities for developing novel classes of drugs to treat cancer and other age-related diseases.