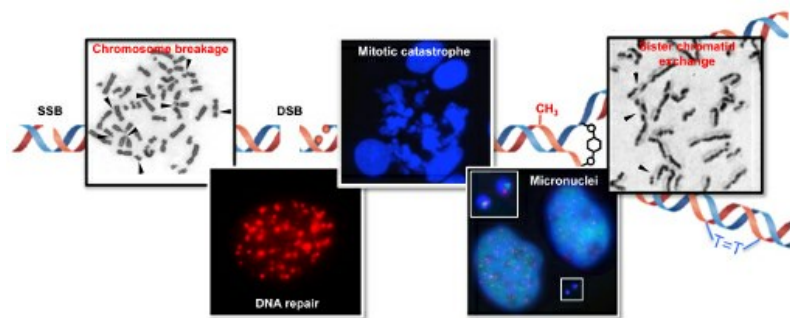


DNA damage and repair



Group leader: **Dr Grant Stewart**
[\(/staff/profiles/cancer/stewart-grant.aspx\)](http://staff/profiles/cancer/stewart-grant.aspx)

Overview

Defective repair of DNA damage is the most frequent underlying cause of genetic instability and cancer development. Our research focuses on understanding how the cell detects and repairs damage to its DNA and how defects in this process contribute to the development of human disease.

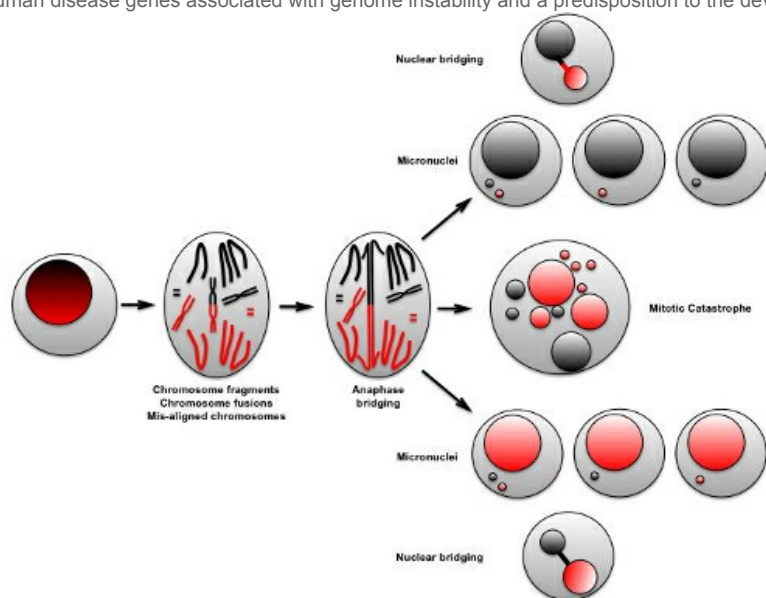
Our research group

Genome instability is a genetic trait that is common to all cancer. Abnormal repair of DNA damage is the most frequent underlying cause of genome instability and probably represents the most important event that contributes to, and in some cases initiates the development of cancer. Therefore, cellular pathways that control the repair of damaged DNA as well as those that regulate cell cycle checkpoints and the apoptotic machinery represent an inherent anti-tumour barrier that must be surpassed for a tumour to develop.

The principal focus of the laboratory is to determine how the cell detects and faithfully repairs damage its DNA. The biochemical pathways involved in this process are collectively termed the DNA damage response (DDR) and consist of those that regulate DNA damage detection, cell cycle checkpoint activation, DNA repair and apoptosis.

Much of our insight about how the proteins involved in regulating the DDR function and the biological consequences if this fails, has come about from the study of rare inherited human syndromes associated with genome instability and a high prevalence of cancer e.g. Ataxia-Telangiectasia.

A large proportion of the research ongoing in laboratory centres around understanding how defects in DDR pathways contribute to human disease, which includes providing a genetic diagnosis for patients with a suspected DNA repair deficiency disorder, characterising human gene mutations and their impact on the DDR and identifying novel human disease genes associated with genome instability and a predisposition to the development of cancer.



Current projects

1. Understanding how the ubiquitin system controls repair of damaged DNA.
2. Identification and characterisation of novel proteins involved in regulating the cellular response to DNA damage.
3. Identifying novel genes mutated in human syndromes associated with the defective repair of DNA damage.
4. Understanding how viruses subvert the host cell DNA damage response pathways.

[Open all sections](#)

Recent publications

- **Stewart GS, Wang B, Bignell CR, Taylor AM, Elledge SJ.** (2003). MDC1 is a mediator of the mammalian DNA damage checkpoint. *Nature* 421:961-6.
- **Stewart GS**, Stankovic T, Byrd PJ, Wechsler T, Miller ES, Huissoon A, Drayson MT, West SC, Elledge SJ, Taylor AM.** (2007). RIDDLE immunodeficiency syndrome is linked to defects in 53BP1-mediated DNA damage signaling. *Proc Natl Acad Sci USA*. 104:16910-5. (** Corresponding author)
- **Stewart GS**, Panier S, Townsend K, Al-Hakim AK, Kolas NK, Miller ES, Nakada S, Ylanko J, Olivarius S, Mendez M, Oldreive C, Wildenhain J, Tagliaferro A, Pelletier L, Taubenheim N, Durandy A, Byrd PJ, Stankovic T, Taylor AMR, Durocher D**.** (2009) The gene mutated in the RIDDLE syndrome mediates a ubiquitin-dependent signalling cascade at sites of DNA damage. *Cell* 136:420-434 (** Corresponding author)
- **Bohgaki T, Bohgaki M, Cardosos R, Panier S, Stewart GS, Sanchez O, Durocher D, Hakem A, Hakem R.** (2011). Genomic instability, defective spermatogenesis, immunodeficiency and cancer in a mouse model of the RIDDLE syndrome. *PLOS Genet*. 7: e1001381.5.
- **Polo SE, Blackford AN, Chapman JR, Baskcomb L, Gravel S, Rusch A, Thomas A, Blundred R, Smith P, Dobner T, Taylor AMR, Turnell AS, Stewart GS, Grand RJA, Jackson SP.** (2012). Regulation of DNA-end resection by hnRNP-like proteins promotes DNA double-strand break signaling and repair. *Mol Cell*. 45:505-16.

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