

**M004** Defective strand break repair and human inheritable diseases

**Miguel G. Blanco, Helen R. Flynn, Stephen C.Y. Ip, Ulrich Rass, Mark Skehel, Tina Thorslund and Stephen C. West**

*London Research Institute, Clare Hall, Cancer Research UK, South Mimms, Herts EN6 3LD, UK*

Defects in basic cellular DNA repair processes have been linked to genome instability, inheritable cancers, premature aging syndromes and neurological diseases. Our understanding of most DNA repair pathways is now well advanced, and it is often possible to pinpoint the underlying defects that lead to disease progression. For example, the breast cancer tumour suppressor BRCA2 controls the nuclear relocalization and activities of RAD51 protein, a key player in homologous recombination-mediated double-strand break repair. Without efficient homologous recombination, BRCA2-deficient cells exhibit high levels of spontaneous chromosome instability, and an inability to promote the repair of DNA breaks caused by ionizing radiation or radiomimetic drugs. Recently a new factor in this BRCA2-regulated pathway of recombinational repair was identified. This protein, GEN1, resolves recombination intermediates (Holliday junctions) a reaction that is essential for proper chromosome segregation. Cleavage occurs by the introduction of symmetrically-related cuts across the junction point, to produce nicked duplex products that can be ligated, in a manner analogous to that exhibited by the *E. coli* Holliday junction resolvase RuvC.