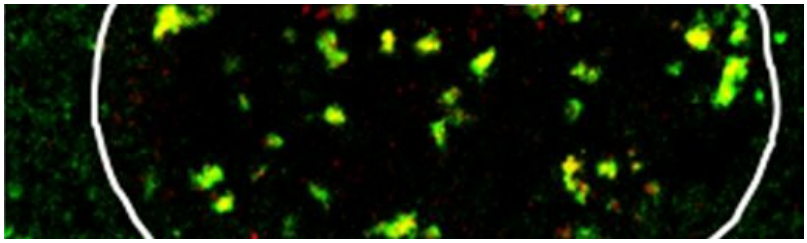
# Cancer predisposition pathways



Group leader: **Dr Jo Morris (/staff/profiles/cancer/morris-joanna.aspx)**

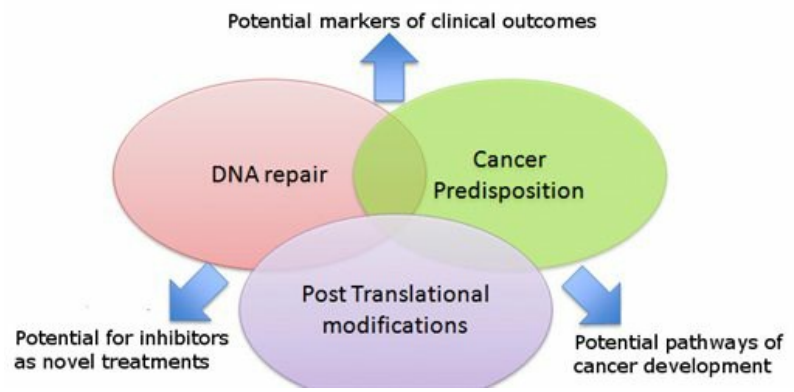
## Overview

The majority of cancer is manifest through changes that occur in cells as they age. However inheritance of a dysfunctional gene important in cancer prevention gives rise to early onset of the disease and disease that affects several family members. Understanding how these changes result in tumour development is currently one of the most powerful means of understanding how cancer arises and how best to treat it. For this reason our lab focuses on the molecular pathways associated with cancer predisposition.

## Our research group

SOUNDCLOUD

We are interested in identifying mechanisms involved in genome integrity and understanding their relationship to cancer development and treatment in people. In particular, we are committed to the elucidation of the contribution of post-translational modifications in this pathway. Our approach centres around BRCA1 function and the cellular pathways necessary for repair of DNA double strand breaks and suppression of breast and ovarian cancer.




## Current projects

Open all sections

**Understanding the BRCA1 N-terminus**
The highest density of amino acid changes in cancer patients are found in the N-terminal portion for BRCA1. While some, largely zinc-ligating residues are known to be pathogenic, others are of unknown clinical significance.

This project aims to map the sensitivity of the N-terminus to known interacting proteins as a means to identifying molecular pathways relevant to BRCA1 dysfunction.

As part of this interest we are part of the AFFECT consortia. Which aims to gather information on the tumours from carriers of BRCA1 missense carriers in order to increase the ability to 'call' the likelihood that currently unclassified variants are or are not pathogenic.

We are using gene editing to generate cell lines bearing some of these changes within the endogenous locus in complement with our animal model of breast cancer development.

**Activity of conserved regions of BRCA1**
Small patches of high levels of conservation occur beyond the N- and C-termini of BRCA1. This project aims to establish whether these, and the patient variants found within them, have any functional role. And if so what that might be.

**Regulation of BRCA1**
Inactivation of BRCA1, such as promoter methylation is a potential 'second hit' in cancer development. In this project other means of BRCA1 regulation are explored to establish whether loss of the supporting mechanisms of BRCA1 expression relate to breast cancer development.

**Ubiquitin conjugation in DNA repair**
Ubiquitin conjugation plays a significant role in the co-ordination of the DNA repair response. Defects in this pathway are associated with immune-deficiency syndromes and cancer. We aim to identify new plays in the ubiquitin conjugation and de-conjugation pathways that may shed new light on this important post-translational modification.

In work in this area we have shown that the proteasomal De-ubiquitinating enzyme, POH1, is key in restricting the presence of Ubiquitin conjugates generated at sites of Double-strand breaks and restricts 53BP1 accumulation regulating DNA repair by non homologous end-joining.SUMO conjugation in DNA repair.

We have recently found that SUMO plays an important part of the BRCA1-pathway in the DNA damage response. In this project we aim to define the role of poly-SUMOlyation in DNA repair, in cancer and in development.

Other pathways of post-translational modifications are also under investigation.

## Recent publications


- **Butler, L.R., Densham, R.M., Jia J., Garvin A.J., Stone H.R., Shah V., Weekes, D. Festy, F, Beesley, J., and Morris J.R**. The proteasomal de-Ubiquitinating enzyme POH1 promotes the double-strand DNA break response. *EMBO J* l Oct 3;31(19):3918-34..
- **Drost, R., P. Bouwman, S. Rottenberg, U. Boon, E. Schut, S. Klarenbeek, C. Klijn, I. van der Heijden, H. van der Gulden, E. Wientjens, M. Pieterse, A. Catteau, P. Green, E. Solomon, J.R. Morris*, and J. Jonkers*,** BRCA1 RING Function Is Essential for Tumor Suppression but Dispensable for Therapy Resistance. *Cancer Cell*, 2011. 20(6): p. 797-809. (*joint senior/comminucating authors).
- **Morris, J.R., C. Boutell, M. Keppler, R. Densham, D. Weekes, A. Alamshah, L. Butler, Y. Galanty, L. Pangon, T. Kiuchi, T. Ng, and E. Solomon,** The SUMO modification pathway is involved in the BRCA1 response to genotoxic stress. *Nature*, 2009. 462(7275): p. 886-90.
- **Morris, J.R., L. Pangon, C. Boutell, T. Katagiri, N.H. Keep, and E. Solomon,** Genetic analysis of BRCA1 ubiquitin ligase activity and its relationship to breast cancer susceptibility. *Hum Mol Genet*, 2006. 15(4): p. 599-606.
- **Morris, J.R. and E. Solomon,** BRCA1 : BARD1 induces the formation of conjugated ubiquitin structures, dependent on K6 of ubiquitin, in cells during DNA replication and repair. *Hum Mol Genet*, 2004. 13(8): p. 807-17.


## Staff

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