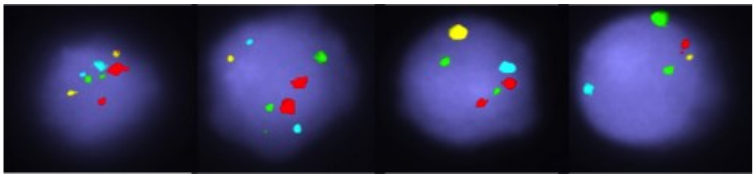
The role of DNA damage response genes in haemopoietic malignancies



Group leader **Prof Tatjana Stankovic (/staff/profiles/cancer/stankovic-tatjana.aspx)**

Overview

A tight regulation of cellular responses to DNA damage prevents generation of chromosome alterations that can lead to tumour development. The integrity of these responses is particularly important in lymphoid progenitor cells that undergo developmentally regulated recombination of immune system genes. Cells with an intact DNA damage response are capable of repairing a moderate level of DNA breaks and respond to an excess of unrepaired breaks by activation of apoptosis. The latter mechanism is utilized by the majority of DNA damaging chemotherapeutic agents. Therefore, defects in DNA damage response can lead not only to tumour development but also to tumour chemoresistance.

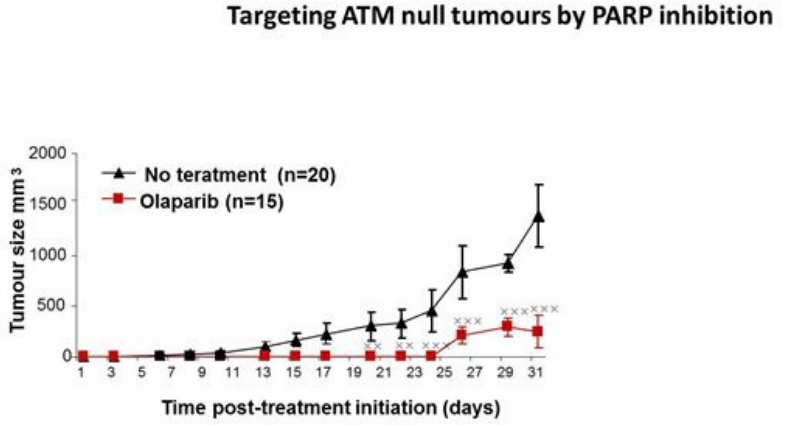
Our current research is focused on an elucidation of the role of Ataxia Telangiectasia Mutated (*ATM)* and other DNA damage response genes in the multistep process of leukaemia/lymphomagenesis. Particular emphasis is given to DNA damage response defects that can be targeted for tumour specific treatment. Therefore, our long-term goal is to translate the understanding of DNA damage response pathways in haematopoietic malignancies into novel therapeutic strategies.

Our research group

The pleiotropic nature of the *ATM* mutant CLL cellular phenotype provides multiple ways for sensitisation of *ATM* mutant tumours. This concept is called synthetic lethality. For example, the current hypothesis is that inhibition of DNA repair pathways that cooperate with ATM could sensitize *ATM* mutant cells by a mechanism that does not involve activation of apoptosis. This lead to the use of a novel, highly specific PARP inhibitor (olaparib) that is already in the phase I/II clinical trials for BRCA mutant tumours in ATM null lymphoid malignancies. The group has shown that ATM null tumour cells exhibit sensitivity to PARP inhibitor both in vitro and in vivo in an ATM null xenograft model. Based on multicentre national collaboration a phase I/II clinical trial with PARP inhibitor in ATM null lymphoid malignancies has been initiated.

Generation of novel therapeutic approaches is hugely facilitated by several mouse models recently produced. One such model ($Atm^{-/-}nu^{-/-}$ double knockout animals lacking a T cell compartment), provides an excellent opportunity to study the role of ATM in a wide range of malignancies. Equally, xenografts for all major leukaemias have been developed to facilitate testing of targeted therapies.

The group has recently undertaken a wide screen of kinome and DNA repair profiles in paediatric ALL and identified deregulated kinases and DNA repair proteins associated with apoptosis resistance. These proteins will be targeted by pharmacological inhibitors.



Open all sections

Current projects

- Identification of a network of ATM dependent cellular responses and DNA repair defects that can be targeted for treatment in chronic leukaemia (CLL)
- Addressing different mechanisms of tumorigenesis and novel therapeutic approaches in mouse models of ATM deficient haematopoietic malignancies.
- Identifying activated kinases and DNA repair proteins that cause chemoresistance in paediatric acute lymphoblastic leukaemia (ALL)

Recent publications

- **Marston E, Weston V, Jesson J, Maina E, McConville C, Agathanggelou A, Skowronska A, Mapp K, Sameith K, Powell JE, Lawson S, Kearns P, Falciani F, Taylor M, Stankovic T.** Stratification of paediatric ALL by in vitro cellular responses to DNA double strand breaks provides insight into the molecular mechanisms underlying clinical response Blood. 2009; 113(1):117-26.
- **Victoria J Weston, Ceri E Oldreive, Anna Skowronska, David G Oscier, Guy Pratt, Martin JS Dyer, Graeme Smith, Judy E Powell, A Malcolm R Taylor, Paul AH Moss, Tatjana Stankovic.** The PARP inhibitor olaparib suppresses growth of ATM mutant lymphoid tumour cells in vitro and in vivo. Blood. 2010;116(22):4578-87
- **Skowronska A, Austen B, Powell JE, Weston V, Oscier DG, Dyer MJS, Matutes E, Pratt G, Fegan C, Moss P, Taylor AM, Stankovic T**. ATM germline heterozygosity does not play a role in CLL initiation but influences rapid disease progression through loss of the remaining ATM allele . Haematologica. 2012;97(1):142-6.
- **Anna Skowronska, Anton Parker, Gulshanara Ahmed, Ceri Oldreive, Zadie Davis, Sue Richards, Martin Dyer, Estella Matutes E, David Gonzalez, AMR Taylor, Paul Moss, David Oscier, Tatjana Stankovic.** Biallelic ATM Inactivation Significantly Reduces Survival in Patients Treated on UK CLL4 Trial. JCO (ahead of print Oct 22nd 2012).

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