Name	STEPHEN WEST
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	1985

Career History

1974–1977 PhD in Biochemistry, Newcastle University
1977–1978 Post-doctoral Research Associate, University of Newcastle
1978–1983 Post-doctoral Research Associate, Yale University USA
1983–1985 Research Scientist, Yale University USA.

Major Awards, Honours and Prizes

1994: Elected, Member of EMBO
1995: Elected, Fellow of the Royal Society
2000: Elected, Fellow of the Academy of Medical Sciences
2000: Elected, Member of Academia Europae
2001: Swiss Bridge Prize Award for Cancer Research
2002: Leeuwenhoek Medal of the Royal Society
2007: Louis-Jeantet Prize for Medicine
2008: Novartis Medal and Prize from the Biochemical Society
2009: Swiss Bridge Prize Award for Cancer Research
2010: GlaxoSmithKline Prize and Medal of the Royal Society
2011: Breast Cancer Campaign 'Team of the Year'
2011: Elected, Fellow of the European Academy of Cancer Sciences
2012: The Genetics Medal
2015: The Genome Stability Network Medal
2016: Elected, US National Academy of Sciences (Foreign Associate)
2018: 'Lifetime Achievement in Cancer Research' Prize (awarded by Cancer Research UK)

Membership of external committees, editorial boards, review panels, SABs etc

Editorial boards:
1996–present: Editorial Board, EMBO Journal
2000–present: Editorial Board, EMBO Reports
2001–present: Editorial Board, DNA Repair

Review panels & SABs etc:
2012–2015: Royal Society Prizes and Awards Nomination Committee
2015: External Review Committee (chair), Fritz Lippmann Institute, Jena, Germany
2012–2016: Scientific Advisory Board, Fritz Lippmann Institute, Jena, Germany
2016 Member, MRC Programmatic Review Committee, Oxford Institute of Radiation Oncology

2016–present Scientific Advisory Board, Center for Chromosome Stability, University of Copenhagen, Denmark
2017–present Scientific Advisory Board, Guangdong Key Laboratory, Shenzen University, Shenzen, China
2018 Scientific Advisory Board, China Medical University, Taiwan
2018–present Scientific Advisory Board, Max Planck Institute, Martinsreid, Germany

Lab Name	***DNA Recombination and Repair Laboratory***

Research programme and achievements

Our genetic material is continually subjected to damage, either from endogenous sources such as reactive oxygen species, produced as by-products of oxidative metabolism, from the breakdown of replication forks during cell growth, or by agents in the environment such as ionising radiation or carcinogenic chemicals. To cope with DNA damage, cells employ elaborate and effective repair processes that specifically recognise a wide variety of lesions in DNA. These repair systems are essential for the maintenance of genome integrity. Unfortunately, some individuals are genetically predisposed to crippling diseases or cancers that are the direct result of mutations in genes involved in the DNA damage response.

For several years, our work has been at the forefront of basic biological research in the area of DNA repair, and in particular we have made significant contributions to the understanding of heritable diseases such as breast cancer, Fanconi anaemia, and the neurodegenerative disorder Ataxia with Oculomotor Apraxia (AOA). In particular, our focus has been directed towards: (i) determining the mechanism of action and high-resolution structure of the BRCA2 breast cancer tumour suppressor, and to provide a detailed picture of the interplay between BRCA2, PALB2, and the RAD51 paralogs, in terms of RAD51 filament assembly/disassembly, using biochemical, electron microscopic and cell biological approaches, (ii) to determine how the nucleases that resolve recombination intermediates are regulated in simple (yeast) and complex (human) organisms, to determine the biological role of a unique six-subunit structure-selective tri-nuclease complex (SLX1-SLX4-MUS81-EME1-XPF-ERCC1), and (iii) to understand the actions of Senataxin, which is defective in AOA2, in protecting against genome instability in neuronal cells. These distinct and yet inter-related areas of the research programme will provide an improved understanding of basic mechanisms of DNA repair and thereby underpin future therapeutic developments that will help individuals afflicted with these diseases.

Research outputs

van Wietmarschen N, Sridharan S, Nathan W, Tubbs A, Chan EM, Callen E, Wu W, Belinky F, Tripathi V, Wong N, Foster K, Noorbakhsh J, Garimella K, Cruz-Mignoni A, Sommers JA, Fugger K, Walker RL, Dolzhenko E, Eberle MA, Hayward BE, Usdin K, Freudenreich CH, Brosh RM, West SC, McHugh P, Meltzer PS, Bass AJ and Nussenzweig A (2020) *Werner helicase prevents cell death in cancers with microsatellite instability by resolving large-scale expanded (TA)n repeats*. Nature, in press.

The RecQ DNA helicase WRN is a synthetic lethal target for cancers with microsatellite instability (MSI). WRN depletion induces widespread DNA double strand breaks (DSBs) in MSI cells, leading by an unknown mechanism to cell cycle arrest and/or apoptosis. Here, we show that TA-dinucleotide repeats are highly unstable in MSI cells, exhibiting large-scale expansions. The expanded TA repeats form non-B DNA secondary structures that stall replication forks, activate the ATR checkpoint kinase, and necessitate unwinding by the WRN helicase. In the absence of WRN, the expanded TA-dinucleotide repeats are susceptible to MUS81 nuclease cleavage, resulting in massive chromosome shattering.

Chan YW, Fugger K and West SC (2018). ***Unresolved recombination intermediates lead to a novel class of ultra-fine bridges, chromosome breaks and aberrations*****. Nature Cell Biol 20:92-103. DOI: 10.1038/s41556-017-0011-1**
The generation of CRISPR-Cas9 GEN1 k/o cell lines (supplemented with MUS81 siRNA) allowed us to develop the first model system to analyse the phenotypes of 'resolvase-deficient' human cells. We discovered that recombination intermediates persist until anaphase (despite the presence of the BLM-TopoIII-RMI1-RMI2 dissolvasome) where they form ultra-fine bridges (UFBs). These UFBs represent a new class of ultrafine bridges (we termed them HR-UFBs) distinct from replication stress induced UFBs or centromeric UFBs. HR-UFBs were targeted and processed by PICH/BLM, leading to the formation of ssDNA bridges that were broken at cytokinesis. Loss of GEN1 and MUS81 activity led to synthetic lethality.

Shah Punatar R, Martin MJ, Wyatt HD, Chan YW and West SC (2017) ***Resolution of single and double Holliday junction recombination intermediates by GEN1*****. Proc Natl Acad Sci USA 114:443-450. DOI: 10.1073/pnas.1619790114**
DNA recombination leads to the formation of DNA intermediates that need to be resolved prior to chromosome segregation. These intermediates contain either single- or double Holliday junctions that from a covalent attachment between interaction duplexes. In this work we found that the GEN1 Holliday junction efficiently resolves both single and double junctions. Moreover, we found that GEN1 exhibits a weak sequence preference for incision between two G residues that reside in a T-rich region of DNA.

Wyatt HDM, Laister RC, Martin SR, Arrowsmith CH and West SC. (2017) ***The SMX DNA repair tri-nuclease*****. Molecular Cell 65:848-860. DOI: 10.1016/j.molcel.2017.01.031**
First description of the SMX tri-nuclease that resolves recombination intermediates. Composed of SLX1-SLX4, MUS81-EME1 and XPF-ERCC1, the six-subunit complex was purified following baculovirus expression in insect cells. Characterization of the Holliday junction cleavage reaction revealed that the first incision was introduced by SLX1-SLX4, while the second was mediated by MUS81-EME1. We also found that MUS81-EME1 was activated by interaction with the SLX4 scaffold, ensuring that the second cut occurs in concert with SLX1-SLX4's initial incision. The formation of SMX and activation of MUS81-EME1 provides a mechanistic basis for restriction of SMX activity to the later stages of the cell cycle.