Name	SIMON BOULTON
Position	Senior Group Leader Ambassador for Translation
Year joined *(Crick or founder institute)*	2002

Career History

1994-1998: PhD awarded from University of Cambridge, UK.
1998-2000: HFSP and EMBO Postdoctoral Research Fellow, MGH Cancer Center, Harvard Medical School, Boston, USA.
2000-2002: Postdoctoral Research Fellow, Dana Farber Cancer Institute, Harvard Medical School, Boston, USA.
2002-2007: Research Scientist, LRI, Clare Hall Laboratories, UK.
2007-2015: Senior Research Scientist, LRI, Clare Hall Laboratories, UK.
2015-present: Senior Group Leader, The Francis Crick Institute, London, UK.
2016-present: VP Science Strategy, Artios Pharma Ltd, Cambridge, UK.

Major Awards, Honours and Prizes

1998: Human Frontiers Science Program Fellowship.
1998: EMBO Long Term Fellowship.
2001: MGH Fund for Medical Discovery Award.
2002: Tosteson Postdoctoral Fellowship Award.
2006: Colworth Medal, Biochemical Society.
2007: EMBO Young Investigator Award.
2008: EACR Young Cancer Researcher of the Year Award.
2008: Eppendorf/Nature Award for Young European Investigators.
2009: Elected member of EMBO.
2010: Royal Society Wolfson Research Merit Award.
2011: EMBO Gold Medal.
2011: Royal Society Francis Crick Medal and Lecture.
2012: Elected Fellow of the Academy of Medical Sciences.
2013: Paul Marks Prize for Cancer Research, MSKCC, New York.

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

EDITORIAL BOARDS
2009-2018 Associate Editor, DNA Repair.
2008-present Editorial board, Biochemical Journal.
2011-present Editorial board, Cell Reports.
2014-present Editorial board, Molecular Cell.
2014-present Editorial board, Genes & Development.
2011-2017 Associate Editor, Chromosoma.
2018-present Editor-in-Chief, Chromosoma.

SCIENTIFIC ADVISORY/REVIEW BOARDS
2009-present Review Board for the Italian Association for Cancer Research.

2009 Review Board for the Institute Gulbenkian de Ciencia, Portugal.
2011 & 2018 Cancer Research UK, Program Grant Review Panel.
2012, 2020 Site review committee, National Cancer Institute, (NKI), Amsterdam.
2012-2019 Scientific Advisory Board, MRC PPU, University of Dundee.
2013 Site Review Committee, Ludwig Institute of Cancer Research, La Jolla, CA.
2013-2019 Expert Review Group, Wellcome Trust, London, UK.
2014-2016 Chair, Expert Review Panel, Research Council of Norway.
2014-present Scientific Advisory Board, Action for A-T (Ataxia Telangiectasia), London, UK.
2015-present GSK-Crick Joint Steering committee, UK (Chair, 2017-).
2015-present Scientific Advisory Board, Mendel Lectures, Brno, CR.
2017-2019 DDR and PARPi Steering Committee, COR2ED.
2017-2018 Crick Ambassador to N4 (Leeds, Sheffield, Manchester, Newcastle)
2018-present Scientific Advisory Board, Centre for Genomic Integrity, UNIST, Ulsan, South Korea.
2018 Chair, Expert Review Panel, NRC, Nordforsk.
2018-present AZ-Crick & MSD-Crick Joint Steering committees, UK.
2019-present Co-Lead, CRUK City of London, Radiation Research Unit.
2019-present Lead, Research Strategy, Tessa Jowell Brain Cancer Mission.
2019-2020 Therapeutic innovation review panel, Cancer Research UK, UK.
2020 Site review committee, Institute of Human Genetics, Montpellier.
2021 Academic Lead, EPSRC Crick-GSK Prosperity Partnership.

COMMERCIAL ENTERPRISE

2016-present Scientific Co-founder and Vice President, Science Strategy, Artios Pharma Ltd, UK.

In 2016, I helped found Artios Pharma Ltd, which was established on the Babraham Research Campus near Cambridge. I was instrumental in helping the company raise £25m Series A (Q3, 2016) and £65m Series B (Q3, 2018) financing to establish/progress the companies lead assets into POC studies in humans. Currently, a syndicate of investors, including Merck, Abbvie, Pfizer and Novartis (strategic investors) finance the company. As VP of Science Strategy, I assist the executive team in the identification and evaluation of new pipeline opportunities from the global academic and industrial DDR network. I also chair the SAB and am a member of the Executive board. Artios are developing new treatments that target DNA repair pathway vulnerabilities to selectively kill cancer cells either as mono-therapies or in combination with existing treatments. The companies leading two assets, ATR and POLQ inhibitors, will enter clinical trials in Q1 and Q3 2021, respectively.

PATENTS SUBMITTED

Composition of matter patent fillings:

- 5 patents filed in relation to series 1 and 2 POLQ inhibitors
- 1 patent filed in relation to PARP sensitization and SL with HRD and ATMD conferred by ALC1 loss (No. 2009477.7)

Compound use patents:

- 1 patent filed for series 2 POLQ inhibitors

Assay technology patents

- 1 patent filed describing bespoke MMEJ assays

NB: None of these patents have yet published.

Lab Name	*DSB Repair Metabolism Laboratory*

Research programme and achievements

Since 2015, my lab has provided insights into the regulation of homologous recombination (HR) in normal and pathological situations. We have gained mechanistic insight into several key factors that promote specific steps during the HR reaction and have identified new genes that contribute to the regulation of HR in metazoans and/or function in various DNA repair pathways. Our discovery of RTEL1 as a key regulator of HR and our subsequent insights into its role in meiosis and during DNA replication, laid the foundations for our most important work on the function of RTEL1 in maintaining the integrity of chromosome ends. In a series of studies, we discovered that RTEL1 is co-opted to telomeres to disassemble t-loops, which had been proposed to protect chromosome ends. Unexpectedly, we discovered that telomere dysfunction caused by loss of RTEL1 could be rescued by inactivating telomerase, the reverse transcriptase that normal extends telomeres to solve the end-replication problem. Rather than being unwound by the replisome, we provided evidence that replication forks stall and undergo reversal at persistent t-loops, which creates a pseudo-telomere substrate that is bound and inappropriately stabilised by telomerase, creating a block to telomere replication. This necessitated the excision of the t-loop by SLX1/4 and loss of a substantial part of the telomere. We went on to establish that t-loop unwinding is also compromised by RTEL1 mutations in the telomere dysfunction disorder Hoyeraal-Hreidarsson syndrome and is subject to cell cycle control via a phospho-switch in TRF2. Importantly, we showed that the phospho-switch in TRF2 regulates the transient recruitment and release of RTEL1 from telomeres, which is required to temporarily disassemble t-loops during S-phase to facilitate telomere replication, whilst also preventing promiscuous t-loop unwinding during other cell cycle stages. This work demonstrated beyond any reasonable doubt that the t-loop is a physiologically important structure required to suppress checkpoint activation at telomere ends.

More recently, we discovered that telomere protection is solved by distinct mechanisms in pluripotent and somatic tissues. It was widely acknowledged that TRF2 is essential for t-loop formation and end protection. However, we discovered that this is only true in somatic cells. Loss of TRF2 in stem cells has no overt phenotype, telomeres remain functional, they form t-loops and remain unfused. This work challenges existing dogma, it raises important questions about how and why telomeres in pluripotent cells differ from somatic cells, and how the switch in telomere maintenance mechanism occurs upon differentiation.

In the last few years, we have begun to explore the HR mechanisms that contribute to telomere maintenance in cancers, which acquire unlimited proliferative capacity by either re-expressing telomerase or inducing alternative lengthening of telomeres (ALT) that relies on telomere recombination. Intriguingly, we have recently discovered that infection of cells with Kaposi's Sarcoma Herpes Virus triggers ALT, which we plan to use as a system to understand the mechanisms responsible for ALT induction and maintenance.

Our ongoing and future work aims to develop our most important discoveries from the last review period in three complementary areas, which share homologous recombination (HR) at their core: 1) telomere maintenance mechanisms; 2) replication-fork conflicts, stabilisation and restart, and; 3) mechanisms of the HR reaction.

Research outputs

Ruis P, Van Ly D, Borel V, Kafer G, McCarthy A, Howell S, Blassberg R, Snijders AP, Howell M, Briscoe J, Niakan K, Marzec P, Cesare AJ & Boulton SJ (2021) *TRF2-independent chromosome end protection during pluripotency*. Nature, 589:103-109 DOI: 10.1038/s41586-020-2960-y
This work revealed that telomere protection is solved by distinct mechanisms in pluripotent and somatic tissues. In somatic cells, TRF2 sequesters the telomere within a t-loop, preventing telomere end-to-end fusions and inviability. In contrast, TRF2 is dispensable for telomere protection in pluripotent cells; ESCs lacking TRF2 grow normally, do not fuse their telomeres and form functional t-loops. Upon differentiation this unique attribute of stem cells is lost and TRF2 assumes its full role in end protection. The retention of end protection in the presence of t-loops, but absence of TRF2, confirmed that t-loops are a key mediator of telomere end protection irrespectively of how they form.

Sarek G, Kotsantis P, Van Ly D, Ruis P, Margalef P, Borel V, Zheng X-F, Flynn H, Snijders B, Choudhury D, Cesare A & Boulton SJ. (2019) *CDK phosphorylation of TRF2 controls t-loop dynamics during the cell cycle*. Nature, 575:523-527. DOI: 10.1038/s41586-019-1744-8
Evidence suggested that the telomere adopts a lasso-like t-loop configuration, which safeguards chromosome ends from being recognised as DNA double strand breaks. However, the regulation and physiological importance of t-loops in end-protection was uncertain. This study uncovered a phospho-switch in TRF2 that coordinates the timely assembly and disassembly of t-loops during the cell cycle, which protects telomeres from replication stress and an unscheduled DNA damage response. These results were the first to definitively establish the t-loop as a physiologically important structure required to suppress checkpoint activation at telomere ends.

Margalef P, Kotsantis P, Borel V, Bellelli R, Panier S & Boulton SJ (2018). *Stabilization of reversed replication forks by telomerase drives telomere catastrophe*. Cell.172: 439-453. DOI: 10.1016/j.cell.2017.11.047
This study defined the mechanism leading to critically short telomeres in the absence of RTEL1 and showed that telomerase, which extends telomeres in normal cells, is pathological when forks encounter an obstacle within the telomere. We showed that replication forks stall and reverse at persistent t-loops, which creates a pseudo-telomere substrate that is inappropriately stabilised by telomerase. Removing telomerase or blocking replication fork reversal rescued telomere dysfunction in *Rtel1* deficient cells. We proposed that when persistent t-loops stall the replisome, telomerase inhibits fork restart, triggering the excision of the t-loop by SLX1/4 and loss of a substantial part of the telomere.

Taylor MRG, Špírek M, Chaurasiya KR, Ward JD, Carzaniga R, Yu S, Egelman EH, Collinson LM, Rueda D, Krejci L & Boulton SJ (2015). *Rad51 paralogs remodel pre-synaptic Rad51 filaments to stimulate homologous recombination*. Cell 162, 271-286. DOI: 10.1016/j.cell.2015.06.015
This study was the first to demonstrate that RAD51 paralogues bind to and structurally remodel the pre-synaptic RAD-51-ssDNA filament to a stabilised, “open”, and flexible conformation, which facilitates strand exchange with the template duplex. We showed that RAD51 paralogues act by binding the end of the presynaptic filament, which induces a conformational change that stabilises RAD-51 bound to ssDNA and primes the filament

for strand exchange. These observations established for the first time the underlying mechanism of HR stimulation by Rad51 paralogues and revealed a new paradigm for the action of HR mediator proteins.

Hewitt G, Borel V, Segura-Bayona S, Takaki T, Ruis P, Bellelli R, Lehmann LC, Sommerova L, Vancevska A, Tomas-Loba A, Zhu K, CooperC, Fugger K, Patel H, Goldstone R, Brough R, Lord CJ, West SC, Ahel I, Ahel D, Chapman JR, Deindl S & Boulton SJ (2021). *Defective ALC1 nucleosome remodelling confers PARPi sensitivity and synthetic lethality with HRD*. Molecular Cell 81(4): 767-783.e11. DOI: 10.1016/j.molcel.2020.12.006.

Homologous recombination (HR) is an essential DNA repair mechanism that is frequently inactivated in cancer. Importantly, deficiencies in the HR pathway creates a vulnerability that can be exploited to selectively kill cancer cells by means of synthetic lethality as exemplified by the success of PARP inhibitors in the clinic. This study sought to identify novel synthetic lethal strategies to target cancers and to combat the emerging problem of innate and acquired PARP inhibitor resistance. We discovered that loss of ALC1 confers both PARP inhibitor sensitivity and synthetic lethality with HR deficiency. As such, targeting ALC1 could be employed to augment existing therapeutic strategies for cancer therapy