BIOGRAPHICAL SKETCH
Simon J. Boulton

NAME
Simon J. Boulton

POSITION TITLE
Senior Group Leader, Francis Crick Institute, London.

Francis Crick Institute, Midland Road, London

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>University of Edinburgh, UK</td>
<td>BSc.</td>
<td>09/94</td>
<td>Molecular Biology</td>
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<tr>
<td>University of Cambridge, UK</td>
<td>Ph.D.</td>
<td>01/98</td>
<td>Molecular Biology</td>
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<tr>
<td>Harvard Medical School, USA</td>
<td>Postdoctoral</td>
<td>02/02</td>
<td>Molecular Genetics</td>
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PERSONAL STATEMENT

Simon Boulton has a long-standing interest in the mechanisms of DNA repair. His work using genetics, biochemistry and biophysical approaches has led to the discovery of novel DNA repair genes and provided molecular insights into human diseases. Boulton’s early career achievements include the identification of non-homologous end joining (NHEJ) factors in budding yeast, and the establishment of their importance in preventing error-prone DNA repair and in maintaining telomere integrity (Boulton & Jackson, EMBO J 1996 & 1998 NAR 1998). He conducted the first large-scale functional genome analysis of the DNA damage response in *C. elegans* and was responsible for the discovery and molecular characterization of novel DNA repair genes and the Fanconi Anemia pathway in worms (Boulton, Science 2002). Boulton’s work has also played an important role in shaping our understanding of the process of homologous recombination (HR), a key DNA double strand break repair pathway required for the maintenance of genome stability. Loss or inappropriate utilisation of HR is a well-documented source of chromosomal instability and a key driver of tumorigenesis (eg. *Brca* loss; Higgins & Boulton Science 2018). Through a genetic screen in *C. elegans*, Boulton identified the helicase RTEL-1 as the first negative regulator of HR in metazoans. His biochemical analysis revealed that RTEL-1 acts by dismantling D-loop intermediates, which reverses DNA strand exchange catalysed by Rad51. Boulton proposed that RTEL1 acts to constrain HR when it is invoked at the wrong time or place within the genome (Barber, Cell 2008). Prompted by this work, Boulton hypothesised that the D-loop disruption activity of RTEL1 might be utilised to control HR in various distinct physiological contexts including meiosis, DNA replication and at telomeres. This hypothesis was first investigated in meiosis where his lab discovered that defects in Rtel1 lead to a failure to effectively dissociate meiotic recombination intermediates required to promote non-crossover repair (Youds, Science 2010). This finding was particularly important as this implicated D-loop disruption by RTEL-1 in crossover homeostasis and the faithful segregation of chromosome at the first meiotic division. More recently, Boulton discovered that RTEL1 and HIM-6/BLM helicases also counteract illegitimate inter-homologue recombination during *C. elegans* meiosis. By extension of this finding to vertebrates, his lab established that these aberrant recombination reactions accelerate genome instability leading to a novel class of complex genome rearrangements in cancers (Leon-Ortiz, Mol Cell 2018). Boulton’s discovery of RTEL1 as a key regulator of HR and his subsequent insights into its role in meiosis, laid the foundations for his ground-breaking work on the function of RTEL1 at telomeres. In a series of studies, Boulton discovered that the D-loop disrupting activity of RTEL1 is co-opted to telomeres to promote the transient disassembly of t-loops, which are normally formed by HR to protect telomere ends but must be transiently unwound during S-phase to allow telomere replication (Vannier, Cell 2012). He also discovered that RTEL1 performs a genetically separable function to facilitate the replication of telomeres. Boulton observed that telomeres are fragile in the absence of RTEL1, and this is exacerbated following treatment with G4-DNA stabilizing drugs. This work marked a major advance in the telomere field as it implicated RTEL1 in t-loop unwinding and telomere replication, which provided a mechanistic understanding for the source of telomere loss observed in Rtel1 deficient cells. Boulton went on to discover that telomere dysfunction caused by loss of RTEL1 could be rescued by inactivating telomerase, the reverse transcriptase that normally extends telomeres to solve the end-replication problem. Rather than being unwound by the replisome, Boulton 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 necessitates the excision of the t-loop by SLX1/4 and loss of a substantial part of the telomere, which refined the mechanism that leads to critically short telomeres in the absence of RTEL1 (Margalef, Cell 2018). Boulton went on to establish that t-loop unwinding is compromised by RTEL1 mutations in the telomere dysfunction disorder Hoyeraal-Hreidarsson syndrome (Sarek, Mol. Cell 2015) and is subject to cell cycle control via a phospho-switch in TRF2. Importantly, he 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 avert telomere catastrophe, whilst also preventing promiscuous t-loop unwinding during other cell cycle stages. Such exquisite control of TRF2 to regulate t-loop opening and the need to "protect" t-loops from promiscuous unwinding by RTEL1 outside of S-phase, demonstrated for the first time that t-loops are indeed essential for physiological telomere homeostasis and chromosome end protection (Sarek, Nature 2019). Boulton also discovered that RTEL1 plays an important role in dismantling DNA secondary structures to facilitating global DNA replication, which he showed is an important tumour suppression mechanism in mice (Vannier, Science 2013; Bellelli Mol Cell, 2019 & Cell Reports 2020). Finally, Boulton has made important contributions to our understand of the mechanisms that promote homologous recombination; he was first to show that BRCA2 binds to and stabilizes Rad51 filaments by inhibiting ATP hydrolysis (Petalcorin PNAS, 2007); he implicated HELQ in promoting the disassembly of Rad51 from post-synaptic HR intermediates (Ward Mol Cell 2010), established a role for HELQ and the Rad51 paralogs in avertting germ cell attrition and tumorigenesis (Adelman Nature 2013); he established that Rad51 paralogs promote HR by remodeling Rad51 filaments to a stable conformation proficient for strand exchange (Taylor Cell 2015 & Mol Cell 2016); and, identified the metalloprotease SPRTN, which is essential for removing DNA protein cross-links that impede DNA replication (Stingele, Mol Cell 2015).

Boulton is also Scientific Co-founder of Artios Pharma Ltd, Cambridge, UK. He 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 SVP of Science Strategy, Boulton assists the executive team in the identification and evaluation of new pipeline opportunities from the global academic and industrial DDR network. He also chairs the SAB and is 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 lead assets, ATR and POLQ inhibitors, will enter the clinic in 2021.

POSITIONS AND EMPLOYMENT

2017-present  Honorary Professor, Kings College London.
             London Research Institute, Clare Hall Laboratories, UK.
2007-present  Honorary Professor, University College London.
2000-2002  Postdoctoral Research Fellow, Dana Farber Cancer Institute,
            Harvard Medical School, Boston, USA.
1998-2000  HFSP and EMBO Postdoctoral Research Fellow, MGH Cancer
            Center, Harvard Medical School, Boston, USA.
1994-1998  CRC Graduate Student, Wellcome/CRC Institute, University of Cambridge, UK.
1990-1994  BSc (Hons) in Molecular Biology, University of Edinburgh, UK.

HONORS AND AWARDS

2020  Wellcome Trust Senior Investigator.
2019  Ambassador for Translation, The Francis Crick Institute.
2017  Lead, Wellcome Trust Collaborative Award.
2017  ERC Advanced Investigator (TelMetab).
2014  Wellcome Trust Senior Investigator.
2013  Mendel Lecture, Brno, CR.
2012  Elected as a Fellow of the Academy of Medical Sciences, UK.
2011  ERC Advanced Investigator (RecMitMei).
2011  EMBO Gold Medal.
2010  Royal Society Wolfson Research Merit Award.
2009  Elected as a member of EMBO.
2008  Eppendorf/Nature Award for Young European Investigators.
2008  EACR Young Cancer Researcher of the Year Award.
2007  EMBO Young Investigator.
2006  Colworth Medal. Awarded from the Biochemical Society.
2002  Tosteson Postdoctoral Fellowship Award.
2001  MGH Fund for Medical Discovery Award.
1998  Human Frontiers Science Program Fellowship Award.
1998  EMBO Long Term Fellowship Award.

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.
2012  Site review committee, National Cancer Institute, Amsterdam.
2012-present Scientific Advisory Board, MRC PPU, University of Dundee.
2013  Site Review Committee, Ludwig Institute of Cancer Research, La Jolla, CA.
2015-present GSK-CRICK Joint Steering committee, UK (Chair, 2017-).
2015-present Scientific Advisory Board, Mendel Lectures, Brno, CR.
2017-present DDR and PARPi Steering Committee, COR2ED.
2017-present 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.
2020.  Site review committee, Institute of human Genetics, Montpellier.

PUBLICATIONS

http://www.ncbi.nlm.nih.gov/pubmed/?term=Boulton+s

20 selected publications (from a totally of 118; h-index = 54) listed in chronological order:


