

## **JOINT NEWS RELEASE**

**Singapore, 21 July 2025**

### **NTU Singapore and Oxford scientists reveal how cells repair toxic DNA damage linked to cancer and premature ageing**

Researchers at the **University of Oxford** and **Nanyang Technological University, Singapore (NTU Singapore)** have uncovered the mechanism by which cells identify and repair a highly toxic form of DNA damage that causes cancer, neurodegeneration, and premature ageing.

The findings, published in *Nucleic Acids Research*, reveal how DNA-protein crosslinks (DPCs) – harmful DNA lesions induced by chemotherapy, formaldehyde, and UV exposure – are recognised and broken down by SPRTN, a key repair enzyme.

The research team discovered a new region within SPRTN that enables it to selectively target DPC lesions, increasing its repair activity 67-fold while leaving surrounding structures unharmed.

Led by **Kristijan Ramadan, Toh Kian Chui Distinguished Professor in Cancer and Stem Cell Biology at the Lee Kong Chian School of Medicine, NTU Singapore and Honorary Senior Researcher at the Department of Oncology, University of Oxford**, the work has important implications for improving cancer therapy and healthy ageing.

#### **The threat of DPC lesions**

Every time a cell divides into two, it must accurately create a copy of all its DNA, a process that involves the tight coordination of sophisticated molecular machinery. DNA-protein crosslinks (DPCs) are bulky lesions in which unwanted proteins attach to DNA, blocking the process of copying the cell's DNA.

If left unrepaired, DPCs can cause neurodegeneration, premature ageing, and cancer. Therefore, understanding how these lesions are repaired is crucial for protecting genome integrity and preventing these conditions.

DPCs can occur through normal cellular metabolism, as well as exposure to chemotherapeutic drugs, UV radiation, and environmental agents like formaldehyde.

Formaldehyde is a Group 1 carcinogen commonly found in household furniture, paint, and air pollution, including haze.

SPRTN is a critical enzyme that protects cells against DPC lesions. It travels along the DNA and degrades the proteins in the lesions, which clears the blockage and enables the DNA copying process to proceed.

Until now, it was unknown how SPRTN specifically breaks down DPC lesions without damaging functional proteins in the cell.

### **Discovery of a damage recognition domain**

The research team discovered a specialised region within SPRTN which drives its activity against DPCs. The region detects chains of ubiquitin – tiny tags that attach to other proteins to modify their function – which DPC lesions have in abundance.

Recognition of these tags directly guides SPRTN to the DPC lesions, triggering a rapid increase in its activity to break down the harmful protein attachments.

“In the absence of ubiquitin chains on DPCs, SPRTN is slow and inefficient, taking hours to clear the DNA lesions. But when the ubiquitin chains are present, SPRTN’s ability to specifically target DPCs and break them down is enhanced 67-fold, enabling rapid removal of DPCs, which is critical due to its role in the rapid repair of DNA,” said Prof Ramadan, who is also the Director of the Cancer Discovery and Regenerative Medicine Programme at NTU Singapore’s Lee Kong Chian School of Medicine.

Importantly, the team showed that longer chains significantly accelerated the repair process compared to when only one or two ubiquitin tags were attached to the DNA lesion. This allows SPRTN to act quickly on DPCs while sparing other proteins that lack these tags.

### **Implications for cancer therapy and healthy ageing**

These findings, which demonstrate the importance of the newly discovered SPRTN region for DPC lesion repair, have important implications in cancer therapy and healthy ageing.

Mutations in the SPRTN gene are known to cause Ruijs-Aalfs syndrome (RJALS), a rare condition characterised by chromosomal instability, premature ageing, and a high risk of early-onset liver cancer. The discovery of SPRTN’s recognition mechanism provides essential insights into our cells’ natural defences and how defects in DPC repair can drive disease.

**First author of the study, Oxford's postdoctoral researcher Dr Wei Song**, said: "Our body's ability to repair DNA damage caused by DPCs has long been a mystery. But now that we know how the repair mechanism works, we've laid the groundwork for developing potential ways to strengthen the body's defences against age-related diseases, as well as reduce the side effects of cancer therapies that damage DNA."

Commenting as an independent expert, **Dr Jens Samol, Senior Consultant in Medical Oncology, Department of Medical Oncology, Tan Tock Seng Hospital, Singapore**, said that the researchers' study is significant as it identified that ubiquitin chains act as the main signal for SPRTN's rapid activation and are very likely the main signal for SPRTN to specifically target and break down DPCs heavily tagged with ubiquitin.

"These findings further the understanding of SPRTN's ability to specifically degrade DPCs and prevent normal cells from becoming cancerous," added Dr Samol. "Moreover, some cancer patients are resistant to chemotherapy that kills tumour cells by inducing DPCs in them."

"The involvement of ubiquitin shown by the study opens the possibility of investigating whether anti-ubiquitin antibodies or ubiquitin-proteasome inhibitors, such as bortezomib, could be potentially used as therapeutic options for overcoming cancer patients' resistance to chemotherapy drugs. This concept could be tested in animal models like mice."

Future studies by the researchers, including ongoing work in zebrafish, mouse models and human tissues, aim to validate their findings and further explore the potential of strengthening DPC repair mechanisms. This research could further revolutionise our understanding of the processes of ageing and cancer, as well as identify potential therapeutic interventions.

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#### **Notes to Editor:**

Paper titled "The dual ubiquitin binding mode of SPRTN secures rapid spatiotemporal proteolysis of DNA–protein crosslinks" published in *Nucleic Acids Research*, 21 July 2025.

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### ***About the University of Oxford***

Oxford University has been placed number 1 in the Times Higher Education World University Rankings for the ninth year running, and number 3 in the QS World Rankings 2024. At the heart of this success are the twin-pillars of our ground-breaking research and innovation and our distinctive educational offer.

Oxford is world-famous for research and teaching excellence and home to some of the most talented people from across the globe. Our work helps the lives of millions, solving real-world problems through a huge network of partnerships and collaborations. The breadth and interdisciplinary nature of our research alongside our personalised approach to teaching sparks imaginative and inventive insights and solutions.

Through its research commercialisation arm, Oxford University Innovation, Oxford is the highest university patent filer in the UK and is ranked first in the UK for university spinouts, having created more than 300 new companies since 1988. Over a third of these companies have been created in the past five years. The university is a catalyst for prosperity in Oxfordshire and the United Kingdom, contributing [£15.7 billion to the UK economy](#) in 2018/19, and supports more than 28,000 full time jobs.

### ***About Nanyang Technological University, Singapore***

A research-intensive public university, Nanyang Technological University, Singapore (NTU Singapore) has 35,000 undergraduate and postgraduate students in the Business, Computing & Data Science, Engineering, Humanities, Arts, & Social Sciences, Medicine, Science, and Graduate colleges.

NTU is also home to world-renowned autonomous institutes – the National Institute of Education, S Rajaratnam School of International Studies and Singapore Centre for Environmental Life Sciences Engineering – and various leading research centres such as the Earth Observatory of Singapore, Nanyang Environment & Water Research Institute and Energy Research Institute @ NTU (ERI@N).

Under the NTU Smart Campus vision, the University harnesses the power of digital technology and tech-enabled solutions to support better learning and living experiences, the discovery of new knowledge, and the sustainability of resources.

Ranked amongst the world's top universities, the University's main campus is also frequently listed among the world's most beautiful. Known for its sustainability, NTU has achieved 100% Green Mark Platinum certification for all its eligible building projects. Apart from its main campus, NTU also has a medical campus in Novena, Singapore's healthcare district.

For more information, visit [www.ntu.edu.sg](http://www.ntu.edu.sg)

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