

## Global Phd Scholarship – St Andrews and Bonn

### Untying the knot: genome-wide recognition and remodelling of G4 structures by the NER machinery- implications in human DNA repair and regulatory pathways

#### Project description

Cancer is one of the leading causes of death worldwide. Smoking, alcohol, and/or UV light can lead to mutations within genomic DNA and drive cancer development. In healthy cells, DNA repair mechanisms exist to prevent mutations and disease generation. To better understand the molecular origins of cancer and improve diagnostic and therapeutic applications an enhanced understanding of repair is required.

The observation that DNA can form knotted-like structures revolutionized modern biology, because they can participate in the regulation of many DNA-mediated processes crucial for life. G-quadruplexes (G4s) are specific DNA structures that have raised considerable attention due to their widespread in humans (~700,000 G4 sites) and their implication in cancer development and ageing. Recently, G4s were shown to impact positively DNA repair, raising the hypothesis if G4s can be used to regulate and target DNA repair.

Nucleotide excision repair (NER) is the major repair pathway that is activated upon UV light, environmental mutagens, and certain chemotherapeutic agents. Defects in NER lead to genetic disorders such as Xeroderma Pigmentosum, Cockayne syndrome and cancer. Multiple proteins participate in NER. Among these proteins are XPD and XPB, which are part of the multi-subunit TFIIH complex, and are the focus of the Penedo's lab. In previous work, the Paeschke lab discovered that induction of G4 structures in cells positively influence NER in yeast. These evidences suggest the exciting possibility that G4 formation facilitates NER function. In this project the PhD candidate we will unravel the protein interaction network and its direct implication on NER efficiency at G4s.

The appointed PhD student will integrate the biophysics, single-molecule microscopy, and cellular and genomics expertise from both labs to determine the role of G4 structures in NER activation.

The project will be managed jointly between the School of Physics and Astronomy and the School of Biology at St Andrews and the University Hospital, Medical Clinic III for Haematology and Oncology at Bonn. The student will be supervised by Prof. Carlos Penedo (St Andrews) and Prof. Dr. rer. nat. Katrin Paeschke (Bonn).

Informal enquiries regarding this scholarship may be addressed to the co-supervisors:

- **Professor Carlos Penedo:** [jcp10@st-andrews.ac.uk](mailto:jcp10@st-andrews.ac.uk)
- **Professor Katrin Paeschke:** [paeschke@uni-bonn.de](mailto:paeschke@uni-bonn.de)

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**Application deadline: March 31, 2023**