

Molecular mechanisms of DNA repair and replication in health and disease

Principal supervisor's name: Dr **Luca Pellegrini**
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Principal supervisor's CRUK CC theme: Cell and Molecular Biology Programme

Department for student registration: Biochemistry
Department or institute where research will take place: Tennis Court Road, Dept of Biochemistry,
University of Cambridge

Postgraduate scheme: **MRes + PhD (1 + 3-year non-clinical applicants only).**

MRes project outline:

The aim of the project is to improve our understanding of the mechanistic basis for some key aspects of DNA metabolism responsible for duplication and maintenance of our chromosome. In the project, the student will use a range of biochemical and biophysical techniques, including Structural Biology techniques such as cryoEM, to investigate the structure and function of protein assemblies important for DNA repair and replication.

MRes experimental plan:

To be determined

PhD project outline:

The aim of the project is to improve our understanding of the mechanistic basis for some key aspects of DNA metabolism responsible for duplication and maintenance of our chromosome. In the project, the student will use a range of biochemical and biophysical techniques, including Structural Biology techniques such as cryoEM, to investigate the structure and function of protein assemblies important for DNA repair and replication.

PhD experimental plan:

To be determined

Main techniques:

In the course of the project, the student will have a chance to learn several experimental techniques, including preparative Biochemistry (DNA cloning and protein expression in various prokaryotic and eukaryotic host system), gel- and solution-based assays for quantitative analysis of macromolecular interactions, enzymatic assays, single-molecule fluorescence assays using optical tweezers and Structural Biology (cryoEM and X-ray crystallography).

Key references:

- 1: Pellegrini L. The CMG DNA helicase and the core replisome. *Curr Opin Struct Biol.* 2023 Aug;81:102612. doi: 10.1016/j.sbi.2023.102612. Epub 2023 May 25. PMID: 37244171.
- 2: Appleby R, Bollschweiler D, Chirgadze DY, Joudeh L, Pellegrini L. A metal ion-dependent mechanism of RAD51 nucleoprotein filament disassembly. *iScience.* 2023 Apr 25;26(5):106689. doi: 10.1016/j.isci.2023.106689. PMID: 37216117; PMCID: PMC10192527.
- 3: Kilkenny ML, Veale CE, Guppy A, Hardwick SW, Chirgadze DY, Rzechorzek NJ, Maman JD, Pellegrini L. Structural basis for the interaction of SARS-CoV-2 virulence factor nsp1 with DNA polymerase α -primase. *Protein Sci.* 2022 Feb;31(2):333-344. doi: 10.1002/pro.4220. Epub 2021 Nov 12. PMID: 34719824; PMCID: PMC8661717.
- 4: Lerner LK, Holzer S, Kilkenny ML, Šviković S, Murat P, Schiavone D, Eldridge CB, Bittleston A, Maman JD, Branzei D, Stott K, Pellegrini L, Sale JE. Timeless couples G-quadruplex detection with processing by DDX11 helicase during DNA replication. *EMBO J.* 2020 Sep 15;39(18):e104185. doi: 10.15252/embj.2019104185. Epub 2020 Jul 23. PMID: 32705708; PMCID: PMC7506991.
- 5: Rzechorzek NJ, Hardwick SW, Jatikusumo VA, Chirgadze DY, Pellegrini L. CryoEM structures of human CMG-ATP γ S-DNA and CMG-AND-1 complexes. *Nucleic Acids Res.* 2020 Jul 9;48(12):6980-6995. doi: 10.1093/nar/gkaa429. PMID: 32453425; PMCID: PMC7337937.
- 6: Syrjänen JL, Heller I, Candelli A, Davies OR, Peterman EJ, Wuite GJ, Pellegrini L. Single-molecule observation of DNA compaction by meiotic protein SYCP3. *Elife.* 2017 Mar 13;6:e22582. doi: 10.7554/eLife.22582. PMID: 28287952; PMCID: PMC5348128.
- 7: Davies OR, Forment JV, Sun M, Belotserkovskaya R, Coates J, Galanty Y, Demir M, Morton CR, Rzechorzek NJ, Jackson SP, Pellegrini L. CtIP tetramer assembly is required for DNA-end resection and repair. *Nat Struct Mol Biol.* 2015 Feb;22(2):150-157. doi: 10.1038/nsmb.2937. Epub 2015 Jan 5. PMID: 25558984; PMCID: PMC4564947.