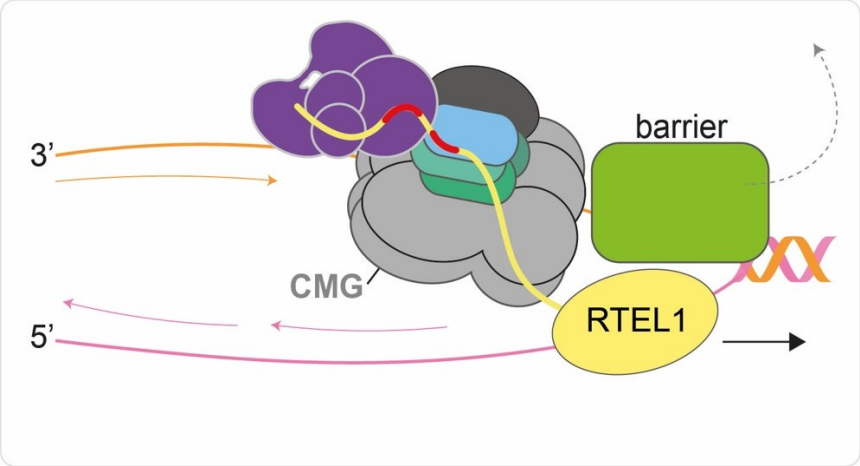
Helper helicases in human genome replication



The DNA replication machinery (replisome) in human cells is built around a core DNA helicase called CMG, which separates the two strands of the double helix during DNA replication, to generate the single strands of DNA that act as templates for new DNA synthesis. Although CMG is capable of supporting the unwinding of the majority of our genome, it is stalled at numerous protein barriers, and when two replisomes meet each other during the final stages of DNA replication.

When CMG stalls, a 2nd accessory or 'helper' helicase is required to support replisome progression, so that genome replication can be completed and genome stability preserved. We have previously identified a new role for these helper helicases during the final stages of DNA replication (Deegan et al., Mol Cell, 2019), and defined a conserved mechanism for how they are recruited to replisome (Olson et al., EMBO J, 2024). We now intend to interrogate the molecular and physical mechanisms for how these helicases are regulated to act only when CMG is blocked, and how these helicases help protect our genomes when DNA replication is perturbed.

This project will combine a range of biochemical, biophysical and cell biological approaches, including reconstituting DNA replication in the test tube with purified human proteins. Ultimately, this work will shed light on both a newly discovered, fundamental feature of eukaryotic replisome organisation, and on the numerous human diseases in which helper helicases are mutated.