

CCS Annual Report 2021

The Center for Chromosome Stability (CCS) is a multidisciplinary research center that aims to further our understanding of fundamental aspects of genome maintenance. As part of this overall aim, we have a particular focus on defining how chromosomal instability impacts on human disease. Our investigations are not, however, focused on any specific disease; instead, we study a variety of disorders in which a failure to maintain the structural and functional integrity of cellular DNA is the underlying defect. These include cancer, selected neurodegenerative disorders, and impaired fertility. Although we have ongoing interests in many aspects of DNA metabolism, a core theme is to understand how chromosomal instability arises as an undesirable byproduct of the process of DNA replication when the genome is duplicated in preparation for the division of a mother cell into two daughter cells (Figure 1).

DNA replication

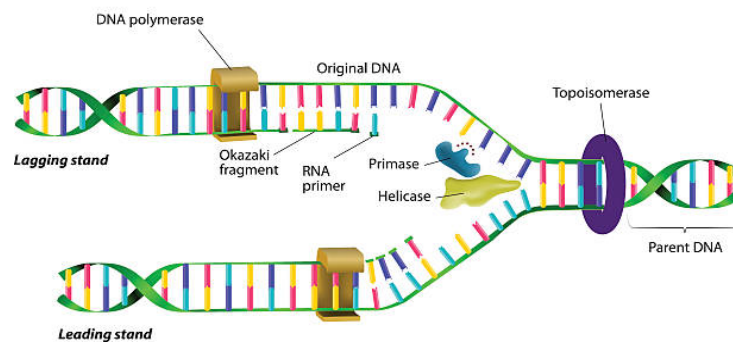


Figure 1: Overview of the DNA replication machinery. Many of the factors indicated, including DNA polymerases, helicases and topoisomerases, are studied in the CCS

DNA replication is perhaps the most remarkable and challenging process that any cell embarks upon. As a result, a high proportion of disease-causing mutations arise in the human genome because of errors made during DNA replication. One major source of replication perturbation (generally referred to as replication stress; RS) arises when cells attempt to replicate a locus while it is being transcribed into RNA at the same time – in these instances, two very large macromolecular complexes try simultaneously to use the same DNA template. Understanding the consequences for genome maintenance of these so-called transcription-replication conflicts has emerged as a new theme of the CCS in the past year.

Conducting research during the reporting period has been a serious challenge for the CCS due to the consequences of the ongoing pandemic. It has not only impacted on the training and progression of many of our young researchers, but also has affected more generally the success of the CCS during the reporting period. Despite this, we have had several major achievements this year. Most notably, we have begun the process of establishing a new research group, headed by Associate Professor Thomas (Tom) Miller, who joined us from the Francis Crick Institute in London. Tom will be developing a new research theme in the CCS focusing on innovative applications of cryo-electron microscopy (cryo-EM) to visualize events during DNA replication. His research will utilize the excellent facilities offered by the Danish National cryo-EM Facility at the University of Copenhagen. Although Tom replaced Andrés Lopez-Contreras as a CCS group leader, we are pleased that our host department (ICMM) has supported us to maintain strong links with Andrés. As such, a formal affiliation between the CCS/ICMM and Andrés has been established, initially for a 3-year period. The CCS has also produced high impact publications in 2021; most notably, a paper in *Nature* from Eva Hoffmann's group that generated considerable scientific interest and media coverage. That study identified genes that impact on reproductive lifespan in women, including a demonstration of how ovarian ageing can be delayed by gene manipulation.