The accurate transmission of the genetic material requires a faithful replication of the chromosomes and their equal segregation to the progeny. The perturbation of the dynamic of DNA replication, known as replication stress, has emerged as a major source of genome instability contributing to the early stages of carcinogenesis.

The causes of replication stress are many and varied, but they ultimately affect the progression of replication forks and can jeopardize the even segregation of chromosome in mitosis. The aim of our research is to decipher the molecular transactions occurring at replication forks in response to replication stress and to understand how these mechanisms trigger genome instability. In particular, the team focuses on the mechanisms of homologous recombination, a well evolutionary conserved pathway, known to prevent genome instability and tumour development in humans. Such questions are important to address in basic cancer research to understand how genetic instability arises from replication stress and contributes to cancer devolvement or genomic disorders.
Figure 1: Cellular model to induce endogenous replication stress at targeted locus. (A) A natural fork obstacle is exploited in fission yeast to induce endogenous replication stress at a targeted locus. The protein Rtf1, which expression is regulated, binds a specific sequence (in blue) and mediates fork arrest. Replication arrest and restart are investigated by combining molecular (B) and cellular biology (C).

Figure 2: Model of replication stress-induced genetic instability at collapsed forks.

To investigate the causes and the consequences of replication stress, the yeast *Schizosaccharomyces pombe* is a powerful model system amendable to genetic, cellular and molecular biology, thus allowing us to manipulate and create endogenous replication stress (Fig 1). Our team has identified that homologous recombination is an efficient pathway to restart replication forks, but that this comes at the expense of potential genetic instability, including tumour-like genome rearrangements (genomic deletion/translocations). Also, we have reported that replication restart by homologous recombination results in the progression of an error-prone replication fork, liable to replication slippage (Fig 2). Finally, we have identified that the DNA Damage Response is involved in regulating the extent of genetics errors.
committed during replication restart by homologous recombination.

By combining genetics screens, cell imaging and molecular biology, the team focuses on deciphering the replication maintenance functions of homologous recombination, from fork-restart to fork-protection functions. As molecular transactions at blocked replication forks occur in a chromatin context, the team has also investigated the links between chromatin assembly pathways and the fidelity of homologous recombination. We have identified CAF-1 as a novel factor that challenges the fidelity of replication restart by homologous recombination.