Our Group uses cryo-electron microscopy (cryoEM) to determine the 3D structure of large macromolecular complexes of relevance in cancer. Structural information, in combination with molecular and cell biology and biochemistry, is then used to propose how these molecules work and increase our understanding of the molecular basis of cancer. Most of our efforts are currently focused on 2 major areas of research: i) the study of chaperones essential for the activation of several macromolecular complexes relevant in cancer such as mTORC1; and ii) the study of complexes implicated in the repair of DNA damage and in genomic instability. In collaboration with other groups, we are also studying the structure and mechanisms of several amino acid transporters, as well as the mechanisms that regulate microtubule nucleation for the assembly of the mitotic spindle.

“We have discovered a mechanism used by aggressive forms of hepatocellular carcinoma to repair broken DNA using a long non-coding RNA. Modulation of this RNA could serve as a therapeutic opportunity.”
Telomeres are structures found at the ends of all human chromosomes in eukaryotes. Telomeres consist of DNA repeats that function as a protective ‘cap’, preventing chromosomes from shortening during genome replication. The regulation of double-strand breaks (DSBs) by the cellular DNA repair machinery is essential in preventing chromosome ends from being recognised as broken DNA. Our model is that NIHCOLE serves as a glue that strengthens both ends of the broken DNA, promoting DNA-end synapsis. We discovered that NIHCOLE interacts with Ku70-Ku80 at both ends of the broken DNA, promoting DNA-end synopsis. Our model is that NIHCOLE serves as a glue that strengthens the bridge between the 2 pieces of the broken DNA, and this increases the efficiency of DNA repair by the NHEJ pathway.

One of our goals is to uncover the mechanism and structural basis of the CST complex in the homeostasis of telomeres. CST participates in regulating telomere extension and is also required to recruit DNA polymerase α-primase for converting the extended tail to dsDNA (C-strand fill-in). We are comparing the structure and function of complexes in humans and yeast to uncover core elements conserved across species, while discriminating adaptations specific for humans.

We have elucidated the molecular organisation of Cdc13, one of the components of the CST complex in the yeast _Candida glabrata_, using several biochemical and biophysical techniques. Cdc13 binds to the telomeric G-overhang during the G2 phase and recruits telomerase during progression into S-phase. We have found that Cdc13 forms a dimeric structure that requires dimerization of the OB2 domain. Dimerization enhances binding to telomeric sequences leading to the unfolding of ssDNA. Once bound to DNA, Cdc13 prevents the refolding of ssDNA through mechanisms involving all its domains. We propose the first detailed model for the molecular architecture of Cdc13 and how its structural organisation underpins its telomeric DNA-binding and centromere binding. Our results suggest that the molecular architecture of CST varies between yeast and humans, as well as between different yeast species, but that some structural and functional elements are conserved.