Immortality is one of the most universal characteristics of cancer cells. We study the mechanisms by which tumour cells are immortal and normal cells are mortal. The enzyme telomerase is present in more than 95% of all types of human cancers and is absent in normal cells in the body. Telomeres are nucleoprotein complexes located at the ends of chromosomes and are essential for chromosome protection and genomic stability. Progressive shortening of telomeres associated with organism ageing leads to ageing. When telomeres are altered, adult stem cells have a maimed regenerative capacity.

Our research focuses on:

- Generating mouse models to validate telomeres and telomerase as therapeutic targets for cancer and age-related diseases.
- Interplay between telomeres and DNA repair pathways.
- Role and regulation of non-coding telomeric RNAs or TERRA.
- Testing telomerase gene therapy in telomere syndromes and age-related diseases.
- Role of telomerase and telomeres in adult stem cell biology and in nuclear reprogramming of differentiated cells to iPSCs.

“Our finding that signals outside the cell, which induce cell proliferation and are implicated in tumorigenesis, regulate telomeres opens the door to new therapeutic avenues targeting telomeres to help treat cancer.”
We have progressed in our quest to unravel the role that telomeres—the chromosome ends responsible for cellular ageing as they shorten—play in cancer. Telomeres are bound by shelterin, a multi-protein complex essential for the protection of chromosome ends and genomic stability. Knowledge is scarce on the regulation of shelterin components by extracellular signals including developmental and environmental cues. Using the gene-editing tool CRISPR/Cas9, we generated knock-in human cell lines carrying non-phosphorylatable mutant forms of the AKT-dependent phosphorylation sites that are present in the shelterin TRF1 and showed that TRF1 is subjected to AKT-dependent regulation. TRF1 mutant cells had decreased TRF1 binding to telomeres as well as increased global and telomeric DNA damage. Human cells bearing non-phosphorylatable mutant TRF1 alleles exhibited accelerated telomere shortening (FIGURE1), demonstrating that AKT-dependent TRF1 phosphorylation regulates telomere maintenance in vivo. TRF1 mutant cells showed an impaired response to proliferative extracellular signals as well as a decreased tumorigenesis potential. Telomere protection and telomere length can thus be regulated by extracellular signals upstream of PI3K/AKT pathway activation, such as growth factors, nutrients, or immune regulators, and can interfere with immortality of cancer cells.

Short and dysfunctional telomeres contribute to renal fibrosis. A connection between short telomeres and the epithelial-to-mesenchymal transition programme

Telomere shortening or telomere dysfunction are responsible for the human pathologies known as telomere syndromes characterised by the loss of regenerative capacity of tissues and fibrotic pathologies. We generated two different mouse models of kidney fibrosis: one that combines telomerase deficiency to induce telomere shortening and a low dose of folic acid (a kidney toxin), and another in which TRF1 is conditionally deleted from the kidneys.

We found that short telomeres make the kidneys sensitive to developing fibrosis in response to folic acid and exacerbate the epithelial-to-mesenchymal transition (EMT) programme. Short telomeres play an important role in the development of renal fibrosis, a finding that could be of use to devise new treatments of this pathology.

Trf1 deletion in kidneys resulted in fibrosis and EMT activation. This is the first time that short telomeres have been linked to EMT, a connection of relevance since EMT, and the genes that regulate this programme, are also involved in cancer.

Telomere shortening or dysfunction may therefore contribute to pathological, age-associated renal fibrosis by influencing the EMT programme.

Shorter telomere lengths in patients with severe COVID-19 disease

Incidence of severe manifestations of COVID-19 increases along with age, with older patients showing the highest mortality rate suggestive of the contribution of the molecular pathways underlying ageing to the severity of COVID-19. The progressive shortening of telomeres (FIGURE 2) is one of the mechanisms of ageing. Critically short telomeres impair the regenerative capacity of tissues and trigger loss of tissue homeostasis and disease. The SARS-CoV-2 virus infects many different cell types, causing turnover and regeneration to maintain tissue homeostasis.

Our starting hypothesis was that short telomeres in older patients could be a driving force to SARS-CoV-2 mechanisms. We measured telomere length in peripheral blood lymphocytes from COVID-19 patients aged 29-85 years and found that patients who manifested severe forms of COVID-19 had significantly shorter telomeres.

We postulate that telomere shortening arising from the viral infection impedes tissue regeneration and that is the reason why a significant number of patients suffer long COVID-19. In this context, telomerase-based gene therapy may be a tool of use in the treatment of post-COVID-19 pulmonary injury.

**REFERENCES**

- Nature Aging.

FIGURE 1 Telomere length is normal upon AKT phosphorylation of TRF1 (top) and shorter in AKT phosphorylation-unresponsive TRF1 cell lines (bottom).

FIGURE 2 Representative immunofluorescence images of human cells bearing either long or short telomeres at the indicated cell cycle phases.

- **PUBLICATIONS**
- **AWARDS AND RECOGNITION**