OVERVIEW

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, 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 iPS cells.

“Our potential preclinical mouse model ki-Pot1aR117C for Li-Fraumeni-Like syndrome presenting with high angiosarcoma incidence could be a very useful tool in the therapeutics of these tumours.”
The BRAF gene, which encodes a master kinase of the RAS-pathway, is frequently mutated in human cancers. The most common genetic mutation is a single nucleotide transition that gives rise to a constitutively active BRAF kinase (BRAFV600E), which in turn sustains continuous telomere dysfunction. This effect is mediated by the telomeric protein POT1, which is mutated in many cardiac angiosarcomas associated to POT1 mutations. A mouse model for Li-Fraumeni-Like Syndrome with cardiac angiosarcomas developed a high incidence of angiosarcomas (FIGURE 1), including CAS, and this is associated with the presence of abnormally long telomeres in endothelial cells as well as in the tumours. The Pot1aR117C mouse model therefore constitutes a useful tool to understand human cancers initiated by POT1 mutations.

Impact of telomere dysfunction in fibroblasts, Club and basal cells on the development of lung fibrosis

Telomeric protein TRF1 is an essential component of the telomeric protective complex that prevents telomeric DNA damage, chromosome end-to-end fusions and telomere fragility. We previously showed that induction of telomere dysfunction in alveolar type II (ATII) cells is sufficient to induce progressive and lethal pulmonary fibrosis in mice. The pathological consequences of telomere dysfunction in lung fibroblasts, Club and basal cells remained to be investigated. We have now conditionally deleted Trf1 in the former mouse tissues. We found that while Trf1 deficiency in fibroblasts does not lead to significant lung pathologies, Trf1 deletion in Club and basal cells from male mice led to lung inflammation and airway remodeling. While dysfunctional telomeres in ATII cells led to alveolar DNA damage, senescence and apoptosis, as well as to interstitial lung fibrosis, their presence in Club and basal cells increased the presence of neutrophils, lymphocytes and macrophages in the lung, as well as airway collagen deposition and fibrillogenesis, features not observed in female mice upon telomere dysfunction. Depletion of TRF1 in fibroblasts, Club and basal cells did not lead to interstitial fibrosis, underscoring ATII cells as the relevant cell type for the origin of interstitial fibrosis (FIGURE 2).