**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. Telomerase is an enzyme present in over 95% of all types of human cancers and absent in normal cells in the body. Telomeres, nucleoprotein complexes located at the ends of chromosomes, are essential for chromosome protection and genomic stability. Telomeres shorten progressively with organism ageing, leading to ageing. If telomeres are altered, adult stem cells have a maimed regenerative capacity.

Our research focuses on:

- 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 (TERRA).
- Telomerase gene therapy in telomere syndromes and age-related diseases.
- Role of telomerase and telomeres in:
  - adult stem cell biology
  - nuclear reprogramming of differentiated cells to iPSCs.
Telomerase defciency and dysfunctional telomeres in the lung tumour microenvironment impair tumour progression in lung cancer

Lung cancer is the leading cause of cancer death. The long-term ineffectiveness of current therapies and late-stage diagnosis result in a five-year survival rate of about 20%. Non-small-cell lung cancer (NSCLC) accounts for 85% of lung cancer-associated deaths. Focusing on the so-called tumour microenvironment, a set of cells and factors surrounding the tumour and playing a crucial role in the development of cancer, and the response to therapies, we used a combination of NSCLC mouse models and patient-derived xenografts to address the effects of telomerase deficiency and the anti-tumour activity of 6-thio-2'-deoxyguanosine (6-thio-dG), a nucleoside analogue that leads to telomere dysfunction, genomic instability, and cell death.

We showed in mice that telomerase deficiency and 6-thio-dG-induced telomere dysfunctionally reduced lung tumour implantation and vascularisation, and increased DNA damage response, cell cycle arrest and apoptosis, while it reduced proliferation, inflammation, and lung tumour immunosuppression and invasion. 6-thio-dG-treated human NSCLC xenografts exhibited increased telomere damage, cell cycle arrest and apoptosis, as well as reduced proliferation, resulting in reduced tumour growth. Targeting telomeres might thus be an effective therapeutic strategy in NSCLC.

A link between short telomeres in alveolar type II cells and lung fibrosis in post-COVID-19 patients with cancer

The severity of COVID-19 increases with each passing decade of life, suggesting that organisational ageing contributes to the fatality of the disease. We and others previously showed that COVID-19 severity correlates with shorter telomeres, a molecular determinant of ageing, in patients’ leukocytes. Lung injury, a predominant feature of acute SARS-CoV-2 infection, can further progress to lung fibrosis in post-COVID-19 patients. Short or dysfunctional telomeres in alveolar type II (ATII) cells suffice to induce pulmonary fibrosis in mouse and humans. Our analyses of telomere length and histopathology of lung biopsies from a cohort of alive post-COVID-19 patients and a cohort of age-matched controls with lung cancer have now revealed a loss of ATII cellularity and the presence of shorter telomeres in ATII cells, concomitant with a marked increase in fibrotic lung parenchyma remodelling in post-COVID-19 patients. Our findings uncovered a link between presence of short telomeres in ATII cells and long-term lung fibrosis sequelae in post-COVID-19 patients.

Expanding the hallmarks of ageing

Aging research explores the decline in function of organisms during adulthood. In collaboration with 4 other groups, in 2013 we suggested 9 molecular, cellular, and systemic hallmarks of ageing: telomere attrition, DNA instability, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Ten years on, we have now updated the previous hallmarks, introduced some new ones, and included the following: (1) their age-associated manifestation, (2) the acceleration of ageing by experimentally accentuating them, and, most decisively, (3) the opportunity to decelerate, stop, or reverse ageing by therapeutic interventions on them. These hallmarks are interconnected among each other, as well as to the recently proposed hallmarks of health, which include organisational features of spatial compartmentalisation, maintenance of homeostasis, and adequate responses to stress (FIGURE 2).

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**FIGURE 2** Integration of hallmarks.
All 12 proposed hallmarks of ageing are functionally related amongst each other. They are also interconnected to the 8 hallmarks of health and, finally, to the 8 proposed strata of organisational organisation and create a multidimensional space of interactions that may contribute to explain some important features of the ageing process.

**FIGURE 1** The hallmarks of ageing. Scheme compiling the proposed 12 hallmarks of ageing. These hallmarks are grouped into 3 categories: primary, antagonistic, and integrative.

**Strata of organisational organisation**
- Meta-organism
- Systemic circuits
- Organ systems
- Organs
- Supracellular units
- Cells
- Organelles
- Molecules

**Hallmarks of ageing**
- Dysbiosis
- Altered cellular communication
- Deregulated nutrient-sensing
- Chronic inflammation
- Stem cell exhaustion
- Senescence
- Disabled autophagy
- Genomic instability

**Hallmarks of failing health**
- Spatial compartmentalization
- Integrity of barriers
- Containment of perturbations
- Maintenance of homeostasis
- Recycling and turnover
- Integration of circulations
- Rhythmic oscillations
- Responses to stress
- Homeostatic resilience
- Hormetic regulation
- Repair and regeneration

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