UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

Development of senolytics of natural origin for anti-aging therapy

2)Abstract (max 500 words)

In most high-income countries the age of the population is constantly increasing. The lifespan expansion is associated with an increased occurrence of many age-related disorders, such as cardiovascular diseases, cancer, metabolic diseases, neurodegenerative diseases, which represent the leading causes of death worldwide. This results in a reduced quality of life for elderly people, which translates into increased healthcare costs, thus representing both a societal and economic burden. For these reasons, current research in the field of aging is aiming at increasing health-span (the number of years a person is in good health), rather than lifespan.

It is now widely accepted that **treating aging as a whole**, rather than single pathologies, may represent a more affordable strategy to tackle age-related disorders and increase the elderly population's health-span. For this reason, there is increasing interest in the discovery of safe and effective anti-aging drugs.

Organismal aging is a very complex process, influenced by many factors, both genetic and environmental. One of the biological causes of aging is the accumulation of **senescent cells**. Senescent cells are unable to proliferate but maintain their capacity to produce and secrete different kinds of molecule, collectively called SASP (Senescence-Associated Secretory Phenotype). While the organism ages, senescent cells accumulate in tissues and, through the SASP, can promote tissue damage, playing a causative role in the aging process. It has been demonstrated that the selective removal of senescent cells can increase the lifespan as well as ameliorate the health conditions of aged animal models. For this reason, the **development of senolytic molecules**, able to selectively eliminate senescent cells, represents a promising strategy for the treatment of aging. However, currently available senolytics are characterized by a general toxicity.

The principal goal of this project is to identify natural sources of safe and effective anti-aging compounds, targeting cellular senescence.

The project will consist of **three phases**:

1. Development of a high-throughput screening platform for the identification of senolytic compounds:
Research and acquisition of screening libraries, focusing in particular on natural products.
Generation of a suitable cellular model to identify senescence-targeting molecules.
High-throughput screening in collaboration with the high-throughput screening facility of the Department of Biology (University of Padova). We have already performed several high-throughput screenings for the identification of molecules active in cancer and aging.
2. *In vitro* validation and selection of promising hits: Validation of the identified hits on a panel of cell lines.
Identification of molecules suitable for pharmaceutical development.

3. Experimentation on *in vivo* models of aging: Selected molecules will be tested on mouse models. In our laboratory we have experience working with the p16-luciferase mouse model, a transgenic mouse expressing a senescence reporter gene, as well as with naturally aged mice. Both models can give important information on the efficacy of the tested molecules, as well as on the pathology(ies) that are more likely to benefit from our therapeutic intervention.