TITLE: Computational and experimental modulation of senescent cells through RNA processing machinery

Summary: Aging is a major risk factor for several chronic age-related diseases, and accumulation of senescent cells is a hallmark of aging in mammals. Eliminating senescent cells has been shown to prolong health and lifespan.
The 5S ribonucleoprotein particle (RNP) complex, consisting of RPL11, RPL5, and 5S rRNA, contributes to p53 activation and promotes cellular senescence following oncogenic or replicative stress. This (senescence) is achieved by the incorporation of MDM2 into the 5S RNP complex, whereas MDM2 binds and degrades p53 under normal conditions.
Using molecular dynamics simulations, we will study the 5S-RNP complex with the bound MDM2 protein (pdb id: 4XXB and 7F5S) to obtain the necessary information about the systems dynamics that will subsequently be used to develop inhibitors of protein-protein interaction that will be experimentally validated for its impact on the time of onset of replicative senescence in IMR90 cells. These inhibitors would provide a novel tool against cellular senescence.

Research techniques used: In the proposed project we will employ in silico techniques of molecular simulations and drug design approaches complemented by artificial intelligence (AI), together with experimental cell assays: molecular dynamics simulations, AI accelerated sampling techniques, variational approach for Markov processes with implemented neural network architecture, in silico drug design (molecular docking, pharmacophore modelling), cell assay (to study a time delay in occurrence of replicative senescence upon treatment with designed inhibitor) and evaluation of senomorphic properties.

The reason why the topic is innovative: Since aging is considered a causative factor in the development of age-related diseases, it could serve as a target for their simultaneous treatment. Senescent cells a proposed target for such an intervention with potentially far-reaching benefits. This project will use both computational and experimental techniques to gain the necessary knowledge of cellular senescence and provide the basis for developing potential new therapeutic interventions. The implementation of AI techniques in simulation protocols will enable a smooth transition into the new area of development of MD simulations.

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The Scientists4Future Slovenia has received funding from Ministry of Higher Education, Science and Innovation. The project is co-executed by University of Ljubljana.

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