The process of aging is becoming more and more important due to prolongation of lifespan in modern societies. The mechanisms of aging are still a biological mystery, despite intensitication and sophistication of research. Aging of the organism depends on changes occurring in its various elements, both in dividing cells and in postmitotic cells, which cannot divide. Aging of dividing cells in vitro is an useful model allowing to understand changes, which ocur in the populations of these cells in the body.
From among numerous hypotheses concerming molecular mechanisms of aging, the free radical hypothesis is especially polular. It ascribes aging to accumulation of products of damage of constituents of cells and organisms by free radicals, more generally reactive oxygen species. A more general hypothesis links aging to all side reactions of metabolism, including also reactions of reactive nitrogen and chlorine species (in particular nitration of protein tyrosyl residues involed by peroxynitrite), non-enzymatic reactions of reducing sugars and reactive aldehydes with proteins (glycation) and reactions of products of lipid peroxidation with proteins (lipoxidation).
We propose that non-enzymatic protein modifications resulting from such reactions contribute significantly to aging and that inhibition of these reactions should slow down aging. We aim at testing this hypothesis at at the cellular level using three models of in vitro aging of human fibroblasts: replicative aging (expressed as limitation of the number of divisions the cells are able to accomplish), postreplciative agng (decrease in the survival of cells under conditions preventing cell divisions) and oxidative-stress induced premature aging (loss of cell survival due to exposure to an agent inducing oxidative stress).
Our previous studies have identified a series of compounds effficiently inhiiting non-enzymatic protein modifications, mainly glycation and nitration. This group of compounds includes polyphenols (especially flavonoids), stable free nitroxide radicals (nitroxides) and newly synthesizeds iron chelators, belonging to quinoline thiosemicarbazones.We aim to test the efficiency of preventing non-enzymatic protein modifications at the cellular level by these compounds and examine if inhibition of non-enzymatic protein modifications (and of which of them) delays cellular senescence.
These studies should results in identification of compounds most effective in preventing non-enzymatic protein modifications in the cells and inhibiting the process of cellular aging. Analysis of results will allow for synthesis of new compound of optimal properties, which can be applied in the future in in vivo studies for delaying aging at the organismal level and attenuation of the development of age-related diseases in which non-enzymatic protein modifications play a crucial role.