ABSTRACT Lucia LATELLA

Aging and senescence: from DNA damage to muscle regeneration
We are interested in studying the relationship between replicative senescence, aging and the ability to achieve the myogenic program in adult stem muscle cells (satellite cells). These studies, in collaboration with Dr. Pier Lorenzo Puri at the Sanford Burnham Medical Prebys Discovery Institute (La Jolla, CA), provide the first evidence of a functional antagonism between senescence and muscle differentiation, mediated by the DNA damage signal (Latella 2017).
Complementarily, we get interested to a premature aging syndrome HGPS leading to the identification of SERPINE1 as a molecule directly involved in the disease. SERPINE1 levels increase in HGPS patients and elevated SERPINE1 levels are shown to be associated with thrombosis and atherosclerosis. In our studies, we used the SERPINE1 inhibitor TM5441 that has been proved useful in reducing the pathogenic aspects associated with the disease such as the accumulation of DNA damage, nuclear malformation and Progerin accumulation, suggesting the use of SERPINE1 inhibitor TM5441 in the treatment of HGPS to counteract fibrosis and senescence.
Recently, we deciphered the essential contribution of autophagy in regulating the function of satellite cells to promote efficient muscle regeneration in normal and pathological diseases, such as Duchenne Muscular Dystrophy (DMD) demonstrating that autophagy is active during the compensatory regeneration phases, but is inhibited in the late phases, where the fibrotic tissue is deposited in the muscle and is the cause of functional alteration (Fiacco et al., 2016).
The productive collaboration with Dr. Sacco at the Sanford Burnham Medical Prebys Discovery Institute (La Jolla, CA) on the study of the transcriptional factor STAT3 and its role during muscle regeneration leads to the identification of the key role of STAT3 in regulating the expansion and differentiation of satellite cells, extending its use as a therapeutic target to counteract muscle loss (Tierney et al., 2014). This led me to investigate on the role of autophagy in mediating STAT3 pro-regenerative function and to explore on interventions aimed at activating autophagy that could be useful in the treatment of DMD to promote muscle regeneration and delay the progression of the disease.