Improving the quality of life in progeria: a first trial in the murine Lmna\textsuperscript{G609G/G609G} model using tocilizumab and different drug combinations

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Most studies on HGPS are aimed at understanding the causes of the disease and identify a successful therapy. Since the discovery of LMNA gene involvement in progeria, our research group was engaged in those studies by focusing both on pathogenesis and possible therapeutic strategies (Mattioli et al 2018-2019; Gargiuli et al 2018; Loi et al 2016; Camozzi et al 2014; Richards et al 2011; Capanni et al 2010; Evangelisti et al 2016; Pellegrini et al 2015; Cenni 2011; Columbaro et al 2005).

Here, we plan to face a parallel aspect of the syndrome, which is critical for people affected by HGPS. The major problem addressed by this project is the quality of life of HGPS patients, which is compromised by symptoms related to a chronic inflammatory state. We will test strategies for reducing the chronic inflammation in the Lmna\textsuperscript{G609G/G609G} progeria mouse model, with the aim to transfer results to patients. An improved life quality represents an important goal for HGPS children. Besides the psychological impact, relieve of disabling symptoms helps patients to face pharmacological treatments, which may be meantime implemented and refined. As a result, pharmacological therapies in patients living in a better health state could attain better efficacy and extend lifespan.

The inflammatory cytokine interleukin 6 (IL6) is a major player in the inflammatory pathway involved in ageing processes. In progeria mouse models, levels of IL6 are significantly increased and inhibition of NF-kB-dependent IL6 pathway extends animal lifespan (Osorio et al 2012). Our preliminary data showed that IL6 secretion is also increased in HGPS fibroblasts. On the other hand, long-lived people (centenarians), who experience healthy ageing, show low levels of IL6 secretion (Storci et al 2019). Importantly, it has been demonstrated that IL6 neutralization blocks the bystander effect of IL6, which propagates DNA damage among cells and tissues and triggers an inflammatory state (Storci et al., 2019). Based on those data, we hypothesized that inhibiting IL6 activity might relieve the disabling symptoms of HGPS. Thus, we set up a study aimed at validating and optimizing the use of a neutralizing antibody (Tocilizumab) directed to the human interleukin 6 receptor (IL6r) and also efficient in mouse models. As increasing evidence shows that a combination of drugs or molecular approaches is synergistic in counteracting premature ageing phenotypes, we will also test tocilizumab in combination with lonafarnib, a farnesyl-transferase inhibitor currently used in HGPS clinical trials. Further, based on our previous studies showing reduction of progeroid features in HGPS cells subjected to rapamycin or ATRA+rapamycin, we will test those drugs in different combinations in the murine mouse model of HGPS.

Funded by:
Progeria Research Foundation (PRF), Boston, MA
EU E-RARE 2017 TREAT-HGPS project
Associazione Italiana Progeria Sammy Basso (AIPROSAB), Tezze sul Brenta, VI
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