

Innovative strategy using mRNA-LNP for the treatment of hematologic disorders

Chantal Lagresle-Peyrou
Biotherapy Clinical Investigation Center, **Groupe Hospitalier Universitaire Ouest-APHP, Université Paris Cité**, Imagine Institute, INSERM UMR 1163, Paris, France

Background: Different missense mutations in the Ras-related C3 botulinum toxin substrate 2 (RAC2) protein have been reported in immune disorders. The constitutive autosomal dominant RAC2 p.G12R form is associated with a life-threatening severe combined immunodeficiency (SCID) characterized by a profound leukopenia and bone-marrow hypoplasia. By multi-omics studies and live cell imaging we observed that RAC2 G12R variant disrupts nucleotide metabolism, prevent cell proliferation and led to a rapid and massive cell death through a necroptosis-like signaling pathway. Taking as a whole, our data suggest that RAC2 signaling pathway is required to maintain cell homeostasis and survival. In this context, we considered that G12R variant expression represents an innovative strategy to treat several hematologic disorders.
Methods: Different LNP formulations containing a GFP reporter gene were delivered into AML cell lines and primary hematopoietic cells. Several doses were tested to evaluate the efficacy and toxicity of the LNPs.
Results: Depending on the nature of the cells, we observed differences between the formulations. Further experiments with a time course kinetic are underway to confirm these preliminary data and select the best LNP formulation.
Conclusion: The next challenge will be to generate antibody-decorated LNP able to deliver the G12R mRNA specifically into AML or hematopoietic cells in order to induce cell death with limited off-target effect. The major innovation of this mRNA-based therapeutic strategy is to transform the deleterious effect of a mutation causing SCID into a new lethal therapeutic weapon that could be included in therapeutic strategies to treat several hematologic disorders.