Targeting RNA conformational ensemble of *LMNA* gene via Small Molecules against Hutchinson-Gilford Progeria Syndrome

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Hutchinson-Gilford progeria syndrome (HGPS) is a very rare, sporadic, autosomal dominant disorder resulting in early death. HGPS is caused by a point mutation in exon-11 of the *LMNA* [1]. This mutation promotes recognition of a cryptic alternative splicing site in exon-11 and reduces the recognition of the authentic splicing site resulting in the production of progerin, a truncated toxic protein leading to an aberrant nuclear morphology, genetic instability, and premature senescence [2, 3]. Progerin accumulates in the cell nuclei of HGPS patients and its accumulation is the biomarker of the disease. Symptomatic treatments of HGPS are available but no disease modifying treatment is existing [2, 4].
In this work, to address the unmet medical need of HGPS, we aim at understanding the relationship between the conformational plasticity of pre-mRNA structure of exon-11 carrying the mutation around its cryptic splice site and the splicing behavior to validate this structural element as a target for small molecules that would abolish the production of progerin.
Different point mutations in exon-11 of *LMNA* gene and 2-Aminopurine tagged RNA hairpins have been designed to assess hairpin conformational plasticity. Various small molecules have been filtered and experimentally tested to appraise their binding and splicing efficiency to *LMNA* mRNA. Two different binding assays were utilized to determine small molecules as suitable hits. Hits were tested according to their RNA-binding ability and their splicing modifying characteristics in patient-derived cells. Results give first insights into the relationship between hairpin conformational plasticity and splicing modulation and suggest ideas for the development of small molecules reducing progerin pre-mRNA, which may open new avenue for other splicing-linked diseases after the first successful example of modifying TSL2 conformation to modulate the splicing of *SMN2* in SMA [5].

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