RNA Horizons 2024
Therapeutics Symposium
Unlocking the RNA's Potential in Medicine
September 25-27, 2024
Alfandega Congress Centre, Porto, Portugal

Evaluating LNP- Encapsulated Decoy Oligonucleotides for the Treatment of Spliceosomal Mutant Myeloid Blood Cancers

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Therapeutic targeting of spliceosome mutations holds great promise due to the high frequency of these mutations in advanced myeloid malignancies, and the lack of effective therapies for the majority of patients. Spliceosomal gene mutations have been identified in ~60% of cases of myelodysplastic syndromes (MDS) and CMML (the common subtype of MDS/MPN-overlap) and ~10% of cases of acute myeloid leukemia (AML) and myeloproliferative neoplasms (MPN). The most prevalent class of genetic alterations in individuals with myeloid neoplasms involves mutations in spliceosomal proteins SF3B1, SRSF2, U2AF1, and ZRSR2. These mutations are almost always heterozygous, mutually exclusive, missense mutations at highly specific residues. We have developed a novel technology to specifically downregulate splicing factor activity by using Decoy Oligonucleotides (decoys) (Denichenko,et al., *Nat Commun,* 2019). We have applied this technology to develop specific inhibitors for the wild type and mutant forms of U2AF1 and SRSF2, which are the most common mutated splicing factors in myeloid neoplasms. We show that the decoys specifically bind the mutated and non-mutated forms of U2AF1 and SRSF2 and inhibit their splicing activity, in addition to affecting the cancerous properties of the cells. To overcome the challenge of efficient delivery to cancer cells *in vivo*, we have developed a lipid nanoparticle-based delivery platform for AML cells. These lipid nanoparticles efficiently deliver the decoy oligonucleotides specifically into myeloid blood cancer cells, with minimal to no uptake by normal white blood cells. This generated lipid nanoparticle platform can be universally used to deliver RNA- based therapeutics into cancer cells, while preventing unwanted non-specific effects on normal blood cells.