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Antisense oligonucleotides, an innovative RNA therapeutic for lung adenocarcinomas

Martina Guerrero, Anna Ribó, Ana Silvina Nacht, Juan Valcarcel

Centre for Genomic Regulation, Barcelona, Spain

Background: Lung adenocarcinoma (LUAD) is the most common form of lung cancer, which is the leading cause of cancer death worldwide. Activation of the Notch pathway plays a key role in LUAD formation and two alternatively spliced isoforms of the Notch regulator NUMB display antagonistic activities on LUAD cell proliferation. Inclusion of exon 9 produces an isoform that promotes, while skipping of exon 9 inhibits, cancer cell growth. Our analysis of cancer transcriptome databases shows that NUMB exon 9 inclusion is significantly increased in most LUAD samples.

Methods: We explored the possibility of modulating NUMB exon 9 inclusion by scanning through the exon and flanking intronic sequences with 2'-O-methyl phosphorothioate antisense oligonucleotides (AONs).

Results: This resulted in changes in ratios between alternative spliced isoforms, and increasing exon skipping tightly correlated with reduced proliferation of a variety of cancer cell lines, including LUAD and other lung cancers. 2 AONs directed against distinct exonic regions efficiently induced NUMB exon 9 skipping. The effects of these AONs have been tested in vivo in four different mouse models of LUAD: 1) a genetic engineered model, 2) a lung orthotopic xenograft model, and 3) two lung orthotopic human patient-derived xenograft (PDX) models.

Conclusion: Reduced tumor growth upon intranasal administration of these AONs were observed along with corresponding changes in NUMB exon 9 inclusion, as well as increased survival in PDX models. No toxicity effects were observed. A variety of AON chemistries, formulations and administration routes are being tested to improve delivery, efficacy and pharmacokinetics. Our results indicate that splicing-modifying AONs targeting NUMB exon 9 can limit tumor growth and provide a potential therapeutic approach for the treatment of lung cancer.