

Biodistribution, safety and efficacy assessment of small RNAs with the new RNAscope™ Plus small RNA-RNA co-detection Assay

Advances in drug development utilizing antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are currently amongst the most promising RNAi therapeutics. The regulatory mechanisms of microRNA (miRNAs) and other small RNAs such as antisense oligos (ASOs) and small interfering RNAs (siRNA) have been exploited to develop oligonucleotide therapies for undruggable protein targets that achieve longer-term effects with lower drug development costs. The ability to visualize the oligonucleotide therapeutics and their targets in intact tissues is crucial to evaluate their safety and efficacy. Since these therapeutics can target a variety of RNA molecules (premRNA, mRNA, long non-coding RNA, miRNA), they offer promising treatment strategies for a broad range of diseases including neurodegenerative diseases, cancer, and rare diseases.

Detection of small RNAs require a highly specific and sensitive assay with quantifiable signal. The new RNAscope™ Plus small RNA-RNA Fluorescent Assay leverages the RNAscope patented core technology that enables signal amplification and background suppression for multiplex visualization of small RNA expression with RNAs in formalin-fixed paraffin-embedded (FFPE) and fresh frozen samples. This assay utilizes Tyramide Signal Amplification (TSA)-based fluorescent readouts and is compatible with the new fluorescent Vivid™ dyes. The RNAscope Plus assay can simultaneously visualize one smRNA target (miRNAs, siRNAs, ASOs) along with three RNA targets and can be automated on the Leica BOND RX autostainer.

RNAscope Plus smRNA-RNA Reagent Kits		
Component	Part number (ACD, Bio-Techne)	Assay Compatibility
RNAscope™ Plus smRNA-RNA HD Reagents Kit	322785	For Manual workflow
RNAscope™ Plus smRNA-RNA LS Reagents Kit	322786	For Leica BOND RX workflow

Key Features

- Visualize ASOs , siRNAs, miRNAs and other small RNA sequences (17-50nt).
- Assess ASO and siRNA delivery, biodistribution, cellular uptake, and persistence over time.
- Examine target gene expression, cell-specific marker, gene expression and evaluate therapeutic efficacy with morphological context.
- Screen for potential toxicity and off-target effects.
- Multiplex with TSA Vivid dyes for increased boost in signal intensity for small RNA targets.



The RNAscope™ Plus small RNA-RNA Fluorescent Assay demonstrates effective suppression of the target gene using a single siRNA therapeutic in FFPE mouse liver tissue.

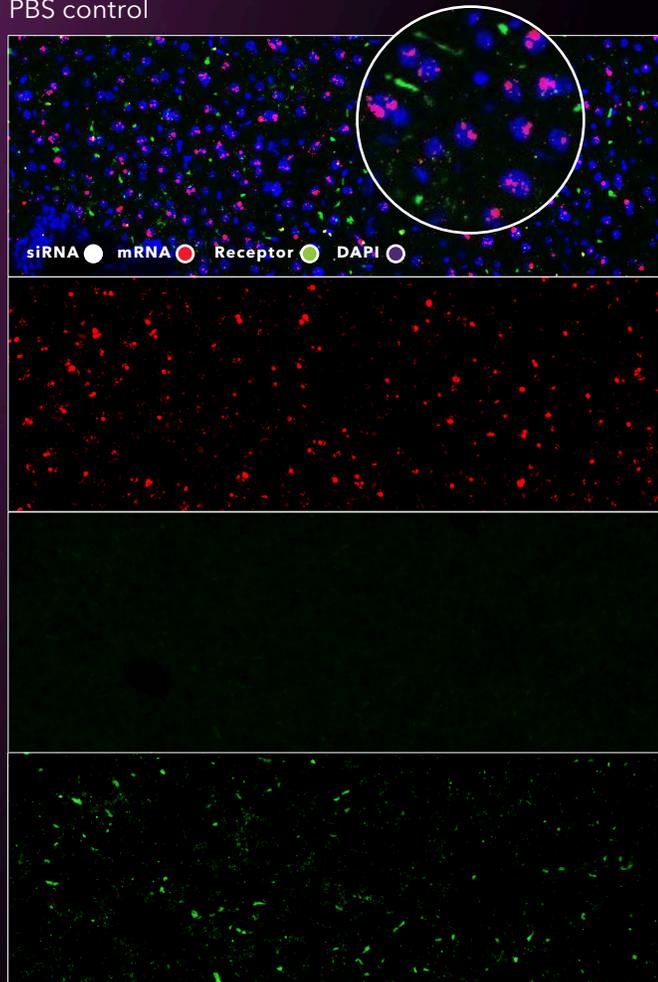
siRNA therapeutics act by silencing specific gene targets. This example from a group at a leading biopharma company demonstrates detection of a single siRNA therapeutic and its cell-specific knockdown of target mRNA using the RNAscope Plus assay. With the multiplexing capability of the RNAscope plus smRNA-RNA assay, researchers were able to simultaneously study the biodistribution of their therapeutic siRNA and detect the target mRNA along with the cell-specific marker, indicating successful delivery and robust knockdown of the target gene by the therapeutic.

Summary

In summary, RNAscope Plus smRNA-RNA assay will enable researchers to visualize regulatory RNA simultaneously with target RNAs, cell-type and morphology markers in intact cells/tissues with single cell resolution. Furthermore, its multiplexing capability allows conservation of precious samples while providing meaningful insights into disease pathology and drive advances in oligonucleotide-based drug development.

Mouse liver tissue

PBS control



Mouse liver tissue

Treated (10mg/kg)

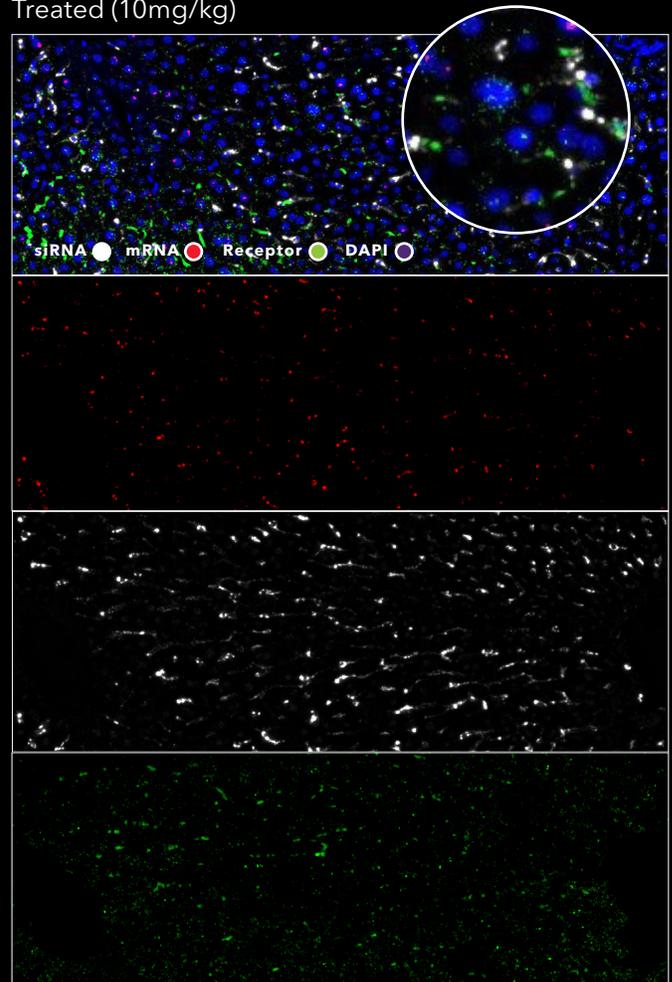


FIGURE 1. siRNA mediated gene regulation of mRNA target in mouse liver tissue using the manual RNAscope Plus assay. Seventy-two hours after dosing animals with the therapeutic siRNA, the efficacy of the siRNA mediated knockdown was evaluated in 5 um FFPE mouse liver tissue using the manual RNAscope Plus assay. The data demonstrates robust knockdown of the target mRNA in response to the siRNA therapy in the treated group as compared to the PBS control group.

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