Feasibility, distribution, and efficacy of an inhaled oligonucleotide mimic of miR-29 for pulmonary fibrosis induced by bleomycin in rats

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Abstract
miRNA-29 targets multiple profibrotic molecules and is down-regulated during fibrosis, including TGF-β. Previously, we showed a synthetic, chemically stabilized oligonucleotide mimic of miR-29b could repress collagen expression and abrogate pulmonary fibrosis in the bleomycin mouse model when administered i.V. Preliminary studies using a Scireq inExpose inhalation system yielded positive results with miR-29 mimic-treated mice. Here, we sought to determine the feasibility of nebulizing miR-29 mimic (MRG-201) and to assess the distribution properties via nose-only inhalation in rats using a more sophisticated system. miR-29 mimic aerosols were generated with an Aeroneb Solo nebulizer, analyzed by HPLC for compound integrity, and connected to a nose-only rat inhalation system. Rats were challenged with bleomycin at day 0 and received a single dose of miR-29 mimic at target doses of 0.5 or 5 mg/kg by nose-only inhalation and were sacrificed 6, 24, or 48 hours later for analysis. Using a dual probe hybridization assay, distribution to the lung was robust and dose-dependent, with significant clearance at 48 hours. Minimal compound was detected in the kidney (4.9 pmol/g) and plasma (46 pmol/mL) at 6 hours in the 5 mg/kg group only, with no detection observed in heart, liver, or spleen. We then looked at target regulation following multiple administrations at two different doses. Daily administration of 1.0 mg/kg demonstrated significantly better target regulation than 0.1 mg/kg. These data demonstrate the feasibility of nebulizing and delivering a mimic of miR-29 by nose-only inhalation, with robust and restricted delivery to the lung.

miR-29 Family: Antifibrotic miRNAs

miR-29 mimics can be nebulized and administered via nose-only inhalation to mice and rats similarly. Daily treatment of miR-29 mimics regulated gene expression in lung, spleen, and plasma of mice and rats. miR-29 mimics are dose-dependently regulated by inhaled miR-29 mimics following bleomycin treatment. Stress markers are increased with bleomycin at day 7 (A). miR-29 mimics and pirfenidone reduce expression of stress markers (B).