Molecular MR Imaging of Pulmonary Fibrosis in a Mouse Model

Peter Caravan[1], Yan Yang[1], Roshini Zachariah[2], David Sosnovik[1], Guangping Dai[1], Bryan Fuchs[2], and Michael Lanuti[2]
[1]*A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, United States,* [2]*Surgery, Massachusetts General Hospital, Boston, MA, United States*

Target audience: Molecular imagers, lung imagers, fibrosis researchers.

Purpose: Idiopathic pulmonary fibrosis is a chronic, progressive fibrosing interstitial pneumonia of unknown cause that primarily affects older adults resulting in dyspnea and functional decline until death. High-resolution CT scanning has proven invaluable in the diagnosis of the disease,[1] but up to 50% of patients do not have clear radiologic hallmarks of fibrosis, and CT has shown limited utility in tracking disease progression. New antifibrotic therapies are being developed, but there are currently no effective noninvasive tools to monitor response to treatment. Over-expression of collagen is a hallmark of fibrosis. We hypothesized that combining ultrashort TE imaging of the lung with a molecular gadolinium-based probe targeted to type I collagen could provide a non-invasive method for assessment of pulmonary fibrosis.

Methods: Collagen-binding probe EP3533 and its non-binding isomer EP3612 were synthesized as reported.[2] To induce pulmonary fibrosis bleomycin sulfate (0.05U) in saline was delivered intratracheally to the lungs of C57BL6 mice. Control sham mice received vehicle. Four groups of mice (n=5) were imaged: fibrotic+EP3533, sham+EP3533, fibrotic+EP3612, sham+EP3612. Mice were imaged at 4.7T under isoflurane anaesthesia with respiratory gating. A 3D ultrashort TE (TE=20 μs) sequence with respiratory gating was used to image the lungs prior to and post injection of probe (10 μmol/kg of either EP3533 or EP3612). A 3D FLASH sequence was used immediately post probe injection to obtain an angiogram that was used to segment the heart and large vessels from the lung. The increase in signal:noise (SNR) following probe administration was measured in 5 ROIs in both lungs and also in the shoulder muscle. Lung tissue was analyzed for hydroxyproline (collagen) and Gd content, and also stained with H&E and for fibrosis (Sirius Red).

Results: Bleomycin mice had 35% higher lung collagen than sham mice ($p<0.0001$). Sirius red staining showed 2.3-fold higher positive staining by area in bleomycin mice compared to sham ($p<0.001$) confirming fibrosis in this model. The SNR increase in the lungs of fibrotic mice following EP3533 administration was twice as high as in sham animals and twice as high as the SNR increase following EP3612 administration in either fibrotic or sham mice, $p<0.0001$, Figure. The post-probe signal enhancement in muscle was similar for all cohorts. Ex vivo analysis showed higher Gd levels in lungs of fibrotic mice post EP3533 compared with lungs of sham mice or in mice that received control probe EP3612 ($p<0.05$). Gd levels in muscle were similar in all 4 cohorts.

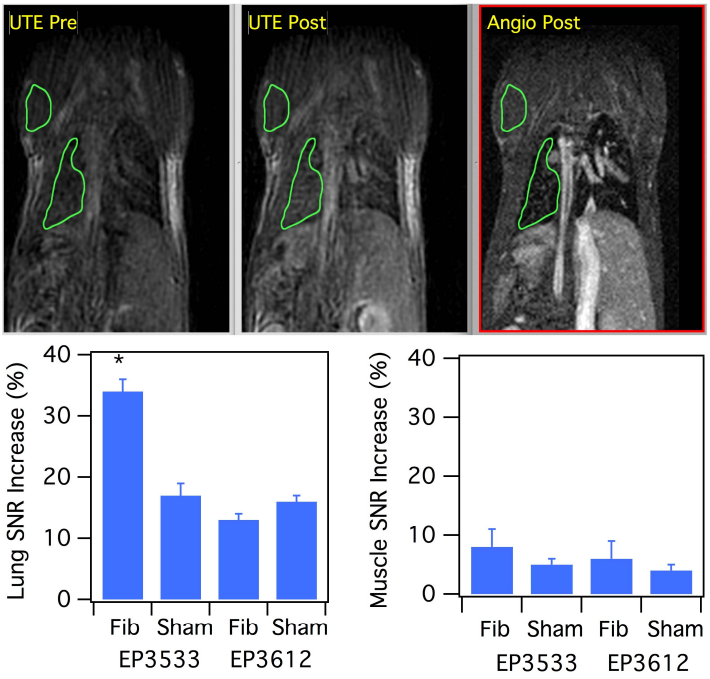

Figure. Top left: coronal UTE image before EP3533 injection, lung and muscle ROIs shown in green; top middle: UTE image post EP3533; top right: MR angiogram immediately post EP3533. Bottom left: lung SNR increase shows that EP3533 enhanced MR detects pulmonary fibrosis (2X higher SNR in fibrotic vs sham mice) by non-targeted probe EP3612 does not. Bottom right: muscle enhancement is similar in fibrotic and control mice with both probes.

Conclusion: Collagen-targeted probe EP3533 enhanced MRI specifically detects pulmonary fibrosis in a mouse model of disease.

References: (1) Hunninghake et al. *Am J Respir Crit Care Med*. 2001;164:193-196. (2) Caravan et al. *Angew Chem Int Ed Engl*. 2007;46:8171-8173.