$^{19}F/^{1}H$ MR Molecular Imaging Following Anti-angiogenic Therapy in a Translatable Preclinical Asthma Model

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An estimated 235 million people worldwide suffer from asthma[1]. For patients with severe debilitating, systemic steroid dependent disease, current diagnosis and treatment approaches are not adequate. A prominent feature of the chronic asthmatic airway is expanded and aberrant bronchial vascularity, which might explain persistent airway wall edema, airway restriction and sustained leukocyte recruitment. A progressive approach to asthma therapy may be to target bronchial angiogenesis in an attempt to improve lung hemodynamics and respiratory function. However, examining this hypothesis presents a challenge because early neovascular expansion in the lungs in preclinical models and patients is very difficult to assess noninvasively, particularly quantitatively.

We have recently used high resolution, dual $^{19}F/^{1}H$ MR molecular imaging (3T) for quantifying the spatiotemporal distribution of angiogenesis in a clinically relevant rat asthma model[2]. In Brown Norway (BN) rats, which have a bronchial vasculature similar to humans, repeated allergen challenge recapitulates the airway remodeling and increased airway vascularity seen in asthma patients[3] (**Fig. 1).** As soon as 1 week after allergen challenge, $^{19}F/^{1}H$ MR imaging with αvβ3-targeted perfluorocarbon (PFC) nanoparticles (NPs) revealed an increase in ^{19}F signal in rat lungs, reflective of neovascular expansion. Other standard pathological and clinical measures of asthmatic changes were not detectable until 2-3 weeks. Based on these results, we hypothesized that $^{19}F/^{1}H$ MR molecular imaging offers a state-of-the-art translatable method to noninvasively quantify the early effect of a targeted antiangiogenic therapy on pulmonary neovascularization in asthma.

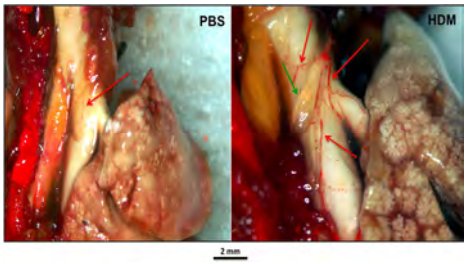

Fig. 1 Airway (white) and vascular casts (red) showing vascular expansion in an HDM rat (3 weeks) compared with a PBS control rat.

PFC NPs were prepared as previously described[2]. A peptidomimetic αvβ3-integrin antagonist was incorporated into the lipid monolayer for targeting angiogenesis. Nominal particle size measured by dynamic light scattering was ~200 nm. αvβ3-targeted anti-angiogenic micelles[4] (~15nm) were formulated with novel phospholipid prodrugs (PD) of either fumagillin[5] or docetaxel[6]. Anesthetized BN rats were administered house dust mites (HDM; 100μg/ challenge) twice weekly by intra-nasal aspiration. Anti-angiogenic PD micelles, or control no-drug micelles, were administered 24 hours after each HDM challenge. At 10 days after the start of HDM treatment, rats (n=5-6/group) were administered αvβ3-targeted PFOB NPs (1.0 ml i.v./kg). After 2 hours, rats were imaged at 3T (Philips Achieva) using an in-house, custom dual-tuned solenoid transmit-receive coil. Simultaneous 3D $^{19}F/^{1}H$ imaging was used employing a novel steady state ultrashort echo time (UTE) technique (TE/TR=0.1ms/1.96ms) with the frequencies set to the resonance of ^{1}H and the CF_2 groups of the PFOB (CF_3-$(CF_2)_6$-CF_2Br) spectrum, representing 12 of 17 total ^{19}F nuclei[7]. Using a highly oversampled 3D radial readout scheme, the reconstructed image datasets have a nominal resolution of ~1.25mm^3, and ultimately, a Nyquist value of 0.20 was chosen for all image reconstructions. Typical total scan time was 28min.

As previously observed, in HDM challenged rats, fluorine signal from αvβ3-targeted PFOB NPs was distributed throughout the superior lung, near the bronchi (**Fig. 2A**). Remarkably, after just two doses of anti-angiogenic drug, the ^{19}F angiogenesis signal at 10 days was significantly decreased in fumagillin-PD treated rats (0.11±0.04 vs 0.33±0.14, average lung mean normalized to reference standard), and was also lower in docetaxel-PD treatment group (0.17±0.05) compared to control (**Fig. 2B,C**). The decrease in ^{19}F signal was consistent with histological results that showed less fluorescently labeled NP binding in lungs of prodrug treated animals. The impact of antiangiogenic treatment on airway reactivity is in progress.

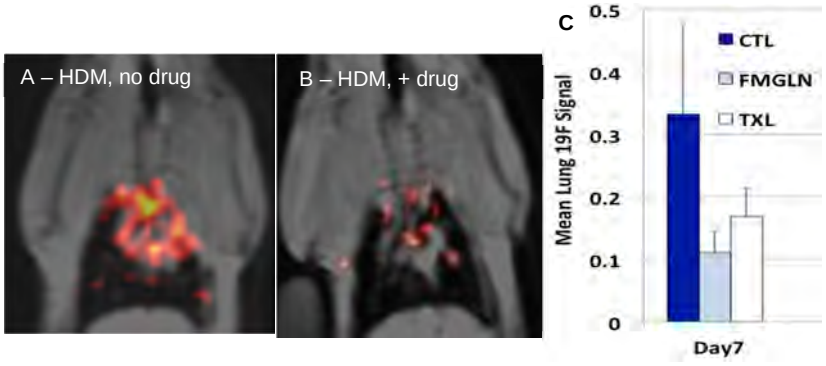

Fig. 2 αvβ3-targeted ^{19}F MR signal (yellow/red) overlaid on ^{1}H image. A – control, no drug. B – Fumagillin-PD treated. C - Mean ^{19}F MR lung signal in HDM rats treated with αvβ3-targeted fumagillin-PD, docetaxel-PD or no-drug

This is the first report of quantitative simultaneous $^{19}F/^{1}H$ MR molecular imaging at 3T for monitoring the effect of antiangiogenic therapy in the asthmatic lung. This is a clinically translatable approach for noninvasive evaluation and optimization of antiangiogenic therapy in chronic airway inflammation, aimed at improved pulmonary function. Early, more aggressive management may be possible in patients with moderate disease impacting quality of life. Also, by furthering our fundamental understanding of the timeline and pathophysiology of disease, this technique could also provide answers on the existing debate of the role of angiogenesis in asthma.

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