Combined off-resonance imaging and relaxation in the rotating frame for positive contrast imaging of infection in a murine burn model testing a novel anti-infective compound

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Introduction–We developed a novel molecular magnetic resonance (MR) imaging method to monitor accumulation of macrophages at the infection site in vivo. Positive-contrast molecular MR imaging provides an alternative to negative-contrast molecular MRI imaging, exploiting the chemical shift induced by ultra-small superparamagnetic iron-oxide (USPIO) nanoparticles to nearby water molecules. We introduced a novel combination of off-resonance (ORI) positive-contrast MRI and $T_2^*-$relaxation in the rotating frame (ORI-$T_2^*$) for positive-contrast MR imaging of USPIO [1,2]. We used this new method for testing a new anti-infective compound M50 following Pseudomonas aeruginosa infection.

Materials and Methods–Ultra-small super-paramagnetic iron oxide (USPIO) nanoparticles, known generically as Ferumoxtran-10 commercially and as Combidex® in the U.S. (Advanced Magnetics, Cambridge, MA) were used as the molecular imaging MRI contrast agent. Six weeks old CD-1 mice were anesthetized according and a leg thermal injury of 5% total burn surface area was produced on the right thigh muscle. Six hours post-burn and infection, 500 mg of Ferumoxtran-10 suspension was injected by intravenous injection.

The ORI-$T_2^*$ was estimated from fitting the image background to a Rician distribution. Error bars shown depict standard error of the mean image intensity in the ROI. The control group is statistically different from the animal model. We observed a significant difference between ORI-$T_2^*$ and O$T_2$, which leads us to suggest that ORI-$T_2^*$ is more sensitive in detecting USPIO signal. To this end, the ORI-$T_2^*$ positive contrast method may prove to be of higher utility in future research. We used this ORI-$T_2^*$ method to image the effects of our anti-infective compound M50 (Fig. 1A). Figure 1A shows negative-contrast images in pseudocolor, thresholded to signal greater than three in (dimensionless) $SNR$ units, and superimposed on anatomical reference images. The images were transformed to SNR images and thresholded in the same manner (units of image standard deviation) for comparisons. Figure 1B shows the signal detection in the controls which was significantly different from the signal detection in the M50-treated group.

Discussion–Our results show that compound M50 attenuates the signals coming from macrophages that accumulate at the infection site and thus support the compound’s anti-infective action. These results may have direct implications in the longitudinal monitoring of infection, and open perspectives for testing our novel anti-virulence compounds.

References