

**Title: *In Vivo* MR Lymphography in Mice at 11.7 T: Contrast Enhancement Imaging for Lymphatics and Phagocytes**

Lymphatic permeability and active-, passive-transport ability in a noninvasive manner is important to understand the dynamics of the immunity system. However, investigation of those lymphatic drainage patterns may be difficult due to the small size of the lymph nodes and vessels in healthy mice. We have tried to elucidate the permeability and antigen-transport ability of lymphatics with noninvasive methods, especially in mice often used in the immunological studies. High field MRI meets the requirements of noninvasive and repeatable investigation whereas we need to get more sufficient spatial resolution for visualize the lymphatic drainage patterns. The purpose of this study is to get sufficient spatio-temporal resolution for *in vivo* MR Lymphography in mice with appropriate contrast agents and specialized coils.

Several different sized superparamagnetic iron oxide (SPIO) particles as MRI probes were injected into the footpads of mice.  $T_2$ - and  $T_2^*$ -weighted MRI were obtained sequentially through 6 weeks. All MRI experiments were performed on an 11.7 T vertical Bruker MRI system. As the result, arrival time of particle into draining lymph node from the injection site strongly depended on particle size, and it may represent the different manner of particle transportation. Small particles, with a diameter 50 and 100 nm, possessed passive targeting effects that enabled the visualization of lymphatic structures via transport across lymphatic walls passively in large quantities. Further, micron-sized particles could potentially demonstrate the active transport of phagocytes with MRI in a noninvasive manner, without *ex-vivo* cell labeling. The distribution of iron particles and also phagocytes containing injected iron particles in the lymph nodes were confirmed by histology.

We further tried to visualize the lymphatic pathways using some contrast agents. Interstitial administration of  $MnCl_2$  can visualize the lymphatic vessels and the accompanying veins, although it was difficult to discriminate between them. When combined with an intravenous injection of SPIO, a subcutaneous administration of  $MnCl_2$  clearly differentiated lymphatic and blood stream with high resolution contrast-enhanced MRI.

In summary, the active-, passive-transport of iron oxide particles from the mice footpads to lymphatic system was observed in vivo using MRI at 11.7 T. Additionally, lymphatic vessels were visualized and discriminated from blood vessels with our method of high resolution contrast-enhanced MRI. MRI gives us the information about the permeability and transport ability of lymphatic vessels and also the migration of phagocytes noninvasively.