A MAGNETIC RESONANCE STUDY OF IRON AND COBALT BASED NANOPARTICLES AS POTENTIAL CONTRAST AGENTS FOR MOLECULAR IMAGING OF CANCER

Barbara Blasiak[1,6], Boguslaw Tomanek[1,6,7], Ulrike Trojahn[2,3], Abedelnasser Abulrob[8,9], Zhijun Zhang[4], Teodor Veres[4,5], Celine Desvaux[4], Umar Iqbal[9], Maureen O'Connor[2,3], Garnette Sutherland[1]

[1]Department of Clinical Neurosciences, University of Calgary, 3330 Hospital Drive NW, Calgary AB T2N 4N1, Canada, [2]Biotechnology Research Institute, National Research Council of Canada, Montreal, QC, Canada, [3]McGill University, Montreal, Canada, [4]Functional Nanomaterials Group, Industrial Materials Institute, National Research Council of Canada, Boucherville, QC, Canada, [5]INRS - Énergie et matériaux Institut national de recherche scientifique, Montreal, QC, Canada, [6]Institute of Nuclear Physics, Polish Academy of Sciences, Krakow, Poland, [7]Institute for Biodiagnostics (West), National Research Council Canada, Calgary, Alberta, Canada, [8]Institute of Biological Sciences, National Research Council Canada, Ottawa, Ontario, Canada, [9]Faculty of Medicine, University of Ottawa, Ottawa, Canada

barbara.blasiak@nrc.ca

Molecular magnetic resonance imaging (MMRI) is an emerging area of research. It integrates several recently developed nano-technologies such as nanostructure, nanosynthesis, molecular biology and molecular magnetic resonance. While standard human MR imaging (MRI) provides resolution of about 1 mm, MMRI allows detection of much smaller biological objects. This technique uses paramagnetic nanoparticles (NP) conjugated with biological probes that target specific cancer cells. Delivery of the NPs to the cancer cell enable much higher sensitivity of MRI thus much earlier and precise diagnosis than with the application of standard non-targeted contrast agents. Because the NPs must be delivered to the cancer cell, antibodies or other binding proteins are used as probes to deliver the contrast to the specific site.

Because MR images are sensitive to changes of the magnetic field, the development of non-toxic NPs with high paramagnetic moments is necessary. Such NPs disturb local magnetic field produced by magnets used in MRI. The field distortion reduces the T_2 relaxation time of surrounding water, making NPs detectable with T_2-weighted MRI technique.

The magnetic properties of the NPs can be measured with different techniques, for example low temperature first order reversal and zero-field cooled magnetization methods. However to measure their MRI efficacy a direct, MR-based, method is needed. Therefore we used 9.4T MRI system to measure directly MR parameter, called T_2 relaxation time.

We have studied the influence of the composition of the NPs, including the core and the shell on their magnetic efficiency thus suitability for contrast enhanced MRI. The NPs were tested with MRI first *ex-vivo* and then *in-vivo*. The experiments *ex-vivo* were carried out using 1% agarose to ensure homogenous distribution of the contrast agents across the imaged glass tube. For the study we selected iron oxide (Fe_3O_4) and iron cobalt (FeCo) core NPs with SiO_2 and Au shell, with the core sizes 5 to 15 nm and the shell of 1 to 40 nm. We found the correlation between the structure of the NP and T_2 of the surrounding water molecules. The larger the core the stronger influence on T_2 and the larger the shell the weaker influence on T_2 was observed in *ex-vivo* studies. Furthermore Au coating had a stronger influence on T_2 than SiO_2. We have also compared the T_2 measurements of the NPs with commercially available iron based NP, Feridex® (Bayer Health Care Pharmaceuticals).

The NPs to become targeted contrast agents used *in-vivo* must have high affinity to specific cells or processes. Therefore antibodies (Ab) or other binding proteins can be used to deliver the NPs to the specific site. To test molecular imaging agents for glioblastoma tumors, we have

selected a glioma specific antibody and conjugated them with the previously tested *ex-vivo* NPs (Fe_3O_4/SiO_2 and FeCo/Au). The NPs were synthesized with poly(ethylene glycol) (PEG) to conjugate the antibody to the NP.

In-vivo experiments with mouse model of glioblastoma were carried out using a 9.4T/21 cm MRI system. T_2-weighted images were collected before and after the injection of the contrast agent. The effects on contrast enhanced MR images depended on the composition of the used agents and corresponded to *ex-vivo* measurements of the T_2 relaxation times.

Based on *ex-vivo* and *in-vivo* experiments we concluded that both the core and the shell and sizes of NPs have to be considered in the design of contrast agents for MRI. The tested NPs provided comparable (for Fe_3O_4) or stronger (for FeCo/Au) influence on T_2 as commercially available contrast agents.

Our final goal is to apply these NPs for enhanced MR imaging of central nervous system neoplasm in human to improve diagnosis and follow-up of cancer patients.

This project was supported by a CIHR team grant in nanomedicine and regenerative medicine.

References:

[1] Pankhurst, Q.A., J. Connolly, S.K. Jones, and J. Dobson, *J. Phys. D: Appl. Phys.*, **36** (2003): 167-181.
[2] Grancharov, S.G., H. Zeng, S. Sun, S.X. Wang, S. O'Brien, C.B. Murray, J.R. Kirtley, and G.A. Held (2005), *J. Phys. Chem. B*,**109** (2005): 13030-13035.
[3] Huang, P.L., R.S. Liu, H.T. Chan, Y.Y. Do, P.L. Chien, T.S. Chan, C.Y. Huang, S.Y. Yang, and H.E. Horng, *J. Magn. Magn. Mater.*, **304** (2006): 415-17.
[4] Desvaux, C., C. Amiens, P. Fejes, P. Renaud, M. Respaud, P. Lecante, E. Snoeck, and B. Chaudret, *Nature*, **4** (2005): 750-753.
[5] Weissleder R, Elizondo G, Wittenberg J, Rabito C, Bengele HH, Josephson L. Radiology, **175** (1990): 489-493.