In vitro and *in vivo* study of iron oxide nanoparticles designed for theranostic targeting EGFR-overexpressing tumors

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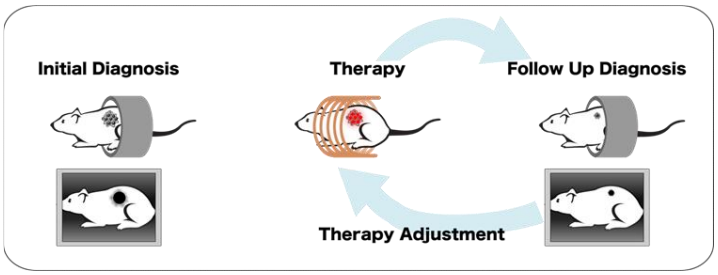
Aim of the study is to develop targeted multifunctional nanoplatforms designed for theranostic (diagnosis, therapy and follow-up diagnosis) in cancer context. MRI and magnetic hyperthermia are used to diagnosis and treat solid tumors respectively. This work is focused on the diagnostic part. Iron oxide nanoparticles (IONPs) are synthesized by thermal decomposition method and coated with dendrons (DNPs)[1]. A targeting ligand, peptide 22 (P22), is conjugated to DNPs. P22 binds specifically to EGFR overexpressing cancer cell such as triple negative breast tumors[2].



First the cytotoxic effect of DNPs was measured on tumoral cell lines. The amount of internalized nanoparticles with and without P22 have been measured by iron quantification in biological matrix methods[3]. In a second time, DNP's biodistribution have been observed on standard mouse strain with a 9.4T MRI machine; mice have been monitored for one month after nanoparticle injection. At last, EGFR-overexpressing cells have been inoculated into to mice. When the tumor size was sufficient, nanoparticles were intravenously injected to mice. The contrast effect of DNPs was evaluated using 9.4T T_2^*-weighted-imaging MRI. Tumors, liver and spleen were collected after sacrifice. Those tissue and organs were digested in hydrochloric acid, and the amount of iron was measured by ICP analysis.

Cytotoxicity tests prove that DNPs are weakly toxic below 150 μg_{iron}/mL after 24h exposure. The presence of P22 on DNPs surface increases the amount of nanoparticles internalized by cells. *In vivo,* no sign of toxicity has been seen during a one-month monitoring. Nanoparticles are mostly found in sinusoid organs (liver and femoral bone marrow) in which cells of the mononuclear phagocytic system should participate in the nanoparticle uptake process. After one month, the signal decrease is still observable in these organs. In the tumoral model, nanoparticle accumulation in tumors is noticeable 1 hour after iv. injection. After 24h, the darkening in the tumor region is stronger for DNPs conjugated with P22 than without. *Ex vivo* ICP analysis of organs also points in this direction; the iron amount in tumors is greater for DNPs+P22 than for DNPs alone.

In conclusion, DNPs are safe to use for *in vitro* and *in vivo* experiments at a controlled iron concentration (<150µg/mL). *In vivo* observations suggest a nanoparticle accumulation in liver but without toxicity signs or side effects on mice. Peptide 22 is of interest as its binding increases the cellular internalisation of DNPs and allows tumor contrast enhancement on T_2^*-weighted images.

References

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