A nanohybrid consisting of titanate nanotubes and docetaxel for the treatment of prostate cancer in preclinical developments

J. Boudon[1], C. Mirjolet[2], A. Loiseau[1], G. Créhange[2] and N. Millot[1]

[1]Laboratoire Interdisciplinaire Carnot de Bourgogne, UMR 6303 CNRS-Université Bourgogne Franche-Comté, BP 47870, 21078 Dijon cedex, France
[2] Centre Georges-François Leclerc, BP 77980, 21079 Dijon cedex, France

Contacts: julien.boudon@u-bourgogne.fr; nadine.millot@u-bourgogne.fr

Titanate Nanotubes (TiONts) with controlled parameters are obtained from a hydrothermal synthesis [1, 2]. TiONts are able to increase the ionizing effect of radiation therapy [3] and can also be used as novel transfection agents [4]. On the other hand, the clinically well-established docetaxel molecule is used for the treatment of breast, ovarian and prostate cancers. Systemic injections of the classical formulation lead to only 2-5% uptake by tumors; adverse side effects are a crucial problem and consequently limit injectable drug doses. Thus effective vectorization of anti-cancer drugs is required and nanomaterial-mediated strategies have been developed in recent years. In addition, prostate cancer is one the most frequently diagnosed cancer in men and as 50% of patients treated by brachytherapy undergo a local recurrence, they have to renew the treatment. In this context, docetaxel-based TiONts appear as versatile nanovectors.
This project is based on intraprostatic injection of the nanohybrids. A particular attention was paid to the elaboration of docetaxel-based TiONts nanohybrids in order to control the surface properties by chemical functionalization. Docetaxel molecules were grafted onto TiONts by an original pathway and suspension stability was increased by the addition of biocompatible polyethylene oxide polymers. In addition DOTA macrocycles are grafted to TiONts with a view to monitor their location after injection *in vivo* on mice by SPECT-CT. Exhaustive physico-chemical characterizations were realized to assert the good match of the custom-engineered nanohybrid properties (TGA-MS, XPS, UV-Vis spectroscopy, HR-TEM/EDS, FTIR, ζ-potential, ^{1}H-NMR). *In vitro* results on two cancer cell lines originating from human prostate tumors (PC3 and 22RV1) and results of *in vivo* SPECT-CT images will be presented as well as first irradiation tests on prostate tumors [2, 5].Biodistribution kinetics showed that more than 70% of nanohybrids were localized into the tumor 96 hours after injection. Mice receiving nanohybrid-RT (Radiation Therapy) exhibited a significant tumor growth delay to reach a volume of 1,000 mm^3 compared to mice receiving free DXL-RT [5].

References.

[1] A.-L. Papa, N. Millot, L. Saviot, R. Chassagnon, O. Heintz, *J. Phys. Chem. C*, 113, 12682 (2009)
[2] J. Boudon, A.-L. Papa, J. Paris, N. Millot, in *Nanomedicine*, One Central Press, Manchester UK, 2014, ISBN 978-1-910086-00-1
[3] C. Mirjolet, A.L. Papa, G. Créhange, O. Raguin, C. Seignez, C. Paul, G. Truc, P. Maingon, N. Millot, Radiother. Oncol., 108, 136 (2013)
[4] A.-L. Papa, L. Dumont, D. Vandroux, N. Millot, Nanotoxicology, 7, 1131 (2013)
[5] C. Mirjolet, J. Boudon, A. Loiseau, S. Chevrier, T. Gautier, R. Boidot, J. Paris, N. Millot, G. Créhange, Eur. J. Cancer 50 (6), 67 (2014)