Reversal of temporal and spatial heterogeneities in tumor perfusion identifies the tumor vascular tone as a tunable parameter to improve drug delivery. Philippe Martinive, Julie DeWever, Caroline Bouzin, *Christine Baudelet, Pierre Sonveaux, §Vincent Grégoire, *Bernard Gallez and Olivier Feron. Unit of Pharmacology and Therapeutics (FATH 5349), *Laboratory of Biomedical Magnetic Resonance; §Center for Molecular Imaging and Experimental Radiotherapy, University of Louvain (UCL) Medical School, B-1200 Brussels, Belgium. (***philippe.martinive@imre.ucl.ac.be***)

The maturation of the tumor vasculature implies the recruitment of pericytes covering and protecting the endothelial tubes from a variety of stresses including anti-angiogenic drugs. Mural cells also provide mature tumor blood vessels with the ability to either relax or contract in response to substances present in the tumor microenvironment. The observed cyclic alterations in tumor blood flow (TBF) and the associated deficit in chemotherapeutic drug delivery could arise from the influence of such vasomodulators.

To challenge this hypothesis, we focused our work on endothelin-1 (ET-1) which, besides its largely ubiquitous, autocrine effects on tumor cell growth, is a powerful vasoconstrictor. We first documented that an ET_A receptor antagonist could induce the relaxation of microdissected tumor arterioles, and selectively and quantitatively increase TBF in experimental tumor models. We then combined dye staining of functional (perfused) vessels, fluorescent microspheres-based mapping and dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) to identify TBF heterogeneities and examine the reversibility of such phenomenon. We found that administration of ET_A receptor antagonist could indeed acutely reduce the extent of underperfused tumor areas, thereby proving the key role of vessel tone variations in the TBF heterogeneities. Importantly, we also provided evidence that the ET_A antagonist administration could, despite an increase in tumor interstitial fluid pressure, improve the access of the contrast agent used in DCE-MRI and of conventional chemotherapy to the tumor compartment. We showed that the combinatory administration of cyclophosphamide with the ET_A antagonist led to a significant increase in tumor growth delay when using low doses of cyclophosphamide and even to the tumor control when higher doses were used (*vs* either treatment given separately).

In conclusion, we report here that tumor endogenous ET-1 production largely participates in the temporal and spatial variations in TBF and that ET_A antagonist administration may wipe out such heterogeneities, thereby eliciting an adjuvant strategy to improve the delivery of chemotherapeutic drugs to the tumor.