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| **Title** | Engineered smart nanovehicles for enhanced drug delivery across barriers |
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| **Curriculum** | Scienze Farmaceutiche |
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**Project description:**

Cancer is one of the major causes of death worldwide accounting for about 10 million deaths in 2020, or nearly one in six deaths (source: WHO Fact, February 2022) with breast, lung, colon, prostate, skin, and stomach accounting for about 10 milions new cases in 2020. However there is a lack of ultimate solution to this fatal disease. The majority of available chemotherapeutic treatments suffer from poor pharmacokinetic (PK) profiles, limited biodistribution in the tumor tissue and high off-target toxicity which often hampers the clinical development of new promising molecules raising the need for alternative strategies. Drug delivery approaches based on the use of nanosized vehicles encapsulating drugs represent a suitable strategy to reduce secondary effects and enhance targeted delivery to ultimately improve the therapeutic efficacy of drugs. Recently, the use of nucleic acid has been globally accepted for vaccination treatment during the COVID-2019 pandemic. However, despite their therapeutic potential for a variety of diseases, this class of biotherapeutic agents are not yet clinically used for cancer treatment neither for other deseases which is mostly attributed to the lack of molecular target consensus among different tumors and of efficient delivery. This opens mostly to the crucial *need of efficient delivery* to the target cells upon *biobarrier crossing* which is major requirement for rationally designed colloidal drug nanocarriers.

Two platforms will be investigated as drug nanovehicles to perform logic sequential actions:

1. Lipid based nanocarriers will be engineered for nucleic acid delivery. To this aim, lipidic vesicles will be rationally designed and their composition will be selected to comply the expected functions. Firstly, the combination of natural or synthetic lipids will be chosen to provide for suitable encapsulation and physico-chemical stabilization of the loaded therapeutic agents by looking at the physico-chemical features of the therapeutic molecules (amphiphilicity, charge, etc). Secondly, functional components will be included to ensure the crossing of biobarriers by the nanocarriers and, eventually, the programmed cargo released in the site of action. 2. Colloidal gold will be enginnered as remote activated delivery systems by combining on their surface targeting agents and releasable drugs or enhancers of particle activation by ultrasounds or photoirradiation. Indeed this nanosystem may open a new era of exploitation of dormant colloidal gold that in virtue of a localized activation can either minimize the toxic effects of anticancer drugs released from their surface and maximise their physical activation for site specific tumor apoptosys. Notably, great expectations are raised by externally activatable metal oxide nanoparticles such that those by Nanobiotix now in Phase 3 clinical trial.

The tailoring of the carrier composition and surface properties will be guided by the knowledge of the biobarrier features (composition, thickness, vascularization, layers, etc). The combination of the nanocarrier components will provide for concertated spatially and temporally controlled behaviour as a result of the activation of vehicle functions when in contact with targets (tissues, cells, subcellular organelles). The resulting vehicles operates as “nano-machines” for cancer therapy. Carriers engeering will will be based While lipoplexes are meant for nucleic acids delivery to restore cancer cell impaired functions (siRNA, miRNA), to present antigen for immunestimulation against cancer, to restore missing intracellular functions, to treat locally diseases such as inflammation, colloidal gold can be exploited for delivery of approved anticancer drugs whose activity can be improved upon activation with external physical stimuli in combination with enhancers of the immunogenic cell death.

The bottom-up formulation approaches of drug delivery systems affects their biopharmaceutical features; thus novel microfluidic assembly procedures will be exploited as anticipation of the scale up development.

The PhD student involved in this project will acquire state-of-the-art skills in advanced drug delivery, nano-

technology, development of self-assembling carriers, bioconjugation/polymer chemistry, in vitro and in vivo characterization of novel nanocarriers. The student will learn the most updated physico-chemical and biophysical techniques for colloid system characterization. He/she will be trained at the forefront of material science / pharmacy / nanotechnology / biomedicine. Notably, the tailoring of the interfacial features of these nanosystems must to be initiate by the background knowledge of the bio-barrier characteristics.

**Publications:**

1. Al-Amin MD, et al. (2023) Tailoring surface properties of liposomes for dexamethasone intraocular administration. *J Control Release* 354, 323-336
2. M. Barattin, et al. (2018) pH-controlled liposomes for enhanced cell penetration in tumor environment Appl. Mater. Interfaces 10, 17646–17661
3. Gallon E., et al (2015) Triblock copolymer nanovesicles for pH-responsive targeted delivery and controlled release of siRNA to cancer cells. *Biomacromolecules* 16: 1924–1937
4. Brazzale C., et al. (2016) Enhanced selective sonosensitizing efficacy of ultrasound-based anticancer treatment by targeted gold nanoparticles. *Nanomedicine (Lond.),* 11, 3053-3070
5. Daniele R., et al. (2023) Influence of folate targeted gold nanoparticles on subcellular localization and distribution into lysosomes. *Pharmaceutics,* 15, 864

**Hosting groups for the period abroad** (tentative list, may change):

Prof. Koen Raemdonck (Department of Pharmaceutics, University of Gent); Prof. Kevin Brackmans (Department of Pharmaceutics, University of Gent), Prof. Giovanna Lollo (Faculty of Pharmacy, University of Lyon), Prof. Olivia Merkel (Department Pharmazie, University of Munich).