2017 SCI-STAR project call for applications

Overcoming biological barriers in the post-nano era: unraveling multi-stage delivery vectors uptake by the liver.

Project proposal:

In the past decades much effort has been devoted to the development of selective, efficient, and targeted drugs for the treatment of a variety of diseases. However, despite undoubtable advancements, a major limitation to any type of systemic therapy is the presence of *biological barriers* that hinder the capability of drugs to reach the target (1, 2). Among others, the first and most dramatic barrier that systemically administered drugs encounter is the mononuclear phagocyte system (MPS) (3). The filtering effect on nanoparticles due to MPS is particularly relevant in the treatment of cancer. In fact, cancer's intrinsic heterogeneity and invasive nature make targeted or local therapy virtually impossible for the aggressive clinical cases (i.e. metastasis). Cells of the MPS are found in many different organs that exhibit high filtering capability (i.e. liver, lungs, and spleen). In particular, the liver is responsible for uptake of ~90-99% of nanoparticles (4). Thus, it becomes crucial to identify and describe the working principle of the liver as a biological barrier to transport and delivery of nano- and micro- particles. When nano- and micro- particles enter the blood circulation, the liver is one of the first organs that filters blood. Physiologically structured like a sponge, the liver mass is almost homogeneously filled with capillaries, called sinusoids (3). While the long-term uptake is mostly addressed to the phagocytic activity of resident liver macrophages (Kupffer cells), the synergy between liver cells lining the sinusoidal vascular endothelium in the short-term uptake (adhesion) it is to date not well understood.

The **aim of this project** is to study the synergy in short-term uptake between liver cells lining the sinusoidal capillary bed, where particles stop and exit the blood flow with the ultimate goal of developing rational design of particles for drug delivery. A parallel plate flow chamber coupled with a confocal microscope will be used to evaluate uptake of microparticles by different types of cells in realistic shear flow conditions (5), and study uptake of multistage delivery vectors by different cells types present in the liver. The **first aim** of the project is to quantify particle adhesion on liver cells under physiological shear stress conditions. The **second aim** will include the investigation of Artificial Neural Network (ANN) potential in the design of microparticle for drug delivery. Overall, this systematic analysis of particle uptake by liver cells under physiological flow conditions is expected to shine light on the mechanisms that make the liver the powerful biological barrier it is, and provide guidance to the development of biomimetic particles capable of avoiding uptake by the liver and thus increase accumulation in tumors.

A motivated undergraduate student from Rice University will be selected to conduct research under the supervision of Ms. Sara Nizzero, with the end goal of presenting at the SCI research colloquium in 2108. Research will be conducted at the Houston Methodist Research Insititute in the Nanomedicine department within the group of Dr. Mauro Ferrari. The undergraduate student will be selected within the STEM departments at Rice University. Previous experience in either computational or laboratory work is not required but will be highly valued. Preference will be given to students with expertise in either basic cell culture and biology lab procedures or Artificial Neural Network. The specific project will be tailored to the interest, background and skills of the undergraduate researchers. During this program, the undergraduate trainee will acquire technical skills used in pre-clinical work within nanomedicine laboratories: cell culture protocols, toxicity and particle uptake *in vitro* assays, flow chamber assays, confocal microscopy, cell staining and tissue preparation for confocal microscopy, Matlab coding for data and image analysis and artificial neural network development. During the program the student will also have the opportunity to be exposed to other aspects of research such as participation and presentation to group meetings, writing of scientific articles, preparation of scientific posters and attendance to academic development activities or scientific seminars. Throughout the program, the student will also be stimulated to develop critical thinking, and will be encouraged to progress towards independence through the design of simple experiments within the funded research project. At the end of the program the student will be able to discuss the motivation, methods and procedures, results and conclusions of the project, as well as discuss possible future lines of research. Through this program the student will be encouraged, guided and supported to develop critical thinking capabilities and technical skills that will enable him or her to ideate and design independent projects in the field of multidisciplinary research.

Contact:

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1. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol. 2015;33(9):941-951.
2. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J. Analysis of nanoparticle delivery to tumours. Nat Rev Mater. 2016;1:16014.
3. Gustafson HH, Holt-Casper D, Grainger DW, Ghandehari H. Nanoparticle Uptake: The Phagocyte Problem. Nano Today. 2015;10(4):487-510.
4. Wolfram J, Shen H, Ferrari M. Multistage vector (MSV) therapeutics. J Control Release. 2015;219:406-415.
5. van de Ven AL, Kim P, Haley O, Fakhoury JR, Adriani G, Schmulen J, Moloney P, Hussain F, Ferrari M, Liu X, Yun SH, Decuzzi P. Rapid tumoritropic accumulation of systemically injected plateloid particles and their biodistribution. J Control Release. 2012;158(1):148-155.