NANO-BIO INTERACTIONS FOR PERSONALIZED NANOMEDICINE

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Nanomedicine offers significant advantages over conventional treatments for cancer such as: improved drug solubility, enhanced stability and blood circulation time, increased bioavailability, improved site-specific targeting with the consequent reduction of systemic toxicity, drug protection from premature degradation and possibility to incorporate multiple components inside them. Nanomedicine enhances drug or contrast agent biodistribution and pharmacokinetic profile, with the possibility to improve cancer diagnosis and treatment. Nanoparticle properties, i.e. size, shape, surface charge and decoration and stiffness, define the way in which they are distributed at the tumor target site. In particular, factors affecting transport of nanoparticles in tumor microenvironment, crossing of the biological barriers and targeting of the tumor cells are strictly correlated to the stage of the disease and to the pathophysiological state of the patient, given the high heterogeneity in the tumor microenvironment itself and among all different patients.

Transport phenomena inside tumor microenvironment are, actually, extremely influenced by changes in mechanical and fluidodynamic properties of the targeted tissue. In solid tumors**,** vasculature is abnormal, disordered, and characterized by the presence of leakier and more permeable blood vessels and the absence of a functional lymphatic drainage system. As a result, excessive loss from the vascular system to the interstitial one occurs and an elevated interstitial fluid pressure (IFP) arises within the tumor. IFP equals the microvascular one, making diffusion the main mechanism of transvascular and interstitial mass transport. At the tumor periphery, IFP drops causing a steep pressure gradient that may determine an intravasation of materials back into systemic circulation. Convection flow is, thus, drastically reduced and, furthermore, diffusion has to occur in a tortuous, much denser and stiffer extracellular matrix (ECM). Consequently, the diffusion transport which, by itself, is already much slower than convection is drastically impaired. In these conditions, also oxygen delivery is compromised, resulting in subsequent hypoxia and necrosis; necrosis, together with hypoxia, has been proved to promote angiogenesis and consequent tumor progression, making the tumor cell population around the necrotic area to be more resistant to chemotherapy and radiotherapy.

Nowadays, the clinical translation of nanoparticles is made difficult by the small percentage of injected nanoparticle dose that is, effectively, able to reach the tumor site. All these factors make necessary the development of a nanoparticle design which is disease and patient driven. So, in order to be able to “have access” to the molecular profile of the tumor and to understand and predict nano-bio interactions that guide the way in which nanoparticles interact with cells and biomolecules, big data have to be analyzed and proper information needs to be interpreted and extracted. Coupling of omics, *in vivo* imaging and nano-bio interaction studies pose the foundation of personalized nanomedicine, with the aim to achieve superior therapeutic outcomes for the patients due to a data driven selection of the proper nanomedicine system. Some biomedical datasets are already accessible, but they are characterized by high dimensionality, complexity and heterogeneity. These data can be acquired from multiple tumor analysis techniques, starting from lab tests, histology and biopsy up to imaging and cancer genome sequencing, proteomics, transcriptomics and metabolomics. These data will be analyzed to derive the description of tumor morphology and microenvironment or to choose the proper drug and molecular target. The nanoparticle design will be optimized based on these patient and disease derived parameters.

This highlights the importance of the apriori *in-silico* modelling of nanoparticle design, transport and nano-bio interactions, providing useful computational tools needed for the rational design of safer and more effective nanoparticles, with the aim to develop a treatment for a specific patient, rather than through a generalized approach.

The aim of my PhD thesis will be to categorize the nano-bio interactions of the nanostructured materials and find rational patterns in the available databases, deriving information which could be useful to drive the optimal design of the nanoparticles for subsequent validation and precision nanomedicine.

References:

Paunovska K, Loughrey D, Sago CD, Langer R, Dahlman JE. Using Large Datasets to Understand Nanotechnology. *Adv Mater*. 2019;31(43): e.1902798. doi: 10.1002/adma.201902798

Hare JI, Lammers T, Ashford MB, Puri S, Storm G, Barry ST. Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. Adv Drug Deliv Rev. 2017 Jan 1; 108:25-38. doi: 10.1016/j.addr.2016.04.025. Epub 2016 Apr 29. PMID: 27137110.

Chauhan VP, Stylianopoulos T, Boucher Y, Jain RK. Delivery of molecular and nanoscale medicine to tumors: transport barriers and strategies. Annu Rev Chem Biomol Eng. 2011; 2:281-98. doi: 10.1146/annurev-chembioeng-061010-114300. PMID: 22432620.

Adir O, Poley M, Chen G, Froim S, Krinsky N, Shklover J, Shainsky-Roitman J, Lammers T, Schroeder A. Integrating Artificial Intelligence and Nanotechnology for Precision Cancer Medicine. Adv Mater. 2020 Apr;32(13): e1901989. doi: 10.1002/adma.201901989. Epub 2019 Jul 9. PMID: 31286573; PMCID: PMC7124889.

Xue Bai, Fang Liu, Yin Liu, Cong Li, Shenqing Wang, Hongyu Zhou, Wenyi Wang, Hao Zhu, David A. Winkler, Bing Yan Toward a systematic exploration of nano-bio interactions, Toxicology and Applied Pharmacology, Volume 323, 2017, https://doi.org/10.1016/j.taap.2017.03.011.

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