Blood Flow Dynamics and the Design of Vascular-Targeted Drug Delivery Vehicles

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Overall, localized delivery of therapeutics to or via the vascular wall offers the possibility of increased drug effectiveness while minimizing side effects often associated with systemic drug administration. Targeting of these blood vessel walls for diagnosis or treatment involves (i) selecting known target receptors expressed on vessel endothelial cells that are unique to an organ, tissue, or disease, (ii) decorating surfaces of particulate carriers (loaded with a therapeutic or imaging agent) with molecules that bind to these unique receptors, and (iii) bringing the carriers into sufficiently close proximity to the blood vessel that binding can occur. Early enthusiasm for this strategy in cancer and heart disease has faded in that many VTC systems that were effective in preclinical research have failed in clinical trials. We believe one reason for this is the lack of attention to particle behavior in the intermediate transport step between injection and vessel wall target binding. Existing literature have focused mainly on identifying target epitopes and the degradation/drug release characteristics of a wide range of drug-carrier formulations. Absent in the literature, are work focused on the potential roles of particle shape and size on the ability of vascular-targeted drug carriers to interact with the vessels – an important consideration that will control the effectiveness of drug targeting regardless of the targeted disease or delivered therapeutic. In the context of micro- or nanoparticle delivery, blood is not a homogenous fluid. Rather, it is a dense and anisotropic aqueous suspension of red blood cells (RBCs) with an average diameter of 7 µm. This cellular diameter is critical: particles on the same scale as red blood cells distribute to the RBC free plasma layer adjacent to the blood vessel as RBCs congregate to the center of flow. Our previous work show nanoparticles however distribute into a much larger volume including the interstices of the RBC core in blood flow, and thereby have much less opportunity to make contact with the blood vessel wall. My lab focuses on elucidating the effect of particle geometry (size and shape) along with blood flow dynamics, vessel size and hematocrit on the efficiency of drug carrier interaction with inflamed endothelium in vitro. We utilize microfluidic and parallel plate flow assays to evaluate key carrier-blood cell interactions that affect drug carrier binding to the vascular wall and suggest the optimum drug carrier size(s) and/or shape for vascular-targeted drug delivery applications in a solid tumor microvascular network and in large vessels associated with many cardiovascular diseases. We are currently seeking collaboration for the design of triggersensitive microcarriers for transport of nanoparticles to the blood vessel wall, including fabrication of nanoparticle-loaded microcarriers, surface conjugation of nanoparticles to lipid microcarriers, or in vivo triggered assembly/disassembly of nanoparticles.