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Multistage Mesoporous Silicon Particles for Biomedical Applications

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Abstract

We developed a versatile platform based on mesoporous silicon micro and nano particles for the efficient systemic delivery of therapeutic and imaging agents. Our approach consists in a multistage delivery system where the task of avoiding the sequential biobarriers from the point of entry to the final target is divided among the different stages. The porous silicon microparticles constitute the first-stage vector of the delivery system and are assigned the tasks of proficient navigation of the vasculature, avoidance of macrophage uptake, first order recognition of the target site and delivery of theranostic agents at target. We developed a vast array of methods in order to provide a vector able to fulfill the required tasks in the widest possible range of conditions.

The ability to deliver therapeutic compounds specifically to diseased sites is crucial for effectively treating human illnesses [1]. Nanotechnology is emerging as a tool for resolving challenges in the delivery of poorly administrable drugs (nanotherapeutics) [1]. A large number of nanotherapeutics have been envisioned to date, but the original objective, to increase drug concentration at target sites, has not been fully realized [1]. A series of biological barriers pose as insurmountable obstacles which limit or completely abolish the ability to selectively deliver a therapeutic agent. We hypothesized, engineered, developed and tested a multi-stage system for systemic delivery (MSDS) designed to interact with and successfully overcome sequential biological barriers [2-3] (figure 1). The MSDS is based on biodegradable [4], biocompatible [5] mesoporous silicon particles. Through a combination of state of the art silicon manufacturing technology and electrochemical etch we can produce porous silicon particles with characteristic size from 600nm onwards, and we can control their aspect ratio in the range from 0.1 to 1. We finely control their shape through photolithography (circular, oval, square, et) and their profile through dry silicon etch (discoidal, hemispherical, tubular, et), to obtain a wide variety of three-dimensional shapes optimally designed to travel into the blood flow, avoid macrophage uptake, marginate and adhere to tumor vasculature [6]. We can also manipulate the details of the porous matrix (pore size from 3nm to 130nm, porosity form 40% to 90% and pore morphology from disordered networks to aligned pores) to control not only the loading of the second stage agents, whether they be nanoparticles or molecules but also their degradation-mediated spatio/temporal release. We developed a broad series of surface chemistries in order to convey to the particles additional functionalities (targeting to tissues, cells and subcellular organelles, avoidance of cell internalization, stabilization, stealthing, etc.). Fluorescent and magnetic nanoparticles and molecules can be loaded into the pores of our particles in order to allow for the visualization with multiple modalities (optical, CT, PET, MRI) of the injected MSDS from its administration to its final localization into the body (figure2). We monitored the biodistribution of the silicon carrier and of its payload and characterized their biocompatibility in the different tissues. Taken together, these studies provide first time evidence of silicon nanoporous particles use as effective carriers for the simultaneous delivery of different nanotherapeutics in vivo.

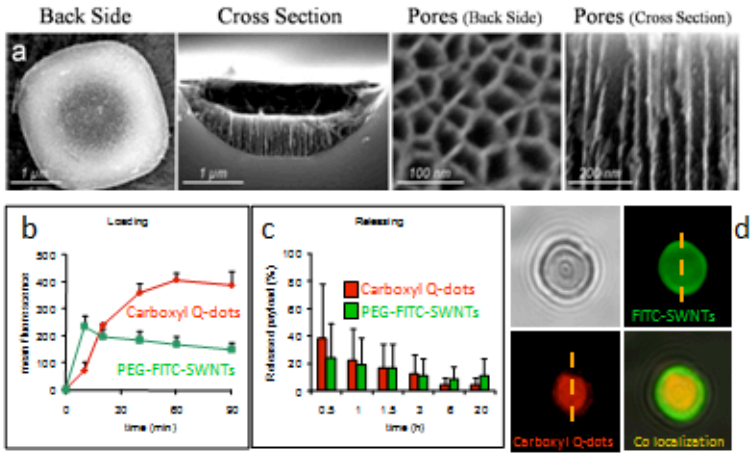

Figure 1: Figure 1. (a) SEM micrographs of the multistage carrier showing the structure of the particle and the pores. Cytofluorimetry analysis showing the load profile of nanoparticles into the pores (b) and of their release from the pores (c). (d) fluorescent confocal microscopy imaging showing the simultaneous loading of SWNTs and Cd-Se Q-dots SSC into a carrier.

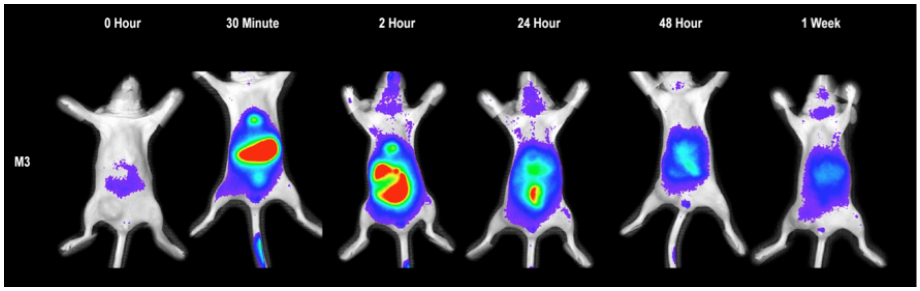

Figure 2: In vivo imaging of FSC biodistribution in a nude mouse bearing a breast tumor in the mammary fat pad. Using a near infra red dye conjugated on the surface of FSC it is possible to monitor in real time and over time the concentration and localization of the FSCs in vivo.

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