Title: Multi-staged delivery system overcoming the physiological barriers for metastatic breast cancer (MBC) therapy

PUBLIC ABSTRACT
Breast cancer is the most common type of cancer and the second most common cause of death among women. Despite the fact that over 90% of women with breast cancer are diagnosed early and cured, a significant number of patients will develop metastatic disease or relapse at metastatic site. Metastatic breast cancer (MBC) is currently incurable, with median survival of less than 60 months, constituting an urgent need for better therapeutic options for this disease. The HER2 protein is overexpressed in a particular subset of breast cancer, i.e., 15-25% of all breast cancer diagnosed. It is also known that HER2-positive MBC patients tend to have a poor prognosis. While the clinical outcomes of this disease have been considerably improved by the development of anti-HER2 targeting therapies such as Trastuzumab, many patients do not benefit from this therapy and eventually succumb to the disease. Trastuzumab emtansine (T-DM1; commercial name Kadcyla) is an anti-HER2 agent that delivers a potent chemotherapy drug directly to tumor cells that overexpress HER2. T-DM1 was approved as second-line therapy for HER2+ MBC, but in recent clinical trials, it failed to show any superiority over treatment with antibody plus drug. The reasons may be the large size of T-DM1, which hinders its deep penetration into tumor tissues, and to its suboptimal clinical pharmacokinetics. To overcome these obstacles and develop a more effective therapy for HER2+ MBC, we propose to translate an innovative technology that allows the encapsulation of anticancer small biologic drug conjugates (SBDCs) in long-circulating, biodegradable polymeric nanoparticles for systemic delivery to tumors. These nanoparticles are designed specifically to degrade in the acidic tumor environment, rapidly releasing the SBDCs, while the SBDCs themselves are designed to deeply penetrate into tumor tissues and efficiently target cancer cells. In this platform we foresee the ultimate "home-run" in a drug-delivery system with long blood circulation, high tumor accumulation, deep tumor penetrability, and specific tumor-cell targeting, culminating eventually in safer and more effective cancer treatment.