A Microfluidic Platform for Combinatorial Synthesis and Optimization of Targeted Polymeric Nanoparticles for Cancer Therapy

By

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The use of nanotechnology to engineer drug delivery vehicles comprised of controlled release polymers with targeting molecules has the potential to revolutionize cancer therapy, among other diseases. Although a myriad of nanotherapeutics have been developed at the bench side, many of them stay at the research stage due to their complexity and difficulty in their optimization. A key challenge for optimization of nanoparticles (NPs) for drug delivery is the ability to systematically and combinatorially create and screen libraries of NPs with distinct physicochemical properties, from which promising formulations can be moved forward to preclinical and clinical studies.

In this work, the development of a controlled method to synthesize libraries of NPs with distinct properties is described. The procedure uses a microfluidic platform that rapidly mixes reagents and provides homogeneous reaction environments, resulting in the reproducible, single-step synthesis of NPs with well-defined properties and narrow size distributions. The microfluidic system is composed of a mixing unit and a NP assembly unit. The mixing unit consists of a multi-inlet, 2-layer mixer where different precursors such as polymers of different MW and charge, ligand- and drug-conjugated polymers, free drugs, and solvents are mixed at different ratios into a homogenous solution. In the assembly unit, the precursor solution is quickly mixed with an anti-solvent (i.e. water) using 3D hydrodynamic flow focusing where NPs self-assemble after complete mixing.

With the microfluidic platform, a library of 100 NPs with different sizes (15-200 nm), charge (-30 to +30 mV), surface chemistry (i.e. PEG coverage), surface ligand density (0-2.510^5 ligands/µm^2), and drug loading (0-5 w/w%) was produced in a high-throughput manner by simply varying the flow ratios of precursors entering the system. This library was implemented for (i) screening for formulations (in vitro and in vivo) with optimal clinical properties for cancer treatment and (ii) deepening the understanding of how NP properties affect their biological behavior.

The platform developed in this work would likely lead to better understanding of the design parameters for polymeric NPs and their smoother transition to the clinic.

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