**Smart Nanofiber Webs for "On-off" Release of Cells and Drugs**

Mitsuhiro Ebara,[1] Young-Jin Kim,[1,2] Takao Aoyagi[1,2]

[1]Biomaterials Unit, International Center for Materials Nanoarchitectonics (WPI-MANA), National Institute for Materials Science (NIMS), [2]Graduate School of Pure and Applied Science, University of Tsukuba

**Statement of Purpose:** Nanofiber webs are finding an ever-increasing range of applications, including as filter fabrics, sensors, and electronic devices, as well as medical/pharmaceutical applications. One new class of nanofiber webs with considerable potential for use in these rapidly growing fields are "smart" nanofiber webs, which are fabricated from stimuliresponsive polymers. Nanoscale structures inherent to stimuli-responsive polymers enable highly sensitive responses to external stimuli, and the incorporation of stimuli-responsive polymers into nanofibers takes advantage of the extremely large surface area and porosity of nanofibers to generate a precision "on-off" switch to control the morphology and function of the nanofiber. Extension of these nanoscale effects to the macroscale enables manipulation of the bulk matter and creates the opportunity to develop profitable new applications. Herein, we report the synthesis and application of cross-linked temperature-responsive polymer-based nanofiber webs with dynamically and reversibly tunable web properties, including swelling/shrinking, mechanical strength, and porosity. We demonstrate the ability to capture, encapsulate, and release cells, drugs, or magnetic nanoparticles in response to alternations of external temperature. This novel nanofiber enables the facile encapsulation and on-demand release of various biomolecules in response to external signals.

**Methods:** For photo-crosslinkable nanofibers, poly(*N*-isopropylacrylamide (NIPAAm)-*co*-2-carboxyisopropylacrylamide (CIPAAm)) with varying monomer ratios was copolymerized by free-radical polymerization (Fig.1a)[1]. A UV-reactive benzophenone (BP) was conjugated to the copolymer. The copolymer was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and then subjected to voltages of 15 kV. The electrospun nanofibers were subsequently exposed to UV illumination to form crosslinked webs. For heat-crosslinkable nanofivers, poly(NIPAAm-*co*-*N*-hydroxymethylacrylamide (HMAAm)) with varying monomer ratios was copolymerized by free-radical polymerization (Fig.1b) [2]. The chemical crosslinking was carried out by thermal curing of the OH groups of HMAAm. The successive fabrication of the nanofibers has been studied in detail by FTIR-ATR, SEM, TEM, and a tensile tester etc. We further demonstrated the on-off release of encapsulated cells or drugs by alternating external temperatures.

**Results:** The photo-crosslinkable smart web was fabricated by an electrospinning method with a newly synthesized photo-cross-linkable temperatureresponsive polymer. By photo-cross-linking, the web showed the ability to trigger "on" or "off" web properties in response to external changes in temperature. By using external signals, we also demonstrated cell capture, encapsulation, and release (Fig.1c). The released cells show excellent viability and proliferation behavior.

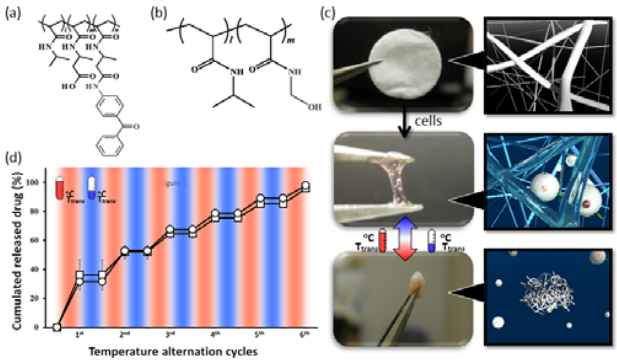


Figure 1. Photo-crosslinkable P(NIPAAm-*co*-BP-CIPAAm) (a) and thermally crosslinkable P(NIPAAm-*co*-HMAAm) (b). (c) Schematic illustration of a facile capture and release concept for cells [1]. (d) Release profiles of dextran from crosslinked nanofibers [2].

Thermally crosslinkable and temperature-responsive poly(NIPAAm-*co*-HMAAm) nanofibers have been fabricated by electrospinning to realize the 'on–off' controllable release of dextran. Approximately 50% of the methylol groups of HMAAm in the polymer were crosslinked by thermal curing without altering the fiber morphology. The LCSTs of the fabricated nanofibers were close to human body temperature. The crosslinked nanofibers exhibited rapid swelling and shrinking in response to cycles of temperature alternation across the LCST. Dextran-loaded nanofibers with a continuous and smooth fibrous structure were fabricated, and the 'on–off' switchable release of dextran from the nanofibers was observed (Fig.1d). Almost all the dextran was released from the nanofibers after six heating cycles, whereas a negligible amount of dextran was evolved during the cooling process. The reported incorporation of smart properties into nanofibers takes advantage of their extremely large surface area and porosity and is expected to provide a simple platform for 'on–off' drug delivery.

**Conclusions:** This study extends the further functionalization of the nanofibers for the immobilization of peptides or antibodies, which are highly promising for separation, purification, preservation, and the delivery of the target molecules and cells.

**References:** [1] Kim YJ et al., Angew Chem Intl Ed. 2012; 51: 10537-10541. [2] Kim YJ et al., Sci Tech Adv Mater. 2012; 13: 064203.