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Supramolecular glycorhodamine-polymer dot ensembles for the homogeneous, fluorogenic analysis of lectins

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ABSTRACT

We have developed a new series of glycoprobe-polymer dot ensembles for the fluorogenic, homogeneous detection of lectins. Electrostatic self-assembly between positively charged rhodamine-based glycosides and negatively charged poly(3-hexylthiophene-2,5-diyl)/poly(styrene-*co*-maleic anhydride) polymer dots produces the ensembles with a quenched fluorescence. Fluorescence spectroscopy showed that the ensembles exhibited a concentration-dependent fluorescence enhancement with selective lectins over a range of unselective lectins and proteins. This research provides insight into the development of simple fluorogenic probes for homogeneous lectin analyses based on the supramolecular assembly between polymeric nanoparticles and fluorescent glycoprobes.

The selective recognition between carbohydrates and lectins is responsible for a number of biological processes. Carbohydrate-lectin interactions (CLIs) are also implicated in many human diseases such as cancer metastasis [1], inflammation [2], viral invasion [3] and gut-flora-related pathological disorders [4]. As a consequence, the effective identification of the lectin selectivity of carbohydrates is of significance for not only deciphering the glycomics, but offering useful tools towards disease diagnosis and therapy [5]. To achieve this goal, a diverse range of solid-phase methods have been employed including surface plasma resonance [6], quartz crystal microbalance [7], electrochemical techniques [8,9], field-effect transistors [10,11] as well as the elegant glycomicroarray technique [12]. Whereas those sophisticated techniques have been proven to be powerful tools for the analysis of CLIs, several problems still exist in terms of the need for surface-immobilization of carbohydrates, the requirement of advanced facilities and the inability to probe the spatiotemporal location of transmembrane lectins (for example the endocytosis of *C*-type lectins) [13].

With a continuing interest in the development of fluorogenic glycoprobes [14–17] and materials [18–21] for the homogeneous detection of lectins, here we describe a polymer dot based glycoensemble for the selective analysis of lectins using fluorescence spectroscopy. Development of fluorescence probes has been a very active research area owing to the sensitivity and simplicity of fluorescence techniques, the flexibility in probe design as well as the usefulness of probes for sensing and bioimaging both *in vitro* and *in vivo* [22,23]. Recently we have demonstrated that "glycosylation" represents a promising strategy for improving the water solubility, lowering the toxicity as well as enhancing the targeting ability of traditional fluorescent dyes [24–27]. Here, we show that glycorhodamine probes synthesized by the effective click reaction, can be used for the electrostatic self-assembly with poly(3-hexylthiophene-2,5-diyl)/poly(styrene-*co*-maleic anhydride) polymer dots, producing fluorogenic glycoensembles suitable for the homogeneous analysis of lectins.

Copper(I)-catalyzed azide-alkyne cycloaddition of propargyl β-*O*-galactoside (**1**) and α-*O*-mannoside (**2**) with azido rhodamine (**3**) produced triazole-linked galacto-rhodamine (**Gal-Rh**) and manno-rhodamine (**Man-Rh**), respectively, in moderate yields (Fig. 1a). Then, we employed poly(3-hexylthiophene-2,5-diyl) (**P3HT**), which is a polymer extensively used for the construction of photovoltaic devices [28], as the material backbone. To increase the water solubility, 20% (w/w) of poly(styrene-*co*-maleic anhydride) (**PSMA**) was mixed with **P3HT** to form the polymer dots (**P3HT-d**) through the established reprecipitation method [29]. The presence of **PSMA** also imparts **P3HT-d** with negatively charged sites for

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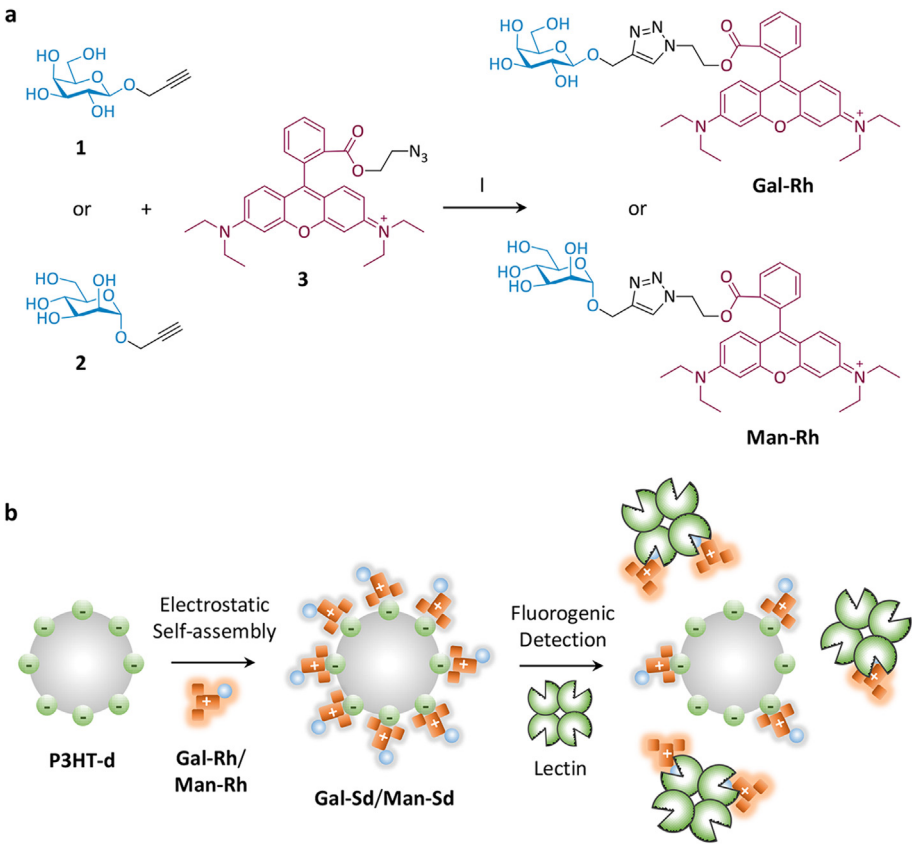

Fig. 1. (a) Synthesis of galactosyl rhodamine (**Gal-Rh**) and mannosyl rhodamine (**Man-Rh**). Reagents and conditions: (I) CuCl in CH_2Cl_2/*t*-BuOH/H_2O (6/4/1, v/v/v) at room temperature. (b) Schematic illustration of the electrostatic self-assembly between negatively charged poly(3-hexylthiophene)/poly(styrene-*co*-maleic anhydride) dots (**P3HT-d**) and **Gal-Rh** or **Man-Rh** to produce the galactosyl supramolecular dots (**Gal-Sd**) and mannosyl supramolecular dots (**Man-Sd**) with a quenched fluorescence, and the use of the resulting **Gal-Sd** or **Man-Sd** for the fluorogenic, homogeneous detection of lectins through selective carbohydrate-lectin recognition that competitively interrupts the binding between **Gal-Sd**/**Man-Sd** and **P3HT-d**.

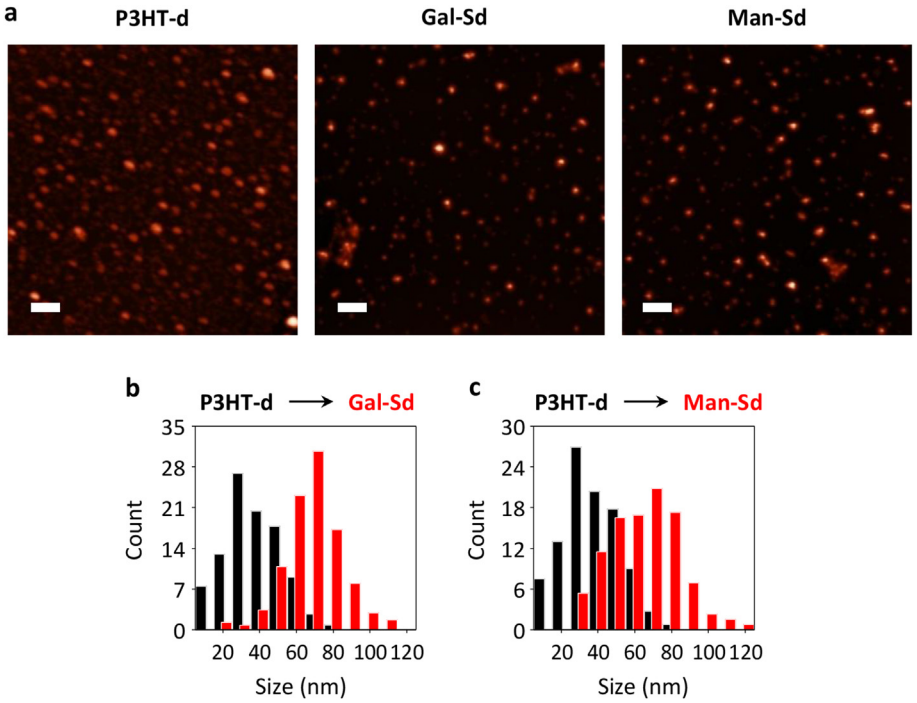

Fig. 2. (a) Atomic force microscopic (AFM) images of **P3HT-d** (Scale bar = 200 nm), **Gal-Sd** (Scale bar = 500 nm) and **Man-Sd** (Scale bar = 500 nm). (b) The size distribution of the materials as determined through measuring the parameters of the particles shown in the AFM images. The AFM images were obtained on a Veeco/DI apparatus (USA).