Dynamically drug-responsive biomaterials

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In biomedicine and analytics, hydrogels are required that specifically respond to a given biologically relevant molecule like a drug, a hormone or a metabolite at a physiologically compatible concentration. Recently, we presented hydrogel concepts based on drug-targets such as bacterial gyrase (Ehrbar M. Nat Mater. 2008;7: 800-804.) and the FK-binding protein (Kämpf MM. Adv Funct Mater. 2010;20: 2534-2538.) conferring sensitivity to small molecule drugs. The suitability of the hydrogel as a stimulus-inducible drug depot was shown *in vivo* by the dose-dependent release of the model therapeutic biomolecule VEGF in a mouse model.

A possible drawback of these hydrogels in regard to clinical applications are the incorporated Ni^{2+} ions possibly leading to toxic or allergic side effects in vivo.

To circumvent these problems, we have designed a hybrid hydrogel scaffold (Fig. 1) consisting of a polyethylene glycol (PEG) which was covalently functionalized by Michael-type addition (Fig. 2) with engineered gyrase B (GyrB). Dimerization of the GyrB subunits with the coumarin antibiotic coumermycin resulted in gel formation which was verified by rheometry.

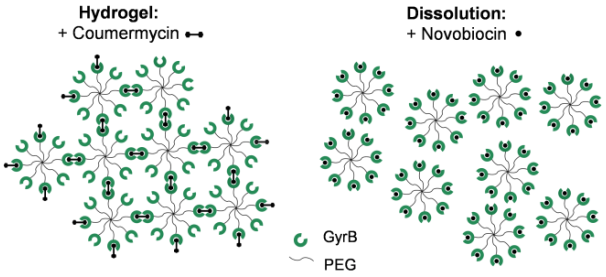

Figure 1. Antibiotic-responsive hydrogel design.

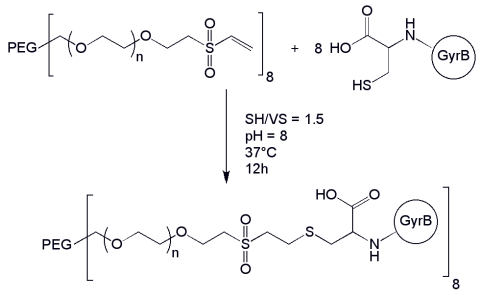

Figure 2. Synthesis of building blocks.

Addition of increasing concentrations of clinically validated novobiocin competitively displaced coumermycin thereby dissociating the GyrB subunits and resulting in dose- and time-dependent dissolution of the hydrogel (Fig. 3).

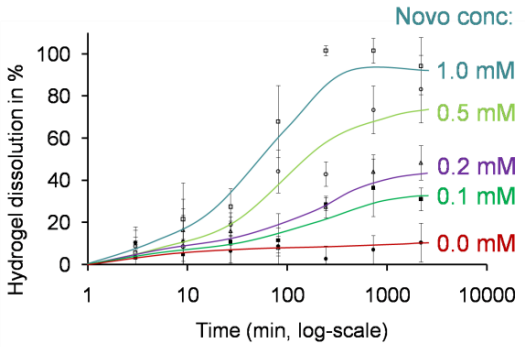

Figure 3. Adjustable pharmacologically triggered hydrogel dissolution.

The hydrogels showed excellent long-time stability still retaining its functionality thereby proving its general suitability as a drug depot.

The presented pharmacologically controlled hydrogels have the potential to fulfill the promises of stimuli-sensing materials as (i) smart devices for spatiotemporally controlled delivery of drugs within patients, (ii) scaffolds for cell growth and differentiation and (iii) valves for microfluidic applications. Additionally, this hydrogel design concept might serve as a blueprint for the synthesis of a new generation of biohybrid materials responsive to drugs, metabolites, pheromones, vitamins or heavy metals by replacing GyrB with proteins showing the desired stimulus specificity selected from the large family of small-molecule binding proteins.

References:

Ehrbar M. Schoenmakers R., Christen EH., Fussenegger M. & Weber W. Drug-sensing hydrogels for the inducible release of biopharmaceuticals. Nat Mater. 2008;7: 800-804

Kämpf MM. Christen EH., Ehrbar M., Daoud-El Baba M., Charpin-El Hamri G., Fussenegger M., and Weber W. A gene therapy technology-based hydrogel for the trigger inducible release of bipharmaceuticals in mice. Adv Funct Mater. 2010;20: 2534-2538