Editorial corner – a personal view

Cell-instructive hydrogels to assemble in biofluids

C. Werner*

Leibniz Institute of Polymer Research Dresden and TU Dresden, Germany

Embedding cells in engineered polymer matrices, which mimic fundamental characteristics of naturally occurring extracellular microenvironments, is a key task in the rapidly progressing fields of tissue engineering and regenerative medicine (DOI: [10.1038/nature08602](https://doi.org/10.1038/nature08602)). Importantly, cell-instructive matrix signals – including matrix-associated growth factors, ligands of cellular adhesion receptors, intrinsic viscoelastic properties and susceptibility for cell-driven reorganization – have to be presented in a spatiotemporally adjusted manner (DOI: [10.1002/marc.201200382](https://doi.org/10.1002/marc.201200382)).

For that purpose, the current practice in cell biology and biotechnology mostly relies on reconstituting non-covalently associating biopolymer meshworks (collagen fibrils, Matrigel). Although effective in numerous *in vitro* approaches to cell signaling, these preparations are hardly compatible with safety requirements for medical applications and are often not suitable for the mechanistic investigation of particular exogenous signals.

Recent approaches have therefore aimed at forming covalent polymer hydrogel networks in the presence of cells in culture or even within living tissue. A range of poly(ethylene glycol) (PEG) conjugates with adhesive peptide ligands and/or degradable peptide crosslinkers were converted in cell-compatible crosslinking schemes, including Michael-type addition, triazole formation, enzymatic (Factor XIIIa/transglutaminase-mediated) crosslinking, and photo-induced polymerization.

Amongst these, the Michael-type addition reaction turned out to be particularly powerful, as it does not require a catalyst, has no side products, and pro-

ceeds rapidly under physiological conditions (DOI: [10.1002/adma.201103574](https://doi.org/10.1002/adma.201103574)). The thiol group of cysteine residues can participate as a nucleophile in this reaction, which massively extends the number of suitable substrates and simplifies the attachment of bioactive peptides or proteins. A very common synthetic scheme for the formation of PEG-peptide hydrogels utilizes dithiol-containing peptides to react with PEG-polymers carrying electron deficient double bonds at the terminal groups.

Recently, this scheme was further extended by incorporating glycosaminoglycan building blocks for the *in situ* formation of biohybrid gel matrices, which allows for the versatile biomimetic functionalization of the obtained materials with a plethora of glycosaminoglycan-binding growth factors: Michael-type reaction schemes were applied for the formation of customized, cell-embedding, PEG-glycosaminoglycan hydrogels with precisely adjusted polymer network properties and independently tunable signaling characteristics (DOI: [10.1002/adma.201300691](https://doi.org/10.1002/adma.201300691)). These materials provide a means for the effective modulation of therapeutically relevant cell fate decisions *in vivo* and are thus expected to become instrumental in medical technologies aimed at regenerating diseased or injured tissues.

Prof. Dr. Carsten Werner
Member of International Advisory Board

*Corresponding author, e-mail: werner@ipfdd.de
© BME-PT