ESSAY

Going Beyond Compromises in Multifunctionality of Biomaterials

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Design, synthesis, processing, and testing, or perhaps better altogether exploration, of biomaterials, which are intended to substitute native tissue, have generally been approached from one of two distinct perspectives (**Figure 1**A). Researchers with a background in chemistry or biology have been inspired by the natural surroundings of cells, the extracellular matrix (ECM). The ECM is a complex nanostructured system of fiber and network forming macromolecules as well as soluble compounds embedded in a hydrogel. The fiber and network forming macromolecules such as collagen and elastin enable the elastic deformability and recoverability of tissues. Water storage in the hydrogel is ruled by polysaccharide and proteoglycan components, such as glycosaminoglycans, for example, hyaluronic acid. The hydrogel furthermore counteracts the contraction by the fibers and the elastic network. At the same time, it allows the diffusion of gasses, ions, nutrients, and metabolites necessary for the supply of and communication between the cells. Anchoring of cells to the matrix as well as of the different macromolecular components is generally ruled by non-covalent, specific adhesion such as the interaction of the RGD sequence in, for example, fibronectin and integrins in cell membranes. The matrix is built up and degraded through hydrolytic as well as enzyme- and cell-mediated events, which in vivo leads to a continuous remodeling and renewal. In an attempt to learn from nature the macromolecular components of the ECM can be used or emulated, and selected functionalities of the ECM can be mimicked. Taking the ECM structure and functions as blueprint led to a much improved understanding of the interplay between cells and materials. However, materials designed in this way have rarely been advanced to technical or clinical applications. Examples for approaches in this field are the coating of polymers or metals with extracellular matrix extracts produced from sarcoma cells which are harvested and decellularized,[1] or the production of ECM on an artificial surface by cells which are removed prior to application. Such approaches suffer from an incomplete knowledge and limited control of the actual composition and chemical structure, as well as batch-to-batch variability of the biotechnologically produced ECM. Alternatively, full tissues are decellularized and used as guiding structure in tissue engineering.[2] From the perspective of the medical device design aiming at a specific clinical need, especially biomedical engineers have concentrated on formulating requirements, and used "from the shelf" materials to reach their goals.

Though, with the latter strategy, devices which are nowadays firmly established in the clinic were developed, the application of engineering plastics originally not intended for clinical use is often connected with compromises regarding the matching of properties and functions of the materials with the requirements of the application. For device design, one function of the material is frequently prioritized to understand, employ, expand, or tailor, while other functions, judged as of lower importance, are accepted as is. An example for a prioritized function is the structural function, which could be realized by existing engineering plastics, for example, for hip implants. An early example for the design of a material with one function (see Figure 1B–D) is the tailoring of degradation rate of synthetic polymers, which was approached through changing comonomer types and ratio as well as molecular weight distribution of, for example, copolyesters.[6] Copolyesters such as poly(lactide-*co*-glycolide) (PLGA) or ε-caprolactone-based copolymers could be adjusted in their degradation rate in a time frame of weeks to years. The desire to change the release profile of bioactives from polymer matrices actually triggered the investigation of polymers with different degradation behavior: on the one hand, bulk degrading materials such as (co)polyesters and, on the other hand, surface degrading polymers such as polyanhydrides or poly(ortho esters).[7] However, the elastic properties of these classical degradable polymers are not comparable to the elastic properties of soft tissues. In some cases, such as in the use of PLGA as matrix of drug delivery systems or surgical sutures, such compromise might be acceptable, while the elastic properties of (co)polyesters are unsuitable for their application as soft tissue implant, for example, for augmentation. The successful application of polymer-based implants in the clinic rapidly stimulated the generation of ideas for novel applications. For each application, a characteristic combination of properties and functions is required. If more of these novel applications are to be realized, this also means that a larger variety of polymers will have to be available fulfilling these diverse requirement profiles.

An essential function of biomaterials is their biocompatibility.[8] The concept of biocompatibility first of all implies the non-toxicity of a material (though, in fact some materials

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should be cytotoxic under certain boundary conditions, such as for cancer cells after specific cellular uptake). This non-toxicity of eluates of the material as well as measured in direct cell-material interactions is based on the fact that components, starting materials, catalysts, or degradation products are not released in toxic amounts and that the direct contact does not impair cellular function. Toxicity tests are typically performed with cells from cell lines, for instance, L929 mouse fibroblasts. A more specific evaluation covering toxicity as well as cell compatibility comprises the investigation with one or few specific cell types associated with a potential application of the materials. The histocompatibility of the materials with, for example, specific soft or hard tissues can be evaluated in vivo. Furthermore, the evaluation of hemocompatibility of materials[9] is of relevance for all implants in contact with blood as well as for extracorporeal devices such as heart-lung-machines or apheresis devices. Finally, the biofunctionality of a device is evaluated in vivo. The above discussed examples for aspects of biocompatibility and the corresponding plethora of toxicity and biofunctionality tests shows that the material function biocompatibility has to be considered with differentiated views. A material's performance has to correspond to each facet of biofunctionality, which increases the complexity of multifunctionality considerably. So, how can the high expectations towards multifunctionality be fulfilled?

Approaches to biofunctional materials have on the one hand to be concentrated on realizing biochemical cues found in nature to be provided by a material. In addition to incorporation of RGD-based cell adhesion sites, options include provision of enzyme-sensitive moieties allowing cell-mediated degradation, or loading with bioactive macromolecules such as growth factors or cytokines. By increasing the complexity of the system, it was hoped that the biological performance of the biomaterial is improved.[10] However, contrasting the success in interesting pilot studies in vitro, the translation into, for example, clinical applications is seriously hampered by the accompanying increase of complexity of synthesis, shown by the increase of synthetic steps necessary to create such systems. The provision of protein cues released from the matrix has been shown to be risk-associated in vivo because of potential overshooting reactions and/or ectopic biological effects.[11] For example, application of bone morphogenic proteins has in some cases resulted in ectopic or excess bone formation as well as potential increase in cancer risk. Potential reasons might be unsuitable levels of the protein released, and/or insufficient feedback and deactivation of the active compounds as natural inhibiting and control mechanisms are not released at the same time. This might be addressed by applying cells as local factor release systems, for example, as suggested for muscle stem cell implantation for VEGF release in ischemic hearts,[12] or by cell-material constructs, in which the living cells communicate with their biological environment and release only the appropriate biological signals in the needed amount.

A fundamentally different approach is the use of physical cues such as substrate elasticity[13] and geometry, for example, of 2D surface patterns to direct stem cell fate.[14] Early examples included the matrix-elasticity directing stem cell differentiation,[15] as well as the importance of pore size in scaffolds for good tissue integration.[16] Recently, the influence of the geometry of 3D microstructured microwells on human adipose-derived mesenchymal stem cells morphology, migration, and proliferation,[17] but also on differentiation and gene expression exemplarily highlights the interdependence of biological biomaterial studies and progress in biomaterial design and processing.

The realization of multifunctional biomaterials as enabling technology for novel biomedical applications requires strategies, which go beyond compromises. Integrative approaches might be a way to achieve this goal. An interdisciplinary research team of chemists, material scientists, biologists, engineers, and physicians has to address one specific application and develop the right material for this purpose. This requires patience from the people nearer to the application as such material invention and exploration might take some time as well as more application motivated thinking in fundamental research. Different concepts for efficiently integrating multiple functions, which are independently from each other, need to

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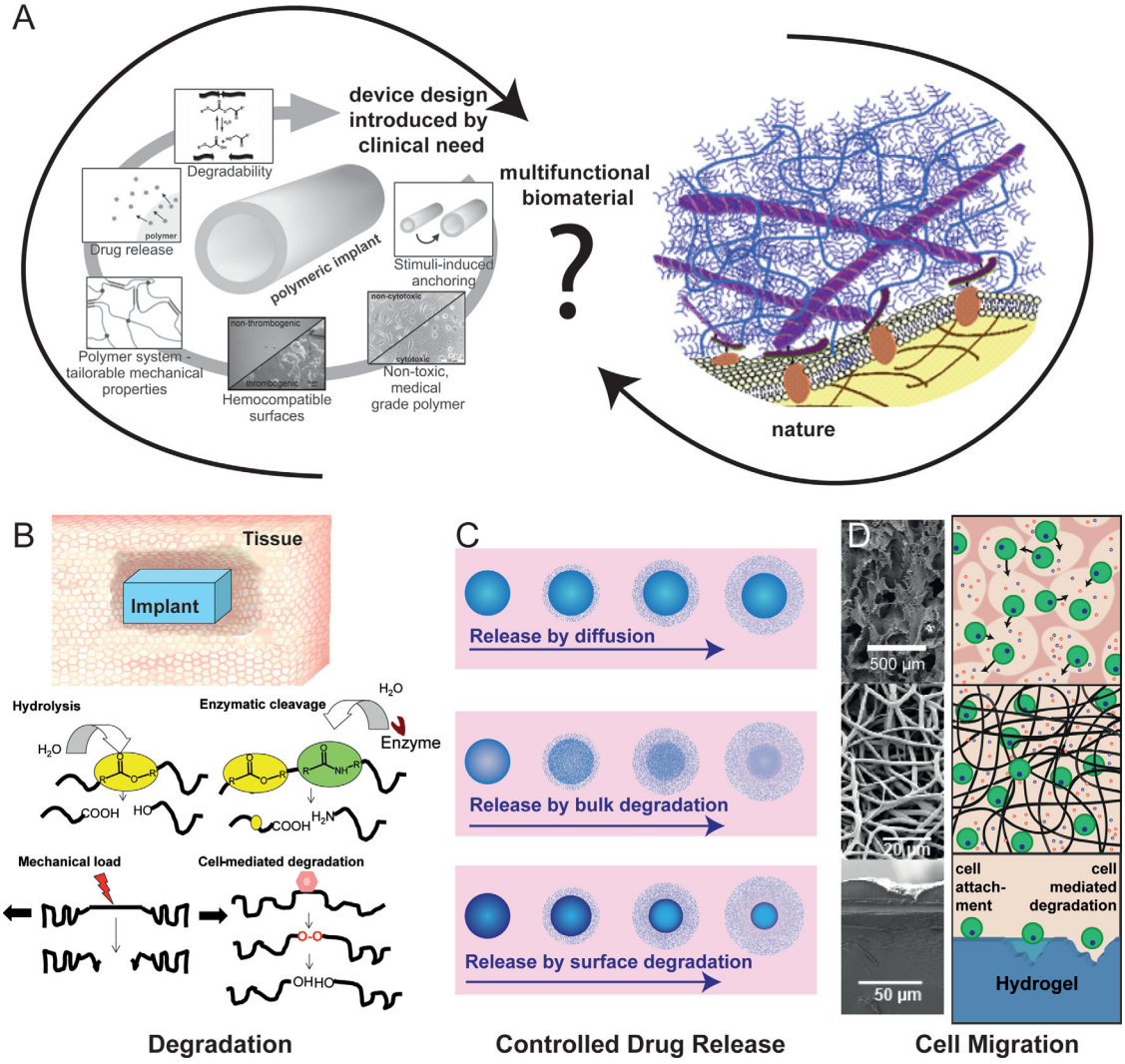

Figure 1. A) The extracellular matrix (ECM) is the natural and self-produced environment of cells. Its structure and functions are explored to gain a fundamental understanding. But the overall complexity of the ECM cannot (yet) be mimicked to enable multifunctional devices. On the other hand, a specific application can give rise to formulate and prioritize functions. However, addressing the prioritized functions with readily available materials often goes hand in hand with compromises for properties and functions of lower importance. Bridging of the two approaches demands novel strategies. Figures reproduced with permission: left,[3] Copyright 2011, IOS Press; right,[4] Copyright 2010, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. B–D) Functions of biomaterials. B) Degradability of materials is complex in vivo, as hydrolysis, enzymatic degradation, mechanical load, and cell-mediated processes contribute to degradation also of materials intended for long-term application. The rate of degradation will be influenced by individual preconditions. C) Control of release can be realized through diffusion or degradation control. D) Biomaterials mimicking different aspects of the ECM structure. Open porous and interconnective 3D structures (top) allow migration of cells through pores of sufficient size. Nanofiber meshes (middle) resembling the collagen fiber network of the ECM, with fiber diameters typically being in the range of 500 nm–2 µm (photo reproduced with permission;[4] Copyright 2010, WILEY-VCH Verlag GmbH & Co. KGaA). Hydrogels (bottom) can only be infiltrated by cells if cell-mediated degradation can take place (photo reproduced with permission;[5] Copyright 2010 of The Royal Society of Chemistry (http://pubs.rsc.org/en/content/articlelanding/2010/jm/c0jm00883d).

be explored. This includes a separation of functions by being recalled not simultaneously but successively, or realizing different functions on different length scales or in different material phases. Finally, integrative processes might play an important role in the future by integrating chemical synthesis and processing in one step procedures. This concept deserves more attention to bridge the gap between the "learning from nature" and "device designer" communities, as in this way the potential drawbacks of multi-step syntheses so far devised for increasing the complexity of a system might be circumvented and translation will be facilitated.

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