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# Engineering of pathways, cells and tissues

## Editorial overview

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**Uwe T. Bornscheuer** studied chemistry and received his PhD in 1993 from Hannover University (Germany) and then was postdoc at Nagoya University (Japan). After his Habilitation at Stuttgart University in 1998, he became Professor at Greifswald University. In 2008, he received the BioCat2008 award. His current research interest is in protein engineering of enzymes from various classes with special emphasis on the synthesis of chiral compounds and for lipid modification.

Most biological systems are highly complex. Therefore to fully utilize biological systems for various applications, there is a great need for understanding the complexity of these systems from molecular to multi-organ levels. Our understanding of biological systems and the resulting complexity has increased significantly over the past few decades. In this issue of *Current Opinion in Biotechnology* we explore the recent advances in understanding and engineering of such systems at molecular, cellular and tissue levels. In particular we highlight the advances in pathway development of bacterial systems as well as those of mammalian cells for engineering of artificial tissues for biomedicine.

The first set of articles in this special issue is related to engineering of biological pathways. Successful engineering of biochemical pathways in the context of systems biology requires input from various disciplines to form desired products in a microbial host. First of all, genetic tools must be available to insert foreign genes and ensure the controlled and functional expression of the gene product, the metabolic flow within the host cell must be well understood and finally the substrate uptake and fate of the product (intramolecular accumulation vs. secretion into the media) must be ensured. **Wiechert and Noack** review bioinformatic approaches to create mechanistic models, which allow to quantitatively describe dynamic and steady states of biochemical pathways. They show recent successes and current limitations of these tools used in bioprocess development for industrial biotechnology. Along these lines, **Pleiss** discusses the importance and strategies of protein engineering to fine-tune bottleneck enzymes in metabolic engineering.

An important, but not yet sufficiently explored source of novel enzymes are hyperthermophiles with a huge potential for various biotechnological processes. Together with the recently developed genetic systems for a number of hyperthermophilic archaea, **Atomi et al.** exemplify in their article how the latest progress in understanding the genetics of archaea of (hyper)thermophiles can be used for hydrogen production serving as potential biofuel.

Two contributions deal with the actual engineering of biosynthetic pathways. **Misawa** reviews the formation of functional isoprenoids containing mono-, sesqui-, di-, triterpenes, and carotenoids (tetraterpenes) through pathway engineering in various microbial and plant hosts, where the products are of high interest to the chemical, pharmaceutical and food industry. An alternative biofuel to ethanol is 1-butanol. **Lütke-Eversloh & Bahl** cover in their article the current status of metabolic engineering of the solvent tolerant *Clostridium* species where already wild-type strains are

capable of producing high levels of 1-butanol. Despite major progress in the past few years, still many issues need to be solved, before sufficiently high yields of this alternative fuel can be achieved.

In addition to molecular pathways, biological tissues are also of great importance for various applications such as biomedical therapeutics and diagnostics. Engineered tissues can be used as replacement organs for transplantation and have the potential to revolutionize the pharmaceutical industry by enabling more predictive *in vitro* testings. In a number of papers in this issue various aspects of the understanding and engineering of these systems are highlighted. The papers in this section cover topics that range from fundamental understanding of cell-microenvironment interactions, and the subsequent engineering of these environments to specific applications related to cardiac, bone, cartilage and neural engineering.

A key to regulating biological systems is to understand the interaction of cells with their surrounding microenvironment. An increasingly important signaling method is through mechanical forces. Mechanotransduction is widely regarded as a complicated process where a cell converts a mechanical stimulus into a biochemical signal. Eventhough all adherent cell types participate in this process, the specific mechanical input and the nature of the corresponding output is known to vary significantly. Furthermore, despite the importance of the problem and two decades of serious scientific inquiry, an agreement on the signaling pathways that undergo mechanosensation and the resulting behaviors that it induces has yet to be understood. In their paper, [Engler \*et al.\*](#) discuss the context in which mechanotransduction occurs, the categories of known mechanosensitive pathways, the systems used to perturb these pathways, and provide an opinion on where consensus can be found within the field of mechanotransduction.

A number of other papers also discuss various approaches to engineer the surrounding microenvironment of cells using degradable scaffolds that enable cells to form three-dimensional (3D) tissues. Scaffolds are routinely used in tissue engineering as a support to seed and hold cells in a 3D environment. For example, by applying different conjugation techniques to the synthesis of novel biomimetic cell-responsive hydrogels it is possible to control cell migration, adhesion, differentiation and proliferation. In a mini review, [Jabbari](#) highlights the exciting developments in bioconjugation of synthetic hydrogels targeted for tissue engineering applications. These approaches include development of conjugated hydrogel matrices, novel hydrogels for self-renewal and pluripotency of stem cells and combining 3D printing with bioconjugation to generate hydrogels including cells and biomolecules.

Another key aspect of forming tissue-like biological systems is the need for vascularization to supply nutrients and gases to the living tissue. Hence there is a pressing need to create scaffolds that allow for the transfer of nutrients and gases. Various techniques have been developed for creating porous scaffolds which include methods such as electrospinning, freeze-drying, and solvent casting/salt leaching. The challenges include lack of control in the dimensions of the pores, as well as limited connectivity between the pores. In their paper, [Annabi \*et al.\*](#) provide an overview of gas-based fabrication methods developed for creating porous scaffolds.

Other approaches to generate tissue complexity are also discussed. For example, the use of robotic biofabrication processes to create functional 3D tissues is becoming more popular. [Mironov \*et al.\*](#) discuss simple printing technologies and describe in detail the challenges and protocols to scale-up such technologies. Furthermore, self-assembly has also been demonstrated as a promising approach for generating tissues. [Elbert \*et al.\*](#) discuss recent advances in the assembly of microscale cell clusters and microgels.

In addition two papers discuss the use of microfabricated environments for enhancing tissue complexity of engineered biological tissues. [Borenstein \*et al.\*](#) discuss the use of microfluidic channels for creating artificial vascular trees, while [Lutolf and colleagues](#) describe the intersection of microfluidics and hydrogel biomaterials for generating *in vitro* tissue models with controllable microscale features.

A number of papers in this issue also discuss the engineering of biological tissues for various clinical applications. Cardiovascular disease is one of the leading causes of death in the United States. Hence there is a strong need for developing functional tissue replacements such as heart valves and cardiac muscle patches. For example, although mechanical heart valves are commonly used, they often fail in pediatric patients as mechanical heart valves do not grow with the patient. Accordingly, a tissue engineering based heart valve may be able to address some of the limitations of mechanical valves. [Schoen](#) provides a brief overview of heart valve tissue engineering field with an emphasis on recent developments and remaining challenges. Also, [Radisic \*et al.\*](#) describe recent advances in the field of cardiac muscle tissue engineering including cell-scaffold approaches, bioreactor designs, cell sheet engineering, stem-cell based approaches and topographical control of tissue organization and function.

Musculoskeletal diseases are also another area where cell and tissue engineering may be of great importance. For example, *in vivo* tissue engineering strategies using conventional approaches (cells, growth factors, scaffolds) are being directly implanted at the damaged tissue site or

within ectopic sites and are capable of supporting novel bone tissue formation. In their contribution, *Stevens et al.* highlight recent advances in the field of *in vivo* tissue engineering and specifically focus on bone tissue formation. Furthermore, *Mikos and colleagues*, highlight recent advances in segmental bone defect animal models, bone tissue engineering, and drug delivery. Their overarching goal is to identify promising approaches that need further exploration towards developing improved tissue engineering techniques to address infection control while at the same time inducing bone regeneration.

The current trend in aging world population combined with sports related injuries create an urgent need for replacement of damaged cartilage tissue. *Reis et al.* provide a review of approaches for current strategies for osteochondral regeneration including the design of multi-layered scaffolds, the use of stem cells and bioreactors. Furthermore, *Yang et al.* provide a review of novel approaches for cartilage tissue engineering such as identifying promising cell sources, designing 3D scaffolds with dynamic and spatially patterned cues to guide

cellular processes, mimicking zonal organization and integrating with host tissue.

Paralysis due to accidents or war related events hinder the lives of many. Despite the years of research and investments, nerve regeneration remains to be a daunting task. *Mao et al.* discuss novel approaches for nerve regeneration mainly focusing on signaling cue presentation and Schwann cell-based therapies. They also examine the approach and efficacy of various methods to effectively present neurotropic factors and utilize potentiated Schwann cells and alternative cell types. The review also provides insight into methods of improving the functional outcome of these approaches and into the potential for combining biomaterials and cell-based approaches to enhance nerve regeneration.

Overall, it is becoming clear that engineering biological systems can be of great benefit for a range of applications. The papers in this issue focus on a small, although important, aspect of this area. These achievements are highly promising in addressing a range of problems in biomedicine, pharmaceuticals and bioenergy.