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Editorial

Smart Biomaterials, Smarter Medicine?

"End of fillings in sight" was The Telegraph's headline in a recent article reporting the promotion of natural tooth repair from a team at King's College London (UK). The study found that when a biodegradable collagen sponge soaked in the drug tideglusib (a glycogen synthase kinase-3 inhibitor) was implanted into a tooth cavity, it mobilized resident stem cells in the dental pulp to stimulate the production of dentine. As the sponge degraded, it was replaced by reparative dentine until the tooth was completely fixed. Although an exciting development, dentists should not worry…yet. The repaired teeth in this study belonged to mice. Whether or not this process can be used to repair larger holes of the size typically found in humans remains to be seen. However, what this research illustrates is the use of a novel biomaterial that might one day replace the need for metal amalgam or ceramic fillings by co-opting the body's natural regenerative process.

Using materials to address a biological problem is not a new concept. As with dental fillings, artificial hips, heart stents and orthopedic implants are all examples of non-biological materials being deployed in the human body to fulfil a health requirement. What these materials have in common is that they provide functional or structural support, but remain relatively inert. What if materials could be designed that responded to physical, chemical and/or biological cues? Advances in manufacturing processes combined with cross-talk between scientific and engineering disciplines have resulted in a rapidly emerging area within bioengineering to develop smart biomaterials. Next-generation biomaterials are rationally designed to better serve a desired function by actively or adaptively responding to dynamic stimuli.

One of the pioneers of smart biomaterial development is Robert Langer, distinguished MIT professor and 2016 recipient of the Benjamin Franklin Medal in Life Sciences. His multidisciplinary team has the expertise to tweak the macromolecular characteristics of a material so that it performs in novel and sometimes unexpected ways. One example of this approach is their creation of an alginate hydrogel that mitigates an inflammatory response when applied in vivo. Using a combinatorial approach to chemically modify alginate, a large library of variants was established. Variants with triazole derivatives were shown to inhibit the activation of macrophages in mice and non-human primates. By alleviating the foreign body response, this class of hydrogels was used to encapsulate human stem cell-derived β-cells and, when implanted in vivo, correct long-term glycemic control in diabetic mice. Such a smart material could be applied to a variety of biomedical indications, for example by coating implantable medical devices that often result in fibrosis and device failure.

As well as immuno-engineering a desired response, smart biomaterials have been developed that can improve drug delivery (e.g., liposomes, nanomaterials, and polymeric controlled release systems that respond to pH, temperature or light), adapt cell microenvironments to enhance particular characteristics (e.g., differentiate, proliferate, migrate), and act as supportive matrices in regenerative medicine (e.g., embedding stem cells in bioactive scaffolds). Anthony Atala and colleagues from Wake Forest Institute for Regenerative Medicine (USA) have developed a 3D bioprinting system to produce human tissue constructs that are of a clinically-relevant size, shape and structure. The group has designed an integrated tissue-organ printer (ITOP) that simultaneously deposits cell-laden composite hydrogels alongside a synthetic biodegradable matrix. This combination offers a supportive milieu for encapsulated cells and mechanical support to allow structural integrity that had been lacking in previous attempts. Because ITOP builds tissue constructs by additive manufacturing, complex shapes can be formed layer-by-layer, allowing the incorporation of features such as microchannels to provide a supply of nutrients and oxygen when implanted in vivo. The hydrogel component can be functionalized by adding chemical or biological moieties, to diversify its behavior. Furthermore, by integrating medical imaging data, regenerated tissue can be tailored as demonstrated by the construction of a bioprinted bone structure that fitted into a defective segment of human jaw bone. Cartilage and skeletal muscle have also been constructed using ITOP and shown to be viable. Implanted skeletal muscle was able to functionally integrate into a nerve injury mouse model and improve muscle action potential. While this technology is extremely promising, current challenges include coordinating the sheer number and diversity of cell types required to recreate printed tissues, and increasing the print speed without damaging cells.

The diversity of preclinical studies involving smart biomaterials is staggering; however, progression into clinical trials has faltered. There are a number of factors that are currently hampering this transition. First is regulatory consideration. The smart biomaterial might constitute a medical device, but contain a mixture of biologic, drug or tissue entities, each having its own distinct regulatory pathway—referred to as Combination Products in the USA and Advanced Therapeutic Medicinal Products (ATMPs) in the EU. This can be a difficult process for respective regulatory bodies to navigate, and might discourage stakeholders from embarking on this potentially risky enterprise. Second, for a product to be used clinically, it is vital that it displays predictable properties and performs reliably when encountering variable physiological conditions. Especially when using biomaterials with a cellular component, achieving this level of consistency is challenging, and is further confounded by the difficulty of quantifying a product's performance once implanted in humans.

Will the potential clinical utility of smart biomaterials overcome these regulatory and quality control hurdles? The EU Framework Program for Research and Innovation, Horizon 2020, has certainly made their intentions clear by publishing a Work Program that focuses on

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four key areas over the next two years: Nanotechnologies, Advanced Materials, Biotechnology, and Advanced Manufacturing and Processing. Within healthcare, this document prioritizes the development of biomaterials with diagnostic and therapeutic modalities, nanotechnologies for imaging cellular transplants and regenerative processes in vivo, and development of a reliable methodology for better risk management of engineered biomaterials in ATMPs. In the USA, the NIH has the Office of Biotechnology Activities to manage the development of public policies in Biomedical Technology Assessment, Biosafety and Biosecurity. We at *EBioMedicine* feel this is an encouraging stance to help turn preclinical fervor into tangible benefits and take healthcare to the next level. We hope other funding bodies agree. Langer once said he could "…envision a whole range of minimally invasive surgical products that you could insert through a small hole in the body and have snap into a desired shape". While not a reality yet, the field is certainly moving towards this realization.

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