



## Preface

Biologically inspired ‘smart’ materials<sup>☆</sup>

Inspiration from nature and its translation to designing the next generation of biomedical devices have received immense attention recently. Biologically inspired materials utilise billions of years of evolution to generate diverse properties that would otherwise be difficult to achieve. These materials have the potential to address many limitations associated with more traditional materials. This issue of *ADDR* highlights some of the most recent advances in the development of biologically inspired smart materials and systems. These materials/systems are defined as structures, material systems, sensors, actuators, or other devices that reflect the functionality found in nature and utilise smart materials [1]. Often such designs do not follow traditional engineering paradigms, but are developed through observations of natural phenomena. Bioinspired materials provide new solutions to treat diseases, support tissue regeneration and rebuild body parts and can be derived from synthetic sources (that replicate biological or natural structure, functionality, geometry of morphology), natural materials (derived from natural sources), or composite/hybrids of both classes [2–7].

Historically, natural materials such as wood or ivory were utilised to support fractured bones. In addition, naturally-derived materials have been used to help wound healing and induce skin regeneration [3,7]. Subsequent technological advances resulted in a significant shift towards synthetic materials such as metals and polymers, which were easily accessible, cheaper and satisfied the need from the functional point of view. However, with increasing knowledge and further technological advances it has been recognised that biological processes and structures can provide solutions to real-world problems [8–10]. For example, bioinspired materials offer potential solutions for addressing problems in tissue regeneration, drug delivery and preventive medicine.

Despite advances in engineering of synthetic materials that were reviewed by Kim [2], Huttmacher [6] and Wallace [8], a massive ‘back to nature’ movement and appreciation of natural materials are currently underway. The most explored examples of natural materials used in biomedical engineering include collagen [7], tropoelastin [3] and silk [5]. In her review, Abou Neel [7] highlighted that collagen is one of the most abundant proteins in mammals and its role is essential to life. Clinical uses of collagen-derived materials include products that have been shown to be effective for neural repair, as cosmetic for the treatment of dermatologic defects, haemostatic agents, mucosal wound dressing and guided bone regeneration membrane. The paper also highlighted that several other applications of collagen are under investigations [7]. Tropoelastin, which dominates the physical performance of human elastic tissue, has also received increasing appreciation in biomedicine, such as for making engineered constructs to augment

and repair human tissues including skin and vasculature [3]. In addition, Kundu and Wang [5], present the latest advances in the biomedical use of silk. Silk is currently used in applications ranging from tissue engineering (e.g. engineering ligaments, bone, bioactive coatings, stitches) to dermatological uses (e.g. hair tonics). The major advantages of silk are its mechanical properties, which are superior to any other construction materials, and its biocompatibility.

This group of naturally-derived materials can be supplemented with materials composed of natural elements that are found in the body such as calcium, phosphorous or silica [2,4]. Kim and Knowles [2,4] developed several such systems predominantly utilising glass and ceramic materials that include phosphate glasses, silica-based glasses and different forms of apatite (i.e. hydroxyl apatite and tri-calcium phosphate) [11–14]. Importantly, these materials can incorporate different ions (e.g. metal ions) which play significant functions in the body; as well as aid the formation, regulation and maintenance of biological processes [4]. Knowles and colleagues [4] reviewed the mechanisms of biological functionality of relevant ions in particular in bone formation that include: calcium, zinc, strontium, magnesium, boron, titanium and also phosphate anions as well as copper and its role in angiogenesis.

The combination of natural and synthetic materials can also be used to generate biomimetic properties [2]. In this manner, the benefits of both types of materials are merged and advanced functional materials are obtained. Strategies to provide smart capabilities to the composite biomaterials focus on achieving matrices that are instructive, inductive to cells, or that stimulate cell responses. In their paper Roach and colleagues [10], presented advances in the area of responsive materials, which can be regulated via internal or external stimuli, including pH, temperature, ionic strength, and magnetism. In fact remote and local control of responsive materials for therapeutic applications offers unique ability to change their characteristics in response to presented stimuli [8,10]. Responsive materials may be useful in biomedical applications particularly for drug delivery, protein adsorption and cell attachment to materials [15–17]. Many of these smart systems are reversible, giving rise to finer control over material properties and biological interaction, useful for various therapeutic treatment strategies [6,8,10].

Another group of ‘smart’ materials constitutes shape memory materials, superelastic materials or materials with negative Poisson ratio described by Huang et al. [18]. Mechanical stimuli are critical in tissue regeneration and this can be achieved by employing shape memory or superelastic effects [18]. Upon severe quasi-plastic deformation, shape memory materials are able to return to their original shape at the presence of the right stimulus. Hence, it makes it possible to apply the mechanical stimuli to tissue with external trigger which controls deformation of the material and directs tissue regenerations [18].

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Due to the responsiveness of the cells to chemical, topographical and mechanical signals in their microenvironment, such features can be used to control biological reactions [9,15,17,19–25]. For example, topographical features at micro- and nanoscale can be used to control cell migration, elongation and other functions [9,26]. In fact, nanotopography has been shown to control stem cell differentiation and self-renewal [27,28]. Suh and his colleagues [9] summarised the use of these approaches in many different areas and discussed the new understanding and discoveries that have emerged from this field of research (e.g. mechanotransduction).

As reviewed by Parkin and colleagues light can also be used as stimuli for activating specific response of a material [29]. Shining light on materials has already been used in activating antimicrobial surfaces [29–31]. These surfaces kill microbes by the action of light and have potential applications in domestic and healthcare settings. It has been demonstrated that both soft polymeric surfaces with either surface bound or impregnated photosensitiser molecules; and hard inorganic surfaces such as modified titanium dioxide can be engineered with such antimicrobial properties [29]. Hard inorganic surfaces also show low bacterial adherence upon light activated photo-wetting [29].

Advances in molecular biology in the past few decades and specifically advances in genomics and proteomics, and increased understanding of biocompatibility have affected the way biomaterials are designed [6]. As indicated in this issue a challenge in the development of smart biomaterials is to mimic the extracellular matrix (ECM) of natural tissues with their multiscale complexity. Despite many advances in this field [24,32,33] we are still far from recreating the molecular architecture of the ECM and dynamic processes that govern their remodelling and interactions within the host environment.

From the advances that are highlighted in this issue, it is clear that new understanding of biological process, combined with technological advances in fabrication as well as new advances in chemical sciences will result in the next generation of innovative biomaterials. Thus, nature provides significant motivation to these developments and bio/nature-inspired materials will continue to become a useful category of materials for various applications including tissue regeneration and drug delivery.

## References

- [1] G. Ephraim, Welcome to the 2013 volume, *Smart Mater. Struct.* 22 (1) (2013) 010201.
- [2] R.A. Pérez, J.-E. Won, J.C. Knowles, H.-W. Kim, Naturally and synthetic smart composite biomaterials for tissue regeneration, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 471–496.
- [3] S.M. Mithieux, S.G. Wise, A.S. Weiss, Tropoelastin – a multifaceted naturally smart material, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 421–428.
- [4] N.J. Lakhkar, I.-H. Lee, H.-W. Kim, V. Salih, I.B. Wall, J.C. Knowles, Bone formation controlled by biologically relevant inorganic ions: role and controlled delivery from phosphate-based glasses, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 405–420.
- [5] B. Kundu, R. Rajkhowa, S.C. Kundu, X. Wang, Silk fibroin biomaterials for tissue regenerations, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 457–470.
- [6] B.M. Holzapfel, J.C. Reichert, J.-T. Schantz, U. Gbureck, L. Rackwitz, U. Nth, et al., How smart do biomaterials need to be? A translational science and clinical point of view, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 581–603.
- [7] E.A. Abou Neel, L. Bozec, J.C. Knowles, O. Syed, V. Mudera, R. Day, et al., Collagen – Emerging collagen based therapies hit the patient, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 429–456.
- [8] Z. Yue, S.E. Moulton, M. Cook, S. OLeary, G.G. Wallace, Controlled delivery for neuro-bionic devices, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 559–569.
- [9] H.N. Kim, A. Jiao, N.S. Hwang, M.S. Kim, D.H. Kang, D.-H. Kim, et al., Nanotopography-guided tissue engineering and regenerative medicine, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 536–558.
- [10] A. Chan, R.P. Orme, R.A. Fricker, P. Roach, Remote and local control of stimuli responsive materials for therapeutic applications, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 497–514.
- [11] E.A. Abou Neel, W. Chrzanowski, S.P. Valappil, L.A. O'Dell, D.M. Pickup, M.E. Smith, et al., Doping of a high calcium oxide metaphosphate glass with titanium dioxide, *J. Non-Cryst. Solids* 355 (16–17) (2009) 991–1000.
- [12] A. Alani, J.C. Knowles, W. Chrzanowski, Y.-L. Ng, K. Gulabivala, Ion release characteristics, precipitate formation and sealing ability of a phosphate glass-polycaprolactone-based composite for use as a root canal obturation material, *Dent. Mater.* 25 (3) (2009) 400–410.
- [13] S.K. Misra, S.E. Philip, W. Chrzanowski, S.N. Nazhat, I. Roy, J.C. Knowles, et al., Incorporation of vitamin E in poly(3hydroxybutyrate)/bioglass composite films: effect on surface properties and cell attachment, *J. R. Soc. Interface* 6 (33) (2009) 401–409.
- [14] S.P. Valappil, D. Ready, E.A. Abou Neel, D.M. Pickup, L.A. O'Dell, W. Chrzanowski, et al., Controlled delivery of antimicrobial gallium ions from phosphate-based glasses, *Acta Biomater.* 5 (4) (2009) 1198–1210.
- [15] H. Tekin, G. Ozaydin-Ince, T. Tsinman, K.K. Gleason, R. Langer, A. Khademhosseini, et al., Responsive microgrooves for the formation of harvestable tissue constructs, *Langmuir* 27 (9) (2011) 5671–5679.
- [16] J. Cheng, B.A. Teply, S.Y. Jeong, C.H. Yim, D. Ho, I. Sherifi, et al., Magnetically responsive polymeric microparticles for oral delivery of protein drugs, *Pharm. Res.* 23 (3) (2006) 557–564.
- [17] A. Khademhosseini, E. Jabbari, *Biologically-Responsive Hybrid Biomaterials: A Reference for Material Scientists and Bioengineers*, World Scientific Publishing Co, 2010.
- [18] W.M. Huang, C.L. Song, Y.Q. Fu, C.C. Wang, Y. Zhao, H. Purnawali, et al., Shaping tissue with shape memory materials, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 515–535.
- [19] W. Chrzanowski, E.A. Abou Neel, D.A. Armitage, K. Lee, W. Walke, J.C. Knowles, Nanomechanical evaluation of nickel-titanium surface properties after alkali and electrochemical treatments, *J. R. Soc. Interface* 5 (26) (2008) 1009–1022.
- [20] W. Chrzanowski, E.A. Abou Neel, K.Y. Lee, A. Bismarck, A.M. Young, A.D. Hart, et al., Tailoring cell behavior on polymers by the incorporation of titanium doped phosphate glass filler, *Adv. Eng. Mater.* 12 (7) (2010) B298–B308.
- [21] W. Chrzanowski, A. Kondyurin, J. Lee, M. Lord, M.M.M. Bilek, H.-W. Kim, Biointerface: protein enhanced stem cells binding to implant surface, *J. Mater. Sci. Mater. Med.* 23 (9) (2012) 2203–2215.
- [22] N. Mitchell, R. Schlapak, M. Kastner, D. Armitage, W. Chrzanowski, J. Riener, et al., A DNA nanostructure for the functional assembly of chemical groups with tunable stoichiometry and defined nanoscale geometry, *Angew. Chem. Int. Ed.* 48 (3) (2009) 525–527.
- [23] R. Schlapak, D. Armitage, N. Saucedo-Zeni, W. Chrzanowski, M. Hohage, D. Caruana, et al., Selective protein and DNA adsorption on PLL-PEG films modulated by ionic strength, *Soft Matter* 5 (3) (2009) 613–621.
- [24] H. Tekin, M. Anaya, M.D. Brigham, C. Nauman, R. Langer, A. Khademhosseini, Stimuli-responsive microwells for formation and retrieval of cell aggregates, *Lab Chip* 10 (18) (2010) 2411–2418.
- [25] P. Koezler, A. Clayton, H. Thissen, G.N.C. Santos, P. Kingshott, The influence of nanostructured materials on biointerfacial interactions, *Adv. Drug Deliv. Rev.* 64 (15) (2012) 1820–1839.
- [26] E. Kang, G.S. Jeong, Y.Y. Choi, K.H. Lee, A. Khademhosseini, S.-H. Lee, Digitally tunable physicochemical coding of material composition and topography in continuous microfibres, *Nat. Mater.* 10 (11) (2011) 877–883.
- [27] M.J. Dalby, N. Gadegaard, R. Tare, A. Andar, M.O. Riehle, P. Herzyk, et al., The control of human mesenchymal cell differentiation using nanoscale symmetry and disorder, *Nat. Mater.* 6 (12) (2007) 997–1003.
- [28] M.J. Dalby, M.O. Riehle, D.S. Sutherland, H. Agheli, A.S.G. Curtis, Morphological and microarray analysis of human fibroblasts cultured on nanocolumns produced by colloidal lithography, *Eur. Cells Mater.* 9 (2005) 1–8, (discussion 8).
- [29] S. Noimark, C.W. Dunnill, I.P. Parkin, Shining light on materials – A self-sterilising revolution, *Adv. Drug Deliv. Rev.* 65 (4) (2013) 570–580.
- [30] W. Chrzanowski, S.P. Valappil, C.W. Dunnill, E.A. Abou Neel, K. Lee, I.P. Parkin, et al., Impaired bacterial attachment to light activated Ni-Ti alloy, *Mater. Sci. Eng. C* 30 (2) (2010) 225–234.
- [31] S. Pemi, C. Piccirillo, J. Pratten, P. Prokopovich, W. Chrzanowski, I.P. Parkin, et al., The antimicrobial properties of light-activated polymers containing methylene blue and gold nanoparticles, *Biomaterials* 30 (1) (2009) 89–93.
- [32] F. Edalat, H. Bae, S. Manoucheri, J.M. Cha, A. Khademhosseini, Engineering approaches toward deconstructing and controlling the stem cell environment, *Ann. Biomed. Eng.* 40 (6) (2012) 1301–1315.
- [33] B.G. Chung, K.-H. Lee, A. Khademhosseini, S.-H. Lee, Microfluidic fabrication of microengineered hydrogels and their application in tissue engineering, *Lab Chip* 12 (1) (2012) 45–59.

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