Size matters

Dr David K Mills explains his methods and the goals behind his work in nanomedicine, and describes his vision for the future of personalised and patient-specific healthcare

How has your non-traditional route into science inspired the way you work today? What attracted you to the field of biomedical engineering?

I believe I think differently compared to my biology and engineering colleagues. My bachelor’s degrees in Ancient History and Classics and Master’s degree in Biological Anthropology enable me to think outside of the box and make connections not easily seen. My humanities and social science training has provided me with a very different world view than my classically trained colleagues. I believe I am on the road less travelled and have met few fellow travellers. I was attracted to biomedical engineering for the opportunities to develop applications, biomaterials and devices that would replace ineffective treatment modalities and bring benefit and reduced costs to patients.

Can you explain what self-assembled nanofilm patterns are and how they can be utilised biologically?

Nanofilms are made up of bilayers of positively and negatively charged polyelectrolytes (proteins or other materials) assembled sequentially. Among the various techniques used for ultrathin nanofilm generation, the one that has seen much attention is layer-by-layer (LbL) nanoassembly. In this technique, oppositely charged macromolecules are placed atop each other in order to create a multi-layered structure of the order 5-500 nm. The procedure is simple and can be applied for branched and linear polymers as well as nanoparticles that are deposited alternately and produce a film that is highly tuneable in composition and properties. We use these nanofilms as biomimetic scaffolding materials. The ultimate goal of such a scaffold or substrate is that it enhances cell adhesion, proliferation and differentiated function, in a regulated or controlled fashion, allowing neotissue formation and subsequent remodelling into a mature and functional tissue.

What challenges have you encountered in developing these scaffolds, especially with respect to the complexity of natural tissue repair processes at the nanoscale?

A major challenge has been in controlling the release of drugs, antibiotics and growth factors. We have mastered sustained release using a clay nanoparticle (halloysite) by loading drugs, antibiotics and growth factors and then encapsulating them within a polyelectrolyte or polymer coating. The construction of the coating architecture can be fine-tuned to regulate the release of drugs, antibiotics and growth factors and other bioactive substances.

In 2011, you founded organicNANO. Can you explain the impetus behind establishing this company, and highlight the products it is currently developing?

The company’s mission is to develop bioactive therapeutics that prevent infection, fight disease and advance tissue repair at the nanoscale. organicNANO is poised to transform the way we fight disease, from customised disease treatments, tunable drug delivery systems, targeted therapies for cancer, and bioactive nanocoatings. A product portfolio along several discrete product lines has been developed and includes:

- Nanoenabled bone cements
- Dental nanocomposites
- Enhanced surgical materials
- Anti-infective and tissue generating bio- and nanocoatings

What has been the significance of the 3D printing approaches that you have been working on for producing personalised medical implants?

Currently, there is an intense research effort focused on applying 3D printing research to a range of health applications, including the development of blood vessels, bioengineered tissues and the production of functional biomedical materials and devices for dental and orthopaedic applications. In medicine, 3D printing and bioplastics are being used in surgical planning, in the creation of anatomical and surgical models, artificial and prosthetic devices, drugs, bio- and medical implants and even human tissue.

The main idea was to produce beads and filaments that would be printed into medical devices that are designed to reduce infection using a standard 3D printer. This novel 3D-printing technique can also incorporate chemotherapeutic drugs or hormones to assist in the treatment of, for example, chronic wounds, bone fractures and cancer.

Finally, how do you see your research aims changing in the future?

The ability to generate new tissue for musculoskeletal use is a major clinical need. Although the field of tissue engineering has progressed significantly in recent years, the promise of engineering viable tissues has not yet materialised.

We are currently working with Dr Yufeng Dung from the Department of Orthopedic Surgery at Louisiana State University Health Shreveport, USA, to create a bioengineered periosteum. We will combine his innovation of a stem cell sheet with a nanosprayed, thin and biodegradable membrane as a carrier during surgical transplantation. Our goal here is to develop well-defined biomimetic microenvironments for the regulation of stem cell behaviour and bioengineering of human tissues, for repair or replacement, through a solid understanding of the nanoscale properties of polymers and cell-matrix interactions.
A new dimension

The BioMorph lab at Louisiana Tech University is leading the way in nanomedicine; it is using 3D printing to develop novel devices for drug delivery and repair tissue damage.

Concerns over the environmental impact of nanomedicine, for example, have led to more complex safety testing of new designs, resulting in a longer pre-clinical stage. While the potential toxicity of nanoproducts has also resulted in more advanced testing. Despite these and other challenges, many experts in the field believe the nanomedical revolution is just beginning.

Leading the line for these advances is Dr David Mills and his team at the Louisiana Tech University. Mills is tackling various nanomedical problems through his BioMorph lab and his commercial arm – organicNANO. His approach is broad, taking in drug delivery, osteogenesis and even creating products compatible with 3D printing of bioactive medical materials.

**SMALL-SCALE REVOLUTION**

One of the team’s main aims is to solve the problem of efficient drug delivery for the individual. The researchers hope that by modifying 3D printing technology they will be able to create safe and cheap implants that can be loaded with antibiotic or other drugs. “The emphasis in the design was based on controlled drug release as far as how much and when. The design would be able to support whatever drugs are needed,” Mills explains. Designing implants for 3D printing means that different prototypes can be easily created and tested. From a medical point of view, the advantages of such technology lie in the personalisation and ease of access of the devices. With 3D printers becoming ever more accessible, it would be possible to download and modify the schematics for an implant that can be adapted according to the patient’s needs.

Tailored healthcare is an underlying theme of Mills’ research: “My research lab envisions a future where medical treatment has become highly personalised, with treatment modalities that are patient specific, not ‘one size fits all,’” he states. This is seen in Nanoseeds; a project aimed at delivering biomolecules capable of promoting cell growth and repair at sites of injury. The idea is to place signalling biomolecules such as bone morphogenic protein (BMP2) and vascular endothelial growth factor (VEGF) in a nanocomposite made of alginate/halloysite clay nanotubes (HNTs). These nanotubes can be made more or less permeable in order to deliver these signalling molecules at a consistent rate over different time periods. In this case, the different molecules will promote osteogenesis in the case of fractured bones. Existing drug delivery implants are both dangerous to create and do not breakdown in the body, even requiring surgery to remove. This is not the case with Nanoseeds, which has been designed to eventually degrade naturally in the body and leave no lasting effects.

Related to Nanoseeds is a broad project aimed at creating novel and dynamic nanofilms for a variety of biological uses. Nanofilms are layers of oppositely charged macromolecules and
Many of the technologies being developed in Mills’ lab have multiple uses with potential to significantly influence healthcare.

A BIG FUTURE
The future of the research is bright. Many of the technologies being developed in Mills’ lab have multiple uses with potential to significantly influence healthcare. Mills is eagerly awaiting the next step in stem cell development, creating two new projects to help facilitate stem cell treatments. Firstly, he hopes to produce structured microenvironments for regulating stem cell differentiation in vivo. This would be done using nanofilms to create a molecular gradient scaffold to allow stem cells to differentiate into different subtypes. Additionally, Mills envisions Nanoseeds being used in conjunction with stem cell therapy in order to deliver the correct signals at the right time to differentiate stem cells into the required cell type. Secondly, he hopes to manipulate substrate properties in order to allow the construction of stem cell-based biomaterials in vitro. These biomaterials would be used in a variety of ways, most notably to create implants that do not trigger a response from the host immune system.

By creating many of these designs using 3D printing technology, there is scope for this work to be adapted to other fields of medicine. The protocols created can be accessed and modified to specialise the implants and devices to tackle particular problems. Mills also envisages a healthy need for his company, organicNANO, as he notes: “Demand for our class of biomedical applications will steadily increase as the USAs ‘baby boomer’ population continues to age. Such ageing populations will be greatly aided by spinal, orthopaedic, dental, and medical devices with nanoenhanced properties”. Not only does Mills hope to meet this growing demand, but he is aiming to create more efficient and personalised treatments.