In Focus

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1. Biomaterials in Tissue Engineering – New Perspectives

In a plenary session dedicated to biomaterials in tissue engineering, Antonios Mikos (Rice University, USA) discussed the synthesis, processing and evaluation of biomaterials for new tissue engineering applications. To accurately mimic the native tissue environment, additive manufacturing techniques can be utilized to fabricate complex 3D scaffolds that traditional manufacturing methods could not otherwise achieve. This structural component can be further modified to comprise physical or biochemical gradients that interact in specific ways with native tissue to leverage a particular response. Physical gradients include altering the porosity of scaffolds to improve the success of host implantation by allowing infiltration of cellular populations, vascularization, and exchange of nutrients and waste. Modulating the stiffness of the substrate can also direct the migration of resident cells and promote differentiation of stem cell populations, acting as conduits for guided tissue growth. Biochemical gradients include modifying scaffolds with precise patterns of bioactive molecules to promote a particular cell behavior. This approach can promote targeted cell adhesion, incorporate vectors for gene delivery, respond to dynamic stimuli using smart biomaterials, or act as depots for controlled drug delivery.

A therapeutic avenue that is actively being pursued in the Mikos laboratory is to develop functionalized scaffolds to treat craniofacial defects, such as those suffered by war veterans. One of the challenges of treating large bone defects is the presence of bacterial infection. To overcome this problem, a biomaterial comprising a porous poly(methylmethacrylate) (PMMA) core was impregnated with the antibiotic clindamycin. The temporary PMMA scaffold was overlaid with a biofilm that is actively being pursued in the Mikos laboratory to develop functionalized scaffolds to treat craniofacial defects, such as those suffered by war veterans. One of the challenges of treating large bone defects is the presence of bacterial infection. To overcome this problem, a biomaterial comprising a porous poly(methylmethacrylate) (PMMA) core was impregnated with the antibiotic clindamycin. The temporary PMMA scaffold was overlaid with an osteogenic membrane to create a material with a dual function; first to clear local bacterial infection, and second to promote the formation of new bone. This implant is currently undergoing preclinical testing and has produced promising results. In a rat femoral defect model, this biomaterial was able to significantly reduce Staphylococcus aureus infection over four weeks, and restore levels of cytokine and growth factors expression. It remains to be seen if PMMA scaffolds are eventually replaced with endogenous bone, but if this is achieved, translating into humans will be the next big step.

2. Controversies in Biomaterial Science

A well-attended “Special Fellows Session” was organized by The International College of Fellows of Biomaterials Science and Engineering. Four Fellows were selected, each presenting a current controversy in the field of biomaterial research. These issues were then opened to the floor for lively debate. Buddy Ratner (University of Washington, USA) initiated proceedings with a talk titled “Patients are dying today while biomaterials experts play nano-games with low probability of future impact.” He argued that current research has moved away from addressing patients’ immediate needs, and called for sharpened focus on clinically-relevant medical devices. He acknowledged the continued need to develop biomaterials of the future, but that short-term goals should be clinically oriented. This sentiment was echoed by Maria Vallet-Regi (Universidad Complutense de Madrid, Spain) who discussed the use of nanocarriers for drug delivery and why their translation from the lab to the clinic is taking so long. Despite decades of research, no more than fifty nanomedicines have made it to market. This huge cost-benefit ratio is difficult to justify, but Maria argued that their clinical potential was great enough to pursue, albeit in a more applied manner. Elizabeth Tanner’s (University of Glasgow, UK) talk called for more rigorous biomechanical testing of biomaterials to increase the probability of clinical success. Using the continued structural failure of hip joints as an example, while past generations of biomaterials were driven by biomechanical demands, structural considerations are being overlooked as other attributes take precedence. To wrap up this session, Dietmar Hutmacher (Queensland University of Technology, Australia), who was also the recipient of the 2017 ESB International Award, spoke about Bioprintonomics. Dietmar argued that to translate bioprinting towards clinical utility, the current paradigm needs to shift from “what can this fabrication method do?” to “how can this fabrication process achieve what we need?” The need to use clinical-grade materials early in the development process would also facilitate clinical translation, with only 1–3% of preclinical publications currently fulfilling this requirement. A healthy discussion followed and consensus was largely reached regarding the need to ensure research was properly directed in a goal-oriented manner, to identify potential problems early, and to facilitate cross-talk between basic scientists, clinicians and engineers to maximize skillsets and experience.

3. Predicting Biomaterial Biocompatibility

In a session dedicated to the Immune Response of Biomaterials, Julio Suay (Universitat Jaume I, Spain) described how a proteomics approach could be used to predict biomaterial biocompatibility. This is a crucial consideration as the success of an implanted biomaterial or medical
device is largely determined by how well it is tolerated by the host. If an immune response is raised against the foreign material this can impair its intended function by becoming fibrotic, or even result in rejection. The biocompatibility of biomaterials is often determined using in vitro tests. Unfortunately there tends to be a discrepancy between in vitro and in vivo performance, usually because the culture system is unable to faithfully recreate an organism’s complex internal milieu. Suay has developed a proteomics approach to predict the in vivo response of a material by analyzing the protein composition of its exterior. The rationale is that the host immune system is most likely to interact with this outermost layer of proteins, therefore determining its outcome. Four distinct sol-gel biomaterials were chosen, all of which demonstrated similar in vitro parameters, but differed when implanted in vivo. Mass spectrometry was used to analyze the composition of the surface proteins. Six of the 171 proteins were significantly more abundant on sol-gel compounds with poor biocompatibility. These proteins were associated with the complement pathway – part of the bodies innate immune system. Using a proteome approach, it is hoped that proteins that elicit a strong immune response can be recognized and suppressed at the implant-host interface. This should help to inform the creation of a new generation of hypoallergenic biomaterials.

4. Controlling the Delivery of Cisplatin using Nanoparticles

Platinum-based compounds such as cisplatin are one of the most widely used chemotherapeutic agents, currently utilized in around half of all cancer treatments. Cisplatin is used to treat a variety of malignancies by interfering with DNA replication, thereby initiating apoptosis in proliferating cells. Unfortunately, this mechanism of action is not cancer-specific and results in the death of non-malignant cells. This is compounded by its intravenous administration, precipitating a number of unpleasant side-effects including nephrotoxicity, neurotoxicity, nausea and hearing loss. To mitigate some of these unintended side-effects, Philip Reardon (University College London, UK) presented a novel nanoparticle approach to enable the controlled-release of cisplatin. Using electrohydrodynamic atomization and adapting its configuration, cisplatin was encapsulated in core-shell nanoparticles (CS NPs) with an efficiency > 80%. Transmission electron microscopy indicated uniform distribution of cisplatin throughout the CS NP core. In vitro drug-release assays indicated a biphasic release profile, featuring an initial short burst release period of about 1 h, followed by a lower sustained release period. This is consistent with previously reported release profiles, and crucially, drug release was tunable by altering the NP shell material and/or thickness. CS NPs were effectively internalized by cultured cancer cells, and demonstrated an increased cytotoxic efficacy compared to free drug. The next step is to translate these promising in vitro findings into preclinical cancer models. To enhance the localization of the nanoparticles to a tumor site, one strategy being tested is to combine NPs with microbubbles. The rationale is that NPs trapped in microbubbles can be intravenously injected into a tumor-bearing host. If an ultrasound probe is applied to the tumor, the ultrasound will burst the bubbles and create a small shock wave that will force the NPs into malignant cells. It is hoped this ultrasound approach will enhance localized delivery of therapeutic NPs, and reduce systemic side-effects for the patient.

5. Developing Electrospun Patches to Treat Oral Candidiasis

Oral candidiasis, also known as oral thrush, is a fungal infection caused by Candida species on the mucous membranes of the mouth. Candida albicans is the most prevalent species and is carried in the mouths of approximately half of the world’s population as part of the regular oral microbiota. While not usually a problem, Candida can become pathogenic and start invading host tissue. Oral candidiasis usually affects individuals with an impaired immune system, for example those with HIV/AIDS, undergoing cancer treatment, or newborn babies with immature immune systems. The most common treatment are anti-fungal drugs, usually applied to the affected area as a topical cream. This method of delivery is sub-optimal as it is rapidly removed from the oral surface, limiting its effectiveness. In the Translational Research Symposium, Katharina Clitheroe (University of Sheffield, UK in collaboration with Dermtrat ApS) presented a solution to this challenge by creating an electrospun polymer patch incorporating antifungal agents. Due to the high surface area-volume ratio of electrospun materials, the patch can adhere to mucosal tissue and provide local and sustained release of the fungicide.

A range of fatty acids (FAs) were tested to assess their antifungal properties. Various FAs were blotted onto the electrospun membranes and tested on clinical isolates containingazole-resistant fungal species. Several longer chain FAs, such as decanoic acid, showed remarkable fungicidal activity when tested in culture. The antifungal mode of action of FAs has been previously attributed to their ability to target fungal cell membranes and increase its fluidity such that intracellular components can leak out. FAs offer an advantage over chemical fungicides as they are biodegradable, highly specific and less prone to pathogen resistance. The next step is to test these patches on superior in vitro models that incorporate mature biofilm isolates (instead of the juvenile biofilm isolates described here), before testing in vivo to see how factors such as saliva and movement of the tongue affect its fungicidal activity. If the patch proves effective under these more rigorous conditions, this approach could be translated into humans and used to treat other oral mucosal lesions.

6. Nanovaccines – An Alternative Immunization Strategy

The World Health Organization estimate that up to 1.5 million children die each year due to diseases that could have been prevented by vaccination. In a thought-provoking presentation, Noemi S Csaba (University of Santiago de Compostela, Spain) described the rational design of protamine nanocapsules as antigen delivery carriers that could offer advantages over current vaccination approaches. To demonstrate the ability of this nanocarrier platform, H1N1 influenza hemagglutinin (HI) was selected as a model viral antigen. Fabricated nanocarriers consisted of an oily core and a protamine shell, surrounded by pegylated surfactants and HI antigen. Protamine is a cationic polypeptide that can easily cross biological membranes and promote the internalization of associated molecules. It can also stabilize proteins, making it a promising compound to incorporate into drug delivery modalities. In vitro, nanocarriers were shown to enter macrophages in great numbers, without affecting cell viability. Mice immunized with HI-loaded nanocarriers exhibited a significant and sustained humoral immune response against influenza when tested 28 weeks after immunization. The response was similar to that observed in control mice treated with alum-adsorbed HI, even when lower doses of HI were incorporated into the nanocarriers, indicating adjuvant properties. Furthermore, nanocarriers could be freeze-dried and reconstituted without affecting its physicochemical characteristics, underscoring the thermostability of these nanocapsules. This feature offers a huge advantage over current vaccines that typically require refrigerated transport and storage of liquid formulations. Although currently in an early phase of development, promising proof-of-concept studies indicate that nanovaccines are tremendously versatile and effective, and warrant further testing to establish if they really do overcome the challenges that current vaccines face.