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editorial

Long-lived biomaterials

The design of implantable biomaterials with lasting function is rooted in biomolecular and cellular principles.

Implanted biomaterials that are expensive to replace or painful on failure, such as hip replacements and dental implants, should ideally stay put for a lifetime. Historically, the emphasis on increased longevity is rooted in the role of most biomaterials: to repair and replace damaged tissues and to restore function. For example, the longevity of joint replacements pivots on their mechanical compatibility with bone and on their ability to bond with the host tissue. In 1964, the Swedish physician Per-Ingvar Brånemark, who was investigating the bone-healing process using cylindrical titanium cages screwed into rabbit bone, made the incidental observation that the cages were immobile because the bony tissue surrounding them had integrated with the titanium; Brånemark had unwittingly discovered osseointegration (a term that he coined). And around that time, Sir John Charnley, who pioneered the use of metal- and plastic-bearing surfaces for total hip replacements, recognized the importance of a sterile surgical environment in preventing periprosthetic infection, a major contributor to implant loosening and failure.

Infection rates can also be significantly reduced by the introduction of antibiotics within bone cement (poly(methyl methacrylate)). The standard treatment for preventing bacterial infection around total joint replacements is a one- or two-stage revision procedure that involves the debridement of the joint cavity from bacterial biofilm before a new implant is inserted. However, infection can reoccur (requiring additional surgery), despite the use of antibiotics in the cement used to fix the new artificial joint in place (or, in the two-stage procedure, in the cement spacer that is used between implant removal and the placement of a new implant). Strategies whereby antibiotics are coated on the metal surfaces of implants or are integrated within the implant itself can prevent infection, yet they may compromise the implant's mechanical integrity. Ebru Oral and colleagues (article no. 0080) have now demonstrated long-term antibiotic elution from ultrahigh-molecular-weight polyethylene by incorporating antibiotics into the polymer in eccentrically shaped (pictured; left), rather than spherical, drug clusters. When implanted in the tibial canal of rabbits infected with *Staphylococcus aureus*, the drug-eluting polymer remained free of bacterial infection after two weeks (pictured; right) without compromising mechanical strength or increasing the expected wear rate. Because elution can continue for 12 months in the optimized material, implants could last longer and perhaps avoid the requirement for a two-stage revision in some patients.

Naturally, there are many strategies that can increase the function of implanted biomaterials. Four other advances included in this issue showcase three common approaches: enhanced integration with the host via vascular anastomosis, biological mimicry, and controlled degradation.

Foremost, vascularization is essential for the proper integration of implanted and host tissues (except for avascular tissues such as cartilage). Christopher Chen and colleagues (article no. 0083) investigated how to best achieve integration by using 3D-printed fibrin scaffolds incorporating channels seeded with endothelial cells and implanted at the injury sites in rodent models of hind-limb ischaemia and myocardial infarction. The researchers showed that large parallel channels led to a higher degree of tissue integration, anastomosis and blood perfusion than smaller channels or channels organized in other geometries. And Juan Melero-Martin and co-authors (article no. 0081), also by using implantable pre-vascularized grafts, containing either an unassembled suspension of human vascular cells or an assembled mature network of them, demonstrated that non-inflammatory host neutrophils (which are unable to engage with mature vasculature) are indispensable mediators of vascularization.

Biomaterial integration can also be enhanced by harnessing biological mimicry, which in addition can impart new function. As discussed by Lonnie Shea and collaborators in a Review Article (article no. 0077), easily implantable hydrogels with cell-surface receptors commonly expressed on tumour cells and hosting tumour-shed exosomes, soluble factors and immune-cell factors can act as metastatic niches that capture circulating tumour cells and that can later be removed for analysis. Modulating the chemistry, porosity, stiffness and degradability of a subcutaneously implantable hydrogel, as well as its biological content, could provide a test bed for the study of metastatic-cell homing and colonization, and for the discovery of biomolecular targets for the treatment of metastatic cancer.

Subcutaneously implanted gels can also act as degradable, drug-releasing depots. For example, type-2 diabetes can be treated with depots of agonists of the receptor for glucagon-like-peptide 1 (GLP-1), which stimulates insulin secretion while supressing glucagon production, thereby lowering blood-glucose levels. However, delivery of GLP-1 formulations through gel depots or via frequent (often daily) intravenous injections lead to 'peak-and-valley-shaped' drug-concentration profiles in the body. Ashutosh Chilkoti and colleagues (article no. 0078) now demonstrate that a single subcutaneous injection of an optimized formulation of a GLP-1 receptor agonist fused with a thermoresponsive polymer forms a depot that releases GLP-1 at a constant rate for extended periods in mice (over a week) and monkeys (over two weeks).

From hip and knee replacements to vascular tissue grafts to cell-trapping scaffolds to drug depots, extending the life and function of the implanted biomaterials are foremost considerations. Yet implant durability is not always crucial; the design of implanted biomaterials that are resorbed at a commensurate rate with new-tissue formation or with decreasing needs in function is a common strategy in the design of engineered tissues. After all, retention of function might be more important than retention of the biomaterial itself. ❐

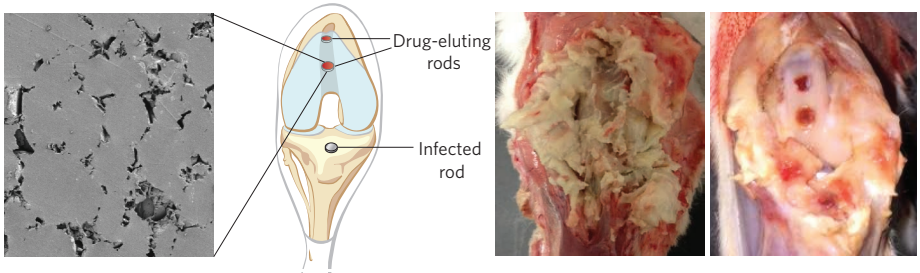

Figure adapted from article no. 0080, Macmillan Publishers Ltd.