

TISSUE ENGINEERING

A glue for biomaterials

Wall paint gives the best result if the surface is primed with an undercoat. The same concept, applied to biomaterials, yields successful fixation of implant and tissue integration.

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The cartilage that lines our moveable joints serves to support mechanical loads and facilitate movements. Its degeneration, which affects over 36 million people in the US (ref. 1), leads to great pain and impairment of mobility. During the past two decades, strategies to engineer or regenerate cartilage tissue have been bedeviled by the need to structurally integrate the implanted materials with the native cartilage. On page 385 of this issue, Dongan Wang and colleagues propose an exciting new concept based on a 'glue' capable of binding the proteins present in the existing cartilage to the materials used for tissue reconstruction or regeneration².

Cartilage has distinct functions depending on type and location, and hyaline cartilage found in joint surfaces provides shock absorption, stable movement and low friction. However, cartilage heals very poorly after injury, often leading to gradual degradation over time, which is accompanied by severe pain and a dramatic decline in quality of life. In spite of tremendous effort, cartilage has remained a particularly challenging tissue to engineer. To date, efforts to regenerate cartilage have focused on identifying the types, sources and biology of cells capable of forming cartilage, and the bulk mechanical properties of the constructs formed with these cells. The first cellular product licensed by the US Food and Drug Administration — Carticell³ — is based on a patient's own cartilage cells, sampled and multiplied outside the body. Cells derived from bone marrow⁴ have also been widely investigated as a readily available source of cells to form cartilage. Meanwhile, significant effort has been devoted to understanding the unique

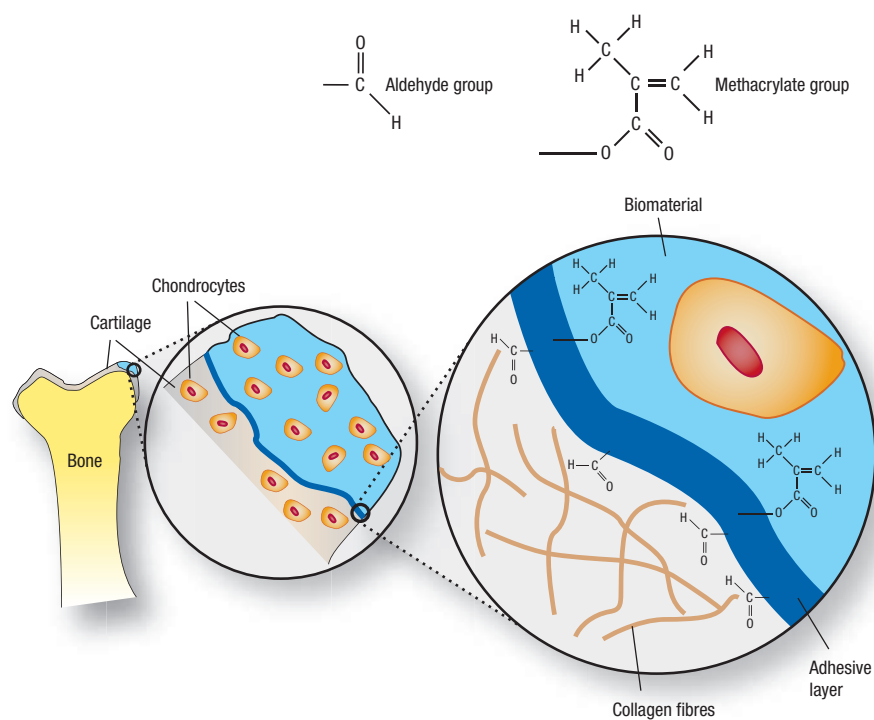


Figure 1 New tissue glued to old. Existing and implanted tissues can be glued together using an adhesive agent that binds to both. Cartilage defects are filled with a biomaterial (light blue) that is also a vehicle for transplanted cells. A very thin layer (tens of nanometres) of the adhesive (dark blue) is present at the interface between the native and new tissue. The adhesive agent is chondroitin sulphate functionalized with aldehydes, which can form covalent bonds with the amine groups of the collagen in the host tissue, and methacrylate groups, which participate in the polymerization of the biomaterial used to fill the defect.

mechanical properties of cartilage and duplicating these properties in bioactive and composite materials^{5,6}.

Unfortunately, even the most advanced biological and materials science approaches to form cartilage replacements will not find success if the new tissue does not become structurally and mechanically integrated with the native cartilage. Many of the failures associated with engineered cartilage⁷ are likely to be due to poor integration between the new and the native matrix^{8,9}. Current approaches to cartilage regeneration merely place the implanted construct in contact with native tissue and hope that long-term

stability will be achieved through entanglement of the newly synthesized matrix with the existing matrix. But the rate at which this process occurs seems to be rather slow and the resulting adhesion is poor.

The new approach described by Wang and colleagues does not attempt to attach the new tissue directly to the old. Instead it relies on an adhesive agent as an intermediary that can chemically bind both the native tissue and the material used to fill the defect. The authors provide an analogy to the primers that are widely used to fix paint to walls. A more direct connection can be drawn

with the primers used by dentists to bond restorative materials to our teeth, as these also provide for the formation of strong chemical bonds between the restorative and the native tooth structure¹⁰. Wang and colleagues functionalized chondroitin sulphate, which is one of the components of native cartilage, with two distinct organic moieties: methacrylate and aldehyde groups. The aldehydes form a covalent bond with the native cartilage tissue (presumably reacting with the amine groups of the collagen). At the same time this adhesive can bind to the biomaterial, as the methacrylate groups participate in the polymerization reaction used to solidify the biomaterial once it is introduced in the tissue defect. Together, these modifications yield a unique architecture illustrated in Fig. 1. Notably, this tissue primer provides a strong mechanical bond to the native

cartilage, and does not damage the cells delivered through the biomaterial or the native cartilage. Ultimately, this approach led to significantly greater tissue repair of cartilage defects in two different *in vivo* experiments using rabbits and goats.

Future studies will clearly be required to determine if these specific chemistries and procedures can lead to long-term functional cartilage repair in animals, and ultimately humans, but this general concept seems to be full of promise. It may be further extended by the incorporation of specific cytokines or growth factors that direct the metabolic activity of cartilage cells, potentially enhancing cross-talk between the host and new tissue. The work of Wang *et al.* will most likely be applicable, not only to orthopaedic tissue repair, but also more broadly to any situation in which separate tissues (native or engineered) need to be adhered. It is

an excellent example of the high level of sophistication that can be achieved in tissue engineering, and introduces the perspective that native tissue is to be considered as a partner in determining the fate of new tissues.

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ELECTRONIC TEXTILES

A logical step

The integration of electronics and clothing promises a variety of new technologies, but constructing electronic circuits on fabrics is complex. Coating fibres to create electrodes and forming transistors at their crossing points offers an elegant solution.

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The concept of multifunctional — electronic or ‘smart’ — fabrics was suggested several years ago¹, but only recently has their true potential to make life safer, healthier and more comfortable been recognised. Multifunctional fabrics are conceived as innovative and high-knowledge-content apparel, integrating sensing, actuation, processing and power functions into a single garment². Perhaps the most compelling application is that of providing quality health care in modern society, delivered by means of easy-to-use wearable interfaces, to enable prevention, diagnosis, therapy and even rehabilitation³.

Although considerable progress towards these goals has been made in some areas, the realization of viable textile fibres endowed with active electronic functions has proved to be more elusive. On page 357 of this issue, Olle Inganäs and

colleagues take a step in this direction⁴. By coating fibres with conducting polymer, they can join them with solid electrolyte at cross-points to form micrometre-sized organic electrochemical transistors (OECTs). They then use the OECTs as components for logic circuits, offering an alternative approach to organic field effect transistors (OFETs) commonly used in flexible electronics⁵. The wire OECTs provide an easier route to weaving electronics directly into fabrics.

Common OFETs operate like electrical valves, with the flow of current between the source and drain electrodes controlled by the voltage of the gate electrode. Increasing the gate voltage injects charges into the conducting polymer next to the gate electrode, creating a conduction channel, through which the source-to-drain current flows (Fig. 1a). The magnitude of the voltage applied by the gate controls the size of this conduction channel. OFETs can be flexible, but printing them onto fibres^{6,7} is a complex process — their successful operation depends on the accurate control of the electric field applied to the polymer

by the gate electrode, which in turn requires a very thin and uniform insulating layer to be deposited between the gate and active polymer. Precise micropatterning of source drain and gate electrodes on a fibre is therefore needed. These requirements make the implementation of OFET-based knitted or woven structures very impractical.

In the OECTs used by Inganäs and colleagues, the conducting channel is made by ions being injected from or removed to a solid electrolyte reservoir (Fig. 1b), which is in turn controlled by the gate electrode. This means very large conductivity changes can be easily induced, and these conductivity changes control the source-to-drain current in the same way as the injected charges from the gate electrode in the OFET. Because of the differences in the way the devices work, the need for accurate dimensions and precise positioning of the transistor subparts is greatly relaxed in OECTs compared with OFETs. OECTs also benefit from needing very low operating voltages — of the order of a couple of volts.