PERSPECTIVE

Work with, not against, biology

Advances in technology have outpaced our understanding of organ development and injury response. It's time to reassess, says **Stephen Badylak**.

Medical science is failing to translate promising bench research on engineered tissues and organs into clinical practice. The original, and still dominant, template for creating replacement tissues was established in the 1980s and involves the culture of cells on a degradable scaffold in the shape of the target body part, which is then implanted into the recipient. Numerous reports of human ears[1], blood vessels[2], bladders[3] and other body parts manufactured using this approach have generated a great deal of enthusiasm and, in the 1990s, gave rise to the field of tissue engineering.

But, with only a few exceptions, these replacement tissues are not being implanted in patients. There are the usual regulatory, manufacturing and reimbursement challenges, although most of these are manageable. One possible, and crucial, problem is that the tissues created by this generic approach lack many of the supportive elements that sustain the viability and function of the cells. Organs and tissues need effective vascular, lymphatic and innervation networks, but these are not part of the current design template; nor do they have enough time to develop organically before the transplant organ dies. Tissue engineers have also failed to consider the cells' microenvironment, which includes factors such as mechanical forces, pH and oxygen concentration, as well as signalling molecules embedded in the extracellular matrix. As a result, once implanted, the carefully engineered tissue is treated like a foreign body. Instead of being a drop-in, friendly replacement tissue, these grafts rapidly die from a lack of nutrients, appropriate growth factors and innervation[4].

Then there is the immune system: the body's highly regulated method for orchestrating processes such as tissue and organ development, response to injury and infection, response to foreign cells and, importantly, regulation of tissue repair and reconstruction. Such processes may seem obvious to developmental biologists, immunologists and molecular biologists, but the tissue-engineering community has tended to either ignore the inevitable immune-system recognition of scaffolds and engineered tissues until the later stages of development, or conduct studies in immunocompromised rodent models that fail to take into account the potential effect of these factors on downstream clinical outcomes.

In spite of (or, in some cases, because of) incredible advances in genomic mapping, 3D cell printing, stem-cell biology, biomaterial development and bioreactor design, we have stubbornly adhered to the old approach. With current technology, a 3D replica of a patient's ear, based on a template created from elegant imaging techniques, can be fabricated by devices that deposit different types of cell layer by layer. As the 3D structure is recreated before our eyes, it is easy to forget that the natural intercellular connections necessary for cell-to-cell communication and support are not present.

Failure to consider the effect of these robotic techniques on cell viability and phenotype, the omission of extracellular matrix molecules and the inability to 'print' the appropriate sensory and motor nerves and lymphatic networks, mean that these constructs will remain visually impressive but non-functional examples of state-of-the-art technology.

What can be done to advance the field and deliver on the promises of tissue engineering? It is time to combine forces with cross-disciplinary colleagues to first identify, then overcome, the biological obstacles that currently prevent the creation of functional tissue and organ replacements. These challenges are not insurmountable, but they must be acknowledged.

Of particular interest is the potential for tissue and organ regeneration that exists within the human genome (see page S58). Much has already been learned from salamanders, which can regrow an impressive array of body parts following injury[5]. The innate immune system has an active role in such developmental and regenerative processes[6]. Macrophages, for example, a cell type long identified with chronic inflammation, are necessary for limb regeneration in salamanders. This requirement suggests that it may be possible to reactivate similar signals in humans by working with the natural immune system rather than attempting to evade or suppress the host immune response. Successful tissue replacement may be as simple as placing an appropriate template embedded with biological cues at the intended anatomical site and using the body as the ultimate bioreactor, instead of attempting to recreate the organ or tissue externally.

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Incredible progress has been made in the field of tissue engineering and regenerative medicine, but it is time for a course correction. The promises of the 1990s can still be fulfilled, but this will require willingness among tissue engineers to identify the processes that are working well, abandon the approaches that have inherent limitations and incorporate, where possible, the fundamental principles of normal mammalian development and regeneration. ■

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