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# Biomaterials and scaffolds for tissue engineering and regenerative medicine

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**Abstract**

Methods in tissue engineering and regenerative medicine are constantly evolving to address the complex challenges of repairing damaged tissues and modeling diseased organs using a library of various biomaterials, cellular therapies, and biofabrication techniques. The *BMC Methods* Collection 'Biomaterials and scaffolds for tissue engineering and regenerative medicine' will host the most recent advances in tissue engineering and regenerative medicine approaches, providing a comprehensive resource for researchers in the field.

## Main text

During the last three decades, the number of approaches to engineer new functional tissues has exponentially grown to build an extensive library of methodologies.

Since the initial attempts of Langer and Vacanti [1], tissue engineering and regenerative medicine (TERM) methodologies have gathered extensive expertise in harnessing biomaterials and cellular components for the fabrication of functional substitutes. Today, new technologies (e.g., 3D bioprinting and organoids) are empowering laboratories worldwide to develop new approaches for engineering functional implants [2].

In the *BMC Methods* Collection 'Biomaterials and scaffolds for tissue engineering and regenerative medicine' (https://www.biomedcentral.com/collections/bsterm), we aim to collect original articles on the latest methodologies for the characterization of biomaterials and fabrication of scaffolds for TERM purposes.

## Methods in tissue engineering and regenerative medicine

TERM approaches extensively rely on using biomaterials to build scaffolding structures with or without cells to produce viable implantable tissues [3]. Engineered constructs are composed of biomaterials, which are biocompatible and biodegradable, to allow the ultimate degradation of the implantable tissues as well as support tissue maturation and regeneration. Typically, scaffolding materials provide a framework for cells to adhere, proliferate and differentiate. However, decades of research on un-modified biomaterials have now produced the understanding of the need for functional polymers. New methodologies have been developed to decorate biomaterials with bioactive peptides that might resemble adhesive (e.g., RGD), biomimetic (e.g., laminin-mimetic) and degradable (e.g., MMP-sensitive) moieties. New methods to engineer functional materials are constantly evolving, including approaches to investigate cellular functionality and implant bioactivity. However, there is an unmet need for biomimetic functional biomaterials capable of sustaining cell differentiation and tissue growth following implantation or model fabrication. Moreover, the number of technologies capable of processing biomaterial for

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scaffold fabrication (e.g., electrospinning and 3D printing) have evolved, resulting in the development of new approaches yet to be exploited by the tissue engineering and regenerative medicine research fields. However, the need for more standardized protocols and procedures currently limits the adoption of such new technologies by many researchers.

## Emerging approaches for regeneration and modelling

Technological advancements are rapidly revolutionizing TERM methodologies. New frontiers in biomaterial design and strategies are supporting the functional engineering of new tissue models for either regeneration or disease modelling [4].

### Bioactive materials

Natural and synthetic polymers have been extensively used in tissue engineering approaches, from single material scaffold preparation to complex 3D bioprinting with multi-material approaches. However, the lack of functional sites that resemble the physiological extracellular matrices (ECMs) has greatly limited the advancement towards a biomimetic approach. Thus, the decoration of polymers with functional moieties is being explored to improve the physicochemical properties and biological functionality of biomaterials.

### ECM-based materials

Researchers are developing new approaches for decellularising tissues to produce ECM-based materials that better resemble human physiology. Tissue-derived materials are ideal candidates for encapsulating new cellular and biologics components, supporting *in vivo* delivery for ad-hoc degradation and tissue maturation. Native matrices typically recapitulate physiological ECM, thus providing the support needed for cell division, differentiation and further maturation *in vitro* and *in vivo* [5].

### Organoids

A powerful approach to engineering organ-like constructs is based on the self-assembling ability of cells in 3D forming organoids upon uncoated surface exposure. Organoids are cellular aggregates capable of recapitulating a wide variety of physiological functions *in vitro* without the need of supporting biomatrices [6]. Nevertheless, there are still limitations associated with the use of organoids for drug screening, such as the poor viability due to the absence of vasculature, and the limited scalability in laboratory facilities.

## Challenges and opportunities for clinical impact

Researchers and clinicians developing biomaterials for tissue engineering and regenerative medicine face many unsolved challenges. Below, we describe some significant obstacles to the clinical translation of tissue-engineered constructs.

(i) *Vasculature*. To date, we can considerably scale up the fabrication of implantable tissues. For example, 3D bioprinting technologies have facilitated the fabrication of large implantable constructs. However, insufficient vascularisation during tissue regeneration is associated with poor repair outcomes. Therefore, improving the biocompatibility of engineered constructs and enhancing the integration and vascularisation of post-implantation is crucial. There is a need to explore viable methods to drive new vasculature formation within engineered tissues [7].

(ii) *Interfacial tissues*. Current methods used for tissue fabrication are limited in stacking more than a single tissue at a time. Nevertheless, human tissues are always in contact with other/different tissue types, making tissue interfaces essential for the functional repair of damaged organs. New approaches are needed to guide the spatial transition from one tissue type to another (e.g., bone-cartilage, bone-neuro, tendon-muscle) [8].

(iii) *Cell density and maturation*. Cells are the major component of human tissues. Tissues have unique cell numbers in the order of tens of millions [9]. To date, we are still unable to gain such density, failing to ultimately recapitulate tissue functionality. Lately, the rapid surge of lab-based meat production has drastically augmented interest in *ex vivo* cell expansion. Advancements in cell culture are yet to be implemented, along with robust methodologies for cell expansion [10]. The immaturity of the structure and function of tissues created using stem cell derived cells is also a bottleneck for translation to the clinic. Further research is needed into the maturation of such cells for therapeutic purposes [11].

(iv) *Immunomodulation*. Tissue regeneration is a temporal process including i) inflammation, ii) soft/hard tissue formation, and, iii) regeneration. The immune response to a biomaterial plays a pivotal role in the subsequent stages of repair and, when ineffective, can cause a stagnated inflammatory state that delays tissue formation. Immune cells, typically macrophages, play a key role in the body's response to implanted materials. New methodologies to engineer new classes of implants that can modulate macrophage response

to accelerate the tissue regeneration process are urgently needed [12].

## Conclusions

The incremental effort that has allowed the rapid evolution of TERM has stimulated the engineering of unique protocols for functional tissue fabrication approaches. To date, there has been a limited effort in gathering TERM protocols to optimize a library of methods.

With this new collection, we aim to offer new perspectives on the latest advancements in TERM methodologies. Spanning from biomaterial design to novel tissue fabrication methodologies, we will collect unique work focusing on innovative methods for tissue regeneration or disease modelling.

### Abbreviations

TERM Tissue engineering and regenerative medicine
ECM Extracellular matrix

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### Authors' contributions

Y.K., S.V., and G.C. wrote the main manuscript text. All authors reviewed the manuscript.

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### Availability of data and materials

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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