Editorial

Special Issue: Application of Extracellular Matrix in Regenerative Medicine

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Abstract: The present Special Issue comprises a collection of articles addressing the many ways in which extracellular matrix (ECM), or its components parts, can be used in regenerative medicine applications. ECM is a dynamic structure, composed of a three-dimensional architecture of fibrous proteins, proteoglycans, and glycosaminoglycans, synthesized by the resident cells. Consequently, ECM can be considered as nature's ideal biologic scaffold material. The articles in this Special Issue cover a range of topics from the use of ECM components to manufacture scaffold materials, understanding how changes in ECM composition can lead to the development of disease, and how decellularization techniques can be used to develop tissue-derived ECM scaffolds for whole organ regeneration and wound repair. This editorial briefly summarizes the most interesting aspects of these articles.

Keywords: extracellular matrix; scaffold; wound healing; regenerative medicine; tissue engineering; decellularization

Citation: Turner, N.J. Special Issue: Application of Extracellular Matrix in Regenerative Medicine. *Appl. Sci.* **2021**, *11*, 3262. <https://doi.org/10.3390/app11073262>

Received: 10 March 2021

Accepted: 19 March 2021

Published: 6 April 2021

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Regenerative medicine is an interdisciplinary field that uses the principles of bioengineering, developmental biology, immunology, and stem cell biology to restore diseased and injured tissues and whole organs. The field of regenerative medicine encompasses a number of strategies, but these can broadly be grouped into approaches using scaffolds, cells, soluble factors or various combinations thereof. The focus of this Special Issue is on scaffolds and the use extracellular matrix (ECM) and its components in the development of biologic scaffolds. The primary role of a scaffold is to provide structural support and a suitable environment to modulate cell attachment and cell behavior. In addition to their structural role, biologic scaffolds also have a microenvironmental role delivering bioactive molecules such as growth factors and cytokines, functional molecules such as antimicrobial or anti-inflammatory drugs, as well as morphogenic cues from the structural ECM components such as collagen, laminin, and fibronectin. The articles in the present issue cover a range of topics including the use ECM components to manufacture biologic scaffold materials, understanding how changes in ECM composition can lead to the development of disease, and how decellularization techniques can be used to develop tissue-derived ECM scaffolds for whole organ regeneration and wound repair.

All tissues and organs contain a mixture of cells and structural and functional molecules. These structural and functional molecules form on an organized network called ECM. ECM not only provides structure support to the tissues and organs but also regulates many cellular processes including proliferation, migration, differentiation, helping to define the function of each tissue and organ. In fact, the ECM is responsible for, and responsive to, the continually changing mechanical, metabolic, and functional needs of these cells. Thus, ECM plays a vital role in response to injury and disease where the mechanical and physiological states of tissues are altered. ECM consists of a large variety of fibrillar macromolecules including collagens, laminins, elastin, fibronectin, glycoproteins, proteoglycans, and glycosaminoglycans that form the major structural components of ECM. In addition,

all cell types synthesize and secrete matrix macromolecules, growth factors, cytokines, and other signaling molecules and result in ECMs that are unique to each tissue and organ in the body. New discoveries about ECM composition and function continue to be made, and this wealth of knowledge has allowed researchers to utilize components of ECM to engineer scaffold to attract cells and promote cell growth or differentiation. Others have used the native ECM, derived from decellularized tissues, as nature's ideal biological scaffold material to promote site-appropriate tissue repair and potentially grow new tissues and organs in vitro.

In this Special Issue, Dussoyer et al. provide a review of the use of decellularized scaffolds for skin repair and regeneration [1]. This provides an excellent introduction to the topic and describes in detail the different source tissue from which the scaffold materials are derived and the different techniques that can be used to successfully remove cells from tissue. The article highlights the diversity of decellularized scaffolds that are now in clinical use, showing that it is not necessary to use a tissue-specific scaffold material to promote constructive tissue remodeling and that scaffold materials derived from intestine, bladder or amniotic membrane are equally practical for promoting skin wound repair. In their review of whole organ engineering, Sohn et al. describe how the decellularization techniques described by Dussoyer et al. have been adapted and applied to the field of organ transplantation to develop decellularized organs with the long-term goal of having "off the shelf" organ transplants available for patients [2]. This comprehensive review describes the long history of tissue engineering and longstanding goal to develop functional organs in vitro. The review article highlights the important steps in cell culture, scaffold development, and surgical technique that have allowed advances in organ engineering to take place. The article describes the different potential approaches to using ECM for organ engineering, from using decellularized cadaveric organs to using engineered ECM scaffolds such as films or sponges through to more modern approaches such as 3D printing of ECM gels. Importantly, in addition to highlighting the advances that have been made, Sohn et al. also discuss the challenges and barriers to market that still need to be overcome. These are challenges that not only affect whole organ engineering but are limiting factors to translating all ECM-based regenerative medicine strategies into therapeutic products.

In addition to ECM scaffolds derived from decellularized tissues, researchers also use components of ECM to manufacture novel scaffold materials for regenerative medicine, and several examples are included in this Special Issue. Norris et al. describe their work fabricating engineered scaffolds from collagen and fibronectin [3]. In this study, the authors expose the collagen and fibronectin gels to ultrasound waves during the polymerization phase. This results in a distinct pattern of collagen fibril formation and closer association of the fibronectin component to the collagen fibrils. While the ultrasound-treated gels reduced initial cell attachment, they promoted the formation of more multicellular spheroids, and refinement of this technique could result in scaffolds with defined ECM structures that could promote specific cell behaviors. The paper by Goller and Turner also focuses on the development of an engineered ECM scaffold, in this case a hybrid scaffold combining chitosan with an ECM hydrogel derived from decellularized urinary bladder [4]. In this study, the authors show that by varying the proportions of the chitosan and ECM gels, they can produce scaffolds with different physical properties. Moreover, they show that these scaffolds can be augmented with antibiotics and that the release characteristics of the antibiotics are also influenced by the composition of the scaffold. Bellrichard et al. take a slightly different approach to engineering a scaffold. The authors use decellularized tendon as the scaffold material but augment the scaffold with gold nanoparticles with the goal of reducing the inflammatory response [5]. In this proof of principle study, the authors showed that they could successfully attach gold nanoparticles to the ECM scaffolds using genipin crosslinking and that these gold nanoparticles had no detrimental effects on cell viability or cell attachment. The effects of these nanoparticles on the host response to the ECM scaffolds is still unknown, but all these manuscripts demonstrate how researchers can modify or engineer ECM materials to develop scaffolds that enhance the beneficial

effects of the ECM while minimizing some of the factors that are detrimental to wound healing and tissue repair.

If regenerative medicine approaches are to be successful in promoting tissue repair, it is important to understand the role ECM plays in modifying cell behavior and how changes in ECM composition can lead to the development of disease. Chaher et al. have provided a detailed review on the structure of ECM and how the ECM changes in cardiovascular diseases such as atherosclerosis and myocardial infarction [6]. The review highlights the changes in ECM composition that occur and how these changes in the ECM can alter the mechanical properties of the tissue, leading to further progression of the disease and associated morbidity for the patients. Importantly, the authors highlight the imaging techniques that can be employed to detect and monitor the ECM changes associated with cardiovascular diseases. It is by using these imaging techniques that the role ECM plays in disease progression can be determined, and this information has an important role to play in developing therapeutic strategies to prevent or reverse disease progression in the future. Finally, Ghanemi et al. provide a brief review of the role ECM-associated proteins play in tissue homeostasis and may play a role in disease progression [7]. ECM-associated proteins are non-structural proteins that are embedded within the ECM and are increasingly seen as vital to maintaining a healthy tissue microenvironment. In their review, Ghanemi et al. focus on the SPARC protein due to its importance in tissue remodeling. They highlight its role in both metabolic functions such as energy metabolism or adipose tissue formation as well as its homeostatic roles in modulating inflammation and cell development. This review highlights the complex role ECM plays in maintaining tissue health and complex interactions that occur between cells and ECM.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: This Special Issue would not be possible without the contributions of the authors, hardworking and professional reviewers, and dedicated editorial team members of the *Applied Sciences* journal. I would like to take this opportunity to thank everyone for their valuable contribution to this collection.

Conflicts of Interest: The author declares no conflict of interest.

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