Natural Fibrous Polymers for Tissue Engineering
Thais Sayuri Iguma\textsuperscript{1}, Sonia Maria Malmonge\textsuperscript{2} and Arnaldo R. Santos Jr\textsuperscript{1*}

\textsuperscript{1}Centro de Ciências Naturais e Humanas (CCNH), Universidade Federal do ABC, Brazil.
\textsuperscript{2}Centro de Engenharias, Modelagem e Ciências Sociais Aplicadas, Universidade Federal do ABC, Brazil.

\textsuperscript{*}Correspondence: Arnaldo R Santos Jr, Centro de Ciências Naturais e Humanas, Universidade Federal do ABC, Brazil, E-mail: arnaldo.santos@ufabc.edu.br.

Received: 10 August 2019; Accepted: 07 September 2019

Citation: Iguma TS, Malmonge SM, Santos Jr AR. Natural Fibrous Polymers for Tissue Engineering. Stem Cells Regen Med. 2019; 3(1): 1-4.

ABSTRACT
As life expectancy grows, many age-related diseases are becoming increasingly evident such as osteoporosis, diabetes or cardiovascular disorders. Not only that, some studies are also pointing up an increase of road accidents and trauma injuries boosting the implants market. Many techniques have been developed in order to repair damaged organs, and Tissue Engineering (TE) is a promising one. In order to reduce the dependence on transplanted tissues and organs, TE combines the field of life science with engineering by developing a 3D template (scaffold) which temporarily mimics an extracellular matrix (ECM) and provides a support for cells to grow and proliferate with the right stimuli (signals). Not only may the source of the cells and signals vary, but also the scaffold itself. Depending on the purpose, there are many possibilities in which the scaffold can be designed: ceramic materials, synthetic or natural polymers with a vast range of architecture. Creating a system as similar as possible to ECM is advantageous for the cells, for this reason fibrous structures and natural polymers, such as collagen and gelatin, are outstanding regarding TE.

Keywords
Tissue engineering, Disease study, Organs, Polymers, Implants.

Introduction
Over the years, life expectancy has been growing considerably. According to the Global Burden of Disease Study 2017, People are living approximately 23 years longer in 2017 than they were in 1950 [1]. On the other hand, many age-related diseases are becoming increasingly evident, for example, osteoporosis, diabetes or cardiovascular disorders [2], and researchers have been striving to improve the quality of life of those in need. In the same way, not only the elderly citizens are under the spotlight of medical researches, but also people of all ages who have suffered tissue lesions from mechanical trauma or degenerative diseases. Some studies are also pointing up an increase of road accidents and trauma injuries [3,4], boosting the implants market [5]. Many techniques have been developed in order to repair damaged organs, such as the replacement of the injured tissue or regeneration stimulus of the patient’s own tissue [6].

Two main procedures used for repairing lesions can be mentioned: transplant and implant [6]. In the first one, organs or tissues are provided from living donors, cadavers or even from other species (xenotransplantation), and it is commonly associated with rejection and microbial contamination, which requires immunosuppressive medications. Moreover, transplant techniques have some obstacles concerning religion and ethical issues [6,7]. Implants, on the other hand, have many advantages comparing to transplants. For instance, an implant (or bioimplant) does not necessarily need a donor, since it is an engineering device designed specifically for replacing or assisting natural tissues [5]. The prostheses can be made with a huge variety of biomaterials among the three major classes: metallic, ceramic, and polymeric materials [8].

Biomaterials can be described as “Any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ or function of the body” [9,10], and it can be classified into three groups: bioinert, bioactive or bioresorbable. The essential characteristic of bioinert materials is the almost nonexistent interaction between material-tissue interface, providing to the tissue a minimum response, frequently resulting in the formation of a fibrous capsule around the implant. Bioactive materials have the
ability to supply with considerable interaction between the tissue and the device, as a consequence of strong chemical bonds. Finally, bioresorbable materials do not have to be surgically removed from the body, i.e., they can be absorbed and eliminated by the organism itself without harmful responses. Bioinert materials are frequently associated with metals, bioactive with ceramics and bioresorbable with polymers, but those materials are often found associated as a composite [8,12,13].

Nowadays, polymers are widely used in biomedical field, because they are versatile and have several advantages comparing to metals and ceramics. Polymeric materials usually exhibit low density, and low resistance to temperature. Nonetheless, they can be easily tailored with an extensive range of desirable properties. There are many particular ways to classify polymers. One of them is related to their origin: natural or synthetic. Natural biopolymers are derived from renewable or biological sources whereas synthetic are chemically synthesized. Polymer biological applicability is ample: from medical supplies (blood bags and surgical tools), to therapeutic treatment (implants) and recently reaching regenerative medicine and tissue engineering [14,15].

**Tissue Engineering**

Tissue engineering (TE), as the name suggests, combines the field of life science with engineering in order to reduce the dependence on transplanted tissues and organs from a donor (allogeneic) or the same patient (autogenic). The essence of TE is to provide a solution prompting repair, replacement or even regeneration of damaged tissues caused by diseases or injuries instead of replacing them. TE is founded on the combination of three pillars: cells, signaling mechanism and a three-dimensional template (scaffold) [16]. To summarize, it involves the production of a 3D template which temporarily mimics an extracellular matrix (ECM), providing a support for cells to grow and proliferate with the right stimuli (signals). The system can be firstly cultured in vitro and subsequently implanted in the patient, or directly applied in vivo [16,17].

The cellular sources in TE may vary: cells can be provided from a different individual, other species (both can cause immunological rejection) or stem cells from the patient himself [17]. To assist the cells proliferations, many techniques can be adopted, such as chemical stimuli substances (growth factors and adhesion molecules) or mechanical stimuli (bioreactors). The TE success also depends on the implantable matrices: scaffolds must guarantee an environment for cells to adhere and proliferate. In order to provide that, the device must have biocompatibility and a propitious architecture with interconnected pores to assist cell incorporation and allow movement of fluids as nutrient delivery and waste removal [16,17].

Khademhosseini & Langer (2016) have put forward several advances concerning TE over the last decade. Not only novel methods regarding cellular sources and stimuli (iPSCs and CRISPR-Cas9), but also state-of-the-art technologies creating efficient scaffolds (programmed modular self-assembly and bioprinters). Furthermore, besides the well-known applications for organs such as skin, bone, cartilage, liver and intestine [18], they pointed up a few potential applications of TE designed to assist, for example, neuronal connections, vascular tissue or lateral collateral ligaments. Additionally, the authors mentioned applications beyond medical purpose, such as biological actuators, robotic and food industry [19].

Depending on the purpose, there are many possibilities in which the scaffold can be designed. Firstly, the biomaterial is usually ceramic or polymer (natural or synthetic), or even both combined as a composite. Ceramics are brittle, with low elasticity and hardly molded, which may be an obstacle for implantation. However, its high mechanical stiffness shows similarities to bone tissue [16]. On the other hand, for soft tissue applications, polymers might present better results. As such, one of the advantages of polymers in TE is the different fabrication techniques resulting in unique scaffold architectures as similar as possible to the original tissue. Polymer fibrous structures, for instance, have shown to have promising potential in TE due to its morphological resemblance to ECM [20].

**Fibrous Materials**

Regarding fibrous scaffolds, not only the nature of the material is important, but also the morphology and fiber pattern play a pivotal role to guarantee success in TE. Several tissues and organs have their own particular pattern of fiber organization, and the topographic and mechanical feature is crucial for cells to survive and proliferate in order to become functional tissues. Thus, it is necessary to understand the interaction between cell and ECM. Depending on the chosen technique, it allows to organize the fiber orientation pattern, fiber dimensions, pore size, and so forth. Also, there are several methods available on the market with a different range of cost, availability, processability and results [20].

So far, electrospinning is probably the most common technique to design fibrous scaffolds [20]. The method uses electrostatic interaction to produce fibers with solution or melted polymer. Even though it can reach finer diameters, it has several disadvantages comparing to others, e.g., smaller pore sizes, hindering cell infiltration, and inefficiency in building 3D structures [21-23]. Centrifugal spinning is a different technique which uses a centrifugal force provided from a rotating spinning head to produce fibers. The fluid is ejected when the centrifugal force exceeds its surface tension, and the liquid is deposited on the collector, solidifying. The method is safer, and it has higher production rate comparing to electrospinning [24]. Considerable novel techniques have been developed as an alternative to both methods described previously. Solution blow spinning (SBS) is a versatile and accessible method consisting in spraying a polymer solution jet accelerated by compressed gas. The injection rate and pressure can be regulated and, once the fibers are extruded and deposited on the collector, the solvent evaporates. Airbrushing is another accessible technique (similar to airbrushing for painting), which uses compressed nitrogen stream to push the polymer onto the collector. This method is easier to handle, even though the solution rate cannot be controlled. Comparing to electrospinning,
Crosslinking gelatin not only increases mechanical properties, but also enhances stability and provides insolubility. The three main routes to crosslinking gelatin are through chemical, physical or enzymatic methods. Crosslinking gelatin using glutaraldehyde (GTA) is a chemical method, and one of the most common mechanism in the biomedical field literature, essentially because of its efficiency. GTA, however, is cytotoxic and, without proper removal, the residue can be harmful to the cells [36]. There are two main methods of crosslinking by GTA: solution or vapor phase. The GTA solution makes it harder to remove residues after the process, even though it is faster and efficient. Vapor phase, on the other hand, it is a time-consuming method and, whether the structure of the scaffold is a thick/bulk material (e.g., sponge), it is difficult to reach the core, resulting in worse crosslinking degree. However, when it comes to fibrous gelatin structures, the contact surface area of the material is usually wider, and the pores, larger. Thus, vapor GTA might have greater potential [36,37].

Fibrous scaffolds made with pure gelatin are not common in TE literature. As previously mentioned, they are usually combined with other materials, improving mechanical properties and stability. Plus, the predominant scaffold manufacturing technique is still electrospinning, which might even allow crosslinking during the process (in situ) in order to control the degradation rate and final morphology, instead of using GTA solution or vapor [38]. Gelatin fibrous scaffolds may have significant potential for soft tissue injuries, such as skin regeneration [39] and others.

**Conclusion**

It is not possible to define the best technique to use in all TE applications. The chosen method and material always depend on the purpose, since every choice has its own advantages and disadvantages. It is crucial to understand the structure and function of the original tissue, designing the apparatus with great potential to mimic the tissue, e.g., fibrous materials with structural similarities to ECM. For soft tissue, for example, polymers can do a greater job than ceramics, but still, there is a vast range of options among them. Usually, natural polymers, such as collagen and gelatin, are preferable than synthetic due to their better biodegradability and biocompatibility. However, their lack of mechanical properties and uneven characteristics can be disadvantageous. To solve that problem, crosslinking may be applied. Several techniques are described in literature to produce fibrous materials, and electrospinning is the most used method. Nonetheless, it would be appealing to attempt other techniques such as SBS and airbrushing, because of all the advantages listed on this work.

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