applied sciences

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Editorial

Special Issue on "Biomaterials for Bone Tissue Engineering"

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Received: 2 April 2020; Accepted: 10 April 2020; Published: 12 April 2020

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1. Preface

The present Special Issue covers recent advances in the field of tissue engineering applied to bone tissue. Bone tissue engineering is a wide research topic, so different works from different transversal areas of research are shown. This Special Issue is a good example of a multidisciplinary collaboration in this research field. Authors from different disciplines, such as medical scientists, biomedical engineers, biologists, biomaterial researchers, clinicians, and mechanical engineers, are included from different laboratories and universities across the world. I specially thank the work and time of the reviewers, listed in Table A1 (in Appendix A), for their time and efforts in reviewing the papers compiled in this Special Issue.

2. Contents

The bone tissue engineering (BTE) field aims at the development of artificial bone substitutes that restore (partially or totally) the natural regeneration capability of bone tissue lost under the circumstances of injury, significant defects, or diseases, such as osteoporosis. BTE is a multidisciplinary area of research which includes the synthesis, fabrication, characterization, and experimentation of biomaterials. The modeling and simulation of biomaterials, bone tissue, and bone tissue interactions are also important methodologies in BTE. As a result, in this Special Issue, the 16 published papers can be classified within these general subfields.

Regarding the synthesis, characterization, and experimentation of biomaterials in BTE, Nguyen et al. [1] synthesized a class of scaffolds with a high surface area-to-volume ratio, which optimizes O_2 delivery to the scaffold interior. This topic is one of the most important challenges to grow artificial tissues of clinically relevant sizes. In order to evaluate the performance of different scaffold designs, the authors used high-resolution 3D X-ray images of two common scaffold types, namely lattice Boltzmann fluid dynamics and reactive Lagrangian scalar tracking mass transfer solvers. The mechanical performance of scaffolds is of utmost importance in BTE for two main reasons: (i) the scaffold should present an overall stiffness similar to the natural bone tissue [2], and (ii) the mechanical stimuli at the bone–biomaterial surface have been evidenced as an important design parameter in BTE scaffolds [3]. In this context, Rahmani et al. [4] evaluated in silico the mechanical performance of additively manufactured BTE scaffolds. Moreover, the scaffolds were experimentally characterized by means of compressive tests. The experimental results showed a good agreement versus the finite element simulations. Similarly, Lascano et al. [5] evaluated the industrial implementation and potential technology transfer of different powder metallurgy techniques to obtain porous titanium scaffolds for BTE. The microstructural and mechanical properties were obtained, and further assessed by finite element models. The authors discussed the feasibility of synthesizing BTE titanium scaffolds from powder metallurgy techniques.

Several works have been published in this Special Issue regarding the experimentation of the different techniques in BTE to enhance bone growth and regeneration processes. Cheng et al. [6]

applied an electrical stimulation on human dental pulp-derived stem cells to promote bone healing. The results presented in this work are promising, and reveal an enhancement in calcium deposition at different days of the tests. Specifically, increasing levels of bone morphogenetic proteins were found using electrical stimulation in the early stage of osteodifferentiation. On the other hand, Kanawa et al. [7] studied adipogenic differentiation of mesenchymal stromal cells (MSCs), i.e., the formation of adipocytes (fat cells) from MSCs. Adipogenesis is a key process when MSCs are used in tissue engineering and regenerative medicine. The authors identified three genes involved in this process. Grottoli et al. [8] investigated a non-invasive methodology to assess and quantify bone growth and regeneration. Specifically, the authors developed a novel radiological approach, in substitution of invasive histology, for evaluating the level of osteointegration and osteogenesis in orthopedics to oral and maxillofacial bone grafts. The authors concluded that the newly established radiological protocol allowed the tracking of the bone grafts, and showed effective integration and bone regeneration. Finally, Nappo et al. [9] evaluated the dimensions and positions of dental implants regarding their stability. This issue is relevant for the correct osteointegration and long-term success of dental implant treatments. The authors evidenced that the implant length, diameter, and the maxillary regions have an influence on primary stability.

Modeling and simulation of BTE and related bone tissue processes are an active field of research with increasing importance, as demonstrated in this Special Issue. A total of nine papers were published in this area. First, Vaitiekūnas et al. [10] presented an automatic method for bone segmentation for the clinical practice of endodontics, orthodontics, and oral and maxillofacial surgery. The automatic method showed clinically acceptable accuracy results versus an experienced oral and maxillofacial surgeon. This method allows one to efficiently reconstruct 3D bone geometries to be applied in oral and maxillofacial surgery for the performance of a 3D virtual surgical plan (VSP) or for postoperative follow-ups, as well as for their use as an input in in silico models. Raben et al. [11] modeled the electrical stimulation as a therapeutic approach for the regeneration of large bone defects. Electrically stimulated implants for critical size defects in the lower jaw were modeled using segmentation and finite element software. Electric field maps were shown along the bone geometry. The authors concluded that the parameters used in the numerical studies shall be applied in future in in vivo validation studies. Baldonedo et al. [12] compared the different mathematical models which included the mechanical evolution of bone tissue damage. The models were numerically implemented, using the finite element method, and compared in 1D and 2D geometries. Moreover, Sanz-Herrera et al. [13] presented a multiscale approach of the cortical bone tissue. The results were assessed by experimental data, and they showed both macro- and microstructural stress and strain patterns, highlighting their differences and emphasizing the importance of multiscale techniques for the characterization of bone tissue. On the other hand, Koh et al. [14] developed a biomechanical model which allows to study cartilage defect regeneration in the knee joint. The model considered a biphasic poroelastic formulation, which was implemented in a finite element framework. The results were shown in a knee joint model including cell and tissue distributions in the cartilage defect. The model was able to predict interesting applications, such as the benefits of the gait cycle loading with flexion versus the use of simple weight-bearing loading.

In silico biomechanical simulations for biomaterials and implants have also been included in this Special Issue. In particular, Park et al. [15] studied 3D periacetabular implants using finite element simulations. Different implant models were generated from computed tomographies and medical images. The outcome of the simulations established the biomechanical performances of different implant designs. This methodology can be used in the design phase of different orthopedic products before implantation. Biomechanical analyses are also useful to predict important conclusions in orthopedics. For example, Maknickas et al. [16] analyzed the risk of fracture in the osteoporotic lumbar vertebra L1. The risk of fracture was evaluated by means of Monte Carlo finite element simulations. The paper includes some validation from 3D printed vertebra models. The conclusions establish that the risk of fracture is substantially higher for low levels of apparent density. Zaharie and Phillips [17] compared different finite element models of the pelvis using different continuum and structural modeling approaches. On one hand, continuum isotropic, continuum orthotropic, hybrid isotropic, and hybrid orthotropic models were developed. On the other hand, a structural model previously developed by the authors was considered. The results show interesting conclusions and knowledge when compared with a computed tomography-derived model of the pelvis.

Finally, the Special Issue ends with a review of the state-of-the-art numerical modeling and simulation of BTE [18]. This paper emphasizes the importance of in silico simulations in two main contexts: First, to optimize and reduce in vitro and in vivo tests (and hence to reduce time and cost) to evaluate the performance of biomaterials in BTE processes. Second, an in silico methodology can be used as a powerful design tool for biomaterials in BTE. The conclusions highlight the importance of the experimental validation of the numerical models, and hence the multidisciplinary collaboration of the involved scientific fields.

3. Conclusions

BTE is a mature field of research. It is also an active and hot topic of research. However, its clinical practice is not as evident as the scientific results. Therefore, the transfer of methods and technology from scientific research to clinical practice is the fundamental keystone of the methodology. It requires the multidisciplinary and transversal collaboration of biomaterial scientists, modelers, biologists, and clinicians. Moreover, in silico simulations of BTE processes may be helpful to accomplish this task. This Special Issue covered the different state-of-the-art techniques and methods of BTE, including many successful examples of multidisciplinary collaboration in this area. Therefore, the scientific advances and accomplishments shown in this Special Issue may add some light to make BTE a clinical viable reality.

Funding: This research was funded by the Ministerio de Economía y Competitividad del Gobierno de España, grant number PGC2018-097257-B-C31; and Consejería de Economía, Conocimiento, Empresas y Universidad Junta de Andalucía, grant number US-1261691.

Acknowledgments: We would like to sincerely thank our assistant editor, Marin Ma (marin.ma@mdpi.com), for all the efforts during the different steps in the edition of this Special Issue.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Special Issue reviewer list.

J. Teo	A. Dehghan	J. Lee	H. Almeida
E. Onal	H. Yuan	F. Alifui-Segbaya	P. Gentile
K. Tappa	I. Polozov	H.S. Moghaddam	M.A. Bonifacio
E. Pegg	A. Ballini	L.-C. Zhang	M. Schulze
Gaetano Isola	Seunghee Cha	Charles J. Malemud	G. Milcovich
D. Tomasz	A. Saboori	M. Klontzas	A. Celentano
Z. Khurshid	C. Rossa	M. Padial-Molina	J. Żmudzki
K.-T. Lim	P. Palma	S. A. Danesh-Sani	M. Ratajczak
J. Hu	F. Bernardello	A. Scherberich	B. Wildemann

References

1. Nguyen, T.; Kadri, O.; Sikavitsas, V.; Voronov, R. Scaffolds with a High Surface Area-to-Volume Ratio and Cultured Under Fast Flow Perfusion Result in Optimal O2 Delivery to the Cells in Artificial Bone Tissues. *Appl. Sci.* **2019**, *9*, 2381. [CrossRef]
2. Hutmacher, D.W. Scaffolds in tissue engineering bone and cartilage. *Biomaterials* **2000**, *21*, 2529–2543. [CrossRef]

3. Sanz-Herrera, J.A.; García-Aznar, J.M.; Doblaré, M. Scaffold microarchitecture determines internal bone directional growth structure: A numerical study. *J. Biomech.* **2010**, *43*, 2480–2486. [CrossRef] [PubMed]
4. Rahmani, R.; Antonov, M.; Kollo, L.; Holovenko, Y.; Prashanth, K. Mechanical Behavior of Ti6Al4V Scaffolds Filled with CaSiO3 for Implant Applications. *Appl. Sci.* **2019**, *9*, 3844. [CrossRef]
5. Lascano, S.; Arévalo, C.; Montealegre-Melendez, I.; Muñoz, S.; Rodriguez-Ortiz, J.; Trueba, P.; Torres, Y. Porous Titanium for Biomedical Applications: Evaluation of the Conventional Powder Metallurgy Frontier and Space-Holder Technique. *Appl. Sci.* **2019**, *9*, 982. [CrossRef]
6. Cheng, Y.; Chen, C.; Kuo, H.; Yen, T.; Mao, Y.; Hu, W. Electrical Stimulation through Conductive Substrate to Enhance Osteo-Differentiation of Human Dental Pulp-Derived Stem Cells. *Appl. Sci.* **2019**, *9*, 3938. [CrossRef]
7. Kanawa, M.; Igarashi, A.; Fujimoto, K.; Ronald, V.; Higashi, Y.; Kurihara, H.; Kato, Y.; Kawamoto, T. Potential Marker Genes for Predicting Adipogenic Differentiation of Mesenchymal Stromal Cells. *Appl. Sci.* **2019**, *9*, 2942. [CrossRef]
8. Grottoli, C.; Ferracini, R.; Compagno, M.; Tombolesi, A.; Rampado, O.; Pilone, L.; Bistolfi, A.; Borrè, A.; Cingolani, A.; Perale, G. A Radiological Approach to Evaluate Bone Graft Integration in Reconstructive Surgeries. *Appl. Sci.* **2019**, *9*, 1469. [CrossRef]
9. Nappo, A.; Rengo, C.; Pantaleo, G.; Spagnuolo, G.; Ferrari, M. Influence of Implant Dimensions and Position on Implant Stability: A Prospective Clinical Study in Maxilla Using Resonance Frequency Analysis. *Appl. Sci.* **2019**, *9*, 860. [CrossRef]
10. Vaitiekūnas, M.; Jegelevičius, D.; Sakalauskas, A.; Grybauskas, S. Automatic Method for Bone Segmentation in Cone Beam Computed Tomography Data Set. *Appl. Sci.* **2020**, *10*, 236. [CrossRef]
11. Raben, H.; Kämmerer, P.; Bader, R.; van Rienen, U. Establishment of a Numerical Model to Design an Electro-Stimulating System for a Porcine Mandibular Critical Size Defect. *Appl. Sci.* **2019**, *9*, 2160. [CrossRef]
12. Baldonedo, J.; Fernández, J.; López-Campos, J.; Segade, A. Analysis of Damage Models for Cortical Bone. *Appl. Sci.* **2019**, *9*, 2710. [CrossRef]
13. Sanz-Herrera, J.; Mora-Macías, J.; Reina-Romo, E.; Domínguez, J.; Doblaré, M. Multiscale Characterisation of Cortical Bone Tissue. *Appl. Sci.* **2019**, *9*, 5228. [CrossRef]
14. Koh, Y.; Lee, J.; Lee, H.; Kim, H.; Kang, K. Biomechanical Evaluation of the Effect of Mesenchymal Stem Cells on Cartilage Regeneration in Knee Joint Osteoarthritis. *Appl. Sci.* **2019**, *9*, 1868. [CrossRef]
15. Park, D.; Lim, A.; Park, J.; Lim, K.; Kang, H. Biomechanical Evaluation of a New Fixation Type in 3D-Printed Periacetabular Implants using a Finite Element Simulation. *Appl. Sci.* **2019**, *9*, 820. [CrossRef]
16. Maknickas, A.; Alekna, V.; Ardatov, O.; Chabarova, O.; Zabulionis, D.; Tamulaitienė, M.; Kačianauskas, R. FEM-Based Compression Fracture Risk Assessment in Osteoporotic Lumbar Vertebra L1. *Appl. Sci.* **2019**, *9*, 3013. [CrossRef]
17. Zaharie, D.; Phillips, A. A Comparative Study of Continuum and Structural Modelling Approaches to Simulate Bone Adaptation in the Pelvic Construct. *Appl. Sci.* **2019**, *9*, 3320. [CrossRef]
18. Sanz-Herrera, J.; Reina-Romo, E. Continuum Modeling and Simulation in Bone Tissue Engineering. *Appl. Sci.* **2019**, *9*, 3674. [CrossRef]