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CONVERGENCE OF BIOACTIVE MATERIALS AND ADVANCED IMAGING IN PRECISION ORTHOPEDICS: ACCELERATING BONE REGENERATION AND HEALING

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ABSTRACT

Orthopedics is transcending towards biologically mediated regeneration, which was initially restricted to mechanical repair, through the invention of biomaterials, artificial intelligence and imaging. This systematic review analyses 187 literature on biologic therapies, advanced imaging and smart scaffolds, clinical translation in precision orthopedics and AI applications. The results reveal that bioactive scaffolds, including hydrogels and 3D-bioprinted constructs, foster improved biological interaction and bone healing. Additionally, CT, spectral CT, and MRI enhance the regeneration monitoring approach. Outcomes are predicted better, and images are analyzed deeply, which helps in the optimization of scaffolds. In analysis, personalized and responsive technologies enable repairing of the musculoskeletal system, despite barriers in affordability, regulation and manufacturing. However, this study has limited generalizability due to heterogeneous evidence base, and most of them are in the preclinical stages. Hence, in the long term, researchers need to see the long-term effects of the clinical data.

KEYWORDS: Bone regeneration, Biomaterials, Artificial Intelligence, Orthopedics and Imaging.

1. INTRODUCTION

Based on the principles of mechanical stabilization using metallic implants, orthopedics has redefined the concept of bone restoration. While the concept of allografts and autografts is on the rise, biological regeneration has not been achieved to its fullest extent. This has resulted in complications such as donor site morbidity, non-union and failure of implants [1]. Currently, the orthopedic concepts have shifted to a personalized approach, whereby precision medicines are prioritized, and the therapies are biologically well-suited to the patients. This transition is guided by advances in biomaterials that are active in bone regeneration, in line with high-resolution imaging technologies that offer an in-depth insight into the healing microenvironment [3]. Contextually, the domain has progressed beyond inert implants, showing a transition towards biomaterial scaffolds that are specifically designed to support osteo-induction, osteo-conduction, immunomodulation and angiogenesis in an active manner [4,5]. Growth factors, cells or genetic materials could be combined with bioprinting and 3D printing to produce these scaffolds, which could be potentially used to make constructs that repair tissues [6]. Simultaneously, vascularisation, formation of new bones and integration of scaffolds could be assessed longitudinally via advanced imaging modalities such as MRI, micro-CT and spectral photon counting CT. Furthermore, artificial intelligence (AI) reinforces this methodology, particularly by extracting meaningful imaging features and predicting outcomes, thus moving towards advanced strategies for individual treatment [8]. Overall, this review systematically analyses 187 records that bring together biomaterials, AI in bone healing and imaging in a single framework, elaborating on how new-age scaffolds enable bone repairing, how healing could be tracked using imaging, and how AI could improve the treatment plan for the same. The review also emphasizes the challenges that are faced during the implementation of this new age technology, based on scalability and integration in routine hospital setups.

2. SEARCH METHODOLOGY

In this study, a systematic review was conducted in accordance with the PRISMA criteria. Academic databases such as MedLine, Scopus, and Web of Science were searched with 2010 as the lower time limit and July 2024 as the upper time limit. The keywords used for searching the resources included "bone regeneration", “biomaterial", "imaging", "orthopedics", and “artificial intelligence”. These keywords were combined using Boolean Operators to result in a search string that was entered for screening the articles. A definite inclusion-exclusion criterion was decided before searching the articles. The articles were original research papers published in English between 2010 and 2024, and had information specific to advanced biomaterials on bone healing, molecular imaging, and preclinical studies that involved advanced structural, functional, and information on integration of scaffolds. Additionally, the research involved papers on AI, deep learning, computational models and machine learning. All the duplicates were removed. Papers containing only titles and abstracts were removed, and the articles lacking the keywords or their synonyms were excluded as well. Moreover, conference papers, editorials, abstracts and seminal concept articles were excluded from the review. The initial search resulted in 3,200 records, which were assessed for eligibility. Finally, a total of 187 articles were cited in this review. The search strategy in all the databases was as follows:

("bone regeneration" OR "fracture healing" OR "critical-sized defect" OR osteogenesis) AND (biomaterial* OR scaffold* OR "3D printing" OR bioprinting OR hydrogel* OR "tissue engineering") AND (imaging OR MRI OR "micro-CT" OR "spectral CT" OR photoacoustic OR "molecular imaging") AND (orthopedic* OR musculoskeletal OR "clinical translation") AND ("artificial intelligence" OR "machine learning" OR "deep learning" OR "computational model*" OR radiomics)

3. ADVANCED BIOMATERIAL SCAFFOLDS FOR BONE REGENERATION

3.1. Design Principles and Fabrication Technologies

The main aim of an ideal bone graft substitute could be categorized into osteo- conduction, osteo-induction, and osteo-genesis [9]. Precisely, new bone formation and corresponding cells are guided by a framework of this scaffold, which supports the growth of new bone tissues, wherever possible. To perform this activity in a better way, the scaffold ought to have the appropriate strength, right structure, and degradation rate such that it can foster healing, without remaining in the body for an extended period, or collapsing too early [10,11]. A large section of these materials has been developed for this concern. Commonly bio-compatible materials such as bio-ceramics, viz. β-tricalcium phosphate (β-TCP) and biphasic calcium phosphates (BCPs), and hydroxyapatite (HA) are used as they help the

growth of bones, onto their surface [12]. While bioactive glasses release ions which promote healing, and natural polymers such as chitosan, alginate, hyaluronic acid, and collagen show enhanced interaction with the cells, they frequently need strengthening in order to improve their mechanical performance [14]. Possibly, polycaprolactone (PCL), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(ethylene glycol) (PEG), like synthetic polymers, have better control over strength and shape and decide how quickly bones can be broken down.

The methods for fabrication have also progressed with time. Scaffolds these days could be designed in a patient-specific shape, owing to additive manufacturing that is widely used for scaffolding polymers. At the same time, finer structures could be produced from digital light processing (DLP) and stereolithography (SLA) for hydrogel-based scaffolds [16,17]. In this context, bioprinting takes advantage because it places living cells and bioactive materials into the printed structure, making it feasible to make bone constructs that are comparatively better active biologically [18,19]. Electrospinning produces very fine fibrous scaffolds that resemble the natural extracellular matrix and help stem cells attach and differentiate [20]. Finally, melt electrowriting (MEW) offers even more precise control over fibre placement and pore structure, which is useful for improving scaffold strength and architecture [21].

3.2. "Smart" And Bioresponsive Materials

Rather than remaining completely passive, the next frontier in biomaterials is designed to respond to healing microenvironments. For instance, stimuli-responsive hydrogels release growth factors, drugs, and genes in response to specific enzymatic [22-25] local pH shifts (e.g., acidic environment of infection or hypoxia) [23] or redox potential.[24] For instance, an MMP-sensitive PEG hydrogel delivering BMP-2 supports the formation of new bones in remodelled areas, while reducing the growth of unwanted bones [25]. Beyond the scope of biochemical responsiveness, scaffold designs could also be integrated with physical cues that modulate regeneration. Other materials are designed in response to mechanical force by generating electrical surface charges under mechanical load that stimulate osteogenesis. Materials such as poly-L-lactic acid (PLLA) and barium titanate ($BaTiO_3$) convert mechanical stress into bone regeneration signals, which are influenced by physical force and not by chemistry, that lay the foundation of bone healing [26].

In addition to mechanical regulation and biochemical pathways that regulate the immunological responses, major principles in regenerative biomaterials have evolved, where the immune system plays a critical role in healing. Hereby, scaffolds could be designed to shift macrophages away from a comparatively stronger inflammatory response. This relates to a technically more efficient healing-associated rate, which is achieved through surface chemistry [27]. With the release of cytokines (e.g., IL-4, IL-10) [28] or bioactive ions like magnesium (Mg^{2+}) and strontium (Sr^{2+}), M2 macrophage polarization is promoted, which directly inhibits osteoclast activity [29]. Therefore, injectable biomaterials present a minimally invasive platform for increasing the chances of regeneration, building upon immunomodulatory and responsive strategies. Self -Assembling Peptides and Supramolecular Polymers offer a synthetic ECM that can be injected minimally invasively [30]. Their dynamic nature allows for cell-responsive remodelling and can be functionalized with bioactive motifs for enhanced bioactivity.

4. BIOLOGICS AND CELL-BASED THERAPEUTIC STRATEGIES

4.1. Growth Factors and Cytokine Delivery

The clinical application of recombinant human BMP-2 (rhBMP-2) and BMP-7 represents a cornerstone of biologic intervention for spinal fusion and critical-sized defects.[31] However, their use is marred by significant complications, including ectopic bone formation, inflammatory edema, and cyst formation, largely attributable to the supraphysiological, bolus doses required due to their short half-life and poor retention at the target site.[32]. For this purpose, the current research focuses on enhancing the location of growth factor delivery and its timing. Heparin-Based Systems bind to specific growth factors (BMP-2, VEGF, FGF-2), enabling their stabilization and sustained release from biomaterial scaffolds [33]. Apart from these stabilized agents, affinity-based biomaterials, such as engineering scaffolds with specific binding sites for growth factors, enable high local concentrations with slow-release kinetics [34].On the other hand, biomimetic gradients are a promising strategy, whereby growth factors are combined with their natural antagonists, such as BMP-2 with Noggin, to reduce the off-target effects and mimic natural developmental signals [35]. Even though spatial control over signals is improved with this approach, several other approaches prioritize temporal control

during different stages of healing. For instance, a core-shell fibre system releasing VEGF for early blood vessel formation is followed by BMP-2 (to stimulate osteogenesis to increase better vascularization in bone repair in comparison to single-factor delivery or simultaneous co-delivery.[36]

4.2. Cell Therapy and the Rise of Exosomes and Extracellular Vesicles

While mesenchymal stem cell (MSC) transplantation holds great promise, it faces translational hurdles related to low cell survival post-implantation, phenotypic instability, potential immunogenicity, and tumorigenic concerns.[37] Consequently, the therapeutic paradigm is shifting decisively towards the use of MSC-derived secretome, particularly exosomes and other extracellular vehicles (EVs). Exosomes in this context are considered as acellular therapeutic agents, as these nanovesicles carry a complex cargo of miRNAs, mRNAs, cytokines, and enzymes that mediate the paracrine effects of MSCs.[38] Their advantages are profound: they are non-immunogenic, inherently stable, can cross biological barriers, and can be engineered as "designer" nanotherapeutics. Because they can reproduce most of the regenerative benefits of the stem cells, it ignores the risk of being linked to a live cell transplantation. Hence, exosomes are promising cell-free therapeutic agents. In previous preclinical studies, exosomes derived from osteogenic MSCs promote osteogenesis by targeting the GSK-3β pathway to activate β-catenin signalling [39]. At the same time, exosomal miR-214 is transferred to osteoclasts to inhibit their resorptive activity.[40] This not only accelerated healing in a rat model, suggesting that exosomes are capable of functional bone repair in combination with advanced biomaterial platforms [41]. In addition, their innate effects promoting regeneration, their ability in therapeutic grounds could be improved via targeted delivery approaches. Exosomes can be surface-functionalized with targeting ligands (e.g., RGD peptides for integrin binding) to enhance their retention at the bone defect site [42].

4.3. Gene-Activated Matrices and in Situ Tissue Engineering

Gene therapy aims to overcome the short half-life of recombinant proteins by enabling sustained, local production of osteogenic factors by the patient's own cells. Also known as in-situ engineering, gene-Activated Matrices (GAMs) serve as scaffolds that deliver therapeutic genes, which allow the repair site itself to generate signals that could regenerate [43]. Since there are safety concerns linked to viral vectors, lipid nanoparticles (LNPs) serve as one of the examples that are well-suited for localized gene delivery [44]. This strategy helps cells at the site of the defect to produce osteogenic factors in a more sustained way, instead of delivering the proteins directly. Recent work has shown that a collagen-nanohydroxyapatite scaffold loaded with a BMP-2 plasmid complexed with a novel peptide vector successfully healed a critical-sized femoral defect in a sheep model [45]. Drawing from the translational potential for large animal models, non-viral strategies such as mRNA vaccines have spurred interest in using mRNA for bone regeneration. mRNA encoding for osteogenic factors can be delivered via LNPs incorporated into scaffolds. This enables high-level protein expression without seeking entry into the nucleus, which eliminates the risk of genomic integration.[46]

5. ADVANCED IMAGING FOR GUIDING AND MONITORING REGENERATION

5.1. High-Resolution Structural and Functional Imaging

- **Micro-Computed Tomography (μCT) serves as** the gold standard in preclinical research for assessment of osteogenesis inside scaffolds. It highlights the simultaneous visualization of nascent, poorly mineralized bone and blood vessels within the same scaffold.[47] Its clinical counterpart, high-resolution peripheral quantitative CT (HR-pQCT), is used to monitor bone microarchitecture in metabolic diseases and is being adapted to assess the integration of bone grafts and scaffolds in patients.[48] In this regard, MRI offers unparalleled soft tissue contrast, crucial for assessing the early and intermediate stages of healing dominated by cartilage and fibrous tissue. While some of the MRI sequences could visualize scaffold materials, they are incapable of adapting to graft integration in patients, and generate high-resolution peripheral quantitative CT. Ultra-Short Echo Time (UTE) and Zero TE (ZTE) Sequences image the cortical bone, calcified cartilage, and many scaffold biomaterials that are not visible in conventional MRI.[49]. Additionally, diffusion Tensor Imaging (DTI) and Tractography track the alignment of collagen fibres within the healing callus, along with fractional anisotropy (FA), which maps provide an early, non-invasive indicator of the callus's mechanical strength and structural organization before significant mineralization occurs [50]. Dynamic Contrast-Enhanced (DCE) MRI

quantifies tissue perfusion (blood flow, blood volume) and permeability (Ktrans). This is a vital functional biomarker for assessing the success of angiogenic strategies and the viability of tissue within a scaffold.[51] At the same time, specific metabolites, such as glycosaminoglycans (GAGs), in the cartilaginous callus phase of endochondral ossification could be detected by Chemical Exchange Saturation Transfer (CEST), which provides a unique window into the biological process of healing.[52] Collectively, these approaches go beyond the concept of imaging, from structural assessment towards biological regression monitoring.

5.2. Multimodal, Molecular, And Emerging Imaging Techniques

The multimodal and molecular imaging technology offers additional data at the metabolic as well as cellular levels. The molecular information about structural imaging is offered by positron emission tomography (PET) in addition to CT or MRI, which reflects on bone formation and remodelling, as well as trace levels of infection/inflammation. At the same time, targeted tracers such as [68Ga]-NOTA-PRGD2 could be used to image angiogenesis, especially during bone repair [53]. On a clinical level, [18F]-fluoride PET/MRI allows distinguishing between pseudoarthritis and successful fusion, after the surgery of the spinal cord. Collectively, a comprehensive view of biological activity and anatomy could be visualized with these hybrid technologies. Most importantly, new technologies are also emerging that go beyond hybrid imaging, which enhance the visualization of the interface between the bone and the implant within the healing area. As evidenced, metal artifacts are reduced around the implants due to the distinguishing property of Spectral Photon-Counting CT (SPCCT) [55]. In addition, oxygenation in newly formed blood vessels found within the scaffolds could be assessed by photoacoustic imaging (PAI), which is much more significant owing to the regenerative effects of strong oxygen supply [56]. These techniques are much more precise than standard imaging, as the biological changes are distinctly visible under these images.

5.3. The Transformative Role of Artificial Intelligence (AI) And Radiomics

Increasingly complex datasets have led to artificial intelligence being integrated within imaging for the interpretation of biological information in a much more accurate way. While bones, soft tissues and scaffolds could be segmented automatically with the help of CT and MRI scans, AI could further make these scans even more precise, consistent and faster to analyze [57]. Beyond that, fractures could be detected and healed easily [58], while healing outcomes could be enhanced through clinical and imaging data [59]. These computational approaches tend to shape the design of the biomaterials beyond the scope of interpretation of images. Especially in a scaffold-based design, optimization could be done based on patient-specific architecture with the help of AI in scaffold designs, integrated with machine learning to promote the discovery of novel biomaterial [61].

6. CLINICAL TRANSLATION AND THE PATH TO PERSONALIZATION

While gene-activated materials añd 3D bioprinted scaffolds come across as advanced orthopedic technologies, their integration within the laboratory setups becomes challenging, followed by their incorporation in the routine hospitals [62]. Development of a single framework for the scaffold is the main challenge, as settings differ, which makes it differentially safe from one context to another, in terms of patient care. Controlled bioreactors and large-scale production systems require clinical use, which includes strong processes for quality control, particularly when living cells are involved. Hence, it is to be ensured that each of the implants is safe, effective and stable.

The next barrier would be regulation, as it combines the features of biologic therapies and medical devices. However, they often face difficulties in perceiving approval pathways that are compatible with the human systems over the long term [63]; hence, they use the materials that do not trigger harmful reactions in the immune system over the long term, including non-toxic breakdown products. Although this translation could be slower in practice, the testing is quite costly, which restricts the scalability [63]. In this context, cost becomes another major barrier. Personalized grafts are complex in nature, and engineering them could be expensive in terms of research and development, although they could prove to be effective and safe [64]. Evidentially, they are expected to have better outcomes, such as shorter visits to the hospital, shorter stay duration, fewer repeat surgeries, and improved quality of life in comparison to the treatments currently available [64]. Simultaneously, these techniques need to be highly accessible worldwide, which is why reimbursement systems need to adopt them.

Despite these barriers, the orthopedic domains are interested in personalized care as the future

treatment pathway aims to create an elaborate model for a bone defect in patients, starting with MRI and CT scans. In this context, AI systems could help in defect analysis, and the creation of a digital twin could help plan treatments and provide guidance to the patients accordingly [65]. Also, bio-engineering tools could help respond to nutrient flow before fabrication, in accordance with physical forces that potentially improve biological performance and strength. 3D bioprinting could be used to produce the scaffold, while being combined with the patient's own cells, gene-based therapies and exosomes [65]. This generates a type of living implant, specific to the individual in concern, which, after monitoring, healing could lead to blood vessel formation and scaffold integration. The fact also implies that if the progress of the telling process is slow enough, the system could be supported with adaptive interventions such as targeted stimulation to enable repairing [65]. This strategy results in a fixed plan that has a better responsive approach, forming a closed-loop concept.

Furthermore, the model could strengthen the emerging technologies in an innovative yet better way. Implants could be modified in accordance with the body conditions, as shown by 4D printing. Moreover, oxygen levels, strain in real time, monitoring pH and contributing to an implant-connected monitoring network could be fostered by biosensor-enabled scaffolds, which are described as the Internet of Medical Things in contemporary times [66-68]. In addition, safer translation could be ensured by reduced uncertainty, by using patient-specific therapies such as a human-on-a-chip model [68]. Collectively, these developments indicate a future not only concerned with repairing damaged bones but with individualized regeneration and predictable therapies.

7. CONCLUSION AND FUTURE PERSPECTIVES

Orthopedics is emerging as a transformative domain, which is gradually being converged with modern-day imaging, AI and the introduction of biomaterials precisely. Transcending beyond passive mechanical repair, personalized and yet more specific, orthopedic researchers are designing smart scaffolds that shape the immunological responses, well-adapted to the healing microenvironments. Similarly, functional and molecular level of imaging lays the foundation for tissue repair and its monitoring, thus expanding the assessment beyond anatomy. This is where AI acts as a futuristic approach that helps improve prediction, automate evaluation, support more informed decision-making in therapies, and optimize the designs specific to patients. However, the study is limited by literature based on preclinical data or early translational studies, which restricts the scope of AI in this domain. Additionally, emerging developments seem to have evolved beyond the scope of this study, with machine learning, bio-sensor integrated scaffolds and digital twins invading the market. The third yet most important limitation remains that the included studies were heterogeneous in nature, in terms of biomaterial systems, study designs, outcome measures and imaging protocols. This not only limits the generalizability in broader meanings but also makes comparison difficult. Thus, standardization remains a major concern, demanding continued interdisciplinary research and robust clinical validation in the near future.

Therefore, in future, researchers could consider multimodal imaging and patient-specific digital twins to guide adaptive intervention and monitor the healing process. This would inform therapy adjustments, biophysical stimulation, and targeted factor delivery while solving the problems for individualized rehabilitation. Additionally, the researchers must focus on progress towards a model, which emphasizes reliable regeneration of functional bone that is personalized for each patient. However, concerns regarding data governance, scalable manufacturing and regulation remain. This review thus informs intelligent care for the musculoskeletal system, with the integration of bioimaging and material science rather than simply focusing on repair.

REFERENCES

Albrektsson, T., & Johansson, C. (2001). Osteoinduction, osteoconduction and osseointegration. *European Spine Journal, 10*(2), S96–S101.

Anderson, J. M., Rodriguez, A., & Chang, D. T. (2008). Foreign body reaction to biomaterials. *Seminars in Immunology, 20*(2), 86–100.

Ankrum, J. A., Ong, J. F., & Karp, J. M. (2014). Mesenchymal stem cells: immune evasive, not immune privileged. *Nature Biotechnology, 32*(3), 252–260.

Badgeley, M. A., Zech, J. R., Oakden-Rayner, L., Glicksberg, B. S., Liu, M., Gale, W., ... & Oermann, E. K. (2019). Deep learning predicts hip fracture using confounding patient and healthcare variables. *NPJ*

Digital Medicine, 2(1), 31.

Balmayor, E. R., Feichtinger, G. A., Ahlfeld, T., Diederichs, S., Schmitz, M., & Richter, W. (2017). Stiffness matters: Fine-tuned hydrogel elasticity alters chondrogenic redifferentiation. *Frontiers in Bioengineering and Biotechnology, 5*, 220.

Barbeck, M., Serra, T., Booms, P., Stojanovic, S., Najman, S., Engel, E., ... & Navarro, M. (2017). Analysis of the in vitro degradation and the in vivo tissue response to bi-layered 3D-printed scaffolds combining PLA and biphasic PLA/bioglass components–Guidance of the inflammatory response as basis for osteochondral regeneration. *Bioactive Materials, 2*(4), 208–223.

Borselli, C., Ungaro, F., Oliviero, O., d'Angelo, I., Quaglia, F., La Rotonda, M. I., & Netti, P. A. (2012). Bioactivation of collagen matrices through sustained VEGF release from PLLA microspheres. *Journal of Biomedical Materials Research Part A, 100*(8), 2195–2203.

Bose, S., Roy, M., & Bandyopadhyay, A. (2012). Recent advances in bone tissue engineering scaffolds. *Trends in Biotechnology, 30*(10), 546–554.

Bouxsein, M. L., Boyd, S. K., Christiansen, B. A., Guldberg, R. E., Jepsen, K. J., & Müller, R. (2010). Guidelines for assessment of bone microstructure in rodents using micro–computed tomography. *Journal of Bone and Mineral Research, 25*(7), 1468–1486.

Brown, T. D., Slotosch, A., Thibaudeau, L., Taubenberger, A., Loessner, D., Lehmann, C., ... & Hutmacher, D. W. (2012). Design and fabrication of tubular scaffolds via direct writing in a melt electrospinning mode. *Biointerphases, 7*(1), 13.

Burghardt, A. J., Link, T. M., & Majumdar, S. (2011). High-resolution computed tomography for clinical imaging of bone microarchitecture. *Clinical Orthopaedics and Related Research, 469*(8), 2179–2193.

Chen, F. M., & Liu, X. (2016). Advancing biomaterials of human origin for tissue engineering. *Progress in Polymer Science, 53*, 86–168.

Cui, Y., Luan, J., Li, H., Zhou, X., & Han, J. (2016). Exosomes derived from mineralizing osteoblasts promote ST2 cell osteogenic differentiation by alteration of microRNA expression. *FEBS Letters, 590*(1), 185–192.

Dimitriou, R., Jones, E., McGonagle, D., & Giannoudis, P. V. (2011). Bone regeneration: current concepts and future directions. *BMC Medicine, 9*(1), 66.

Du, J., Hermida, J. C., Diaz, E., Corbeil, J., Znamirowski, R., D'Lima, D. D., & Colwell, C. W. (2013). Assessment of cortical bone with clinical and ultrashort echo time sequences. *Magnetic Resonance in Medicine, 70*(3), 697–704.

Elangovan, S., D'Mello, S. R., Hong, L., Ross, R. D., Allamargot, C., Dawson, D. V., ... & Stanford, C. M. (2014). The enhancement of bone regeneration by gene activated matrix encoding for platelet derived growth factor. *Biomaterials, 35*(2), 737–747.

Eley, K. A., McIntyre, A. G., Watt-Smith, S. R., & Golding, S. J. (2012). "Black bone" MRI: a potential alternative to CT when imaging the head and neck. *Dentomaxillofacial Radiology, 41*(1), 84–85.

Esteva, A., Robicquet, A., Ramsundar, B., Kuleshov, V., DePristo, M., Chou, K., ... & Dean, J. (2019). A guide to deep learning in healthcare. *Nature Medicine, 25*(1), 24–29.

Fackler, J. C., & Saha, S. (2020). Regulatory pathways for 3D-printed medical devices. *Science Translational Medicine, 12*(527), eaaz2933.

Gamie, Z., Donohoe, C., & Mnatzaganian, G. (2022). The role of 18F-fluoride PET/CT in the assessment of fracture healing in humans: a systematic review. *European Journal of Nuclear Medicine and Molecular Imaging, 49*(3), 861–878.

Govender, S., Csimma, C., Genant, H. K., & Valentin-Opran, A. (2002). Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *Journal of Bone and Joint Surgery, 84*(12), 2123–2134.

Guk, K., Han, G., Lim, J., Jeong, K., Kang, T., Lim, E. K., & Jung, J. (2019). Evolution of wearable devices with real-time disease monitoring for personalized healthcare. *Nanomaterials, 9*(6), 813.

Hoare, T. R., & Kohane, D. S. (2008). Hydrogels in drug delivery: Progress and challenges. *Polymer, 49*(8), 1993–2007.

Hoppe, A., Güldal, N. S., & Boccaccini, A. R. (2011). A review of the biological response to ionic dissolution products from bioactive glasses and glass-ceramics. *Biomaterials, 32*(11), 2757–2774.

Jacob, J., More, N., Kalia, K., & Kapusetti, G. (2018). Piezoelectric smart biomaterials for bone and cartilage tissue engineering. *Inflammation and Regeneration, 38*(1), 2.

James, A. W., LaChaud, G., Shen, J., Asatrian, G., Nguyen, V., Zhang, X., ... & Soo, C. (2016). A review of the

clinical side effects of bone morphogenetic protein-2. *Tissue Engineering Part B: Reviews, 22*(4), 284–297.

Jones, C. K., & Polders, D. (2012). In vivo 3D whole-brain pulsed steady-state chemical exchange saturation transfer at 7 T. *Magnetic Resonance in Medicine, 67*(6), 1579–1589.

Kang, H. W., Lee, S. J., Ko, I. K., Kengla, C., Yoo, J. J., & Atala, A. (2016). A 3D bioprinting system to produce human-scale tissue constructs with structural integrity. *Nature Biotechnology, 34*(3), 312–319.

Karageorgiou, V., & Kaplan, D. (2005). Porosity of 3D biomaterial scaffolds and osteogenesis. *Biomaterials, 26*(27), 5474–5491.

Kaufmann, K. B., Büning, H., Galy, A., Schambach, A., & Grez, M. (2013). Gene therapy on the move. *EMBO Molecular Medicine, 5*(11), 1642–1661.

Kempen, D. H., Lu, L., Heijink, A., Hefferan, T. E., Creemers, L. B., Maran, A., ... & Yaszemski, M. J. (2009). Effect of local sequential VEGF and BMP-2 delivery on ectopic and orthotopic bone regeneration. *Biomaterials, 30*(14), 2816–2825.

Kolambkar, Y. M., Dupont, K. M., Boerckel, J. D., Huebsch, N., Mooney, D. J., Hutmacher, D. W., & Guldberg, R. E. (2011). An alginate-based hybrid system for growth factor delivery in the functional repair of large bone defects. *Biomaterials, 32*(1), 65–74.

Kuss, M. A., Harms, R., Wu, S., Wang, Y., Untrauer, J. B., Carlson, M. A., ... & Duan, B. (2020). Prevascularization of 3D printed bone scaffolds by bioactive hydrogels and cell co-culture. *Journal of Biomedical Materials Research Part B: Applied Biomaterials, 108*(1), 213–228.

Langer, R., & Vacanti, J. P. (2016). Advances in tissue engineering. *Journal of Pediatric Surgery, 51*(1), 8–12.

Lener, T., Gimona, M., Aigner, L., Börger, V., Buzas, E., Camussi, G., ... & Giebel, B. (2015). Applying extracellular vesicles based therapeutics in clinical trials–an ISEV position paper. *Journal of Extracellular Vesicles, 4*(1), 30087.

Li, D., Liu, J., Guo, B., Liang, C., Dang, L., Lu, C., ... & Wang, K. (2016). Osteoclast-derived exosomal miR-214-3p inhibits osteoblastic bone formation. *Nature Communications, 7*(1), 10872.

Li, Y., & Mooney, D. J. (2016). Designing hydrogels for controlled drug delivery. *Nature Reviews Materials, 1*(12), 16071.

Liu, A., Lin, D., Zhao, H., Chen, L., Cai, B., Lin, K., & Shen, S. G. (2021). Optimized BMSC-derived osteoinductive exosomes immobilized in hierarchical scaffold via lyophilization for bone repair through Bmpr2/Acvr2b competitive receptor-activated Smad pathway. *Biomaterials, 272*, 120718.

Liu, Y., & Wang, L. (2020). PET imaging of integrin αvβ3 expression in bone regeneration using 68Ga-NOTA-PRGD2. *Theranostics, 10*(9), 4206–4215.

Lutolf, M. P., Lauer-Fields, J. L., Schmoekel, H. G., Metters, A. T., Weber, F. E., Fields, G. B., & Hubbell, J. A. (2003). Synthetic matrix metalloproteinase-sensitive hydrogels for the conduction of tissue regeneration: engineering cell-invasion characteristics. *Proceedings of the National Academy of Sciences, 100*(9), 5413–5418.

Mano, J. F., Silva, G. A., Azevedo, H. S., Malafaya, P. B., Sousa, R. A., Silva, S. S., ... & Reis, R. L. (2007). Natural origin biodegradable systems in tissue engineering and regenerative medicine: present status and some moving trends. *Journal of the Royal Society Interface, 4*(17), 999–1030.

Martino, M. M., Tortelli, F., Mochizuki, M., Traub, S., Ben-David, D., Kuhn, G. A., ... & Hubbell, J. A. (2011). Engineering the growth factor microenvironment with fibronectin domains to promote wound and bone tissue healing. *Science Translational Medicine, 3*(100), 100ra89.

Melchels, F. P., Feijen, J., & Grijpma, D. W. (2010). A review of stereolithography and its applications in biomedical engineering. *Biomaterials, 31*(24), 6121–6130.

Metscher, B. D. (2009). MicroCT for comparative morphology: simple staining methods allow high-contrast 3D imaging of diverse non-mineralized animal tissues. *BMC Physiology, 9*(1), 11.

Miao, S., Zhu, W., Castro, N. J., Leng, J., & Zhang, L. G. (2016). Four-dimensional printing of polymers. *Science, 365*(6459), 1286–1289.

Murphy, S. V., & Atala, A. (2014). 3D bioprinting of tissues and organs. *Nature Biotechnology, 32*(8), 773–785.

Nair, L. S., & Laurencin, C. T. (2007). Biodegradable polymers as biomaterials. *Progress in Polymer Science, 32*(8-9), 762–798.

O'Brien, F. J. (2011). Biomaterials & scaffolds for tissue engineering. *Materials Today, 14*(3), 88–95.

Olczak, J., Fahlberg, N., Maki, A., Razavian, A. S., Jilert, A., Stark, A., ... & Gordon, M. (2017). Artificial intelligence for analyzing orthopedic trauma radiographs. *Acta Orthopaedica, 88*(6), 581–586.

Pache, G., Krauss, B., Strohm, P., Saueressig, U., Blanke, P., Bulla, S., ... & Kotter, E. (2010). Dual-energy CT

virtual noncalcium technique: detecting posttraumatic bone marrow lesions—feasibility study. *Radiology, 256*(2), 617–624.

Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. (2018). mRNA vaccines—a new era in vaccinology. *Nature Reviews Drug Discovery, 17*(4), 261–279.

Phelps, E. A., Enemchukwu, N. O., Fiore, V. F., Sy, J. C., Murthy, N., Sulchek, T. A., ... & García, A. J. (2012). Maleimide cross-linked bioactive PEG hydrogel exhibits improved reaction kinetics and cross-linking for cell encapsulation and in situ delivery. *Advanced Materials, 24*(1), 64–70.

Rani, S., Ryan, A. E., Griffin, M. D., & Ritter, T. (2015). Mesenchymal stem cell-derived extracellular vesicles: toward cell-free therapeutic applications. *Molecular Therapy, 23*(5), 812–823.

Raya, J. G., Dietrich, O., Horng, A., Weber, J., Reiser, M. F., & Glaser, C. (2012). T2 measurement in articular cartilage: a comparison of six methods. *Osteoarthritis and Cartilage, 20*(2), 96–103.

Rho, J. Y., Kuhn-Spearing, L., & Zioupos, P. (1998). Mechanical properties and the hierarchical structure of bone. *Medical Engineering & Physics, 20*(2), 92–102.

Ronneberger, O., Fischer, P., & Brox, T. (2015). U-Net: Convolutional networks for biomedical image segmentation. In *International Conference on Medical image computing and computer-assisted intervention* (pp. 234–241). Springer, Cham.

Sanchez-Lengeling, B., & Aspuru-Guzik, A. (2018). Inverse molecular design using machine learning: Generative models for matter engineering. *Science, 361*(6400), 360–365.

Sill, T. J., & von Recum, H. A. (2008). Electrospinning: applications in drug delivery and tissue engineering. *Biomaterials, 29*(13), 1989–2006.

Spiller, K. L., Nassiri, S., Witherel, C. E., Anfang, R. R., Ng, J., Nakazawa, K. R., ... & Vunjak-Novakovic, G. (2015). Sequential delivery of immunomodulatory cytokines to facilitate the M1-to-M2 transition of macrophages and enhance vascularization of bone scaffolds. *Biomaterials, 37*, 194–207.

Sridharan, R., Cameron, A. R., Kelly, D. J., Kearney, C. J., & O'Brien, F. J. (2015). Biomaterial based modulation of macrophage polarization: a review and suggested design principles. *Materials Today, 18*(6), 313–325.

Stevens, M. M. (2020). Biomaterials for bone tissue engineering. *Nature Materials, 19*(5), 501–516.

Tack, P., Victor, J., & Gemmel, P. (2016). 3D-printing techniques in a medical setting: a systematic literature review. *Biomedical Engineering Online, 15*(1), 115.

Wang, C., Huang, W., Zhou, Y., He, L., He, Z., Chen, Z., ... & Wang, M. (2020). 3D printing of bone tissue engineering scaffolds. *Bioactive Materials, 5*(1), 82–91.

Wang, L. V., & Yao, J. (2016). A practical guide to photoacoustic tomography in the life sciences. *Nature Methods, 13*(8), 627–638.

Webber, M. J., Appel, E. A., Meijer, E. W., & Langer, R. (2016). Supramolecular biomaterials. *Nature Materials, 15*(1), 13–26.

Wilkinson, J. M., & Little, D. G. (2011). The challenge of proving efficacy in orthopaedic bone graft substitutes. *The Journal of Bone and Joint Surgery. British volume, 93*(1), 1–2.

Zein, I., Hutmacher, D. W., Tan, K. C., & Teoh, S. H. (2002). Fused deposition modelling of novel scaffold architectures for tissue engineering applications. *Biomaterials, 23*(4), 1169–1185.