Li-Doped Bioactive Ceramics: Promising Biomaterials for Tissue Engineering and Regenerative Medicine

Ahmad Reza Farmani 1,2,3, Mohammad Ali Salmeh 4, Zahra Golkar 5, Alaa Moeinzadeh 6,7, Farzaneh Farid Ghiasi 6, Sara Zamani Amirabad 9, Mohammad Hasan Shoormeij 9, Forough Mahdavinezhad 10,11, Simin Momeni 12, Fatemeh Moradbeygi 13,14, Jafar Ai 1, John G. Hardy 15,16,* and Amir Mostafaei 17,∗

1 Tissue Engineering and Applied Cell Sciences Department, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran 14166-34793, Iran
2 Tissue Engineering Department, School of Advanced Technologies in Medicine, Fasa University of Medical Sciences, Fasa 74615-168, Iran
3 Students’ Scientific Research Center, Tehran University of Medical Sciences, Tehran 14166-34793, Iran
4 Department of Biotechnology, School of Chemical Engineering, College of Engineering, University of Tehran, Tehran, 14155-6619, Iran
5 Department of Midwifery, Firoozabad Branch, Islamic Azad University, Firoozabad 74715-117, Iran
6 Department of Tissue Engineering and Regenerative Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran 14496-14535, Iran
7 Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran 14496-14535, Iran
8 Department of Chemical Engineering, Faculty of Engineering, Yasar University, Yasar 75918-74934, Iran
9 Emergency Medicine Department, Shariati Hospital, Tehran University of Medical Sciences, Tehran 14166-34793, Iran
10 Anatomy Department-School of Medicine, Tehran University of Medical Sciences, Tehran 14166-34793, Iran
11 Department of Infertility, Velayat Hospital, Qazvin University of Medical Sciences, Qazvin 34199-15315, Iran
12 Chemistry Department, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz 83151-61355, Iran
13 Department of Pharmaceutical Biotechnology, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz 71348-14336, Iran
14 Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz 71348-14336, Iran
15 Department of Chemistry, Faraday Building, Lancaster University, Lancaster LA1 4YB, UK
16 Materials Science Institute, Lancaster University, Lancaster LA1 4YW, UK
17 Department of Mechanical, Materials, and Aerospace Engineering, Illinois Institute of Technology, 10 W 32nd Street, Chicago, IL 60616, USA

* Correspondence: j.g.hardy@lancaster.ac.uk (J.G.H.); mostafaei@iit.edu (A.M.)

Abstract: Lithium (Li) is a metal with critical therapeutic properties ranging from the treatment of bipolar depression to antibacterial, anticancer, antiviral and pro-regenerative effects. This element can be incorporated into the structure of various biomaterials through the inclusion of Li chloride/carbonate into polymeric matrices or being doped in bioceramics. The biocompatibility and multifunctionality of Li-doped bioceramics present many opportunities for biomedical researchers and clinicians. Li-doped bioceramics (capable of immunomodulation) have been used extensively for bone and tooth regeneration, and they have great potential for cartilage/nerve regeneration, osteochondral repair, and wound healing. The synergistic effect of Li in combination with other anticancer drugs as well as the anticancer properties of Li underline the rationale that bioceramics doped with Li may be impactful in cancer treatments. The role of Li in autophagy may explain its impact in regenerative, antiviral, and anticancer research. The combination of Li-doped bioceramics with polymers can provide new biomaterials with suitable flexibility, especially as bio-ink used in 3D printing for clinical applications of tissue engineering. Such Li-doped biomaterials have significant clinical potential in the foreseeable future.

Keywords: lithium; bioceramics; bioactive biomaterials; tissue engineering; cancer treatment; autophagy; drug delivery
1. Introduction

Tissue engineering and regenerative medicine approaches have a variety of applications in human healthcare, including bone reconstruction and fertility treatments [1–10]. Tissue engineering combines three components, cells, biomaterials, and bioactive molecules (e.g., drugs and growth factors), to repair the body’s damaged tissues and restore their normal function [11–14]. Stem cells can self-renew, proliferate, and differentiate into target tissue cells in the presence of relevant growth factors when in biomaterials with supportive architecture, composition, and mechanics [15,16]. However, some studies have shown that stem cells are the cause of pathological conditions and have a role in cancer [17–20].

Biomimetic biomaterials with similar properties to the extracellular matrix play a crucial role in cell proliferation and differentiation, and consequently tissue regeneration. Generally, biomaterials used in tissue engineering can be divided into four main categories: metal-based, ceramic-based, polymer-based, and their composites [21–30]. Due to their structure and similarity to the extracellular matrix of hard tissues (such as bone and teeth), bioceramics have been widely investigated for their potential application in the regeneration of hard tissues [31,32]; however, by contrast, there has been limited research into their application in soft tissue regeneration [33–35], which is in part due to challenges related to engineering bioceramics with mechanical properties mimicking the natural tissues in which they will be implanted [24,36–44]. Bioceramic biomaterials can release drugs and/or therapeutic metal ions in regenerative medicine applications and cancer treatment [45–50], yet doping the right amount of ions/therapeutics and the controlled/sustained release of the therapeutic payloads are remaining challenges (Figure 1) [51–53].

Li is an essential ion that has a multitude of biological effects on the body, such as increasing the activity of chemical messengers in the brain [54–56]. The discovery that Li is effective in treating bipolar disorder happened more than 70 years ago, and it is a widely prescribed bipolar disorder medication [57–59]. However, it is associated with adverse effects and teratogenicity [60]. Li affects hematopoiesis, embryonic development, glyco- gen synthesis, and other processes [61–63]. Its mechanism of action in mood disorders was unknown in the past; it was thought that Li exerts its effect by affecting cation transport in nerve and muscle cells [64]. In pharmacy, Li is prepared in the form of carbonate, acetate, citrate, sulfate, and orotate salts, and it is most commonly prescribed in the form of carbonate or citrate salts in tablets (up to 2.0 g per day) [55,65]. However, concerns related to Li include hand tremor, downbeat nystagmus, and hypothyroidism [66–68]. In acute mania, Li doses can reach 1.2 mEq/L. Li is toxic when its concentration exceeds 1.5 mEq/L and can be lethal above 3.5 mEq/L [69,70]. The main side effects of Li are dose-dependent; thus, therapeutic doses should be employed to reduce any side effects [71–74]. Retrospective studies showed lower cancer incidence in psychiatric patients treated with Li therapy for bipolar disorder than in a control group not receiving Li therapy [75,76], which was suggested to be due to Li controlling cancer cell growth via inhibiting GSK-3β [77]. Interestingly, Li can inhibit 17 human magnesium-dependent phosphate transfer enzymes, which represents another potential anticancer mechanism of Li. Meanwhile, system biology studies demonstrated that 13 KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway categories are most statistically enriched in the 265 genes that interact directly with GSK-3β. Given that the Li therapy impact is mostly systemic and the ability of Li to inhibit cancer cell growth has been shown, Li may also inhibit metastasis [54,76,78]. Li monotherapy (or in combination) was effective in inducing cancer cell apoptosis in breast cancer [79–81], colon cancer [82–86], esophageal cancer [82,87], glioblastoma [88], ovarian cancer [89], pancreatic cancer [88,90], prostate cancer [91–93], and thyroid cancer [94–97]. In vitro studies showed that Li induces apoptosis in lung cancer cell lines [98], and changes mRNA in leukemia [99,100] and lymphoma [101,102]. Given these studies, Li may have an anticancer effect through the induction of apoptosis and autophagy [103–106]. Li-induced autophagy may have other therapeutic applications beyond cancer treatment and regenerative medicine, such as treating autoimmune diseases [107,108].
This review discusses the biological effects of Li ions and prospects for the application of Li-doped bioactive ceramics (Li-doped bioceramics) in regenerative medicine (abbreviations used throughout the article are summarized in Table 1). Current research trends in applications of Li-doped bioceramics are summarized in Figure 2; the bioceramics that have attracted most attention are BGs; bone and osteochondral regeneration are the predominant focus of the existing research, and despite the great potential of lithium-doped bioceramics for cancer treatment, wound healing, and nerve regeneration, these are comparatively nascent in their development.

Figure 1. Common loading techniques for therapeutic inorganic ion entrapment in nanoparticles/microparticles, granules, hydrogels, and fibers. Reproduced from [53] with permission.

Table 1. Abbreviations used in this review.

| Abbreviation | Word or Phrase           |
|--------------|--------------------------|
| ALP          | Alkaline phosphatase     |
| AP-1         | Activator protein-1      |
| BG           | Bioactive glass          |
| Abbreviation | Description |
|--------------|-------------|
| BMSC         | Bone marrow mesenchymal stem cell |
| β-TCP        | Beta-three calcium phosphate |
| cAMP         | Cyclic adenosine monophosphate |
| CNS          | Central nervous system |
| CREB         | Response element binding protein |
| DEXA         | Dual-energy X-ray absorptiometry |
| Dspp         | Dentin sialophosphoprotein |
| EPO          | Erythrogenin |
| ERK          | Extracellular signal-regulated kinase |
| 5-FU         | Fluorouracil |
| GAG          | Glycosaminoglycan |
| GIONFH       | Glucocorticoid-induced osteonecrosis of the femoral head |
| GSK-3β       | Glycogen synthase kinase-3 beta |
| HA           | Hydroxyapatite |
| Hh           | Hedgehog pathways |
| HIF-1α       | Hypoxia-inducible factor 1-alpha |
| HSC          | Hematopoietic stem cell |
| HUVEC        | Human umbilical vein endothelial cell |
| IGF1         | Insulin growth factor 1 |
| iTENG        | Ionic triboelectric nanogenerator |
| KEGG         | Kyoto Encyclopedia of Genes and Genomes |
| Klk4         | Axin2, Kallikrein 4 |
| LCS          | Lithium-doped calcium silicate |
| LD           | Lithium disilicate |
| Li-BG        | Lithium-doped bioactive glass |
| Li-BBG       | Lithium-doped borate-based bioactive glass |
| Li-MBG       | Lithium-doped mesoporous bioactive glass |
| LMNS         | Lithium-doped mesoporous silica nanosphere |
| Li-nHA/GMs/rhEP | Gelatin/lithium-doped-hydroxyapatite nanoparticles/gelatin microspheres/rhEPO |
| Li-PBG       | Lithium-doped phosphate-based bioactive glass |
| LPPEEK       | Lithium-doped silica nanospheres coated on polyetheretherketone surface |
| LSN          | Lithium-doped silica nanosphere |
| MACI         | Matrix-associated autologous chondrocyte implantation |
| MAPK         | Mitogen-activated protein kinase |
| micro-CT     | Micro-computed tomography |
| MSC          | Mesenchymal stem cell |
| MSN          | Mesoporous silica nanosphere |
| NPWT         | Negative pressure wound therapy |
| OA           | Osteoarthritis |
| OIM          | Osteoimmunomodulation |
| p38MAPK      | P38 mitogen-activated protein kinase |
| PCL          | Poly-ε-caprolactone |
| PDA          | Polydopamine |
| PEEK         | Polyetheretherketone |
| PI3-K        | Phosphatidylinositol 3 kinase |
| PNS          | Peripheral nerve system |
| qPCR         | Quantitative polymerase chain reaction |
| rBMSC        | Rabbit mesenchymal stem cell |
ROS Reactive oxygen species
Runx2 Runt-related transcription factor 2
SBF Simulated body fluid
SCI Spinal-cord injury
TGF-β Transforming growth factor beta
VEGF Vascular endothelial growth factor
ZLS Zirconia-reinforced lithium silicate

Figure 2. Current trends of research on the application of Li-doped bioceramics.

2. Lithium and Its Biological Effects

2.1. Lithium and Stem Cell Fate

Li affects stem cells in various ways, mainly related to the inhibition of glycogen synthase kinase-3 beta (GSK-3β) and the activation of other pathways, such as activator protein-1 (AP-1), cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), mitogen activated protein kinase (MAPK), WNT, and β-catenin signals. WNT and MAP kinase activation have a significant role in stem cell proliferation, wound healing, neural, and bone regeneration. Hence, Li affects stem cell fate, such as differentiation, proliferation, and regeneration. The neuroprotective and anti-inflammatory effects of Li are mainly related to GSK-3β inhibition, the deterrence of the pro-inflammatory cytokine response, and the production of reactive oxygen species (ROS), and they are stimulated by polymicrobial sepsis [109–113].

Angiogenesis-related gene expression can be attributed to the crosstalk between the canonical WNT and hypoxia-inducible factor 1-alpha (HIF-1α) signaling pathway [114]. The enhancement in vascular endothelial growth factor (VEGF) expression was observed through phosphatidylinositol 3 kinase (PI3-K)/(GSK-3β)-dependent and independent pathways in the brain endothelium and astrocytes, respectively, in the presence of Li [115]. Activating the WNT/β-catenin signaling impelled proliferation, survival, and migration, which are normal procedures in angiogenesis. These features were observed in vitro in human microvascular endothelial cells with LiCl [116]. A study demonstrated that
Li improved self-renewal, stem cell homing, ability to build colonies, and self-renewal of hematopoietic stem cells (HSCs). Li can positively affect the maintenance and proliferation of mesenchymal stem cells (MSCs) [117], and Li impacts stem cells fate by enhancing autophagy, which has a crucial role in tissue development, remodeling, and regeneration [103,118,119].

2.2. Lithium and Osteogenesis

The mechanical properties of bone are of fundamental importance to its biological role [120,121] and a key property of tissue scaffolds for bone tissue engineering [122,123]. Li boosts β-catenin signaling, which stimulates bone growth in reply to mechanical load. In expanding sutures, Li enhances cell proliferation and β-catenin expression; the initial retardation in the differentiation of osteoprogenitors cells into mature osteoblasts by Li therapy was associated with the development of preosteoblasts, which pave the way for the enhancement of new bone regeneration in the vicinity of sutures. β-catenin influences osteoprogenitors proliferation and osteoblast maturation during mid-palatal suture osteogenesis. Li enhances β-catenin expression, boosting bone repair. Therefore, Li may boost the durability of orthodontic therapies, such as rapid palatal dilatation [124]. Evaluating the impact of GSK-3β deficiency in the mice model demonstrated that in vivo bone healing can be accelerated by GSK-3β inhibition; moreover, the results may be attributed to the impact of the higher activity of WNT/β-catenin in deficient mice [125]. In a similar study, rats were treated daily with LiCl or NaCl from 7 days before socket extraction up to 14 days after surgery. New bone development after tooth extraction was 37.5% (control), 23.8% (continuously treated), 53.9% (post-treated), and 63.2% (pre-treated) groups. Before or after socket extraction, Li enhances bone healing, and tooth removal during Li therapy may slow bone repair [126].

In a study on rats, it was observed that the administration of Li carbonate (45 mg/kg/day) caused bone deterioration in sexually mature healthy rats [127]. Another study reported that Li chloride (LiCl) debilitates BMP-2 signaling and creates a hindrance for osteogenic differentiation through an independent novel GSK-3β/WNT during the early stages of osteogenic differentiation [128]. In contrast to this study, others showed improving bone regeneration by the administration of Li, for example, it was reported that proliferation and osteogenic differentiation were enhanced at 4 mM and 10–12 mM of LiCl, respectively [129]. An important aspect of bone tissue is its mechanical properties and its ability to withstand forces exerted on it [120,121]. The effect of a 28-day Li therapy (140 mg/kg/day) on the mechanical properties of the bones of estrogen-deprived rats was investigated and, although a remarkable increase in the mechanical properties of cancellous bone was observed, increases in the mechanical properties of compact bone were small; this suggests that the use of Li in improving the mechanical properties of bone holds promise for long-term clinical applications [130]. A comparable study revealed that 150 mg/kg/2 days of LiCl could enhance bone regeneration substantially in osteoporotic mice. Higher bone volume, trabecular thickness, trabecular number, and osseointegration were assessed with Micro-CT, and the maximum push-out force (N) and implant–bone contact shear strength (N/mm²) were stronger in the LiCl group (36 ± 6 N vs. 105 ± 12 N, 1.9 ± 0.4 vs. 5.6 ± 0.7 N/mm², respectively) [131]. The effects of systemic LiCl administration on the socket healing of estrogen-deficient rats were evaluated, finding that LiCl improved bone regeneration in rats with estrogen deficiency, especially in the initial healing [132]. Bone regeneration by Li treatment is therefore dose-dependent and the dosage may be dependent on the stem cell source [133].

Li acts via hedgehog pathways (Hh). By simultaneously impacting the Hh and WNT pathways, LiCl diminishes adipogenesis and improves osteogenesis in bone marrow mesenchymal stem cells (BMSCs) [134]. The adipogenic gene (CEBPA, CMKLR1, and HSD11B1) expression of human mesenchymal stem cells (hMSCs) after exposure to Li was reduced, while the expression of alkaline phosphatase (ALP), Runx-related transcription factor 2 (Runx2), bone sialoprotein (BSP), and collagen 1 synthesis were elevated [135]. A
key clinical challenge is fracture healing, which can be a lengthy process and fails in 5–10% of cases. Femoral fracture in rats was used as a model to optimize Li administration variables (such as onset time, curing duration, and dose); administrating a low dose of Li (20 mg/kg) for two weeks after fracture revealed the most promising results [136]. Furthermore, another effect of Li on bone regeneration is increasing bone mineral density after the administration of Li. Dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and hip in 75 normal participants and 75 Li-treated patients showed that bone density was raised by 5.3% at the femoral neck, 7.5% at the trochanter, and 4.5% at the spine. Li-treated patients had reduced ALP, osteocalcin, and serum CTX [137].

The immune system plays a significant role in bone regeneration. Osteoimmunomodulation (OIM) is an area of focus that has been developed to study the immune response during osteogenesis [138,139]. Li modulates immune cells, especially macrophages through chemokine gene expression [140]. Osseal macrophages (osteomacs), especially CD169+ osteomacs pro-anabolic support contribute to osteoblasts during bone hemostasis and regeneration [141]. In vitro studies revealed that Li reprograms macrophages to the M2 phenotype, leading to improvement in osteogenic differentiation in rat BMSCs. Additionally, LiCl prevents p38mitogen-activated protein kinase (p38MAPK) and extracellular signal-regulated kinase (ERK) from phosphorylation. Hence, it accelerates bone regeneration, for which these studies help to find new treatments wearing debris-induced osteolysis [142,143].

The results of computerized tomography and bone histomorphometry showed that the local Li:CO3 administration can accelerate bone healing in rat tibia defective lesions by raising lamellar bone ratios versus controls, and the acceleration in the recovery of bone damage through boosting osteoblastogenesis and preventing osteoclastogenesis was achieved effectively by the local delivery of Li [144]. However, decreasing immune-responsive genes (CXCL1, CXCL12, CCL20, IL7, and IL8) and osteoclastogenic factors were reported before [135]; therefore, increasing bone mineral density can result from inhibiting osteoclastogenesis caused by Li. The crucial roles of Li in different stages of bone regeneration is summarized in Figure 3 [145].
2.3. Lithium and Bone and Cartilage Regeneration

The majority of the work on Li focuses on bone regeneration. Given the similarity in the development of bone and cartilage, Li may also induce cartilage regeneration. An in vitro study showed the growth of cartilage on LiCl-polydopamine (PDA)-coated 3D-printed poly-ε-caprolactone (PCL)-based scaffolds, and glycosaminoglycan (GAG) production was increased as was chondrogenic marker gene expression [146]. Teeth are another hard tissue and activating WNT/β-catenin signaling affects the rate of dentin secretion and cementoblastic differentiation [147–150]. An in vivo study in a rat pulp capping model showed that the local administration of LiCl leads to the induction of compensatory dentin formation through WNT/β-catenin signaling [151]. Another study reported that the WNT signaling pathway is crucial in regulating dentin sialophosphoprotein (Dspp) expression, and LiCl promotes mRNA levels of Axin2, Kallikrein 4 (Klk4), and Dspp while attenuating the expression of osteopontin. Therefore, using LiCl as a capping-material for dentine regeneration may be promising [152]. Since Li effects are dose-dependent, the overuse of Li can result in severe dental putrefaction and deterioration in the tooth structure, which is linked with dentin mineral loss [153]. Therefore, using Li in dentistry still requires extensive studies [154].
2.4. Lithium and Wound Healing

Li activates the WNT pathway; WNT7a has a crucial role in wound healing, especially regenerating damaged vessels and diminishing the inflammatory response in diabetic wounds (with or without obesity) and epithelial differentiation [155]. The size of the wound is regulated by canonical WNT/β-catenin signaling, which also mediates the role of transforming growth factor beta (TGF-β) in cutaneous healing [156–158]. Therefore, Li-ions are a suitable target for wound healing. In live animals, initiating the WNT signaling pathway by employing a pump specialized for negative pressure wound therapy (NPWT) and LiCl promoted the migration of cells into simulated wound sites. The minimum LiCl demanded to fill the simulated wound is 10 mM [159]. Similar results were achieved by loading LiCl in chitosan hydrogel wound dressings in male C57BL/c mice [160].

One of the most important applications of Li is in energy storage as Li-ion batteries, which are the most promising electrochemical energy storage devices [161]. Electrotherapy creates new opportunities in wound healing [162], and wearable ionic triboelectric nanogenerator (iTENG) patches (created from a stretchable platform based on LiCl-loaded organogels and elastomeric microtubular structures) utilized the therapeutic effects of Li-ions in wound healing, and moreover contributed to creating and transmitting electrical stimulation (Figure 4) [163], which is very promising in wound healing applications [164].

2.5. Lithium and Nerve Regeneration

Li was shown to promote the proliferation of progenitor cells in the hippocampus’s dentate gyrus and to boost the mitosis of Schwann cells; neurogenesis is connected to Li’s neuroprotective and neurotrophic effects, synaptic plasticity improvement, cell survival enhancement, and apoptosis reduction [117]. GSK-3β inhibitors, especially mood stabilizers such as LiCl, could be neuroprotective or anti-inflammatory agents. Li can enhance remyelination by boosting the expression of MPZ and PMP22 promoter activity, as well as transcripts, and protein levels. LiCl promotes myelin gene expression, maintains myelin integrity, and catalyzes the recovery of mouse whisker movements following facial nerve compression injury; it also promotes the remyelination of sciatic nerves. Moreover, the mechanism of LiCl interaction with Schwann cells can be attributed to raising the amount of β-catenin and provoking its nuclear localization [165].

The hypothesized neuroprotective effects of Li include the inactivation of N-methyl-D-aspartate receptors, the activation of PI3-K/Akt cell survival pathway, boosting expression of cytoprotective Bcl-2, and the suppression of GSK-3β [166]. Schwann cell viability and proliferation rates were increased at 5, 10, 15, and 30 mM LiCl. Wound healing was due to suppressing the migration of Schwann cells [167]. Thus, in peripheral nerves, Li improved remyelination by enhancing the expression of peripheral myelin genes, resulting in their proliferation and attenuating the migration of Schwann cells. In addition to peripheral nerves, Li has a significant neuroprotective role in central nervous system (CNS). For example, it has been reported that Li attenuates neuronal damage after acute spinal cord injury (SCI) and promotes neurological recovery by inducing autophagy [168]. Brachial plexus damage is one of the most common spinal cord injuries that often involves intense root avulsion resulting in the permanent paralysis of the innervated muscles. The impaired regeneration of motoneurons from the spinal to the peripheral nerve system (PNS) is one of the leading causes of inadequate treatment. By inhibiting GSK-3, Li therapy can improve motoneuron regeneration from the CNS to the PNS [169]. The outcomes of daily intraperitoneal LiCl administration after a 20-week rehabilitation on the immediate reimplantation and avulsion of the C7 and C8 ventral roots were studied, and Li along with reimplantation permitted 45.1% of motoneurons to be rescued from the injury as well as improving the quantity and median diameter of nerve fibers [170]. Another study demonstrated that Li, started during the early remyelination phase, preserved it, despite the late stage of the process [171]. Locally releasing Li from hyaluronic acid in a silicon
conduit on a rat sciatic nerve injury was observed to increase nerve regeneration in rats [172].

Figure 4. An ionic TENG (iTENG) patch and its potential wound-healing applications. (A) Schematic illustration of an iTENG patch for accelerated wound healing based on tribotronics. (B) Schematic depiction of accelerated wound healing due to the secretion of biological molecules and the formation of new cutaneous tissue under a self-powered EF driven by an iTENG patch. (C) Optical image of the ionic fabric (scale bar: 1 cm. Inset: Schematic diagram of a cross-section of the ionic fabric and magnified image of a fiber.) Conductive organogel is injected into an HDFS-treated silicone tube (scale bar: 500 μm). (D) Schematic illustration of the biomechanical energy harvesting mechanism of the iTENG, which relies on friction between the iTENG and skin. (E) Voltage generated upon bending at 30°, 60°, and 90° (scale bar: 3 cm. Inset: Optical image of wearable ionic fabric on a bent index finger). (F) Voltage generation of a self-motion-driven iTENG patch applied to the back of a BALB/c nude mouse. Reproduced from [163] with permission.

2.6. Lithium and Antibacterial and Antiviral Activities

The antibacterial and antiviral activities of biomaterials are beneficial because infection and the presence of pathogens are among the most critical problems that inhibit tissue regeneration [173–176], and moreover, it is recognized that bacteria and viruses are recognized to have the potential to induce carcinogenesis [177–180]. The main metal-mediated antibacterial mechanisms are membrane disruption, ROS generation, macrophage activation, and protein/DNA damage [181,182]. In the case of Li, immunostimulating, anti-prostaglandin actions, inhibiting viral replication, and reducing lymphopenia are reported as being the primary antibacterial and antiviral mechanisms [183,184]. Moreover, Li affects autophagy, and it has been reported that autophagy has a vital role in virally infected cells; hence, further studies to investigate the antiviral mechanism of Li are important [103,185].
Given the impact of SARS-CoV-2 in global health, various anti-inflammatory and antiviral treatments are under investigation, including Li [186–192]. To date, the antiviral activity of Li in different viruses (including porcine epidemic diarrhea, pseudorabies herpesvirus, Orthoreoviruses, and Coxsackievirus B3 virus) has been proved [193–196]. Additionally, its antibacterial activity against Gram-negative bacteria (including Porphyromonas gingivalis, Francisella tularensis, Aggregatibacter actinomycetemcomitans, Klebsiella pneumoniae, Escherichia coli, Burkholderia pseudomallei, and Pseudomonas aeruginosa) and Gram-positive bacteria (including Streptococcus pneumoniae, Streptococcus mutans, and Staphylococcus aureus) has been reported [197–202]. A summary of the biological effects of Li and the relation between these effects and autophagy is presented in Figure 5.

**Figure 5.** An overview of the biological effects of lithium. (A) Regenerative effects and their main signaling pathways that are activated in each tissue. Lithium can cause regeneration in several tissues, including bone, cartilage, dentin, nerve, skin, and vascular system. A WNT/β-catenin signaling pathway is the primary signaling pathway activated by lithium. Additionally, it has an anti-inflammatory response by inhibiting the GSK-3β pathway. (B) The anticancer effects of lithium in several types of prevalent cancers with a high mortality rate, including pancreatic cancer, thyroid cancer, esophageal cancer, colon cancer, prostate cancer, ovarian cancer, breast cancer, lung cancer, leukemia, and glioblastoma. Lithium has shown an anticancer effect and has been used as a singular or adjunct treatment. Hence, lithium can be considered a chemosensitizer in chemotherapy. (C) Antibacterial properties. Lithium has antibacterial properties against both Gram-positive and Gram-negative bacteria. (D) Lithium has antireplicative effects against several types of viruses. (E) The crucial point of the biological properties of lithium, including its antiviral, anticancer, and regenerative effects, is the effect of lithium on autophagy.
3. Lithium-doped Bioceramics in Regenerative Medicine

Bioceramics can be used in both hard and soft tissue regeneration. The three main groups of bioceramics that incorporate Li-ions in their structure include bioactive glass (BG), calcium phosphates (including hydroxyapatite (HA) and beta-three calcium phosphate (β-TCP)), and silicates.

3.1. Lithium-Doped Bioactive Glasses (Li-BGs)

Bioactive glasses (BGs) are bioceramics promoting hard tissue regeneration by creating a layer of HA on their surfaces [203,204]. An advantage of BGs is the inclusion of various ions to their structure to improve their performance. In recent years, one of the ions added to the structure of BG is Li; Li-BG is commonly used in bone regeneration and osteochondral repair [205]. For instance, a study investigated the biocompatibility and bioactivity of 45S5 Li-BG that was prepared by a melt quenching method. Li in low concentrations inhibited apatite formation, resulting in the compactness of the structure [206]. Additionally, Li-substituted bioglasses caused increasing ALP activity and cell proliferation in a dose-dependent manner, reducing the rate of ion release and apatite formation [207]. Li2O contents within the therapeutic range (below 8.3 ppm) have been reported, which should be between 2.5 and 5 wt% in Li silicates, 45S5 Li-BG, and their scaffolds. Li-BGs generally crystallize into the phases Li6P6O18 and Li3PO4, as well as combeite (Na2Ca2Si3O9) and silicorhenanite (SiO4(PO4)2Ca5) [208]. Investigating the effect of Li precursors on the structure–property relationships of Li–silicate sol–gel BG revealed that nitrate, in comparison to citrate, has a higher affinity for Li. In contrast, citrate has a lower decomposition temperature that is advantageous [209].

One of the areas in which bioceramics have a wide range of applications is dentistry [210]. A new class of glass–ceramics based on Li2O-SiO2 called Li disilicate (LD) was conceived for dentistry due to its aesthetics, chemical durability, high fracture strength, and inertness in the buccal environment [211,212]. LD bioactivity begins after 14 days, and after 21 days, a mineralized matrix develops from a demineralized matrix [213]. Similar results were reported in a case report for zirconia-reinforced Li silicate (ZLS) [214]. The remineralization process induced by 45S5 Li-BG containing 5-wt% of Li and its great antibacterial activity is prevalent in oral diseases [202].

BGs are used in bone regeneration due to release crucial ions [215]. The release of Li from different 45S5 BGs, which is designed for bone regeneration, has been explored by Da Silva et al. [216]. Similar to LiCl treatment, local Li-ion release upregulated WNT pathway expression in 171A4 cells. However, high concentrations of BG may cause cytotoxicity due to changes in the pH of the solution. Compared to Li-doped phosphate-based bioactive glasses (Li-PBGs), Li-doped borate-based bioactive glasses (Li-BBGs) release Li at a slightly higher rate and amount. The quantitative polymerase chain reaction (qPCR) analysis of AXIN2 expression found that Li-BBGs had a higher gene expression. Li-BBGs release more Li, explaining these results [217].

The synergistic effect of dopant ions and the ease of preparing polymer composites are two significant advantages of BGs. For example, the use of Sr-doped BGs for bone regeneration is well established [218]. The impact of single and binary strontium and Li doping on BG scaffolds in vivo has been investigated employing histochemical and micro-computed tomography (micro-CT) analysis of a femoral defect of rabbits as a model at 2, 4, and 6 months. Li-doped scaffolds have mild bone regeneration, while Sr and Li + Sr-doped scaffolds had excellent osseous tissue formation. Moreover, micro-CT data showed that Li + Sr samples have the highest degree of vascularity, peripheral cancellous tissue formation, and cortical tissue inside implanted samples. Thus, doping Sr and Li to BG can improve bone regeneration, especially in early in vivo osseointegration [219]. Nanobiocomposite scaffolds consisting of Li-doped mesoporous bioactive glass (Li-MBG) and a block copolymer (mPEG-PLGA-b-PLL) were observed to significantly improve MC3T3-
E1 cell proliferation, attachment, and ALP activity [220]. Thus, doping Li and other beneficial ions for bone regeneration to BGs such as Sr may synergistically enhance its regenerative effect. They may also be used to prepare polymeric nanocomposite scaffolds.

The majority of BGs’ regenerative applications are orthopedic. Osteochondral lesions are common worldwide and pose significant treatment challenges for orthopedic specialists due to unsatisfactory treatments [221]. Although regenerative medicine has proposed new treatment strategies, such as matrix-associated autologous chondrocyte implantation (MACI), layered scaffolds in acellular or cellular approaches for use in the clinic [222], the most challenging task is to create biomaterials that can regenerate both bone and cartilage. These requirements make this field difficult [223]. Gradient scaffolds for osteochondral tissue engineering are exciting, but designing them for clinical application is challenging [224]. Because of these reasons, simplifying biomaterial system design is critical. Li-releasing BGs derived from sol-gel processes are suitable for cartilage regeneration [146,225]. Thus, using Li-doped BGs for osteochondral tissue engineering is promising but not well investigated. For example, Li-MBG was used in a rabbit osteochondral defect study. After 8–16 weeks of implantation in osteochondral defects, Li-MBG scaffolds outperformed pure MBG scaffolds in terms of the regeneration of subchondral bone and hyaline cartilage-like tissues, suggesting Li-doped BGs have great potential in osteochondral regeneration [226].

Although bioceramics and BGs appear limited to orthopedics and hard tissue reconstruction, these materials have found many applications in soft tissue reconstruction due to one of their pro-angiogenesis properties. The lack of mature and functional vasculature has severely hampered the clinical translation of tissue-engineered constructs [227]. As stated previously, Li-ions can induce angiogenesis, making Li-doped BGs promising materials for improving angiogenesis [114,116]. Exposure to 45S5.5 Li-BG ionic dissolution products improved angiogenesis by increasing integrin αvβ3 subunit β3 expression and vascular density in quail embryo CAMs. The ionic dissolution products of 45S5.5 Li-doped BGs can be considered inorganic angiogenic agents, which can be used in place of expensive and potentially harmful growth factors [205,228,229]. It has also been claimed that Si and Li-ions have synergistic effects on the activation of the WNT/β-catenin canonical pathway and the production of proangiogenic cytokines (insulin growth factor 1 (IGF1) and TGF-β) [205,230]. A separate study demonstrated that 45SS Li-BG could improve human umbilical vein endothelial cells’ (HUVECs) pro-angiogenic ability by down-regulating PTEN protein and activating the AKT pathway, which increases endothelial cell proliferation, migration, and tube formation and enhances the expression of pro-angiogenic genes [231]. Therefore, it appears that adding Li-ions to BGs can stimulate angiogenesis, though more research is required to fully grasp the mechanism.

Finally, given Li’s neuroprotective and neurogenic properties and the use of BGs in neural regeneration, Li-doped BGs may be helpful in neural tissue engineering scaffolds [232,233]. Despite the several neuroprotective advantages of Li, there are relatively few studies related to Li-doped bioceramics for neural regeneration. Extensive burns, for example, can cause nerve damage, and different Li2O contents have been added to BGs to support nerve healing and angiogenesis. In the proper dilution ratio, Li-BG extracts advanced the proliferation of Schwann cells and HUVECs. Li-BG extracts with adequate Li- and Si-ions promoted Schwann cell migration [234]. A new strategy for neural regeneration may be Li-BGs and their polymeric composites.

3.2. Lithium-Doped Calcium Phosphates

Calcium phosphates, including HA and β-TCP, have always been considered the first bioceramics used in regenerative medicine due to their extracellular matrix nature. HA, which is found in the body, is one of the bioceramics whose function is improved by adding ions such as Li [235]. For example, improving fracture bone healing with Li-doped calcium phosphate cement (Li/CPC) has been studied; Li/CPC extracts can stimulate the in vitro proliferation and differentiation of osteoblasts by releasing Li-ions (Li+) at 25.35–
50.74 mg/L via the WNT/β-catenin pathway. The effects of the local Li+ release in rat tibia defects were also studied in vivo using CPC and Li/CPC. Compared to CPC, Li/CPC showed better osteoconductivity, osteogenesis, and osseointegration by increasing bone mass and promoting defect repair [236]. Calcium phosphate/Li coatings improved MG63 cell attachment, early proliferation, and biocompatibility [237], so doping Li-ion to calcium phosphate can improve its potential biomedical application. For example, the glucocorticoid-induced osteonecrosis of the femoral head (GIONFH) affects young people and middle-aged adults, and to treat GIONFH, a composite scaffold with Li as a WNT signal activator and erythrogenin (EPO) to upregulate the HIF-1/VEGF pathway was designed. To this end, a porous gelatin/Li-doped-hydroxyapatite nanoparticles/gelatin microspheres/rhEPO (Li-nHA/GMs/rhEPO) composite scaffold was created. The in vitro results showed increased osteogenic and angiogenic factors and activating factors in the WNT and HIF-1/VEGF pathways. Additionally, in the GIONFH rabbit model, this scaffold improved new bone formation and repaired femoral head defects [238]. Consequently, more research on Li-doped HA and its nanocomposites in treating GIONFH or similar conditions seems logical.

Orthopedic implants are another possible application for Li-doped HA. In simulated body fluid (SBF), Li-HA scaffolds were hydrolyzed, and they can also be degraded by cells. Li-HA scaffolds increased PO43- release in a degradation medium, which increased osteoblast physiological activity and sped up Li-HA degradation. The addition of Li to HA also increased its compressive strength. Moreover, SEM and MTT assays showed that the degradation products of Li-HA scaffolds aided osteoblast proliferation [239]. Although adding Li to HA did not affect the degradation rate, doping Li into HA scaffolds increased bone formation by decreasing GSK-3β and β-catenin mechanisms, but did not have a significant angiogenic effect [240]. The incorporation of Li in HA causes densification [241], with greater crystallinity for Li-doped HA than undoped HA. Li also reduces the dielectric constant, which is good for dental and orthopedic applications [242]. A study evaluated the physical, mechanical, and biological properties of Li-doped calcium phosphates, which showed the growth of an apatite layer in SBF [243]. Metallic implants coated with Li-HA thin films have been studied. FTIR spectra revealed the coatings' high biomineralization potential; Li3PO4 and Li2CO3 as doping reagents were observed to increase the growth of hMSCs on film surfaces, suggesting Li-doped bio-derived materials as a promising next-generation coated implant material with rapid osteointegration [244].

Seeding stem cells on the new generation of implants may improve clinical applications. For instance, simultaneous nerve and bone tissue regeneration in spinal cord injuries are required (SCI). Hydroxyapatites are bioreabsorbable materials with good biocompatibility and osteoconductivity, so their use in spinal surgery is possible. The theranostic agent nanocrystalline calcium HAs, incorporating Li+ (Li-nHA) doped with europium (Eu3+), have excellent potential for treating SCI. Human olfactory ensheathing cells (hOECs) and adipose tissue-derived multipotent stromal cells were used to assess the biocompatibility of the nanoparticles. The results show a promising approach to SCI treatment using regenerative strategies [245]. A Li-HA porous scaffold seeded with hypoxia-preconditioned BMSCs for bone regeneration was also evaluated in vitro and in vivo. The data revealed that 1.5% Li-HA had the best in vitro cell proliferation and bone formation, with a decrease in GSK-3β and an increase in β-catenin, though Li did not affect angiogenesis significantly. Hypoxia-preconditioned BMMSCs improved angiogenesis and osteogenesis by activating the WNT and HIF-1 signal pathways [246]. A new strategy for improving the clinical efficacy of Li-doped HA scaffolds seeded with stem cells appears to be emerging.

B-TCP scaffolds based on excellent biocompatibility and compositional similarity to the natural bone have received attention as ceramic implants for bone repair and augmentation. However, the high solubility of β-TCP may cause refracture due to implant degra-
dation and inflammatory reactions [247]. Li-doping β-TCP increases dissolution and thermal stability [248,249], so doping β-TCP with Li-ions appears to have potential to improve clinical applications.

3.3. Other Lithium-Doped Bioceramics

Calcium silicate bioceramics are widely applied in tissue engineering and drug delivery [250–253]. The apatite mineralization of a bioactive composite based on poly (dopamine) (PDA) and Li-doped silica nanospheres (LSNs) coated on polyetheretherketone (PEEK) [254] surfaces (LSN-PDA-PEEK) in SBF was evaluated, and the bioactivity was observed to be higher than that of neat PDA coated on PEEK (PDA-PEEK) and PEEK. LSN-PDA-PEEK also stimulated rBMSC responses more than PDA-PEEK and PEEK. Moreover, in vivo, LSN-PDA-PEEK increased bone tissue responses compared to PDA-PEEK and PEEK [255]. Adding 5% Li to mesoporous silica nanospheres (MSNs) increases their degradability. Moreover, Li-doped mesoporous silica nanospheres (LMSNs) had more significant stimulatory effects on BMSC attachment and proliferation than MSNs due to Li-ion release. LMSNs may also improve BMSC ALP activity and the expression of osteogenesis-related genes (osteopontin (OPN), osteocalcin (OCN), Runx2, and ALP). Thus, LMSNs have a potential application in bone regeneration [256].

As a result of the synergistic interaction of Li and Si-ions, Li-ions can enhance the biological effectiveness of calcium silicates. This synergistic effect can be seen in osteochondral regeneration. Osteoarthritis (OA) causes cartilage lesions that spread to the subchondral bone. The regeneration of both tissues is required to repair osteochondral OA defects. Extracts of biomaterials containing Li and silicon have significantly increased chondrocyte proliferation and maturation, and favored the osteogenic differentiation of rabbit mesenchymal stem cells (rBMSCs). A histological and micro-CT analysis revealed that Li-doped calcium silicate (LCS) scaffolds promoted osteochondral regeneration in vivo; Li- and Si-ions released from LCS scaffolds are important in osteochondral regeneration, suggesting that LCS scaffolds are promising biomaterials for osteochondral repair [257]. In a similar study, pure phase LCS (Li₂Ca₄Si₄O₁₃ and L₂C₄S₄) scaffolds were synthesized by the sol–gel method and then 3D printed. These scaffolds have controlled biodegradability and good apatite mineralization capacity. The ionic products of L₂C₄S₄ also significantly increased chondrocyte proliferation and maturation and rBMSC osteogenic differentiation. In osteochondral defects of the rabbit, the L₂C₄S₄ scaffolding favored both cartilage and subchondral bone regeneration (Figure 6) [258]. Three-dimensional-printed LCS and its composites offer opportunities to generate scaffolds to treat difficult-to-treat disease (such as OA) conditions (particularly as the printing process facilitates the inclusion of macropores for vascularization). Another study evaluated the in vitro and in vivo osteogenic properties of 3D-printed lithium magnesium phosphate (Li₀.₅Mg₂.₇₅ (PO₄)₂, Li₁Mg₂.₅ (PO₄)₂, and Li₂Mg₂ (PO₄)₃) prepared by the sol–gel method. Interestingly, the lithium magnesium phosphate has a lower porosity and higher compressive strength, and raises cellular proliferation, osteogenic differentiation, and proangiogenic activity; moreover, lithium magnesium phosphate significantly improved bone regeneration in critical-size calvarial defects of rats [259]. Recent developments in dental restorations used Li germanosilicate glass-ceramics doped with rare-earth oxides [260].
Figure 6. (A) Schematic illustration of the application of Li2Ca4Si4O13 scaffolds for osteochondral reconstruction. Pure-phase Li2Ca4Si4O13 powders were successfully synthesized by the sol–gel method. Three-dimensional-printed Li2Ca4Si4O13 scaffolds not only promoted cartilage maturation, but also stimulated osteogenic differentiation in vitro. On the other hand, Li2Ca4Si4O13 scaffolds significantly accelerated cartilage regeneration as well as promoting subchondral bone reconstruction in vivo. (B–I) Surface morphology and XRD analysis of Li2Ca4Si4O13 scaffolds. Digital photograph (B), optical microscope image (C), and SEM images (D,E) of 3D-printed Li2Ca4Si4O13 scaffolds. The prepared porous Li2Ca4Si4O13 scaffolds possessed a controlled pore size (~250 μm). XRD analysis (F) of Li2Ca4Si4O13 scaffolds before/after soaking in the simulated body fluids for 14 days, and SEM images (G–I) of Li2Ca4Si4O13 scaffolds after soaking in the simulated body fluids for 14 days. Li2Ca4Si4O13 scaffolds induced distinct apatite mineralization on their surface. Reproduced from [258] with permission.

3.4. Lithium-Doped Bioceramics for Anticancer Applications

Drug delivery is an important potential application of bioceramics, especially nano-bioceramics [261]. Additionally, as previously stated, Li has anticancer properties. Some researchers have found that using Li with other drugs has a synergistic effect on cancer cells and may be used for combinational therapy [88,262]. Li may cause tumor chemosensitization [106]. Thus, the use of Li-doped bioceramics could be an exciting research area. However, there are few reports in the literature exploiting these bioceramics for such applications. Li-BG nanoparticles loaded with vancomycin or Fluorouracil (5-FU) were designed to deliver Li-ions and drugs simultaneously to treat osteomyelitis, bone cancer, and osteoporosis; drugs are released via a diffusion-controlled process, and the release profile is dependent on the drug concentration applied in the loading stage (Figure 7) [263].
4. Conclusions

Li is widely used to store energy, particularly in batteries [265–268] and capacitors [269,270], and we foresee nanogenerators [271] (including stimuli-responsive nanogenerators, e.g., photoactivatable nanogenerators [272]) will have broad applications in medical fields, such as regenerative medicine, rehabilitation, and cancer treatment [273–276], particularly as nanogenerators have been shown to increase the efficacy of chemoimmunotherapy for non-small-cell lung cancer [277]. Therefore, Li-doped bioceramics may be
good candidates for nanogenerators for advanced multifunctional systems in cancer treatments and regenerative medicine [272,278]. Li has anti-replication properties in viruses and is anti-mitotic in cancer cells, but it simultaneously stimulates stem cell proliferation, which may be an evolved regulatory system. However, more studies on the effects of Li on autophagy in cancer cells, virally infected cells, and stem cells and their related signaling are also necessary.

Li has a variety of biological properties that can be influential in stem cell therapy, in the development of the next generation of antibacterial, antiviral, and anticancer agents, as well as in tissue regeneration, and opportunities exist for fundamental studies to understand the role of Li in biological processes. Li is a widely used medication for various mental illnesses [279–282], and we foresee significant potential for further clinical applications of biomaterials incorporating Li in some manner (e.g., doped ceramics and gels), supported by the large number of ongoing clinical trials employing Li in some fashion (>3000 clinical trials in the Cochrane Central Register of Controlled Trials [283]). The purpose of this review was to provide to interested readers an overview of some of these clinical trials.

**Author Contributions:** conceptualization, all authors; writing—original draft preparation, all authors; writing—review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Data Availability Statement:** Not applicable.

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

**References**

1. Farmani, A.R.; Nekoofar, M.H.; Barough, S.E.; Azami, M.; Rezaei, N.; Najafipour, S.; Ai. J. Application of Platelet Rich Fibrin in Tissue Engineering: Focus on Bone Regeneration. *Platelets* **2021**, *32*, 183–188.
2. Khademi, F.; Soleimani, M.; Verdi, J.; Tavangar, S.M.; Sadroddiny, E.; Massumi, M.; Ai, J. Human endometrial stem cells differentiation into functional hepatocyte-like cells. *Cell Biol. Int.* **2014**, *38*, 825–834.
3. Asadpour, S.; Kargoza, S.; Moradi, L.; Ai, A.; Nosrati, H.; Ai, J. Natural biomacromolecule based composite scaffolds from silk fibroin, gelatin and chitosan toward tissue engineering applications. *Int. J. Biol. Macromol.* **2020**, *154*, 1285–1294.
4. Rezapour-Lactoe, A.; Yeganeh, H.; Ostad, S.N.; Garibi, R.; Mazaheri, Z.; Ai, J. Thermoresponsive polyurethane/siloxane membrane for wound dressing and cell sheet transplantation: In-vitro and in-vivo studies. *Mater. Sci. Eng. C* **2016**, *69*, 804–814.
5. Asadpour, S.; Yeganeh, H.; Ai, J.; Kargoza, S.; Rashbar, M.; Seifalian, A.; Ghanbari, H. Polyurethane-Polycaprolactone Blend Patches: Scaffold Characterization and Cardiomyoblast Adhesion, Proliferation, and Function. *ACS Biomater. Sci. Eng.* **2018**, *4*, 4299–4310.
6. Hasanzadeh, E.; Ebrahimi-Barough, S.; Mirzaei, E.; Azami, M.; Tavangar, S.M.; Mahmoudi, N.; Basiri, A.; Ai, J. Preparation of fibrin gel scaffolds containing MWCNT/PU nanofibers for neural tissue engineering. *J. Biomed. Mater. Res. Part A* **2019**, *107*, 802–814.
7. Noory, P.; Navid, S.; Zanganeh, B.M.; Talebi, A.; Borhani-Haghighi, M.; Gholami, K.; Manshadi, M.D.; Abbasi, M. Human menstrual blood stem cell-derived granulosa cells participate in ovarian follicle formation in a rat model of premature ovarian failure in vivo. *Cell. Reprogramming* **2019**, *21*, 249–259.
8. Jabari, A.; Gilani, M.A.S.; Koruji, M.; Gholami, K.; Mohsenzadeh, M.; Khadivi, F.; Gashhi, N.G.; Nikmahzar, A.; Mojaverrostami, S.; Talebi, A.; et al. Three-dimensional co-culture of human spermatogonial stem cells with Sertoli cells in soft agar culture system supplemented by growth factors and Laminin. *Acta Histochem.* **2020**, *122*, 151572.
9. Gholami, K.; Vermeulen, M.; Del Vento, F.; de Michele, F.; Giudice, M.G.; Wyns, C. The air-liquid interface culture of the mechanically isolated seminiferous tubules embedded in agarose or alginate improves in vitro spermatogenesis at the expense of attenuating their integrity. *In Vitro Cell. Dev. Biol.-Anim.* **2020**, *56*, 261–270.
10. Ashouri Movassagh, S.; Ashouri Movassagh, S.; Dehkordi, M.B.; Fourmand, G.; Gholami, K.; Talebi, A.; Esfandyari, S.; Jabari, A.; Samadian, A.; Abbasi, M. Isolation, identification and differentiation of human spermatogonial cells on three-dimensional decellularized sheep testis. *Acta Histochem.* **2020**, *122*, 151623.
11. Bakhshandeh, B.; Zarrintaj, P.; Oftadeh, M.O.; Keramati, F.; Foulaadiha, H.; Sohrabi-Jahromi, S.; Ziraksaz, Z. Tissue engineering: strategies, tissues, and biomaterials. *Biotechnol. Genet. Eng. Rev.* **2017**, *33*, 144–172.
12. Han, F.; Wang, J.; Ding, L.; Hu, Y.; Li, W.; Yuan, Z.; Guo, Q.; Zhu, C.; Yu, L.; Wang, H.; et al. Tissue Engineering and Regenerative Medicine: Achievements, Future, and Sustainability in Asia. *Front. Bioeng. Biotechnol.* **2020**, *8*, 83.
13. Khademhosseini, A.; Langer, R. A decade of progress in tissue engineering. *Nat. Protoc.* **2016**, *11*, 1775–1781.
14. Pina, S.; Ribeiro, V.P.; Marques, C.F.; Maia, F.R.; Silva, T.H.; Reis, R.L.; Oliveira, J.M. Scaffolding strategies for tissue engineering and regenerative medicine applications. Materials 2019, 12, 1824.

15. Kwon, S.G.; Kwon, Y.W.; Lee, T.W.; Park, G.T.; Kim, J.H. Recent advances in stem cell therapeutics and tissue engineering strategies. Biomater. Res. 2018, 22, 36.

16. Willerth, S.M.; Sakiyama-Elbert, S.E. Combining stem cells and biomaterial scaffolds for constructing tissues and cell delivery. StemJnl 2019, 1, 1–25.

17. Hayat, H.; Hayat, H.; Dwan, B.F.; Gudi, M.; Bishop, J.O.; Wang, P. A Concise Review: The Role of Stem Cells in Cancer Progression and Therapy. OncoTargets Ther. 2021, 14, 2761.

18. Pérez, L.M.; de Lucas, B.; Gálvez, B.G. Unhealthy stem cells: When health conditions upset stem cell properties. Cell. Physiol. Biochem. 2018, 46, 1999–2016.

19. Dhesi, A.S.; Morelli, S.S. Endometriosis: A role for stem cells. Women’s Health 2015, 11, 35–49.

20. Mahdavinezhad, F.; Gharaei, R.; Farmani, A.R.; Hashemi, F.; Kouhestani, M.; Amidi, F. The Potential Relationship Between Different Human Female Reproductive Disorders and Sperm Quality in Female Genital Tract. Reprod. Sci. 2021, 29, 695–710.

21. Lee, E.J.; Kasper, F.K.; Mikos, A.G. Biomaterials for tissue engineering. Ann. Biomed. Eng. 2014, 42, 323–337.

22. Sharma, K.; Mujawar, M.A.; Kaushik, A. State-of-Art Functional Biomaterials for Tissue Engineering. Front. Mater. 2019, 6, 172.

23. Kohane, D.S.; Langer, R. Polymeric Biomaterials in Tissue Engineering. Pediatr. Res. 2008, 63, 487–491.

24. Bano, F.; Novajra, G.; Vitale-Brovarone, C. Bioceramics and Scaffolds: A Winning Combination for Tissue Engineering. Front. Bioeng. Biotechnol. 2015, 3, 202.

25. Zhao, H.; Liu, M.; Zhang, Y.; Yin, J.; Pei, R. Nanocomposite hydrogels for tissue engineering applications. Nanoscale 2020, 12, 14976–14995.

26. Prasad, K.; Bazaka, O.; Chua, M.; Rockfard, M.; Fedrick, L.; Spoor, J.; Symes, R.; Tieppo, M.; Collins, C.; Cao, A.; et al. Metallic Biomaterials: Current Challenges and Opportunities. Materials 2017, 10, 884.

27. Prakasam, M.; Locs, J.; Salma-Ancane, K.; Loca, D.; Largeteau, A.; Berzina-Cimidina, L. Biodegradable Materials and Metallic Implants—A Review. J. Funct. Biomater. 2017, 8, 44.

28. Yusop, A.H.; Bakir, A.A.; Shaharom, N.A.; Abdul Kadir, M.R.; Hermawan, H. Porous Biodegradable Metals for Hard Tissue Scaffolds: A Review. Int. J. Biomater. 2012, 2012, 641430.

29. Bazaka, O. Metallic Implants for Biomedical Applications. In Metallic Implants for Biomedical Applications; Royal Society of Chemistry: London, UK, 2021.

30. Chowdhury, S.K.; Nagarjunna, V.; Bhaskar, B. Metallic Biomaterials in Tissue Engineering: Retrospect and Prospects. In Biomaterials in Tissue Engineering and Regenerative Medicine: From Basic Concepts to State of the Art Approaches; Bhaskar, B.; Rao, P.S.; Kasoju, N.; Nagarjunna, V.; Baadhe, R.R. Eds.; Springer: Singapore, 2021; pp. 19–60.

31. Jedati, H.; Yilmaz, B.; Evir, Z. A review of bioceramic porous scaffolds for hard tissue applications: Effects of structural features. Ceram. Int. 2020, 46 Part B, 15725–15739.

32. Zhou, Y.; Wu, C.; Chang, J. Bioceramics to regulate stem cells and their microenvironment for tissue regeneration. Mater. Today 2019, 24, 41–56.

33. Mazzoni, E.; Ilaquinta, M.R.; Lanzillotti, C.; Mazzotti, C.; Maritati, M.; Montesi, M.; Sprio, S.; Tampieri, A.; Tognon, M.; Martini, F. Bioactive Materials for Soft Tissue Repair. Front. Bioeng. Biotechnol. 2021, 9, 613787.

34. Wang, X.; Xue, J.; Ma, B.; Wu, J.; Chang, J.; Gelinsky, M.; Wu, C. Black Bioceramics: Combining Regeneration with Therapy. Adv. Mater. 2020, 32, 2005140.

35. Yu, Q.; Chang, J.; Wu, C. Silicate bioceramics: From soft tissue regeneration to tumor therapy. J. Mater. Chem. B 2019, 7, 5449–5460.

36. Hench, L.L. Bioceramics: From Concept to Clinic. J. Am. Ceram. Soc. 1991, 74, 1487–1510.

37. Gerhardt, L.-C.; Boccaccini, A.R. Bioactive Glass and Glass-Ceramic Scaffolds for Bone Tissue Engineering. Materials 2010, 3, 3867–3910.

38. Eliaz, N.; Metoki, N. Calcium Phosphate Bioceramics: A Review of Their History, Structure, Properties, Coating Technologies and Biomedical Applications. Materials 2017, 10, 334.

39. Ben-Nissan, B.; Pezzotti, G. Bioceramics processing routes and mechanical evaluation. J. Ceram. Soc. Jpn. 2002, 110, 601–608.

40. Swain, M.V.; He, L.H. 4—Mechanical properties of bioceramics. In Bioceramics and their Clinical Applications; Kokubo, T.; Ed.; Woodhead Publishing: Sawston, UK; 2008; pp. 78–105.

41. Ginebra, M.P.; Espanol, M.; Maazouz, Y.; Bergez, V.; Pastorino, D. Bioceramics and bone healing. EFTOR Open Rev. 2018, 3, 173–183.

42. Kokubo, T. Bioceramics and Their Clinical Applications; Elsevier: Amsterdam, The Netherlands, 2008.

43. Glasses, B. An. Introduction to Bioceramics; Structure; World Scientific: Singapore, 2019.

44. Hench, L.L. An. Introduction to Bioceramics; World Scientific: Singapore, 1993.

45. Vallet-Regi, M.; Izquierdo-Barba, I.; Colilla, M. Structure and functionalization of mesoporous bioceramics for bone tissue regeneration and local drug delivery. Philos. Trans. R. Soc. A Math. Phys. Eng. Sci. 2012, 370, 1400–1421.

46. El-Ghannam, A. Bioceramic Drug Delivery System for Cancer Treatment and Regenerative Medicine. Key Eng. Mater. 2016, 696, 245–249.
47. Zhuang, H.; Lin, R.; Liu, Y.; Zhang, M.; Zhai, D.; Huan, Z.; Wu, C. Three-Dimensional-Printed Bioceramic Scaffolds with Osteogenic Activity for Simultaneous Photo/Magneto-thermal Therapy of Bone Tumors. ACS Biomater. Sci. Eng. 2019, 5, 6725–6734.

48. Zhang, K.; Zhou, Y.; Xiao, C.; Zhao, W.; Wu, H.; Tang, J.; Li, Z.; Yu, S.; Li, X.; Min, L.; et al. Application of hydroxyapatite nanoparticles in tumor-associated bone segmental defect. Sci. Adv. 2019, 5, eaax6946.

49. Sedighi, O.; Alaghmandfard, A.; Montazerian, M.; Baino, F. A critical review of bioceramics for magnetic hyperthermia. J. Am. Ceram. Soc. 2021, 105, 1723–1747.

50. Mourino, V.; Catalini, J.P.; Boccaccini, A.R. Metallic ions as therapeutic agents in tissue engineering scaffolds: An overview of their biological and clinical applications and new developments for their future applications. J. R. Soc. Interface 2012, 9, 401–419.

51. Schatkoski, V.M.; do Amaral Montanheiro, T.L.; de Menezes, B.R.C.; Pereira, R.M.; Rodrigues, K.F.; Ribas, R.G.; da Silva, D.M.; Thim, G.P. Current advances concerning the most cited metal ions doped bioceramics and silicate-based bioactive glasses for bone tissue engineering. Ceram. Int. 2021, 47, 2999–3012.

52. Sprio, S.; Dapporto, M.; Preti, L.; Mazzoni, E.; Iaquinta, M.R.; Martini, F.; Tognon, M.; Pugno, N.M.; Restivo, E.; Visai, L.; et al. Enhancement of the Biological and Mechanical Performances of Sintered Hydroxyapatite by Multiple Ions Doping. Front. Mater. 2020, 7, 224.

53. Mourino, V.; Vidotto, R.; Catalini, J.P.; Boccaccini, A.R. Enhancing biological activity of bioactive glass scaffolds by inorganic ion delivery for bone tissue engineering, Curr. Opin. Biomed. Eng. 2019, 10, 23–34.

54. Jakobsson, E.; Arquiello-Miranda, O.; Chiu, S.W.; Fazal, Z.; Krucezk, J.; Nunez-Corrales, S.; Pandit, S.; Pritchet, L. Towards a unified understanding of lithium action in basic biology and its significance for applied biology. J. Membr. Biol. 2017, 250, 587–604.

55. Oruch, R.; Elderbi, M.A.; Khattab, H.A.; Pryme, I.F.; Lund, A. Lithium: A review of pharmacology, clinical uses, and toxicity. Eur. J. Pharmacol. 2014, 740, 464–473.

56. Lodders, K. Solar system abundances and condensation temperatures of the elements. Astrophys. J. 2003, 591, 1220.

57. Coppen, A. Lithium in unipolar depression and the prevention of suicide. J. Clin. Psychiatry 2000, 61, 52–56.

58. Shorter, E. The history of lithium therapy. Bipolar Disord. 2009, 11 (Suppl. 2), 4–9.

59. Ruffalo, M.L. A brief history of lithium treatment in psychiatry. Prim. Care Companion CNS Disord. 2017, 19, 27325.

60. Hashimoto, Y.; Kotake, K.; Watanabe, N.; Fujiwara, T.; Sakamoto, S. Lamotrigine in the maintenance treatment of bipolar disorder. Cochrane Database Syst. Rev. 2021, 9, CD013875.

61. MAEDA, Y. Influence of ionic conditions on cell differentiation and morphogenesis of the cellular slime molds. Dev. Growth Differ. 1970, 12, 217–227.

62. Klein, P.S.; Melton, D.A. A molecular mechanism for the effect of lithium on development. Proc. Natl. Acad. Sci. USA 1996, 93, 8455–8459.

63. Corbella, B.; Vieta, E. Molecular targets of lithium action. Acta Neuropsychiatr. 2003, 15, 316–340.

64. Ward, M.E.; Musa, M.N.; Bajend, L. Clinical pharmacokinetics of lithium. J. Clin. Pharmacol. 1994, 34, 280–285.

65. Ishii, N.; Terao, T.; Hirakawa, H. The Present State of Lithium for the Prevention of Dementia Related to Alzheimer’s Dementia in Clinical and Epidemiological Studies: A Critical Review. Int. J. Environ. Res. Public Health 2021, 18, 7756.

66. Shine, B.; McKnight, R.F.; Leaver, L.; Geddes, J.R. Long-term effects of lithium on renal, thyroid, and parathyroid function: A retrospective analysis of laboratory data. Lancet 2015, 386, 461–468.

67. Gitlin, M. Lithium side effects and toxicity: Prevalence and management strategies. Int. J. Bipolar Disord. 2016, 4, 27.

68. Feng, Y.-Y. Reversible hand tremors, downbeat nystagmus, and an unsteady gait with nontoxic lithium level. Clin. Case Rep. 2019, 7, 599–600.

69. Lehman, A.F.; Lieberman, J.A.; Dixon, L.B.; McGlashan, T.H.; Miller, A.L.; Perkins, D.O.; Kreyenbuhl, J.; McIntyre, J.S.; Charles, S.C.; Altshuler, K.; et al. Practice guideline for the treatment of patients with schizophrenia. Am. J. Psychiatry. 2004, 161 (Suppl. 2), i–iv+ 1–56.

70. Mitchell, P.B. Therapeutic drug monitoring of psychotropic medications. British J. Clinical Pharmacol.; 2001, 52 (Suppl. 1), 45–54.

71. Baek, J.; Kinrys, G.; Nierenberg, A. Lithium tremor revisited: Pathophysiology and treatment. Acta Psychiatr. Scand. 2014, 129, 17–23.

72. Lee, M.S.; Lessell, S. Lithium-induced periodic alternating nystagmus. Neurology 2003, 60, 344–344.

73. Özerdem, A.; Tunca, Z.; Cınmın, D.; Hdroğlu, C.; Ergör, G. Female vulnerability for thyroid function abnormality in bipolar disorder: Role of lithium treatment. Bipolar Disord. 2014, 16, 72–82.

74. Albert, U.; De Cori, D.; Blengino, G.; Bogetto, F.; Maina, G. Lithium treatment and potential long-term side effects: A systematic review of the literature. Riv. Psichiatr. 2014, 49, 12–21.

75. Martiñsson, L. Lithium treatment and cancer incidence in bipolar disorder. Bipolar Disord. 2016, 18, 33–40.

76. Ge, W.; Jakobsson, E. Systems biology understanding of the effects of lithium on cancer. Front. Oncol. 2019, 9, 296.

77. Ryves, W.J.; Harwood, A.J. Lithium Inhibits Glycogen Synthase Kinase-3 by Competition for Magnesium. Biochem. Biophys. Res. Commun. 2001, 280, 720–725.

78. Greenblatt, D.Y.; Ndiaye, M.; Chen, H.; Kunnimalaiyaaan, M. Lithium inhibits carcinoid cell growth in vitro. Am. J. Transl. Res. 2010, 2, 248.

79. Arena, A.; Capozza, A.B.; Orlando, M.E.; Curro, F.; Losi, E.; Chillemi, S.; Mesiti, M.; Merendino, R.A. In vitro effects of lithium chloride on TNFα and IL-6 production by monocytes from breast cancer patients. J. Chemother. 1997, 9, 219–226.
80. Suganthi, M.; Sangeetha, G.; Gayathri, G.; Ravi Sankar, B. Biphasic dose-dependent effect of lithium chloride on survival of human hormone-dependent breast cancer cells (MCF-7). *Biol. Trace Elem. Res.* **2012**, *150*, 477–486.

81. Rouhani, M.; Goliaei, B.; Khodagholi, F.; Nikoofar, A. Lithium increases radiosensitivity by abrogating DNA repair in breast cancer sphere culture. *Arch. Iran. Med.* **2014**, *17*, 352-60.

82. O’Donovan, T.R.; Rajendra, S.; O’Reilly, S.; O’Sullivan, G.C.; McKenna, S.L. Lithium modulates autophagy in esophageal and colorectal cancer cells and enhances the efficacy of therapeutic agents in vitro and in vivo. *PLoS ONE* **2015**, *10*, e0134676.

83. Vidal, F.; De Araujo, W.M.; Cruz, A.L.; Tanaka, M.N.; Niola, J.P.; Morgado-Díaz, J.A. Lithium reduces tumorigenic potential in response to EGF signaling in human colorectal cancer cells. *Int. J. Oncol.* **2011**, *38*, 1365–1373.

84. Li, H.; Huang, K.; Liu, X.; Liu, J.; Lu, X.; Tao, K.; Wang, G.; Wang, J. Lithium chloride suppresses colorectal cancer cell survival and proliferation through ROS/GSK-3β signal pathway. *Oxidative Med. Cell. Longev.* **2014**, *2014*, 241864.

85. de Araujo, W.M.; Robbs, B.K.; Bastos, L.G.; de Souza, W.F.; Vidal, F.C.; Viola, J.P.; Morgado Diaz, J.A. PTEN overexpression cooperates with lithium to reduce the malignancy and to increase cell death by apoptosis via PI3K/Akt suppression in colorectal cancer cells. *J. Cell. Biochem.* **2016**, *117*, 458–469.

86. Cammarota, F.; Conte, A.; Aversano, S.; Muto, P.; Ametrano, G.; Riccio, P.; Turano, M.; Valente, V.; Delrio, P.; Izzo, P.; et al. Lithium chloride increases sensitivity to photon irradiation treatment in primary mesenchymal colon cancer cells. *Med. Mol. Rep.* **2020**, *21*, 1501–1508.

87. Wang, J.S.; Wang, C.L.; Wen, J.F.; Wang, Y.J.; Hu, Y.B.; Ren, H.Z. Lithium inhibits proliferation of human esophageal cancer cell line Eca-109 by inducing a G2/M cell cycle arrest. *World J. Gastroenterol.* *WJG* **2008**, *14*, 3982.

88. Elmaci, I.; Altinoz, M.A. A metabolic inhibitory cocktail for heavy cancers: Metformin, pioglitazone and lithium combination in treatment of pancreatic cancer and glioblastoma multiforme. *Biochem. Genet.* **2016**, *54*, 573–618.

89. Novetsky, A.P.; Thompson, D.M.; Zigbelboim, L; Thaker, P.H.; Powell, M.A.; Mutch, D.G.; Goodfellow, P.J. Lithium chloride and inhibition of glycosen synthase kinase 3β as a potential therapy for serous ovarian cancer. *Int. J. Gynecol. Cancer* **2013**, *23*, 361–366.

90. Wang, X.; Luo, C.; Cheng, X.; Lu, M. Lithium and an EPAC-specific inhibitor ESI-09 synergistically suppress pancreatic cancer cell proliferation and survival. *Acta Biochim. Biophys. Sin.* **2017**, *49*, 573–580.

91. Hossein, G.; Zavareh, V.A.; Fard, P.S. Combined treatment of androgen-independent prostate cancer cell line DU145 with chemotherapeutic agents and lithium chloride: Effect on growth arrest and/or apoptosis. *Avicenna J. Med. Biotechnol.* **2014**, *4*, 75.

92. Erguven, M.; Oktem, G.; Kara, A.N.; Bilir, A. Lithium chloride has a biphasic effect on prostate cancer stem cells and a proportional effect on midline levels. *Oncol. Lett.* **2016**, *12*, 2948–2955.

93. Sun, A.; Shannugam, I.; Song, J.; Terranova, P.F.; Thrasher, J.B.; Li, B. Lithium suppresses cell proliferation by interrupting E2F–DNA interaction and subsequently reducing S–phase gene expression in prostate cancer. *Prostate* **2007**, *67*, 976–988.

94. Koong, S.S.; Reynolds, J.C.; Movius, E.G.; Keenan, A.M.; Ain, K.B.; Lakshmanan, M.C.; Robbins, J. Lithium as a potential adjuvant to 131I therapy of metastatic, well differentiated thyroid carcinoma. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 912–916.

95. Adler, J.T.; Hottinger, D.G.; Kunnimalaiyaan, M.; Chen, H. Inhibition of growth in medullary thyroid cancer cells with histone deacetylase inhibitors and lithium chloride. *J. Surg. Res.* **2010**, *175*, 162–175.

96. Lan, Y.; Liu, X.; Zhang, R.; Wang, K.; Wang, Y.; Hua, Z.C. Lithium enhances TRAIL-induced apoptosis in human lung carcinoma A549 cells. *Biometals* **2013**, *26*, 241–254.

97. Matsubatela, T.; Gallicchio, V.; Becker, R. Lithium modulates cancer cell growth, apoptosis, gene expression and cytokine production in HL-60 promyelocytic leukaemia cells and their drug-resistant sub-clones. *Biol. Trace Elem. Res.* **2012**, *149*, 323–330.

98. Li, L.; Song, H.; Zhong, L.; Yang, R.; Yang, X.Q.; Jiang, K.L.; Liu, B.Z. Lithium chloride promotes apoptosis in human leukemia NB4 cells by inhibiting glycogen synthase kinase-3 beta. *Int. J. Med. Sci.* **2015**, *12*, 805.

99. Chen, H.; Wang, N.; Burmeister, M.; McInnis, M.G. MicroRNA expression changes in lymphoblastoid cell lines in response to lithium treatment. *Int. J. Neuropsychopharmacol.* **2009**, *12*, 975–981.

100. Maeng, Y.S.; Lee, R.; Lee, B.; Choi, S.I.; Kim, E.K. Lithium inhibits tumor lymphangiogenesis and metastasis through the inhibition of TGFβp expression in cancer cells. *Sci. Rep.* **2016**, *6*, 20739.

101. Motoi, Y.; Shimada, K.; Ishiguro, K.; Hattori, N. Lithium and autophagy. *ACS Chem. Neurosci.* **2014**, *5*, 434–442.

102. Thorburn, A.; Thamm, D.H.; Gustafson, D.L. Autophagy and cancer therapy. *Mol. Pharmacol.* **2014**, *85*, 830–838.

103. Yun, C.W.; Lee, S.H. The roles of apoptosis in cancer. *Int. J. Mol. Sci.* **2018**, *19*, 3466.

104. Pérez-Hernández, M.; Arias, A.; Martínez-Garcia, D.; Pérez-Tomás, R.; Quesada, R.; Soto-Cerrato, V. Targeting autophagy for cancer treatment and tumor chemosensitization. *Cancers* **2019**, *11*, 1599.

105. De Sarno, P.; Axtell, R.C.; Raman, C.; Roth, K.A.; Alessi, D.R.; Jope, R.S. Lithium prevents and ameliorates experimental autoimmune encephalomyelitis. *J. Immunol.* **2008**, *181*, 338–345.

106. Wu, M.Y.; Wang, E.J.; Feng, D.; Li, M.; Richard, D.Y.; Lu, J.H. Pharmacological insights into autophagy modulation in autoimmune diseases. *Acta Pharm. Sin. B* **2021**, *11*, 3364–3378.
109. Gallicchio, V.S. Lithium effects on stem cells-advances in stem cell application in clinical medicine. *Adv. Cell Sci. Tissue Cult.* 2018, 2, 14–24.

110. Leucht, P.; Lee, S.; Yim, N. Wnt signaling and bone regeneration: Can’t have one without the other. *Biomaterials* 2019, 196, 46–50.

111. Zhu, Z.; Yin, J.; Guan, J.; Hu, B.; Niu, X.; Jin, D.; Wang, Y.; Zhang, C. Lithium stimulates human bone marrow derived mesenchymal stem cell proliferation through GSK-3β-dependent β-catenin/Wnt pathway activation. *FEBS J.* 2014, 281, 5371–5389.

112. Nassar, A.; Azab, A.N. Effects of lithium on inflammation. *ACS Chem. Neurosci.* 2014, 5, 451–458.

113. Albayrak, A.; Halici, Z.; Polat, B.; Karakus, E.; Cadirci, E.; Bayir, Y.; Kunak, S.; Karcioglu, S.S.; Yigit, S.; Unal, D.; et al. Protective effects of lithium: A new look at an old drug with potential antioxidative and anti-inflammatory effects in an animal model of sepsis. *Int. Immunopharmacol.* 2013, 16, 35–40.

114. Tan, Z.; Zhou, B.; Zheng, J.; Huang, Y.; Zeng, H.; Xue, L.; Wang, D. Lithium and Copper Induce the Osteogenesis-Angiogenesis Coupling of Bone Marrow Mesenchymal Stem Cells via Crosstalk between Canonical Wnt and HIF-1α Signaling Pathways. *Stem Cells Int.* 2021, 2021, 6662164.

115. Guo, S.; Arai, K.; Stins, M.F.; Chuang, D.M.; Lo, E.H. Lithium upregulates vascular endothelial growth factor in brain endothelial cells and astrocytes. *Stroke* 2009, 40, 652–655.

116. Zellbeck, L.F.; Müller, B.; Knobloch, V.; Tamm, E.R.; Ohlmann, A. Differential angiogenic properties of lithium chloride in vitro and in vivo. *PLoS ONE* 2014, 9, e95546.

117. Ferensztajn-Rochowiak, E.; Rybakowski, J.K. The effect of lithium on hematopoietic, mesenchymal and neural stem cells. *Pharmacol. Rep.* 2016, 68, 224–230.

118. Tettamanti, G.; Carata, E.; Montali, A.; Dini, L.; Fimia, G.M. Autophagy in development and regeneration: Role in tissue remodelling and cell survival. *Eur. J. Cell Biol.* 2019, 86, 113–131.

119. Perrotta, C.; Cattaneo, M.G.; Molteni, R.; De Palma, C. Autophagy in the Regulation of Tissue Differentiation and Homeostasis. *Front. Cell Dev. Biol.* 2020, 8, 1563.

120. Morgan, E.F.; Unnikrisnan, G.U.; Hussein, A.I. Bone Mechanical Properties in Healthy and Diseased States. *Annu. Rev. Biomed. Eng.* 2018, 20, 119–143.

121. Hart, N.H.; Nimphius, S.; Rantalainen, T.; Ireland, A.; Siafarikas, A.; Newton, R.U. Mechanical basis of bone strength: Influence of bone material, bone structure and muscle action. *J. Musculoskelet. Neuronal Interact.* 2017, 17, 114–139.

122. Chao, L.; Jiao, C.; Xie, D.; Shen, L.; Liu, Z. Analysis of Mechanical Properties and Permeability of Trabecular-Like Porous Scaffold by Additive Manufacturing. *Front. Bioeng. Biotechnol.* 2021, 9, 779854.

123. Ghassemi, T.; Shahroodi, A.; Ebrahimzadeh, M.H.; Mousavian, A.; Movaffagh, J.; Moradi, A. Current Concepts in Scaffolding for Bone Tissue Engineering. *Arch. Bone Jt. Surg.* 2018, 6, 90–99.

124. Tang, G.H.; Xu, J.; Chen, R.J.; Qian, Y.F.; Shen, G. Lithium delivery enhances bone growth during midpalatal expansion. *J. Dent. Res.* 2011, 90, 336–340.

125. Arioka, M.; Takahashi-Yanaga, F.; Sasaki, M.; Yoshihara, T.; Morimoto, S.; Takashima, A.; Mori, Y.; Sasaguri, T. Acceleration of bone development and regeneration through the Wnt/β-catenin signaling pathway in mice heterozygously deficient for GSK-3β. *Biochem. Biophys. Res. Commun.* 2013, 440, 667–682.

126. Zeng, Y.T.; Fu, B.; Tang, G.H.; Zhang, L.; Qian, Y.F. Effects of lithium on extraction socket healing in rats assessed with micro-computed tomography. *Acta Odontol. Scand.* 2011, 71, 1335–1340.

127. Lewis, M.; Paer, H.; Mandalunis, P.M. Effect of lithium carbonate on subchondral bone in sexually mature Wistar rats. *Exp. Toxicol. Pathol.* 2006, 58, 197–201.

128. Li, J.; Khavadgar, Z.; Lin, S.H.; Murshed, M. Lithium chloride attenuates BMP-2 signaling and inhibits osteogenic differentiation through a novel WNT/GSK3-independent mechanism. *Bone* 2011, 48, 321–331.

129. Baghaban Eslaminejad, M.; Talkhabi, M.; Zeynali, B. Effect of Lithium chloride on proliferation and bone differentiation of rat marrow-derived mesenchymal stem cells in culture. *Irnn. J. Basic Med. Sci.* 2008, 11, 143–151.

130. Bolek, D.; Pytlík, M. Effects of lithium on bone mechanical properties in the presence and deficiency of estrogens in rats. *Pharmacol. Rep.* 2010, 62, 74–75.

131. Jin, Y.; Xu, L.; Hu, X.; Liao, S.; Pathak, J.L.; Liu, J. Lithium chloride enhances bone regeneration and implant osseointegration in osteoporotic conditions. *J. Bone Miner. Metab.* 2017, 35, 497–503.

132. Duarte, P.M.; Miranda, T.S.; Marins, L.M.; Perez, E.G.; Copes, L.G.; Tonietto, C.B.; Montalli, V.A.; Malta, F.S.; Napiomgra, M.H. Systemic Lithium Chloride Administration Improves Tooth Extraction Wound Healing in Estrogen-Deficient Rats. *Braz. Dent. J.* 2020, 31, 640–649.

133. Chattanawarawipa, P.; Pavasant, P.; Osathanon, T.; Sukarawan, W. Effect of lithium chloride on cell proliferation and osteogenic differentiation in stem cells from human exfoliated deciduous teeth. *Tissue Cell* 2016, 48, 425–431.

134. Tang, L.; Chen, Y.; Pei, F.; Zhang, H. Lithium chloride modulates adiopogenesis and osteogenesis of human bone marrow-derived mesenchymal stem cells. *Cell. Physiol. Biochem.* 2015, 37, 143–152.

135. Satija, N.K.; Sharma, D.; Afrin, F.; Tripathi, R.P.; Gangenahalli, G. High throughput transcriptome profiling of lithium stimulated human mesenchymal stem cells reveals priming towards osteoblastic lineage. *PLoS ONE* 2013, 8, e55769.

136. Vachhani, K.; Pagotto, A.; Wang, Y.; Whyne, C.; Nam, D. Design of experiments confirms optimization of lithium administration parameters for enhanced fracture healing. *J. Biomech.* 2018, 66, 153–158.
of Wnt/β-catenin signaling directs the odontoblastic differentiation of dental pulp-derived stem cells. Rahman, S.U.; Oh, J.H.; Cho, Y.D.; Chung, S.H.; Lee, G.; Baek, J.H.; Ryoo, H.M.; Woo, K.M. Fibrous topography-potentiated canonical Wnt signaling directs the odontoblastic differentiation of dental pulp-derived stem cells. ACS Appl. Mater. Interfaces 2018, 10, 17526–17541.

Zhao, Y.; Yuan, X.; Bellido, T.; Helms, J.A. A correlation between Wnt/beta-catenin signaling and the rate of dentin secretion. J. Endod. 2019, 45, 1357–1364. e1.

Hara, M.; Horibe, K.; Mori, H.; Nakamura, H. The role of canonical Wnt signaling in dentin bridge formation. J. Oral Biosci. 2021, 63, 199–209.

Ali, M.; Okamoto, M.; Komichi, S.; Watanabe, M.; Huang, H.; Takahashi, Y.; Hayashi, M. Lithium-containing surface pre-reacted glass fillers enhance hDPSC functions and induce reparative dentin formation in a rat pulp capping model through activation of Wnt/beta-catenin signaling. Acta Biomater. 2019, 96, 594–604.

Ishimoto, K.; Hayano, S.; Yanagita, T.; Kurosaka, H.; Kawanabe, N.; Itoh, S.; Ono, M.; Kuboki, T.; Kamioka, H.; Yamashiro, T. Topical application of lithium chloride on the pulp induces dentin regeneration. PLoS ONE 2015, 10, e0121938.

Eduardo, C.D.P.; Simões, A.; de Freitas, P.M.; Arana, M.; Okamoto, M.; Komichi, S.; Watanabe, M.; Huang, H.; Takahashi, Y.; Hayashi, M. Lithium-containing surface pre-reacted glass fillers enhance hDPSC functions and induce reparative dentin formation in a rat pulp capping model through activation of Wnt/beta-catenin signaling. Acta Biomater. 2019, 96, 594–604.

Yang, C.; Wang, W.; Zhu, K.; Liu, W.; Luo, Y.; Yuan, X.; Wang, J.; Cheng, T.; Zhang, X. Lithium chloride with immunomodulatory function for regulating titanium nanoparticle-stimulated inflammatory response and accelerating osteogenesis through suppression of MAPK signaling pathway. Int. J. Nanomed. 2019, 14, 7475.

Geng, D.; Wu, J.; Shao, H.; Zhu, S.; Wang, Y.; Zhang, W.; Ping, Z.; Hu, X.; Zhu, X.; Xu, Y.; et al. Pharmaceutical inhibition of glycogen synthetase kinase 3 beta suppresses wear debris-induced osteolysis. FASEB J. 2016, 30, 244–253.

Yang, C.; Wang, W.; Zhu, K.; Liu, W.; Luo, Y.; Yuan, X.; Wang, J.; Cheng, T.; Zhang, X. Lithium chloride with immunomodulatory function for regulating titanium nanoparticle-stimulated inflammatory response and accelerating osteogenesis through suppression of MAPK signaling pathway. Int. J. Nanomed. 2019, 14, 7475.

Gao, S.; Wang, Y.; Wang, X.; Lin, P.; Hu, M. Effect of lithium ions on cementoblasts in the presence of lipopolysaccharide in vitro. Exp. Ther. Med. 2015, 9, 1277–1282.

Wang, W.; Yan, X.; Lin, Y.; Ge, H.; Tan, Q. Wnt7a promotes wound healing by regulation of angiogenesis and inflammation: Issues on diabetes and obesity. J. Dermatol. Sci. 2018, 91, 124–133.

Fathcke, C.; Wilson, L.; Shah, K.; Kim, B.; Hocking, A.; Moon, R.; Isik, F. Wnt signaling induces epithelial differentiation during cutaneous wound healing. BMC Cell Biol. 2006, 7, 4.

Cheon, S.S.; Wei, Q.; Gurung, A.; Youn, A.; Bright, T.; Poon, R.; Whetstone, H.; Guha, A.; Alman, B.A. Beta-catenin regulates wound size and mediates the effect of TGF-beta in cutaneous healing. FASEB J. 2006, 20, 692–701.

Houshary, K.S.; Momeni, A.; Pyles, M.N.; Maan, Z.N.; Whittam, A.J.; Siemers, F. Wnt signaling induces epithelial differentiation during cutaneous wound healing. Organogenesis 2015, 11, 95–104.

Pandit, V.; Nesbitt, S.R.; Kim, D.Y.; Mixon, A.; Kotha, S.P. Combinatorial therapy using negative pressure and varying lithium dosage for accelerated wound healing. J. Mech. Behav. Biomed. Mater. 2015, 44, 173–178.

Yuan, J.; Hou, Q.; Chen, D.; Zhong, L.; Dai, X.; Zhu, Z.; Li, M.; Fu, X. Chitosan/LiCl composite scaffolds promote skin regeneration in full-thickness loss. Sci. China Life Sci. 2019, 63, 552–562.

Ma, Y.; Li, L.; Qian, J.; Qu, W.; Luo, R.; Wu, F.; Chen, R. Materials and structure engineering by magnetron sputtering for advanced lithium batteries. Energy Storage Mater. 2021, 39, 203–224.

Farber, P.L.; Isoldi, F.C.; Ferreira, L.M. Electric Factors in Wound Healing. Adv. Wound Care 2020, 10, 461–476.

Jeong, S.H.; Lee, Y.; Lee, M.G.; Song, W.J.; Park, J.U.; Sun, J.Y. Accelerated wound healing with an ionic patch assisted by a triboelectric nanogenerator. Nano Energy 2021, 79, 105463.

Rajendran, S.B.; Challen, K.; Wright, K.L.; Hardy, J.G. Electrical Stimulation to Enhance Wound Healing. J. Funct. Biomater. 2021, 12, 40.
165. Makoukji, J.; Belle, M.; Meffre, D.; Stassart, R.; Grenier, J.; Shackelford, G.G.; Feldrich, R.; Fonte, C.; Branchu, J.; Goulard, M.; et al. Lithium enhances remyelination of peripheral nerves. Proc. Natl. Acad. Sci. USA 2012, 109, 3973–3978.

166. Nouri, M.; Rasouli, M.R.; Rahimian, R.; Asadi-Amoli, F.; Dehpour, A.R. Lithium improves regeneration after sciatic nerve traumatic injury in rat. J. Reconstr. Microsurg. 2009, 25, 151.

167. Gu, X.K.; Li, X.R.; Lu, M.L.; Xu, H. Lithium promotes proliferation and suppresses migration of Schwann cells. Neural Regen. Res. 2020, 15, 1955.

168. Zhang, D.; Wang, F.; Zhai, X.; Li, X.H.; He, X.J. Lithium promotes recovery of neurological function after spinal cord injury by inducing autophagy. Neural Regen. Res. 2018, 13, 2191.

169. Su, H.; Yuan, Q.; Qin, D.; Yang, X.; Wong, W.M.; So, K.F.; Wu, W. Lithium enhances axonal regeneration in peripheral nerve by inhibiting glycogen synthase kinase 3β activation. BioMed Res. Int. 2014, 2014, 658753.

170. Fu, R.; Tang, Y.; Ling, Z.M.; Li, Y.Q.; Cheng, X.; Song, F.H.; Zhou, L.H.; Wu, W. Lithium enhances survival and regrowth of spinal motoneurons after ventral root avulsion. BMC Neurosci. 2014, 15, 84.

171. Fang, X.Y.; Zhang, W.M.; Zhang, C.F.; Wong, W.M.; Li, W.; Wu, W.; Lin, J.H. Lithium accelerates functional motor recovery by improving remyelination of regenerating axons following ventral root avulsion and reimplantation. Neuroscience 2016, 329, 213–225.

172. Kocman, A.E.; Dąg, I.; Sjengel, T.; Soztutar, E.; Canbek, M. The effect of lithium and lithium-loaded hyaluronic acid hydrogel applications on nerve regeneration and recovery of motor functions in peripheral nerve injury. Rendiconti Lincei. Sci. Fis. Nat. 2020, 31, 889–904.

173. Hasan, J.; Crawford, R.J.; Ivanova, E.P. Antibacterial surfaces: The quest for a new generation of biomaterials. Trends Biotechnol. 2013, 31, 295–304.

174. Arnold, C.P.; Merryman, M.S.; Harris-Arnold, A.; McKinney, S.A.; Seidel, C.W.; Loethen, S.; Proctor, K.N.; Guo, L.; Alvarado, A.S. Pathogenic shifts in endogenous microbiota impede tissue regeneration via distinct activation of TAK1/MKK/p38. eLife 2016, 5, e16793.

175. Abnave, P.; Ghigo, E. Role of the immune system in regeneration and its dynamic interplay with adult stem cells. In Seminars in Cell & Developmental Biology; Elsevier Ltd.: Amsterdam, The Netherlands, 2019.

176. Huang, X.; Xu, W.; Li, M.; Zhang, P.; Zhang, Y.S.; Ding, J.; Chen, X. Antiviral biomaterials. Matter 2021, 4, 1892–1918.

177. Vandeven, N.; Nghiem, P. Pathogen-driven cancers and emerging immune therapeutic strategies. Cancer Immunol. Res. 2014, 2, 9–14.

178. Vogelmann, R.; Amieva, M.R. The role of bacterial pathogens in cancer. Curr. Opin. Microbiol. 2007, 10, 76–81.

179. Rajagopalan, D.; Jha, S. An epi(c)genetic war: Pathogens, cancer and human genome. Biochim. Biophys. Acta (BBA)-Rev. Cancer 2018, 1869, 333–345.

180. Morales-Sánchez, A.; Fuentes-Panáñez, E.M. Human Viruses and Cancer. Viruses 2014, 6, 4047–4079.

181. Godoy-Gallardo, M.; Eckhard, U.; Delgado, L.M.; de Roo Puente, Y.J.; Hoyos-Nogués, M.; Gil, F.J.; Perez, R.A. Antibacterial approaches in tissue engineering using metal ions and nanoparticles: From mechanisms to applications. Bioact. Mater. 2021, 6, 4470–4490.

182. Lieb, J. Lithium and antidepressants: Stimulating immune function and preventing and reversing infection. Med. Hypotheses 2007, 69, 8–11.

183. Lieb, J. The immunostimulating and antimicrobial properties of lithium and antidepressants. J. Infect. 2004, 49, 88–93.

184. Spuch, C.; López-García, M.; Rivera-Baltanás, T.; Rodrigues-Amorim, D.; Olivares, J.M. Does lithium deserve a place in the treatment against COVID-19? A preliminary observational study in six patients, case report. Front. Pharmacol. 2020, 11, 1347.

185. Choi, Y.; Bowman, J.W.; Jung, J.U. Autophagy during viral infection—a double-edged sword. Nat. Rev. Microbiol. 2018, 16, 341–354.

186. Farmani, A.R.; Mahdavinezhad, F.; Moslemi, R.; Mehrabi, Z.; Noori, A.; Kouhestani, M.; Noroozi, Z.; Ai, J.; Rezaei, N. Anti-IgE monoclonal antibodies as potential treatment in COVID-19. Immunopharmacol. Immunotoxical. 2021, 43, 259–264.

187. Nowak, J.K.; Walkowiak, J. Lithium and coronaviral infections. A scoring review. F1000Research 2020, 9, 93.

188. Murr, A.; Manchia, M.; Hajek, T.; Nielsen, R.E.; Rybakowski, J.K.; Sani, G.; Schulze, T.G.; Tondo, L.; Bauer, M. Lithium’s antiviral effects: A potential drug for COVID-19 disease? Int. J. Bipolar Disord. 2020, 8, 21.

189. Qaswal, A.B.; Suleiman, A.; Guzu, H.; Harb, T.A.; Atiyat, B. The potential role of lithium as an antiviral agent against SARS-CoV-2 via membrane depolarization: Review and hypothesis. Sci. Pharm. 2021, 89, 11.

190. Farmani, A.R.; Mahdavinezhad, F.; Scagnolari, C.; Kouhestani, M.; Mohammadi, S.; Ai, J.; Shoormeij, M.H.; Rezaei, N. An overview on tumor treating fields (TTFie lds) technology as a new potential subsidiary biophysical treatment for COVID-19. Drug Deliv. Transl. Res. 2021, 12, 1605–1615.

191. Mahdavinezhad, F.; Farmani, A.R.; Pakniat, H.; Taghavi, S.; Gharaei, R.; Valipour, J.; Amidi, F. COVID-19 and varicocoele: The possible overlap factors and the common therapeutic approaches. Am. J. Reprod. Immunol. 2021, 87, e13518.

192. Farmani, A.R.; Swanson, R.J.; Mahdavinezhad, F.; Shoormeij, M.H.; Mohammadi, S.; Moeinzadeh, A.; Ghazipour, F.; Ai, J. Potential Application of Picosecond Pulsed Electric Field (PPEF): Advanced Bioelectrical Technology for Potential COVID-19 Treatment. J. Neu Mater. Electrochem. Syst. 2021, 24, 293–296.

193. Li, H.J.; Gao, D.S.; Li, Y.T.; Wang, Y.S.; Liu, H.Y.; Zhao, J. Antiviral effect of lithium chloride on porcine epidemic diarrhea virus in vitro. Res. Vet. Sci. 2018, 118, 288–294.
Influence of single and binary doping of strontium and lithium on in vivo biological properties of bioactive glass scaffolds.  
Khan, P.K.; Mahato, A.; Kundu, B.; Nandi, S.K.; Mukherjee, P.; Datta, S.; Sarkar, S.; Mukherjee, J.; Nath, S.; Balla, V.K.; et al.

Physicochemical and Antibacterial Properties of Experimental Adhesives Doped with Lithium Niobate.  
Canno, M.; Bellucci, D.; Roether, J.A.; Boccaccini, A.R.; Kurtzman, G.M.; Moore, C.  
Reinforced Lithium Silicate Ceramic: A Case Report.  
Miguel-Pacheco, V.; Büttner, T.; Maçon, A.L.B.; Jones, J.R.; Fey, T.; De Ligny, D.; Greil, P.; Chevalier, J.; Malchere, A.; Boccaccini, A.R.  
Development and characterization of lithium-releasing silicate bioactive glasses and their scaffolds for bone repair.  
Jones, J.R.  
Review of bioactive glasses: From Hench to hybrids.  
Acta Biomater. 2013, 9, 4457–4486.

Cannio, M.; Bellucci, D.; Roether, J.A.; Boccaccini, A.R.; Cannillo, V.  
Bioactive Glass Applications: A Literature Review of Human Clinical Trials.  
Materials 2021, 12, 14400.

Durand, L.A.H.; Vargas, G.E.; Gomez-Gramajo, F.; Vera-Mesones, R.; Miguez-Pacheco, V.; Boccaccini, A.R.; Gorustovich, A.  
A Chapter 7—Lithium-Containing Bioactive Glasses for Bone Regeneration.  
In Biomedical, Therapeutic and Clinical Applications of Bioactive Glasses; Kaur, G.; Ed.; Woodhead Publishing: Sawston, UK, 2019; pp. 201–217.

Khorami, M.; Hesaraki, S.; Behnamghader, A.; Nazarian, H.; Shahrabi, S.  
In vitro bioactivity and biocompatibility of lithium substituted 4555 bioglass.  
Mater. Sci. Eng. C 2011, 31, 1584–1592.

Kavitha, R.J.; Subha, B.; Shanmugam, S.; Ravichandran, K.  
Synthesis and in vitro characterisation of lithium doped bioactive glass through quick alkali Sol-Gel method.  
Int. J. Innov. Res. Sci. Eng. 2014, 2, 2347–2307.

Miguez-Pacheco, V.; Büttner, T.; Maçon, A.L.B.; Jones, J.R.; Fey, T.; De Ligny, D.; Greil, P.; Chevalier, J.; Malchere, A.; Boccaccini, A.R.  
Development and characterization of lithium-releasing silicate bioactive glasses and their scaffolds for bone repair.  
J. Non-Cryst. Solids 2016, 432, 65–72.

Maçon, A.L.; Jacquemin, M.; Page, S.J.; Li, S.; Bertazzo, S.; Stevens, M.M.; Hanna, J.V.; Jones, J.R.  
Lithium-silicate sol–gel bioactive glass and the effect of lithium precursor on structure–property relationships.  
J. Sol.-Gel Sci. Technol. 2017, 81, 84–94.

Malik, Q.U.A.; Ifitikhar, S.; Zahid, S.; Safi, S.Z.; Khan, A.F.; Nawshad, M.; Ghafoor, S.; Khan, A.S.; Shah, A.T.  
Smart injectable self-setting bioceramics for dental applications.  
Mater. Sci. Eng. C 2020, 113, 110956.

Zaronf, F.; Di Mauro, M.I.; Ausiello, P.; Ruggiero, G.; Sorrentino, R.  
Current status on lithium disilicate and zirconia: A narrative review.  
BMC Oral Health 2019, 19, 134.

Chen, Y.; Yeung, A.W.; Pow, E.H.; Tsoi, J.K.  
Current status and research trends of lithium disilicate in dentistry: A bibliometric analysis.  
J. Prosthet. Dent. 2021, 126, 512–522.

Daguano, J.K.; Milesi, M.T.; Rodas, A.C.; Weber, A.F.; Sarkis, J.E.; Hortellani, M.A.; Zanotto, E.D.  
In vitro biocompatibility of new bioactive lithia-silica glass-ceramics.  
Mater. Sci. Eng. C 2019, 94, 117–125.

Kurtzman, G.M.; Moore, C.  
Reinforced Lithium Silicate Ceramic: A Case Report.  
Dent. Today 2017, 36, 102–105.

El-Rashidy, A.A.; Roether, J.A.; Harhaus, L.; Kneser, U.; Boccaccini, D.N.; Cannillo, V.  
Bioactive Glass Applications: A Literature Review of Oral Diseases.  
Chapter 7—Lithium-Containing Bioactive Glasses for Bone Regeneration.  
In Biomedical, Therapeutic and Clinical Applications of Bioactive Glasses; Kaur, G.; Ed.; Woodhead Publishing: Sawston, UK, 2019; pp. 201–217.

Zaronf, F.; Di Mauro, M.I.; Ausiello, P.; Ruggiero, G.; Sorrentino, R.  
Current status on lithium disilicate and zirconia: A narrative review.  
BMC Oral Health 2019, 19, 134.
223. Mororó, P.; Fernandes, C.; Lattanzi, W. Challenges and Innovations in Osteochondral Regeneration: Insights from Biology and Inputs from Bioengineering toward the Optimization of Tissue Engineering Strategies. *J. Funct. Biomater.* **2021**, *12*, 17.

224. Zhang, B.; Huang, J.; Narayan, R.J. Gradient scaffolds for osteochondral tissue engineering and regeneration. *J. Mater. Chem. B* **2020**, *8*, S149–S170.

225. Li, S.; Macon, A.L.; Jacquemin, M.; Stevens, M.M.; Jones, J.R. Sol–gel derived lithium-releasing glass for cartilage regeneration. *J. Biomater. Appl.* **2017**, *32*, 104–113.

226. Wu, Y.; Zhu, S.; Wu, C.; Lu, P.; Hu, C.; Xiong, S.; Chang, J.; Heng, B.C.; Xiao, Y.; Ouyang, H.W. A Bi-lineage conducive scaffold for osteochondral defect regeneration. *Adv. Funct. Mater.* **2014**, *24*, 4473–4483.

227. Mastrullo, V.; Cathery, W.; Vellion, E.; Madeddu, P.; Campagnolo, P. Angiogenesis in tissue engineering: As nature intended? *Front. Bioeng. Biotechnol.* **2020**, *8*, 188.

228. Barrientsos, S.; Brem, H.; Stojadinovic, O.; Tomic Canic, M. Clinical application of growth factors and cytokines in wound healing. *Wound Repair Regen.* **2014**, *22*, 569–578.

229. Mitchell, A.C.; Briquez, P.S.; Hubbell, J.A.; Cochran, J.R. Engineering growth factors for regenerative medicine applications. *Acta Biomater.* **2016**, *30*, 1–12.

230. Haro Durand, L.A.; Varqas, G.E.; Vera-Mesones, R.; Baldi, A.; Zago, M.P.; Fanovich, M.A.; Boccaccini, A.R.; Gorustovich, A. In vitro human umbilical vein endothelial cells response to ionic dissolution products from lithium-containing 4555 bioactive glass. *Materials* **2017**, *10*, 740.

231. Liu, L.; Liu, Y.; Feng, C.; Chang, J.; Fu, R.; Wu, T.; Yu, F.; Wang, X.; Xia, L.; Wu, C.; et al. Lithium-containing biomaterials stimulate bone marrow stromal cell-derived exosomal miR-130a secretion to promote angiogenesis. *Biomaterials* **2019**, *192*, 523–536.

232. Zanni, G.; Michno, W.; Di Martino, E.; Tjärnlund-Wolf, A.; Pettersson, J.; Mason, C.E.; Hellspng, G.; Blomgren, K.; Hanrieder, J. Lithium Accumulates in Neurogenic Brain Regions as Revealed by High Resolution Ion Imaging. *Sci. Rep.* **2017**, *7*, 40726.

233. Kargozar, S.; Mozafari, M.; Ghenaatgar-Kasbi, M.; Bano, F. Bioactive Glasses and Glass/Polymer Composites for Bio-Medical and Orthopedic Applications. *Front. Bioeng. Biotechnol.* **2020**, *8*, 17.

234. Bose, S.; Fielding, G.; Taraifer, S.; Bandyopadhyay, A. Understanding of dopant-induced osteogenesis and angiogenesis in wound healing with nerve repair potential. *Mater. Lett.* **2021**, *292*, 126269.

235. Wei, R.; Zhang, Z.; Xing, M.; Zhou, Y.; Chang, J. Preparation and in vitro evaluation of Lithium-doped bioactive glasses for wound healing with nerve repair potential. *Mater. Lett.* **2021**, 126269.

236. Badran, H.; Yahia, I.S.; Hamdy, M.S.; Awwad, N.S. Lithium-doped hydroxyapatite nano-composites: Synthesis, characterization, gamma attenuation coefficient and dielectric properties. *Radiat. Phys. Chem.* **2022**, *139*, 84–91.

237. Drlík, D.; Slama, M.; Hadraba, H.; Drlíková, K.; Cihlar, J. Physical, mechanical, and biological properties of electrophoretically deposited lithium-doped calcium phosphates. *Ceram. Int.* **2018**, *44*, 2884–2891.

238. Popescu, A.C.; Florian, P.E.; Stan, G.E.; Popescu-Pelin, G.; Zgura, I.; Enculescu, M.; Oktar, F.N.; Trusca, R.; Sima, L.E.; Roseanu, A.; et al. Physical-chemical characterization and biological assessment of simple and lithium-doped biological-derived hydroxyapatite thin films for a new generation of metallic implants. *Appl. Surf. Sci.* **2018**, *439*, 724–735.

239. Marycz, K.; Sobierajska, P.; Smieszek, A.; Maredziak, M.; Wiglus, K.; Wiglus, R.J. Li+ activated nanohydroxyapatite doped with Eu3+ ions enhances proliferative activity and viability of human stem progenitor cells of adipose tissue and olfactory ensheathing cells. Further perspective of nHAP: Li+. *Appl. Sci.* **2017**, *7*, 151–162.

240. Li, D.; Huijiang, L.; Zhao, J.; Yang, Z.; Xie, X.; Wei, Z.; Li, D.; Kang, P. Porous lithium-doped hydroxyapatite scaffold seeded with hypoxia-preconditioned bone-marrow mesenchymal stem cells for bone-tissue regeneration. *Biomed. Mater.* **2018**, *13*, 055002.

241. Wei, X.; Ugurlu, O.; Ankit, A.; Acar, H.Y.; Akinc, M. Dissolution behavior of Si, Zn-codoped tricalcium phosphates. *Mater. Sci. Eng. C* **2009**, *29*, 126–135.

242. Matsumoto, N.; Yoshida, K.; Hashimoto, K.; Toda, Y. Dissolution mechanisms of β-tricalcium phosphate doped with monovalent metal ions. *J. Ceram. Soc. Jpn.* **2010**, *118*, 451–457.
249. Matsumoto, N.; Yoshida, K.; Hashimoto, K.; Toda, Y. Thermal stability of β-tricalcium phosphate doped with monovalent metal ions. Mater. Res. Bull. 2009, 44, 1889–1894.

250. No, Y.J.; Li, J.J.; Zreiqat, H. Doped calcium silicate ceramics: A new class of candidates for synthetic bone substitutes. Materials 2017, 10, 153.

251. Bertucci, A.; Kim, K.H.; Kang, J.; Zuidema, J.M.; Lee, S.H.; Kwon, E.J.; Kim, D.; Howell, S.B.; Ricci, F.; Ruoslahti, E.; et al. Tumor-targeting, microRNA-silencing porous silicon nanoparticles for ovarian cancer therapy. ACS Appl. Mater. Interfaces 2019, 11, 23926–23937.

252. Cui, H.; Zhu, G.; Qiu, L. and Ye, X.; et al. Facile synthesis of Mg-doped calcium silicate porous nanoparticles for targeted drug delivery and ovarian cancer treatment. Ceram. Int. 2021, 47, 24942–24948.

253. Zhu, Y.-J.; Guo, X.-X.; Sham, T.-K. Calcium silicate-based drug delivery systems. Expert Opin. Drug Deliv. 2017, 14, 215–228.

254. Lowe, S.; Ghita, O.; Hardy, J.G. Special issue: PAEKing ahead into the 21st century. Polym. Int. 2021, 70, 997–998.

255. Zhang, J.; Cai, L.; Wang, T.; Li, Q.; Tang, T.; Wei, S.; Qian, J.; Wei, J.; Su, J. Lithium doped silica nanospheres/poly(dopamine) composite coating on polyetheretherketone to stimulate cell responses, improve bone formation and osseointegration. Nanomed. Nanotechnol. Biol. Med. 2018, 14, 965–976.

256. Zhang, J.; Cai, L.; Tang, L.; Zhang, X.; Yang, L.; Zheng, K.; He, A.; Boccaccini, A.R.; Wei, J.; Zhao, J. Highly dispersed lithium doped mesoporous silica nanospheres regulating adhesion, proliferation, morphology, ALP activity and osteogenesis related gene expressions of BMSCs. Colloids Surf. B Biointerfaces 2018, 170, 563–571.

257. Deng, C.; Yang, Q.; Sun, X.; Chen, L.; Feng, C.; Chang, J.; Wu, C. Bioactive scaffolds with Li and Si ions-synergistic effects for osteochondral defects regeneration. Acta Mater. Today 2018, 10, 203–216.

258. Chen, L.; Deng, C.; Li, J.; Yao, Q.; Chang, J.; Wang, L.; Wu, C. 3D printing of a lithium–calcium–silicate crystal bio scaffold with dual bioactivities for osteochondral interface reconstruction. Biomaterials 2019, 196, 138–150.

259. He, F.; Yuan, X.; Lu, T.; Wang, Y.; Feng, S.; Shi, X.; Wang, L.; Ye, J.; Yang, H. Preparation and characterization of novel lithium magnesium phosphate bio ceramic scaffolds facilitating bone generation. J. Mater. Chem. B 2022, 10, 4040–4047.

260. Salman, S.; Salama, S.; Mahdy, E.A. Crystallization characteristics and properties of lithium germanosilicate glass-ceramics doped with some rare earth oxides. Boletin Soc. Española Cerámica Vidrio 2019, 58, 94–102.

261. Arcos, D.; Vallet-Regi, M. Bio ceramics for drug delivery. Acta Mater. 2013, 61, 890–911.

262. Razmi, M.; Rabbani-Charadegani, A.; Hashemi-Niasari, F.; Ghadam, P. Lithium chloride attenuates mitomycin C induced necrotic cell death in MDA-MB-231 breast cancer cells via HMGB1 and Bax signaling. J. Trace Elem. Med. Biol. 2018, 48, 87–96.

263. El-Kady, A.M.; Farag, M.M.; El-Rashed, A.M. Bioactive glass nanoparticles designed for multiple deliveries of lithium ions and drugs: Curative and restorative bone treatment. Eur. J. Pharm. Sci. 2016, 91, 243–250.

264. Yazdanpanah, A.; Moztarzadeh, F.; Arabayazi, S. A heat-generating lithium-ferrite doped bioactive glass for cancer hyperthermia. Phys. B Condens. Matter 2020, 593, 412298.

265. Xie, J.; Lu, Y.-C. A retrospective on lithium-ion batteries. Nat. Commun. 2020, 11, 2499.

266. Grey, C.P.; Hall, D.S. Prospects for lithium-ion batteries and beyond—A 2030 vision. Nat. Commun. 2020, 11, 6279.

267. Wu, F.; Maier, J.; Yu, Y. Guidelines and trends for next-generation rechargeable lithium and lithium-ion batteries. J. Energy Storage 2021, 34, 102019.

268. Nitta, N.; Wu, F.; Lee, J.T.; Yushin, G. Li-ion battery materials: Present and future. Mater. Today 2015, 18, 252–264.

269. Soltani, M.; Beheshti, S.H. A comprehensive review of lithium ion capacitor: Development, modelling, thermal management and applications. J. Energy Storage 2018, 13, 102019.

270. Karimi, D.; Behi, H.; Van Mierlo, J.; Berecibar, M. A Comprehensive Review of Lithium-Ion Capacitor Technology: Theory, Development, Modeling, Thermal Management Systems, and Applications. Molecules 2022, 27, 3119.

271. Liang, X.; Qi, R.; Zhao, M.; Zhang, Z.; Liu, M.; Pu, X.; Wang, Z.L.; Lu, X. Ultrafast lithium-ion capacitors for efficient storage of energy generated by triboelectric nanogenerators. Energy Storage Mater. 2020, 24, 297–303.

272. Zheng, X.; Jin, Y.; Liu, X.; Liu, T.; Wang, W.; Yu, H. Photoactivatable nanogenerators of reactive species for cancer therapy. Bioact. Mater. 2021, 6, 4301–4318.

273. Zhang, S.; Bick, M.; Xiao, X.; Chen, G.; Nashalian, A.; Chen, J. Leveraging triboelectric nanogenerators for bioengineering. Matter 2021, 4, 845–887.

274. Wang, Y.M.; Zeng, Q.; He, L.; Yin, P.; Sun, Y.; Hu, W.; Yang, R. Fabrication and application of biocompatible nanogenerators. iScience 2021, 24, 102274.

275. Sun, M.; Li, Z.; Yang, C.; Lv, Y.; Yuan, L.; Shang, C.; Liang, S.; Guo, B.; Liu, Y.; Li, Z.; et al. Nanogenerator-based devices for biomedical applications. Nano Energy 2021, 89, 106461.

276. Yoon, H.-J.; Kim, S.-W. Nanogenerators to Power Implantable Medical Systems. Joule 2020, 4, 1398–1407.

277. Liang, L.; Wen, L.; Wang, Y.; Song, J.; Li, H.; Zhang, Y.; He, X.; Zhao, W.; Zhan, M.; Li, Y.; et al. Homologous-targeted and tumor microenvironment-activated hydroxyl radical nanogenerator for enhanced chemoinmunotherapy of non-small cell lung cancer. Chem. Eng. J. 2021, 425, 131451.

278. Chowdhury, A.R.; Abdullah, A.M.; Hussain, I.; Lopez, J.; Cantu, D.; Gupta, S.K.; Mao, Y.; Danti, S.; Uddin, M.J. Lithium doped zinc oxide based flexible piezoelectric-tri boelectric hybrid nanogenerator. Nano Energy 2019, 61, 327–336.

279. Leucht, S.; Helfer, B.; Dold, M.; Kissling, W.; McGrath, J.J. Lithium for schizophrenia. Cochrane Database Syst. Rev. 2015, 2015, CD003834.
280. McKnight, R.F.; Chesney, E.; Amit, B.H.; Geddes, J.; Cipriani, A. Lithium for acute mania. *Cochrane Database Syst. Rev.* 2019, 2019, CD004048.

281. Burgess, S.S.; Geddes, J.; Hawton, K.K.; Taylor, M.J.; Townsend, E.; Jamison, K.; Goodwin, G. Lithium for maintenance treatment of mood disorders. *Cochrane Database Syst. Rev.* 2001, 2001, CD003013.

282. Cipriani, A.; Smith, K.A.; Burgess, S.S.; Carney, S.M.; Goodwin, G.; Geddes, J. Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. *Cochrane Database Syst. Rev.* 2006, 2006, CD003492.

283. Cochrane. *Cochrane Central Register of Controlled Trials;* Cochrane: London, UK, 2022.