processes

MDPI

Review

Biomaterials and Their Biomedical Applications: From Replacement to Regeneration

Silvia Todros, Martina Todesco and Andrea Bagno *

Department of Industrial Engineering, University of Padova, via Marzolo 9, 35131 Padova, Italy; silvia.todros@unipd.it (S.T.); martina.todesco@unipd.it (M.T.)
* Correspondence: andrea.bagno@unipd.it

Abstract: The history of biomaterials dates back to the mists of time: human beings had always used exogenous materials to facilitate wound healing and try to restore damaged tissues and organs. Nowadays, a wide variety of materials are commercially available and many others are under investigation to both maintain and restore bodily functions. Emerging clinical needs forced the development of new biomaterials, and lately discovered biomaterials allowed for the performing of new clinical applications. The definition of biomaterials as materials specifically conceived for biomedical uses was raised when it was acknowledged that they have to possess a fundamental feature: biocompatibility. At first, biocompatibility was mainly associated with biologically inert substances; around the 1970s, bioactivity was first discovered and the definition of biomaterials was consequently extended. At present, it also includes biologically derived materials and biological tissues. The present work aims at walking across the history of biomaterials, looking towards the scientific literature published on this matter. Finally, some current applications of biomaterials are briefly depicted and their future exploitation is hypothesized.

Keywords: biomaterials; biocompatibility; tissue engineering; artificial organs; regenerative medicine

Citation: Todros, S.; Todesco, M.; Bagno, A. Biomaterials and Their Biomedical Applications: From Replacement to Regeneration. *Processes* **2021**, *9*, 1949. https://doi.org/10.3390/pr9111949

Academic Editor: Maurizio Ventre

Received: 1 October 2021
Accepted: 28 October 2021
Published: 29 October 2021

1. When the History Began

The use of the word "biomaterials" had been largely anticipated by the practical use of materials as biomaterials. Indeed, the presence of exogenous materials in the human body can be dated back to prehistory [1]. The spear point embedded in the hip of the Kennewick Man (around 7000 BC) and the use of carbon particles for tattooing are examples of foreign bodies that had been tolerated by the host. It is also well known that linen threads were used by Ancient Egyptians to facilitate wound healing as much as 4000 years ago; catgut was applied as suturing material by Europeans in the Middle Ages [2]. In South Africa and India, the heads of large, biting ants were exploited to clamp wound edges together [1]. An interesting historical review on materials for suturing was published by Muffly, Tizzano and Waters [3]. Metallic sutures go back to Ancient Greece, when the physician, surgeon and philosopher Galen of Pergamon (II century AC) described golden wires used as ligatures. Over the centuries, other metals have been exploited: lead and silver among others, with and without evidence of adverse reactions.

Cases of intended applications of non-biological materials to repair bone tissue can be attributed to Inca surgeons, who repaired cranial fractures with golden plates; moreover, ancient Mayan populations used seashells to create artificial teeth, which properly achieved osseointegration [4,5]. Moreover, 4000 years ago the Chinese carved bamboo sticks in the form of natural teeth to be inserted into jaws just like current dental implants. Egyptians used precious metals for dental implants [6]. More recently, iron was utilized to produce artificial teeth in Europe (around 200 AC) [7]. A timeline illustrating the most important milestones in the history of biomaterials is depicted in Figure 1. Table 1 lists some of the most relevant applications of biomaterials for clinical use.

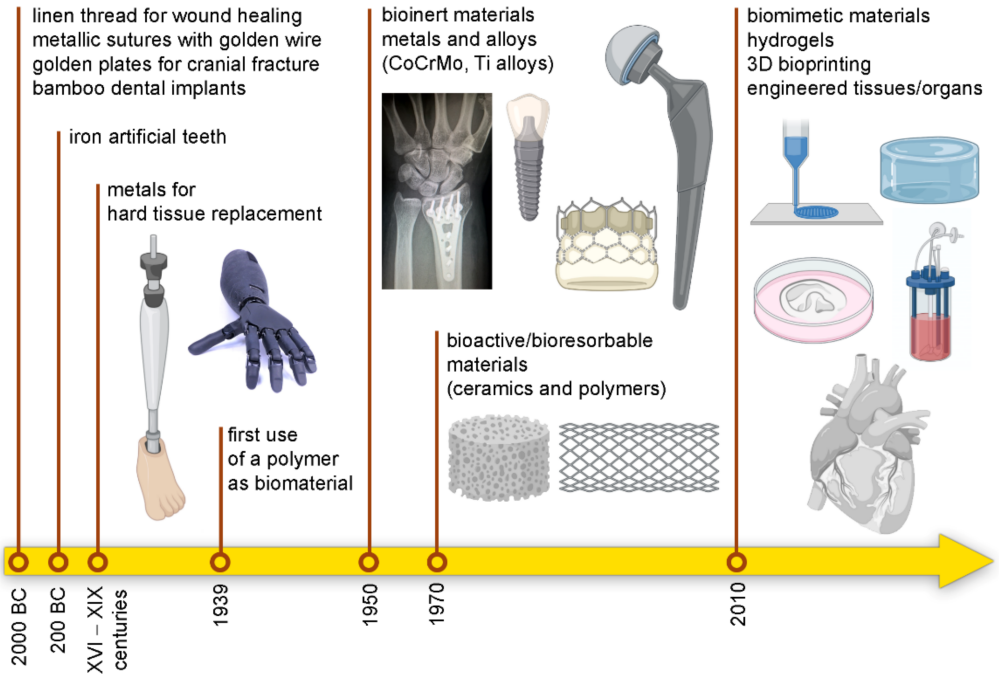

Figure 1. The history of biomaterials: from replacement to regeneration.

Table 1. Classes of biomaterials and their most relevant clinical applications.

	Pros and Cons	Examples	Applications
Metals	Pros: - high mechanical properties - high fatigue resistance - ductility Cons: - poor biocompatibility - stiffness - high specific weight - corrosion	stainless steel, CoCrMo, titanium, Ti6Al4V, nitinol, nickel, platinum, tantalum	orthopedic, orthodontic, cardiovascular
Ceramics	Pros: - good biocompatibility - chemical inertness - high compressive strength - corrosion resistance Cons: - low impulsive tensile strength - high specific weight - brittleness - not easy to process	alumina, zirconia, hydroxyapatite, beta tri-calcium phosphate, pyrolytic carbon	orthopedic, orthodontic, cardiovascular
Polymers	Pros: - toughness - low specific weight - processability Cons: - low mechanical strength - degradability over time - deformability over time	polymethylmethacrilate (PMMA), ultra-high molecular weight polyethylene (UHMWPE), polylactic acid (PLA), poly tetrafluoroethylene (PTFE), nylon, polyethylene, polyurethane, celluloid, cellophane, polycaprolactone (PCL), polyglycolic acid (PGA), polylactic acid (PLA), poly-lactic-co-glycolic acid (PLGA), poly(ethers) including polyethylene glycol (PEG), polyvinyl alcohol (PVA) and polyurethanes (PUs)	orthopedic, orthodontic, cardiovascular, breast implants, scaffold for soft tissues
Biologically-derived materials	Pros: - biocompatibility Cons: - poor reliability - difficult handling and storage	porcine/bovine pericardium	bioprosthetic heart valves, total artificial heart

Additionally, the purpose to replace diseased/damaged parts of the human body has been pursued for centuries. During the sixteenth century, Gaspare Tagliacozzi and other pioneering plastic surgeons successfully used autogenous skin flaps to replace missing noses [8]. All these original surgical procedures had been performed without any awareness of the problems and limitations related to material science and biological phenomena; moreover, no knowledge of sterilization, immunological reaction, inflammation, and biodegradation was available at those times [1]. However, their "unconscious" success clearly demonstrates that the human body has an impressive ability to adapt itself and accommodate foreign materials. This allowed for traveling on the road to biomaterials evolution before taking into account the fundamental interactions between the body and the implanted materials; the systematic examination thereof only began about 150 years ago, when scientists and physicians started to scientifically evaluate how the body reacts to the presence of exogenous materials. The practical exploitation of materials as biomaterials then began to face the issue of biocompatibility.

2. Biocompatibility as the Crucial Item

Biocompatibility assessment is a complex procedure aimed at verifying the capacity of a given material to avoid adverse reactions and also to correctly perform the intended function when in contact with (or inserted into) the biological environment. Some basic but fundamental concepts related to biocompatibility are available at the FDA [9]: it is worthy to pinpoint that the "FDA assesses the biocompatibility of the whole device and not just the component materials". Analogously, the ISO 10993-1 establishes criteria for the biological evaluation of medical devices, again confirming that biological tests have to be "performed on the final medical device, or representative samples from the final device or materials processed in the same manner as the final medical device (including sterilization, if needed)" [10].

Thus, the term "biocompatibility" has not only to include what is commonly meant as "biological compatibility", but also a functional evaluation of the entire implantable system. There are many cases of biologically compatible materials that did not pass the functional check. A clear example is represented by Teflon (polytetrafluoroethylene): it does not evoke any particular biological reaction, and therefore it can be considered "biologically" compatible. When Teflon was used for replacing the temporomandibular joint, it resulted in substantial fragmentation and caused huge foreign body giant cell responses that progressively eroded adjacent structures [11]. So, Teflon is not "functionally" compatible with respect to the foreseen application.

For sure, several aspects determine the biocompatibility of a given material also considering the duration of the contact with the biological counterparts: chemical composition, mechanical behavior and also physical shape. With specific regard to this latter, readers are invited to read the review written by T. G. Moizhess [12] where carcinogenesis (carcinogenesis induced by foreign bodies is the appearance of sarcomas in the immediate vicinity of an implanted material) is related not only to the chemical composition but also to the shape of different discs implanted in an animal model. Briefly, highly tumorigenic polymeric plates exhibited lower carcinogenicity after perforation, while their fragmentation resulted in almost complete loss of carcinogenicity.

The reactions induced by metals were studied early in the XIX century since metals were exploited at that time. Gold, silver, lead, nickel and platinum were studied in animals, and platinum was found to be well tolerated [1]. Other metals resulted in fast corrosion (iron and steel); others in tissue discoloration (copper, magnesium, aluminum alloy, zinc, and nickel); others exhibited not adequate mechanical features (gold, silver, lead, aluminum). CoCrMo alloys, titanium and its alloys were then proposed as promising candidates for biomedical applications due to their biocompatibility, which is combined with good mechanical properties.

Indeed, the major limitation of metals in contact with biological fluids is due to corrosion, which is the sum of (electro) chemical phenomena that commonly take place in

the presence of water and oxygen. After surgical implantation, all metallic devices (i.e., articular prostheses, plates and screws) are exposed to the attack of the body's structures that act as a defense system. Under these circumstances, some metals are oxidized: they release ions that can be toxic both locally and systemically. Consequently, the device degrades and it is no longer able to appropriately perform the intended function.

Polymeric materials entered the field of biomaterials quite recently: the first plastic material (celluloid) was developed in the 1860s and others followed thereafter [13]. Ratner and Zhang dated the first use of a polymer (cellophane) as implantable material in 1939: it was applied to wrap blood vessels, inducing a fibrotic reaction to limit the further expansion of the aneurysm. Interestingly, the Nobel Prize recipient Albert Einstein was diagnosed with an abdominal aortic aneurysm and treated with cellophane wrapping [14]. Two years later, nylon and poly(methyl methacrylate) were tested in vivo, then polyethylene followed [1].

The world of polymeric materials is continuously growing and now includes a huge number of different substances that can be produced in a variety of physical shapes with a variety of physical features: from solids to fibers, from thin sheets to thick plates, from hard to soft components, from inert to bioactive products. Manufacturing techniques were recently boosted by the introduction of electrospinning apparatuses and 3D printers: they both help to customize polymers with respect to an increasing number of applications.

The major aspect limiting polymers' biocompatibility is due to their chemical formulation: they always include additives that can be released in vivo resulting in adverse reactions. They are plasticizers, pigments, antioxidants, radiopaque agents, polymerization inhibitors/initiators, and, of course, monomers. Their undesired effects were observed as early as the mid-1900s [15].

Ceramics can be defined as inorganic non-metallic materials [16]: they are widely used as biomaterials especially for dental restoration and bone-contacting applications. Indeed, ceramics were suggested as an alternative to metals and polymers with the purpose to enhance bone fixation/integration. Generally, they are biologically compatible, in the sense that they are inert or bioactive, but do not elicit adverse reactions. Their marked limitation is due to stiffness and brittleness, which both represent severe drawbacks in many practical applications. Only alumina and zirconia have been used for the production of hip prostheses. Interestingly, some ceramics (e.g., bioactive glasses) are able to form a direct bond with living tissues [17]. An exhaustive review on the mechanisms of action and applications of bioactive glasses was published by Larry Hench, who discovered this class of biomaterials in 1969 [18]. Very briefly, the multistage process taking place on bioactive glasses surfaces in vivo results in the formation of a strong interface between bone and a dense layer of hydroxyapatite and carbonate-apatite [19]. Thus, a stable bond to bone is established, which promotes osteoconduction and also osteoinduction [20].

3. Evolving Definitions of Biomaterials

As was described in the previous paragraph, biomaterials are characterized by a wide range of chemical compositions and properties, and they can be exploited in very many applications. Therefore, it is quite difficult to define them unambiguously.

Marin et al. [21] ascribed to Jonathan Cohen one of the earliest definitions of biomaterials, which dates to 1967 [22]. Not by chance, Dr. Cohen was an orthopedic surgeon: exogenous materials had entered orthopedic surgery for many years. He simply defined "biomaterials" as all materials that are used as implants, with the exception of drugs and soft biological tissues. Indeed, this definition comes from the practical use of biomaterials in surgery focusing on "hard" materials that are typically applied in orthopedics.

In April 1974, the Society for Biomaterials (SFB) was formally established and organized its inaugural annual symposium one year later at Clemson University (SC, USA) [23]. This was the occasion to formalize a new definition: "A biomaterial is a systematically, pharmacologically inert substance designed for implantation within or incorporation with a living system" [24]. The inert nature of biomaterials was then confirmed as was their

difference from a drug; moreover, the role of biomaterials for implantation was stressed again. Professor Hench, who was a member of the SFB board, accepted the definition, even though he had already discovered bioactive glasses. Apparently, at that time the absence of adverse responses to the presence of biomaterials in vivo was prioritized with respect to their bioactive effects [21].

A broader definition was formulated in 1982 during the "National Institutes of Health Consensus Development Conference Statement on the Clinical Applications of Biomaterials" (Bethesda, MD, USA): biomaterial is "A substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body" [25]. The difference from a drug is maintained, but now the definition includes materials of "natural" origin and specifies what biomaterials are intended for: they are part of a system that is conceived not only to replace but also to potentially treat and augment each tissue, each organ and each function of the body. In our opinion, this definition marked a step forward to the most recent exploitation of biomaterials: they are not only simply "spare parts" of the body, but they can also play an active role whatever their nature is. As an immediate consequence, possible applications increase as much as the availability of biomaterials increases. In this sense, we consider the definition given by Prof. D. F. Williams ("A biomaterial is a non-viable material used in a medical device, intended to interact with biological systems" [26]) a step back: the exclusion of viable materials was (and is still) anachronistic! Besides the current use of biological tissues from human cadavers (tissue banks) and from animals (after chemical treatments), tissue engineering techniques appear as extremely promising approaches to create viable tissues (and organs) by combining cells, scaffolds (biomaterials!) and biochemical signals.

During the European Society for Biomaterials 9th European Conference (Chester, UK) in 1991, the definition, approved in 1982, was improved including "in order to maintain or improve the quality of life of the individual" [27]. What does this imply? It clearly affirms that the aim of any biomaterial is not only the "survival" of the patient but also the maintenance/improvement of their quality of life. The huge impact of this statement can be easily understood considering that the WHO foresees that the proportion of the world's population over 60 years will nearly double (from 12% to 22%) between 2015 and 2050 [28].

Given the faster and faster advances of scientific research and technological applications, especially in the biomedical field and in the clinical practice as well, we deem it opportune to apply the most inclusive definition of biomaterials.

4. Biomaterials in the Scientific Literature

While biomaterials were originally conceived as substitutes to replace impaired biological tissues, anatomical structures and organs, the idea of using them for regenerative medicine was first proposed in the 1980s by several scientists, including Ioannis Yannas, Joseph Vacanti, Charles Vacanti, Robert Langer and Stephen Badylak [29–32]. Since that time, there has been a massive increase in research activities in the field of biomaterials for regenerative medicine and tissue engineering. The number of Scopus records concerning biomaterials for both replacement and regeneration is reported in Figure 2 for each year from 1994 to 2020. It is clearly shown that, while the research activities on biomaterials for organ and tissue replacement have been producing about one hundred publications per year over the last decades, the research papers on biomaterials for regeneration are strongly increasing, with a number of more than 1200 records just in the year 2020.

In order to better understand the directions taken in the worldwide biomaterials research, the Scopus database was searched for full-text original articles in English using some keywords that characterize this field, such as "biomaterial", "bioactive materials", "smart material", "medical devices", "biocompatibility", "tissue engineering", "engineered organ", "biomaterials replacement" and "biomaterials regeneration". The cumulative number of Scopus records for each of these keywords up to June 2021 is reported in Figure 3a. Emerging trends in recent scientific progress are highlighted by comparing the number

of records in the years 2000 and 2020 for the selected keywords, as shown in Figure 3b. A range of advanced biomaterials is increasingly designed with bioactive behavior or smart and stimuli-responsive biomaterials with multiple functionalities. Polymeric hydrogels have received considerable attention in several biomedical applications due to their structural similarities to the native extracellular matrix (ECM) as well as their ability as carriers for controlled drug delivery. The development of engineered tissues and organs is rapidly displacing the concept of biomaterials for tissue substitution. Therefore, the following sections of this review are focused on some of the emerging trends in biomaterials for a wide range of biomedical applications.

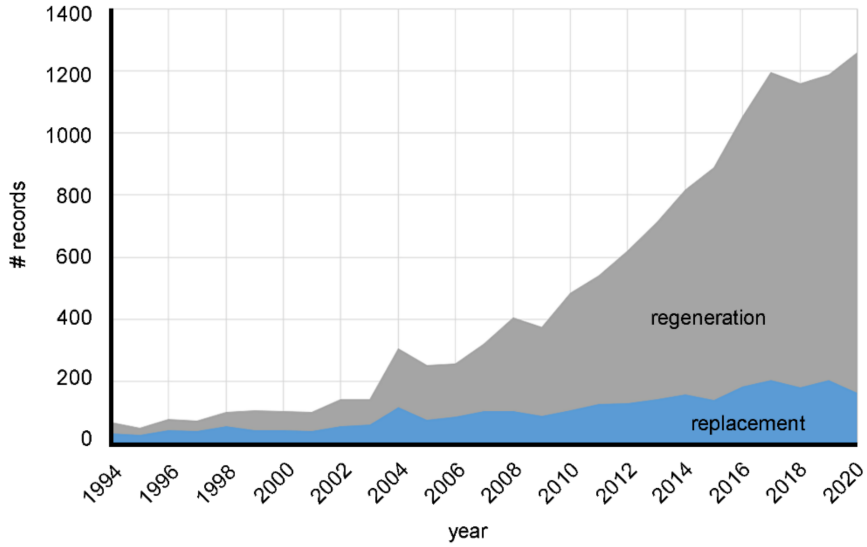

Figure 2. Trend in the number of Scopus records from 1994 to 2020 for the keywords "biomaterials replacement" and "biomaterials regeneration".

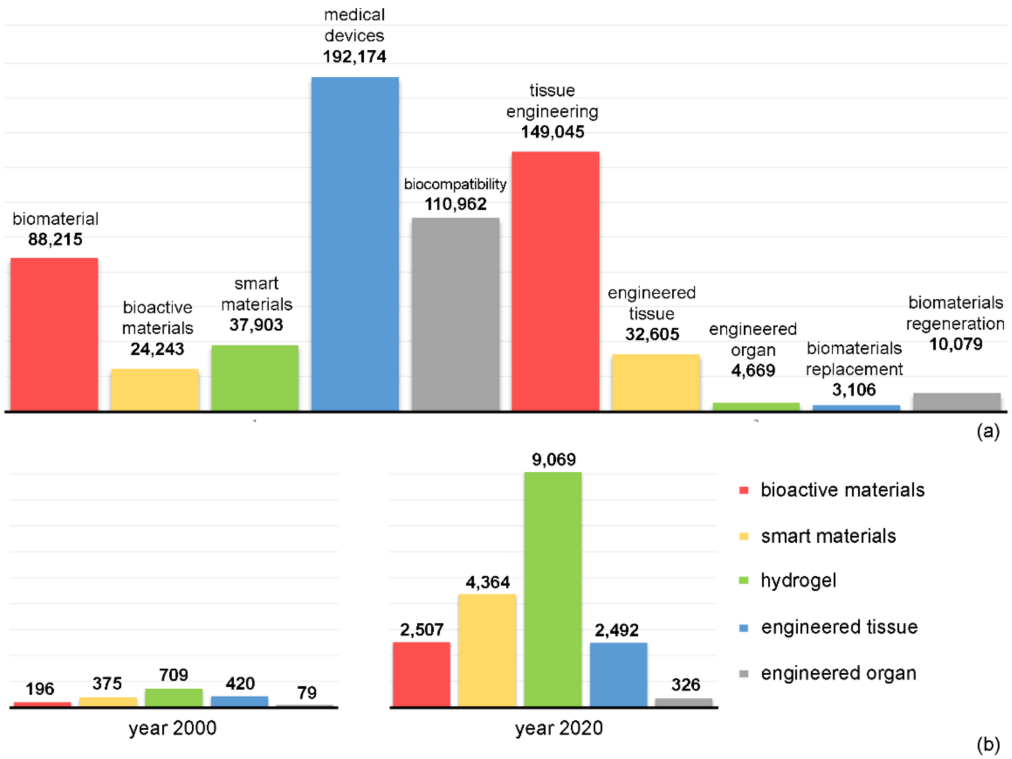

Figure 3. Cumulative number of Scopus records for different keywords related to biomaterials, up to June 2021 (**a**); comparison of the number of records in years 2000 and 2020 for selected keywords (**b**).

4.1. Biomaterials for Tissue Engineering

Since the 1980s, biomaterials began to be used as scaffolds seeded with living cells, to restore, maintain, or enhance damaged or missing anatomical structures. The term "tissue engineering" was then formally established at a National Science Foundation workshop in 1988 [33] to mean "the application of principles and methods of engineering and life sciences toward the fundamental understanding of structure–function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function". A crucial aspect of tissue engineering is the selection of the biomaterial from which scaffolds are developed [34]. Scaffolds are porous degradable structures, which may have a sponge-like random architecture or a highly complex structure with specifically designed pores and channels, suitable for cell adhesion, proliferation and growth. They are intended to degrade after implantation while being replaced by autologous newly-grown tissue. Scaffolds can also be designed to release growth factors [35–37], which promote cellular differentiation and tissue growth in vitro, or cell migration into the wound site in vivo. Thanks to the functionalization with biochemical factors, the scaffold biomaterial should be able to selectively interact with the specific receptors expressed by target cells in surrounding tissues, in order to guide their migration to the injury site and stimulate their adhesion, growth and differentiation [38]. After seeding with cells, scaffolds are often subjected to biophysical stimulation by means of a bioreactor [39–42], which is a device able to apply different stimuli (mechanical, hydraulic, electrical, chemical) to cells, mimicking the physiological conditions that cells are expected to experience in vivo and thus affecting gene expression and significantly increasing the biosynthetic activity.

Synthetic ceramics and polymers have been widely investigated as scaffolds for tissue engineering. Ceramic scaffolds, based on hydroxyapatite (HA) and tri-calcium phosphate (TCP), were mainly applied for bone regeneration [43–45]. Ceramics exhibit an excellent biochemical and biomechanical compatibility with bone tissue, due to their compositional and structural similarity to bone mineral phase, and are well known to enhance osteoblast differentiation and proliferation [46,47]. However, up to now their clinical applications for tissue engineering have been limited due to their brittle mechanical behavior and to the difficulties in tuning their biodegradation rate [48].

Several synthetic polymers have been proposed to develop scaffolds for soft tissue regeneration, namely poly(α-hydroxy esters) including polycaprolactone (PCL), polyglycolic acid (PGA), polylactic acid (PLA) and their copolymer poly-lactic-co-glycolic acid (PLGA), poly(ethers) including polyethylene glycol (PEG), polyvinyl alcohol (PVA) and polyurethane (PU) [49–51]. These polymers exhibit physicochemical and mechanical properties similar to biological tissues, they can be easily fabricated with tailored structural conformation and geometry, and their biodegradation profile can be controlled by varying their chemical composition. Nonetheless, they often lack cell adhesion sites and require chemical modifications to enhance cellular attachment. Moreover, it should be mentioned that PEG is not easily produced: due to the thermal instability and high reactivity of ethylene oxide, sophisticated reactors and safety measures are needed during the ethoxylation reaction [52].

To overcome these limitations, biological materials such as collagen, proteoglycans, alginate, fibrin, chitosan, gelatin and agarose were used for scaffolds manufacture [53–55]. Natural polymers are biologically active and able to promote excellent cell adhesion and growth. Nonetheless, they often show poor mechanical properties, especially in load-bearing applications, and they are not easily achieved in homogeneous batches with reproducible features, due to their inherent biological variability.

Both synthetic and natural polymers are frequently used to develop hydrogels for tissue engineering [55–59]. Hydrogels are composed of hydrophilic polymeric chains crosslinked through either covalent or non-covalent bonds. Due to their ability to absorb large amounts of water and soft mechanical properties, they present physicochemical and mechanical properties comparable with the ones of many soft tissues. They can be also

used as injectable materials able to adapt to the shape of the damaged tissue. According to their structure, both natural and synthetic hydrogels can be amorphous or semi-crystalline, while depending on their response to environmental stimuli, hydrogels can be divided into conventional and smart hydrogels, with the latter being able to reversely change their swelling behavior or structure in response to light, pressure, temperature, pH, ionic strength, electric or magnetic field, and other stimuli [56]. They are appropriate materials for scaffolds due to the possibility of tailoring their mechanical properties, modifying hydrogel chemical composition and crosslinking [60]. Hydrogels are also suitable for cell seeding because they offer immuno-isolation and concurrently allow gaseous exchange and nutrient diffusion [56]. To date, hydrogels are largely used as scaffolds for bone or soft tissue regeneration, especially in cartilage healing, and for wound dressing and drug or growth factor delivery [61].

To develop scaffolds that closely resemble natural tissues, decellularized extracellular matrix (dECM) is frequently adopted [62]. The ECM is primarily composed of structural molecules, such as collagen and proteoglycan, which provide tissue mechanical resistance and elastic behavior. Moreover, several cellular functions, as proliferation, migration or differentiation, are regulated by the ECM [63].

The dECM is obtained by removing from a tissue all the cellular and nuclear components that are responsible for the host immune response while maintaining ECM composition, structural conformation, mechanical properties and biological activity. Several decellularization methods were developed, owing to three main categories, i.e., physical, chemical and biological [64–67]. Physical methods comprise freeze–thawing cycles, high hydrostatic pressure, electroporation, ultrasonic waves and supercritical CO_2; chemical methods involve ionic or non-ionic detergents, hypertonic or hypotonic salt solutions, acids and bases; biological methods adopt enzymes such as trypsin, dispase and phospholipase or nucleases, such as DNase. The selection of the proper decellularization protocol is a key aspect in each specific application, considering that any treatment may have some drawbacks: for instance, physical methods can induce damages to the matrix, while chemical methods may change the chemical composition of ECM [64,68,69]. Several aspects, such as cell density, matrix density, thickness and tissue morphology affect the decellularization process and consequently the physicochemical and mechanical properties of the obtained dECM. In fact, the decellularized structure is intended to preserve its 3D geometry and leave the whole organ intact: thereby, tissue-engineered heart [70], lungs [71], urethra [72] and bladder [73] were developed in recent years.

4.2. Three-Dimensional Printing of Biomaterials

Due to the increasing trend towards a patient-specific approach, additive manufacturing techniques are playing a major role in the biomedical industry for the production of several devices, including customized orthopedic and dental implants, craniofacial reconstruction and plastic surgery, anatomical models for surgical planning, scaffolds for tissue engineering, diagnostic platforms, and drug delivery systems [74–77]. Three-dimensional (3D) printing is a layer-by-layer manufacturing process that creates 3D objects directly from patient anatomical data. Medical images acquired by means of Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) can be processed with Computer-Aided Design (CAD) software and then translated into customized implants. Three-dimensional printing techniques are generally classified into three classes, namely liquid-based, solid-based and powder-based techniques, depending on the initial form of the ink material, i.e., metals, ceramics and polymers [76]. Liquid-based techniques mainly involve the use of UV light to selectively cure a photocrosslinkable polymer layer by layer; specific commercial set-ups may differ in terms of type and wavelength of the light source, scanning or exposure method and suitable resin features. Solid-based systems entail the cutting and joining or melting of extruded material in the shape of pellets, wires or laminates, while powder-based techniques, including—among others—Selective Laser Sintering (SLS) and Electron

Beam Melting (EBM), use a high-energy beam for scanning subsequent layers of powder to create a 3D object [78].

A relevant area of application of 3D printed objects is tissue engineering since scaffolds can be developed with both micro and macro porosity where cells are able to attach, grow and differentiate. In this context, bioprinting is an innovative technique in which live cells are printed along with other biomaterials, generally hydrogels [79–82]. The aim of bioprinting is the production of fully functional human organs and tissues on a large scale. There are currently three major bioprinting systems on the market, namely inkjet, microextrusion and laser-assisted bioprinters. At present, the main limitations of bioprinting include the low mechanical strength of hydrogels that is responsible for a reduced 3D structure fabrication ability, the need of keeping cells viable during the overall process and eventually to include multiple cell types in the bioink, and the challenges in tuning the design and print strategy towards an effective biofabrication. Indeed, the maturation of a 3D printed tissue is strongly dependent on porosity and permeability, allowing nutrient delivery, gas exchange and vascularization. Notwithstanding some limitations and open issues, future progress in bioprinting techniques and bioinks formulation will lead to the development of patient-specific optimized functional tissues for transplantation and surgical repair.

4.3. Smart Biomaterials

Another class of innovative biomaterials that are pushing forward pioneering medical approaches are the ones taking the name of smart biomaterials, due to their ability to respond to changes in physiological parameters or external stimuli [83–85]. These biomaterials are able to modify their physicochemical and mechanical properties as a reaction to biological, chemical and physical signals, i.e., temperature, humidity, pH, redox potential, enzymatic activity, light and mechanical stimuli. Among these biomaterials, smart hydrogels are frequently exploited for tissue engineering and drug delivery applications [86–88]. Indeed, the hydrogel structure can be cross-linked also using reversible methods, such as physical cross-linking, thermally induced entanglement and self-assembly, which may allow for controlling drug release and biodegradation rate [89,90]. Biodegradable hydrogels are often obtained by means of cleavable cross-linkers, which can be dissolved through hydrolysis, proteolysis or disentanglement following a specific stimulus [91].

Moreover, in this framework, a new concept named "four-dimensional (4D) bioprinting" was introduced, considering time as the 4th dimension [92–94]. This technique is based on the principle that 3D bioprinted tissues need to remodel in vivo: using a bioink based on a smart hydrogel loaded with cells, the ability of the engineered tissue to grow and replace damaged tissue can be triggered by means of specific stimuli.

Other biomaterials such as Shape Memory (SM) alloys and polymers own the unique ability to recover to their original geometry and structure after exposure to an external stimulus, such as temperature, magnetic field, electric field, light or relative humidity [95]. The SM effect and the superelastic mechanical properties of these materials have been widely used in the development of minimally invasive implantable devices and surgical tools. Moreover, the SM behavior was recently exploited to confer self-healing properties to medical devices, preventing sudden damages by fast recovery to the original structure and shape [96].

Electroactive Polymers (EAPs) are another emerging class of smart materials that have attracted attention as actuators for the development of artificial muscles [97,98]. These polymers present some similarities with the functional response of biological muscles in terms of resilience, resistance and large actuation stretching or bending. Based on their activation mechanism, EAPs can be split into two classes: electronic EAPs, which are generally dry and driven by Coulomb forces, and ionic EAPs, which usually contain an electrolyte and involve the transport of ions or molecules in response to an external electric field. However, due to the need for high actuation voltages and to their poor stability in

a wet environment, these smart polymers have mainly found application in biomimetic devices, robotics and wearable electronics.

Nanomaterials and nanostructured biomaterials [99] have also been adopted in bioinspired robotics to simulate specific actuation and sensing properties, such as, by way of example, the tactile features of human skin or the ability of some animals to sense subtle vibrations in the environment.

4.4. Biomaterials Functionalized with Vesicles

One of the most recent applications of biomaterials to regenerative medicine is represented by their use as systems to release extracellular vesicles (EVs) and soluble factors [100]. Mesenchymal stem cells (MSCs) are pluripotent progenitor cells able to self-renew, differentiate into multiple lineages, and also accomplish trophic effects [101]. These effects are due to the secretion of EVs, which transport a variety of intracellular molecules (e.g., lipids, proteins, RNA, and DNA) suitable for guiding the regenerative process during tissue repair. These molecules control different cellular functions (e.g., migration, proliferation, differentiation, and synthesis of extracellular matrix components); furthermore, they suppress the local immune system, inhibit fibrosis and apoptosis, enhance angiogenesis, and stimulate mitosis and differentiation of reparative cells. The therapeutic effects of MSC-derived EVs were observed in many preclinical studies: for brain diseases, lung diseases, cardiac injury, liver injury, kidney injury, and skin lesions [100].

Biomaterials are used to create platforms for in situ delivery of EVs, binding them to (or embedding into) a matrix to extend their bioavailability. In the work published by Wang and coauthors [102], an injectable, self-healing and antibacterial polypeptide-based hydrogel was enriched with adipose-derived MSCs exosomes to enhance chronic wound healing and complete skin regeneration. The system was applied to full-thickness diabetic wounds with promising results. In another recent paper by Mardpour et al. [103], the therapeutic effect of EVs from MSCs was demonstrated for the treatment of liver diseases. In this case, an in situ-forming biodegradable hydrogel was used to encapsulate EVs upon intraperitoneal injection: it provided a sustained release with access to the systemic circulation. The hydrogel was obtained by clickable poly(ethylene glycol) (PEG) macromeres. A further example is given by the incorporation of exosomes into a chitosan-based hydrogel to treat hindlimb ischemia in an animal model [104]. Independently on the specific application, biomaterials are necessary to target cell-derived EVs locally and to deliver them in therapeutically effective amounts.

5. Biomaterials and Biomedical Devices

Is the clinical need that forces the development of new biomaterials, or the availability of new biomaterials that allow the development of innovative devices suitable for facing the clinical need? This question resembles the old one: egg or chicken first? Maybe the issue is trivial and meaningless. Indeed, we believe that the evolution of many practical applications in clinics goes hand in hand with the discovery of biomaterials to be used alone or as parts of biomedical devices. Sometimes the translation of already available materials into the clinical practice permits management of a specific need; sometimes a specific need guides the development of a newly conceived material. Two examples of prosthetic devices are herewith presented and discussed.

5.1. Total Hip Prosthesis

The hip is the joint that supports the body joining the femurs and the pelvis. The smooth and spherical head of the femur is perfectly hosted into the seat of the acetabulum; the stability of the joint is ensured by very resistant ligaments. The hip has to withstand the weight of the body and the mechanical stresses due to movements: excessive loading conditions, pathologies and aging can result in alterations of joint function with pain [105]. Osteoarthritis is a degenerative pathology that often compels the replacement of the damaged joint with a prosthetic device. This is designed to perform the same functions

as the natural joint; it usually consists of three basic components: a stem (that is inserted into the femur), a ball (the femoral head that is connected to the top of the stem), and a cup (that is hosted in the pelvis). The surgical operation is referred to as Total Hip Arthroplasty (THA).

After designing the prosthetic device to best simulate the kinematics of the joint, the choice of the material(s) to use represent a very critical issue. The selection has to be guided by the awareness that several constraints have to be matched: biocompatibility, fatigue resistance, stiffness, toughness, ability to withstand static and dynamic loads, and high resistance to mechanical and chemical wear [106]. Different materials are commonly exploited for the production of prosthetic components, briefly: CoCrMo, Ti6Al4V, alumina and zirconia for the femoral stem; CoCrMo, UHMWPE, alumina for the cup. Thus, different bearings are currently exploited to find the ideal combination that yields the fewest complications and best long-term survival [101]: metal-on-polyethylene (M-on-PE), metal-on-metal (M-on-M), ceramic-on-ceramic (C-on-C).

Therefore, why was one of the first recorded attempts (dr. Carnochan is sometimes cited as the first surgeon to insert a prosthetic device (a wooden piece!) between the hip joint [J.V. Bono, J.C. McCarthy, T.S. Thornhill, B.E. Bierbaum, and R.H. Turner, Eds, Revision Total Hip Arthroplasty, Springer-Verlag:New York, 1999]) to replace the arthritic hip performed using ivory ball and socket fixed to the bone by screws [107,108]? Simply, at that time (the year 1891) ivory was available and it was considered a good material in terms of mechanical resistance and compatibility; moreover, it was characterized by a smooth surface for movements. Other available materials were then exploited: rubber, glass, Bakelite. It was only in the mid-1900s that metals were used to fabricate the first generation of metal-on-metal bearing [109]. It happened when metal processing technology allowed it. Steel was used first, then replaced by chrome–cobalt–molybdenum and titanium alloys. Nevertheless, failures of metal-on-metal bearings were discovered and be attributed to the "high friction" due to inadequate manufacturing process.

The development of materials for the hip prosthesis is still in progress in order not to simply exploit available materials but also to design specifically conceived ones. At present, ceramics are widely used since they assure the best tribological features, but other materials are under investigation. About this, it is worthy to mention that, besides any other requirement, the materials for the production of the hip prosthesis have to minimize the so-called "stress shielding" effect, which received more and more attention over the years [110]. It occurs when a metallic device is in deep contact with bone: the higher stiffness of the device causes bone loss (atrophy) as a result of decreased loading conditions or produces denser bone where the load is increased. In other words, the presence of the device alters the physiological remodeling process of bone tissue, which is not properly stimulated. Stress shielding can result in periprosthetic bone resorption, and eventually in joint prosthesis failure: this leads to the need for a revision surgery, which is associated with increased risks, complications, and costs [110].

Two approaches were suggested to limit the stress shielding effect: (i) to investigate geometry and shape of the device, with specific regard to the surface characteristics; (ii) to properly select the material of choice depending on its stiffness. Numerical simulations [111] and experimental studies [112] are both fundamental for optimizing hip prosthesis configuration and composition. In particular, the exploitation of composite polymeric materials seems a promising strategy for the design of hip prostheses with adjustable stiffness.

A first example is given by the carbon/PEEK (PEEK stands for polyetheretherketone) composites, whose mechanical performances were compared to those of stainless steel and titanium [113]: the stress distribution was investigated by numerical simulations to check the suitability of the composites as an alternative to metals. Another example is the Carbon Fiber polyamide 12 (CF/PA12) composite: its capacity to provide a uniform density distribution across the bone, resulting in a reduced stress shielding effect was compared to CoCrMo and Ti alloys by numerical simulations [114].

A couple of considerations have necessarily to be advised: first, recent developments of total hip prosthesis design are moving the choice of candidate materials from the already available ones to those that have to be specifically produced for this application; second, composite materials, as those obtained by inserting ceramic/polymeric fibers into a polymeric matrix, are expected to assure better performances when compared to traditional ones.

5.2. Total Artificial Heart (TAH)

Heart failure (HF) is a complex clinical condition that severely impairs the heart's functions; up to now, cardiac transplantation is the only definitive solution for refractory end-stage HF [115]. Indeed, cardiac transplantation is limited by the short availability of organs from donors, which increases the waitlist time, and by the adverse effects due to immunosuppression (immunosuppression is mandatory to make the recipient able to host the biological organ from donor without rejection). These are the main reasons pushing the search for an alternative solution: the replacement of the failed heart with mechanical pumps. Pumps can "simply" assist one ventricle (Ventricular Assist Device, VAD) or replace the whole heart (Total Artificial Heart, TAH): they both give the patients a satisfactory quality of life and increase the rate of survival.

As plainly stated by Gino Gerosa et al. "Total replacement of the failing heart with a mechanical pump has been the Holy Grail for cardiac surgeons for decades" [116]. Indeed, very preliminary investigations aimed at supporting/replacing the biological heart with a man-made device date back to the beginning of the 1800s (more than 150 years before the first cardiac transplantation performed by Dr. Barnard in 1967), when the idea to assist a failing heart with extracorporeal perfusion was conceived [117]. In the late 1920s, the famous surgeon Alexis Carrel, in an unlikely partnership with the aviator Charles Lindbergh, tried to develop a mechanical heart: this purpose was not achieved, but they created a pump oxygenator for temporary perfusion of tissues and organs [118]. In 1957, Willem Kolf and Tetsuzo Akutso performed the first successful TAH implantation in a dog, whose circulation was sustained for 90 min [119]. The heart "was made of polyvinylchloride; subsequently we used polyurethane; and then for many years, Silastic" [120]. Silastic is a trademark registered in 1948 by Dow Corning Corporation for flexible, inert silicone elastomer.

After a sequence of trials in pre-clinical models, the first TAH implantation in humans was performed in 1969 by Denton Cooley and Domingo Liotta [121]. Over the years, many other prototypes were developed [122], but up to now, only two devices have entered the clinical practice: the CardioWest TAH (SynCardia, Tucson, AZ, USA) and the Aeson CARMAT TAH (Vélizy-Villacoublay, France), which very recently received the CE marking and the FDA approval for beginning enrollment in the US [123].

Following a clinical trial started in 1993 and concluded in 2002 [124], the CardioWest TAH (inspired by the predecessor Jarvik 7 developed in the 1980s, and now marketed as Syncardia TAH) experienced a great clinical success: to date, more than 1700 patients received this device. It is lined with polyurethane and has four-layer, pneumatically-driven diaphragms (polyurethane) to separate blood and compressed air in each ventricular chamber [124]; four mechanical valves (single leaflet tilting disc) regulate the blood flow.

Polymeric materials, not dependently on their specific chemical composition, and mechanical valves exhibit a certain level of thrombogenicity. In particular, polymers are able to assure promising features with regard to the manufacturing process and mechanical performances, but they cannot assure the required hemocompatibility. This imposes the administration of lifelong anticoagulation therapy to prevent thromboembolic complications; unfortunately, unbalanced anticoagulation can result in bleedings and hemorrhages [115].

Thus, is it possible to improve the biocompatibility of the device by choosing (or developing) a more compatible material for coating the blood-contacting surfaces? The CARMAT TAH offers two major innovations with respect to the existing TAHs: (i) the valves are not mechanical but biological and (ii) the membranes separating the blood compartment from the actuation fluid are made of a bioprosthetic material [125]. This latter

is obtained by coupling a polyurethane (at the fluid-contacting surface) with chemically treated bovine pericardium (at the blood-contacting side); its intended benefit is an improved hemocompatibility, potentially reducing the need for prolonged anticoagulation and the risk of bleeding/thrombosis [126]. Therefore, a new biomaterial was created, not only polymeric nor only biologic, but "hybrid". The idea is appealing and it can open the way for the development of other blood-contacting devices, but does it really work? In particular, what does it mean "chemically treated bovine pericardial tissue"?

Bovine and porcine pericardia have been used for manufacturing bioprosthetic heart valves but they have to be properly treated to avoid any adverse reaction when implanted into humans. So, animal pericardia are usually fixed with glutaraldehyde: it is a cheap and effective fixation agent, but it is also acknowledged to result in cytotoxic effects and to make the biological tissue prone to calcification [127]. To avoid (or at least limit) calcific degeneration, modifications to glutaraldehyde processed tissue and non-glutaraldehyde processes were proposed. We do not discuss the effectiveness of these methods, we only pinpoint that, whatever the method used to prevent calcification, treated tissues are no more vital: it means that they are not able to integrate with the host and their durability is limited. In other words, they are biological in nature, but they still remain "foreign bodies" after implantation.

Taking advantage of the progress in the field of tissue engineering, a different approach to the production of hybrid materials was recently proposed by our group. We applied a decellularization treatment to native biological tissues by removing cells and nuclear components from the matrix [128]: biological scaffolds with improved immunocompatibility and unvaried biological and biomechanical properties with respect to native tissues were obtained. They are still vital in the sense that they can be repopulated by circulating cells after implantation [129]: an endothelial layer will be generated in vivo over the blood-contacting side of the hybrid membrane that is produced by coupling the decellularized pericardium with a synthetic polymer, e.g., a commercial polycarbonate urethane [130]. The hemocompatibility of these innovative materials was investigated by assessing their capacity to promote thrombin generation and induce platelet activation. Our preliminary results demonstrated that the proposed hybrid membranes are compatible with blood [131].

6. What Are Biomaterials Intended for from 2021 Onwards?

In 2019 Prof. Buddy Ratner, one of the most prominent scientists in the field of biomaterials science authored an illuminating review on the future of biomaterials. He stated, and we do agree with him, that the biomaterials field was (and is still) characterized by multidisciplinarity. He wrote, "The field of biomaterials started with physicians, then embraced engineers, and was energized and legitimized by the molecular biology revolution" [132]. Prof. Ratner borrowed the term "convergence" from Sharp and Langer [133] to indicate a kind of "revolution" in the biomedical science aimed at integrating different skills with an equal role: future clinical needs will be faced by a joint collaboration of engineers, physical scientists, biologists and clinicians. Sharp and Langer offered a number of examples of this revolutionary cooperation: tissue-engineering is typically based on the exploitation of developmental biology with engineering and materials methods to replace tissues and organs; microfabrication techniques allow analyzing single cells, developing targeted nanoparticle therapeutics; algorithms for data mining improve personalized medicine; microsensors can detect the onset of disease [133]. Let us add the massive role that will be played by Artificial Intelligence all along the care pathway [134].

We believe that the present review demonstrated the incredible growth of the biomaterials field in terms of research interests and, consequently, scientific publications: but is it a real success? Professor Ratner raised doubt about that, arguing that tangible advances in medicine driven by biomaterials science are much less than the number of published papers. He sadly concluded, "these new developments, described in thousands of papers, have had limited impact on clinical medicine" [132]. Major causes for the lack

of clinical progress in biomaterials-based medical devices are mainly due to three factors: compatibility, durability and infections.

As previously discussed (see paragraph 2), compatibility implies the ability of a given material/device to not evoke adverse reactions after implantation and to assure the expected functionality; in the specific case of blood-contacting materials/devices, the term hemocompatibility is used to emphasize the absence of thrombogenicity and hemolysis. In general, no implantable material/device can guarantee absolute compatibility with the host. At present, all materials/devices intended for implantation are "foreign bodies", therefore responsible for a reaction that inevitably raises after surgery. This reaction is due to inflammation that is physiologically triggered by the healing process. Being a physiological event, inflammation cannot be avoided: indeed, it is crucial to maintain inflammation as acute and not chronic, to achieve the so-called "restitutio ad integrum" (this Latin term is used to indicate the successful restoration of tissue/organ functionality after completion of the healing process) of the tissue/organ involved.

In the case of materials and devices in permanent contact with blood, the lack of perfect hemocompatibility can be highly dangerous for patients: to prevent thromboembolic complications, they have to be administered with anticoagulant therapy. Indeed, anticoagulation can present deleterious side effects if not properly managed.

As all man-made products, current biomaterials and biomedical devices have limited durability, which is very often much less than patients' life expectancy: for instance, the average durability of a total hip prosthesis is 15 years; a mechanical heart valve is expected to be replaced after 30 years, whereas a bioprosthetic one after 12 years.

Fundamental progresses to enhance both compatibility and durability of materials/devices can be obtained when the shift from the perspective of "replacement" toward "regeneration" will be successfully completed. Indeed, bioengineered tissues and organs are autologous in nature, thus they are perfectly compatible; moreover, they completely integrate with the recipient's body, thus they follow the remodeling processes able to assure better performances and longer durability.

7. Some Words to Conclude

Is the regeneration perspective close to clinical translation? The answer depends on the complexity of the tissue/organ to be regenerated: with the term "complexity" we refer not only to the anatomical structure and histological architecture but also to the number of cells (and cell types) that are necessary for the complete regeneration. Bioengineered skin and cartilage (often, but improperly, termed "artificial") have entered the clinical practice so far, even though they do not reach the structural and functional complexity of native counterparts yet.

With regard to more complex organs, great emphasis was given to the publication of the first transplantation of tissue-engineered airway performed by the Italian surgeon Paolo Macchiarini in 2008 [135], and other attempts were announced subsequently. Afterward, the clinical success of Macchiarini's engineered airway was questioned by the scientific community for several reasons [136], and he had to retract some of his papers. Nevertheless, the way toward the clinical translation of tissue-engineered constructs was opened and several tissues and organs are currently under development: heart and heart valves [137,138], liver [139], kidney [140], lung [141], bladder [142], bone [143] and, of course, skin [144], cartilage [145] and trachea [146], are some examples from the scientific literature.

Undoubtedly, tissue engineering, boosted by 3D printing techniques and decellularization methods, will offer a ground-breaking solution for tissue/organ regeneration and, eventually, for safe and effective treatments of patients. In this context, biomaterial science has to play a crucial role in promoting what Tibbit and coworkers described as "The transition . . . from permissive to promoting biomaterials that are no longer bioinert but bioactive" [147].

With regard to the bioactivity issue, searching for biomaterials able to stimulate tissue repair opened the way for exploiting synthetic peptides for the biochemical functionaliza-

tion of materials surfaces. A wide number of synthetic sequences were already discovered and tested [148]: they are pro-angiogenic, anti-inflammatory, and pro-adhesive peptides, which are able to guide cells behavior and control the fate of a given material/device upon contact with the biological environment.

Gathered together, all these improvements in biomaterials science will be translated to clinics when companies renounce to use well-established biomaterials that are familiar to the regulatory authorities [132].

Whichever the nature of the materials used (synthetic or biological), for sure future biomaterial-based therapeutic approaches will be addressed towards the so-called "personalized medicine". It overcomes the traditional "one-size-fits-all" approach and considers each patient as an individual, tailoring the required therapy on the basis of the specific needs. This is a real revolution in medical care and it requires advances in biomaterials research that enable innovative biomaterials design to diagnose and treat patients' diseases [149].

Future Perspectives

Biomaterials science has advanced from pioneering practices to a field dominated by engineers, chemists, and physicists, to the present time with bioengineers and biologists as the "key players" [1].

It is not likely to draw the future perspectives of biomaterials science since biomaterials are (and will be) successfully exploited in a huge number of different applications. As argued by Prof. Ratner [132], the development of new biomaterials will be probably driven by the necessity to reduce the gap between scientific research and clinical practice. Undoubtedly, this step ahead will require stronger cooperation among researchers from different fields, who have to be able (and available!) to "mix" their competencies for a common purpose. Additionally, the design of novel biomaterials requires a "mix" of different components, combining the features of both biological and synthetic substances with cells and biochemical molecules.

Let scientists unleash their imagination and work together, provide them with an adequate amount of money, and they will get the goal! The abatement of current technical limitations will surely follow.

Author Contributions: Conceptualization, S.T. and A.B.; methodology, S.T. and A.B.; data curation, S.T. and A.B.; writing—original draft preparation, S.T., M.T. and A.B.; writing—review and editing, S.T., M.T. and A.B.; visualization, S.T.; supervision, A.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

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

References

1. Ratner, B.D.; Zhang, G. A History of Biomaterials. In *Biomaterials Science. An Introduction to Materials in Medicine*, 4th ed.; Ratner, B.D., Hoffman, A.S., Schoen, F.J., Lemons, J.E., Eds.; Elsevier Academic Press: London, UK, 2020.
2. Gentleman, E.; Ball, M.D.; Stevens, M.M. Medical Sciences—Vol.II—Biomaterials. Available online: https://www.eolss.net/ebooklib/home.aspx (accessed on 29 September 2021).
3. Muffly, T.M.; Tizzano, A.P.; Walters, M.D. The history and evolution of sutures in pelvic surgery. *J. R. Soc. Med.* **2011**, *104*, 107–112. [CrossRef]
4. Bobbio, A. The first endosseous alloplastic implant in the history of man. *Bull. Hist. Dent.* **1972**, *20*, 1–6.
5. Anjard, R. Mayan dental wonders. *J. Oral Implantol.* **1981**, *9*, 423–426. [PubMed]
6. Ali, F. History of dental implants, in memoriam: Dr. Per-Ingvar Branemark, the man who made people smile. *Int. J. Adv. Res. Ideas Innov. Technol.* **2019**, *5*, 123–124.
7. Crubézy, E.; Murail, P.; Girard, L.; Bernadou, J.-P. False teeth of the Roman world. *Nat. Cell Biol.* **1998**, *391*, 29. [CrossRef] [PubMed]

8. Barker, C.F.; Markmann, J.F. Historical Overview of Transplantation. *Cold Spring Harb. Perspect. Med.* **2013**, *3*, a014977. [CrossRef]
9. Biocompatibility Assessment Resource Center. FDA. Available online: https://www.fda.gov/medical-devices/premarket-submissions/biocompatibility-assessment-resource-center (accessed on 2 July 2021).
10. ISO 10993-1:2009 Biological Evaluation of Medical Devices—Part 1. Available online: https://www.iso.org/standard/44908.html (accessed on 29 September 2021).
11. Lee, K.C.; Eisig, S.B.; Perrino, M.A. Foreign Body Giant Cell Reaction to a Proplast/Teflon Interpositional Implant: A Case Report and Literature Review. *J. Oral Maxillofac. Surg.* **2018**, *76*, 1719–1724. [CrossRef] [PubMed]
12. Moizhess, T.G. Carcinogenesis induced by foreign bodies. *Biochemistry* **2008**, *73*, 763–775. [CrossRef]
13. Feldman, D. Polymer History. *Des. Monomers Polym.* **2008**, *11*, 1–15. [CrossRef]
14. Castro, J.C. Albert Einstein and his abdominal aortic aneurysm. *Gac. Med. Mex.* **2011**, *147*, 74–76.
15. LeVeen, H.H.; Rarberio, J.R. Tissue reaction to plastics used in surgery with special reference to teflon. *Ann. Surg.* **1949**, *129*, 74–84. [CrossRef]
16. Vallet-Regí, M. Ceramics for medical applications. *J. Chem. Soc. Dalton Trans.* **2001**, 97–108. [CrossRef]
17. Hench, L.L. Bioactive Ceramics. *Ann. N. Y. Acad. Sci.* **1988**, *523*, 54–71. [CrossRef] [PubMed]
18. Hench, L.L.; Jones, J.R. Bioactive Glasses: Frontiers and Challenges. *Front. Bioeng. Biotechnol.* **2015**, *3*, 194. [CrossRef] [PubMed]
19. Nordström, E.G.; Muñoz, O.L.S. Physics of bone bonding mechanism of different surface bioactive ceramic materials in vitro and in vivo. *Bio-Med. Mater. Eng.* **2001**, *11*, 221–231.
20. Baino, F.; Hamzehlou, S.; Kargozar, S. Bioactive Glasses: Where Are We and Where Are We Going? *J. Funct. Biomater.* **2018**, *9*, 25. [CrossRef]
21. Marin, E.; Boschetto, F.; Pezzotti, G. Biomaterials and biocompatibility: An historical overview. *J. Biomed. Mater. Res. Part A* **2020**, *108*, 1617–1633. [CrossRef] [PubMed]
22. Cohen, J. Biomaterials in orthopedic surgery. *Am. J. Surg.* **1967**, *114*, 31–41. [CrossRef]
23. Society for Biomaterials (SFB). Available online: https://biomaterials.org/ (accessed on 15 June 2021).
24. Park, J.B. Introduction. In *Biomaterials Science and Engineering*; Springer: Boston, MA, USA, 1984; ISBN 978-1-4612-9710-9.
25. Bergmann, C.P. Stumpf Aisha Biomaterials. In *Dental Ceramics*; Springer: Berlin, Germany, 2013; pp. 9–13; ISBN 978-3-642-38224-6.
26. Williams, D.F.; David, F. European Society for Biomaterials Definitions in biomaterials. In Proceedings of the Consensus Conference of the European Society for Biomaterials, Chester, UK, 3–5 March 1986; Elsevier: Amsterdam, The Netherlands; Chester, UK; Volume 4.
27. The European Society for Biomaterials 9th European Conference on Biomaterials Chester, UK 9–11th September, 1991 in conjunction with 2nd Consensus Conference on Definitions in Biomaterials 7–8th September, 1991 and IUPAC working party on blood compatibility. *J. Mater. Sci. Mater. Electron.* **1991**, *2*, 62. [CrossRef]
28. World Health Organization. Ageing and Health. Available online: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (accessed on 14 June 2021).
29. Yannas, I.V.; Burke, J.F. Design of an artificial skin. I. Basic design principles. *J. Biomed. Mater. Res.* **1980**, *14*, 65–81. [CrossRef]
30. Badylak, S.; Lantz, G.C.; Coffey, A.; Geddes, L.A. Small intestinal submucosa as a large diameter vascular graft in the dog. *J. Surg. Res.* **1989**, *47*, 74–80. [CrossRef]
31. Vacanti, C.A.; Vacanti, J.P. Functional Organ Replacement, The New Technology of Tissue Engineering. *Surg. Technol. Int.* **1991**, *1*, 43–49.
32. Langer, R.; Vacanti, J.P. Tissue Engineering. *Science* **1993**, *260*, 920–926. [CrossRef] [PubMed]
33. Skalak, R.; Fox, C.F. Tissue engineering. In Proceedings of the Workshop Held at Granlibakken, Lake Tahoe, CA, USA, 26–29 February 1988; Liss: New York, NY, USA, 1988.
34. Griffith, L.G.; Naughton, G. Tissue Engineering—Current Challenges and Expanding Opportunities. *Science* **2002**, *295*, 1009–1014. [CrossRef] [PubMed]
35. Kowalczewski, C.J.; Saul, J.M. Biomaterials for the Delivery of Growth Factors and Other Therapeutic Agents in Tissue Engineering Approaches to Bone Regeneration. *Front. Pharmacol.* **2018**, *9*, 513. [CrossRef] [PubMed]
36. Ren, X.; Zhao, M.; Lash, B.; Martino, M.M.; Julier, Z. Growth Factor Engineering Strategies for Regenerative Medicine Applications. *Front. Bioeng. Biotechnol.* **2020**, *7*. [CrossRef]
37. Chen, L.; Liu, J.; Guan, M.; Zhou, T.; Duan, X.; Xiang, Z. Growth Factor and Its Polymer Scaffold-Based Delivery System for Cartilage Tissue Engineering. *Int. J. Nanomed.* **2020**, *15*, 6097–6111. [CrossRef] [PubMed]
38. Palecek, S.P.; Loftus, J.C.; Ginsberg, M.H.; Lauffenburger, D.A.; Horwitz, A.F. Integrin-ligand binding properties govern cell migration speed through cell-substratum adhesiveness. *Nature* **1997**, *385*, 537–540. [CrossRef]
39. Korossis, S.; Bolland, F.; Kearney, J.N.; Fisher, J.; Ingham, E. Bioreactors in tissue engineering. *Top. Tissue Eng.* **2005**, *2*, 1–23.
40. Selden, C.; Fuller, B. Role of Bioreactor Technology in Tissue Engineering for Clinical Use and Therapeutic Target Design. *Bioengineering* **2018**, *5*, 32. [CrossRef]
41. Ahmed, S.; Chauhan, V.M.; Ghaemmaghami, A.M.; Aylott, J.W. New generation of bioreactors that advance extracellular matrix modelling and tissue engineering. *Biotechnol. Lett.* **2018**, *41*, 1–25. [CrossRef]
42. Todros, S.; Spadoni, S.; Maghin, E.; Piccoli, M.; Pavan, P. A Novel Bioreactor for the Mechanical Stimulation of Clinically Relevant Scaffolds for Muscle Tissue Engineering Purposes. *Processes* **2021**, *9*, 474. [CrossRef]
43. Hench, L.L. Bioceramics. *J. Am. Ceram. Soc.* **2005**, *81*, 1705–1728. [CrossRef]

44. Fernandes, J.S.; Gentile, P.; Pires, R.A.; Reis, R.L.; Hatton, P.V. Multifunctional bioactive glass and glass-ceramic biomaterials with antibacterial properties for repair and regeneration of bone tissue. *Acta Biomater.* **2017**, *59*, 2–11. [CrossRef]
45. Zhou, Y.; Wu, C.; Chang, J. Bioceramics to regulate stem cells and their microenvironment for tissue regeneration. *Mater. Today* **2018**, *24*, 41–56. [CrossRef]
46. Safari, B.; Aghanejad, A.; Roshangar, L.; Davaran, S. Osteogenic effects of the bioactive small molecules and minerals in the scaffold-based bone tissue engineering. *Colloids Surfaces B Biointerfaces* **2020**, *198*, 111462. [CrossRef]
47. Sethu, S.N.; Namashivayam, S.; Devendran, S.; Nagarajan, S.; Tsai, W.-B.; Narashiman, S.; Ramachandran, M.; Ambigapathi, M. Nanoceramics on osteoblast proliferation and differentiation in bone tissue engineering. *Int. J. Biol. Macromol.* **2017**, *98*, 67–74. [CrossRef]
48. Wang, M. Developing bioactive composite materials for tissue replacement. *Biomaterials* **2003**, *24*, 2133–2151. [CrossRef]
49. Liu, S.; Qin, S.; He, M.; Zhou, D.; Qin, Q.; Wang, H. Current applications of poly(lactic acid) composites in tissue engineering and drug delivery. *Compos. Part B Eng.* **2020**, *199*, 108238. [CrossRef]
50. Reddy, M.; Ponnamma, D.; Choudhary, R.; Sadasivuni, K. A Comparative Review of Natural and Synthetic Biopolymer Composite Scaffolds. *Polymers* **2021**, *13*, 1105. [CrossRef]
51. Place, E.S.; George, J.H.; Williams, C.K.; Stevens, M.M. Synthetic polymer scaffolds for tissue engineering. *Chem. Soc. Rev.* **2009**, *38*, 1139–1151. [CrossRef]
52. Salzano, E.; Di Serio, M.; Santacesaria, E. The evaluation of risks of ethoxylation reactors. *Process. Saf. Prog.* **2007**, *26*, 304–311. [CrossRef]
53. O'Brien, F.J. Biomaterials & scaffolds for tissue engineering. *Mater. Today* **2011**, *14*, 88–95. [CrossRef]
54. Nikolova, M.P.; Chavali, M.S. Recent advances in biomaterials for 3D scaffolds: A review. *Bioact. Mater.* **2019**, *4*, 271–292. [CrossRef] [PubMed]
55. Gomez-Florit, M.; Pardo, A.; Domingues, R.M.A.; Graça, A.L.; Babo, P.S.; Reis, R.L.; Gomes, M.E. Natural-Based Hydrogels for Tissue Engineering Applications. *Molecules* **2020**, *25*, 5858. [CrossRef]
56. El-Sherbiny, I.M.; Yacoub, M.H. Hydrogel scaffolds for tissue engineering: Progress and challenges. *Glob. Cardiol. Sci. Pr.* **2013**, *2013*, 316–342. [CrossRef] [PubMed]
57. Hoffman, A.S. Hydrogels for biomedical applications. *Adv. Drug Deliv. Rev.* **2001**, *54*, 3–12. [CrossRef]
58. Barbon, S.; Stocco, E.; Dalzoppo, D.; Todros, S.; Canale, A.; Boscolo-Berto, R.; Pavan, P.; Macchi, V.; Grandi, C.; De Caro, R.; et al. Halogen-Mediated Partial Oxidation of Polyvinyl Alcohol for Tissue Engineering Purposes. *Int. J. Mol. Sci.* **2020**, *21*, 801. [CrossRef]
59. Barbon, S.; Contran, M.; Stocco, E.; Todros, S.; Macchi, V.; Caro, R.; Porzionato, A. Enhanced Biomechanical Properties of Polyvinyl Alcohol-Based Hybrid Scaffolds for Cartilage Tissue Engineering. *Processes* **2021**, *9*, 730. [CrossRef]
60. Schmedlen, R.H.; Masters, K.S.; West, J.L. Photocrosslinkable polyvinyl alcohol hydrogels that can be modified with cell adhesion peptides for use in tissue engineering. *Biomaterials* **2002**, *23*, 4325–4332. [CrossRef]
61. Guadalupe, E.; Ramos, D.; Shelke, N.B.; James, R.; Gibney, C.; Kumbar, S.G. Bioactive polymeric nanofiber matrices for skin regeneration. *J. Appl. Polym. Sci.* **2015**, *132*. [CrossRef]
62. Rana, D.; Zreiqat, H.; Benkirane-Jessel, N.; Ramakrishna, S.; Ramalingam, M. Development of decellularized scaffolds for stem cell-driven tissue engineering. *J. Tissue Eng. Regen. Med.* **2015**, *11*, 942–965. [CrossRef] [PubMed]
63. Frantz, C.; Stewart, K.M.; Weaver, V.M. The extracellular matrix at a glance. *J. Cell Sci.* **2010**, *123*, 4195–4200. [CrossRef] [PubMed]
64. Crapo, P.M.; Gilbert, T.; Badylak, S.F. An overview of tissue and whole organ decellularization processes. *Biomaterials* **2011**, *32*, 3233–3243. [CrossRef] [PubMed]
65. Mendibil, U.; Ruiz-Hernandez, R.; Retegi-Carrion, S.; Garcia-Urquia, N.; Olalde-Graells, B.; Abarrategi, A. Tissue-Specific Decellularization Methods: Rationale and Strategies to Achieve Regenerative Compounds. *Int. J. Mol. Sci.* **2020**, *21*, 5447. [CrossRef]
66. Rabbani, M.; Zakian, N.; Alimoradi, N. Contribution of physical methods in decellularization of animal tissues. *J. Med. Signals Sens.* **2021**, *11*, 1–11. [CrossRef] [PubMed]
67. Keane, T.; Swinehart, I.T.; Badylak, S.F. Methods of tissue decellularization used for preparation of biologic scaffolds and in vivo relevance. *Methods* **2015**, *84*, 25–34. [CrossRef]
68. Fernández-Pérez, J.; Ahearne, M. The impact of decellularization methods on extracellular matrix derived hydrogels. *Sci. Rep.* **2019**, *9*, 1–12. [CrossRef] [PubMed]
69. White, L.; Taylor, A.; Faulk, D.M.; Keane, T.; Saldin, L.T.; Reing, J.; Swinehart, I.T.; Turner, N.; Ratner, B.D.; Badylak, S.F. The impact of detergents on the tissue decellularization process: A ToF-SIMS study. *Acta Biomater.* **2016**, *50*, 207–219. [CrossRef] [PubMed]
70. Zia, S.; Mozafari, M.; Natasha, G.; Tan, A.; Cui, Z.; Seifalian, A. Hearts beating through decellularized scaffolds: Whole-organ engineering for cardiac regeneration and transplantation. *Crit. Rev. Biotechnol.* **2015**, *36*, 705–715. [CrossRef]
71. Crabbe, A.; Liu, Y.; Sarker, S.F.; Bonenfant, N.R.; Barrila, J.; Borg, Z.D.; Lee, J.J.; Weiss, D.J.; Nickerson, C.A. Recellularization of Decellularized Lung Scaffolds Is Enhanced by Dynamic Suspension Culture. *PLoS ONE* **2015**, *10*, e0126846. [CrossRef]
72. Chen, F.; Yoo, J.J.; Atala, A. Acellular collagen matrix as a possible "off the shelf" biomaterial for urethral repair. *Urology* **1999**, *54*, 407–410. [CrossRef]

73. Rasti, H.; Saghiri, N.; Baharara, J.; Mahdavi-Shahri, N.; Marjani, M.; Alavi, S.H.; Hoseini, B. Differentiation of Blastema Cells in Decellularized Bladder Scaffold in vitro. *Zahedan J. Res. Med. Sci.* **2015**, *17*. [CrossRef]
74. Chia, H.N.; Wu, B.M. Recent advances in 3D printing of biomaterials. *J. Biol. Eng.* **2015**, *9*, 1–14. [CrossRef] [PubMed]
75. Bose, S.; Ke, D.; Sahasrabudhe, H.; Bandyopadhyay, A. Additive manufacturing of biomaterials. *Prog. Mater. Sci.* **2017**, *93*, 45–111. [CrossRef] [PubMed]
76. Touri, M.; Kabirian, F.; Saadati, M.; Ramakrishna, S.; Mozafari, M. Additive Manufacturing of Biomaterials—The Evolution of Rapid Prototyping. *Adv. Eng. Mater.* **2019**, *21*. [CrossRef]
77. Atala, A. Introduction: 3D Printing for Biomaterials. *Chem. Rev.* **2020**, *120*, 10545–10546. [CrossRef]
78. Shirazi, S.F.S.; Gharehkhani, S.; Mehrali, M.; Yarmand, H.; Metselaar, H.S.C.; Kadri, N.A.; ABU Osman, N.A. A review on powder-based additive manufacturing for tissue engineering: Selective laser sintering and inkjet 3D printing. *Sci. Technol. Adv. Mater.* **2015**, *16*, 033502. [CrossRef]
79. Murphy, S.V.; Atala, A. 3D bioprinting of tissues and organs. *Nat. Biotechnol.* **2014**, *32*, 773–785. [CrossRef]
80. Rawal, P.; Tripathi, D.M.; Ramakrishna, S.; Kaur, S. Prospects for 3D bioprinting of organoids. *Bio-Design Manuf.* **2021**, *4*, 627–640. [CrossRef]
81. Boso, D.; Carraro, E.; Maghin, E.; Todros, S.; Dedja, A.; Giomo, M.; Elvassore, N.; De Coppi, P.; Pavan, P.; Piccoli, M. Porcine Decellularized Diaphragm Hydrogel: A New Option for Skeletal Muscle Malformations. *Biomedicines* **2021**, *9*, 709. [CrossRef] [PubMed]
82. Elkhoury, K.; Morsink, M.; Sanchez-Gonzalez, L.; Kahn, C.; Tamayol, A.; Arab-Tehrany, E. Biofabrication of natural hydrogels for cardiac, neural, and bone Tissue engineering Applications. *Bioact. Mater.* **2021**, *6*, 3904–3923. [CrossRef] [PubMed]
83. Kowalski, P.S.; Bhattacharya, C.; Afewerki, S.; Langer, R.S. Smart Biomaterials: Recent Advances and Future Directions. *ACS Biomater. Sci. Eng.* **2018**, *4*, 3809–3817. [CrossRef]
84. Tibbitt, M.W.; Langer, R. Living Biomaterials. *Accounts Chem. Res.* **2017**, *50*, 508–513. [CrossRef]
85. Holzapfel, B.M.; Reichert, J.C.; Schantz, J.-T.; Gbureck, U.; Rackwitz, L.; Nöth, U.; Jakob, F.; Rudert, M.; Groll, J.; Hutmacher, D.W. How smart do biomaterials need to be? A translational science and clinical point of view. *Adv. Drug Deliv. Rev.* **2013**, *65*, 581–603. [CrossRef]
86. Mantha, S.; Pillai, S.; Khayambashi, P.; Upadhyay, A.; Zhang, Y.; Tao, O.; Pham, H.; Tran, S.D. Smart Hydrogels in Tissue Engineering and Regenerative Medicine. *Materials* **2019**, *12*, 3323. [CrossRef]
87. Kasiński, A.; Zielińska-Pisklak, M.; Oledzka, E.; Sobczak, M. Smart Hydrogels—Synthetic Stimuli-Responsive Antitumor Drug Release Systems. *Int. J. Nanomed.* **2020**, *15*, 4541–4572. [CrossRef] [PubMed]
88. Zhang, Y.; Huang, Y. Rational Design of Smart Hydrogels for Biomedical Applications. *Front. Chem.* **2021**, *8*. [CrossRef]
89. Parhi, R. Cross-Linked Hydrogel for Pharmaceutical Applications: A Review. *Adv. Pharm. Bull.* **2017**, *7*, 515–530. [CrossRef]
90. Zhao, X. Multi-scale multi-mechanism design of tough hydrogels: Building dissipation into stretchy networks. *Soft Matter* **2013**, *10*, 672–687. [CrossRef]
91. Buwalda, S.J.; Vermonden, T.; Hennink, W.E. Hydrogels for Therapeutic Delivery: Current Developments and Future Directions. *Biomacromolecules* **2017**, *18*, 316–330. [CrossRef]
92. Amukarimi, S.; Mozafari, M. 4D bioprinting of tissues and organs. *Bioprinting* **2021**, *23*, e00161. [CrossRef]
93. Ionov, L. 4D Biofabrication: Materials, Methods, and Applications. *Adv. Health Mater.* **2018**, *7*, e1800412. [CrossRef]
94. Yang, G.H.; Yeo, M.; Koo, Y.W.; Kim, G.H. 4D Bioprinting: Technological Advances in Biofabrication. *Macromol. Biosci.* **2019**, *19*, e1800441. [CrossRef]
95. Zheng, Y.; Liu, J.; Lu, X.; Li, Y. Shape Memory Biomaterials and Their Clinical Applications. In *Biomedical Materials*; Narayan, R., Ed.; Springer: Berlin, Germany, 2020; pp. 195–255; ISBN 978-3-030-49205-2.
96. Diba, M.; Spaans, S.; Ning, K.; Ippel, B.D.; Yang, F.; Loomans, B.; Dankers, P.Y.W.; Leeuwenburgh, S.C.G. Self-Healing Biomaterials: From Molecular Concepts to Clinical Applications. *Adv. Mater. Interfaces* **2018**, *5*. [CrossRef]
97. Mirfakhrai, T.; Madden, J.D.; Baughman, R.H. Polymer artificial muscles. *Mater. Today* **2007**, *10*, 30–38. [CrossRef]
98. Nemat-Nasser, S.; Thomas, C. Ionomeric polymer-metal composites. In *Electroactive Polymer (EAP) Actuators as Artificial Muscles: Reality, Potential and Challenges*; SPIE: Bellingham, WA, USA, 2001; pp. 171–230.
99. Li, J.; Xin, M.; Ma, Z.; Shi, Y.; Pan, L. Nanomaterials and their applications on bio-inspired wearable electronics. *Nanotechnology* **2021**, *32*, 472002. [CrossRef]
100. Brennan, M.; Layrolle, P.; Mooney, D.J. Biomaterials Functionalized with MSC Secreted Extracellular Vesicles and Soluble Factors for Tissue Regeneration. *Adv. Funct. Mater.* **2020**, *30*. [CrossRef]
101. Yuan, Q.; Zhang, Y.; Chen, Q. Mesenchymal Stem Cell (MSC)-Derived Extracellular Vesicles: Potential Therapeutics as MSC Trophic Mediators in Regenerative Medicine. *Anat. Rec. Adv. Integr. Anat. Evol. Biol.* **2019**, *303*, 1735–1742. [CrossRef]
102. Wang, C.; Wang, M.; Xu, T.; Zhang, X.; Lin, C.; Gao, W.; Xu, H.; Lei, B.; Mao, C. Engineering Bioactive Self-Healing Antibacterial Exosomes Hydrogel for Promoting Chronic Diabetic Wound Healing and Complete Skin Regeneration. *Theranostics* **2019**, *9*, 65–76. [CrossRef]
103. Mardpour, S.; Ghanian, M.H.; Sadeghi-Abandansari, H.; Mardpour, S.; Nazari, A.; Shekari, F.; Baharvand, H. Hydrogel-Mediated Sustained Systemic Delivery of Mesenchymal Stem Cell-Derived Extracellular Vesicles Improves Hepatic Regeneration in Chronic Liver Failure. *ACS Appl. Mater. Interfaces* **2019**, *11*, 37421–37433. [CrossRef]

104. Zhang, K.; Zhao, X.; Chen, X.; Wei, Y.; Du, W.; Wang, Y.; Liu, L.; Zhao, W.; Han, Z.; Kong, D.; et al. Enhanced Therapeutic Effects of Mesenchymal Stem Cell-Derived Exosomes with an Injectable Hydrogel for Hindlimb Ischemia Treatment. *ACS Appl. Mater. Interfaces* **2018**, *10*, 30081–30091. [CrossRef] [PubMed]
105. Merola, M.; Affatato, S. Materials for Hip Prostheses: A Review of Wear and Loading Considerations. *Materials* **2019**, *12*, 495. [CrossRef]
106. Aherwar, A.; Singh, A.K.; Patnaik, A. Current and future biocompatibility aspects of biomaterials for hip prosthesis. *AIMS Environ. Sci.* **2015**, *3*, 23–43. [CrossRef]
107. Knight, S.R.; Aujla, R.; Biswas, S.P. Total Hip Arthroplasty—over 100 years of operative history. *Orthop. Rev.* **2011**, *3*, e16. [CrossRef]
108. Muster, D. Themistocles Gluck, Berlin 1890: A pioneer of multidisciplinary applied research into biomaterials for endoprostheses. *Bull. Hist. Dent.* **1990**, *38*, 3–6.
109. Triclot, P. Metal-on-metal: History, state of the art (2010). *Int. Orthop.* **2011**, *35*, 201–206. [CrossRef]
110. Moussa, A.A.; Fischer, J.; Yadav, R.; Khandaker, M. Minimizing Stress Shielding and Cement Damage in Cemented Femoral Component of a Hip Prosthesis through Computational Design Optimization. *Adv. Orthop.* **2017**, *2017*, 1–12. [CrossRef]
111. Reimeringer, M.; Nuño, N.; Desmarais-Trépanier, C.; Lavigne, M.; Vendittoli, P.-A. The influence of uncemented femoral stem length and design on its primary stability: A finite element analysis. *Comput. Methods Biomech. Biomed. Eng.* **2013**, *16*, 1221–1231. [CrossRef]
112. Kim, Y.-H.; Kim, J.-S.; Cho, S.-H. Strain distribution in the proximal human femur. An in vitro comparison in the intact femur and after insertion of reference and experimental femoral stems. *J. Bone Jt. Surgery. Br. Vol.* **2001**, *83*, 295–301. [CrossRef]
113. Rezaei, F.; Hassani, K.; Solhjoei, N.; Karimi, A. Carbon/PEEK composite materials as an alternative for stainless steel/titanium hip prosthesis: A finite element study. *Australas. Phys. Eng. Sci. Med.* **2015**, *38*, 569–580. [CrossRef] [PubMed]
114. Avval, P.T.; Samiezadeh, S.; Klika, V.; Bougherara, H. Investigating stress shielding spanned by biomimetic polymer-composite vs. metallic hip stem: A computational study using mechano-biochemical model. *J. Mech. Behav. Biomed. Mater.* **2015**, *41*, 56–67. [CrossRef] [PubMed]
115. Sasso, E.D.; Bagno, A.; Scuri, S.T.; Gerosa, G.; Iop, L. The Biocompatibility Challenges in the Total Artificial Heart Evolution. *Annu. Rev. Biomed. Eng.* **2019**, *21*, 85–110. [CrossRef] [PubMed]
116. Gerosa, G.; Scuri, S.; Iop, L.; Torregrossa, G. Present and future perspectives on total artificial hearts. *Ann. Cardiothorac. Surg.* **2014**, *3*, 595–602. [CrossRef] [PubMed]
117. Cooley, D.A. The total artificial heart. *Nat. Med.* **2003**, *9*, 108–111. [CrossRef] [PubMed]
118. Lindbergh, C.A. An apparatus for the culture of whole organs. *J. Exp. Med.* **1935**, *62*, 409–431. [CrossRef]
119. Akutsu, T. Components of artificial hearts. *Bull. N. Y. Acad. Med.* **1972**, *48*, 362–378.
120. Kolff, W. The Invention of the Artificial Heart. *Int. J. Artif. Organs* **1990**, *13*, 396–403. [CrossRef]
121. Cooley, D.A.; Liotta, D.; Hallman, G.L.; Bloodwell, R.D.; Leachman, R.D.; Milam, J.D. Orthotopic cardiac prosthesis for two-staged cardiac replacement. *Am. J. Cardiol.* **1969**, *24*, 723–730. [CrossRef]
122. Cook, J.A.; Shah, K.B.; Quader, M.A.; Cooke, R.H.; Kasirajan, V.; Rao, K.K.; Smallfield, M.C.; Tchoukina, I.; Tang, D.G. The total artificial heart. *J. Thorac. Dis.* **2015**, *7*, 2172.
123. Han, J.J. Aeson—The Carmat total artificial heart is approved for enrollment in the United States. *Artif. Organs* **2021**, *45*, 445–446. [CrossRef]
124. Copeland, J.G.; Smith, R.G.; Arabia, F.A.; Nolan, P.E.; Sethi, G.K.; Tsau, P.H.; McClellan, D.; Slepian, M.J. Cardiac Replacement with a Total Artificial Heart as a Bridge to Transplantation. *N. Engl. J. Med.* **2004**, *351*, 859–867. [CrossRef]
125. Mohacsi, P.; Leprince, P. The CARMAT total artificial heart. *Eur. J. Cardio-Thoracic Surg.* **2014**, *46*, 933–934. [CrossRef]
126. Jansen, P.; Van Oeveren, W.; Capel, A.; Carpentier, A. In vitro haemocompatibility of a novel bioprosthetic total artificial heart. *Eur. J. Cardio-Thoracic Surg.* **2012**, *41*, e166–e172. [CrossRef]
127. Gross, J.M. Calcification of bioprosthetic heart valves and its assessment. *J. Thorac. Cardiovasc. Surg.* **2001**, *121*, 428–430. [CrossRef]
128. Zouhair, S.; Sasso, E.D.; Tuladhar, S.R.; Fidalgo, C.; Vedovelli, L.; Filippi, A.; Borile, G.; Bagno, A.; Marchesan, M.; De Rossi, G.; et al. A Comprehensive Comparison of Bovine and Porcine Decellularized Pericardia: New Insights for Surgical Applications. *Biomolecules* **2020**, *10*, 371. [CrossRef]
129. Jana, S. Endothelialization of cardiovascular devices. *Acta Biomater.* **2019**, *99*, 53–71. [CrossRef]
130. Todesco, M.; Zardin, C.; Iop, L.; Palmosi, T.; Capaldo, P.; Romanato, F.; Gerosa, G.; Bagno, A. Hybrid membranes for the production of blood contacting surfaces: Physicochemical, structural and biomechanical characterization. *Biomater. Res.* **2021**, *25*, 1–12. [CrossRef]
131. Todesco, M.; Pontara, E.; Cheng, C.; Gerosa, G.; Pengo, V.; Bagno, A. Preliminary hemocompatibility assessment of an innovative material for blood contacting surfaces. *J. Mater. Sci. Mater. Med.* **2021**, *32*, 1–7. [CrossRef]
132. Ratner, B.D. Biomaterials: Been There, Done That, and Evolving into the Future. *Annu. Rev. Biomed. Eng.* **2019**, *21*, 171–191. [CrossRef]
133. Sharp, P.A.; Langer, R. Promoting Convergence in Biomedical Science. *Science* **2011**, *333*, 527. [CrossRef]
134. Davenport, T.; Kalakota, R. The potential for artificial intelligence in healthcare. *Futur. Health J.* **2019**, *6*, 94–98. [CrossRef] [PubMed]

135. Macchiarini, P.; Jungebluth, P.; Go, T.; Asnaghi, M.A.; Rees, L.E.; Cogan, T.A.; Dodson, A.; Martorell, J.; Bellini, S.; Parnigotto, P.P.; et al. Clinical transplantation of a tissue-engineered airway. *Lancet* **2008**, *372*, 2023–2030. [CrossRef]
136. Delaere, P.R.; Van Raemdonck, D. The trachea: The first tissue-engineered organ? *J. Thorac. Cardiovasc. Surg.* **2014**, *147*, 1128–1132. [CrossRef]
137. Taylor, D.A.; Parikh, R.B.; Sampaio, L.C. Bioengineering Hearts: Simple yet Complex. *Curr. Stem Cell Rep.* **2017**, *3*, 35–44. [CrossRef] [PubMed]
138. Fioretta, E.S.; Motta, S.E.; Lintas, V.; Loerakker, S.; Parker, K.K.; Baaijens, F.P.T.; Falk, V.; Hoerstrup, S.P.; Emmert, M.Y. Next-generation tissue-engineered heart valves with repair, remodelling and regeneration capacity. *Nat. Rev. Cardiol.* **2020**, *18*, 92–116. [CrossRef]
139. Mirdamadi, E.S.; Kalhori, D.; Zakeri, N.; Azarpira, N.; Solati-Hashjin, M. Liver Tissue Engineering as an Emerging Alternative for Liver Disease Treatment. *Tissue Eng. Part B Rev.* **2020**, *26*, 145–163. [CrossRef] [PubMed]
140. Katari, R.; Edgar, L.; Wong, T.; Boey, A.; Mancone, S.; Igel, D.; Callese, T.; Voigt, M.; Tamburrini, R.; Zambon, J.P.; et al. Tissue-Engineering Approaches to Restore Kidney Function. *Curr. Diabetes Rep.* **2015**, *15*. [CrossRef] [PubMed]
141. Tebyanian, H.; Karami, A.; Nourani, M.R.; Motavallian, E.; Barkhordari, A.; Yazdanian, M.; Seifalian, A. Lung tissue engineering: An update. *J. Cell. Physiol.* **2019**, *234*, 19256–19270. [CrossRef] [PubMed]
142. Horst, M.; Eberli, D.; Gobet, R.; Salemi, S. Tissue Engineering in Pediatric Bladder Reconstruction—The Road to Success. *Front. Pediatr.* **2019**, *7*, 91. [CrossRef]
143. Petite, H.; Viateau, V.; Bensaïd, W.; Meunier, A.; De Pollak, C.; Bourguignon, M.; Oudina, K.; Sedel, L.; Guillemin, G. Tissue-engineered bone regeneration. *Nat. Biotechnol.* **2000**, *18*, 959–963. [CrossRef]
144. Sierra-Sánchez, A.; Kim, K.H.; Blasco-Morente, G.; Arias-Santiago, S. Cellular human tissue-engineered skin substitutes investigated for deep and difficult to heal injuries. *NPJ Regen. Med.* **2021**, *6*, 1–23. [CrossRef]
145. Keeney, M.; Lai, J.H.; Yang, F. Recent progress in cartilage tissue engineering. *Curr. Opin. Biotechnol.* **2011**, *22*, 734–740. [CrossRef]
146. Law, J.X.; Liau, L.L.; Aminuddin, B.S.; Ruszymah, B.H.I. Tissue-engineered trachea: A review. *Int. J. Pediatr. Otorhinolaryngol.* **2016**, *91*, 55–63. [CrossRef]
147. Tibbitt, M.W.; Rodell, C.B.; Burdick, J.A.; Anseth, K.S. Progress in material design for biomedical applications. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 14444–14451. [CrossRef] [PubMed]
148. Hosoyama, K.; Lazurko, C.; Muñoz, M.; McTiernan, C.D.; Alarcon, E.I. Peptide-Based Functional Biomaterials for Soft-Tissue Repair. *Front. Bioeng. Biotechnol.* **2019**, *7*, 205. [CrossRef]
149. Aguado, B.A.; Grim, J.C.; Rosales, A.M.; Watson-Capps, J.J.; Anseth, K.S. Engineering precision biomaterials for personalized medicine. *Sci. Transl. Med.* **2018**, *10*. [CrossRef]