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Overview and general ideas of the development of constructions, materials, technologies and clinical applications of scaffolds engineering for regenerative medicine

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ABSTRACT

Purpose: of this paper is the general presentation of the synergic utilisation of medical knowledge, tissue engineering and materials engineering for fabrication of functional substitutes of damaged tissues in the case of which medical indications show that classical prosthetics/implantation cannot be completely avoided, and that it is also appropriate to achieve natural ingrowth of the implanted elements into a living tissue in the implant area.

Design/methodology/approach: This refers to post-injury losses, post-resection losses, as well as those originating from operative treatment of cancerous tumours or inflammation processes. Implantable biomedical devices are currently aggregately considered to be medical bionic implants where bionics is understood as production and investigation of biological systems to prepare and implement artificial engineering systems which can restore the lost functions of biological systems.

Findings: The development of new hybrid technologies of bioactive and engineering materials for personalised scaffolds of tissues and bones requires a number of basic research and application work. They are presented numerous examples of the needs of the research for application of various bioactive and engineering materials, and their respective materials processing and tissue engineering technologies for manufacturing of the hybrid personalised implants and scaffolds.

Research limitations/implications: There are no reports in the references about an original concept presented by the Author of introduction of prosthetics/implantation and tissue engineering techniques for the purpose of natural ingrowth of the implanted elements into a living tissue in the implant area without having to use mechanical devices, at least in the connection (interface) zone of bone or organ stumps with prosthetic/implant elements.

Practical implications: They are open up vast possibilities for the application of the hybrid technologies of bioactive and engineering materials for personalized scaffolds of tissues and bones in accordance with the concept of the Author, presented in this paper.

Medical bionic implants encompass numerous solutions eliminating various disfunctions of a human organism, among other implants of the cardiovascular system (stents, vessel prostheses, heart valves, pacemakers, defibrillators), digestive system implants, neuron devices (implants and neuronal prostheses to the central (CNS) and peripheral nervous system (PNS), the cochlea, retina), orthopaedic prostheses (bone grafts, bone plates, fins and other connecting and stabilising devices, including screws applied in the area of ankles, knees and hands, bars and pins for stabilising fractured limbs), screws and plates in skull-jaw-face reconstructions, dental implants, and also scaffolds of bones and tissues in tissue engineering.

Originality/value: The Author's idea for the embracing hybrid technologies of bioactive and engineering materials with titanium alloys including personalised scaffolds of tissues and bones will be created. It is also a challenge to achieve a synergy of clinical effects obtained with classical prosthetics/implantation of large lost post-injury or post-resection recesses together with the use of achievements in advanced tissue engineering methods at least in the interface zone of bone or organ stumps with prosthetic elements/implants.

Keywords: Regenerative medicine; Scaffolds engineering; Tissue engineering; Prosthetics; Implantation; Medical bionic implants; Interface zone

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GENERAL REVIEW

1. Introduction

The dynamic growth of cases of organ or tissue loss or damage in the human population due to post-injury losses, post-resection losses, as well as those originating from operative treatment of cancerous tumours or inflammation processes and as a result of other disorders and the related necessity to replace or supplement such organs or tissues aimed at the **prevention of biological and social degradation of patients and restoration of their living functions**, either normal functions or such acceptably similar to normal, constitutes a significant and costly problem of modern medicine. It is hard to overestimate, nowadays, the achievements of modern implantology, where courage, imagination and knowledge of doctors supported by accomplishments of engineers have, on a global scale, given many people an opportunity to return to their normal or quasi-normal conditions of functioning, and very often to have their health restored after experiencing severe injuries or losses, and also other disorders. One of the challenges for regenerative medicine is to reconstruct sections of bone losses in maxillo-facial surgery, restorative dentistry, laryngology, including otolaryngology, orthopaedics and traumatology, and to supplement soft tissues, e.g. in case of oesophagus and blood vessels prosthetics/implantation, where in particular bone or organ stumps are not in contact. This refers to post-injury losses, post-resection losses, as well as those originating from operative treatment of cancerous tumours or inflammation processes. Implantable biomedical devices are currently aggregately considered to be **medical bionic implants** where bionics is understood as production and investigation of biological systems to prepare and implement artificial engineering systems which can restore the lost functions of biological systems [1]. In general, medical bionic implants encompass numerous solutions eliminating various dysfunctions of a human organism, among other implants of the cardiovascular system (stents, vessel prostheses, heart valves, pacemakers, defibrillators), digestive system implants, neuron devices (implants and neuronal prostheses to the central (CNS) and peripheral nervous system (PNS), the cochlea, retina), orthopaedic prostheses (bone grafts, bone plates, fins and other connecting and stabilising devices, including screws applied in the area of ankles, knees and hands, bars and pins for stabilising fractured limbs), screws and plates in skull-jaw-face reconstructions, dental implants, and also scaffolds of bones and tissues in tissue engineering [1].

It is expected that the development rate of each of the existing **global medical products market** segments will differ depending on multiple objective factors. On one hand, it is associated with civilisational progress, longer life expectancy, many societies becoming richer, including definitely the Polish society. The global biomaterials market was valued at USD 25,277.8 million in 2012

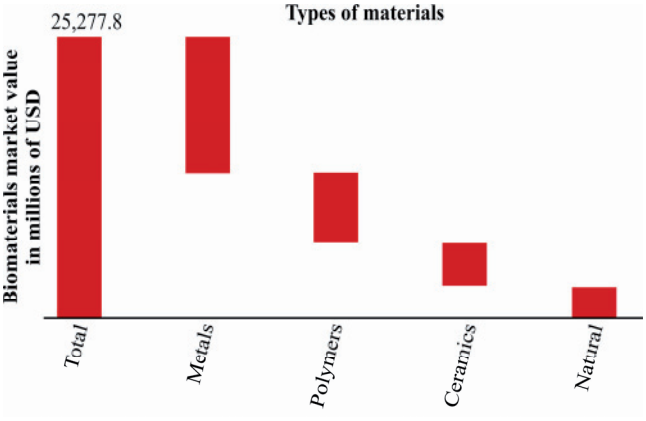

Fig. 1. The global biomaterials market value in 2012; according to data from [2]

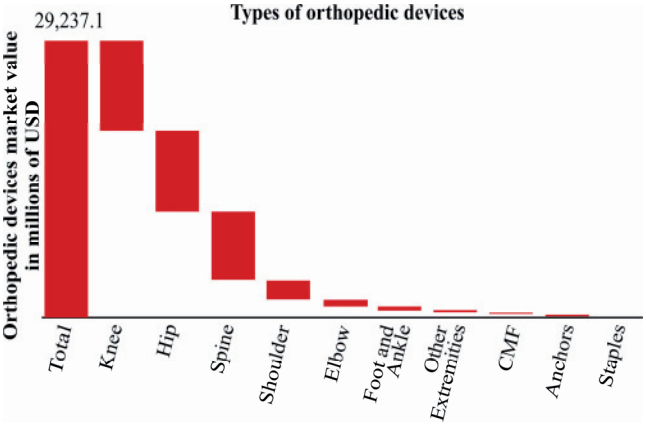

Fig. 2. The global orthopaedic devices market value in 2012; according to data from [3]

(Fig. 1) [2]. On the figure is presented the division of the biomaterials for the main group of materials. The global orthopaedic devices market was valued at USD 29.2 billion in 2012 (Fig. 2) [3]. Orthopaedic devices are used to restore skeletal structure and joint movements in various types of fractures, abnormal growth of bones, soft tissue damage, trauma or other deformities. The statistics of the Central Statistical Office (GUS) show that healthcare expenditures in Poland are constantly on the rise in billions of PLN (Fig. 3) (lines on the figure above show expenses for: current expenses, related investments – no-investment and investment expenses). The radar chart (Fig. 4) [4] shows that public spendings, as a share in overall healthcare spendings, in Poland in 2011 are merely about 15% lower than in the top ranking OECD countries. It should nevertheless be admitted that challenges in Poland in this context are very serious considering huge civilisational backwardness in this field. The OECD's analyses presented in the same paper show that overall healthcare expenditures, by purchasing power per capita in thousands of USD in OECD countries in 2011 (Fig. 5), rank Poland on one of the last positions among such countries. On the other hand, the development rate of segments of the medical products market is linked to sharp development of civilisational diseases, including cancer. The **incidence rate of malignant cancers in Poland has been regularly rising** from 124,407 in 2005 to 138,227 in 2010 [5]. The number of traffic accidents' victims has been growing systematically, as well. The European Commission informs in its Press Announcement of 19 March 2013 that, according to the Eurostat's data for 2011, Poland has a worryingly unfortunate first position in the European Union with 109 fatalities per million inhabitants, while the same figure for the Great Britain is lowest in the European Union of 31, and average decline in this indicator in Latvia and Estonia is 10%, is 543, which is the highest for the European Union, whilst in, e.g. Estonia, Finland and the Netherlands is below 20. Followed by this, almost proportionally, the number of people injured in such accidents and requiring usually **long-lasting medical care grows**. Along with the intensification sports activity, especially among young people, and with promotion of leisure practise of sports by propagating healthy lifestyle, more and more mature people start to practise sports, which is inherent to the **growing number of sports accidents** and the related serious bodily injuries of many people on a global scale. Globally, rise in aging

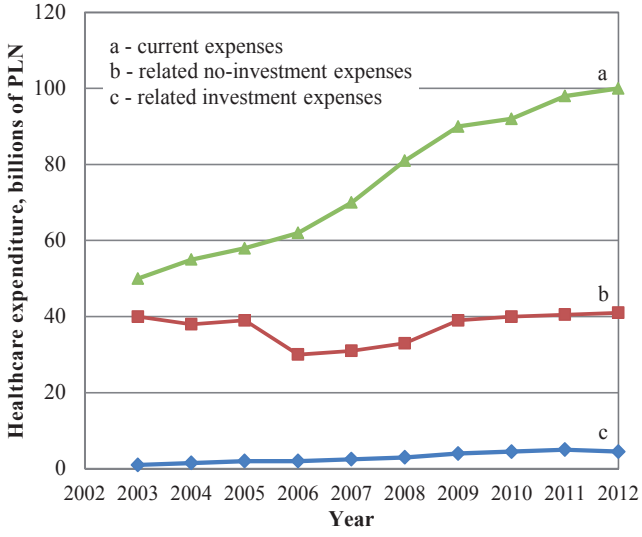

Fig. 3. The changes of the healthcare expenditures in Poland; according to data from [4]

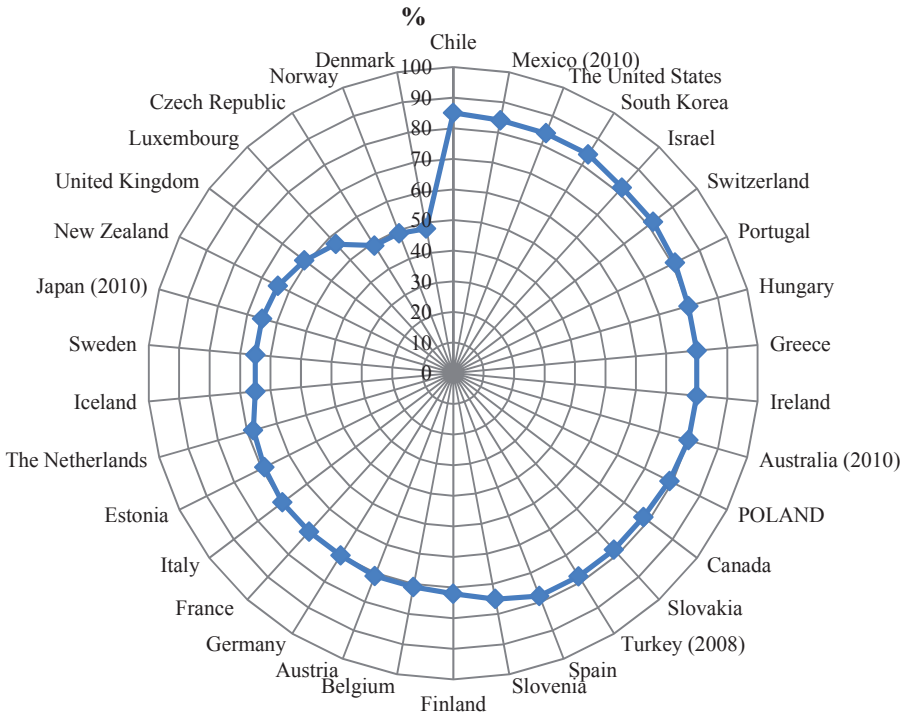

Fig. 4. The public spendings, as a share in overall healthcare spendings in 2011 in OECD countries; according to data from [4]

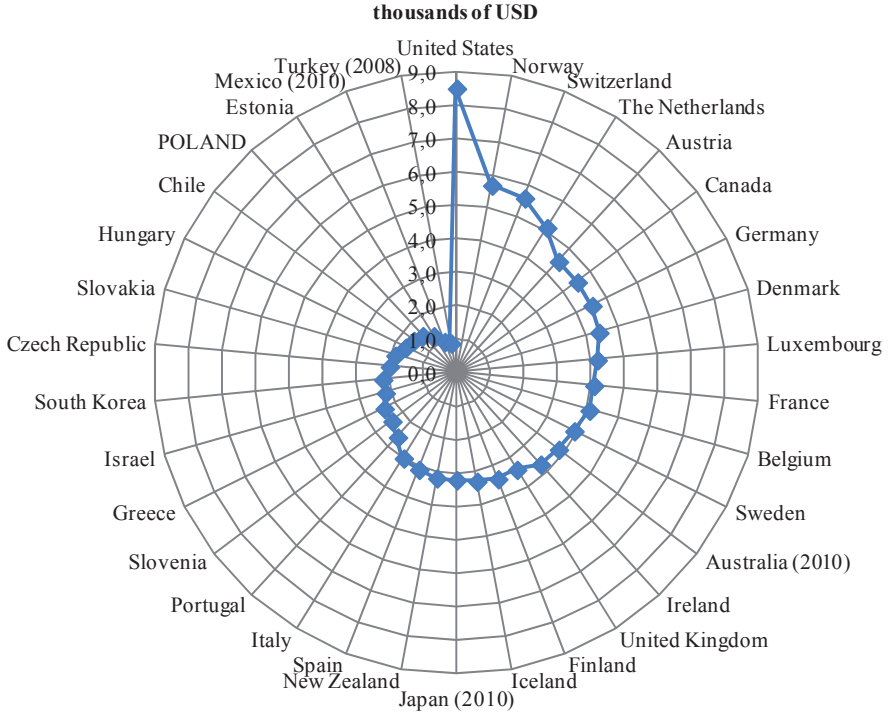

Fig. 5. The overall healthcare expenditures, by purchasing power per capita in 2011 in OECD countries; according to data from [4]

population plays a major role in increasing the incidence of sports injuries as aging diminishes body whilst it goes up by 4% on average annually in Poland. Analogously, the number of fatalities in railway accidents functions and movements which makes the body more prone to injuries. For instance, according to the European Injury Database (EU IDB) catalogue, annually on an average 6.1 million people in the European Union are treated in hospitals for sports injuries. Patients' healthcare expectations are also growing, and economic aspects at the domestic scale call for efficient elimination of disabilities, in particular motoric disabilities and restoring previously handicapped persons to physical fitness and usually most often to full or at least partial professional activity, which considerably lessens pressure on the diminishing social insurance funds.

In the paper the state-of-the-art of the **constructions, materials, technologies, applications and clinical experiences of the scaffolds engineering for regenerative medicine** is presented. Furthermore the Author's idea of the synergy of classical prosthetics/implantation of bone and organ post-injury or post-resection losses together with the methods of tissue engineering in the connection (interface) zone of bone or organ stumps with prosthetic elements/ implants, call for the use of porous and high-strength non-graded metal and/or composite and/or polymer materials (which is strongly, but not exclusively, dependent on the specificity of the clinical application) together with using at the same time biodegradable materials for tissue scaffolds is presented. Numerous actions are undertaken in general by the Author in his own research,

which most generally requires a differentiated methodological approach, materials and technologies used and clinical application methods, concerning the filling of bone losses, joint cartilage cells, oesophagus and/or blood vessels, dental and skin restorations. The lack of procedures for solving synergistically the above issues in the case it is not possible to apply exclusively tissue engineering methods, for instance due to extensive bone or tissue losses, but also for other reasons, substantiates the appropriateness of addressing the challenges outlined by the Author. The aforementioned concept of the synergic use, for this purpose, of the existing achievements in surgery and regenerative medicine in scope of prosthetics/implantation in treatment of the above-mentioned civilisational diseases and their effects, production engineering and materials engineering in scope of design and manufacture of prostheses/implants with different engineering materials and tissue engineering in scope of selection of materials and scaffold fabrication technologies, has been outlined in the earlier own works and projects of the Authors and another Polish researchers [6-21]. At the same time, accomplishments and clinical experiences of distinguished surgeons confirm the necessity to address the said research and implementation path due to urgent needs experienced immediately at the operating table [22-27], and the accomplishments of the tissue bank workers confirm, on the other hand, it is possible to use their own achievements in the field of tissue engineering for this idea [28-31], and that it is also possible to use different highly-specialised technologies, considering the outcomes of the theoretical Author's own works and another Polish researchers attained in this field to date [10, 11, 32-48].

The objective of the paper is the general presentation of the synergic utilisation of medical knowledge, tissue engineering and materials engineering for fabrication of functional substitutes of damaged tissues in the case of which medical indications show that classical prosthetics/implantation cannot be completely avoided, and that it is also appropriate to achieve natural ingrowth of the implanted elements into a living tissue in the implant area. For this reason, Author's idea for the embracing **hybrid technologies of bioactive and engineering materials with titanium alloys including personalised scaffolds of tissues and bones** will be created. It is also a challenge to achieve a synergy of clinical effects obtained with classical prosthetics/implantation of large lost post-injury or post-resection recesses together with the use of achievements in advanced tissue engineering methods at least in the interface zone of bone or organ stumps with prosthetic elements/implants.

2. Description of the state of research of the materials and technologies applied in the scaffolds engineering for regenerative medicine

The dynamic growth of cases of organ or tissue loss or damage in the human population due to post-injury losses, post-resection losses, as well as those originating from operative treatment of cancerous tumours or inflammation processes and as a result of other disorders and the related necessity to replace or supplement such organs or tissues aimed at the prevention of biological and social degradation of patients and restoration of their living functions, either normal functions or such acceptably similar to normal, constitutes a significant and costly problem of modern medicine. It is hard to overestimate, nowadays, the achievements of modern implantology, where courage, imagination and knowledge of doctors supported by accomplishments of engineers have, on a global scale, given many people an opportunity to return to their normal or quasi-normal conditions of functioning, and very often to have their health restored after experiencing severe injuries or losses, and also other disorders. One of the challenges for regenerative medicine is to reconstruct sections of bone losses in maxillo-facial surgery, restorative dentistry, laryngology, including otolaryngology, orthopaedics and traumatology, and to supplement soft tissues, e.g. in case of esophagus and blood vessels prosthetics/implantation, where in particular bone or organ stumps are not in contact. This refers to post-injury losses, post-resection losses, as well as those originating from operative treatment of cancerous tumours or inflammation processes. Implantable biomedical devices are currently aggregately considered to be medical bionic implants where bionics is understood as production and investigation of biological systems to prepare and implement artificial engineering systems which can restore the lost functions of biological systems [1]. In general, **medical bionic implants** encompass numerous solutions eliminating various disfunctions of a human organism, among other implants of the cardiovascular system (stents, vessel prostheses, heart valves, pacemakers, defibrillators), digestive system implants, neuron devices (implants and neuronal prostheses to the central (CNS) and peripheral nervous system (PNS), the cochlea, retina), orthopaedic prostheses (bone grafts, bone plates, fins and other connecting and stabilising devices, including screws applied in the area of ankles, knees and hands, bars and pins for stabilising fractured limbs), screws

and plates in skull-jaw-face reconstructions, dental implants, and also scaffolds of bones and tissues in tissue engineering [1].

Diagnostic methods of medical imaging, including Advanced Computed Tomography (ACT) including X-ray tomography, CAT Computerized Axial Tomography, HRCT High Resolution Computed Tomography, MSCT Multi-Slice Computed Tomography or MDCT Multi-row-Detector Computed Tomography, and also PET Positron Emission Tomography and MRI Magnetic Resonance Imaging [49], modelling and design methods of Computer Aided Design/Manufacturing CAD/CAM [50] and Rapid Manufacturing (RM) and Rapid Prototyping (RP) methods could be employed to accomplish the assumptions of this idea to enable the connection (interface) of bone or organ stumps with prosthetic elements/implants for their synergic manufacturing [51-53]. The solutions proposed by the Author strive to achieve **bioactive connections**, as most advantageous in terms of bond strength, which are formed between bone tissue and implants/scaffolds made or coated with bioactive materials, considerably improving the stability and durability of connection, especially for porous scaffolds/implants. Another acceptable approach is a very durable biological connection characteristic for porous implants/scaffolds whereby the bone tissue grows through the material pores and is mechanically "anchored" in the bone. **Porous resorbable bioglass** may be used for scaffold fabrication [47, 54], e.g. from the CaO-SiO_2-P_2O_5 system, Hench bioglass [55], produced both, with classical melting methods and with sol-gel methods, and also bioglass from the SiO_2-Al_2O_3 system endowed with silver [56], due to their biocompatibility [57] and bacteriocidity [58], and with pore walls coated with hydroxy carbonate apatite (HCA) [48], ensuring enhanced activity of osteoblasts [59] and expression of genes connected with bones [60]. The formation methods of **porous structures from ceramic materials**, in particular such as aluminium oxide, zirconium oxide, calcium carbonate, hydroxyapatite (HA), titanium oxide, include casting of sections from mass containing a fine-grained ceramic material with additives facilitating foaming and then material sintering, and also the use of other methods, e.g. an organic matrix and lyophilisation of ceramic slip [47]. The basic bioactive ceramic materials used for scaffolds is calcium phosphate (CaPs), as the main component of bone, and in hydroxyapatite (HA), β-tricalcium phosphate (β-TCP) or a mixture of HA and β-TCP, known as biphasic calcium phosphate [61-63]. A classical solution in the domain of ceramics, are porous scaffolds/corundum implants completely biocompatible, growing through the fully viable bone tissue, possessing mechanical strength sufficient for many types of clinical procedures and ensuring freedom of manipulation during a surgical procedure, and after growing through, have an appropriate modulus of elasticity, which ensures their good interworking with the bone and also allow for sterilisation with any method. Both, **bioactive and biodegradable polymers** can be employed [64, 65], including in particular natural polymers such as: collagen, fibrin, alginate, silk, hyaluronic acid and chitosan used, e.g. for bone reconstruction [66], as well as synthetic ones, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and polycaprolactone (PCL) and poly(propylene fumarate) (PPF) with high compressive strength, comparable to this of a cortical layer of bone [65], and some of them, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA) may cause negative tissue reactions [67]. **Composite materials** satisfy mechanical and physiological requirements, e.g. CaP-polymer scaffolds, interconnected tricalcium phosphate (TCP) scaffolds coated inside pores with polycaprolactone (PCL) [68], hydroxyapatite HA/poly(ester-urethane) (PU) [69] or a nanocomposite of collagen and Bioglass [70]. **Porous metal materials**, though not biodegradable, are used for scaffolds, mainly Ti and Ta [71], also after treatment of pores' surface [72] and biodegradable Mg and its alloys [73, 74, 75], including Mg-Ca alloys [76], and have found their application primarily due to relatively high compressive strength and fatigue strength [65, 77]. An innovative approach consists of introducing pure Mg with interconnected porosity onto bearing plates, bolts and networks made by rapid pressure assisted densification methods, such as rapid hot pressing/Spark Plasma Sintering (SPS) [78]. Pure Mg represents an optimum solution due to its biocompatibility, and the manufacturing technology also ensures good mechanical strength and recovery of the bone. In order to reduce the rate of in-vivo corrosion and prevent necrosis and the blocking of blood flow, Mg with Ca, Zn and Mn alloys can be used, well tolerated by a human organism [79, 80], and also coatings adapted to bioresorbable implants [81-84]. In consideration of biocompatibility, reinforcements in magnesium MMCs include usually, notably, HA [85-90], FA [91], calcium polyphosphate [92], and calcium [91]. Third-generation scaffolds not only allow to create a new bone and allow biomineralisation, but are also osteoinductive, and made of CaP, Si-TCP/HA [93], collagen hydrogel [94]. Substitute scaffolds of bones are often administered with medicines, including gentamycin, vancomycin, alendronate, methotrexate and ibuprofen

[95, 96] and with growth factors and transcription factors [64, 97, 98].

The treatment strategy developed these days are **tissue engineering** methods, respectively, scaffold-based vascularised bone tissue engineering (SBV BTE), Vascular Tissue Engineering (VTE) or scaffold-based tissue engineering (SBTE). Promising results are achieved by the application of tissue scaffolds in combination with autologous bone marrow stem cells and growth factors (mainly BMP-2). Tissue engineering, experiencing rapid growth since the mid-90's of the last century, as a field of technical sciences using medical knowledge and materials engineering methods, has been involved in construction and fabrication of scaffolds maintaining the developing tissues, in manipulation of somatic and stem cells, in influencing the tissues growth conditions and their structure and in maintaining the physiochemical conditions of the environment supporting this growth, in order to produce functional substitutes of damaged tissues and entire organs [99, 100]. Tissue engineering provides technical support for **regenerative medicine**, enabling utilizasation the achievements of life sciences and modern technologies to develop biological materials capable of restoring, maintaining or improving the functions of particular tissues or organs [101]. The concept of "tissue engineering" was introduced in 1985 by Y.C. Fung [102]. The current methods of organ and tissue replacement employ primarily autographs, allografts or metal devices or such made of other engineering materials [103]. Methods are commonly applied in tissue engineering in which three-dimensional engineering constructions permit ex vivo tissue transplantation, injection or implantation for the initiation of stem cells regeneration. Opposite to pure therapies in which stem cells are injected directly into peripheral circulation or located in particular tissues, in numerous clinical cases it is necessary to use stem cells carriers for their transport and scaffolds for three-dimensional grouping in a particular place of an organism. Research into the use of stem cells in this context has constantly evolved and has considerably intensified in the last decade [103-113]. Obviously, the efficiency of cell-based therapies depends on the preservation of their viability after implantation [114, 115], and this problem is still relevant. One of the main challengers in scaffold transplantation based on cells is the lack of implantation and the related shortage of mass transport of oxygen and nutrients required for the correct functioning and survival of cells in a damaged avascular tissue [116-120], which may lead to ischaemia of tissues and necrosis [121]. The use of scaffolds usually leads to positive results because, as substitutes of an extracellular matrix (ECM), they ensure structural stability for development of tissues and provide an environment of appropriate signals which stimulate cells for proliferation and differentiation as the functional tissue is becoming mature. Scaffolds, apart from ensuring three-dimensional geometrical characteristics, must exhibit adequate mechanical properties, enable adhesion of cells and facilitate their development in order to form a three-dimensional tissue structure in conditions simulating a natural micro-environment [103, 122]. It is a task of **tissue and bone scaffolds** to ensure mechanical preservation of living tissues in a three-dimensional structure and ensure an appropriate environment of development for them. Bone scaffolds are usually made of porous biodegradable material, ensuring mechanical support during regeneration of the damaged or injured bone [65, 123]. The role of scaffolds, including also bone scaffolds, is to ensure adhesion and migration of cells and ensure the necessary conditions of their growth by promoting the growth of new blood vessels [65, 124-126], serving to deliver organic substances and diffusion of nutrients and other necessary substances, as well as to ensure appropriate mechanical and physiochemical properties supporting tissue integration and development. Valuable research into the selection of materials for scaffolds is also purused in Poland [122, 127-136]. The general criteria of materials selection for tissue scaffolds relate to material type and its structure, ability to osteoconductivity, mechanical strength, ease of production and manipulation in clinical applications. A microscopic, porous structure of scaffolds is required, enabling diffusion of nutrients and metabolism products by them. The sizes of pores should be adapted to the specific cell type and be large enough to enable migration of cells and creation of an extracellular matrix (ECM), the supply of developmental signals to cells and the promotion of cells acquisition from the surrounding tissues, and small enough to prevent the sealing of pores in a scaffold [103]. It is necessary to ensure conditions to fill up scaffold pores by the reconstructed cells and to guarantee neovascularisation [137] for preventing blood clots [138]. Regeneration in a natural condition forces the removal of an artificial scaffold [139], most advantageously through bioabsorption, which is ensured by numerous natural and synthetic substances used for creation of scaffolds [140, 141]. The rate of bioabsorption should correspond to the rate of the given tissue's regeneration which allows, in particular, to gradually accept a mechanical load by the tissue.

Among others, **cell therapies**, which in case of many disorders enjoy an unrivalled position, have become attractive along with the advancement of tissue engineering

and regenerative medicine. Autologous cells (obtained directly from an organism of the future recipient), isogenic (syngeneic) cells (coming from organisms with an identical genetic material: monozygotic twins, clones, animal lines subject to inbreeding for long time), allogeneic cells (coming from a donor of the same species , e.g. fibroblasts from connective tissue of the prepuce, for producing skin transplants), xenogenic (obtained from other living organisms) represent a source of cells for tissue engineering [142]. They can be primary cells at the same time (coming directly from a living organism) or secondary cells (taken from the cells and tissues bank). Stem cells (cells from the stem) used, e.g. for craniofacial reconstruction [143-150], are characteristic for their lack of differentiation and ability to the unlimited number of divisions in order to obtain more highly specialised cells which, depending on the source, are classified as germ cells (obtained from an embryo) or somatic cells (coming from an adult organism), although the both categories can be crossed by embryonic cloning and by somatic-cell nuclear transfer (SCNT) [151], also in combination with the use of biodegradable scaffolds [152]. Autologous stem cells are the ones most beneficial as they do not cause an immunological response and thus do not cause harmful immunosuppressive side effects. Depending on the tissue development stage, stem cells can be divided into the category of adult and stem embryotic cells [145-147]. Autologous stem cells and progenitor cells may come from umbilical cord blood [153] or tissue [154]. Adult stem cells occur, in particular, in bone marrow, peripheral blood, fatty tissue, nervous tissue, muscles and dermis, and have an ability of transformation into multiple tissues, including bones, gristle, muscles, tendons. Stem cells originating from bone marrow and fatty tissue may be used for breeding mesenchymal cells and tissues, in adipocytes, chondrocytes, osteoblasts and skeletal myocytes and can be used for producing tissues, e.g. fat, gristle, bones and muscles [155-158]. Stem cells originating from bone marrow exhibit a large potential for autologous therapies [147], without immunosuppresive treatment [159-161]. Differentiated cells forming structures of an adult organism represent a more difficult material for breeding. The development of breeding techniques of human stem cells leads to the introduction of the next, new clinical regenerative procedures having no competition in other clinical methods used to date, including treatment of cancer, injuries, inflammation or diseases related to advanced age, and potentially even in treatment of Parkinson's disease and Alzheimer's disease, osteoporosis and heart and liver diseases, metabolic coronary diseases and autoimmune disorders [103]. It is nevertheless thought that, compared to embryonic stem cells, adult stem cells are usually useful to a limited extent for restoration of different types of cells and tissues [103].

The traditional, and also the oldest fabrication technologies of scaffolds with porous structure differentiate the method of **emulsifying/lyophilisation** [162], to **Thermally Induced Phase Separation** (TIPS) [163], **Solvent Casting & Particulate Leaching** (SCPL), where solvent residues may have an adverse effect on cellular structures [164]. The use of the aforementioned classical methods has not been abandoned altogether, despite being unable to control accurately the size, shape, distribution and interconnections of pores, as well as a general shape of the scaffold. It is used as a modern method in tissue engineering replication technologies with **micro/nano patterned surfaces** [165-167]. The **master moulds**, for the reason of mould rigidity, are produced using a hard or a soft material. Synthetic and natural biodegradable polymers can be cast onto micro/nanofabricated moulds to produce structures with small feature resolution [168, 169], including **hot embossing** (also known as nanoimprint lithography) and **soft lithography** (micro-casting) for achieving patterns with dimensions about of 5 nm [170-173].

The methods currently in use do not require moulds (**solid freeform fabrication SFF**) for fabrication of scaffolds made of different materials, including polymer materials, hydrogels, ceramic materials and metallic materials [50, 65, 174-176]. The key tasks in this field include wide application of the particular fabrication methods, not only for the mentioned biocompatible engineering materials, but also for the processing of biological materials [113]. In the **three-dimensional printing method (3DP)** [177], the particular layers of powder are sprayed with an adequate biocompatible binding agent, e.g. for merging powder to fabricate scaffold from collagen [178], and a 25% acrylic acid solution in a mixture of water with glycerine [179] is used for the integration of hydroxyapatite used for bone regeneration and an aqueous citric acid solution is used for integration of ceramics based on calcium phosphate [180]. A replica of the scaffold surface, e.g. for manufacturing bone and gristle substitutes, can be fabricated with the SFF method of **three-dimensional printing hot wax droplets** [181]. The limitations of the method originate from wax impurities with biologically incompatible solvents [182], which is not exhibited by new generation materials such as BioBuild and BioSupport dissolving in ethanol or water [182]. The **stereolithography** method permits to shapen three-dimensional form of liquid polymer [183], in particular

using poly(propylene fumarate) (PPF) [184, 185], poly-(ethylene glycol) (PEG) [186, 187]. Polymer materials without solvents, including poly(ε-caprolactone) PCL [188, 189], poly(ethylene glycol)–poly(ε-caprolactone)–poly(lactide), PEG-PCL-PLA [189, 190] acrylonitrile-butadiene-styrene (ABS) [191] and hydroxyapatite-poly(ε-caprolactone) HA-PCL [189, 192] are used in **Fused Deposition Modelling (FDM)** [193]. The particular layers are placed from a computer controller and using Computer Aided Design (CAD) methods. **Selective Laser Sintering (SLS)** is similar to 3D printing starting with uniform spreading of a thin layer of powder onto the surface and then the merging of powder grains as a result of sintering with the neighbouring grains with partial pre-melting, according to the assumed constructional characteristics of the element produced, in particular a scaffold, using a computer controlled laser beam according to CAD software. The next layers are manufactured subsequently according to the same method, until the full dimensions of the manufactured element are achieved. This technique, used commonly for additive manufacturing from metallic and ceramic materials [131, 194], including, notably, implants for dental purposes [46], was utilised for scaffolds preparation [50] from biodegradable polymers, e.g. polyether polymer, poly(vinyl alcohol), polycaprolactone [195] and poly(L-lactic acid) [196], and also hydroxyapatite [197] and from composites composed of some of such polymers and hydroxyapatite [196, 198, 199].

Nanofibrous scaffolds are manufactured by **electrospinning**, and the so obtained nanofibres with the diameter of 5 nm to over 1 mm are continuous and randomly interconnected [200, 201]. Due to the character of electrospinning, fibres are oriented randomly [202] or are arranged in an orderly manner [203], they exhibit their structure similar to the extracellular matrix (ECM), have a large specific surface area, high porosity, small size of pores and small density [204]. Natural and engineering materials can be used as a material, including, in particular, collagen, gelatine, chitosan [200]. The ability of certain biopolymers, such as peptides and nucleic acids, to self-organisation, consisting of non-covalent interactions for spontaneous fabrication of a three-dimensional structure in response to the activity of environmental factors [205-207] is utilised for scaffolds fabrication. Such types of scaffolds were used, e.g. for regeneration of nervous tissue to stop bleeding and repair infarcted myocardia, as well as in medical products for slow release of a medicine [208, 209] and for DNA, where the branched DNA particles hybrydise with each other in the presence of ligases in hydrogel [210]. The scaffold fabrication method employing **self-organisable nanofibres** is one of few allowing to produce biocomponents with their properties similar to the natural extracellular matrix (ECM), and scaffolds containing hydrogel, made using such technology, employ more advantageous toxicological properties and higher biocompatibility than traditional materials. Conventional hydrogels are particularly useful for three-dimensional placement of cells [211]. Hydrogels used in tissue engineering should have low viscosity before injection and should be gelling fast in the physiological environment of the tissue, and the most important is gelling (sol-gel transition) by cross-linking, which may take place when producing them in vitro and in vivo during injection. **Physical cross-linking** is used in particular in the case of Poly(N-isopropyl-acrylamide) (poly(NIPAAM)), which may be used in tissue engineering after introducing acrylic acid (AAc) or PEG [212, 213] or biodegradable polymers, including such as chitosan, gelation, hyaluronic acid and dextran [214-218] to block copolymers, such as poly(ethylene oxide) PEO-PPO-PEO (Pluronic), poly(lactide-co-glycolide) PLGA-PEG-PLGA, PEG-PLLA-PEG, polycaprolactone PCL-PEG-PCL and PEG-PCL-PEG [219-223], and also agarose (a polysaccharide polymer material, extracted from seaweed as one of two principal components of agar) [211], as thermo-sensitive systems [224], to avoid the use of potentially cytotoxic ultraviolet radiation. Poly(NIPAAM) and block copolymer hydrogels may undergo cross-linking as a consequence of temperature and pH acting at the same time, as in the case of acrylates [225, 226], such as 2-(dimethylamino) ethyl methacrylate (DMAEMA) or 2-(diethylaminoethyl) methyl methacrylate. Self-assembling peptides hydrogels, including such containing peptide amphiphiles (PAs), can form nonofibres [227, 228] used for three-dimensional formation of tissue cultures [227, 229-232]. **Chemical cross-linking** hydrogels having convalescent bonds include photo-crosslinkable poly(ethylene glycol)-diacrylate (PEGDA), poly(ethylene glycol)-dimethacrylate (PEGDMA), poly(propylene fumarate) (PPF) and oligo(poly(ethylene glyco) fumarate) (OPF) [233-237], and also natural hydrogels such as dextran, alginate, chitosan and hyaluronic acid synthesised from PEGDA/PEGDMA [238-241] and **Michael-type addition reaction** [242-244] and **Schiff base – crosslinked hydrogels** [216, 245-247]. In the case of **enzyme-mediated cross-linking** [210], transglutaminases (including Factor Xllla) and horseradish peroxidases (HRP) [211] are used for the catalysis of star-shaped PEG hydrogels [248] and tissue transglutaminase catalysed PEG hydrogels [249] and also tyrosinase, phosphopantetheinyl transferase, lysyl oxidase, plasma amine oxidase, and phosphatases [250],

which in particular have enabled to develop new gels by engrafting tyramine groups into natural and synthetic polymers such as dextran, hyaluronic acid, alginate, cellulose, gelatin, heparin and PEG-PPO [251-257]. **Ionic cross-linking** hydrogels include calcium-crosslinked alginate [211] and chitosan–polylysine, chitosan–glycerol phosphate salt and chitosan–alginate hydrogels [258-260]. Different synthetic and natural polymers were used for this purpose, including polyethylene glycol (PEG), and copolymers containing PEG [261], hyaluronic acid (HA) [241, 262] after an oxidation reaction through HA–tyramine conjugates [251] and as a result of formation between HA–SH [242, 263] and Michael addition [243, 264], collagen and gelatin hydrogels mostly cross-linked using gluteraldehyde, genipin or water-soluble carbodiimides [265-267], chitosan [268-271], dextran 192 [272, 273] and alginate [274]. Hydrogels were used for reconstruction of the retina [275], ligament [276], fatty tissue [216], kidneys [277], muscles [278], blood vessels [279, 280], and also heart, neural cells, invertebral discs, bones and gristle [211]. Hydrogels were used to prevent adhesions [281, 282], to promote cellular adhesion [244, 283, 284]. So-called strong hydrogels were developed to improve mechanical properties [285]. Three-dimensional representation is possible of placement of cells with energy in hydrogel to vascular structures using a laser [286, 287], notably for recording directly the endothelial cell [287]. The most technologically advanced methods of three-dimension printing include at present **direct organ printing** [288, 289], ensuring the highest currently possible degree of control over the structure of the regenerated tissues. Many layers of different types of cells can be printed to create an organ [290]. A polymer-cell mixture can be dosed using this technique, leading to formation of cell hydrogel [291], microfluidics allows for the creation of three-dimensions systems of cells [292], and hydrogels from photopolymerisation polymer solutions can also be used [293], and also SFF techniques, including stereolithography techniques to create scaffolds made of PEG hydrogels [187]. The first production system for three-dimensional printing of tissues was delivered only in 2009 based on the NovoGen **bioprinting technology** [294]. A three-dimensional structure is obtained by subsequent formation of layers of living tissues on the gel or sugar matrix substrate [295].

Unfortunately, despite immense progress in the production of complicated tissue structures in the last several years, the progress in **vascularisation** control is limited. Vascularisation, even for organ printing, still remains a big challenge in tissue engineering. The development of a vascular network in metabolically functional tissues enables the transport of nutrients and removal of wastes, ensuring maintenance of cells' viability for long time [136]. Micro-formation techniques, by the three-dimensional printing of templates made of agarose fibres, are used for creation of a micro-channel network inside hydrogel products, including, in particular, inside methacrylated gelatin (GelMA), star poly(ethylene glycol-co-lactide) acrylate (SPELA), poly(ethylene glycol) dimethacrylate (PEGDMA) and poly(ethylene glycol) diacrylate (PEGDA) with different concentrations. The efficient formation of endothelial monolayers within the fabricated channels has also been confirmed [296]. Press reports announce, on the other hand, that China has invested nearly 0.5 billion USD to establish 10 national institutes for development of organ printing [297], in which the printing of ears, liver and kidneys from living tissues was started in 2013 and it is expected that fully functional printed organs can be achieved over the next dozens years or so [298, 299]. In the meanwhile, there were reports in the first weeks of the second quarter of this year that an Australian team obtained a kidney tissue print with this method for the first time [300], and an American team confirmed on 1 August 2014 it is ready to print a heart [301].

3. The actual development results of the global markets of biomaterials and various medical products

The existing **global medical products market** is split into numerous segments. In the next part of the paper selected informtion on the few most important segments of the global markets of biomaterials and various medical products are presented.

The undertaken foresight research shows that the **global market of Medical Bionic Implants (Artificial Organs)**, as defined above, will grow in 2012-2017 by 7.1% (with the expected compound annual growth rate (CAGR)), reaching the value of USD 17.82 billion in 2017 [302], and the **market of tissue engineering and regenerative medicine** will grow in the USA from only USD 6.9 billion in 2009 to USD 32 billion in 2018 [51]. This constitutes a realistic and tangible reason for the intensification of research and implementation works combining activities, notably, in scope of pharmacy, bioengineering, biotechnology, chemistry, electronics and biophysics, which inevitably leads to higher industrial expenditures for investments associated with the acquisition of know-how and expansion of manufacturing capacities in this field.

A market potential analysis indicates clear development tendencies of global markets relating to the paper's subject, although none of them corresponds to this topic directly. From among the **global medical product markets**, directly relevant in connection with the subject of the paper are, most of all, development tendencies of the biomaterials market, medical bionic implant/artificial organs market, orthopaedic devices market, orthopaedic soft tissue repair market, orthopaedic trauma fixation devices market, orthopaedic soft tissue repair market, and 3D Printing in Medical Applications Market. The topics included in the paper's content are supplementary to such markets.

The comparison of the selected segments of the global markets of biomaterials and various medical products is presented in the Table 1.

Table 1.
Examples of the selected segments of the global markets of biomaterials and various medical products

The selected segments of the global markets	The expected compound annual growth rate (CAGR) %	The value of global market USD	The estimated value of global market USD	The source
Global biomaterials market	2013-2019 4.1	2012 25,277.8 million	2019 33,600 million	[2]
Global market of Medical Bionic Implants (Artificial Organs)	2012-2017 7.1	2012 12.67 billion	2017 17.82 billion	[303]
Global orthopaedic devices market	2013-2019 4.9	2012 29.2 billion	2019 41.2 billion	[3]
Global orthopaedic trauma fixation devices market	2014-2019 7.2	2014 6.1 billion	2020 9.3 billion	[304]
Global orthopaedic soft tissue repair market	2013-2019 7.2	2013 5.6 billion	2019 8.5 billion	[305]
3D Printing in Medical Applications Market	2013-2019 15.4	2012 354.5 million	2019 965.5 million	[306]

The **global biomaterials market** was valued at USD 25,277.8 million in 2012 and is expected to grow at a CAGR of 4.1% from 2013 to 2019, to reach an estimated value of USD 33,600 million by 2019 [2]. A generic structure of the global biomaterials market valued at USD billion was shown according to KOL Opinions, Company Annual Reports, Expert Interviews, Investing Publications, Press Releases & TMR Analysis, as well as the global orthopaedic devices market. Biomaterials are used to treat effectively various diseases, such as, in particular, bone cancer, orthopaedic injuries, tissue damages, cardiovascular diseases, dental diseases. Biomaterials are biocompatible and do not cause any immunological reactions in a human organism. The dramatic growth of the market and usage of implants has been seen in developed countries such as the United States, Canada, Germany, France, Great Britain, Italy and Spain, due to a high utilisation rate of medical implantology procedures as compared to weaker growth elsewhere in the world. North America is the biggest market of biomaterials, lying ahead of Europe. Demand for numerous medical implants and implantation procedures across the world has been rising due to aging population, and longer life expectancy – due to improved healthcare standards – leads to a high incidence rate of arthritis and osteoporosis. The incidence of bone diseases and fractures is more and more common. Orthopaedic applications enjoyed a large share in the global biomaterials market in 2012 due to the growing number of implanted hip and knee joint endoprosthesis. The studied circumstances are closely linked also to the scaffolds with orthopaedic and

craniofacial implants. Society aging has also a great effect on the incidence of eye diseases and dental problems also covered in the paper. Safe, reliable and affordable biomaterials include metals, ceramics, polymers and biomaterials of natural origin. All of the materials are listed within the scope of the multi-aspect focus of the paper. Metallic materials had the largest share in the global biomaterials market in 2012, with a rapidly growing portion of polymer biomaterials. It is estimated that the share of polymers will grow fastest between 2013 and 2019, including nanofibres made of biodegradable polymers as skin and soft tissue scaffolds. Polymers are used in many prostheses such as percutaneous transluminal coronary angioplasty (PTCA) catheters, heart valves, contact lenses, intraocular lenses and for constructing rigid bases for dental prosthesis and dentures, in ophthalmic applications, and in urology and gastroenterology, and to an artificial esophagus. North America and Europe maintain their leading position on the global biomaterials market for the entire projected period of 2013 to 2019, but countries of Asia and Pacific, such as Japan, South Korea, China, India and Taiwan play more and more crucial part in biomaterials market development, and development will also be seen in Latin America in the years to come.

The **medical bionic implant and artificial organs market** is a potentially growing one with a global market of $12.67 billion in 2012 as it is expected to grow at a CAGR of 7.1% to reach $17.82 billion in 2017 [303]. The development trend of the medical bionic implant and artificial organs industry has maintained over the past two decades and it is expected that will continue until the 20's. The global medical bionic implant and artificial organs market has been segmented into five categories based on the type of products, technology used, and type of fixation, including vision bionics, ear bionics, orthopaedic bionics, heart bionics, and neural/brain bionics. New and improved technologies, increasing organ failure owing to aging and age-related disorders, increasing accidents and injuries leading to amputations, and rise in number of people awaiting organ transplants are the major drivers slated to propel the growth of this market. North America dominates the artificial organs market in 2012, followed by Europe.

The **global orthopaedic devices market** was valued at USD 29.2 billion in 2012 and is expected to grow at a CAGR of 4.9% from 2013 to 2019, to reach an estimated value of USD 41.2 billion in 2019 [3]. Orthopaedic devices are used to restore skeletal structure and joint movements in various types of fractures, abnormal growth of bones, soft tissue damage, trauma or other deformities. These devices can be surgically implanted or externally attached through minimally invasive procedures and hence can be classified as joint implants, internal and external fixation devices. Demand for orthopaedic procedures is expected to grow in the near future owing to the increase in geriatric population and obesity across the globe. The major orthopaedic device segments such as joint implants, internal and external fixation devices have been further analysed on the basis of anatomical locations namely, hip, knee, shoulder, elbow, foot and ankle and other extremities. Spinal orthopaedic devices have been segmented into joint implants and internal fixation devices, while the craniomaxillofacial devices market include estimations only for internal fixation devices.

The **global orthopaedic trauma fixation devices market** is estimated at USD 6.1 billion in 2014 and is expected to grow at a CAGR of 7.2% from 2014 to 2019, to reach an estimated value of USD 9.3 billion in 2020 [304]. The key market drivers include rising healthcare spendings, popularisation of sports activity, a growing number of road accidents and growing geriatric population, leading to higher number of fractures and injuries. The impediments for development are high treatment costs, poor knowledge among many people and disregarding such type of disorders in healthcare systems, especially in developing countries. Internal fixators have the largest share in the orthopaedic trauma fixation devices market and are projected to grow at a CAGR of 6.8% until 2020. Plate and screw systems are used most often and their development in this period will be 7.1%, and internal fixators are used more and more often with bioabsorbable material and development of their production will be even higher and will be 8.4%. North America, including the U.S., has the largest orthopaedic trauma fixation devices market, while Asia, especially China, Japan and other Southeast Asia countries and also countries of the eastern Mediterranean countries are growth markets.

The **global orthopaedic soft tissue repair market** was valued at USD 5.6 billion in 2013 and is expected to grow at a CAGR of 7.2% from 2013 to 2019, to reach an estimated value of USD 8.5 billion in 2019 [305]. The key market development drivers include society aging, increase in obesity, a higher number of damaged soft tissues, including largely due to sports injuries, and also introduction of new medical technologies, and no other alternatives to repair soft tissues, apart from surgical ones, and also growing healthcare expenditures. The constraints encountered by the market are associated especially with a tendency of forcing out metal implants by biodegradable materials, which requires a technology change and usage of

robot-assisted surgeries at the expense of traditional surgical methods related to growth of costs. ACL/PCL reconstruction is the largest practiced procedure in the orthopaedic soft tissue repair market and it is expected to grow at a CAGR of about 8.3% during 2013-2019. Other widely used orthopaedic soft tissue repair procedures include Meniscal Repair, Hip Arthroscopy, Rotator Cuff, Shoulder Labrum and Biceps Tenodesis. North America, including the USA, has the largest share in the soft tissue repair market, whilst Asia, China, India and Japan witness the fastest global growth.

The **3D Printing in Medical Applications Market** was valued at USD 354.5 million in 2012. Its growth is estimated at a high CAGR of 15.4% from 2013 to 2019, to USD 965,500,000 [306]. 3D printing technologies have delivered multiple solutions in the medical industry and have revolutionised the healthcare segment by facilitating the manufacturing of medical implants and surgical guides such as dental, orthopaedic and cranio-maxillofacial ones, usually with enhanced efficiency. Fabrication takes place with various materials, such as metals, polymers, ceramics and natural biological cells. New technologies evolve, such as laser beam melting (LBM), electron beam melting (EBM), droplet deposition manufacturing (DDM) and photopolymerisation. The North America region was the biggest 3D printing market for medical applications in 2012, while it is estimated that Europe enjoys the highest growth rate by over 15% between 2013 and 2019.

The analysis made clearly shows a clear development trend of all the world markets of biomaterials and various medical products, with division into traditional sectors of such a market, though. The facts described above substantiate the determination the state of knowledge in this area, which will be the basis for new lines of research and to increase the level of knowledge among engineers and medical doctors.

4. The estimated future research of the hybrid technologies of bioactive and engineering materials for personalised scaffolds of tissues and bones

The development of new **hybrid technologies of bioactive and engineering materials for personalised scaffolds of tissues and bones** requires a number of basic research and application work. These include generally, among others:

- **analysing clinical cases** in the field of maxillo-facial surgery, restorative dentistry, laryngology, orthopaedics and traumatology, oesophagus and blood vessels prosthetics, for an inventory and classification of typical cases of the necessity to personalise hybrid scaffolds of tissues and bones,
- **designing and constructing of the new generations of implants** using the currently available methods of advanced medical imaging and simulation of mechanical loads with methods of numerical approximation and Computational Materials Science (CMS) and engineering material, constructional and technological design – Computer Aided Materials Design/Design/Manufacturing CAMD/CAD/CAM and experimental verification of models and calculations in laboratory conditions,
- **introducing the bioactive and engineering materials** for above applications and investigating the structure and properties of the examined materials subject to the applied technological processes, among others using advanced methods of light and confocal microscopy, scanning probes, transmission and scanning methods including HRTEM, spectral methods EDS, WDS, EBSD, GDOS, FTIR, Raman's method, X-ray structure analysis, dilatation investigations, mechanical investigations, including micro- and nano-hardness, investigations of physiochemical, corrosive and tribological properties,
- **biological and biocompatibility investigations, cytotoxic investigations**, investigations of biotrans- formation mechanisms and processes using immonu- cytochemistry, immunofluorescence and molecular biology techniques,
- preparatory works for **implementation in industrial conditions** at the semi-technical scale, including market research for the prospect product, preparation of technical documentation necessary for implementation, preparation of procedures related to the market use of a future product originating from the research, obtaining a certificate of conformity entitling to mark a product with a mark for conformity to national or foreign standards, certification and actions directly related to procedures for granting the rights.

The following Table 2 presents numerous examples of the application of various bioactive and engineering materials, and their respective materials processing and tissue engineering technologies for manufacturing of the hybrid personalised implants and scaffolds.

Table 2.
Examples of the application of various bioactive and engineering materials, and their respective materials processing and tissue engineering technologies for manufacturing of the hybrid personalised implants and scaffolds

Fabrication stage	Investigated materials	Technologies applied	Areas of application
Fabrication of implant bearing structure	Ti, Ti alloys with V or Nb, Mg (possibly with additives of Ca, Zn and Mn), ceramic materials Al_2O_3 and ZrO_2, TiO_2, resorbable bioglass, e.g. Hench bioglass, from the CaO-SiO_2-P_2O_5 and SiO_2-Al_2O_3 system, hydroxyapatites, polymers, composites	Selective Laser Sintering, sintering, the use of organic matrix, lyophilisation of ceramic slip, rapid pressure assisted densification methods, such as rapid hot pressing/Spark Plasma Sintering (SPS), skeletal casting, plastic working, cutting micro-treatment, Computer Aided Manufacturing, sol-gel methods, 3D printing, electrospinning, atomic layer deposition, Physical Vapour Deposition	filling the losses of long bones, hip and knee joints, facial-skull bone, losses of joint cartilage cells, oesophagus losses and/or blood vessel losses, dental restorations, skin restorations
Fabrication of implant porous part	Ti, Ti alloys with V or Nb, Mg (possibly with additives of Ca, Zn and Mn), ceramic materials Al_2O_3 and ZrO_2, TiO_2, resorbable bioglass, e.g. Hench bioglass, from the CaO-SiO_2-P_2O_5 i SiO_2-Al_2O_3 system, hydroxyapatites, polymers, composites		
Fabrication of coatings inside pores of implant porous part	natural protein, synthetic and polysaccharide polymers, including thermosetting, including collagen, fibrin, alginate, silk, hyaluronic acid, chitosan, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), polycaprolactone (PCL) and poly(propylene fumarate) (PPF), polyethylene glycol, Al_2O_3, resorbable bioglass, hydroxy carbonate apatite (HCA), calcium phosphate (CaPs), hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), biphasic calcium phosphate, composites: collagen + hydroxyapatite CaP-polymer tricalcium phosphate (TCP)-polycaprolactone (PCL), hydroxyapatite HA/poly(ester-urethane)(PU), collagen-Bioglass	Inflirtation, 3D printing, selective laser sintering, electrospinning, atomic layer deposition, Physical Vapour Deposition, pressing, sol-gel methods	
Fabrication and application of tissue cultures	adipocytes, chondrocytes, osteoblasts, fibroblasts and skeletal myocytes	Cell transplantation, matrix implantation, cell implantation with matrix, breeding of xenogeneic and autologous cells and the stage of clinical activities	

5. General conclusion

A thorough undertaken state-of-the-art shows the high technological advancement of tissue engineering methods. The high advancement of prosthetics/implantation techniques used in the clinical practice should also be noted, which is not detailed in this description as the issues are commonly known. The positioning and fixing of implants takes place in all those methods in a classical way using mechanical devices and solutions. There are no reports in the references about an original concept presented by the Author of introduction of prosthetics/implantation and tissue engineering techniques for the purpose of natural ingrowth of the implanted elements into a living tissue in the implant area without having to use mechanical devices, at least in the connection (interface) zone of bone or organ stumps with prosthetic/implant elements. This opens up vast possibilities for the application of the hybrid technologies of bioactive and

engineering materials for personalized scaffolds of tissues and bones in accordance with the concept of the Author, presented in this paper.

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