# 1. Materials Challenges in Regenerative Medicine

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## Outline

## 1.1. The importance of tissue engineering methods for the development of global markets of medical products

The OECD's analyses [1] show that healthcare spendings by purchasing power per capita in thousands of USD have grown continuously, which entails the inherent development of the medical products market (Fig. 1.1 & 1.2).

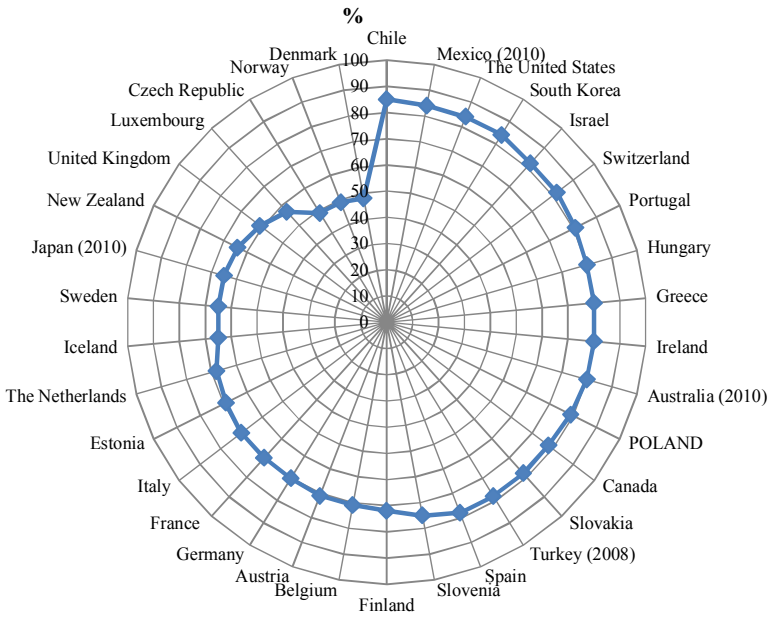


***Figure 1.1.*** *The public spendings, as a share in overall healthcare spendings in 2011 in OECD countries; according to data from [1]*

On the other hand, the development rate of segments of the medical products market is linked to sharp development of civilisational diseases, including cancer, and the incidence rate of malignant cancers in Poland has been regularly rising. The number of traffic accident victims has been growing systematically, as well [2], and, e.g. the rate for Poland is highest in the European Union, i.e. 109 fatalities per million inhabitants, while the same figure for the Great Britain is lowest in the European Union, i.e. 31, and average decline in this indicator in Latvia and Estonia is 10%, whilst it goes up by 4% on average annually in Poland. Analogously, the number of fatalities in railway accidents is 543 in Poland, which is highest

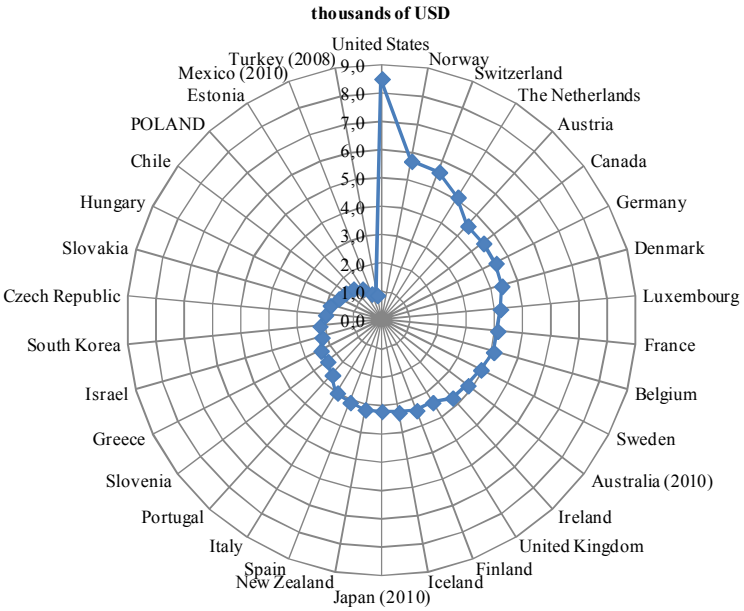


***Figure 1.2.*** *The overall healthcare expenditures, by purchasing power per capita in 2011 in OECD countries; according to data from [1]*

for the European Union, whilst in, e.g. Estonia, Finland and the Netherlands it is below 20. Followed by this, almost proportionally, grows the number of people injured in such accidents and requiring usually long-lasting medical care. Along with the intensification of sports activity, especially among young people, and with the promotion of leisure practise of sports by propagating a 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 at a global scale. Globally, rise in aging population is playing a major role in increasing the incidence of sports injuries as aging diminishes body 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 the efficient elimination of disabilities, in particular motoric disabilities, and the restoration of 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 resources of social insurance funds. Of great importance is the shortened waiting time for service or therapy, a reduced price

and availability of a medical product and service and therapy, a reduced risk of treatment failure, in particular with customised medical products according to a patient's individual anatomical features, and last but not least, a reduced therapy discomfort for the patient and his/her family. The people suffering from civilisational diseases, as shown above, including malignant cancers, often require bone reconstruction, e.g. of legs and hands and in the craniofacial area, as well as skin and other soft tissue reconstruction, and also oesophagus and/or blood vessels.

A market potential analysis indicates clear development trends of the global medical product markets, and directly relevant 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 development of a complementary market should also be expected, associated with the popularisation of the concept and newly established technical and clinical solutions of hybrid implants featuring a porous zone, acting as scaffolds for the ingrowth of living tissues and hybrid engineering-biological implants, according to the author's original concepts [3],[4]. Implantable biomedical devices are currently aggregately considered to be medical bionic implants where bionics is understood as the fabrication and investigation of biological systems to create and implement artificial engineering systems which can restore the lost functions of biological systems [5]. In general, medical bionic implants encompass numerous solutions eliminating various dysfunctions of a human organism, among others orthopaedic prostheses (bone grafts, bone plates, fins and 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 [5].

The undertaken foresight research shows that the global the medical bionic implant and artificial organs market is a potentially growing one with a global market of USD 12.67 billion in 2012 as it is expected to grow at a CAGR of 7.1% to reach USD 17.82 billion in 2017 [6], and the market of tissue engineering and regenerative medicine will grow in the USA only from USD 6.9 billion in 2009 to USD 32 billion in 2018 [7]. 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 [8]. 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 craniomaxillo facial 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 [9]. The key drivers crucial for the growth of this market 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 include 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 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 [10]. The key drivers crucial for the growth of this market 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 linked to the 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, including China, India and Japan, are witnessing 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 [11]. 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 are evolving, 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 growth of the global biomaterials market is showing most truly the general growth tendencies of markets related to technical protection of medical activities, including mainly regenerative medicine. New applications are emerging for biomaterials, in particular for restoration of body parts lost due to a disease or in an accident. The global demand for

biomaterials has been rising constantly. The global biomaterials market was valued at USD 25,277.8 million in 2012 and is expected to reach an estimated value of USD 33,600 million by 2019 [12]. Such high market dynamics is linked to a growing number of people at the retirement age representing at present, according to the World Health Organisation (WHO), 7% of the global population, i.e. approx. 500 million people and will exceed 1 billion until 2020 [13]. All the EU states will be affected by the issue of demographic changes. Demographic changes will lead to economic changes. Activities securing diverse needs of the growing group of people at the retirement age will have to be planned and organised as a result, and this is inherent to ensuring the highest possible comfort of life and health. In particular, a new generation of engineering materials for regenerative medicine purposes will be forced by the growing needs. This aspect is a significant and costly problem of modern medicine. 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, described further. 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, staying ahead of Europe. Demand for numerous medical implants and implantation procedures across the world has been rising due to ageing 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 a growing number of implanted hip and knee joint endoprosthesis. North America and Europe maintain their leading position at 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 are playing more and more crucial part in biomaterials market development, and development will also be seen in Latin America in the years to come. Safe, reliable and affordable biomaterials include metals, ceramics, polymers and biomaterials of natural origin. Metal 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. The dynamic advancement of polymer nanofibers is signified by year-to-year growth of a variety of research areas, the number of nanofibers-related publications as well as the number of new companies specialising in the polymer nanofiber fabrication industry [14]-[17]. The global consumption of carbon nanofibers has weakened over this time span, from 21% in 2010 to 16% of the CAGR predicted in 2016 [18]. The mechanical and chemical industry accounted for 73.2% of overall revenues in 2010. The compound annual growth rate in this industry is estimated at 33.4% in 2010-2015 and 35.3% in 2015-2020. The electronic industry is experiencing the fastest growth with the forecast annual growth rate in 2010-2015 of 45.3% and 50.7% in 2015 to 2020 [19]. The application potential of nanofibers appears to be most surprising, which, despite so diversified directions of research, is currently estimated at 0.5-1%. The remaining 99-99.5% of potential applications for this group of nanomaterials will be explored in the coming years. A characteristic that is decisive for their unique properties, i.e. a diameter of not more than 100 nm, is now also very often a barrier for application at a scale greater than laboratory research. Efforts have been made for this reason to produce hierarchical, three-dimensional structures and to combine them with other materials, i.e. to produce nanocomposite materials. The global nanocomposites market at the onset of 2015 should outrun the compound annual growth rate of 27.1%. Global consumption of nanocomposites, including silicides, will exceed the compound annual growth rate of 32.2%. As projected, the CAGR for the entire global nanocomposite market including ceramics is to be 12.5% by the end of 2014 [20].

A market potential analysis indicates clear development trends of the global medical product markets, and directly relevant 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. This constitutes a real and tangible reason for the intensification of research and implementation works, which inevitably leads to higher industrial spendings for investments associated with know-how acquisition and expansion of manufacturing capacities in this field. The current methods of organ and tissue replacement employ primarily autographs, allografts or metal devices or such made of other engineering materials [21]. The problem of organ transplantation proves how

important are activities consisting of the creation of state-of-the-art biomaterials and how much there is still to do in this area. The necessity to perform another operation, with such an operation being a discomfort for patients and an additional burden for health service finances, will be avoided by replacing non-biodegradable implants with materials undergoing complete resorption. Tissue scaffolds have been intensively developed for several years apart from transplantable implants, and in fact instead of them. Very high demand for various types of organs, a low number of donors, the necessity to take medicines after implantation, have become a driving force for tissue engineering, allowing to fabricate organs without risking rejection after transplantation. Tissue engineering seeks innovative methods of restoring a natural tissue and provides an alternative solution to the currently used conventional methods. The concept of 'tissue engineering' was introduced in 1985 by Y.C. Fung [22]. Tissue engineering, as a field of technical sciences using medical knowledge and materials engineering methods [23],[24], 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 or entire organs. ECM (extracellular matrix) natural tissue scaffolds are an organic or inorganic component forming a tissue when joined with cells. A scaffold forms an integral part of each tissue, supports cells, makes tissues elastic, flexible and strong. The ECM consists of protein components (type I collagen mainly), polysaccharide components (such as hyaluronic acid), as well as inorganic components (including hydroxyapatite being the main building block of a bone tissue). The majority of current works is focussed on designing and fabricating a scaffold using various fabrication technologies, including also materials of natural origin, such as: chitosan (a derivative of chitin), collagen or elastin, as well as of synthetic origin, such as PCL (polycaprolactone), PLA (polylactide), PEO (poly(ethylene oxide). The polymers mentioned, after implantation into a recipient's body, are subject to degradation to products easily removed by a human organism, in particular in the citric acid cycle called the Krebs cycle [25]. Methods are commonly applied in tissue engineering, in which three-dimensional engineering constructions are employed permitting 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 to transport them and scaffolds for three-dimensional grouping in a particular place of an organism.

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 market, though. There are no procedures for solving synergically 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. A treatment strategy developed these days includes tissue engineering methods, respectively, scaffold-based vascularised bone tissue engineering (SBV BTE), Vascular Tissue Engineering (VTE) or scaffold-based tissue engineering (SBTE). Promising outcomes are achieved by the application of tissue scaffolds in combination with autologous bone marrow stem cells and growth factors (mainly BMP-2). Special focus is laid in this work on the possible use of polymer nanofibers and composite materials, in which they can be used, as scaffolds in tissue engineering.

The analysis and research included to the 3 chapters of this work have been implemented among other within the framework of the project financed by the National Science Centre in Poland granted on the basis of the decision number DEC-2012/07/B/ST8/04070, entitled "NANOCOPOR – Determining the importance of the effect of the one-dimensional nanostructural materials on the structure and properties of newly developed functional nanocomposite and nanoporous materials", headed by Prof. Leszek A. Dobrzański.

## 1.2. Biological conditions of restoration of body parts lost due to disease or in accident and general assumptions of tissue engineering

The continuity of tissues requiring tissue regeneration in order to restore their normal condition is interrupted as result of bodily injuries related to numerous accidents, most often work accidents, traffic accidents and sports accidents, as well as due to surgical interventions resulting from the applied therapeutic methods of treating many disorders, most frequently cancerous diseases or removal of inflammatory conditions. Tissue regeneration triggered upon tissue continuity interruption is a very complex and time-consuming process. The regeneration time depends on the type of the tissue and damage extensiveness. A wound is started to be healed in natural conditions from the phase of cleaning, called the inflammation phase, after which a reconstruction phase takes place, initiating the restoration process of blood vessels, nerves and migration of cells. The last phase is the phase of restoring the tissue's natural function consisting of shrinkage and formation of a scar, in which cells produce collagen, and then transform the created collagen structure into an ordered structure providing strength properties of the tissue. The rate of regeneration also depends on the presence of growth factors in the wound environment. PDGF (platelet-derived growth factor) is an example of a growth factor important in the regeneration process. This factor, in contact with fibroblasts, triggers processes in cells responsible for collagen production, i.e. a protein being a foundation of each scaffold in a living organism. Next, the collagen structure being formed is inhabited by cells of the respective tissue, whose presence leads to the creation of blood vessels. As blood vessels are being developed, the regeneration process is intensified, because nutrients and oxygen are flowing together with blood, which accelerates cell division, i.e. regeneration.

An exudation is often formed in a wound healing process which, in chemical terms, contains a mixture of cytokines, growth factors and proteolytic enzymes destroying growth factors such as PDGF. At the same time, the presence of an exudation leads to production of protease by cells, i.e. a compound released by healthy cells to destroy, decompose the dead cells. The presence of protease also contributes to reconstruction of the already formed collagen ECM towards the scar tissue with maximum strength. In normal conditions, the process of releasing protease is strictly controlled by an organism, which controls its presence

by a system of biochemical paths. In unsterile conditions, i.e. conditions in which bacteria appear in the wound environment, the regeneration process is disrupted. The presence of microorganisms is leading to excessive production of protease, while the excess of protease produced by cells is inhibiting the regeneration process at the stage of inflammatory condition. If microorganisms are not removed from the wound environment, an exudation continues to be formed, and this causes excessive production of protease in the cells, which may lead to the formation of wounds that heal from several days to several months and even years. For this reason, it is so important to modify a material to include chemical compounds or particles eliminating microorganisms from the wound environment. This is not an easy task as wounds subjected to surgical operations are especially prone to infections, and also wounds containing impurities, ulcerations, decubitus and such with extensive and deep tissue destruction caused by burning [26]-[39]. An additional impediment in combating micro-organisms occurring in wounds is more and more frequent occurrence of drug-resistant bacteria, the combating of which, due to their antibiotic resistance, is substantially hindered. An antibiotic resistance ability of a bacterium may lead to the creation of strains resistant to all the antibiotics used to date in treatment, and more and more of them have been appearing recently. An example of a 'super-bacterium', i.e. a bacterium fully resistant to all the antibiotics used to date, and there are more than 150 of them so far, is Klebsiella pneumoniae bacterium [40]. Super-bacteria are associated with a risk of causing a global pandemic; the risk is related to the ability to exchange DNA (deoxyribonucleic acid) information between the bacteria of a different strain. The exchange of DNA between a super-bacterium strain resistant to the antibiotics used and a bacterium strain occurring in the natural environment such as Escherichia coli bacterium, may lead to changes taking place at the level of the cellular biochemistry of Escherichia coli, by making it resistant to the antibiotics which have been effective against it to date [41].

Tissue engineering, experiencing rapid growth since the mid-90's of the last century, provides technical support for regenerative medicine and enables to utilise 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 [42]. Research into the use of stem cells in this context has constantly evolved and has considerably intensified over the last decade [21],[43]-[52]. The efficiency of cell-based therapies depends on the presser-vation of their viability after implantation [53],[54], and this problem is still valid.

Scientific advancements in this area ensure the unique laboratory possibilities of producing living cells/tissues from a combination of engineered extracellular matrices scaffolds, cells and biologically active molecules. The application of therapies based on living cells in medicine is a relatively new concept as the first successful allogeneic transplantation of human haemato-poietic stem cells (HSC) was seen as late as in 1968 [55], which is a routine clinical procedure these days, used for bone marrow regeneration. Two decades later, cells were used for regeneration of skeleton tissues [56], and only later for other therapeutic applications [57]. The intensive growth of this discipline was seen in the mid-90's of the 20th cent., and modern skin and cartilage implants have found their application in the existing clinical practices, and the last decade witnessed a constant increase in the number of clinical trials of cell-based therapies [58]. The application of therapeutic cells or cell-based therapies boasts a global market with the revenue of more than half a billion USD [59]. Therapeutic strategies include direct trans-plantation of the desired type of cells collected by means of biopsy or such originating from cultures of stem cells, both in the autologous and allogeneic system, e.g. for treating a heart stroke or when placing the implanted cells inside a polymer sheath, e.g. as one of diabetes treatment methods; matrix implantation consisting of placing a scaffold itself containing substances inducing cells migration and growth, which is subsequently gradually colonised by the donor cells, e.g. in treatment of burns and severe injuries, and the implantation of matrices with cells, where complete structures are implanted, cultured in *in vitro* conditions, not requiring long-lasting adaptation to the conditions prevailing in a recipient organism, and satisfactory, promising clinical results were achieved for restoration of such tissues as gristles and skin layers. The dynamic growth of cases of organ or tissue loss or damage in the human population due to post-injury defects, post-resection defects, 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 to prevent biological and social degradation of patients and restore their living functions, either normal functions or such acceptably similar to normal, constitutes a significant and costly problem of the modern medicine. It is hard to overestimate, nowadays, the achievements of modern implantology, where courage, imagination and expertise of doctors supported by accom-plishments of engineers and biologists 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. An overview of the present situation [60] indicates a scale and diversity of the currently available therapeutic methods based on cells, undergoing the phase of clinical studies. Amidst the ever-growing array of applications of types of cells and clinical recommendations being appraised, it is important how cell-based products are fabricated and then delivered to patients at a clinically meaningful scale. The current clinical research uses both, Embryonic Stem Cells (ESC), as well as Induced Pluripotent Stem Cells (iPS) [61], despite technical, ethical and product safety barriers and problems [62].

A limited clinical application of embryonic stem cells is associated with the current ethical dilemma and concerns about tumorigenesis in patients [63], however, somatic stem cells, in particular hematopoietic stem cells (HSC) from bone marrow, have a much higher translational potential [64],[65], but it is difficult to expand them in vitro, supporting bone marrow stromal cells BMSCs [66], which are commonly studied and applied clinically these days, and the sub-population of which possesses mesenchymal properties regenerating the tissue [57]. Such natural multipotent and self-renewing cells (MSCs) are present not only in bone marrow, they occur in large amounts in synovial fluid, skeletal muscles and fat tissue [66]. Adipose-Derived Stem Cells (ASCs) have a well-established position in research over stem cells and in regenerative medicine and reconstructive surgery [67]. The terms Mesenchymal Stem Cells (MSCs) and Bone Marrow Stromal Cells (BMSCs) have been used alternately, which is not accurate and not fully justified [68]. As cells, termed by many institutions as Mesenchymal Stem Cell (MSCs), may embrace multipotential cells coming from other tissues than bone marrow, such as placenta [69], umbilical cord blood, fat tissue, muscles of adults, stroma of cornea [70], amniotic fluid [71] or deciduous teeth pulp in infants, even though they are unable to restore the entire organ, the term Multipotent Stromal Cells (MSCs) was proposed alternatively as a better term. The most primitive multipotent stromal (MSCs) cells can be derived from umbilical cord tissue and umbilical cord blood [72]. The developing bud cells of wisdom teeth are a very rich source of stem cells for mesenchymal cells and although considered multipotential, they may prove to be pluripotential and most certainly, in the future, will become the main source for personal banking, research and numerous therapies, including hepatocyte production. A fatty tissue is the richest source of multipotent stromal cells, whilst their presence in peripheral blood is controversial and few of their groups in peripheral blood is capable of expanding a cells culture. A type of pluripotential stem cells which have been obtained artificially from non-pluripotential cells, usually somatic cells of an adult by forcing

the expression of relevant genes in such cells [73], are Induced Pluripotent Stem Cells, obtained for the first time from mouse cells in 2006 and from human cells in 2007 by [74]-[76]. They are similar to natural pluripotential stem cells in many aspects, such as: expression of genes, proteins and receptors; division time; morphology and differential potential; however, their properties and similarities are still being analysed [75]. It was reported in 2010 that mesenchymal cells in the pulp of third molars are very promising in terms of iPS cells production, as the differentiation procedure with their presence is up to 100 times more effective than using skin fibroblasts [77]. 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 [78]. 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 [57],[79]-[85], are characteristic for their lack of differentiation and the 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) [86], also in combination with the use of biodegradable scaffolds [87]. Autologous stem cells are the ones most beneficial as they do not cause an immunological response and thus do not cause harmful immuno-suppressive side effects. Depending on the tissue development stage, stem cells can be divided into the category of adult and stem embryonic cells [57],[81],[82]. Autologous stem cells and progenitor cells may come from umbilical cord blood [88] or tissue [89]. 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 [90]-[93].

Stem cells originating from bone marrow exhibit a large potential for autologous therapies [57], without immunosuppressive treatment [94]-[96]. Differentiated cells, forming structures of an adult organism, represent a more difficult material for breeding. The development of breeding techniques of human stem cells is leading 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 [21]. 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 [21].

Stringent safety requirements must be considered in cell-based therapies, especially that raw materials of animal origin are used in many cell culturing processes, which poses a potential threat of transmitting a pathogen to a recipient or of immunological complications [97]. Safety requirements relating to post-production cleaning must be observed for pluripotential stem cells, which is limiting a possibility of unlimited growth of cells delivered to patients [98]. An approval of the American Food and Drug Administration (FDA) is a globally recognised proof of safety and efficiency of new therapeutic methods and such validation has been awarded up till know to several living skin substitutes produced with human fibroblasts, a swine submucosal layer of a small intestine replacing dura mater or used for treating skin injuries, autologous chondrocytes for regeneration of cartilage losses or acellular scaffolds supporting skin regeneration. A review of cell-based therapies, both, from the standpoint of clinical prospects as well as fabrication challenges, indicates that such therapies have a high potential, despite numerous needs of patients not satisfied until now, however, intensified development of the technology and the fabrication potential of cell-based products is necessary at a scale corresponding to clinical requirements and enabling to eliminate or at least tighten the production gap in this field. Although several production systems are already available for development and therapeutic manipulations of some types of cells, an optimum and universal type of a production platform has not been yet created due to differentiated types of cells and clinical applications. It is necessary to overcome multiple challenges and to better define the production requirements in relation to different technologies to facilitate the application of products and further technology development. Except for mesenchymal stem cells, the fabrication of the majority of therapeutically meaningful cell

types has not yet been mastered at a technologically satisfactory scale, although the outcomes achieved to date are promising. It is therefore necessary that the current clinical activity involving elements of tissue engineering is widely promoted in industry and in academic circles and that gaps are identified in production capacities contributing to cell-based therapies. More detailed considerations concerning the in vivo therapeutic activity mechanism based, notably, on mesenchymal stem cells, are required to achieve progress in this domain and multiple impediments have to be surmounted to facilitate process development and optimisation. There is an urgent need for optimising a delivery system of products based on dedicated cells for each of therapeutic indications. Progress in clinical research is closely linked to fabrication of products in evolving automated processes enabling improved quality and efficiency control [99]-[103] and to establishment of reference standards and implementation of functionally closed production systems. It becomes necessary to build strong market brands at a competitive manufacturer market of cell-based products and to minimise manufacturing costs, to enable refundable therapeutic applications of the products offered, regardless the fact that high quality and safety requirements considerably increase manufacturing costs on all stages. The necessity and possibility of accommodating manufacturing conditions to the scale corresponding to the real clinical needs must be taken into account in the development of the introduced technologies. Certainly, the limits of usable groups of cells and their culturing time, in relation to particular products, must also be analysed, which surely differs from laboratory conditions of bioprocesses' performance. The aim of manufacturing processes is to markedly increase the number of cells as compared to the laboratory scale, without affecting adversely cells' therapeutic potential deteriorating during culturing [104]. A risk of losing the cells' function [105] is especially vital for ensuring cell-based product efficiency and quality, which is of particular significance for adherent cells, hence – prior to further processing – they must be individually separated from the substrate on which they are grown. Production batches for cells, reaching trillions of cells, are thus achievable, although this is each time dependent on individual requirements of a given patient and on the development of a product market for a particular therapeutic indication [106]. In case of many technologies based on cells, there is no comparable credible data available, though, for performance of production processes in conditions deviating many times from those existing in laboratory reactors. When products exhibit long-term stability, as is the case for allogeneic therapies, a manufacturing technology management model for the applied cell-

based products is similar to this used in biopharmaceuticals production [107]. Autologous therapies, which are essentially personalised, are complex due to short-term cells availability and conservation, hence the management methods mentioned above cannot be employed [108], and substantial product losses are associated with maintenance of continuous therapeutic availability of a cell-based product due to expiry, which undoubtedly contributes to increased number of product batches produced, thus their overall costs. Considering a variety of cell types and clinical indications, as well as a diversity of business models of the current and prospect manufacturers of cell-based products, it is necessary to develop, preferably at a global scale, multiple self-complementary, and maybe even alternative production platforms, which poses a challenge to many research institutions in different countries. Full interpretation of the therapeutic activity mechanism of Multipotent Stromal Cells (MSCs) in vivo is an important driver conditioning advancements in this field, and this still remains to be an open issue [109]. Immunomodulation properties of mesenchymal stem cells [110],[111], were pointed out at the turn of the 20th and 21st century, in particular in osteoarthritis and in Crohn's disease, which is related to release of trophic factors also showing that a donor's DNA is retained in a recipient's lungs, lymph nodes and intestine after infusion of mesenchymal stem cells [112]. The contemporary allogeneic technologies using mesenchymal stem cells are used for heart stroke treatment [113] requiring 35-350 million of cells per dose, allowing to deliver appropriate products for 10,000 patients annually. A manufacturing process, which decreases a biological disparity, unavoidably ensures a higher product quality. Small changes in the cells environment at the beginning of cells culturing are leading to big final changes as indicated in particular in the culturing of embryonic stem cells where changes in the level of the dissolved oxygen in a culture medium lead to changes in the cells growth characteristics [114] and differentiation potential [115], which can be prevented, e.g. by mixing in such a way that the microenvironment of cells is determined during culturing. A well-known physical mixing characteristic of a reactor system adapted to traditional biological procedures [116]-[118] and used in the biopharmaceutical industry [119] can be a basis for cell-based processes. The lack of constant process control is, however, a key barrier for consistent implementation of cell-based therapies. Process control strategies are routine in tank bioreactors with mixing [120],[121], and weakly defined in case of more avant-garde bioprocesses. An efficient pool of cell-based technologies, not only with mixing [122]-[124], but also such as tank reactors [125], rocking-motion [126], [127], pneumatically driven rectors [118],[128], T-flasks [99], rotating flasks [129],[130] and

multilayer ones [131], with a fluidised bed [132], made of hollow fibers [133], with air blowing generally [134], requires that cells' sensitivity and product time constraints is considered. The involvement of industry, chiefly small- and medium-sized private biotechnological enterprises, in cell-based technologies has been considerably growing since 2004, and the ranking of therapeutic involvement includes, respectively, digestive tract diseases (48%), lung diseases (40%), cartilage diseases (36%), neurological diseases (28%), diabetes (26%) and bone diseases (25%) [135]. About 100 companies specialised in this area are operating at the American and European market, with one or maybe several at most in Poland. The works conducted must be based on the intensification of basic research to better characterise the conditions of cell-based therapies, which is absolutely necessary to improve the standard of technology, repeatability, quality and mass-volume of manufacturing processes and to develop manufacturing capacities. A few potential business models are dominant in connection with cell-based industrial production, especially "point-of-care" and "off-the-shelf" equipment model [135]. Furthermore, it is necessary to optimise a therapeutic method of delivering cell-based products [136], due to the lack of full clinical evidence in this area. Similar as in the case of production processes, there is a need for customised selection of a cell-based product delivery system in terms of particular therapeutic indications [137].

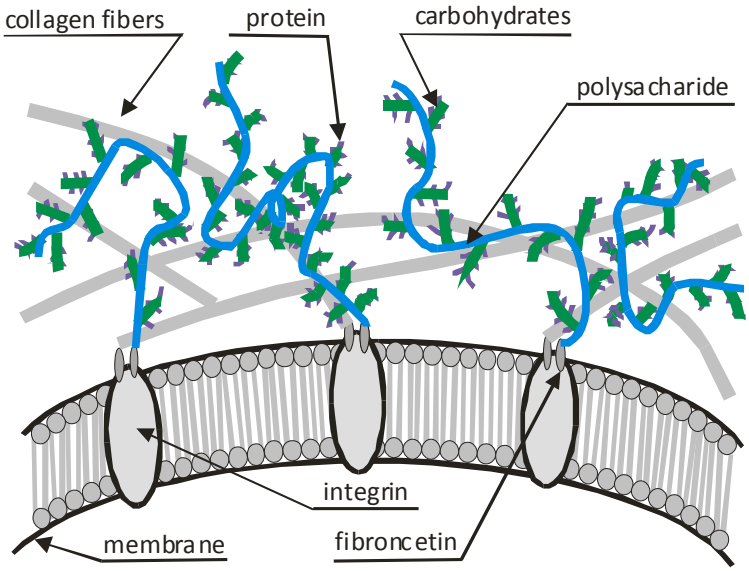


***Figure 1.3.*** *Graphical representation of the natural tissue scaffold joined with the cell surface*

Tissue engineering, as one of the branches of medicine witnessing fastest development, is based on the strategy of establishing tissue scaffolds in order to restore a natural EMC scaffold, called an **e**xtra**c**ellular **m**atrix [138], present in each tissue of a living organism (Fig. 1.3).

Three basic strategies of damaged tissue reconstruction can be distinguished in tissue engineering, with two of them being scaffold-based [139],[140]. These include:

The 1st strategy – cells are implanted in the place of the loss – it consists of injecting (usually as a suspension) the cells directly in the place of the damage occurring. The task of the cells introduced in the place of the loss is to seal the loss formed or to produce the absent chemical substances. It is a non-invasive method employed for small recesses and is unsuitable for regenerating complex tissues (Fig. 1.4) in which a structure encompasses more than one type of cells.

The 2nd strategy – a scaffold is implanted in the place of the defect – it consists of preparing scaffolds, and then placing the so prepared material in the place of the damage

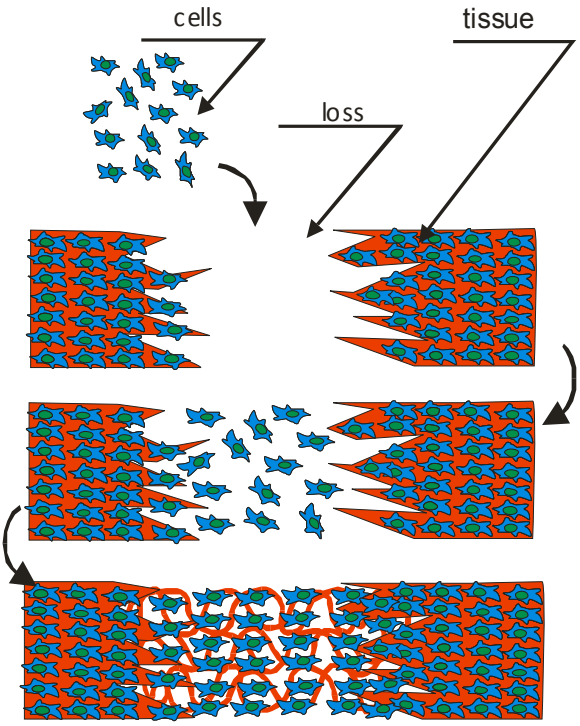


***Figure 1.4.*** *1st strategy – injection of cells in the place of the loss*

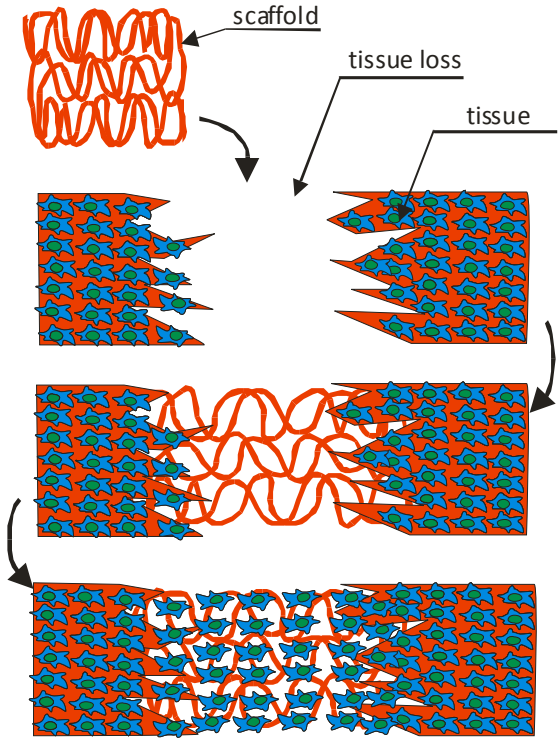


***Figure 1.5.*** *2nd strategy – injection of scaffold in the place of the damaged tissue*

occurring (Fig. 1.5). Scaffolds act as a membrane used in controlled tissue regeneration. The prepared membrane allows – from the side of the defect – to develop only one type of cells, by cutting off any other cells from the place of such a defect. Such a solution dissects a field, in which bone cells are multiplied, from fibrous cells whose multiplication time is much shorter.

The 3rd strategy – a scaffold with cells is implanted in the place of the defect – a scaffold is obtained in this strategy, on which cells are settled and cultured in in vitro conditions. After specific time, a scaffold with cells is implanted into a donor's organism where it joins the existing blood system. Such a measure accelerates a regeneration process (Fig. 1.6).

Two systems of the prepared tissue scaffolds can be differentiated under the 3rd strategy:

- closed systems where cells are placed in a semi-permeable membrane,
- and then such type of structures is placed in a recipient's organism (Fig. 1.7).

Such semi-permeable capsules (Fig. 1.7) have the three basic functions:

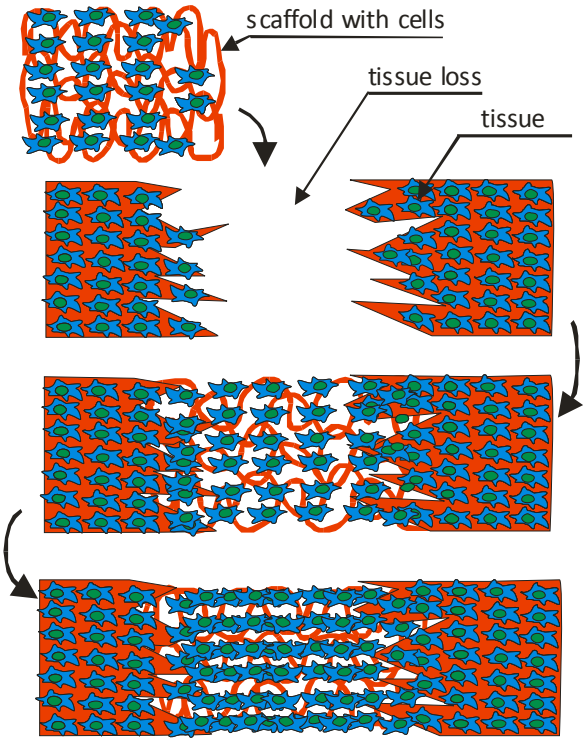


***Figure 1.6.*** *The 3rd strategy – injection of tissue scaffold with cells in the place of the damage occurring*

- protective function – the membrane applied protects the cells placed inside against the recipient's immunity system, which identifies the implanted cells as a foreign body,
- nutritional function – where cells are capable of consuming substances maintaining their existence (vitamins, amino acids, ions, glucoses, $O_2$) from the environment and releasing the metabolites being created (urea, $CO_2$),
- replacement function – where a function of a natural tissue releasing enzymes and hormones vital for the maintenance of life is replaced by a donor's cells encapsulated in a semi-permeable capsule.

The primary disadvantage of such solutions is limited space for the multiplication of cells, dependent upon the size of the capsule in which they were placed. Additionally, the organism fails to remove the damaged cells from inside the capsule, which poses an additional issue, and open systems are being developed for this reason. Open systems are the solutions in which

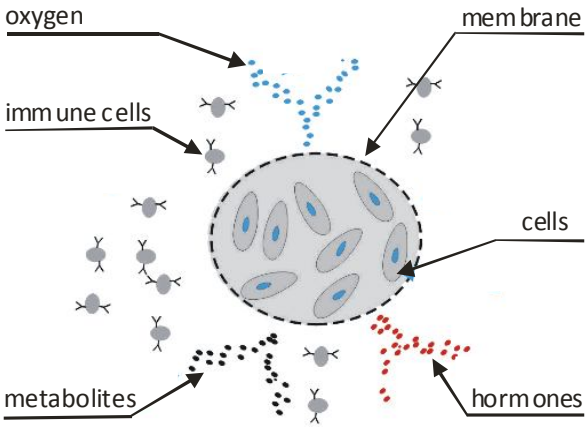


***Figure 1.7.*** *Open system*

materials with a varied shape and functions are obtained by using diverse materials, including mainly biodegradable polymers and technologies.

The properties of tissue scaffolds are largely dependent on the properties of the material used to fabricate them, on the form (solid, porous material), spatial structure, physical and chemical properties. The materials intended for tissue scaffolds should not be toxic, should not release toxic elements, metabolites or compounds.

The scaffolds fabricated should have the following properties, regardless their intended use:

a) the required mechanical properties,

b) optimum porosity,

c) biodegradability depending on regeneration time of the damaged tissue,

d) possibility of sterilisation,

e) structure enabling access of all the cells situated on the scaffold surface to nutrients (glucoses, amino acids, $O_2$),

f) allow to remove metabolic products ($CO_2$, nitrogen compounds),

g) prevent or support the creation of angiogenesis, i.e. where a system of blood vessels is growing through a scaffold.

The selection of a material for tissue scaffolds represents therefore an important engineering task. Table 1.1 provides general criteria of materials selection for tissue scaffolds, including bone scaffolds.

***Table 1.1.*** *General criteria of materials selection for tissue scaffolds, including bone scaffolds*

| General selection criteria of materials for tissue scaffolds, including bone scaffolds, ensuring porous structure, relate to: |
|---|
| material type and material structure, |
| osteoconductivity ability of the material, |
| mechanical strength of the material, |
| easy implant/scaffold fabrication, |
| easy handling in clinical applications of the implant/scaffold. |

A microscopic, porous structure of scaffolds is required, enabling the diffusion of nutrients and metabolism products through 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 [21]. One of the primary challenges in scaffold transplantation based on cells is the lack of nesting 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 [142]-[146], which may lead to the ischaemia of tissues and necrosis [147]. The use of scaffolds usually leads to positive results because, as the substitutes of an extracellular matrix (ECM), they ensure structural stability for the development of tissues and provide an environment of appropriate signals which stimulate cells to proliferation and differentiation as the functional tissue is becoming mature. It is necessary to ensure conditions to fill up scaffold pores by the reconstructed cells and to guarantee neovascularisation [148] for preventing blood clots [149].

## 1.3. Overview of material and technological concepts concerning the fabrication of tissue and bone scaffolds used in tissue engineering

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 [21],[150]. It is a task of tissue and bone scaffolds to ensure mechanical preservation of living tissues in a three-dimensional structure and to ensure an appropriate environment of their development. Bone scaffolds are usually made of a porous biodegradable material, ensuring mechanical support during regeneration of the damaged or sick bone [151],[152]. The role of scaffolds, including also bone scaffolds, is to ensure adhesion and migration of cells and the necessary conditions of their growth by promoting the growth of new blood vessels [151]-[155], serving to deliver organic substances and physical signals and the diffusion of nutrients and other necessary substances, as well as to ensure appropriate mechanical and physiochemical properties supporting tissue integration and development.

The development of tissue scaffolds is currently concentrated on the three types of materials:

- natural materials, including collagen, chitin, elastin, lyophilised bone: a mineralised bone, i.e. a bone from which collagen has been removed and an inorganic part was only left (hydroxyapatite), a demineralised bone – a bone from which inorganic material has been removed, by leaving a structure of organic material (collagen) e.g. coral,
- ceramic ones, including notably hydroxyapatite, bioglass,
- polymer ones, including synthetic polymers.

Neither of the listed three groups is a perfect material for all types of the existing tissues. Natural materials, especially allogeneic and xenogeneic materials ones, pose a risk of transferring viruses from their source of origin to the place of their application. Ceramic materials have a very long time of degradation and are brittle, whereas polymer materials, such as PLA, when decomposed rapidly, acidify the tissue environment. Solutions have been sought for this reason to maintain and expedite a natural process of regeneration, in which the material used, apart from the function of maintaining and restoring the natural scaffold, will release

medicinal or antibacterial agents, i.e. will replace functions of the immunity system which fights microorganisms in natural conditions, and whose interaction with the environment of the damage formed is impossible due to extensively damaged blood vessels and the presence of microorganisms.

Owing to the advancement of state-of-the-art biomaterials, it is currently feasible to employ biomaterials, in particular in controlled tissue regeneration, whose purpose is to create conditions supporting the development of a privileged type of the tissue only (Fig. 1.8). Materials intended for use as membranes for controlled tissue regenerations should meet the conditions set for all biomaterials [156],[157].

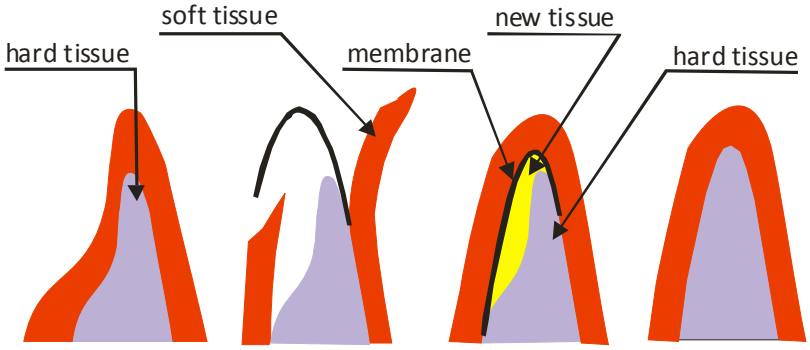


***Figure 1.8.*** *Membrane fixation procedure with example of bone tissue, A – cutting and exposing soft tissues from hard tissues, B – introducing and fixing the membrane, C – protected area, D – membrane decomposition and restoration of the appropriate arrangement of tissues*

Porous resorbable bioglass [158], with the pore walls coated with hydroxy carbonate apatite (HCA), ensuring an enhanced activity of osteoblasts [159] and the expression of genes connected with bones [160] can be used for fabrication of scaffolds. The basic bioactive ceramic material 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 [161]-[163]. Both, bioactive and biodegradable polymers can be employed [151],[164], including, in particular, natural polymers such as: collagen, fibrin, alginate, silk, hyaluronic acid and chitosan used, e.g. for bone reconstruction [165], 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 [151], and some of them, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), may cause negative tissue reactions [166]. Composite materials satisfy mechanical and physiological requirements, e.g. CaP-polymer scaffolds, interconnected tricalcium phosphate (TCP) scaffolds coated inside pores with polycaprolactone (PCL) [167], hydroxyapatite HA/poly(ester-urethane)(PU) [168] or a nano-composite of collagen and Bioglass [169]. The 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 [170], collagen hydrogel [171]. Substitute scaffolds of bones are often administered with medicines, including gentamycin, vancomycin, alendronate , methotrexate and ibuprofen [171],[172] and with growth factors and transcription factors [164],[174],[175]. Regeneration in a natural condition is forcing the removal of an artificial scaffold [176], most advantageously through bioabsorption, which is ensured by numerous natural and synthetic substances used for creation of scaffolds [177],[178]. 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. A natural tissue in a human organism is subject to the activity of body temperature of 36.6°C, aquatic environment, enzymes, proteins, cellular metabolites and forces acting on the tissue, leading to the formation of stresses promoting the creation of microcracks in the tissue structure. The microcracks being formed in natural tissues are regenerated in an organism, whereas when a natural tissue is replaced by an implant, the microcracks created in an engineering material are not undergoing regeneration, what in the longer term poses a fatigue risk for the material, cracks and, in consequence, the necessity to perform transplantation again. Tissue damage is often accompanied by an inflammatory condition caused by the presence of microorganisms which, after entering an organism due to interrupting tissue continuity, intensify the sensation of pain, delay a regeneration process and pose a threat to human life and health. For this reason, modern medicine is seeking materials which, owing to their properties, enable to reconstruct and restore functions of the damaged tissue and are able to protect the environment of the tissue being restored. Moreover, such materials are so designed that, after fulfilling their function, are completely resorbed, into products included in the natural metabolic paths of a living organism, so that, after fulfilling their function, they are decomposed to products non-toxic for a recipient organism such as: $CO_2$ and $H_2O$ [179]. An example of the materials satisfying the above

criteria are biodegradable polymers. A trend for establishing such type of solutions derives from the growing demand for innovative engineering materials which, after implantation, could directly replace the function of the damaged tissue, help to restore it, and then undergo gradual decomposition without leaving the traces of their presence.

The approach described is currently considered to be classical, although it is not clinically applicable in all cases due to medical recommendations. Porous metal materials, though not biodegradable, are also used for scaffolds, mainly Ti and Ta [180], including after treatment of pores' surface [181] and Mg [182] or biodegradable Mg-Ca alloys or biodegradable Mg-Ca alloys [183], have found their applications primarily due to relatively high compressive strength and fatigue strength [151],[184].

A very extensive state-of-the-art in scope of scaffolds materials and fabrication technologies was presented in the earlier own works [3] and 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 [185]-[198]. It is also possible to use different highly-specialised technologies, considering the outcomes of the theoretical own works attained in this field to date [199]-[216].

The traditional, and also the oldest fabrication technologies of scaffolds with a porous structure differentiate the method of emulsifying/lyophilisation [217], to Thermally Induced Phase Separation (TIPS) [218], Solvent Casting & Particulate Leaching (SCPL), where solvent residues may have an adverse effect on cellular structures [219]. 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 [220]-[222]. 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 [223],[224], including hot embossing (also known as nanoimprint lithography) and soft lithography (micro-casting) for achieving patterns with dimensions about of 5 nm [225]-[228].

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 [151],[229]-[232]. 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 [52]. In the three-dimensional printing method (3DP) [233], the particular layers of powder are sprayed with an adequate biocompatible binding agent, e.g. for merging powder to fabricate a scaffold from collagen [234], and a 25% acrylic acid solution in a mixture of water with glycerine [235] 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 [236]. 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 [237]. The limitations of the method originate from wax impurities with biologically incompatible solvents [238], which is not exhibited by new generation materials such as BioBuild and BioSupport dissolving in ethanol or water [238]. The stereolithography method permits to shapen three-dimensional form of liquid polymer [239], in particular using poly(propylene fumarate) (PPF) [240],[241], poly(ethylene glycol) (PEG) [242],[243]. Polymer materials without solvents, including poly(ε-caprolactone) PCL [244],[245], poly(ethylene glycol)–poly(ε-caprolactone)–poly(lactide), PEG-PCL-PLA [245],[246] acrylonitrile-butadiene-styrene (ABS) [247] and hydroxyapatite-poly(ε-caprolactone) HA-PCL [245],[248] are used in Fused Deposition Modelling (FDM) [249]. 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 [206],[250], including, notably, implants for dental purposes [216], was utilised for scaffolds preparation [232] from biodegradable polymers, e.g. polyether polymer, poly(vinyl alcohol), polycaprolactone [251] and poly(L-lactic

acid) [252], and also hydroxyapatite [253] and from composites composed of some of such polymers and hydroxyapatite [252],[254],[255].

Polymer nanofibers have become quite important materials used for scaffolds. At present, many methods are employed to fabricate nanofibers and the most essential ones comprise: Spontaneous Growth, Template-based Synthesis, Electrospinning and Lithography. The first three methods are classified as bottom-up techniques, whereas lithography is classified as a top-down technique. It is also possible to obtain polymer nanofibers in a direct or indirect fashion [256]. The structure of the nanofibers achieved depends on the method selected – Spontaneous Growth allows to formulate crystalline nanostructures, whereas Template-based Synthesis usually leads to the formulation of polycrystalline and amorphous structures. There are about 10,000 polymer chains with average length of macroparticles of 100 μm in the nanofiber cross-section with the diameter of d = 50 nm. Nanofibers with the diameter of 50 to 500 nm are achieved most often in practice. Several polymer nanofiber fabrication technologies exist [26],[179]. The one developed most intensively is electrospinning, permitting to fabricate polymer nanofibers with an electric field from molten polymers (melting electrospinning) where the following polymers are melted in advance: PP, PE, PMMA or PET, and then by subjecting the liquid to the activity of a strong electrostatic field in order to transform it into a nanofiber; and from solutions – solution-electrospinning, where a polymer is transformed into a solution, and then by subjecting the liquid to the activity of a strong electrostatic field in order to elongate the stream and evaporate a solvent, which consequently leads to formation of nanofibers [179],[257]-[260]. 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 [261],[262]. Due to the character of electrospinning, fibres are oriented randomly [263] or are arranged in an orderly manner [264], 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 [261]. Natural and engineering materials can be used as a material, including, in particular, collagen, gelatine, chitosan [261].

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 [265]-[267] is utilised for

scaffolds fabrication. Such types of scaffolds were used, e.g. for regeneration of nervous tissue to stop bleeding and repair infarctuated myocardia, as well as in medical products for slow release of a medicine [268],[269] and for DNA, where the branched DNA particles are hybrydising with each other in the presence of ligases in hydrogel [270]. 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 a technology, employ more advantageous toxicological properties and higher biocompatibility than traditional materials. Conventional hydrogels are particularly useful for three-dimensional placement of cells [271]. 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 [272],[273] or biodegradable polymers, including such as chitosan, gelation, hyaluronic acid and dextran [274]-[278] 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 [279]-[283], and also agarose (a polysaccharide polymer material, extracted from seaweed as one of the two principal components of agar) [271], as thermo-sensitive systems [284], 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 [285],[286], such as 2-(dimethylamino) ethyl methacrylate (DMAEMA) or 2-(di-ethylaminoethyl) methyl methacrylate. Self-assembling peptides hydrogels, including such containing peptide amphiphiles (PAs), can form nonofibres [287],[288] used for three-dimensional formation of tissue cultures [287],[289]-[291]. 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) [293]-[297], and also natural hydrogels such as dextran, alginate, chitosan and hyaluronic acid synthesised from PEGDA/PEGDMA [298]-[301] and Michael-type addition reaction [302]-[304] and Schiff base – crosslinked hydrogels

[305]-[308]. In the case of enzyme-mediated cross-linking [270], transglutaminases (including Factor Xllla) and horseradish peroxidases (HRP) [271] are used for the catalysis of star-shaped PEG hydrogels [309] and tissue transglutaminase catalysed PEG hydrogels [310] and also tyrosinase, phosphopantetheinyl transferase, lysyl oxidase, plasma amine oxidase, and phosphatases [311], 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 [312]-[318]. Ionic cross-linking hydrogels include calcium-crosslinked alginate [271] and chitosan–polylysine, chitosan–glycerol phosphate salt and chitosan–alginate hydrogels [319]-[321]. Different synthetic and natural polymers were used for this purpose, including polyethylene glycol (PEG), and copolymers containing PEG [322], hyaluronic acid (HA) [301],[323] after an oxidation reaction through HA–tyramine conjugates [312] and as a result of formation between HA–SH [302],[324] and Michael addition [303], [325], collagen and gelatin hydrogels mostly cross-linked using gluteraldehyde, genipin or water-soluble carbodiimides [326]-[328], chitosan [329]-[332], dextran 192 [333],[334] and alginate [335]. Hydrogels were used for reconstruction of the retina [336], ligament [337], fatty tissue [276], kidneys [338], muscles [339], blood vessels [340],[341], and also heart, neural cells, invertebral discs, bones and gristle [271]. Hydrogels were used to prevent adhesions [342],[343], to promote cellular adhesion [344]-[346]. So-called strong hydrogels were developed to improve mechanical properties [347]. Three-dimensional representation is possible of placement of cells with energy in hydrogel to vascular structures using a laser [348],[349], notably for recording directly the endothelial cell [349]. The most technologically advanced methods of three-dimension printing include at present direct organ printing [350],[351], 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 [352]. A polymer-cell mixture can be dosed using this technique, leading to formation of cell hydrogel [353], microfluidics allows for the creation of three-dimensions systems of cells [354], and hydrogels from photopolymerisation polymer solutions can also be used [355], and also SFF techniques, including stereolithography techniques to create scaffolds made of PEG hydrogels [243]. The first production system for three-dimensional printing of tissues was delivered only in 2009 based on the NovoGen bioprinting technology [356]. A three-dimensional structure is obtained by subsequent formation of layers of living tissues on the gel or

sugar matrix substrate [357]. 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 [358]. 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 [359]. Press reports announce, on the other hand, that China has invested nearly USD 0.5 billion to establish 10 national institutes for development of organ printing [360], in which the printing of ears, livers 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 [361],[362]. 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 [363], and an American team confirmed on 1 August 2014 it is ready to print a heart [364].

A thorough state-of-the-art undertaken shows the high technological advancement of fabrication methods of tissue scaffolds, including bone scaffolds, as a technical basis in tissue engineering. Special attention is drawn further in the work on the possible use of polymer nanofibers for the manufacture of scaffolds employed in tissue engineering.

## 1.4. Final remarks on the development prospects of scaffolds in view of the challenges of regenerative medicine and tissue engineering

This work draws attention to the special importance of development tendencies of the medical bionic implant/artificial organs market, orthopaedic devices market, orthopaedic soft tissue repair market, orthopaedic trauma fixation devices market, orthopaedic soft tissue repair market, 3D Printing in Medical Applications Market and the biomaterials market. The analysis made shows beyond any doubts a clear development trend of all the world markets of biomaterials and various medical products, with division into traditional sectors of such market, though. Forecasts are very promising. As pointed out earlier, the medical bionic implant and artificial organs market is estimated to reach USD 17.82 billion in 2017 [6] at a CAGR of 7.1% from 2012 to 2017, the global orthopaedic devices market a value of USD 41.2 billion in 20195 at a CAGR of 4.9% from 2013 to 2019, the global orthopaedic trauma fixation devices market will grow to a value of USD 9.3 billion in 20206 at a CAGR of 7.2% from 2014 to 2019, the value of the global orthopaedic soft tissue will be USD 8.5 billion in 20197 at a CAGR of 7.2% from 2013 to 2019, while the 3D Printing in Medical Applications Market will reach the value of USD 965,500,000 8 in 2019 with a high CAGR of 15.4% from 2013 to 2019, whilst the global biomaterials market will grow to a value of USD 33,600 million in 2019 [12] at a CAGR of 4.1% from 2013 to 2019. The underlying reasons of such dynamic growth are seen to be, notably, increased healthcare spendings, development of state-of-the-art medical technologies due to a substantially improved condition and possibilities of diagnosing various disorders, as well as robotisation and computerisation of many medical procedures enabling effective treatment of many diseases, which could not have been treated just a few years ago. On the other hand, the dynamic growth of the aforementioned markets stems from a higher incidence of different diseases, including civilisational diseases, e.g. malignant tumours [1],[365], cardiovascular diseases and such related to society ageing, including geriatric arthritis and osteoporosis, and also a sharp increase in bodily injuries due to traffic accidents, particularly due to a constantly growing number of cars, and also the development of sports, including grassroots sports and a huge number of accidents connected with diverse sports disciplines being practised massively. The related organ or tissue loss or

damage due to post-injury defects, post-resection defects, as well as those originating from operative treatment of cancerous tumours or inflammation processes and as a result of other disorders necessitates, and frequently gives a possibility at present to replace or supplement such organs or tissues to prevent biological and social degradation of patients and restore their living functions, either normal functions or such acceptably similar to normal. The achievements of modern implantology, owing to the accomplishments of doctors and 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 and to return to their full social and professional activity after experiencing severe injuries or losses, and also other disorders.

Considering the specific topics discussed further in this work, nanoporous materials can be considered a special material which can be used for some tissue scaffolds according to the own author's concepts [4], with such materials consisting of nanofibers, as a special kind of a nanocomposite material, where the matrix function is played by empty space (air, vacuum). The properties of such nanocomposites are determined by the properties of their matrix, the properties of the reinforcing phase, the geometry of the reinforcing phase (quantity/number, length, diameter, structure and orientation of fibers) and the quality of linkage between the matrix and the reinforcing phase. There are many fabrication methods of polymeric composites with air acting as a matrix and a reinforcing phase are fibers with a different diameter (standard fibers, thin fibers, microfibers) [188]. Textile technologies are most popular, i.e.: Melt-blown [366], needlepunching [367] and spunlacing (hydroentanglement) [368], Spunbond Technology [369], Thermal Bonding of Nonwoven Fabrics [370] and others. Porous polymer materials, with their reinforcing phase being nano- and sometimes microfibers with the diameter of 50-500 nm, and the matrix function played by the air, have their usage prospects resulting most of all from their geometric characteristics. Efforts have been continued to produce a polymer-air composite featuring high porosity, air permeability, absorptivity, barrierity, bacteriocidity, biocompatibility, intoxicity, a possibility of releasing medicinal agents in a controlled way, appropriate mechanical strength and its structure supporting regeneration. The efforts require multiple interdisciplinary investigations, including those connected with research into polymer nanofibers with a different diameter, made both, of natural polymers and synthetic polymers, including the newly established ones, in particular: PLLA, PGA, PLA, PLGA, PCL, PEO, chitosan, collagen, elastin, hyaluronic acid and others

[3]. The efficiency of the additives introduced, such as silver, iodine, characterised by bacteriocidity, has been ascertained with multiple studies. Chitosan, a derivative of chitin, a second, after cellulose, natural polymer most often occurring in nature, has been observed attentively for several years. It exhibits precious properties, especially antibacterialness, antifungalness, biocompatibility, biodegradability and intoxicity. Chitosan nanofibers can be deposited onto a textile carrier surface, mixed with other polymeric nanofibers such as PEO, PVA, PLA, PET, collagen or produced as hybrid nanofibers (chitosan-second polymer). The additives introduced often reduce absorptivity, elasticity, stretchability and even reduce chitosan bacteriocidity. Designing and producing a composite material exhibiting the above properties for application to extensive wounds sustained from burning and to pathogenic lesions remains to be a challenge, and especially to put into life the concept of a biological and engineering material [4]. A large surface area in relation to the mass, a ratio between the diameter and length of nanofibers, low density of damages on the surface of nanofibers as compared to standard fibers are just some of the advantages of the materials discussed [371]-[379]. Porous composite materials, due to their properties and similarity to a natural extra-cellular matrix, can be used as scaffolds supporting the restoration of natural tissue and can thus be ultimately applied in medicine. Fibers and mats made of nanofibers produced using selected polymer materials can also be used as membranes enabling to control the development of certain tissues, e.g. after implantation or applying a dressing. A new generation of dressings has been sought for defects formed at the surface of a body having characteristics supporting the healing of wounds, such as: ensuring physical wound continuity, maintaining a humid wound environment, correct thermal regulation, active absorption of exudation, interaction with the wound by releasing medicinal agents and easy attaching and removing from the wound surface [380]-[385]. For dressings, membranes and scaffolds, nanofibers can act as a carrier of bactericidal agents, notably silver, iodine [386]-[390]. Polymeric nanofiber mats and fleece can be used in personal hygiene as cosmetic pellets. Due to the presence of air, porous composite materials possess low heat conductivity and can be applied as heat insulation materials and as vibration or sound damping materials. Moreover, high air permeability and an ability to retain a wide spectrum of differently sized particles by a mat allows to filter air and liquid. A chance for fabricating new porous nanocomposite materials, featuring innovative properties, is offered by appropriate selection and correct application of nanofibers with a diverse chemical composition, structure and morphology, the use of the available

technologies or the establishment of new composite fabrication technologies and the use of the available or the establishment of new technologies for nanofiber structure and surface modification and other processes leading to the improved combination/improved wettability/ adhesion of nanostructural composite materials components, as well as the utilisation of the available or modification of the known methods of nanofibers manufacturing. In the light of the above information, knowledge about polymer nanofibers and their manufacturing technologies, which are the main topic of interest in the next parts of this work, is becoming more important, both theoretically and practically.

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