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The concept of biologically active microporous engineering materials and composite biological-engineering materials for regenerative medicine and dentistry

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ABSTRACT

Purpose: The concept presented in this study proposes indirect solutions, both, rigid ones involving high strength and transmission of high mechanical loads, and ones which are elastic, thin and light as fog, when a very light dressing supplying living cells is applied to an extensive wound, e.g. on skin, in a way ensuring their fast fusion with the defected surface of body. They are proposed implant-scaffolds, i.e. rigid devices composed of a solid metal core and a surface or transition porous zone into which living cells may grow. The pores are so small that hair or even a very thin needle can be placed there. The interior of such openings, extending along the entire part of material, needs to be covered from the inside with a very thin coating which can be accepted by living cells so that they can develop in such conditions and penetrate such openings deep inside.

Design/methodology/approach: The material solutions proposed in the study result from a synergy of methods of technical sciences, including materials engineering and chemical sciences, in consistency with the adopted author's assumptions, but, in particular, depending on the specificity of clinical conditions and biological sciences, also tissue engineering, in the context of medical sciences, including tissue therapy, require a multi-aspect state-of-the-art analysis and the resulting specific scientific problems which should be solved and their pioneering character. Taking into consideration the lack of references in the literature to the overall analysis of the issue, separate aspects are analysed further in this study concerning biologically active cellular structures and a substrate with an engineering composite material matrix used for scaffolds and newly developed implant-scaffolds.

Findings: In consideration of the principal research intention of the presented research concept, pertaining to the development of hybrid and multilayer biological-engineering composite materials, including rigid and elastic ones, composed not only of biologically active cellular structures, the state-of-the-art of which is presented earlier, but also of a substrate with an engineering material matrix, with an optimally selected type, chemical composition and a nanometric structure, fulfilling a carrier function, and in fact a scaffold for biological structures required to have an appropriate array of mechanical properties

and rigidity, allowing applications in therapeutic conditions, as well as physiochemical properties, permitting to fully control the behaviour of the whole biological- engineering composite material upon achieving the therapeutic aims defined by medical reasons, it is necessary to consider the material and technological aspects allowing to accomplish the abovementioned assumptions in the current state of technology.

Practical implications: Despite obvious technological progress seen in the recent period in the fabrication of cell-based products and in cell-based therapies, it should be acknowledged that therapies based on implantable devices together with the participation of growing cells, and especially the mass technological processes required by such therapies, are still in a relatively incipient phase of technological development, leaving a lot of space for original and pioneering basic research. The basic research performed in the study will represent a solid basis for undertaking application works in the future, allowing to fabricate a new generation of concrete products unknown today, which will find their application in regenerative medicine and dentistry for treating various internal and external disorders associated with, e.g. burning, healing or severe wounds and injuries, removal of consequences of oncological or post-injury disorders.

Originality/value: The primary scientific aim of the presented research concept is to verify a research thesis that it is possible and relevant to develop multilayer biological-engineering composite materials having clinical readiness, partially artificial ones, using Selective Laser Sintering (SLS), to fabricate microporous rigid titanium and titanium alloy skeletons or for polymer nanofiber electrospinning to produce microporous elastic mats, and partially biological ones consisting of living cells filling the appropriately prepared pores in the mentioned microporous materials. Cognitive aspects concern the recognition of phenomena and mechanisms associated with fabrication of the so understood biologically active microporous engineering material being, in essence, a biological-engineering composite material, and of surface phenomena and mechanisms taking place between individual layers of this unique material and their influence on manufacturing processes, both, in the engineering as well as biological part, and on the behaviour of particular layers and joint zones between such layers during material fabrication, as well as in conditions simulating therapy preparation and duration, and alternatively during the non-destructive separation of cellular structures from a substrate from a composite engineering material substrate on which cells are grown, but already after fulfilling the intended therapeutic function, if the material is not permanently left in the organism.

Keywords: Implants; Implants-scaffolds; Biological-engineering composites; Tissue engineering; Regenerative medicine

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CONCEPTUAL STUDY

1. Introduction

Empathy forces each of us to show concern for human misery, and pragmatism calls for the adequate response to the phenomena observed. Severe cases of diseases and different types of accidents at work, transport accidents, travel accidents and sports accidents are known in each family. People tend to live longer and longer, for the purpose of which numerous programmes are put into life, e.g. healthcare and social care programmes. People want to spend their time actively, so they practise sports for leisure, but it turns out that this way they expose themselves to severe health complications and accidents. Human joints are often wearing. Many people suffer from extensive burns, persistent ulcerations, often threatening directly one's life. People lose their teeth. Sometimes due to long term neglect people lose some or all of their teeth or extensive losses are caused by tooth decay, but also by natural wear or accidents. Sick teeth cause complications for many organs, heart, joints. Over 35 thousand accidents happen on Polish roads each year with a death toll of about 3.5 thousand people, and nearly 45 thousand people suffer injuries. About 150 thousand Poles develop cancer each year, and 90 thousand people a year die because of cancer. In the Table 1 the main reasons of the biological and social degradation of patients at the European Union scale are

Table 1.
The main reasons of the biological and social degradation of patients at the European Union scale

No.	The main reasons of the biological and social degradation of patients
1	the marked growth of 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 in the human population
2	the necessity to replace or supplement such loses in organs or tissues to prevent biological and social degradation of patients and to restore their living functions, either normal functions or such acceptably similar to normal
3	population aging (the official HORIZON 2020 Programme documents report that the number of people in the EU aged over 65 will have grown by 70% by 2050), which considerably increases the number of patients requiring either surgical intervention with replacement or supplementation of loses in organs or tissues inclusively
4	the growing number of sports accidents and the related serious bodily injuries of many people (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), often requiring surgical intervention with replacement or supplementation of loses in organs or tissues inclusively
5	the growing number of road accidents and the related severe injuries of more and more people (the data of the Association for Improving Safety of Road Traffic reveals that about 1.7 million people suffer injuries in the EU every year), requiring many times surgical intervention with replacement or supplementation of loses in organs or tissues inclusively

specified. It happens very close around us. It, of course, must appal. But it is not enough. These people cannot be left alone with their suffering.

One of the fundamental tasks globally, considered to be one of the European Union's and Poland's priorities, is to improve the society's condition of health, medical care and health safety. The numerous tasks related to this topic include the prevention of health risks, early recognition of diseases, rapid and effective implementation of medical procedures, comprehensive and continued therapies leading to improved health condition and the improved health condition and improved quality of the society's life. The European Health Strategy regards health-related aspects to be a central focus of the Community's policy and proposes a programme of actions for citizens, by recognising their right to own health and healthcare and the promotion of the ageing society's health, the protection of citizens against risks for health and life and to support dynamic healthcare systems and new technologies. The idea is to protect against serious health risks, especially such as civilisational diseases, pandemics and bioterrorism and to support research, especially such applying modern technologies, to ensure the fullest prophylactics of diseases and safe treatment of patients, taking into account the relationships between health and economic well-being. A significant and costly problem of modern medicine is the necessity to replace or supplement organs or tissues, in particular in orthopaedics and traumatology and maxillo-facial surgery and restorative dentistry, to prevent the biological and social degradation of patients and to restore their living functions. Intervention medicine, surgery, saves lives in many cases. But the price for saving one's life are sometimes extensive mutilations caused by the amputation of different organs, limbs, bones, skin losses. Naturally, patients are offered prostheses, even implants. A range of mechanical devices, screws, fixation plates, nails, glues is required to fixate such medical devices to a body and the implanted device, although serves the patient, is artificial. More advanced methods concern the implantation of living cells, and even entire organs or their restoration. The delicacy of such solutions needs to be realised. A concept has come into life of specific 3D spatial scaffolds containing numerous pores into which living cells may grow, and such meshes after some time may disappear in an organism or may stay there permanently provided they are not harmful. It should be known, however, that temporary loads on, e.g. a leg bone near a hip joint may reach even several tonnes, hence it is hard to imagine that it is enough to wait until cells restore the lost or surgically removed bodily parts, to finally transfer such loads.

The concept presented in this study proposes indirect solutions, both, rigid ones involving high strength and transmission of high mechanical loads, and ones which are elastic, thin and light as fog, when a very light dressing supplying living cells is applied to an extensive wound, e.g. on skin, in a way ensuring their fast fusion with the defected surface of body. Implant-scaffolds, i.e. rigid devices composed of a solid metal core and a surface or transition porous zone into which living cells may grow are proposed. The pores are so small that hair or even a very thin needle

can be placed there. The interior of such openings, extending along the entire part of material, needs to be covered from the inside with a very thin coating which can be accepted by living cells so that they can develop in such conditions and penetrate such openings deep inside. After performing suitable radiographs with a method similar to computer tomography, a shape of such a device – accurately adapted to a patient's anatomical features and to the loss – can be designed. Cells can be cultured in a laboratory on the so prepared metal and such an engineering and biological material can be introduced during surgery, in a single procedure, into a patient's body and ensure the fusion of cells from such implant surface with the own cells of the patient's body. This also applies to a removed tooth which can be replaced with a suitably shaped implant with own cells of a patient's bone cultured in a laboratory, but also to an artificial oesophagus and prostheses of some blood cells, although the endings connecting with post-operative stumps will only be made as rigid here. When burns and skin losses are treated, a multilayer engineering and biological plaster with cultured skin cells has to be provided outside and, inside, having a layer which will disappear without detaching the outer cover carrying such cells, which is shaped like a mat with very thin fibres of special polymers which are at least 5 times thinner than human hair. There can be several such amyotrophic layers and they may disappear due to slightly elevated temperature or flow of electric current, if an appropriate number of carbon nanotubes is introduced there. The thing seems simple if not for the fact that it is unknown how to make those particular layers adhere to each other permanently, and even more difficult to make such living cells to develop on such surfaces, also inside such small openings. This mutual interaction on the contacting surfaces of different layers and their selection and interaction with living cells should be recognised and explicated under this concept. Moreover, a method is to be elaborated of producing such sophisticated layered composite biological-engineering materials, where the whole physical problem comes down to sizes much smaller than the diameter of human hair. If such basic aspects are resolved, appropriate implants with own cells can be produced in the future on demand, with the shape and dimension accommodated to the individual size of the damaged and removed part of a given patient's body. This will create for many people better conditions of recovery and of returning to normal life after experiencing severe operations, sometime as the only life-saving solution. Many families will be relieved because there is hope their relatives will suffer at least a little bit less. The problem was presented earlier in a few invited [1-12] and contributed [13-23] lectures in important international conferences, the selected detailed information as results of the own preliminary investigations were presented in studies and papers [24-45] and in patent applications [46-52] awarded in important international innovative fairs [53-60] prepared by the Author with the group of closest co-operators. This study is continuation and development of the ideas presented in the work [41] and the main assumptions of the concept of biologically active microporous engineering materials and composite biological-engineering materials for regenerative medicine and dentistry are presented in it.

2. State-of-the-art

The material solutions proposed in the study result from a synergy of methods of technical sciences, including materials engineering and chemical sciences, in consistency with the adopted author's assumptions, but, in particular, depending on the specificity of clinical conditions and biological sciences, also tissue engineering, in the context of medical sciences, including tissue therapy, require a multi-aspect state-of-the-art analysis and the resulting specific scientific problems which should be solved, their pioneering character and the impact of their outcomes on the evolvement of research and the mentioned scientific disciplines, as well as societal and economic relevance. Taking into consideration the lack of references in the literature to the overall analysis of the issue, separate aspects are analysed further in this study concerning biologically active cellular structures and a substrate with an engineering composite material matrix used for scaffolds and newly developed implant-scaffolds.

The development of regenerative medicine, with the first reports dating back to 1992 [61], as a relatively new field of medicine the purpose of which is treatment – by replacing old and sick cells with young cells, also using tissue engineering methods and cell-based therapies or organism regeneration by means of a gene therapy, raises numerous new challenges, notably in counteracting the symptoms and consequences of diseases, and even their causes [62-66]. On the other hand, tissue engineering is an interdisciplinary field employing the principles of engineering and life sciences for development of biological substitutes, for restoration, maintenance and improvement of functions of tissues or entire organs [67,68] and is based on understanding the principles of tissue growth and on applying this for functional production of a replacement tissue for clinical use [69]. Tissue engineering, introduced in 1985 by Y.C. Fung [70], as a field of technical sciences which utilises medical knowledge and materials engineering

methods, evolving dynamically since the mid-90's of the last century, has been involved in the construction and fabrication of scaffolds maintaining the developing tissues, in the 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 [71,72]. It should be noted that the notion of scaffolds is quite comprehensive, as it may refer to engineered extracellular matrices "scaffolds", but also rigid microporous materials into which osteoblasts may grow, and also to microporous mats made of polymer nanofibres, into which living cells are growing and may be used as specific plasters, to treat for example burns or to reconstruct large fragments of skin.

Tissue engineering provides technical support for regenerative medicine, enabling 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 [67]. The current methods of organ and tissue replacement employ primarily autographs, allografts or metal devices or such made of other engineering materials [73]. The application of therapies based on living cells in medicine is a relatively new concept as the first successful allogeneic transplantation of human haematopoietic stem cells (HSC) was seen as late as in 1968 [74], then the cells were used for generation of skeletal tissues [75] and later for other therapeutic applications [76] as dramatic growth was seen in the mid-90's of the 20th century [77]. Advanced skin and cartilage implants have found their common application in the clinical practices until now. The application of therapeutic cells or cell-based therapies boasts a global market with the revenue of more than a billion USD [78]. Therapeutic strategies include direct transplantation 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. Implantable biomedical devices encompass numerous solutions eliminating various dysfunctions of a human organism and 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 [79]. An overview of the present situation [80] indicates a scale and diversity of the currently available therapeutic methods based on cells, undergoing the phase of clinical studies. Opposite to pure therapies, in which stem cells are injected directly into peripheral circulation or are 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, and such research has constantly evolved [73,81-90]. The efficiency of cell-based therapies depends on the preservation of their viability after implantation [91,92], to prevent the ischaemia of tissues and necrosis [93-98]. Scaffolds must exhibit adequate mechanical properties, enable the adhesion of cells and facilitate their development in order to form a three-dimensional tissue structure in conditions simulating a natural microenvironment [73,99], and ensure mechanical preservation of living tissues in a three-dimensional structure and ensure an appropriate environment of development for them. The role of scaffolds, including also bone scaffolds, is to ensure the adhesion and migration of cells and the necessary conditions of their growth by promoting the growth of new blood vessels [100-103].

Bioactive and biodegradable polymers can be employed for scaffold fabrication [102,104]. Although composite materials satisfy mechanical and physiological requirements [105-107], however, due to the specificity of the envisaged therapeutic applications they are not covered by this study, the same as the third-generation scaffolds, which not only allow to create a new tissue and its biomineralisation, but are also osteoinductive [108,109], and are also administered with medicines [110,111], and growth factors and transcription factors [104,112,113]. Porous metal materials, mainly Ti and Ta [114], are used for non-biodegradable scaffolds, including after treatment of the pore surface [115] and Mg [116] or biodegradable Mg-Ca alloys [117], applied primarily due to relatively high compressive strength and fatigue strength [104,118]. 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 the migration of cells and conditions to fill up scaffold pores by the reconstructed cells and to guarantee neovascularisation [119] for preventing blood clots [120], and small enough to prevent the sealing of pores in a scaffold [73]. Regeneration in a natural condition is forcing the removal of an artificial scaffold [121-123]. 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 clinical application of embryonic stem cells is limited [124], and there is a much higher potential for somatic and especially hematopoietic stem cells (HSC) from bone marrow stromal [125,126], supporting bone marrow stromal cells (BMSCs) as a standard [76,127]. Naturally multipotent and self-renewing cells (MSCs) are present in bone marrow, synovial fluid, tendons, skeletal

muscles and fat tissue – ASCs (adipose-derived stem cells) [127,128]. Mesenchymal Stem Cells (MSCs) may embrace multipotential cells coming from other tissues than bone marrow, such as placenta [129], umbilical cord blood, fat tissue, muscles of adults, stroma of cornea [130], amniotic fluid [131] or deciduous teeth pulp in infants, and the term Multipotent Stromal Cells (MSCs) was proposed as a better term. Autologous stem cells are the ones most beneficial [76], as they do not cause an immunological response and thus do not require immunosuppressive treatment [132-134]. Depending on the tissue development stage, stem cells can be divided into the category of adult and stem embryonic cells [76,135,136]. Autologous stem cells and progenitor cells may come from umbilical cord blood [137] or tissue [138]. 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 [139-142]. 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, although it is thought that adult stem cells are usually useful to a limited extent [73]. Stringent safety requirements must be considered in cell-based therapies because raw materials of animal origin are used, which poses a potential threat of transmitting a pathogen to a recipient or of immunological complications [143] and as post-production cleaning is required [144]. 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. More detailed considerations concerning the mechanism of in vivo therapeutic activity are required to achieve progress in this domain and to facilitate process development and optimisation. Progress in clinical research is closely linked to fabrication of products in the developing automated processes, enabling improved quality and efficiency control [145-148] and with the establishment of reference standards and the implementation of functionally closed production systems. The involvement of industry, chiefly small- and medium-sized private biotechnological enterprises, in cell-based technologies has been considerably growing since 2004. 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. The issue of removing structural parts of cell-based products once they fulfil their therapeutic function, including engineered extracellular matrices, and most often scaffolds indispensable for technological and therapeutic reasons, is becoming a separate and highly important issue. It is therefore also necessary to create methods and clarify reasons and conditions of separating unnecessary pieces of cell-based products provided patients' own cells are not interfered with, with such cells being restored as a result of a therapy performed with such products. It is hence substantiated to intensively draw the scientific environment's attention to the elaboration and explanation of the phenomena accompanying the growing of tissue structures in conditions allowing their industrial production for the purpose of well developed and adequately organised therapeutic processes; and also to physiochemical fundamentals of introducing appropriate engineering materials and technological processes utilised for them, including nanotechnology; to elaborate and explain the role of a substrate for culturing tissue structures and the interaction between the surface structure of engineering materials forming the substrate and the tissue structures deposited onto it.

In consideration of the principal research intention of the presented research concept, pertaining to the development of hybrid and multilayer biological-engineering composite materials, including rigid and elastic ones, composed not only of biologically active cellular structures, the state-of-the-art of which is presented earlier, but also of a substrate with an engineering material matrix, with an optimally selected type, chemical composition and a nanometric structure, fulfilling a carrier function, and in fact a scaffold for biological structures required to have an appropriate array of mechanical properties and rigidity, allowing applications in therapeutic conditions, as well as physiochemical properties, permitting to fully control the behaviour of the whole biological-engineering composite material upon achieving the therapeutic aims defined by medical reasons, it is necessary to consider the material and technological aspects allowing to accomplish the above-mentioned assumptions in the current state of technology. The pioneering solutions proposed in this study, resulting from a synergy of tissue engineering methods and material engineering methods, call for the use of porous and high-

strength non-degradable composite and/or polymer materials for the substrate (which is strongly, but not exclusively, dependent on the specificity of the clinical application) together with applying, at the same time, biodegradable and non-biodegradable materials for tissue scaffolds.

Literature analyses concerning two technologies are only described here considering the assumptions of the presented research concept, namely additive manufacturing, especially Selective Laser Sintering (SLS) with reference to rigid composite biological-engineering materials, and polymer nanofiber electrospinning with reference to elastic materials. Selective Laser Sintering (SLS) is similar to 3D printing, and is a technique used commonly for additive manufacturing from metallic and ceramic materials [13-15,17-20,22,25,28-31,34,37,38,41,43,44,149], including, notably, implants for dental purposes and was also utilised for scaffolds preparation [150] from biodegradable polymers and composites [151-155]. Nanofibrous scaffolds forming microporous mats are manufactured by electrospinning [26,35,39,40,51,52] and the so obtained nanofibres with the diameter of 5 nm to over 1 mm are continuous and randomly interconnected [156,157]. Due to the character of electrospinning, fibres are oriented randomly [158] or are arranged in an orderly manner [159], 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 [160]. Natural and engineering materials can be used as a material [157]. The earlier own works [34,41] present in much detail the state of the art in scope of scaffold materials and manufacturing technologies and a concept of the synergic use, for this purpose, of the existing achievements in surgery and regenerative medicine in the field of prosthetics/implantation for treatment of civilisational diseases and their effects, materials engineering and manufacturing engineering in the field of design and manufacture of prostheses/implants made of various engineering materials and tissue engineering in the field of selection of materials and fabrication technologies of scaffolds [161-168], and it is also possible to use different highly-specialised technologies, considering the outcomes of the theoretical own works attained in this field to date [27,46-50,149,169-180]. Valuable research into the selection of materials for scaffolds is also pursued by research institutions in Poland [99,181-188]. 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.

Despite obvious technological progress seen in the recent period in the fabrication of cell-based products and in cell-based therapies, it should be acknowledged that therapies based on implantable devices together with the participation of growing cells, and especially the mass technological processes required by such therapies, are still in a relatively incipient phase of technological development, leaving a lot of space for original and pioneering basic research.

3. Research objectives and hypothesis

Undertaking a scientific issue presented in this study, consists of the synergic utilisation of the existing achievements in materials engineering and manufacturing engineering, in the field of design and manufacture of prostheses/implants made of various porous high-strength engineering materials, surgery and regenerative medicine in the field of prosthetics/implantation for the treatment of civilisational diseases affecting continuously a considerable part of the society and their consequences, and tissue engineering in the field of selection of materials and fabrication technologies of implant-scaffolds and scaffolds and biological-engineering composites, allowing the growth of living cells and of researching, identifying and describing their structure and the properties of the newly created materials, is an interesting and pioneering cognitive issue serving to acquire new knowledge on the fundamentals of the phenomena and facts. The essence of the discussed scientific problem is to research, identify and describe the structure and properties of hybrid multilayer biological-engineering composite materials manufactured with completely separate newly developed custom technologies according to two variants, which are completely different in terms of the technology, structure and applications: rigid and elastic ones, with various therapeutic application possibilities, fulfilling at the same time several functions, including mainly the readiness of the biologically active layer of a biological-engineering composite – composed of artificially cultured cellular structures – for assimilation with natural humans cells and for separation of a composite engineering material from the structure, after meeting the clinical requirements related to the therapy applied; an ability of adhesion of a layer of different types of artificially cultured cellular structures to a multilayer composite engineering material substrate and the proliferation of cells inside its pores, ensuring the required mechanical properties, including rigidity and numerous physiochemical properties; and an ability for separating non-destructively the cellular structures from a composite engineering material substrate on which they are cultured, after meeting the clinical requirements, by controlling the interaction of various physiochemical factors. It is an interesting and

pioneering cognitive issue serving to acquire new knowledge on the fundamentals of the phenomena and observable facts without focussing on immediate practical applications.

An inspiration to undertake the mentioned, very complex and hybrid research topic are Albert Einstein's words that imagination is more important than knowledge, and Martin Luther King's words saying that he had a dream. The Author's dream, suggested by his imagination, is the vision to alleviate the fate of many people afflicted by severe diseases, including an oncological disease, so that in a single procedure, together with removing sick tissues, including also bone or even teeth, reconstruction can be performed, by placing implant-scaffolds made of biological-engineering composite with autologous cells, which will immediately grow into a patient's tissues after surgical procedures. Stated below are the principal, fully original and pioneering research intentions justifying the implementation of the planned research pertaining only to thorough basic investigations encompassing a broad, original, author's concept:

- to introduce the custom-made original hybrid prosthetics/implantation techniques and tissue engineering methods for the natural growth of a living tissue at least in the connection (interface) zone of prosthetic elements/implants into bone or organ stumps, without the necessity to use constantly for a patient the classical mechanical devices and solutions required for the positioning and fixation of implants,
- to develop a new generation of custom, original, hybrid, microporous high-strength, partially artificial, engineering and biological materials, using Selective Laser Sintering (SLS) to fabricate microporous stiff titanium and titanium alloy skeletons or for polymer nanofiber electrospinning to produce microporous elastic mats and partially biological ones consisting of living cells filling the appropriately prepared pores in the mentioned microporous materials,
- to develop a custom, original, hybrid construction of a new generation of personalised tissue implants/ scaffolds, especially bones, consisting of a solid zone, typical for the implants used to date, and a porous hybrid zone located in contact with bone stumps or damaged tissues, lined inside the pores with bioactive materials, enabling the living tissue to grow into zones after performing implantation,
- to prepare custom original hybrid fabrication technologies of the new generation of personalised tissue implants/scaffolds, of especially bones, with the use of locally dedicated surface micro-treatment with bioactive materials inside micropores, in the connection (interface) zone of prosthetic/implant elements with bone or organ stumps.

An old Chinese proverb says that the first step needs to be made to reach the destination. This step, when implementing the assumed vision, is to recognise the scientific and theoretical basis, separated from a holistic area outlined by the presented vision. The topic of the study is a subject of own scientific concepts depicted in own, earlier works and projects [1-61,168]. Undertaking a scientific issue consisting of the synergic utilisation of the existing achievements in materials engineering and manufacturing engineering, in the field of design and manufacture of pioneering implant-scaffold solutions, as well as composite biological- engineering materials allowing the growth of living cells and of researching, identifying and describing their structure and the properties of the newly created materials, is an interesting cognitive notion serving to acquire new knowledge on the fundamentals of the phenomena and observable facts and is of a pioneering nature. This is explained by the author's own publications and confirmed by own patent applications [46-52]. The concept is of the basic character, and is related to recognising the physical and biological basis accompanying the fabrication of pioneering and fully original biologically active microporous engineering materials, hence it does not pertain to the manufacturing of specific products which could be applied directly in regenerative medicine and dentistry. As no procedures exist for solving synergically the above issues in the case where it is not possible to apply exclusively tissue engineering methods, for instance due to extensive bone or tissue losses, and when implants have to be applied to replace such losses, this original engineering concept, constituting the essence of this study, provides an opportunity to solve patients' problems. The implants fabricated this way do not undergo degradation and remain in an organism permanently and do not require re-operation, and in the connection zone with bone stumps, they contain a porous zone, with surface treatment inside pores, enabling the living tissues to grow into. The implant is at least partially losing its artificial character. This, beyond any doubts, highlights the original and pioneering approach. The clinical experiences of distinguished surgeons collaborating with the Author reassert the necessity to address this research path, due to the urgent needs experienced immediately at the operating table.

The primary scientific aim of the presented research concept is to verify a research thesis that it is possible and relevant to develop multilayer biological-engineering composite materials having clinical readiness, partially artificial ones, using Selective Laser Sintering (SLS), to fabricate microporous rigid titanium and titanium alloy

skeletons or for polymer nanofiber electrospinning to produce microporous elastic mats, and partially biological ones consisting of living cells filling the appropriately prepared pores in the mentioned microporous materials. Cognitive aspects concern the recognition of phenomena and mechanisms associated with fabrication of the so understood biologically active microporous engineering material being, in essence, a biological-engineering composite material, and of surface phenomena and mechanisms taking place between individual layers of this unique material and their influence on manufacturing processes, both, in the engineering as well as biological part, and on the behaviour of particular layers and joint zones between such layers during material fabrication, as well as in conditions simulating therapy preparation and duration, and alternatively during the non-destructive separation of cellular structures from a substrate from a composite engineering material substrate on which cells are grown, but already after fulfilling the intended therapeutic function, if the material is not permanently left in the organism.

4. The detailed scope of the planned research

The modern methods of designing and manufacturing engineering materials and of culturing the cells of biological material, forming a hybrid, multilayer composite biological-engineering material, are the embryonic, experimental or prototype technologies, together with planned substrate technologies [189], with very strong development outlooks, as evidenced mainly by the outcomes of foresight research [165], nonetheless, the technologies and methods have not been satisfactorily investigated, and the available literature lacks the description of similar initiatives, and they are practically unknown with reference to a hybrid, multilayer composite biological-engineering material. This signifies, on one hand, that the interdisciplinary scientific and research problem considered is difficult and complex, on the other hand, it shows that the investigated subject is new and incipient. This represents a crucial reason to change such status quo and to undertake comprehensive interdisciplinary research studies in this domain, including a major methodological contribution concerning research into porous and biological-engineering materials of this type.

It is envisioned to examine two possible solutions required in therapeutic conditions due to the character of work, and especially mechanical loads after placement into a human organism: rigid and elastic ones. The general assumption of the research concept is to recognise the basis for developing hybrid and multilayer biologically active microporous composite engineering materials consisting of biologically active cellular structures or implant-scaffolds with microporous zones acting as scaffolds, alternatively:

- made of a stiff substrate in the form of a microporous stiff titanium or titanium alloy skeleton, produced by selective laser sintering, if left permanently in an organism, or
- from an elastic substrate manufactured by electrospinning of one- or two-layer coaxial nanofibres from biodegradable polymer materials used for producing microporous mats and in such case permitting to control engineering material delamination from the biological layer, upon achieving the therapeutic aims defined by medical reasons, as a result of one or several appropriately chosen and selected physiochemical factors, e.g. temperature, magnetic field, electric current, active

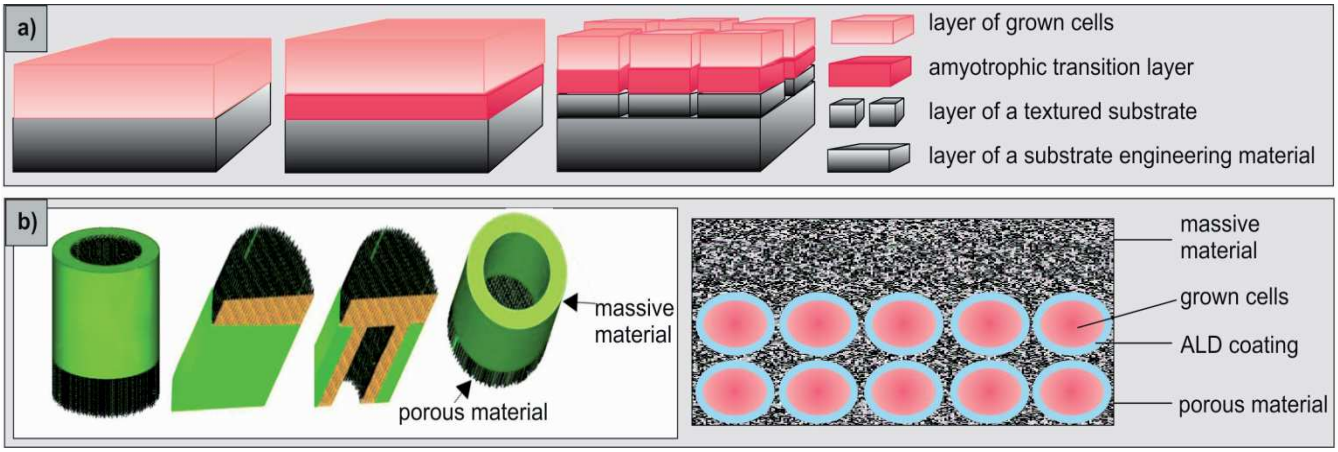

Fig. 1. Structural concepts of biological-engineering materials

enzymatic or chemical activity, by suitably selecting the active medium, and – in necessary cases – as a result of natural biodegradation.

Some variants of structural concepts of the investigated hybrid biologically active microporous engineering materials presented in Figure 1 have been considered. The generalisation relates to the both groups of: (a) rigid and (b) elastic materials, depending on which of them is used as appropriate.

In case of rigid biological-engineering materials which may represent a microporous part of original implant-scaffolds, an original hybrid technology will be employed, comprised of selective laser sintering of a microporous skeleton and of surface treatment, e.g. by the atomic layer deposition (ALD) method inside the pores in order to deposit coatings supporting the growth and proliferation of living cells. In case of elastic biological-engineering materials, an engineering layer into which living cells are growing, will be a mat created by nanofiber electrospinning. Own research experience connected with polymer matrix composite materials reinforced with carbon nanotubes, graphene and/or nanowires Cu, Pt or similar, which – if appropriate conditions connected with percolation are satisfied – may conduct electric current, will be used to develop a technology of a bearing amyotrophic layer. If thermodegradable polymers are used as a matrix, the planned effect of an amotrophic layer can be achieved under the influence of the flowing electric current. The possible use of conductive polymers as well as other research hypotheses will also be analysed.

The Figure 2 shows some examples of the structure of the investigated materials obtained as a result of the own preliminary research performed to date, but mainly in scope of the engineering aspects of producing a rigid or elastic substrate of biological-engineering materials.

An important premise in this action is a thought of Adolf Maciejny, one of the creators of materials engineering in Poland who, in a simplified but a very clear way, made a distinction between technology and engineering as the way of production and science. Engineers answer the question how?, whilst science explains why? Hence, when fulfilling the Author's dream and caring for the hybrid field of knowledge specified in this study, the Table 3 contains numerous questions why? which are essential for formulating the particular research tasks.

The goals of the research should be the achievement of the following effects:

- to identify the effect of chemical, phase and compositional composition on the structure and properties of the newly created hybrid porous high-strength composite biological-engineering materials enabling joining with living cells,
- to determine the effect of the newly developed technologies of fabrication and surface micro-treatment inside pores on the structure and properties of the newly created hybrid porous high-strength composite biological-engineering materials enabling joining with living cells,
- to establish the impact of porosity and coating, with bioactive materials, of the surface inside the pores on the mechanical properties of the newly developed hybrid porous high-strength composite biological-engineering materials and a possibility of combining with living cells,
- to determine the models of the structure and properties of the researched, newly created hybrid porous high-strength composite biological-engineering materials and their joining with living cells depending on the compositional, phase and chemical composition and the applied technological processes of fabrication and surface micro-treatment inside pores using the method of finite elements (FEM) and artificial intelligence methods, mainly neural networks.

The basic research performed in the study will represent a solid basis for undertaking application works in the future, allowing to fabricate a new generation of concrete products unknown today, which will find their application in regenerative medicine and dentistry for treating various internal and external disorders associated with, e.g. burning, healing or severe wounds and injuries, removal of consequences of oncological or post-injury disorders. The Figure 3 illustrates schematically the examples of applications of multilayer biological-engineering composite materials with a microporous zone in a rigid implant-scaffold substrate, which can be manufactured after finishing the basic research.

In the case of elastic multilayer biological-engineering composite materials manufactured by the electrospinning of nanofibers in the form of mats with an outer surface in the form of artificially cultured living cells growing into an organism's cells, it is predicted that specific plasters can be produced for the treated places (Fig. 4).

The essential cognitive aspects of the works planned for the realisation of the research concept are as follows:

- to better characterise the conditions of cell-based therapies and to interpret a therapeutic function mechanism of multipotent stromal cell (MSCs) for biological-engineering composites, which is necessary to improve the level of technology, repeatability, quality and mass-volume of manufacturing processes and to develop production capacities of cell-based products,

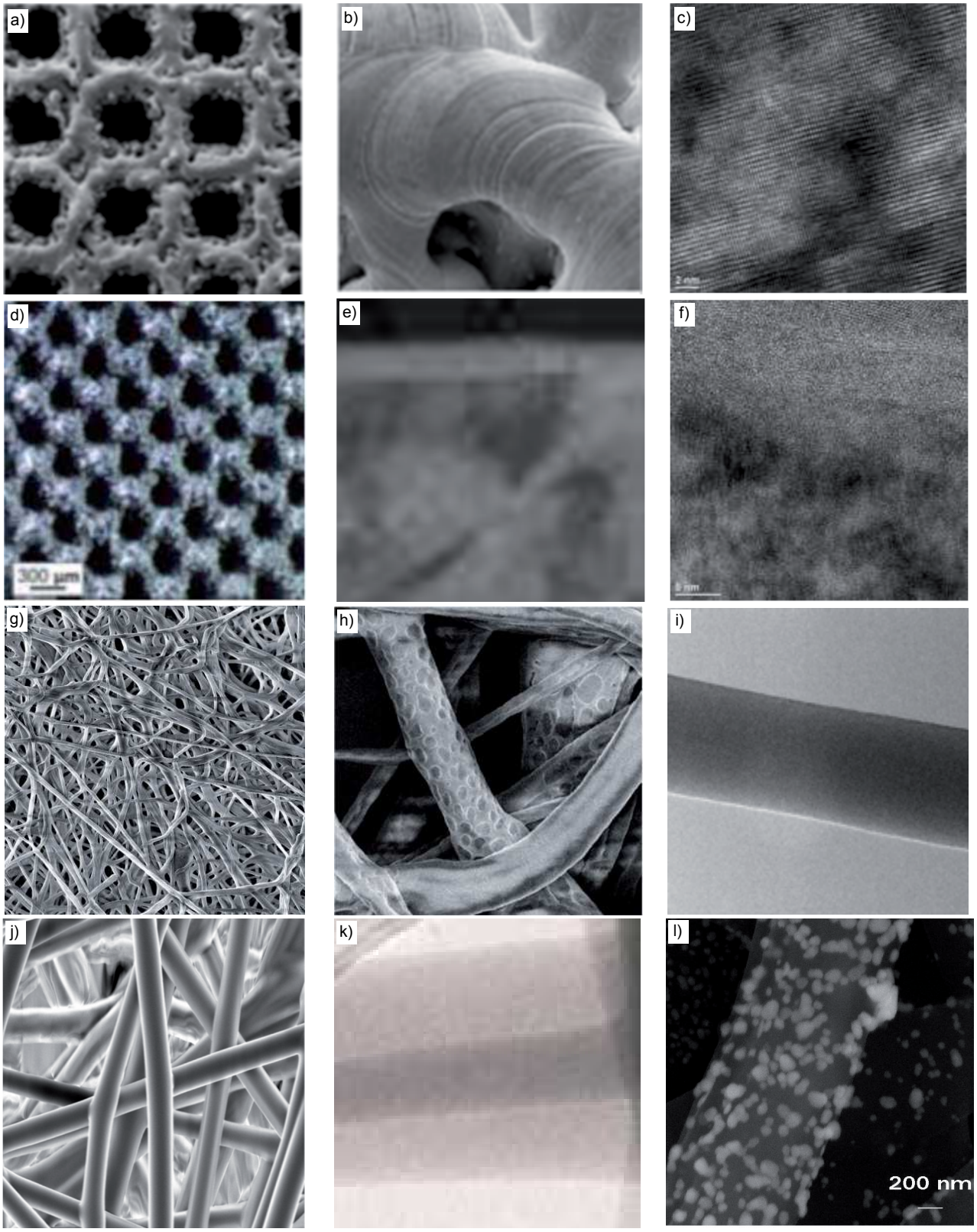

Fig. 2. The examples of the structure of the investigated materials (description in Table 2)

Table 2.
The description to the Figure 2

No.	Description to the Figure 2 - the examples of the structure of the investigated materials obtained as a result of the own preliminary research performed to date:
a	selectively laser sintered titanium microskeleton with the pore size of approx. 250 μm
b	the structure details of the selectively laser sintered titanium microskeleton
c	the structure of crystalline titanium after laser sintering at atomic scale (HRTEM)
d	the inner surface of pores coated in the ALD process
e	the structure of the coating on the inner surface of pores (TEM)
f	intermediate the zone between the microskeleton and the coating
g	a material made of polymer nanofibres from polycaprolactone
h	single monolayer nanofibres
i	single monolayer nanofibres at large magnification
j	two-layer nanofibre
k	two-layer nanofibre at high magnification (TEM)
l	monolayer nanofibre with silver nanoparticles with antibacterial activity (TEM)

Table 3.
The set of the research questions

No.	Detailed research questions
1	Why, in what conditions and how ALD layers and other layers cover the interior of pores of a metallic microskeleton designed for implant-scaffolds?
2	Why, in what conditions and how living cells, mainly osteoblasts, connect with and interact with the inner surface of pores of coated and uncoated metallic microskeletons in implant-scaffolds?
3	Why, in what conditions and how materials are combined in microporous polymer mats in biological- engineering composites inside nanofibres and between them ?
4	Why, in what conditions and how living cells, mainly osteoblasts, connect with and interact with the inner surface of pores and the outer surface of elastic composite microporous mats made of polymer nanofibres?
5	Why, in what conditions and how the artificially cultured cells of different type, as the layers of a biological-engineering composite, assimilate with natural human cells and exhibit the ability to ensure the function of cells during their culturing, supply and application?
6	Why, in what conditions and how the adhesion takes place of a layer of artificially cultured cells of a biological-engineering material with a layer of living cells?
7	Why, in what conditions and how the particular layers adhere to each other in a multilayer composite engineering material and how artificially cultured cells of different type combine with such a substrate?
8	Why, in what conditions and how natural biodegradation occurs of a substrate layer of a composite engineering material, on which artificially cultured cells are located or, alternatively, one or two indirect layers are removed through the controlled interaction of various physiochemical factors?
9	Why, in what conditions and how selective, controlled biodegradation of some fragments of co-axial polymeric nanofibers takes place and medicines are supplied, at a controlled rate, when a patient's cells are growing into the artificially cultured cells on the outer surface of an elastic biological-engineering composite?
10	Why, in what conditions and how controlled delamination of elastic engineering material takes place from a biological layer or natural biodegradation of indirect layers?
11	Why, in what conditions and how are constructional characteristics of implant-scaffolds and scaffolds selected for medical or dental applications?

Fig. 3. The examples of applications of multilayer biological-engineering composite materials with a microporous zone in a rigid implant-scaffold substrate

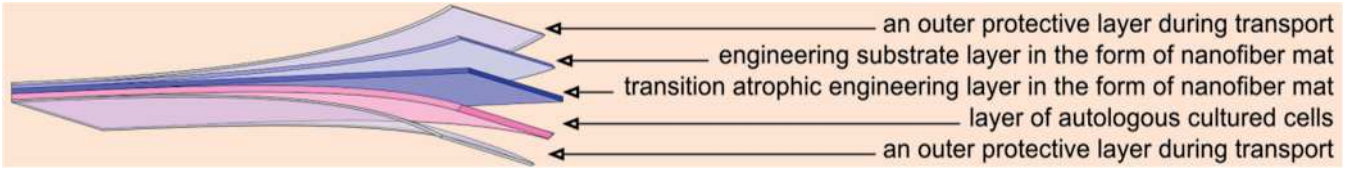

Fig. 4. The schematic idea of the elastic multilayer biological-engineering composite material

- to elaborate and explain the phenomena accompanying the culturing of tissue structures in conditions allowing their industrial production as biological-engineering composites for the purpose of well-developed and adequately organised therapeutic processes,
- to establish and explain the role of a substrate with a physiochemical basis of introducing appropriate engineering materials and the technological processes utilised for them, including nanotechnology, for the culturing of tissue structures and interaction between the surface structure of engineering materials forming the substrate and the cells deposited onto it,
- to formulate a methodological basis of alternative production platforms of cell-based products for biological and engineering composites taking into account the scale corresponding to the real clinical needs and the limits of the usable groups of cells and their culturing time, in relation to particular therapeutic functions,
- to establish methods and explain the causes and conditions of removing, in clinical conditions, once the therapeutic functions are fulfilled, the structural parts of cell-based products for biological-engineering composites, including engineered extracellular matrices, and most often scaffolds indispensable for technological and therapeutic reasons, provided patients' own cells are not interfered with, with such cells being restored as a result of a therapy performed using such materials.

A new pioneering generation of biological-engineering materials has to be prepared when preparing the material for the research, and special attention has to be paid to the aspects presented below linked to the assumed research intentions relate to developing and thoroughly researching the basic, multilayer biological-engineering composite materials consisting of:

- biologically active cellular structures and such enabling the development of biological materials allowing to restore, maintain or improve the functions of individual tissues and even organs and influencing the growth conditions of such tissues and their structure and the maintenance of physiochemical environmental conditions supporting such growth,
- a substrate featuring a composite engineering material matrix with an optimally selected type, phase and chemical composition and a nanometric structure, rigid or elastic as appropriate, fulfilling a carrier function, and in fact a function of a scaffold for biological structures, required to have an appropriate array of mechanical and rigidity properties, allowing applications in therapeutic conditions, notably high porosity, air permeability, absorptivity of liquids and gases, barrierity, bacteriocidity, antibacterialness, antifungalness, biocompatibility, biodegradability, intoxicity, a possibility of releasing medicinal agents in a controlled way, appropriate mechanical strength and its structure supporting regeneration processes,
- zones of biological-engineering connections, and even intermediate layers, with an appropriate structure and the required physiochemical properties, permitting to fully control the behaviour of the whole biological-engineering composite material and permitting controlled elastic engineering material delamination from the

biological layer, upon achieving the therapeutic aims defined by medical reasons, as a result of one or several appropriately chosen and selected physiochemical factors, e.g. temperature, magnetic field, electric current, active enzymatic or chemical activity, by suitably selecting an active medium, and – in necessary cases – as a result of natural biodegradation.

5. Summary

The materials planned for manufacturing in consistency with the custom idea, which are planned to be recognised, investigated and described under the presented research concept, belong to a group of most avant-garde, relatively little known to date, but highly promising biological-engineering materials, therefore the cognitive importance of the described research efforts should be clearly underlined. With reference to the entire chosen scientific topic, a paradigm of materials science and materials engineering has been assumed extensively, established over 50 years of the history of such scientific branches. The paradigm states that in order to satisfy products' usable functions, in this case biological-engineering ones, it is necessary to design and apply biological-engineering materials which, when undergoing the relevant technological processes of shapening their structure, including connecting living cells with the substrate made of engineering composite materials, will ensure the relevant physiochemical properties of the material and the biological activity of cells. The works conducted must be based on the intensification of basic research to better characterise the conditions of cells' adhesion and proliferation, which is possible only in case of recognising holistically all the surface phenomena occurring between an implantable medical device and the cells grown on the surface, as well as between the individual layers of the device. Such expectations are addressed by the concept of developing, manufacturing, investigating and describing newly developed hybrid cellular-nanostructured composites delaminated in a controlled manner under the influence of selected physiochemical factors. Research into the materials produced will make it possible to scrutinise more thoroughly the phenomena and processes of their fabrication, surface micro-treatment and in the conditions of clinical applications. Hypotheses will be tested practically concerning the feasibility of fabricating the developed and porous hybrid materials using advanced hybrid technologies. The research's innovativeness should be considered in terms of investigating the impact of the applied input technologies, especially rapid manufacturing technologies, on the properties of the obtained porous materials, as well as internal treatment methods of pores in order to apply bioactive materials enabling the growth of living tissues. In the long run, by finding the practical applications of the newly developed innovative biological-engineering materials, a contribution will be brought towards sustainable development and growth of a knowledge- and innovation-based economy and this will inscribe into a long-term strategic development plan of Poland and the European Union. The products made with the newly developed avant-garde materials can be potentially produced in the manufacturing activity of highly specialised micro-, small- and medium-sized enterprises. The activities aimed at making the innovating technologies available to such entities indicate the research's economic importance.

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