Nanomedicine and Nanotechnology Journal

CASE REPORT

The Nanobiotechnology - Based Development of New Orthopedic Implants

Marcelo Kropf[1*] and Adelaide Maria de Souza Antunes[2]

[1]National Institute of Traumatology and Orthopedics, Brazil
[2]Chemical and Biochemical Process Technology Department, Federal University of Rio de Janeiro, Brazil

ARTICLE INFO

Received Date: September 18, 2017
Accepted Date: November 01, 2017
Published Date: November 09 , 2017

KEYWORDS

Prosthetics;
Implants;
Nanobiotechnology;
Innovation;
Trends

Citation this article: Kropf M, Antunes AM. The Nanobiotechnology - Based Development of New Orthopedic Implants. Nanomed Nanotechnol J. 2017; 1(1):111.

Corresponding Author :

Marcelo Kropf, Innovation Manager, National Institute of Traumatology and Orthopedics, Brazil,
Email: mkropf@into.saude.gov.br

ABSTRACT

The choice of a bone substitute can determine the success or failure of orthopedic treatments and procedures. In modern medicine, the most widely used bone substitute is the orthopedic implant. The global market for orthopedic devices is expected to be worth some 61 billion dollars by 2023. In this article, technology trends in orthopedic implants are identified by analyzing technological information extracted from patent applications listed in the Derwent World Patents Index between 2000 and 2014. The data obtained express a varied set of trends that describe the profile of innovation and technology developments in converging areas of knowledge, such as nanobiotechnology, indicating the promise of orthopedic implants capable of mimicking the normal physiology of bone tissue, making the "perfect" bone substitute.

INTRODUCTION

Orthopedics is an area concerned with the treatment of musculoskeletal disorders, lesions, diseases, and deformities, like arthritis, osteoporosis, fractures, back pain, scoliosis, soft tissue disorders, etc [1].

Demographics have a major influence on the epidemiology of trauma and orthopedic diseases. For instance, there are over 50 million fractures every year around the world, mostly caused by accidents, falls, and injury-inducing activities. Fifty-one percent of these fractures occur in people under 45 years of age, 21% in adults aged 45-64, and 29% in people aged 65 and over. In the oldest age group, there is an increasing need for fracture repair, which is exacerbated by osteoporosis. Around nine million osteoporotic fractures occur each year annually; in Europe alone, there is one osteoporotic fracture every 30 seconds [2].

In cases such as these, the choice of the bone substitute may dictate the success or failure of the treatment. The best clinical results are achieved when bone grafts are taken from the patient themselves, as the immune responses (in which the graft is perceived as a foreign body and is rejected) are lower. However, there are downsides to bone grafts, including the extra cost of the surgery, pain when harvesting the graft, and the fact that only very small grafts can be taken. Bone grafts from deceased donors – which would resolve the shortage of material issue – have the disadvantage of incurring an increased risk of disease transmission and immune response. Further, the bones would not be viable because they would not have living osteoblasts. As such, synthetic bone substitutes, such as orthopedic implants, are the most widely used and accepted choice in modern medicine [3].

Orthopedic implants are medical devices that are implanted for orthopedic purposes, used directly in joint replacement, bone synthesis, ligament replacement, and spinal maintenance in human beings [4].

The global market for orthopedic devices is expected to be worth some 61 billion dollars by 2023 [5].

The top ten companies in the market for orthopedic devices (as measured by their annual revenues in 2016) are: 1) Stryker (US$ 11.3 billion), 2) DePuy Synthes (US$ 9.3 billion), 3) Zimmer Biomet (US$ 7.7 billion), 4) Smith & Nephew (US$ 4.7 billion), 5) Medtronic Spine (US$ 2.9 billion), 6) DJO Global (US$ 1.2 billion), 7) Integra LifeSciences (US$ 992 million), 8) NuVasive (US$ 962 million), 9) Wright Medical (US$ 690 million), and 10) Globus Medical (US$ 564 million) [6].

Orthopedic implants and prostheses are technologies that offer some of the greatest innovation potential in the healthcare market, and are the target of research and development by converging areas of knowledge, resulting in technology convergence in the form of nanobiotechnology and biomechatronics [7].

In this article, we characterize the technological trends in the latest orthopedic implants and prostheses based on an analysis of the technological information extracted from patent applications listed in the Derwent World Patents Index between 2000 and 2014.

INNOVATIVE ORTHOPEDIC IMPLANTS

Ideally, implants should be osteogenic (producing bone tissue), osteoinducing (inducing the differentiation of stem cells into osteogenic bone cells), osteoconducting (allowing the bone tissue to migrate over the biomaterial at the tissue-material interface), biocompatible (capable of preventing inflammatory and immunogenic reactions), biodegradable/bioabsorbable (so that the material can be substituted by growing bone), capable of providing structural support, easy to use clinically, and cost-effective [7].

Combining all these properties in a single device could seem impossible in view of the current state of technological developments. However, there are new orthopedic implants that could fulfill this promise, drawing on the latest nanobiotechnological breakthroughs [7,8].

Creating the "perfect" bone substitute is the main aim of regenerative medicine, an emerging interdisciplinary research area with clinical applications that focuses on the repair, replacement, and regeneration of cells, tissues, and organs to restore their normal function. When the physiological capacity for self-regeneration is compromised or lacking and there is no other way to recuperate the tissue, modern biotechnology, gene therapy, stem-cell, cell reprogramming, and tissue engineering techniques are used to create new tissue that exactly replicates the tissue that was damaged [7-9].

The principal area of regenerative medicine is tissue engineering, which draws on several areas of knowledge, especially clinical medicine, mechanical engineering, nanobiotechnology, and genetic engineering. The aim of tissue engineering is to use methods that stimulate cell growth by manipulating different natural or artificial biomaterials, which serve as the support for controlled growth in specific types of tissues. These supports are called scaffolds, and have the physical, mechanical, and chemical properties necessary for cell adhesion and the formation of new tissue. The new tissue may be grown in vivo or in vitro. In the former case, scaffolds with or without seeded cells are implanted directly at the injured site in the patient with the aim of rectifying the defect using the body's own regenerative capacity. The latter is when the new tissue is cultured on scaffolds in a controlled medium with characteristics that are propitious for cell growth (bioreactors); once the tissue has been regenerated this way, it is implanted in the patient [7-9].

The success of an implant depends on the tissue response of the receptor site and the type of interface and adhesion between the implant and the live tissue of the host. Any material implanted in a living organism will trigger some reaction, which can be modulated and corrected in different ways. The choice of the right biomaterial when producing an implant must therefore take the possibility of such reactions into account. Today, the biomaterials used in orthopedic implants last between ten and 15 years. As people's life expectancy is lengthening, these materials can exceed their useful life, resulting in the release of debris and bone loss by osteolysis, calling for immediate implant replacement surgery [10].

When tissue-material interactions are ineffective, the implant can suffer wear. It is not yet clear what mechanisms actually lead to the wear of biomaterials. It is believed that the micromechanical conditions at the tissue-material interface regulate the structural stability of the implant. When they become unstable (e.g., debris is released, infections occur, or bone healing is impaired), the implant can fail completely, calling for extensive, costly revision surgery [11].

The application of nanobiotechnology to tissue engineering and orthopedic medicine has emerged as the main technological trend in orthopedic implants. Nanotechnology holds out the promise of new nanomaterials capable of interacting optimally with the bone tissue on a cellular level, while biotechnology techniques introduce the capacity to accelerate bone regeneration by releasing genes that encode osteogenic growth factors or by fine-tuning this process by regulating cell triggers capable of controlling the functions of osteoblasts and osteoclasts [7,8,12].

Therefore, investigating the contact surfaces in tissue-material interactions is clearly a matter of some importance. This is currently one of the main targets of research and development for new types of implants.

Nanomaterials form the basis of the surfaces of implants and the different types of coatings applied to them. The atoms concentrated at the surface of these systems account for up to 90% of their total mass and result in enhanced reactivity. Nanoparticle coatings are generally used to release growth factors that stimulate osseointegration, or else for the delivery of medicines, like antibiotics, which are applied uniformly across the nanomaterial's surface. In other words, the design of the new coatings and surfaces is what lends the latest orthopedic implants their novel properties. Modifying the surface of a nanomaterial in different ways can produce materials with different biological functions and properties for a specific end application and biomimetic properties. This imitation of the cell environment is fundamental for cell replication mechanisms, which also have nanometric dimensions and combine to form extracellular matrices. Furthermore, implants with nanomaterials are capable of forming a larger surface area, which helps cultivate a healthy environment for bone growth, reducing infection rates [12-19].

The surface where tissue-material interaction takes place is responsible for the biological behavior and cell morphology needed for adhesion, enabling cell growth and tissue repair in fractures. The surface properties that affect this adhesion mechanism are topography, wettability, charge, and chemical composition [20].

The most important property from a nanobiotechnolgoical perspective is arguably the topography of the nanomaterial, given that this is directly related to cell adhesion in the valleys, peaks, and dips (i.e. roughness) of the implants. Manipulating surface topography on the nanoscale has been shown to have a positive impact on cell behavior by stimulating and controlling the fixation, migration, propagation, gene expression, proliferation, differentiation, and secretion of components in the matrix. Osteogenesis begins more quickly at surfaces organized on a nanometric scale than on smooth surfaces [21,22].

The nanobiotechnological developments in the latest orthopedic implants are promising. However, it is of the utmost importance that new products, especially those developed in areas of technology convergence, be followed up in clinical studies in order to validate their effectiveness and biosecurity in human beings [7,23].

METHODOLOGY

The methodology employed in this article replicates the one used previously.8 The information and knowledge contained in a technology can be inferred from scientific papers and patents. Patents contain information on protected technology developments ready to be launched on the market. There is an established tradition of using them as indicators of inventive activity [24].

Patents are sources of technological information because: [25] 1) they qualify the state-of-the-art in a given technology at the patent application stage; 2) they orient and form the basis for investment decisions about the acquisition of technologies; 3) they differentiate technologies from their potential alternatives; 4) they serve to identify emerging technologies, market trends, and potential new products; 5) they distinguish potential routes for the improvement of existing products and processes; 6) they can be used to monitor the activities of competitors; and 7) they enable technology tracking, so that companies, inventors, patent assignees, partnerships, countries, areas of high patenting activity, and other strategic information can be gathered and characterized.

This study only focuses on analyses geared towards the technologies identified by executing the methodology described.

The graphics in the results and discussion section are based on data from patent applications for orthopedic implants listed in the Derwent World Patents Index between 2000 and 2014.

To obtain the data, the International Patent Classification (IPC), organized by the World Intellectual Property Organization, and the Derwent Manual Codes were consulted. The IPC has proved effective for identifying trends in technology convergence, and can be used to ascertain the predominant areas of knowledge and technology trends [26].

Implants and prostheses can be classified according to the type of technology used to develop them. The search strategy was created using the IPC subclasses for orthopedic implants, materials used in such implants, biotechnology, and nanotechnology. The search strategy and procedure are presented below:

Implants: IP=(A61F-002/00 OR A61F-002/02 OR A61F-002/08 OR A61F-002/28 OR A61F-002/30 OR A61F-002/32 OR A61F-002/34 OR A61F-002/36 OR A61F-002/38 OR A61F-002/40 OR A61F-002/42 OR A61F-002/44 OR A61F-002/46 OR A61F-002/54 OR A61F-002/56 OR A61F-002/58 OR A61F-002/60 OR A61F-002/62 OR A61F-002/64 OR A61F-002/66 OR A61F-002/68 OR A61F-002/76 OR A61F-002/78 OR A61F-002/80 OR A61L-031/00 OR A61L-031/02 OR A61L-031/04 OR A61L-031/06 OR A61L-031/08 OR A61L-031/10 OR A61L-031/12 OR A61L-031/14 OR A61L-031/16 OR A61L-031/18 OR A61L-033/00 OR A61L-033/02 OR A61L-033/04 OR A61L-033/06 OR A61L-033/08 OR A61L-033/10 OR A61L-033/12 OR A61L-033/14 OR A61L-033/16 OR A61L-033/18)

Implants developed using biotechnology: IP=(C12N-001/00 OR C12N-001/00 OR C12N-003/00 OR C12N-007/00 OR C12N-009/00 OR C12N-011/00 OR C12N-013/00 OR C12N-013/00 OR C12N-015/00 OR C12N-005/00 OR C12N-005/02 OR C12N-005/06 OR C12N-005/08 OR C12N-005/10 OR C12N-005/12 OR C12N-005/16 OR C12N-005/18 OR C12N-005/20 OR C12N-005/24 OR C12N-005/26 OR C12N-005/26 OR C12N-005/28) AND (IPC for implants).

Implants developed using nanotechnology: IP=(B82B-001/00 OR B82B-003/00 OR B82Y) OR MAN=(E05-U06 OR E27-B02A OR E27-B01A OR E27-B03A OR E31-U04 OR J01-C04 OR S05-Y02 OR N06-C09 OR U11-A14 OR U11-C13 OR U21-B01T OR X12-D01D OR X12-D07E2A) AND (IPC for implants).

Data on implants developed using nanobiotechnology can be extrapolated from patents for implants developed using nanotechnology and biotechnology.

The technological information was grouped according to the Technology Focus fields from the Derwent World Patents Index. The patents with no Technology Focus information were allotted to a particular group by analyzing their abstracts: 1) cell and tissue technologies, 2) gene technologies, 3) pharmaceutical technologies, 4) technologies for ceramic materials, 5) technologies for inorganic materials, 6) technologies for testing and diagnostics, 7) technologies responsible for chemical modifications, 8) technologies for metal materials, 9) technologies for (bio) polymeric materials, 10) technologies for chemically engineered processes, 11) (bio)mechanical technologies, 12) computer technologies, 13) electrical and electronic technologies, 14) technologies for industrial standardization, and 15) other technologies.

All these technologies were encountered using the methodology described above, but not all of them indicate a trend. A complete description of these technologies is contained in a previous study by the authors [8].

RESULTS AND DISCUSSION

The search and sorting procedure yielded a total of 22,615 patent applications for implants listed in the Derwent World Patents Index, which can be broken down into their base technologies as follows:

- implants developed using biotechnology – 861 patent applications (3.81%);
- implants developed using nanotechnology – 301 patent applications (1.33%);
- implants developed using nanobiotechnology – 53 patent applications (0.23%);
- conventional implants/prostheses – 21,400 patent applications (94.63%).

It is clear from the number of patents per category that conventional implants and prostheses still prevailed between 2000 and 2014, with cutting-edge technologies still accounting for a very small proportion of the claims.

Implants developed using biotechnology (Figure 1)

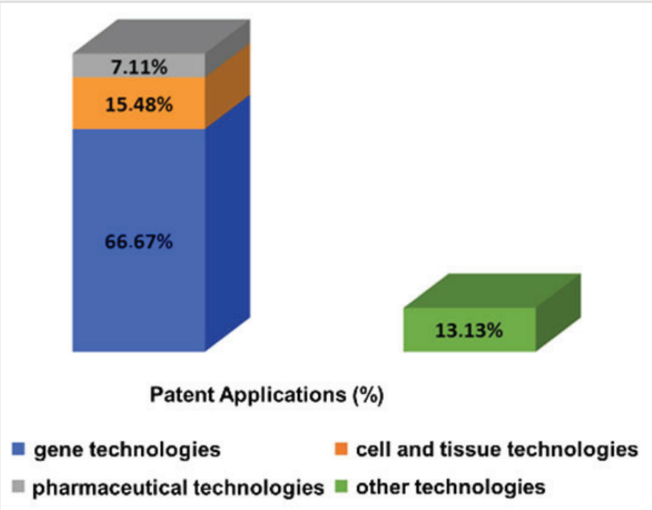

Figure 1: Trends in implants developed using biotechnology, 2000-2014. Own research based on analysis of Derwent World Patents Index.

can be broken down into the following trends:

- 66.67% of the patent applications are for claims related to gene technologies – i.e. technologies designed to genetically modify properties and structures of the bone tissue or substances from the organic component of the bone matrix with the purpose of identifying, modifying or suppressing a given cellular, biochemical or physiological mechanism or property;
- 15.48% of the patent applications are for claims related to technologies that use cell and tissue biology with the purpose of improving bone cell functions or structures in order to improve fracture repair;
- 7.11% of the patent applications are for claims related to pharmaceutical technologies applied to tissue regeneration, the induction of cell-like properties, and the enhancement of different biomaterials with therapeutic properties;

- 13.13% of the patent applications do not correspond to any of the trends identified.

ide The trends in the implants developed using biotechnology indicate progress in tissue engineering resulting from the genetic modification of cells, proteins, adhesins, and other components of the bone matrix to enhance bone repair.

Properties like osteoinduction, osteogenesis, and biocompatibility are optimized in loco in the fracture. The use of drugs like antibiotics and anticoagulants in biomaterials or directly on the tissue is designed to reduce or eliminate risks of infection or bleeding.

Implants developed using nanotechnology (Figure 2)

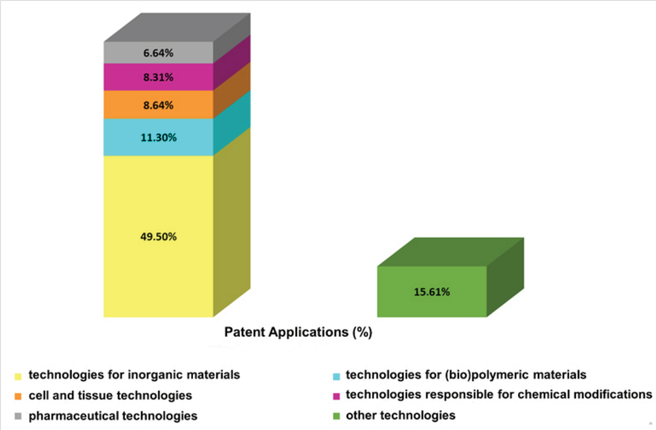

Figure 2: Trends in implants developed using nanotechnology, 2000-2014. Own research based on analysis of Derwent World Patents Index.

can be broken down into the following trends:

- 49.50% of the patent applications are for claims related to inorganic materials constituted of different bone-like composites in different forms, sizes, and rearrangements, and associated with the most varied of agents capable of improving their functions and their applications as biomaterials, including interaction with components of the bone matrix and bone tissue;
- 11.30% of the patent applications are for claims related to (bio) polymer technologies in different forms, sizes, and rearrangements, and associated with the most varied of agents capable of improving their functions and their applications as biomaterials, including interaction with the components of the bone matrix and bone tissue;
- 8.64% of the patent applications are for claims related to cell and tissue biology with the purpose of improving bone cell functions or structures in order to improve fracture repair;
- 8.31% of the patent applications involve the chemical modification of substances, bioactive agents, and (bio) chemical reactions to improve biological properties and tissue-material interactions;
- 6.64% of the patent applications are for claims related to pharmaceutical technologies applied to tissue regeneration, the induction of cell-like properties, and the enhancement of different biomaterials with therapeutic properties.
- 15.51% of the patent applications do not correspond to any of the trends identified.

The trends in the patents whose claims are based on nanotechnology developments have features that directly involve nanomaterial's and their interactions with the inorganic materials of the bone matrix (e.g. between the hydroxyapatite crystals in the bone matrix and the carbon nanotubes in the biomaterials). There is a predominance of nanoforms, their arrangement, surface interactions of biomaterials, and the preparation of the implant to receive nanoparticles for drug delivery (e.g. nanodrugs). Drug delivery systems applied directly to the biomaterials of these implants are designed to eliminate the risk of infection, improve biocompatibility, and reduce the risks of immunogenicity arising from tissue-material interactions. The adequate bioabsorption of these biomaterials tends to reduce the risks inherent to the loss of implants caused by osteolysis.

The polymers contained in the claims are both synthetic (polyethylene, polyurethane, polymethacrylate, etc.) and natural (chitosan, collagen, and animal- and plant-derived polymers) and both biodegradable and non-biodegradable, with nanostructures that interact mainly with the organic bone matrix.

Differentiating stem cells into osteoprogenitor cells is one of the main strategies for bone regeneration. Biologically active molecules, such as growth factors, integrins, and adhesins, and even drugs (immunomodulators) are used as a way to promote cell proliferation and reduce immunogenicity.

Organic solutions are used in the preparations for in-vitro and in-vivo scaffolds. Other chemical products prepare the surface of the implants, operating as a protective nanofilm or as reagents for components from the organic component of the bone matrix.

Patents for implants developed using nanotechnology are set to outnumber those for conventional implants by around 2049 [8].
Implants developed using nanobiotechnology (Figure 3)

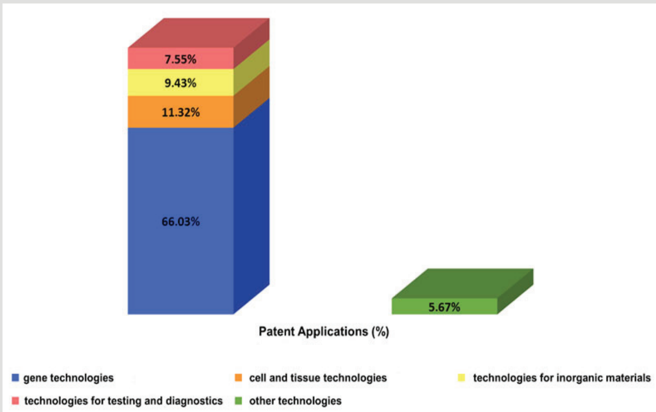

Figure 3: Trends in implants developed using nanobiotechnology, 2000-2014. Own research based on analysis of Derwent World Patents Index.

can be broken down into the following trends:

- 66.03% of the patent applications are for claims related to biotechnologies designed to genetically modify properties and structures of the bone tissue or substances from the organic component of the bone matrix or substances from the organic component of the bone matrix with the purpose of identifying, modifying or suppressing a given cellular, biochemical, or physiological mechanism or property;
- 11.32% of the patent applications are for claims related to cell and

tissue biology with the purpose of improving bone cell functions or structures in order to improve fracture repair;

- 9.43% of the patent applications are for claims related to materials constituted of different bone-like composites in different forms, sizes, and rearrangements, and associated with the most varied of agents capable of improving their functions and their applications as biomaterials, including interaction with components of the bone matrix and bone tissue;
- 7.55% of the patent applications are for claims related to implants and devices of different sizes with different characteristics and functions, which may be impregnated with bioactive agents or other substances, mostly used for biomaterial testing, diagnostics, and support for cell growth (scaffolding);
- 5.67% of the patent applications do not correspond to any of the trends identified.

Implants developed using nanobiotechnology are at the cutting edge of this field. Technology convergence occurs when knowledge from different fields is combined. The merging of these two areas is fundamental from a health science perspective. This is arguably the leading trend for the production of implants in the future, since it combines tissue engineering and materials engineering in a bid to attain the "perfect" implant. The trajectory of the developments and technological pathways could guide production and innovation in health from the perspective of orthopedic medicine and tissue engineering.

The use of biotechnological and genetic engineering techniques to create customized substances (e.g. chemicals, drugs, proteins, cytokines, adhesins) applied to nanomaterials gives the new implants unique properties. Properties only to be found in certain types of biomaterials can be combined in a nanostructured biomaterial. These implants stand out from all others because properties such as osteogenicity, osteoinduction, osteoconduction, biocompatibility, biodegradability, and bioabsorption can be attained by genetic engineering or by preparing nanostructures that interact "perfectly" with these biologically modified products. Implants for testing and diagnostics are likely to be increasingly important in the future. Tests using nanoscaffolds (nano-implants) for in-vitro and in-vivo cell growth are becoming more widespread in the field of regenerative medicine [27]. It is quite possible that nanoscaffolds will replace conventional implants in simple surgical procedures or ones where there is no need for the damaged bone tissue to be completely replaced.

Patents for implants developed using nanobiotechnology are set to outnumber those for biotechnology-based implants by around 2037 [8].

The percentages of patent applications for nanobiotechnology-based implants show that the main trends are for genetic technologies and cell and tissue technologies (from the fields of biotechnology and biology). Taken together, these account for 77.35%. According to the technological information extracted from the patent applications, in the coming decades, new orthopedic implants may well be based primarily on products that have genetic interactions or act on the molecular level of cells and tissues with a view to maximizing interactions with different kinds of nanomaterials.

Conventional implants (Figure 4)

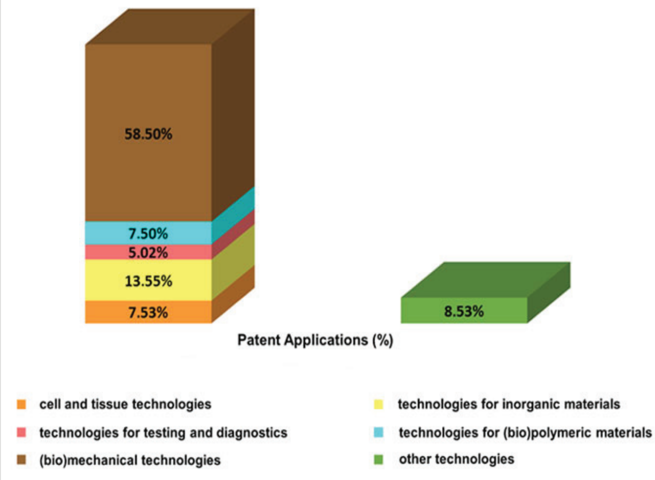

Figure 4: Trends in implants developed using conventional technology, 2000-2014. Own research based on analysis of Derwent World Patents Index.

can be broken down into the following trends:

- 58.60% of the patent applications are for claims related directly to the (bio) mechanics of implants and their properties, like fixation, connection, reconstruction, flexibility, elasticity, surface coatings, and implant systems;
- 13.55% of the patent applications are for claims related to inorganic materials constituted of different bone-like composites in different forms, sizes, and rearrangements, and associated with the most varied of agents capable of improving their functions and their applications as biomaterials;
- 7.53% of the patent applications are for claims related to bone-like (bio)polymeric composites in different forms, sizes, and rearrangements, and associated with the most varied of agents capable of improving their functions and their applications as biomaterials, including interaction with the components of the bone matrix and bone tissue;
- 7.50% of the patent applications are for claims related to cell and tissue biology with the purpose of improving bone cell functions or structures in order to improve fracture repair;
- 5.02% of the patent applications are for claims related to implants and devices of different sizes with different characteristics and functions, which may be impregnated with bioactive agents or other substances, mostly used for biomaterial testing, diagnostics, and support for cell growth (scaffolding);
- 8.53% of the patent applications do not correspond to any of the trends identified.

Patent claims for conventional prosthetics tend to be for the development of biomechatronic devices. Robotic prosthetics can be used very effectively as partial or total substitutes for upper or lower limbs [28]. Different technologies converge in what have come to be called "smart prosthetics," such as myoelectric prostheses, muscle reinnervation, and other technologies that enable interaction between tissue and biomechatronic materials [29]. The technological information encountered in these patent applications showed a plethora of inventive solutions for prosthetics and ways of fixing them to the human body.

Technologies developed for inorganic materials and cells and tissues are

the second and third biggest trends, respectively, which could suggest that even for conventional prosthetics, effort is being put into finding technological enhancements to optimize tissue-material interactions.
Another trend worth noting is the use of (bio) polymers as materials applied to prostheses. Not only are such materials biodegradable and biocompatible, but they also have the important property of elasticity, mimicking the elastic properties of the bone tissue conferred by collagen fibers.
Just 5.02% of these technologies were for diagnostics and testing. This is in line with the percentage of nanobiotechnology-based claims of the same nature (7.55%). This could indicate that such technologies are well established and are fit for the purpose of ascertaining the efficacy, safety, and quality of the new implants/prostheses, or that research, development, and innovations in the area must keep pace with the growing trend for new orthopedic implants around the world.

FINAL CONSIDERATIONS

This survey of technological trends based on patent applications filed between 2000 and 2014 indicates that nanobiotechnology is the main area, strategically speaking, for the production of orthopedic implants and prosthetics in the future. Considering the data obtained, technological developments suggest that the pace at which conventional implants will be overtaken by nanotechnology- and nanobiotechnology-based implants will be slow. Nanobiotechnological implants are nonetheless developing as a feasible future alternative to conventional implants, capable of mimicking the normal physiology of bone tissue and making the “perfect” bone substitute.

REFERENCES

1. Orthoworld. (2017). The Orthopaedic Industry Annual Report. Executive Summary.
2. Orthoworld. (2013). The Orthopaedic Industry Annual Report. Executive Summary.
3. Campana V. Milano G, Pagano E, Barba M, Cicione C, et al. (2014). Bone substitutes in orthopaedic surgery: from basic Science to clinical practice. J Mater Sci: Mater Med. 25: 2445–2461.
4. Brazilian Agency for Industrial Development sectoral progress report. (2013). Nanotechnology for health: market, safety and regulation. Brazil.
5. Global Information Inc. (2017). Global Orthopedics Devices Market - Analysis and Forecast 2017-2023: Focus on China Market, Market Share Analysis, Competitive Landscape, Material, Product, Country Analysis and End User.
6. Orthopedic Design & Technology. (2017). Top 10 Global Orthopedic Device Firms.
7. Kropf M, Adelaide Maria de Souza Antunes. (2015). Trends in the Research and Development of Orthopedic Prostheses. Supervisor: Emeritus Professor Adelaide Maria de Souza Antunes. Doctoral Thesis. School of Chemistry, Technologies in Chemical and Biochemical Processes, Management and Technological Innovation Area, Federal University of Rio de Janeiro, Brazil.
8. Kropf M, Antunes, AMS (2016). Analysis of Trends in Orthopedic Prosthetics. Bio Core 1:1,9-19
9. O’Brien FJ (2011) Biomaterials & scaffolds for tissue engineering. Material Today. 14: 88-95.
10. Sato M, Webster TJ. (2004). Nanobiotechnology: implications for the future of nanotechnology in orthopedic applications. Expert Rev. Medical Devices. 1: 105-114.
11. Garimella R, Eltorai AEM. (2016). Nanotechnology in orthopedics. Journal of Orthopaedics. 14: 30–33
12. Makhdom AM, Nayef L, Tabrizian M, Hamdy RC. (2015). The potential roles of nanobiomaterials in distraction osteogenesis, Nanomedicine: Nanotechnology, Biology and Medicine. 11: 1–18
13. Laurencin CT, Kumbar SG, Nukavarapu SP. (2009). Nanotechnology and orthopedics: a personal perspective. Wiley Interdiscipl. Rev. Nanomed. Nanobiotechnol. 1: 6–10.
14. Thomas JB, Peppas NA. (2005). Nanotechnology and Biomaterial. Nanotecnology Handbook. 605-636.
15. Anselme K. (2011). Biomaterials and interface with bone. Osteoporose Int. 22: 2037–2042.
16. Liu D, Yang F, Xiong F, Gu N. (2016). The smart drug delivery system and its clinical potential. Theranostics. 6: 1306–1323.
17. Zhang BGX, Myers DE, Wallace GG, Brandt M, Choong PFM. (2014). Bioactive Coatings for Orthopaedic Implants—Recent Trends in Development of Implant Coatings. Int. J. Mol. Sci. 15, 11878-11921.
18. Garimella R, Eltorai AEM. (2017). Nanotechnology in orthopedics. Journal of Orthopaedics. 14 30–33.
19. Jaggessar A, Shahali H, Mathew A, Yarlagadda PKDV. (2017). Bio-mimicking nano and micro-structured surface fabrication for antibacterial properties in medical implants. J Nanobiotechnol 15:64.
20. Chen Z, Kang L, Wang Z, Xu Fei, Gu G, et al. (2014). Recent progress in the research of biomaterials regulating cell behavior. RSC Adv. 4: 63807–63816.
21. Ramos AP, Cruz MAE, Tovani CB, Ciancaglini P (2017) Biomedical applications of nanotechnology Biophys Rev. 9: 79–89.
22. Klymov A, Prodanov L, Lamers E, Jansen JA, Walboomers XF. (2013). Understanding the role of nano-topography on the surface of a bone-implant. Biomater Sci. 1: 135–151.
23. Mazaheri M, Eslahi N, Ordikhani F, Tamjid E, Simchi A. (2015). Nanomedicine applications in orthopedic medicine: state of the art. International Journal of Nanomedicine. 10: 6039–6054.
24. Alencar MSM. (2008). Future study by the application of technology foresight techniques: the case of nanotechnology. Supervisor: Emeritus Professor Adelaide Maria de Souza Antunes. Doctoral Thesis. School of Chemistry, Technologies in Chemical and Biochemical Processes, Management and Technological Innovation Area, Federal University of Rio de Janeiro, Brazil.
25. Guerrante RS. (2011). Strategies for Innovation and Technology in Seeds. Supervisor: Emeritus Professor Adelaide Maria de Souza Antunes. Doctoral Thesis. School of Chemistry, Technologies in Chemical and Biochemical Processes, Management and Technological Innovation Area, Federal University of Rio de Janeiro, Brazil.
26. Grilichez Z. (1990). Patent statistics as economic indicators: a survey. The Journal of Economic Literature. 28: 1661-1797.
27. Ghoraishizadeh S, Ghorishizadeh A, Ghoraishizadeh P, Daneshvar N, Boroojerdi MH. (2014). Application of Nanoscaffolds in Mesenchymal Stem Cell-Based Therapy. Hindawi Publishing Corporation. Advances in Regenerative Medicine.
28. Robotics Virtual Organization (2013). A Roadmap for U.S. Robotics From Internet to Robotics. Edition.
29. Dehghani A (2010) Intelligent Prosthesis – a Biomechatronics Ap-

proach. 11: 173-195 in: Bradley D, Russel DW (editors). Mechatronics in Action. Case Studies in Mechatronics – Applications and Education. Springer-Verlag London Limited.