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Review

Scientific and industrial status of tissue engineering

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Tissue engineering is a newly emerging field targeting many unresolved health problems. So far, the achievements of this technology in the production of different tissue engineered substitutes were promising. This review is intended to describe, briefly and in a simple language, what tissue engineering is, what the achievements of this technology are, what the market volume for its products is, what knowledge is needed for practice of this science, how different countries approached this field, and the effects of tissue engineering on national development. This report is primarily written to raise awareness of health authorities and policy makers in developing countries to this technology and help them to approach this multidisciplinary field in a proper way.

Key words: Tissue engineering, regenerative medicine, health care sector, health planning, economics, marketing, developing countries, research.

INTRODUCTION

As a tissue engineering graduate, I was expected by health authorities and policy makers to describe the usefulness and applications of this newly emerging field, and show how it can help the health system in a developing country. The authorities were interested to know the achievements of this field, the potential market volume, and the impact of tissue engineering on the national development. Although, many in-depth studies have been performed on different aspects of tissue engineering by various national and international committees, a concise, and yet comprehensive report has not been published so far to address the above issues for health policy makers of developing countries. Using the data of previous comprehensive studies, this review is aimed to bringing the technology of tissue engineering to the attention of busy health authorities of developing countries and helping them to understand what tissue engineering is, and how it could be approached.

Despite modern advances in the fields of medicine and surgery, the problem of tissue loss and its consequent functional impairment is still considered one of the major challenges for practicing physicians. The oldest available description of a method for replacement of a lost tissue dates back to a thousand years BC when an Indian surgeon reconstructed the cut nose of a patient with the skin of his forehead (Grikscheit and Vacanti, 2002). Currently, five different strategies are employed for replacing the lost tissues: (1) Replacement of the lost tissue with a tissue from another part of the body, e.g. replacement of a lost thumb with big toe. This strategy is not applicable for all cases, for example a myocardium cannot be replaced by another tissue. (2) Replacement with artificial materials e.g. replacement of aortic artery with Dacron. The problem is the artificial material may not be able to adapt properly with all the physiological conditions. Also, in a young patient in growing age, the material may not be able to increase its size proportionate to the growth of the body. (3) Xenograft or allografts are other approaches. The problems with these methods are their limited availability and immunological incompatibility. (4) Use of an artificial device such as hemodialyzder to restore the lost physiological function. But, the limitations in continuous use of the device and the limited potential to adapt to all physiological needs of the body in different conditions are of major concerns. (5) Employment of living cells to replace the lost tissue, which is the basis of tissue engineering.

The term tissue engineering was officially defined in a National Science Foundation (NSF) workshop (USA) in 1988 as “the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and

pathological mammalian tissues and the development of of biological substitutes to restore, maintain or improve tissue function" (Skalak and Fox, 1988). For legislative purposes, in 2005, European Commission Directorate General for Enterprise and Industry proposed recognition of cells and tissues as "engineered" if they fulfil one of the following criteria: (1) the cells or tissues that have been subjected to substantial manipulation, so that their original biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement, are altered. Manipulations such as cutting, grinding, shaping, centrifugation, soaking in antimicrobial solutions, sterilization, irradiation, cell separation, centrifugation or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification are not considered as substantial. (2) The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor. (3) The cells or tissues form part of a combined advanced therapy medicinal product (Anon, 2005c).

The intention of the field of tissue engineering, which is also called regenerative medicine, is to produce living substitutes using live cells, usually in an interactive environment with biomaterials. These substitutes are aimed to have the potential to proliferate and adapt morphologically and functionally to their transplanted environment. The complexities of manufacturing of such products necessitate a multidisciplinary effort and interaction between the fields of medicine, biomaterials, cellular and molecular biology, and even nanotechnology.

Tissue engineering and regenerative medicine can help to improve the quality of healthcare in a wide range of non-communicable health problems. Non-communicable diseases need special attention in developing countries. In the 2003 report of WHO it has been pointed out that these diseases were ignored in developing countries (Anon, 2003b). It is estimated that by 2020, 70% of deaths will be caused by non-communicable diseases in these countries (Boutayeb and Boutayeb, 2005). The point is the conditions that are currently considered as tissue engineering targets are more prevalent in developing countries (Hofman et al., 2005; Folch et al., 2003; Jamison et al., 2006). For example 80% of the world mortalities due to chronic diseases (Anon, 2005b) and 90% of the world mortalities following traumatic injuries (Hofman et al., 2005; Jamison et al., 2006) occur in the developing countries.

ACHIEVEMENTS OF TISSUE ENGINEERING

Several years of scientific efforts in different countries have led to the manufacturing of several tissue engineered products, which either have passed all the regulatory issues and gained access to the healthcare markets or are still in the clinical trial phase. The main tissue engineered products are as follow:

Tissue engineered skin products

These products are indicated for use in burns injury (Jones et al., 2002), chronic ulcers (Harding et al., 2002), and cosmetic surgery. The first skin products were manufactured for treatment of burns victims. These products include: Integra (Integra Lifesciences Corporation, USA), (Heimbach et al., 2003; Winfrey et al., 1999) Epicel (Genzyme Biosurgery, USA) (Wright et al., 1998; Compton et al., 1989), and TransCyte (Smith and Nephew, UK) (Kumar et al., 2004; Noordenbos et al., 1999). Due to higher rate of chronic skin ulcers, the commercial value of the products that are licensed for treatment of this condition is higher than others (Jones et al., 2002). Therefore, various products are available for management of chronic skin ulcers including Apligraf (Organogenesis, USA) (Eaglstein and Falanga, 1997; Cavorsi et al., 2006; Curran and Plosker, 2002), Dermagraft (Smith and Nephew, UK and Advanced Tissue Sciences, USA) (Marston, 2004; Omar et al., 2004; Gentzkow et al., 1996), EpiDex (Euroderm, Germany) (Tausche et al., 2003), Epibase (Laboratoires Genévrier, France) (Vaillant, 2002; Soler, 2002), Myskin (CellTran, UK) (Moustafa et al., 2004), OrCel (Ortec, USA) (Still et al., 2003), BioSeed-S (BioTissue Technologies, Germany) (Johnsen et al., 2005), Hyalograft 3D, and Laserskin, (all by Fidia Advanced Biopolymers, Italy) (Caravaggi et al., 2003). The products that are marketed for cosmetic surgery applications include BioSeed-M (BioTissue Technologies AG, 2002) and MelanoSeed (both by BioTissue Technologies AG, Germany) (Westerhof et al., 2001).

Tissue engineered cartilage products

These products are aimed to repair cartilage defects, especially in lower extremities. Cartilage defects, especially in the knee joint, lead to erosion of articular surfaces and painful movement of the affected knee. In case of extensive degeneration of the joint, prosthetic replacement will be necessary. Application of tissue engineered cartilage products to the site of defect causes regeneration and obviates the need for major surgical operations. Current products are obtained by *in vitro* proliferation of autologous chondrocytes including Carticel (Genzyme Biosurgery, USA) (Beary III et al., 1998), Hyalograft C (Fidia Advanced Biopolymers, Italy) (Marcacci et al., 2005), Matrix-induced Autologous Chondrocyte Implantation (MACI) (Verigen, Germany) (Vibe-Hansen and Aesculai, 1998), ChondroArt (Educell, Slovenia) (Drobnic et al., 2002), co.don chondrotransplant (Grifka et al., 2000) and co.don chondrosphere (the latter is marketed as ARTHROcell as well) (both by co.don, Germany) (Litzke et al., 2004), BioSeed-C (BioTissue Technologies, Germany) (Erggelet et al., 2003), NOVOCART (TETEC, Germany) (Gaissmaier et

al., 2005; Gaissmaier et al., 2006), Cartilage Repair System (CaReS) (Arthro Kinetics, Germany) (Andereya et al., 2006), ArthroMatrix, which is also marketed as Chondrokin (Orthogen, Germany) (Anon., 2002a), ChondroTec (CellTec, Germany) (Anon, 2001a), and ChondroCelect (TiGenix, Belgium) (Vanlauwe, 2005).

Tissue engineered bone products

These products are used for treatment of remaining defects after extensive fractures, surgical operations for bone tumours and plastic maxillofacial surgeries. The advantage of tissue engineered products over prostheses that do not biologically interact with the bone tissue is their ability to increase the rate and quality of healing. These products include BioSeed-Oral Bone (BioTissue Technologies, Germany) (Strietzel, 2006; Schmelzeisen et al., 2003), co.don osteotransplant (co.don, Germany) (Bobic, 2000), and Osteocel, an allograft with proprietary name of Trinity (Osiris Therapeutics, USA) (Melnikova, 2006).

Tissue engineered vascular products

These products are in the clinical trial stage and are aimed to be used to replace coronary heart and peripheral vessels. These trials are conducted by co.don (Germany) (the products are Vascuplant (Josimovic´-Alasevic´ and Fritsch, 2001) and Vascular Biotech (Lamm et al., 2003)), the Heart Institute of Japan (Matsumura et al., 2003; Naito et al., 2003; Shin'oka et al., 2001), and Ludwig Boltzman Institute of Austria (Meinhart et al., 2001).

Cellular products for treatment of myocardial infarction

These products are used to prevent heart failure and shorten the recovery period after myocardial infarction. All these products are in the clinical trial stage. The institutes involved in development of these products are Genzyme Biosurgery (USA) with cooperation of Myosix (France) (Hagege et al., 2006), Diacrin (USA) (Pagani et al., 2003), BioHeart Inc (USA) (the product under trial is MyoCell (Smits et al., 2003)), Osiris Therapeutics, Inc (USA) (the product under trial is Provacel (Hare, 2006)), Neuronyx (USA) (the product under trial is Human Adult Bone Marrow Derived Somatic Cells [hABM-SC] (Neuronyx, 2006)), the German universities including Johann Wolfgang Goethe-University Frankfurt (Schachinger et al., 2004; Britten et al., 2003), University of Frankfurt (Assmus et al., 2002), University of Rostock (Stamm et al., 2003), Heinrich-Heine-University of Duesseldorf (Ghodsizad et al., 2004; Strauer et al., 2002), and Hanover Medical School (Wollert et al., 2004), Instituto de Ciencias del Corazón (Spain) (Fernández-Avilés, 2006), Texas Heart Institute (USA) (Perin et al., 2003), Seoul National University (South Korea) (Kang et al., 2004), University School of Medical Sciences, Poznan (Poland) (Siminiak et al., 2005), and Russian State Institute for Transplantation (Belenkov et al., 2003).

Tissue engineered products for treatment of diabetes

These products are applied for better control of diabetes and reduction of morbidity and mortality of this disease. They are produced by processing of pancreatic islet cells and are in the clinical trial stage. The institutions dealing with these products include AmCyte (USA) (AmCyte Inc,), Living Cell Technologies (Australia) (the product is DiabeCell) (Anon, 2005d), and Novocell (USA) (Novocell, 2006).

Tissue engineered liver products

These products are aimed to be used in acute liver failure that leads to a high mortality in a few days. All these products are in the clinical trial stage including Extracorporeal Liver Assist Device (ELAD): the study on this product started by Vitagen company (USA) (formerly called Hepatix) and is continued by Vital Therapies (USA) (Millis et al., 2002; Millis et al., 1999; Ellis et al., 1996; Sussman et al., 1994); HepatAssist: this product was initially developed by Circe Biomedical (USA) but has been handed over to Arbios Systems (USA) (Demetriou et al., 2004; Watanabe et al., 1997; Demetriou et al., 1995); Bioartificial Liver Support System (BLSS) by Excorp Medical (USA) (Mazariegos et al., 2002; Mazariegos et al., 2001; Kuddus et al., 2002); and Modular Extracorporeal Liver System (MELS) by Hybrid Organ (USA) (Sauer et al., 2003b; Sauer et al., 2003a).

Tissue engineered neural products

All these products are in the clinical trial stage including HuCNS-SC cells by StemCells, Inc (USA) for treatment of Infantile or late infantile neuronal ceroid lipofuscinosis (NCL) (StemCells Inc, 2006); dopamine-producing cells with proprietary name of Spheramine for treatment of Parkinson's disease by cooperation of Titan Pharmaceuticals (USA) and Schering AG (USA) (Grosset and Grosset, 2005; Bakay et al., 2004). The products on clinical trial for application in spinal cord injuries include activated macrophages with the proprietary name of ProCord by Proneuron Biotechnologies (USA) (Knoller et al., 2005), olfactory ensheathing cells by Capital University of Medical Sciences (China) (Huang et al., 2003) and Griffith University (Australia) (Feron et al.,

2005), Schwann cells by Tehran University of Medical Sciences (Iran) (Saberi et al., 2006), and bone marrow stem cells by three organizations including Institute of Experimental Medicine (Czech Republic) (Syková et al., 2006), Inha University College of Medicine (South Korea) (Park et al., 2005), and the Hematology and Hemotherapy Service of São José dos Campos (Brazil) (Callera and do Nascimento, 2006).

ESTIMATION OF MARKET VOLUME

According to the fact that tissue engineered products can be used for treatment of a wide spectrum of diseases and they are promised to be more curative than other therapeutic modalities, they possess a good marketing potential. The market potential is estimated according to the incidence and prevalence of the target disease, cost of current therapies, and availability and ease of application of tissue engineered products. As mentioned above, skin and cartilage products are approved for clinical application and are commercially available. There is a high demand for these products in countries where they are available. It is anticipated that other products receive the approval of regulatory bodies and come onto the market in near future. According to the U.S. Department of Health and Human Services, the potential worldwide market volume for tissue engineered products was more than $300 billion in 2005 and will be $500 billion in 2010 (Anon, 2006a).

Market for tissue engineered skin products

Cutaneous wounds are managed by traditional dressings, and advanced modalities such as antibiotics, growth factors and tissue engineered products. In 2001, the potential annual market volume for treatment of cutaneous wounds was estimated to be $6.25 billion worldwide, of which 10 - 12.8% ($625-800 million) belonged to the tissue engineered products. But, the manufacturers could only supply 2.5 - 3.2% ($20 million) of the worldwide demand (Hüsing et al., 2003; Anon, 2001b). The high difference between the potential demand and supply is due to the low production level and limited access of health care systems in different countries to these products. New figures show a rise in the actual demand of health systems for these modalities. For example, in 2002, the annual sales of Apligraf was $23 million and that of Dermagraft was $4.5 million (Lysaght and Hazlehurst, 2004).

The retail price is an important factor that should be considered when dealing with these modalities. It varies from $9.92-20.85 for each square centimetre (Jones et al., 2002; Bello et al., 2001; Monstrey et al., 1999; Still, Jr. et al., 1994), which is far more expensive than banked skin obtained from deceased donors. Banked skin is marketed for $0.37 - 8.66 for each square centimetre (Jones et al., 2002; Monstrey et al., 1999; Parente, 1997). But, engineered products decrease the need for medication, dressing changes and nursing care, and the number of operations, which decrease the overall cost of the wound care (Parente, 1997).

Market for tissue engineered cartilage products

According to the 2002 report of CONCORD Corporate Finance Research (Anon, 2002b) about 20 million people are suffering from cartilage defects and injuries worldwide. Also, the worldwide incidence of arthrosis is about 25 - 20 million cases according to the 2001 estimation of Landesbank Baden-Württemberg Equity Research (Anon, 2001b). Accordingly, the worldwide annual market volume for cartilage repair was estimated to be $6.5 million in 2001 and $25 million in 2011 (Anon, 2001b). But the actual worldwide annual sales for tissue engineered cartilage products were reported to be around $40 million (Hüsing et al., 2003). The difference is due to the limited supply of these products. But the other point is available products are only suitable for repair of particular cartilage defects. Different products are needed for regeneration of other types of cartilage injuries, which if engineered, increase the annual sales to $300 million-1 billion only in the US (Russell and Cross, 2001).

Market for tissue engineered bone products

The target market for the engineered bone products include 10% of cases with bone fractures that could not be properly managed by the standard modalities (1.5 million cases worldwide each year), maxillofacial and periodontal surgeries (4.5 million cases worldwide each year), and osteoporosis and bone tumours (300 million cases worldwide each year). In 2002, it was estimated that the bone repair market volume of those cases who are not suitable candidates for bone autograft will be around $300 million worldwide (Hüsing et al., 2003; Bock et al., 2003).

Market for cardiovascular products

Annually, 720 - 880 thousands coronary artery bypass operations are conducted in Europe and US (Hüsing et al., 2003). In 30% of these operations, a suitable autologous vessel cannot be harvested from the patient. This necessitates the use of synthetic prostheses. The maximum 5-year rate of patency of these prostheses is 40-50% (Baguneid et al., 2006). Tissue engineered vascular products are suitable for these patients. The annual market volume of vascular substitutes is estimated to be $1.5 billion (Szycher, 2002). As cell therapy protocols have not been approved by regulatory bodies as standard modalities for treatment of cardiovascular

diseases and their exact indications and contraindications are yet to be determined, estimation of market volume for these products may not yield an accurate figure. However, a rough evaluation of the potential cell therapy market for myocardial infarction estimated that the volume will be $2 million in US (Kuiters and Doering, 2005).

In regards to the heart valves, it should be noted that a tissue engineered product that can be used in a clinical trial has not been achieved in majority of studies. Nonetheless, estimation of market volume for these potential products is needed as heart valves are believed to be one of the major tissue engineered products. According to the published reports, the sales rate of these valves in 2001 amounted to $830 million (Hüsing et al., 2003). This market can be targeted by the tissue engineered products.

Market of tissue engineered products for treatment of diabetes

According to the published reports, the worldwide number of diabetic patients was 170 million in 2000 and will increase to 360 million in 2030 (Wild et al., 2004). The indications of current tissue engineered products aiming to control diabetes have not been precisely defined yet. Depending on the results of current clinical trials, these products may be used in all diabetics or a particular percentage of patients who do not respond to conventional modalities. A British report states that the latter include around 3% of insulin-dependent patients (Smith and Gale, 2005). In 2000, International Diabetes Federation estimated that the number of insulin-dependent diabetics was 5.3 million worldwide (Anon, 2000). If 3% of these patients benefit from tissue engineered products and the cost is $15000 per patient (Anon, 2006c), the estimated worldwide market volume for these products will be $2.4 billion. But, in another assessment, the volume was estimated to be $2 billion for just the US market (Anon, 2003a).

Market for tissue engineered liver products

According to the study performed for Vital Therapies, in 2003 around 21000 patients were eligible to use liver substitute manufactured by this company (Anon, 2004). This figure exceeds the number of patients eligible for liver transplantation in the same year (Anon, 2005a). The report estimates that the annual market volume for liver substitute tissue engineered products will be around $1.08 million (Anon, 2004).

THE SCIENCE BEHIND TISSUE ENGINEERING

As it was mentioned above, tissue engineering is a multidisciplinary field that benefits from different scientific areas including cellular science, biomolecules, biomaterials, manufacturing technology, biomechanics and informatics. This section has been adapted from the 2003 report of SPRU Science and Technology Policy Research, University of Sussex, UK (Senker and Mahdi, 2003).

Cellular science

The field of cellular science plays important functions for tissue engineering including: (1) Identification, control and modification of the cellular behaviour in response to different factors and conditions. The tools needed to deal with this function are cellular biology, extracellular matrix biology, developmental biology and physiology, and immunology. The methodologies needed are genomics and proteomics. (2) Identification of suitable cell sources to be used in the tissue engineered constructs. This is an important field that has been extensively studied. The cells can be obtained as autologous, allogeneic, or xenogeneic. The cells can be obtained from adult, foetus or embryo and may be used with or without *in vitro* manipulation. (3) Identification and control of the factors that influence cellular proliferation and differentiation. Cells are the main structural units of tissue engineered constructs; therefore high numbers of cells are needed for productions of these constructs at the industrial level. One of the best ways to fulfil this demand is manipulation of the cellular proliferation machinery. One of the main reasons that stem cells attracted so much attention in recent years is their high proliferative capacity. But, as they are undifferentiated, they need to be induced to differentiate into the desired phenotype. Therefore, cellular differentiation has been recognized as an important field in tissue engineering.

Biomolecules

Biomolecules are components of the biological systems that can modify the cellular behaviour. Preparation and delivery of biomolecules to the target cells are important parameters in tissue engineering. Biomolecules can be synthetically manufactured and delivered to the cells, or the cells can be modified to produce their required biomolecules themselves. Gene therapy is related to tissue engineering for this purpose. Delivery of biomolecules is another important field. These molecules can be just simply added to the cell culture medium, or for a more controlled and timely release, delivered through extracellular matrix components. Also, encapsulation with materials that allow controlled-release of these molecules is under intense investigation.

Biomaterials

Biomaterials are used for engineering of bioscaffolds on which the seeded cells will proliferate, migrate and diffe-

rentiate. Bioscaffolds will determine the shape and mechanical properties of the construct. They are not only carriers of the seeded cells, but also bridges through which the cells in the recipient site can migrate and accelerate the healing process. Bioscaffolds can be used for delivery of biomolecules to the site of injury as well. The important factors that should be considered for engineering of bioscaffolds are their shape and mechanical properties, biocompatibility and cell attachment properties, biodegradability and the properties of their biodegradation products. Different natural, synthetic and semi-synthetic materials are used for engineering of bioscaffolds.

Manufacturing technology

Different technical aspects should be taken into account when a product is aimed to be manufactured at industrial level. These considerations may not be necessary for laboratory level production of the same products. For example, bioreactors can be employed for mass production of cells and 3-dimentional tissue engineered products. Bioreactors enable employment of mechanical forces and scheduled delivery of biomolecules for cell culture. Preservation of the engineered products is another issue. The shelf life of the product and its storage condition are very important. For example, a product which can be stored in room temperature is much cheaper than a product that should be stored frozen. As freezing is necessary for storage of most products, cryobiology will be an important player in industrial tissue engineering.

Biomechanics

Some organs such as heart, blood vessels, cartilage and bone have mechanical functions in the body. Therefore, the mechanical properties of products aiming to be used in these organs should be taken into account as they affect the functional outcome of the products. The other issue is these properties may change after implantation and interaction with cells and biomolecules in the recipient site.

Informatics

Informatics can help to anticipate the cellular behaviours in different conditions. Currently, informatics has progressed in fields of genomics, proteomics and even microarrays, but the fields of cell, tissue, physiome (physiome is a science that deals with the physiologic dynamic of a healthy organism) and commercial informatics are still in a very primitive stage. Tissue engineering will be greatly benefited from expansion and progression of cell and tissue informatics.

Keys to success

According to what already have been pointed out, a number of factors needed for construction of a successful tissue engineering business model can be listed. But, according to the report of Fraunhofer Institute for Systems and Innovation Research (Germany) (Hüsing et al., 2003), amongst all factors, the most important one is relevant knowledge. Many companies start their activities in this filed merely by a knowledge of cell and tissue culture while this multidisciplinary filed needs knowledge in biomaterials, extracellular matrix, biomolecules, and quality control at the same time. Lack of clinical knowledge is another problem in these companies. Logistical flexibility is another issue because the time of manufacturing of some products should be properly synchronized with the time of surgical operation. The other strategy that is sometimes ignored is direction of research activities to fulfil the market demands. The scientists may get involved into interesting studies which are far away from the market demands. This issue frequently occurred in Europe. For example, not much has been done in critical areas such as length of manufacturing, storability, shelf life, and ease of handling of the products. Economists and merchants should be consulted for identification of commercially important gaps that need to be addressed by more focused research.

WORLDWIDE APPROACH TO TISSUE ENGINEERING

Most tissue engineering studies and companies are concentrated in the United States. But other countries have also realized the importance and the present situation of this field and initiated directed and focused activities in tissue engineering. In 1995, only 5% of active tissue engineering companies were non-American, but this figure rose to 46% in 2002 (Anon, 2006a). In regards to the technological capabilities and advancements, Europe and Japan can be considered as the second and third tissue engineering poles after US. Below, the strategies adopted by different countries to get benefit from this new science are reviewed.

United States

Most investments in this field have been made by private companies. According to the published reports, from early 90s to 2002 the investment of private companies on this field amounted to $4.5 billion (Lysaght and Hazlehurst, 2004), and government's investment from 1998 to 2001 amounted to only $250 million (McIntire et al., 2002). U.S. Department of Health and Human Services states that this trend should be corrected (Anon, 2006a). This department estimates an annual market volume of $500 billion for this technology, and recognizes

it as the first industry of new millennium and a determinative technology. As the anticipated time of entering to the market is not long for a wide range of tissue engineered products, a focused investment and organized direction of financial and human resources and research activities has been recommended for gaining access to this market. Department of Health reiterates that private sector only invests on a few products, which require somewhat similar and easily available technologies. But, many products need complex technologies that necessitate integration of major scientific areas — such as medicine, biology, biochemistry and biomaterials — at different levels. The integration can be optimized if the conditions allow physical and temporal closeness of scientists in appropriate clusters. In addition, the high industrial orientation of tissue engineering requires very close cooperation of academic and industrial sectors for sending the products to the market in a short period of time. So far, the applied aspect of these products were the focus of most American studies and less was done in regards to basic and fundamental aspects and understanding of the involved mechanisms in tissue engineering (McIntire, 2003). Governmental support is necessary for leading scientists to deal with the latter issues. US government has recognized tissue engineering as a profitable industry and planned to increase the growth rate of this sector in all its aspects. For example, to expedite the approval process of tissue engineered products, the Office of Combination Products (OCP) has been established in FDA in 2002. In 2006, Department of Health proposed the establishment of a new institute, the Federal Initiative for Regenerative Medicine (FIRM) (Anon., 2006a), which should be highly supported by the government for up to 20 years to make a proper link between the academic and industrial sectors. Currently, the tissue engineering studies are made on an individual basis in the United States, e.g. the studies on myocardial repair are performed in the departments of cardiology and those of bone tissue repair are performed in the departments of orthopaedics. But these have a lot in common, and therefore, their close interaction is necessary to solve the common questions more efficiently. One of the main functions of FIRM will be establishment of a closer inter-sector cooperation. At this time, award of grants, legislation and other issues of tissue engineering is dealt with by different organs such as Department of Health and Human Services (including NIH and FDA), Department of Defence (including DARPA), NASA, Department of Commerce, the White House Office of Science and Technology Policy, the President's Council of Advisors on Science and Technology, and the National Science Foundation (NSF). It was proposed that FIRM takes over all these functions. To do so, FIRM should employ members from both academia and industry. The proposed expertise of FIRM members is engineering (different branches), medicine (different specialties), biology (cellular, developmental, structural, vascular, and computational), nanotechnology fabrication, immunology, biomaterial, economy, education, sociology, psychology, ethics, biochemistry, and chemistry (Anon, 2006a).

This proposal of a long-term support of tissue engineering by the government is based on previous similar support of other technologies. For example the status of semiconductor technology in late 1980s and early 1990s was similar to the current status of tissue engineering. But a timely $2 billion government investment and establishment of Semiconductor Manufacturing Technology Consortium (SEMATECH) led to the growth of this industry from an annual amount of $8 billion to $170 billion (×21), which captured 50% of the world's market (Anon, 2006a).

Europe

Germany, UK, and France are the most active European countries (in descending order) in the field of tissue engineering. The other active countries are Scandinavia and Benelux (Bock et al., 2005). Government provides most funding in Europe; therefore, more attention has been paid to fundamental and basic studies (McIntire, 2003). But most centres working on tissue engineering are young and have not grown to a suitable size yet. The annual sales of these organizations, which are mostly concentrated on autologous products, do not exceed a few million dollars. The active institutes are working on a wide range of research topics. This necessitates establishment of a central organization, similar to US, for needs assessment and definition of national or European research priorities. Tissue engineering activities have extended to the hospitals and tissue banks as well. The research hospitals closely collaborate with academic tissue engineering centres and have focused on development of products that have not mostly reached to the clinical trial stage yet. Non-research hospitals have concentrated on optimization of the existing products, or produce tissue engineered products for their own use. Tissue banks mostly work on decellularization of allogeneic tissues for using them as scaffolds for culture of autologous cells (Bock et al., 2005). In general, the collaboration between academic and industrial sectors is not as much as expected and research into issues with industrial and commercial values is delayed (Senker and Mahdi, 2003). In Europe, the emphasis on the strategic value of tissue engineering is not as strong as US but, the process needed for a product to receive marketing approval is shorter than United States. Similar to US, due to lack of a central organizing institute, the activities of different groups are not coordinated (Hüsing et al., 2003; Bock et al., 2003). But there are initiatives attempting to define national or even European policies to create a focused and coordinated environment to accelerate the growth of this new technology. One of the main obstacles of marketing of tissue engineered products in Europe was

different regulatory issues in European countries. Therefore, in 2002, European Union started a comprehensive program to determine and unify the existing regulations in different countries. After three years of study and adoption of different and sometimes conflicting strategies, in 2005, European Commission has finalized its regulatory proposal for submission to the European Parliament, the Economic and Social Committee and the Committee of the Regions (Anon, 2005c; Kaiser, 2006). According to this proposal, tissue engineered products together with gene and somatic cell therapies will be regulated as advanced therapy medicinal products.

Japan

This section is adapted from the report of the United Kingdom's Royal Academy of Engineering Mission to Japan (Williams, 2003): The government has heavily invested in this technology and established several advanced centres. Therefore, in Japan, similar to Europe, basic and fundamental studies are performed in the field of tissue engineering. This provides a strong back-ground necessary for manufacturing of complex products (McIntire, 2003). This investment is the result of government's decision to increase the volume of biotechnology products from $10 billion to $212 billion (more than 20 times) in a 10-year program (Anon, 1999). In 2001, a budget of $800 million was allocated to tissue engineering and the closely related fields of genomics, stem cells, and bioinformatics. In 2003, Ministry of Education, Science and Technology was asked to spend $400 million on strategic initiatives to expedite the process needed for new tissue engineered and genetic therapeutic modalities to move from the research laboratories to the clinical practice. Establishment of strong infrastructures such as Tissue Engineering Research Centre (TERC) and Institute of Biomedical Research and Innovation (IBRI) have also been noted.

Tissue Engineering Research Centre (TERC) is affiliated to the National Institute of Advanced Industrial Science and Technology (AIST). Due to high demand for close interaction of tissue engineering with commercial and industrial sectors, TERC has been established under close supervision of the Ministry of Economic, Trade and Industry with an initial budget of $26 million and an annual running budget of $10 million.

Institute of Biomedical Research and Innovation (IBRI) was established with an initial budget of $110 million and an annual running budget of $40 million. The main research themes of this institute are tissue engineering applications, clinical research for production of medicinal products, and medical equipment. IBRI is located in Kobe city that has been transformed into a "Medical Industry City". This city has been designed by the Centre for science, technology and economic development of Stanford Research Institute (SRI) International based on previous successful American models (Mathieson, 2005). Next to IBRI, the RIKEN (RIKEN is an abbreviation of "Institute of Physical and Chemical Research" in Japanese language) Centre of Developmental Biology is built, which is run by an annual budget of $50 million concentrating on areas such as aging, environment and information technology (Anon, 2006b). Kobe International Business Centre, Translational Research Informatics Centre, Biotechnology Training and Research Centre, and Biomedical Accelerator (Biomedical Accelerator is aimed to help commercialization of biological research findings) are located in close proximity to IBRI and RIKEN Centre for Developmental Biology. This campus creates an environment in which the scientists with the knowledge needed for successful manufacturing of industrial biological products communicate more closely and efficiently. This well-thought solid infrastructure makes Japan one of the most successful manufacturers of biological products, and especially, tissue engineered products in Asia (Collins, 2005; Anon, 2006a; Williams, 2003).

Other countries

In a study performed by University of Toronto's Joint Centre for Bioethics (Greenwood et al., 2006), the status of tissue engineering was assessed in 31 low- and middle-income countries. These countries were classified according to 4 criteria including: (1) existence of a national plan for promotion of tissue engineering and government's investment in this sector, (2) existence of marketable tissue engineered products or services (e.g. cartilage repair with autologous cells), (3) existence of active private companies in this field, (4) existence of tissue engineering academic institutions and/or publications. The countries possessing all four criteria were Brazil, China, and India. Argentina, Bulgaria, Chile, Malaysia, Mexico, Poland, Slovakia, South Africa, and Thailand had criteria 2-3. Columbia, Cuba, Egypt, and Russia had criteria 3-4; and Belarus, Hungary, Iran, Latvia, Lithuania, Pakistan, Romania, Saudi Arabia, Serbia, Turkey, Ukraine, Vietnam, Moldova, Philippine, and Uganda possessed only the last criterion.

This study shows that Indian and Chinese approach to tissue engineering is very well planned. This comprehensive look to tissue engineering will lead these pioneer countries to capture the potential markets in the region. The long-standing experience of China to penetrate into different worldwide markets will help this country to expand into the international market of tissue engineered products as well. In Middle East, Iran, Turkey, Saudi Arabia, and Pakistan have adopted similar approaches, mainly academic, to this field. If any of these countries starts a comprehensive initiative for setting up of the required infrastructure, it may be able to win the Middle East market of these products.

EFFECTS ON NATIONAL DEVELOPMENT

In 2002, United Nations Economic and Social Commission for Western Asia in cooperation with International Labour Organization held a meeting in Beirut, in which 170 representatives from different Arabic countries participated (Anon., 2002). This meeting was aimed to identify and determine the best approach for regional capacity building in new technologies to increase the employment rate, establish sustainable development, and alleviate poverty in Arab countries. Final report of this meeting states that adoption of a suitable national strategy for establishment of a planned development in science, technology and special initiatives is a necessity. For this purpose, the first important step would be to identify new technologies, which according to the existing knowledge and resources, expected outcomes, and the trend of international development, could be considered as high priorities for national economic and social developments. In this report, it was emphasized that the countries, which adopt a better approach to the four novel technologies of informatics, biotechnology, genetic engineering, and biomaterials, will develop better capacity for economic and social developments. In regards to biotechnology, it was proposed that Arab countries invest in making a strong infrastructure for plant and pharmaceutical biotechnology, tissue engineering, and biocomputer technology (biocomputers are new generation of computers in which biologic materials are used to increase the speed of data processing).

In 2006, the National Security Research Division of RAND Corporation published the report of a study funded by the US National Intelligence Council, the Intelligence Technology Innovation Centre (ITIC), and the Department of Energy (Silberglitt et al., 2006). This study predicts the status of technology in different countries up to 2020 according to the current trend of technology development plans in those countries. The society was divided into 12 economic sectors including water, food, land, population, governance, social structure, energy, health, economic development, education, defence and conflict, and environment and pollution. It has been mentioned that tissue engineering impacts four sectors of population, governance, health, and economic development (one third of the economic structure). On the other hand, the issues that can hinder the rate of a country's development have been classified into eight groups of rural economic development, economic growth and international commerce, public health, individual health, resource use and environment health, military and warfighters of the future, homeland security and public safety, and governance and social structure. The report emphasizes that tissue engineering will have positive impacts on three (more than one third) issues including economic growth and international commerce, individual health, and governance and social structure.

In this report, tissue engineering has been recognized as one of the top 16 applications, which represent the countries capacity for technology implementation in 2020. According to the current trend of technology development, it was anticipated that except North America, Western Europe, Israel, Japan, North Korea, and Australia, other countries will not be able to acquire this technology at a commercially profitable level until 2020. Lack of success of other countries in acquiring this technology was attributed to the high cost, unbalanced investment in research and development (R&D), legislative and political barriers, inappropriate infrastructure, educational problems, particular social values and public opinions, and social stability. But the study predicts that, until 2020, most countries will be able to utilize the tissue engineered products, which increases the worldwide demand and makes tissue engineering a highly profitable technology.

It has been reiterated that establishment of required infrastructure for advanced technologies will enable many countries to have access to them. For example, Kenya could acquire the technology for production of GM crops in 2005 by proper investment, planning and establishment of a suitable infrastructure. Therefore, establishment of infrastructure and capacity building was recognized more and more important than training of skilled and knowledgeable people. In this report, training of scientists and technicians without establishment of proper infrastructures and production units has been counted as a waste of resources. For example, Philippine has been noted in which many of medical doctors choose to go to the nursing schools to increase their chance of employment in an overseas country (Choo, 2003).

In general, a detailed look at tissue engineering shows that expansion of this technology can help development of academic, industrial, and professional activities in the following fields: enzymes production, recombinant protein production especially growth factors, antibody engineering, culture media production, production of natural and synthetic polymers, engineering and modelling of bioscaffolds, engineering of chemicals for bioscaffolds assembly, transplantation immunology, genetic engineering, live cells and tissues preservation and transportation technologies, engineering of manufacturing equipment, legislation for proper production, distribution and use of these products, standardization of production, ethics, training of doctors and nurses for application of tissue engineered products, and national and international marketing.

CONCLUSION

Tissue engineering is a new technology which can help management of a number of previously unresolved health problems. The estimated market volume for tissue engineered products is promising but capture of this market needs an organized and timely investment to build a strong infrastructure. This infrastructure can advance the national development in developing countries.

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