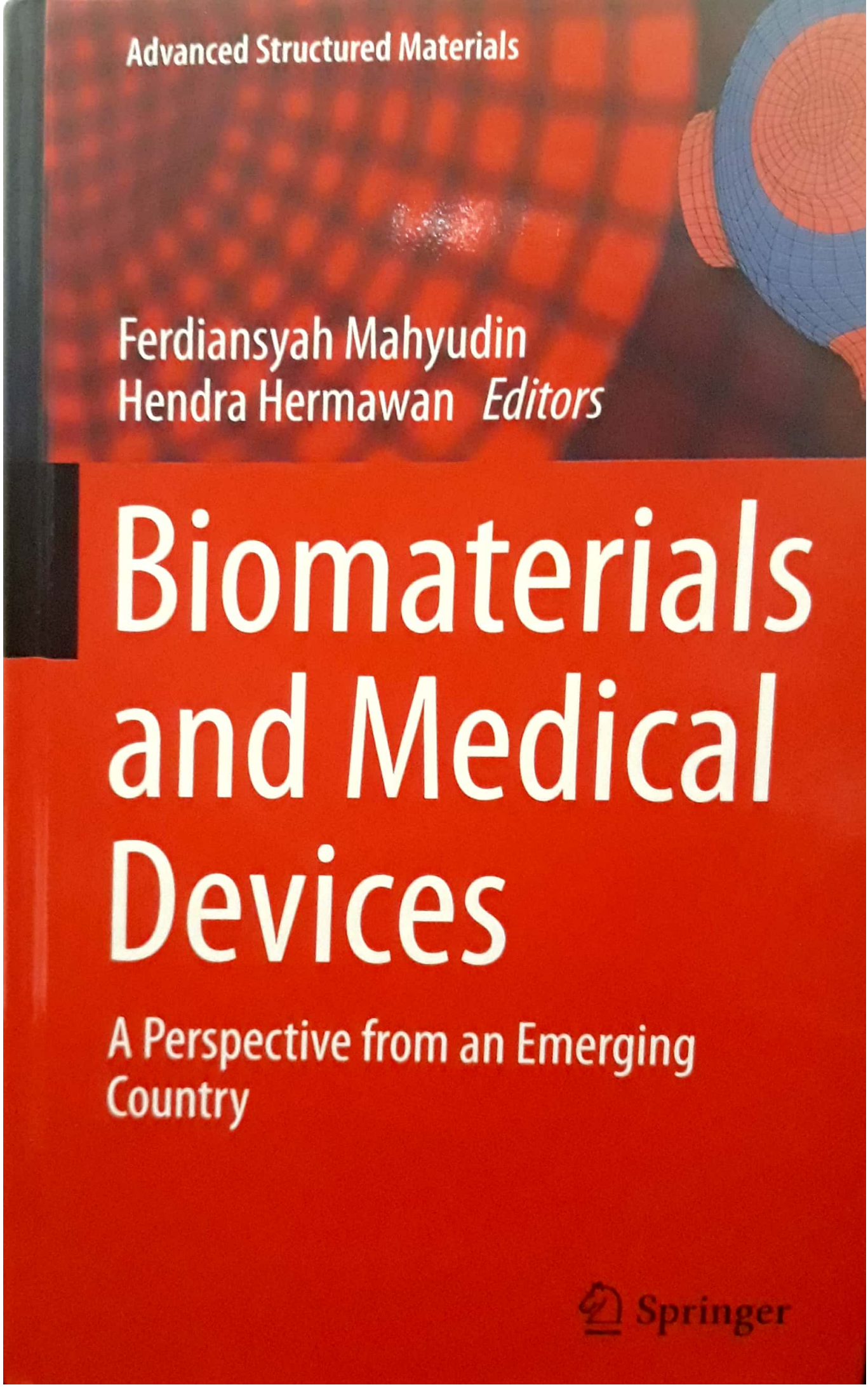

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Editors

Biomaterials and Medical Devices

A Perspective from an Emerging Country

Springer

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Contents

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Tissue Bank and Tissue Engineering

Ferdiansyah Mahyudin and Heri Suroto

Abstract Permanent damage on the tissue or organ are still a major problem and chalenge to be solved in the world of medicine. Humankind has tried to solve the problem using technologies available in their respective era since long time ago. We can read from various literature about the efforts already made to replace and consequently heal the damaged tissue or organ. Tissue or organ damage caused by war and many other causes became the main reason of the tissue bank's estabilishment in many parts of the earth. Tissue bank strife to provide safe and high quality products to be used as natural biomaterial for damaged tissue reconstruction in patients. Several processes started from procurement, processing, and finally sterilization has been done to guarantee safe and useful products for the patients in need. In line with the recent technological advancement, especially with the introduction of stem cell usage, tissue and organ reconstruction has entered a new era that will bring greater hope for patients. If the previous methods that used biomaterial only employ dead tissue in the reconstruction procedures, tissue engineering will make the combination between stem cell and biomaterial as scaffold possible, thus enabling the living tissue to be used in reconstruction. This method, albeit still in the process of research, is expected to yield better results.

Keywords Tissue and organ damage Biomaterial Tissue bank Stem cells Tissue engineering

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1 Introduction

Tissue and organ injuries causing functional damage is the challenge yet to be solved in medical science. In the history of mankind, countless trials and procedures have been tried to solve this problem. Creating an organ, or at least an artificial one, is a long-life dream of mankind, which started to be realized after so many decades and technology advancement until now. The legend of transplantation itself was depicted in the painting of "Healing of Justinian" by St. Cosmas and St. Damien. The painting describe a lower leg transplantation on a soldier who has been injured during war. Cosmas and Damien themselves were Arabic-Christian twin brothers whose profession are doctors and lived in the area that we call Turkey at present (Meyer 2009; Nather and Zheng 2010; Vacanti and Vacanti 2014).

In 600 BC, Shusruta Samhita from Northern India performed a skin graft for war victim soldiers and criminals who received nose mutilation as punishment (Nichter et al. 1983; Ang 2005). A Bolognese surgeon named Gaspare Tagliacozzi (1545–1595) published his idea in a book named De Curtorum Chirurgica per Institionem (Surgery of the Mutilated by Grafting) which describes about forearm flap technique that harvests inner side of forearm to perform reconstruction of the nose and then the termination of pedicle connection several weeks later. The first allogenic skin graft were performed by Jaqcues-Louis Reverdin in 1869 by using epidermal grafts which also known now as split thickness grafts. George Pollock of England introduce epidermal graft on combustion injury in 1871. The following year in 1872 Louis Xavier Edouard Leopold Ollier reported his success in transplanting the skin using whole epidermis and part of dermis. And at last in 1886, Karl Thiersch introduce split thickness skin grafting technique to further extend area of skin graft coverage (Meyer 2009; Nather and Zheng 2010; Phillips 1998a; Vacanti and Vacanti 2014).

The early efforts to replace damaged part of body use metal, ivory, wood and several other as biomaterial for reconstruction. On Galileo-Roman period, teeth replacement which is the early phase of dental implant has been performed. Anthropologic discovery of human skull filled with metal on the showed early effort of tissue reconstruction using substitution material (Crubézy et al. 1998). Ambroise Paré (1510–1590) described in his work Dix livres de la chirurgie measures to reconstruct teeth, noses, and other parts of the body (Pare 1634). Early success of premolar reimplantation due to trauma were reported by John Hunter (1771) on his book titled "The Treatise on the Natural History of the Human Teeth" (Meyer 2009; Nather and Zheng 2010). Reconstruction using donor tissue to cover the defect on musculoskeletal system were reported by MacEwen in 1880. Lexer reported 23 cases of articular cartilage transplantation between 1908 and 1925 and reported 50 % success rate. Noyes and Shino began to use allografts in ligament reconstruction in 1981 and have subsequently reported good results. Milachowski was the first to transplant a human meniscus in 1984 (Shelton et al. 1998).

There are a lot of materials available at present to be used for defect reconstruction procedure on a tissue or organ to restore its function. The materials used to replace the tissue defect are labeled as biomaterials. American National Institute of Health describes biomaterial as "any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to maintain or improve the quality of life of the individual". Biomaterial that is being used came from polymers, metals, ceramic, and composites whether it is obtained from human or animal (natural) or purposely invented by human (synthetic). The usage of biomaterial is varied depend on the disease and tissue that need to be restored. On cardiovascular cases, biomaterial is needed to produce stent in treating coronary diseases, while dentist will need biomaterial for their implant to treat the patient. One of the profession that use implant frequently is orthopedic surgeon. Biomaterial in orthopedic are used as internal fixation for fracture of the bone such as screw, plate, and nail system, to replace damaged joint with artificial one (endoprosthesis), and as bone graft or bone material substitute to promote and stimulation for bone healing (Navarro et al. 2008).

2 Natural Biomaterials

Natural biomaterials refer to organic and inorganic matrix that is obtained from human or animal. The source of biomaterial from human came from tissue or donor donation, or tissue that is being removed after certain procedure such as total joint replacement and craniotomy. Decellularized extracellular matrix tissue can be obtained from hard tissues such as bone and teeth, or soft tissues such as skin, amniotic membrane, intestine, vascular, heart valve, duramater, cornea, etc. There are several advantages using ECM biomaterials as biomaterial ingredients. First of all, each of molecules in ECM can be broken down by using normal enzymatic processes. Another advantage is that the three-dimensional structure and morphology of the ECM copies the structure and morphology of the original tissue that is being transplanted. Lastly, researchers can design a prosthesis that works not only on a macroscopic level, but also on the cellular level due to the innate potential of the biomaterial. There are, of course, several certain disadvantages using ECM. It usually triggers immune system of the recipient thus causing severe reactions. There are also many ancillary molecules that change the way the prosthetic will interact with surrounding recipient tissue when placed in vivo. While there are some molecules that would promote the regenerative capabilities of the recipient tissue, others might stimulate an immune responses. In the end, there is an abundant of potential in ECM biomaterials as well as its problems yet to be solved (Coburn and Pandit 2007).

Natural biomaterials that are being used mostly are intact extracellular matrix, collagen, chitosan, hyaluronoic acid and alginate. Collagen is protein that

construct a human body the most. More than 30 % protein of human body are collagen (Nimni et al. 1987). Chitosans are the second most abundant biopolymer in nature and represent a family of biodegradable cationic polysaccharides consisting of glucosamine and randomly distributed N-acetylglucosamine linked in a β(1–4) manner, and have a chemical structure similar to hyaluronic acid (Dornish et al. 2001). Instead of protein, another substance that frequently used as scaffold is mineral hydroxyapatite (HAp). These minerals can be obtained from nature such as humans, animals, or corrals or made for specific purposes (synthetic). Orthopaedic surgeon applies mineral HAp as bone graft. Mineral HAp can be obtained from bovine bone and corral as scaffold materials. The preparation of HA will decide the composition and structure. First is HA with the organic matrix, unsintered; secondly is without organic matrix, unsintered; and last one is without the organic matrix and sintered. Sintered and unsintered HA differs in their consistency. Unsintered bone mineral consists of small crystals of bone apatite (carbonate HA), while sintered bone mineral consists of larger apatite crystals without carbonate when heated above 1000 °C. The unsintered material has organic matrix that resembles structure in the context of the three dimensional macro- and microstructure of the bone. Natural HAs possess an interconnecting macroporosity that make the cells penetrate into the scaffold possible both in vivo and in vitro (Wiesmann and Meyer 2009).

3 Tissue Bank

Transplantation is an effort to move a cell, tissue, or even an organ from a donor to a recipient in order to restore its function. Tissue transplantation differs from organ transplantation, whereby the process is more complicated, more expensive, and usually is a life-saving procedure. Organ transplantation, such as kidney, heart, liver, lung and many other require a healthy and functional donor to replace the damaged function of the recipient. Consequently, the source of donor organ must be alive or at least in vegetative state in which the function of the organ transplanted is still functional. After harvesting the donor, the organ must be immediately transplanted to the recipient in order to prevent death of the organ's cell. Tissue transplantation, however, can be harvested from cadaver since it consist of non-viable tissue such as cornea, bone, joint, ligament and meniscus. Therefore it is not necessary to perform the transplantation immediately if it is storage properly either in room temperature or deep freezer (Phillips 1998b).

The place to store the donor tissue is called Tissue Bank. Tissue bank, by definition, "is an entity that provides or engages in one or more services involving tissue from living or cadaveric individuals for transplantation purposes. These services include assessing donor suitability, tissue recovery, tissue processing, sterilization, storage, labelling and distribution" (Nather et al. 2007). Tissue bank connects the donor and recipient that needs the tissue. Main function of tissue bank is to provide various type of high quality and safe tissue for recipients.

Korean War is the first trigger to the establishment of first tissue bank in USA. Huge number of war victims that needed various tissue, especially musculoskeletal, as the result of the war inspired George Hyatt to build Bethesda Naval Tissue Bank in the United States in 1950, with Ken Sell becoming Director in 1965. Almost in the same time, Rudolph Klen set up the tissue bank in Hradec Kralove in the old Czechoslovakia in 1952, and then followed by Frank Dexter who established The Leeds Tissue bank in 1956, and then The Charité Hospital Tissue Bank in Berlin in the old East Germany was set up in 1956. Nowadays tissue bank have improved greatly worldwide and several regional organization is formed such as American Association of Tissue Bank (AATB), European Association of Tissue Bank (EATB), Asia-Pacific Association of Surgical Tissue Banking (APASTB) and Latin American Association of Tissue Banks (ALABAT) (Pfeffer 2009; Phillips 2016). In Indonesia there are three tissue banks located at the National Nuclear Research Institute (BATAN) in Jakarta (1988), Dr. Soetomo General Hospital in Surabaya, East Java (1990) and Dr. M. Jamil Hospital in Padang, West Sumatera.

3.1 Regulation

Availability of the tissue is the main requirement on establishing a tissue bank. Tissue donation is an act of humanity, as it enables one to alleviate the sufferings of fellow human beings. Organ donation is a complex situation in which involving many aspects such as social, ethic, regulation, medical, infrastructure and skills of the doctors in charge. Organ donation aims to obtain potential donor that fill the criteria and regulation on its own respective country. The aspects mentioned above, unfortunately, cause an imbalance between supply and demand of a tissue, unavoidably causing longer waiting list for a patient to receive a tissue from the donor (Nijkamp et al. 2008; Anderson and Trias 2009).

Tissue and organ can be obtained from living donor or cadaver. Tissue harvest can be executed if prior agreement exist. Different countries may have different regulations regarding this matter. The first is presumed consent or opt-out system, where a deceased individual which fulfill the criteria may have his/her organ harvested unless there were prior objection from him/herself. The second is informed consent or opt-in system, where people make their agreement with tissue bank regarding the timing and condition of tissue harvest. Usually the donor receive an ID card from tissue bank in exchange. Several countries in Europe adopt opt-out system, while USA, UK, and most of Asia except for Singapore adopt opt-in system (Phillips 1998b; Gevers et al. 2004; Rithalia et al. 2009; Douville et al. 2014; Hutchison 2016; Rid and Dinhofer 2009).

Monetary inducement for donation is subject to the following restrictions. Payment to the donor is prohibited. Monetary payment or advantages for the donation shall not be made to living donors, cadaver donor's next of kin or any donor-related party. As regards compensation for donation-related expenses,

donors or their family shall not be financially responsible for expenses related to retrieval of tissues. Anonymity between donor and unrelated recipient shall be strictly preserved. Anonymity between donor and recipient shall allow tracking of tissues, through anonymous identification numbers (Phillips 2003; Nather et al. 2007).

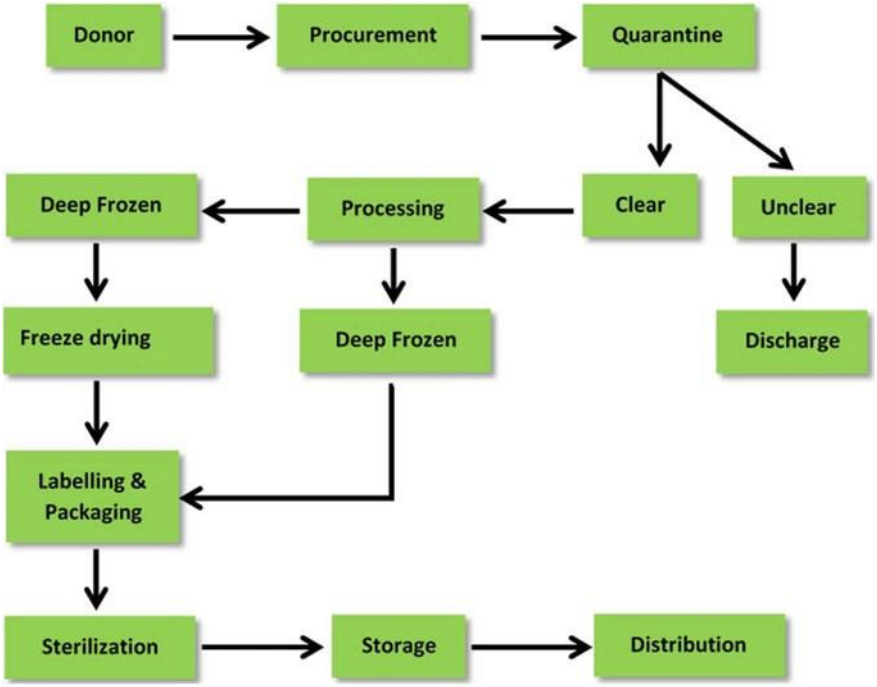

Fig. 9.1 Flow chart of production of human tissue at Surabaya Cell and Tissue Bank

The procedure for tissue harvesting varied in every country depend not only by the consent, but from socio-culture, ethic, religion and nearest family. The role of family is influential in the decision making. In UK on 2006, refusal of donor agreement caused by the family reach 41 % while Spain record 15 % regarding the same problem (Rithalia et al. 2009). A certain belief that a deceased must be buried with its complete parts of body is the main barrier of tissue harvesting and organ donor in Indonesia. Figure 9.1 illustrate the procedure of human tissue production at the Cell and Tissue Bank of Dr. Soetomo General Hospital in Surabaya (hereafter named as Surabaya Cell and Tissue Bank).

3.2 Donors Selection

Main aim of a Tissue Bank is to obtain a safe and high quality tissue to be provided to the patient. Therefore each and every tissue must be examined

thoroughly. Donor suitability for a donation of tissue allograft depend on medical and behavioural, medical records review, physical examination, cadaveric donor autopsy findings (if an autopsy is performed) and laboratory tests (Phillips 2003; Nather et al. 2007; Navarro et al. 2008).

Donor history evaluation includes an interview of the potential living donor or the cadaveric donor's next of kin, performed by suitably trained personnel, using a questionnaire. A qualified physician shall approve the donor evaluation process. According to APASTB Standards for Tissue Bank General Contraindications the use of tissues for therapeutic purposes:

- History of chronic viral Hepatitis.
- Presence of active viral Hepatitis or jaundice of unknown etiology.
- History of, or clinical evidence, or suspicion, or laboratory evidence of HIV infection.
- Risk factors for HIV, HBV and HCV have to be assessed by the Medical Director according to existing National Regulations taking into account national epidemiology.
- Presence or suspicion of central degenerative neurological diseases of possible infectious origin, including dementia (e.g. Alzheimer's disease, Creutzfeldt-Jakob disease or familial history of Creutzfeldt-Jakob disease and multiple sclerosis).
- Use of all native human pituitary derived hormones (e.g. growth hormone), possible history of duramater allograft, including unspecified intracranial surgery.
- Septicaemia and systemic viral disease or mycosis or active tuberculosis at the time of procurement preclude procurement of tissues. In case of other active bacterial infection, tissue may be used only if processed using a validated method for bacterial inactivation and after approval by the Medical Director.
- Presence or history of malignant disease. Exceptions may include primary basal cell carcinoma of the skin, histologically proven and un-metastatic primary brain tumour.
- Significant history of connective tissue disease (e.g. systemic lupus erythematosus and rheumatoid arthritis) or any immunosuppressive treatment.
- Significant exposure to a toxic substance that may be transferred in toxic doses or damage the tissue (e.g. cyanide, lead, mercury and gold).
- Presence or evidence of infection or prior irradiation at the site of donation.
- Unknown cause of death.

Age criteria varied depends on tissue being harvested. There is no age limit for musculoskeletal tissue donor such as cancellous bone. Heart valves and pulmonary valve must be harvested under 65 years old, while aortic valve under 50 years old and mitral valve under 50 years old. Skin tissue is harvested under 75

years old and artery under 50 years old and vein under 60 years old (Phillips 1998c; Nather et al. 2007; Navarro 2010).

There is another way to examine medical and social history that hasn't been reported previously. A physician will perform a thorough examination to a donor candidate to find out any sign of risky behaviour or possibility of infection or viral disease. If any of these signs listed below exist on a donor, it is necessary to ask to the family or the closest relative about the time the sign shows (e.g. skin piercing, tattoo). The donor shall be rejected if the sign is proved to be critical. The physical examination has to be performed systematically in each and every patient with a specific aim to find the signs mentioned before. There are signs that should be specifically looked for, such as risk of sexual transmitted diseases: syphilis, ulcers, herpes simples, chancroid, and perianal lesions. Physical evidence of non-medical percutaneous drug abuse, acupuncture or tattoos including the presence of ear or body piercing. Significant enlarged lymph nodes might be present. Oral thrush, blue spots or purple ones characteristics of Kaposi's sarcoma. Generalized rash that could point to sepsis or unexplained jaundice. Necrotic lesions after previous vaccination. Donor's physical examination shall be recorded in the donor's history and collected by the retrieval team (Phillips 1998c; Nather et al. 2007; Navarro 2010).

The obtained tissues will be tested for transmissible diseases depends on law and practice in each respectful country. In case of living donors, further procedure for blood testing might be performed. Tests will be performed and deemed legitimate on blood samples from the donor using recognized, licensed tests and according to manufacturer's instructions. Tests will be performed by a qualified, licensed laboratory and according to Good Laboratory Practice (GLP). There is 24 hours' time limit for blood screening on deceased donors after death. Blood screening for living donors must be taken at least 7 days before tissue harvesting. For potential tissue donors who experience more than 50 % hemodilution due to additional fluid such as blood, blood components, or plasma volume expanders within 48 h before death, a pre-transfusion blood screening must be done. The physician will be notified of confirmed positive result that has clinical significance according to the existing law. Sample of donor blood examination will be securely sealed and stored frozen for 5 years after the tissue harvested is expired or in accordance to existing law on each country. Minimum Blood Tests shall include (Phillips 1998c; Nather et al. 2007):

- Human Immunodeficiency Virus Antibodies (HIV-1/2-Ab)
- Hepatitis B Virus Surface Antigen (HBs-Ag)
- Hepatitis C Virus Antibodies (HCV-Ab)
- Syphilis: nonspecific (e.g. VDRL) or preferably specific (e.g. TPHA)

Optional Blood Tests could be necessary for compliance with applicable Intergovernmental, National, Regional and Local Law or Regulation and/or to screen for endemic diseases (Phillips 1998c; Nather et al. 2007):

- Hepatitis B core antibodies (HBc-Ab): HBc-Ab should be negative for tissue validation. Though, if the HBc-Ab test is positive and the HBs-Ag is negative, confirmation cascade should be entered. If the antibodies against the surface antigen are found (HBs-Ab), the donor can then be considered to have been recovered from an infection and the tissue can be used for transplantation.
- Antigen test for HIV (p24 antigen) or HCV or validated Molecular Biology Test for HIV and HCV (e.g. PCR), if performed by an experienced laboratory.
- Antibody to HTLV 1: depending on the prevalence in some regions.
- Cytomegalovirus (CMV), Ebstein-Barr Virus (EBV) and Toxoplasmosis Antibodies: for immunosuppressed patients.
- Alanine Aminotransferase (ALT) for Living Donors: In addition to the general testing requirements, testing living donors of tissue for Alanine Aminotransferase (ALT) is recommended.

HIV and HCV retest is recommended in living donors in 180 days after prior examination. Any other method that will yield better result (antigen testing, molecular biology or viral inactivation method) is used rather than retesting with the same method and the result will be recorded in the same document.

Samples of each obtained tissue will be cultured if the tissues are going to be processed without terminal sterilization. Before the tissue exposed to antibiotic containing solution, representative sample shall be taken. The culture procedure must enable the growth of both aerobic and anaerobic bacteria and fungi as well. If the harvest is performed on a cadaver, blood culture might be useful in examining the condition of the cadaver. They must be examined by the experts of this field. If the result shows low virulence or commonly considered non-pathogenic microorganisms growing, the tissue should be distributed after being further processed through decontamination. Tissue which shows high virulence microorganisms growth is not acceptable for transplantation, unless the decontamination is done to render the microorganism inactivate without harmful potential effects, including possibility of residual endotoxins (Phillips 1998c; Nather et al. 2007).

3.3 Tissue Procurement

Tissues can be obtained from either living donors or deceased donors, which can be divided into vegetative state or heart beating donors, deceased due to cardiopulmonary arrest donors, and non-heart beating donors. The available tissue to be obtained are bone, joint, musculoskeletal tissues (ligament, tendon, fascia lata, meniscus), duramater, heart valve, and skin tissues.

The deceased shall had his/her death pronounced or death certificate signed by doctors other than those involved in tissue management. All aspect of law regarding determination of death shall be respected. The cadaver that is going to be used as donor must be identified thoroughly before harvesting began.

Harvesting shall be done in adequate facility such as operating room or mortuary with facilities needed. Sterilization of all equipment shall be done between harvests of different cadaver. Tissues may be obtained using aseptic technique, where harvesting process is prepared using a standard surgical technique and resembling standard operating room practice. Another way is to perform clean or non-sterile technique, only if the sterilization is adequate to remove all pathogens after the procedure (Phillips 1998c; Phillips 2003; Nather et al. 2007):

- Aseptic technique: aseptic technique shall be observed throughout the procurement procedure. Procurement sites shall be prepared using a standard surgical technique; all methods shall be consistent with standard operating room practice.
- Clean/non-sterile technique: allografts procured using clean/non-sterile techniques are suitable for transplantation, if efficient validated sterilizing methods are used to eliminate pathogens after retrieval.

A sample should be taken for microbiological examination if possible. After tissue harvesting, the cadaver must be reconstructed to achieve its previous state before the event of funeral. Time needed to obtain the tissue after the death of the donor is an important issue as well. An optimum time of harvest is between 6 and 24 h (if the cadaver if stored at room temperature), or between 12 and 48 h (if the cadaver is kept in a refrigerator at 4 °C before the first 4 h post-mortem). Residual tissues after a therapeutic surgical procedure (e.g. femoral head, skin and amnion) can be obtained for another therapeutic use in other patient or research purposes. Informed consent is required before the residual tissue can be obtained from the donor.

Potential donor of amnion membrane can be sorted from obstetrician list of patient that is going to undergo elective caesarean section deliveries. Inform consent for amniotic membrane harvest can be made before the patient get the surgery, therefore the possibility of the patient to agree donating the membrane is higher because of longer pre-surgery discussion regarding donation in elective patient compared to those who undergone emergency caesarean section deliveries. The same discussion can also be performed in patient with possible bone donation after a surgical procedure, although the patient list is made according his/her medical and behavioural history (Warwick 2010).

3.4 Quarantine

After procurement, the tissue is temporary kept in a −20 °C freezer to wait for the laboratory test result. If the result is negative, then the process proceeds. If, however, the result is positive, the tissue is deemed unusable and will be terminated.

3.5 Processing of the Tissue

The tissue bank is a storage to keep tissues in non-viable state, which will be sterilized later to prevent disease spread from donor to the patient as well as contamination during processing of the tissue. Non-viable tissue will decrease acute allograft rejection reaction. Cartilage and cornea are exceptions to this rule. Both tissue are normally avascular and will not experience vascularization, render it able to be transplanted in viable condition without causing acute allograft rejection reaction (Kearney 2010).

Tissue preservation are meant to avoid matrix tissue damage due to the enzymatic processes. Enzyme that plays big role in tissue degradation processes is proteolytic. Lipid peroxidation also has great potential to destroy the tissue matrix. Both processes activities mentioned above depends greatly on water availability. Therefore decreasing the amount of water through freeze drying (lyophilisation) or water immobilization using deep freezing technique is very important to preserve the tissue. The methods for tissue preservation depends on the type of tissue being processed (Kearney 2010). Another process to decrease tissue antigenicity is by removing all dead cell and their products (Mirsadraee et al. 2007; Vinci et al. 2013).

Bone can be processed by deep freezing and terminal sterilization using chemical and gamma-irradiation, cryopreservation without irradiation, freeze-dried and demineralized with gamma-irradiation. The obtained bone, both from living or deceased donor, can be processed using methods mentioned above. On deep freezing process, the bone will be stored in deep freezer with temperature of −80 °C. This method will not decrease the mechanical strength of the bone, therefore it is used for large bone graft allograft that will be used as structural bone graft for large bone defect reconstruction. After all examination yield negative result, the bone is wrapped and put into deep freezer. Both cell in the bone and soft tissue will necrotize and disappear microscopically in 2 weeks' time. This process will significantly reduce tissue antigenicity. It is best for the tissue to be issued from tissue bank after 1 month to ensure whole process is completed. Freeze drying, on the other hand, is water reduction process by sublimation where the water will vaporized directly from solid ice state without going through liquid state. The aim of this process is to get biological scaffold that is collagen network containing HAp, decreasing antigenicity, decreasing amount of the microbes, and facilitate sterilization. This process decreased the amount of water in tissue until 5–8 % by sublimation mean. Freeze drying will decrease bone strength significantly. Therefore small bone allograft will be used on small bone defect as filler to facilitate bone healing. Freeze-dried tissue can only be stored in room temperature (Phillips 1998d; Nather and Tay 2010).

Bone demineralization is a chain of process in which soft tissue, blood and fat is removed from the bone, continued by removal of bone mineral using HCl. The process is halted if the amount of the calcium is decreased to 8 % and will be called forth as demineralized bone matrix (DBM). This process exposes mineral trapped within the bone. DBM is a composite of collagens (mostly type I with

some types IV and X), non-collagenous proteins, various growth factors, few residual calcium phosphate mineral (1–6 %) and some small percent cellular debris. DBM is naturally osteoinductive with better potential compared to the unprocessed bone thus provide better bone healing. Final processing of demineralized bone matrix is freeze drying so the demineralized bone matrix can be keep in room temperature (Nather and Tay 2010; Gruskin et al. 2012).

Musculoskeletal soft tissue allograft such as ligament, tendon, fascia, meniscus processed and stored in deep freezer with −80 °C temperature at least 1 month before being used. Tissue sterilization is needed to guarantee there is no disease spreading from the donor to the recipient. Sterilization is needed to ensure there is no proliferating microorganism and to decrease the amount of microorganism until acceptable level called as sterility assurance level (SAL). Tissue sterilization can be done either by chemical sterilization or gamma irradiation therapy. Chemical sterilization is done by using ethylene oxide, glutaraldehyde, and peracetic acid. Each chemical compound have several negative impacts to the tissue therefore its selection and usage require decent knowledge of characteristic and function of each compound to obtain optimal result. Sterilization using gamma ray is usually done with dose of 25 kGy. Gamma irradiation works directly by causing damage on DNA structure of the microorganism and indirectly by forming free radical that will cause damage to the protein, enzyme and nucleus material of the cell. Gamma irradiation might cause decrease on mechanical strength on bone allograft or soft tissue allograft, causing some tissue bank refuse to do terminal sterilization process. On these conditions, allograft harvest must be done in aseptic technique and thoroughly monitored to prevent disease spread or contamination (Kearney 2010; Yusof and Hilmy 2010).

3.6 Tissue Bank Products

Product spectrum produced by tissue bank varied depend on the purpose of the tissue bank itself, available facility, and human resources. Tissue that can be produced by tissue bank are bone, joint, skin, amniotic membrane, ligament, tendon, fascia, heart valve, duramater, and many other cell product.

The Surabaya Cell and Tissue Bank was established in 1990. Earlier, it was called bone bank since the only tissue obtained from cadaver and donor are bone. With additional human resource and equipment, the bone bank started producing human′s soft tissue such as tendon, ligament, duramater and amniotic membrane, hence the name changed into Biomaterial Center—Tissue Bank since 2010. In 2014, the Bank began a research of stem cell in collaboration with the Regenerative Medicine and Stem Cells Center of Dr. Soetomo Hospital, Faculty of Medicine, and Institute of Tropical Disease of Airlangga University Surabaya. The name Biomaterial Center—Tissue Bank changed again into Cell and Tissue Bank in the same year. The Surabaya Cell and Tissue Bank has the signature products such as deep frozen tissue consist of bone, joint, amniotic membrane,

fascia, duramater, tendon and ligament, as well as freeze-dried tissue consist of amniotic membrane, bone, demineralized bone (DBM), and tendon (Figs. 9.2, 9.3 and 9.4). The Indonesian Ministry of Health has appointed Dr. Soetomo Hospital as center of service, education and research for stem cell in Indonesia. According to the regulation in Indonesia, clinical trial can only be done using adult stem cells, while embryonic and animal stem cell are still prohibited.

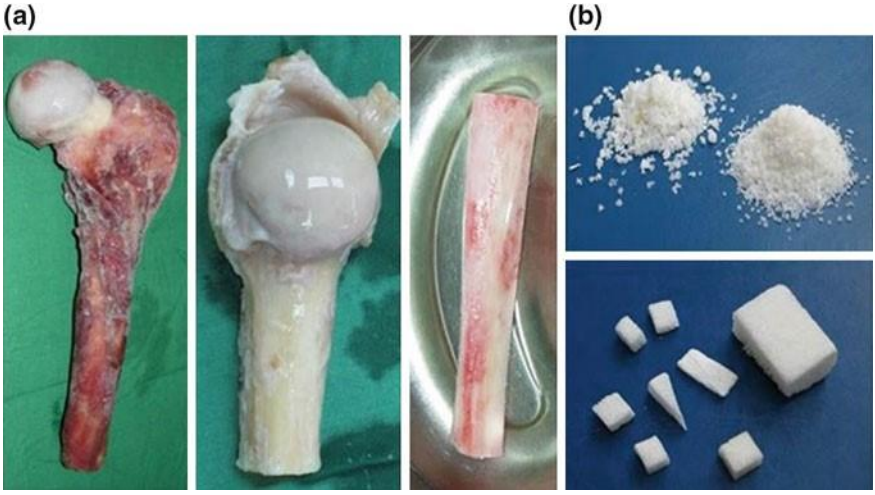

Fig. 9.2 a Left and middle, humerus and femur joint for osteoarticular bone allograft and right shaft of tibia bone for intercalary bone allograft, b various size and shape of freeze dried bone (Courtesy of Dr. Soetomo General Hospital, Surabaya)

Fig. 9.3 Various form of demineralized bone matrix (Courtesy of Dr. Soetomo General Hospital, Surabaya)

Fig. 9.4 a Placenta, b processing of amniotitc membrane, c final product of amniotic membrane (Courtesy of Dr. Soetomo General Hospital, Surabaya)

3.7 Orthopaedic Applications

Spectrum of disease traded by an orthopedist consist of congenital anomaly, infection and inflammation, trauma, arthritis, tumor, metabolic and degenerative disease, and also sensory disturbance and muscle weakness. Most of the diseases mentioned above will cause defect on musculoskeletal system, leading to functional disturbance later on. Reconstruction using bone, ligament, tendon, fascia as graft is performed to treat the defect in musculoskeletal tissue. The tissue graft can be obtained from the patients themselves, which is called autograft, from other person, which is called allograft, and even another species, which is called xenograft. The most ideal graft came from the patient themselves because there will be no rejection reaction, rendering perfect incorporation with the body. Autograft, however, has several weakness that is limited source of harvest, unable to reconstruct large defect, sacrifice some part of normal body structure, need surgical procedure to harvest the graft with risk of pain, infection, and blood loss (Ebraheim et al. 2001; Dimitriou et al. 2011; Loeffler et al. 2012; Shelton and Fagan 2011; Myeroff and Archdeacon 2011). Bone graft is the most tissue transfer transplantation procedure after blood transfusion. Bone autograft has ideal biologic composition to treat bone defect that is osteoconductive matrix, in which the graft act as scaffold or trellis that supports the growth of new bone; second is osteoinductive proteins, which stimulate and support mitogenesis of undifferentiated perivascular cells to form osteoprogenitor cells; and the last one is osteogenic cells, which are capable of forming bone if placed into the proper environment (Finkemeier 2002; Myeroff and Archdeacon 2011). Cancellous bone autograft has osteoconductive, osteoinductive and osteogenesis properties but no structural strength, meanwhile cortical bone autograft has a structural strength but osteoconductive, osteoinductive and osteogenesis properties lower than cancellous autograft. Cancellous bone allograft, both frozen and freeze dried, osteoconductive properties similar to cortical allograft, osteoinduction properties lower than cortical allograft, but no osteogenesis properties also no structural strength. Frozen cortical bone allograft has similar structural strength with cortical bone autograft, osteoconduction lower than cancellous bone allograft and no osteoinduction also osteogenesis properties. Freeze dried cancellous bone allograft has lower structural strength and osteoconduction (same with frozen cortical bone allograft) and no osteoinduction also osteogenesis properties. Demineralized bone matrix (DBM) allograft has osteoconductive properties (similar cortical bone allograft), meanwhile osteoinductive properties is similar to cortical bone allograft and has no mechanical strength and osteogenesis (Greenwald et al. 2001).

Allograft has several advantages compared to the autograft. It doesn't need any extra surgical procedure on the patient means that no further morbidity caused, no need to sacrifice any part of the patient's body, and it is available with different size and shape. With all those advantages, however, it has only osteoconductive and osteoinductive components, therefore it takes longer for the defect to heal and

a good processing is required to prevent disease transmission. Frozen allograft needs to be stored in −80 °C for a minimum 1 month period. The structural strength will never decrease along with the decrease of enzyme degradation and host immune response during the process. Due to its strength, frozen allograft is used for large bone defect reconstruction such as joint replacement (osteoarticular) and bone shaft defect (intercalary). Reports on large bone allograft usage shows satisfactory result with excellent allograft survival, although few complication occurred such as fracture of graft, infection, and graft resorption (Muscolo et al. 2006; Bus et al. 2014; Bus et al. 2015). Reports from Dr. Soetomo General Hospital in 1990–2010 stated that there were 85 large bone allograft procedure performed (Figs. 9.5 and 9.6) with 87 % excellent and good functional evaluation with complication of

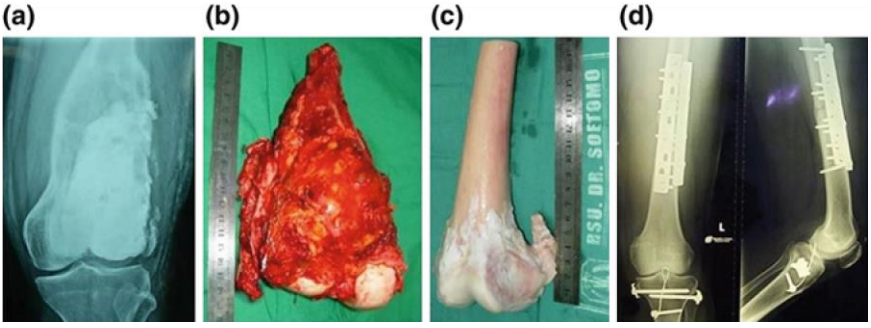

Fig. 9.5 a Giant cell tumor of distal femur, b tumor after resection, c osteoarticular bone allograft (17 cm), d X-ray after reconstruction of the distal femur including knee joint (Courtesy of Dr. Soetomo General Hospital, Surabaya)

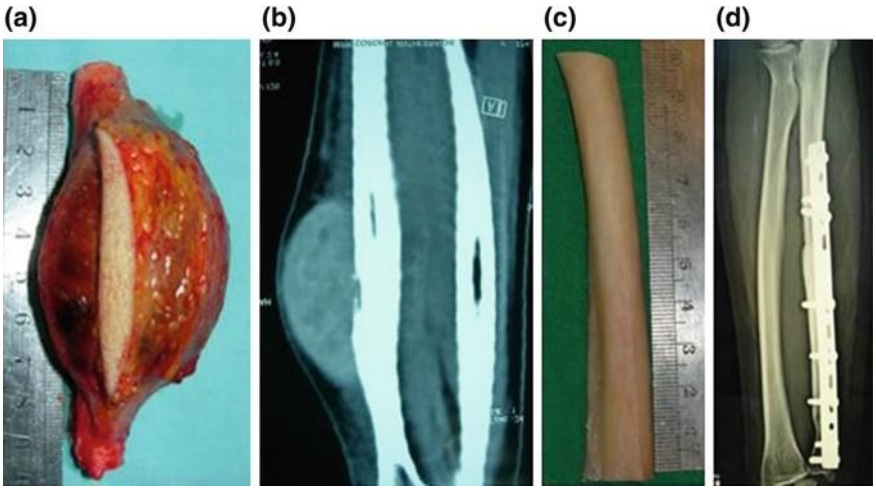

Fig. 9.6 a Malignant soft tissue tumor with ulna bone infiltration, b tumor after bone resection, c intercalary bone allograft (10 cm), d X-ray after ulna bone reconstruction (Courtesy of Dr. Soetomo General Hospital, Surabaya)

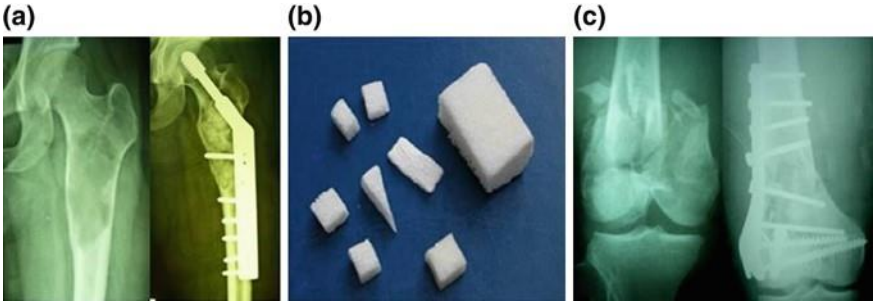

Fig. 9.7 a Left, benign bone tumor, right, after surgery and bone graft; b freeze dried bone allograft; c left fracture of intercondylar femur, right, after surgery and bone graft (Courtesy of Dr. Soetomo General Hospital, Surabaya)

infection in two cases, fracture of bone allograft in two cases, and one case of bone resorption.

Other types of allograft are freeze dried and demineralized bone matrix (Fig. 9.7). Freeze dried bone allograft is processed by decreasing the amount of water in the bone until 5–8 %. The objective of freeze drying is to obtain a chemically stable product at room temperature and to preserve the properties of the tissue, so that the tissue can be kept easily at room temperature and then distributed to the user after being sterilized. Freeze dried bone allograft has osteoconductive and minimal osteoinductive properties, but greatly decreased structural strength instead (Ferdiansyah 2007). While demineralized bone matrix has better osteoinductive properties, structural strength is also decreased, comparable to those of freeze dried bone allograft. Both types of allograft is used to fill small bone defect for procedures in dentistry, maxillofacial, spinal fusion, etc. (Gruskin et al. 2012).

4 Tissue Engineering

In present days, tissue and organ damage can be treated by reconstruction or transplantation surgery. Surgical reconstruction procedure has widely implemented on various tissue damage. On musculoskeletal system, orthopedic surgeons have performed reconstruction surgeries by using biologic biomaterial (allograft) from donor such as bone, joint, meniscus, ligament and tendon. Several other procedures might use synthetic biomaterial (implant and endoprosthesis) that is composed from metal alloy, polymer and ceramic. Reconstruction surgery on cardiovascular, ophthalmology and other medical discipline is also rapidly improving by using biologic or synthetic biomaterial as substitute for damaged tissue and eventually restore its normal function. Nevertheless, there are still problems in using biologic biomaterial that potentially cause morbidity on the patient such as disease transmission, infection, inflammation due to reaction

against foreign component, dislodgment and wear, and also lack of donor (Muscolo et al. 2006; Bus et al. 2014; Bus et al. 2015; Meehan et al. 2014; Illingworth et al. 2013).

Organ transplantation from donor to the recipient is a lifesaving therapy. Transplantable organ are namely kidney, liver, heart, and lung. The technological advancement in medical studies ensured transplantation to be safe and successful procedures to maintain the life of the patient. Transplantation, however, might cause several problems such as immune system process that would lead into chronic rejection and destruction of the organ being transplanted, rendering the recipient to consume lifelong immunosuppressant with risk of infection vulnerability and tendency of tumor formation. The biggest and apparent problem of tissue and organ transplantation is severe discrepancy between available donor and recipients who need the organ, as shown by data from Organ Procurement and Transplantation Network. Up to mid-2015, there are 122,648 total waiting list patient for life saving organ transplant, 79,260 of them are on the active waiting list. On January until July 2015 18,048 transplantation procedure have been performed with 8,757 people as donor. It's displeasing to see 22 patient died each day while waiting for donor availability. There are 4 fold increase of organ demand in the last 20 years, followed only by 2 fold increase of transplantation procedure.

Solution is needed to solve the problem of limited organ donor in transplantation procedures. Tissue engineering might be one of the answers for that. In the late 1980, a meeting was held in Keystone, Colorado, sponsored by National Science Foundation entitled "Tissue Engineering" which emphasize efforts in manipulating tissue or combine it with prosthetic material to restore the function. The article "Functional Organ Replacement: The New Technology of Tissue Engineering" published in 1991 issue of Surgical Technology International recorded for the first time the term "tissue engineering" is used (Vacanti 2006; Vacanti and Vacanti 2014). In the following 25 years, tissue engineering has evolved rapidly not only by using prosthesis or manipulating tissue, but by also integrating the use of cell and protein as well. The definition of tissue engineering is still unclear and is often mistaken for regenerative medicine. According to National Institute of Health US "Tissue engineering evolved from the field of biomaterials development and refers to the practice of combining scaffolds, cells, and biologically active molecules into functional tissues. The goal of tissue engineering is to assemble functional constructs that restore, maintain, or improve damaged tissues or whole organs". "Regenerative medicine is a broad field that includes tissue engineering but also incorporates research on self-healing—where the body uses its own systems, sometimes with help foreign biological material to recreate cells and rebuild tissues and organs". Other definition that is used to identify tissue engineering is "the use of a synthetic or natural biodegradable material, which has been seeded with living cells when necessary, to regenerate the form and/or function of a damaged or diseased tissue or organ in a human patient" (Russell and Bertram 2014).

Tissue engineering is a combination of three component known also as tissue engineering triad that is: cell, scaffold and proteins as signaling (Nerem and Schutte 2014; Moroni et al. 2015). The aim of tissue engineering is to create a living tissue construction to substitute the damaged tissue or organ. The cells can be obtained from stem cells or other progenitor cells or even fully differentiated cells. It might be a mix of several types of cell, mostly known as primary cell with a partner cell. The scaffolds can be manufactured from either synthetic biomaterial or natural extracellular matrix. The scaffold is needed for fabrication of a replacement tissue or as a delivery vehicle for the cells being used in a tissue engineering. There are various types of signals, including growth factors and chemotactic factors. These signals might be ones secreted by the cells employed (Nerem and Schutte 2014).

Tissue engineering works in replacement, repair and regeneration of the damaged tissue. The oldest concept is to replace the tissue rather than repair or regenerate it. Several procedure create a replacement tissue or organ outside of the body which would be implanted within the body. Some of the initial successes were in this category of replacement. This includes such skin substitutes as Integra, a product of Integra Life Sciences and approved by Food and Drug Administration (FDA) in 1996; Apligraf, a product of Organogenesis approved by FDA in 1997; and Dermagraft, a product of Advanced Tissue Sciences approved by FDA in 1999. Dermagraft is now sold by Advanced Biohealing which has been acquired by Shire Medical. Using Integra as an example, the research on this approach was published in a journal in 1982 however, as already noted, FDA approval did not come until 1996, a gap of 14 years. Furthermore, although all three of these skin substitutes were developed as a 'replacement', these products act and categorized as wound healing implants according to the regulation of the US FDA through the Center for Devices and Radiological Health. Therefore they should be in the repair category instead of replacement. Today these might well be regulated as biologics, and one can only speculate about the length of time today that would be required for FDA approval.

4.1 The Cells

Cell is one of major component in tissue engineering to create a fabricated construction to become a living tissue construction. The cells can be obtained from stem cells or other progenitor cells or even fully differentiated cells. A stem cell is defined as a cell that has the capacity for self-renewal and the potential to differentiate into any cell type in the body. Self-renewal is the process by which stem cells divide to make more stem cells, perpetuating the stem cell pool throughout life. Self-renewal is division with maintenance of the undifferentiated state. This requires cell cycle control and often maintenance of multipotency or pluripotency, depending on the stem cell (Shenghui et al. 2009). Progenitor cell,

however, has the ability to generate the exact same cells of the tissue or organ from which it was harvested without ability to change its attributes.

Stem cells have an important role in the process of tissue repair. Manipulating stem cells for applications in tissue engineering and regenerative medicine has caught a lot of attention. The differentiation potential of stem cells is described with different functional terminologies (Samadikuchaksaraei et al. 2014).

- Totipotent stem cells, i.e. the zygote and its descendants up to the eight-cell stage in mammals, which can form the embryo and the trophoblast of the placenta
- Pluripotent stem cells, such as the inner cell mass of the blastocyst, embryonic stem cells and reprogrammed cells, such as induced pluripotent stem (iPS) cells that can differentiate into all the cells of the three embryonic germ layers
- Multipotent stem cells, such as mesenchymal stem cells and several other adult stem cells, which can differentiate into multiple cell lineages like osteoblast, chondroblast and adipocyte, but not all the lineages derived from the three germ layers
- Bipotent stem cells such as mammary gland epithelial stem cells, which can differentiate into two cell lineages such as myoepithelial and luminal cells
- Unipotent stem cells such as spermatogonial stem cells that can differentiate into only one mature cell lineage like male gamete.

Stem cell can be obtained from the patient themselves (autologous) or from another person or donor (allogenic). Using autologous stem cell will diminish any risk of disease transmission and ensure compatibility with the patient. There are some disadvantages, however, such as decreasing potential of stem cells in elderly patient and requiring harvest procedure, which is relatively easy but would still potentially causing morbidity for the patient. Allogenic stem cells are obtained from different individual. It is mainly used for the patient whose stem cells potential decreased for any reason. Some risks must be taken into caution while using allogenic stem cell such as disease transmission and rejection reaction from the host.

Stem cells are classified into embryonic (human embryonic stem cells, hESCs) and adult stem cells. The hESCs isolated in 1998 for the first time from the inner cell mass (ICM) of a pre-implantation human blastocyst in a landmark study by Thompson et al. (Thomson et al. 1998). In theory, hESCs have the capability to change into all tissues of the human body and may provide crucial therapeutic treatment for various diseases. The only method of hESC harvest process in the late 1990s/early 2000s involved destruction of a human embryo, and it is considered by some as the same of terminating a human life. Embryonic stem (ES) cells are considered as immortal version of the ICM in culture; they retain high telomerase activity and can continue to self-renew indefinitely under appropriate culture conditions. When injected into immune-deficient mice, hESC form teratoma tumors that contain derivatives of all three germ layers, the most typical ones being bone, cartilage, neural rosettes and epithelium of the airways and gut (Klimanskaya et al. 2014). Yamanaka et al. discover that Induced

pluripotent stem cells (iPS) is an effort to make a mature cell into pluripotent cell (Takahashi and Yamanaka 2006). Induced pluripotent stem cells (iPSCs) show similarities to embryonic stem cells (ESCs) that are obtained from many somatic cell types and many animal species. Due to accessibility of somatic cell origin, human iPSCs does not have any problem regarding ethical issues that found in human ESCs due to their embryonic origin, but also enable the easy production of patient-specific pluripotent stem cells.
Similar to human ESCs, human iPSCs are capable of massive proliferation in vitro while retaining the developmental potential to differentiate into various types of cells.

Adult stem cell can be obtained from bone marrow, adipose tissue, peripheral blood, umbilical cord, placenta and from other tissues or organ of human bodies. Adult stem cells have lower proliferation and differentiation potential compared to human embryonic stem cells, therefore the risk of teratoma formation is considerably low and diminish the ethical and religion controversy. The most researched adult stem cells is the one obtained from bone marrow. Beside bone marrow, adult stem cells is usually obtained from adipose tissue and umbilical cord. Adult stem cells from organ are rarely used due to the difficulty in harvesting and higher risk of morbidity (Li et al. 2014).

The ideal stem cells in tissue engineering should be: easy to obtain in large numbers, safe to implant, able to differentiate into the expected cells. It resulted in limited types of stem cells which might be useful for tissue engineering. Mesenchymal stem cells, hematopoietic stem cells, adipose stem cells, and skin stem cells are easy to obtain and provided in large numbers. They are basically safe for the patient, being harvested from matured tissues. Although pluripotent stem cells, such as ES cells and iPS cells, are able to provide massive amount cells due to their infinite proliferative potential, one should remember their potential of causing tumor formation, which often prevents their clinical application (Samadikuchaksaraei et al. 2014).

4.2 Scaffolds

Scaffold is an important part in tissue engineering that construct the compound in two or three dimensional shape. Scaffolds will give structural support and shape for new tissue construction in vitro and/or through the initial period after implantation as cells expand, differentiate, and organize.(Stock and Vacanti 2001; Hollister and Murphy 2011). Materials used in these differ from metals and ceramics, to natural and synthetic polymers, as well as micro- and nanocomposites. When used in a three dimensional shape, these materials are processed into micro- and/or nanoporous cell carriers, typically known as scaffolds.

All biological materials for scaffold used in medical applications and regenerative medicine approaches are obtained from naturally materials produced

by the resident cells of each tissue and organ; specifically, the extracellular matrix (ECM). The composition of each ECM is specific depends on the tissue, highly dynamic, and crucially important in organ and tissue development, homeostasis, and response to injury. ECM is consists of separate components such as proteins, glycosaminoglycans, glycoproteins, and small molecules or the intact matrix itself, can be obtained and processed for use as scaffold materials. Individual ECM components, such as collagen and fibronectin, can be used to alter synthetic scaffold materials to enhance their interaction and integration into host tissues, although they have also been used to create both naturally derived scaffold materials and combination products with synthetic materials as biohybrid devices (Pradhan and Farach-Carson 2010; Kular et al. 2014).

Decellularized tissues or organs can be used as sources of biological ECM for tissue engineering. The advanced research of tissue engineering has showed that ECM components allow the use of xenogeneic materials (often porcine). Many types of extracellular matrices have been tried successfully for tissue engineering in animal models, and products incorporating decellularized heart valves, small intestinal submucosa (SIS), and urinary bladder matrix have been approved for human use. The use of decellularized matrices is preferred due to its ability to retain the complex set of molecules and three dimensional structure of original ECM. The right amount in which structural and signaling components are needed depends on the choices of detergents and enzymes used and the washing conditions used to clear these reagents. Despite many advantages, there are also concerns about the use of decellularized materials. Those are potential for rejection reaction, disease transmission, variability among preparations, and the inability to determine the bioactive components of the material expected (Gilbert et al. 2006; Badylak et al. 2011).

Biomaterial synthetic scaffolds used to be implemented as temporary prosthetic devices to fill the void spaces caused by necrosis or surgery. Current biomaterials development aim to copy the function of natural extracellular matrix (ECM), which can support cell adhesion, differentiation, and proliferation. Biomaterial scaffolds should be designed considering the following requirements to be considered successful in copying ECM. First, suitable biomaterials must be selected for certain applications. This is the same with the effort to build up the target-specific biological scaffolds. Second, biomaterial scaffolds must be a highly open porous structure with good interconnectivity, while possessing enough structural strength for cellular in- or outgrowth. Third, the surface of modified scaffolds must be able to support cellular attachment, proliferation, and differentiation. Fourth, substance or cytokine releasing scaffolds are good for tempering tissue regeneration since cytokines such as growth factors and other small molecules have important roles in growing functional living tissues. Fulfilment of the above requirements will ensure excellent biological scaffolds, therefore producing synergic effects on successful tissue healing (Lee 2011).

There are significant advantages in synthetic scaffolds that closely copy key characteristic of the ECM, but it might be manufactured and reproduced more easily than decellularized organs. Electrospinning has enabled the production of a

new generation of highly biocompatible micro- and nano-fibrous scaffolds from materials such as poly(epsilon-caprolactone), from diverse matrix proteins such as collagen, elastin, fibrinogen, and silk fibroin, from polysaccharides, and from carbon nanofibers (Lee et al. 2009; Szentivanyi et al. 2011). Electrospun materials have approximately the same fiber diameters with those found in native ECM and display better structural strength than hydrogels. The electrospun scaffolds can be manufactured using various nano-fibrous structures and can include additional essential ECM components such as particular subtypes of collagen, glycosaminoglycans, and laminin, either in the spun fibers or as coatings, to promote cell adhesion, growth, and differentiation (Ayres et al. 2010; Shin et al. 2012).

One of the method in producing artificial scaffold for tissue engineering is bioprinting. 3D bioprinting is the process of generating custom cell patterns using 3D printing technologies, where cell function and viability are preserved within the printed construct. The 3D bioprinting is applied to regenerative medicine to fill the need for tissues and organs in suitable shape for transplantation. It involves additional modifications, such as the choice of materials, cell types, growth and differentiation factors, and technical challenges related to the sensitivities of living cells and the construction of the tissues. Addressing these modifications requires the integrated effort from several fields such as engineering, biomaterials science, cell biology, physics and medicine. The 3D bioprinting has already been used for the generation and transplantation of several tissues, including multilayered skin, bone, vascular grafts, tracheal splints, heart tissue and cartilaginous structures (Murphy and Atala 2014).

4.3 Development of Tissue Engineering in Indonesia

The development of tissue engineering in Surabaya is centered at Dr. Soetomo General Hospital—Faculty of Medicine University Airlangga, beginning with usage of natural biomaterial from the Surabaya Cell and Tissue Bank. Natural biomaterial application has helped many patients that require tissue reconstruction procedure. On several occasion, these procedure might not yield satisfactory result due to the nature of material being transplanted which are not a living tissue. In massive bone allograft, for instance, the incorporation between the donor and recipient bone are limited only in the contact surface area, while the middle part of the allograft is still considered as dead bone tissue. Consequently, fracture in the middle of the allograft might occur in the future. The fact that it takes longer time to heal compared to the normal tissue should be taken into consideration in performing such procedures. To overcome all of that problems, we need some life constructions that use good cell, mature cell, and stem cells.

Tissue engineering triad that consist of cells, biomaterial as scaffold and protein as signaling (Fig. 9.8) has similar biologic feature compared to the ideal bone graft that is osteogenesis (possess cells that can produce new bone tissue),

osteoinductive (protein to stimulate host cell to produce new bone tissue) and osteoconductive (scaffold as frame for the new bone cell and tissue).

Tissue engineering using stem cells composite along with biomaterial scaffold might become a solution, since the transplanted construction is a living construction. The earliest research in 2008 was bone engineering by using bovine HAp as bone scaffold for bone marrow mesenchymal stem cells (BM-MSCs) in critical size defect reconstruction on rabbit as shown in Fig. 9.9 (Ferdiansyah 2010). It was then followed by tendon engineering research using tendon allograft and cartilage engineering research using processed bovine cartilage as scaffold for bone marrow

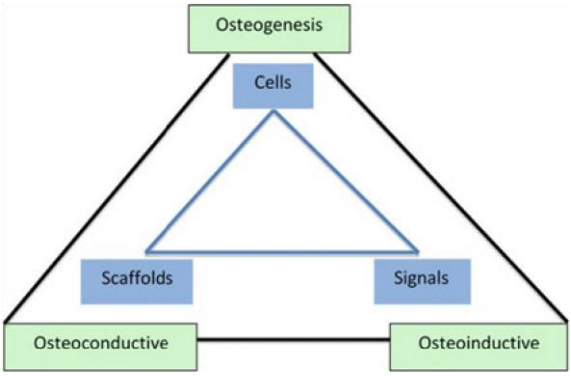

Fig. 9.8 Similarity in the concept of tissue engineering and bone engineering

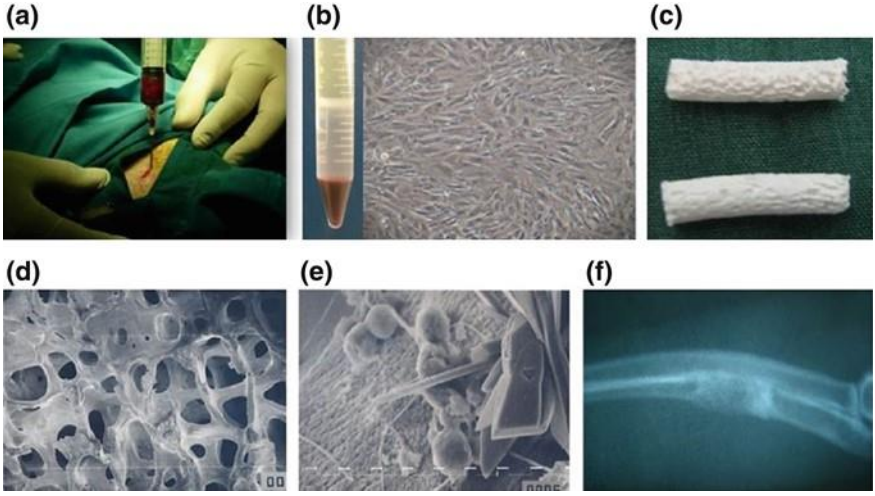

Fig. 9.9 Bone engineering practice: a Bone marrow aspiration, b culture of stem cells, c bovine HAp, d SEM image of bovine HAp, e stem cells growth inside the bovine HAp, f radiograph shows the healing of critical size defect of ulnar bone of rabbit. (Adapted from Ferdiansyah 2010)

mesenchymal stem cells (BM-MSCs) as shown in Fig. 9.10 (Suroto 2011). The first research of tissue engineering in Surabaya showed good products rather than just using only biomaterial.

The above research has triggered more research on stem cells, therapies based on stem cell, and tissue engineering in Indonesia. In order to facilitate the growth of stem cell research in Surabaya, the Surabaya Regenerative Medicine and Stem Center (SRMSC) was founded in 2011 with a collaboration with Dr. Soetomo General Hospital, the Faculty of Medicine, and the Institute of Tropical Disease, Airlangga University. The SRMSC has two laboratories: (1) in the Institute of

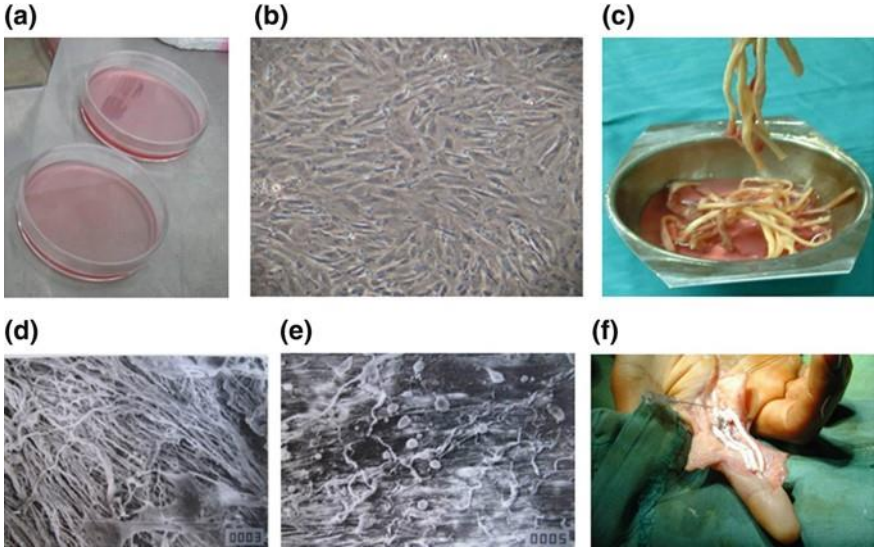

Fig. 9.10 Tendon engineering in practice: a, b Culture of bone marrow mesenchymal stem cells, c tendon allograft, d SEM image of tendon allograft, e stem cells grow inside tendon allograft, f application of tendon engineering. (Adapted from Suroto 2011)

Tropical Disease focuses on basic research, animal and disease model, stem cell banking and stem cell education; (2) in Dr. Soetomo General Hospital focuses on natural production of biomaterial, culture and isolation on stem cell for clinical trial, stem cell banking, education for stem cell, and tissue engineering. Now, the SRMSC has done thousands of stem cell researches and has graduated twenty-two doctors on stem cell studies. In 2014, Dr. Soetomo General Hospital got appointed by Indonesian Ministry of Health as the centre of stem cell educations, researches, and services in Indonesia.

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