



**Review Article**

## **New Medical Options and Promises of Stem Cell Technology in Bioartificial Organ Development: Present Realities and Future Possibilities Particularly In Arab Countries**

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### **ABSTRACT**

The techniques, cells, and knowledge that researchers have now are inadequate to realize the full promise of stem cell-based therapy. Tissue engineering and regenerative medicine technology may provide an alternative to organ and tissue transplantation that is used as a treatment for end-stage organ failures and other diseases. Scientists and researchers these days started to use many principles from organ transplantation, biomaterials and tissue engineering in order to make biological substitutes that will have the ability to restore and maintain normal function in the body. This new technology use the stem cells as a source to build new organs that the patient need to live. The most advantage in this technique is that the patients do not need to use immunosuppressive drugs to stop immune response that leads to organs rejection, thus preventing them from having further complications. Decellularizing and tissue printer are two techniques that are still under research and used to make scaffolds for complicated organs like liver, kidney, heart and lungs. Stem cell scientists from Middle East and around the world hope that one day these technologies will be used successfully and fill the gap between supply and demand of organs needed worldwide. New treatments include graft-versus-tumor therapy for currently incurable cancers, autologous transplants for autoimmune diseases, gene therapy and tissue repair for a host. Key issues for tapping the potential of stem cells will be finding ways to safely and efficiently expand the numbers of transplantable human stem cells in vitro or in vivo.

**Keyword:** Artificial organ; regenerative medicine; tissue printer, Arab countries

### **INTRODUCTION**

Organ transplantation is the established treatment for the failure of vital organs such as the kidney, pancreas, liver, heart or lung. The goal of organ transplantation is to restore organ

to a patient might die from a fatal disease or a vital organ. The need for replacement organs is a great challenge in medicine. Treating and curing people by transplant organs was an idea that begun since many centuries ago. However, as years past this technique is getting older and many unfortunate disadvantages appears including chronic rejection, organ shortage, and other complications that come as a result of immunosuppressive drugs [1-3]. Regenerative medicine and tissue engineering researchers around the world started to search for an alternative way to prevent these disadvantages to occur. One of the breakthroughs was making synthetic organs that can function exactly like a real one. By using stem cells that have the ability to be specialized to any cell and the capability to reproduce their selves to thousand numbers of cells; it gave a solution for the shortage of donor organs in the world for those needing transplants. Urinary bladder was the first complex organ to be implanted in human. Researchers are now trying to build more complex once such as heart, lung, kidney, liver and retina which are a great challenge but possible one to be achieved [4]. In order to make a scaffold suitable for complicated organs, two techniques appeared: Decellularization and recellularization, which is taking the organ and strip it from their cells using mild detergent, then place the patient's cells to the scaffold; and tissue printing using cells as ink and print it layer by layer to make organ. Many researches and conferences have been conducted in Middle East and worldwide about regenerative medicine and they hope that these studies and research would become reality and patients would actually start using them [5, 6, 7]. Until that time would come, scientists are trying to make the synthetic organs work and function properly like a normal organ.

Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) annual data report

for 2013 showed that there are currently 123,175 people waiting for lifesaving organ transplants in the USA of these 101,170 await kidney transplant. Total organ transplant performed in 2013 were 28,953 with 14,257 organ donors. More than 47,000 corneas were transplanted in 2013 and more than 1 million tissue transplants are done and the surgical need for tissues has been steadily rising. In 2013-2014, 61% of living donors were women and 39% were men. The statistics is really reversed for deceased donation: 41% were women and 59% were men. . In 2014, 16, 896 kidney transplant took place in USA of these 11,163 kidney transplant came from deceased donors and 5,733 came from living donors.

Global Observatory on Donation and Transplantation (GODT) in collaboration with World Health Organization report for 2013 showed that total 79,235 kidney transplantations were performed world wide and 298% of increase over 2012. Among them 41.9% of living kidney and 18.3% of living liver are transplanted with 72.7% worldwide making Europe leading other contents (Australia 63%, America 60.8%, Africa 32.4%, Middle East 13.7%, and Asia 4.2%). Eurotransplant report for 2014 showed that 4,928 patients on active organ waiting list on January 1, 2015. There are 10,898 registrations on the waiting list in 2014, and 7,194 organ transplants from deceased donors were carried out in 2014 indicating the highly alarming condition and increase need in organ transplantation field worldwide [8].

### **STEM CELLS**

Stem cells were first isolated from human embryonic stem cells by James Thomson at the University of Wisconsin-Madison in 1998. Soon after that, scientists and researchers begun to grow interest to stem cells and many treatments associated with these cells started to be used in many fields some of them were already discussed previously. The most two basic characteristics the made stem cells

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important in the regenerative technology are that they are unspecialized cells capable of renewing themselves through cell division, and it can become any specialized cell in the body if it exposed to certain signals. As Anthony Atala, a W.H. Boyce professor and director of the Wake Forest Institute for Regenerative Medicine said "Every cell has the right genetic information to create the organ. You just need to put them in the right environment". In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. There are three categories of stem cells are obtained from living tissues and are used for cell therapies which include:

(1) Embryonic stem cells, which are obtained through the aspiration of the inner cell mass of the 3- to 5-day-old embryo, called a blastocyst; or a single cell from this mass. It is broadly pluripotent and can be expanded almost indefinitely to provide an enormous cell replacement supply [9]. Human embryonic stem cells (hESCs) could be an ideal source for regenerative cells because they have the ability to differentiate into cells from all three embryonic germ layers. However, there were some problems that the human embryonic stem cells cause the destruction of embryo making their use limited. Moreover, since they represent an allogenic resource, means that it is not from the same patient, they have the potential to activate the immune response [10].

(2) Fetal and neonatal amniotic fluid and placenta, it may contain multipotent stem cells, are stem cells that can form different cells and tissues, which can be useful in cell therapy applications. It presents a new class of stem cells that have properties between embryonic and adult stem cells. Amniotic fluid stem cells can be obtained by two ways either from amniocentesis or chorionic villous sampling in the developing foetus, or from placenta at the time of birth.

(3) Adult stem cells, they are usually isolated from organ or bone marrow biopsies. In addition, they may provide a more direct route to clinical translation and could be used for bioengineered products. Adult stem cells were found in many adult tissues other than the bone marrow and gastrointestinal tract, such as brain, skin, and muscle. Isolation of these stem cells was problematic and that is because they are presented in extremely low numbers in adult tissue. The best advantage of adult stem cells is that they can be used in autologous therapies in order to prevent immune rejection and other complications.

#### **Stem cell research for solid organs**

After considering how the technology approaches in making a synthetic organs from level one to three which were successful and are used nowadays. The fourth level, the solid organs including heart, kidney, liver and lungs presents a great challenge in the regenerative medicine and tissue engineering field. Since the complex organs have more than one function in the body, when compared with other organs in the body, they are thicker and have more complicated structure, featuring many different types of cells and an extensive network of blood vessels for oxygen, nutrients and wastes exchange. So it is a problem occurred when incorporate these vessels into growing organs, especially at the microscopic scale.

#### **Trachea (Windpipe) and stem cell**

The first synthetic organ in history carried out was the trachea, also called windpipe. Many diseases leads to the resection of the windpipe include trauma, infection disease, tracheomalacia, or treatment with chemotherapy and radiotherapy due to cancer. Tracheal replacement must be strong and flexible, and the conduit must be air tight and, if possible, allow for development of a surface of ciliated epithelium. When engineering a tracheal tissue two essentials should be

reconsidered include the need for complete epithelialization; and the development of hyaline cartilage that possesses suitable mechanical properties and maintain structural integrity of the airway.

The first windpipe operation performed on a 36 years old cancer patient, Andemariam Teklesenbet Beyene, at the Karolinska University Hospital in Stockholm, Sweden in 2011 [11]. The windpipe is a 4.5 inches long hollow tube that leads to the lungs and the tumor of the patient was the size of a golf ball that was obstructing his breathing. A key part of it is a scaffold, which functions like a skeleton for the organ, consisting of tissues such as cartilage and muscle [12]. This achievement became possible by a nanomaterial developed at University College London that serves as a scaffold that allows the stem cells to build upon it [13]. The idea was made in two steps: First Step, to take a three-dimensional CT scan of the patient's windpipe and then by using plastic materials and nanotechnology they made a replica of Beyene's windpipe and his two main bronchial tubes. The material was made from polymers with a spongy and flexible texture with stiff rings around the tube to recreate a more human-like trachea. This procedure was done by Alexander Seifalian at University College London. Second step, the replica was then flown to Sweden where it was coated and soaked, under the supervision of the Spanish surgeon Professor Paolo Macchiarini, with a solution of stem cells that was taken from the patient's bone marrow and then placed in a bioreactor, a vat designed to mimic the conditions inside the human body. After two days, the patient's own tissues had grown to cover the **replica (Figure 1)**.



**Fig. 1: Lab-Grown Trachea**  
(<http://www.visitech.org/know-about-your-eye.html>)

The implantation of this trachea took Professor Macchiarini 12 hours, first removing the tumor and the diseased windpipe and then installing the replacement. After 48 hours of the implant, imaging and other studies showed appropriate cells in the process of populating the artificial windpipe, which had begun to function like a natural one. There was no rejection by the patient's immune system, because the cells used to seed the artificial windpipe came from the patient's own body. After a month, Beyene was discharged from the hospital, cancer-free. Dr. Macchiarini is planning to use the same windpipe implantation technique on three more patients, two from the U.S. and a nine-month-old child from North Korea who was born without a trachea.

#### **Urinary Bladder and stem cell**

Urinary bladder is a hollow organ that is responsible for the excretion of urine. Unfortunately, bladder disease can raise pressure in the bladder leading to kidney problems. As mentioned before, gastrointestinal tissue that is used to repair damaged bladder is the current treatment.

However, disadvantages occurred with this technique that is the gastrointestinal tissues are designed to absorb certain tissues whereas the bladder supposed to be only for excretion. Thus many complications may occur, such as infections, malignancies, metabolic disturbance and urolithiasis. Making a synthetic bladder was

a new hope for patients that will prevent these complications to be present. Urinary bladder was the first complex organ accomplished and actually transplanted in patient body. These bladders that were tissue grown by patients own stem cells implanted in seven patients, who ranged from toddlers to teenagers, successfully in North Carolina's Wake Forest University [14].

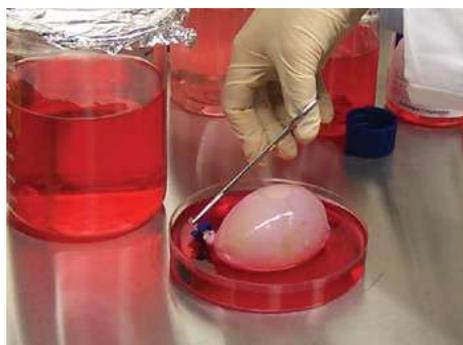
This technique was developed by Anthony Atala in the Wake Forest Institute for Regenerative Medicine in Winston-Salem, North Carolina [15]. This procedure included the reconnection of the bladder with urine tubes, blood supply, and nerve signalling. The seven patients that were under the study all had a congenital condition called spina bifida, birth defect involving incomplete closure of the spine, and myelomeningocele was the type that these patient had. This defect leads to problems in the urinary control that forces the patients to wear pads or diapers and the bladder can flush urine back into the kidney increasing the risk of its damage.

In this new technology, they used a progenitor cell, which are early descendants of stem cells that can differentiate to form one or more kinds of cells. In the procedure, they first took a small bladder biopsy from each patient and isolated muscle cells and special bladder cells, urothelial cells, to multiply them in a glass petri dish in the lab. The cells were then placed onto a three-dimensional bladder-shaped scaffold made partially from collagen, a protein present in cartilage; muscle cells were coated inside whereas the urothelial cells outside then placed into incubation at normal body temperature for 6 to 8 weeks. When these weeks passed, 1.5 billion cells had developed and the researchers attached the synthetic bladder (Figure 2) into the patient's body where it kept maturing. Within a few more weeks, the new bladder has grown to normal size and started to function. The procedure performed was successful and the patients are no longer suffering with

bladder problems and the researchers are now working to grow 20 different tissues and organs in the lab, including blood vessels and hearts [16, 17].

### Eye's Retina and stem cell

Retina is the nerve layer that lines the inside of the back of the eye. When rays of light that comes from the environment are focused by the lens, retina senses them and creates impulses that are sent through the optic nerve to the brain to interpret the picture that the

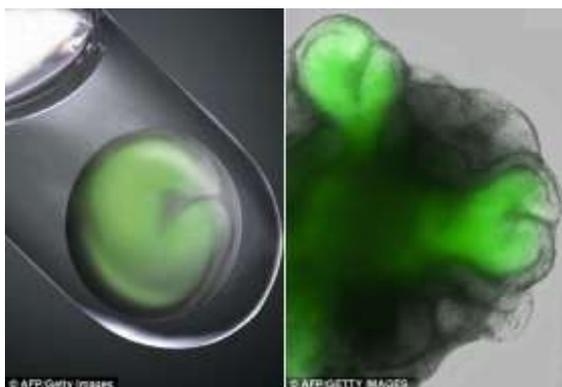


**Fig. 2: Synthetic Bladder**

(<http://sciencetray.com/biology/scientists-have-grown-retina-in-lab/>)

human see. Unfortunately, retinal diseases can cause severe vision loss or blindness if it left untreated. The most common causes of blindness in old age are retinitis pigmentosa and age-related macular degeneration (AMD) which involve the gradual and normally irreversible destruction of retinal cells [18]. A group of Japanese scientists that is led by Yoshiki Sasai of RIKEN Center for Developmental Biology in Kobe opened a new way in treating diseases related to retina by growing them in the lab using the patient's own cell. The experiment in making retina was carried out on mice cells [19]. The researchers used embryonic stem cells, which have the ability to turn into any cell in the body, as their starting material. Then they added proteins and chemicals to develop the cell into a synthetic retina [20]. The cultured stem cells organized themselves into a complex structure that resembled the developing embryonic eye, like optic cup that is a two-

walled structure and it is ultimately develops into the inner and outer layers of the retina (Figure 3). Scientists have yet to show that the cells actually work. However the scientists said that Self-formation of fully stratified 3D neural retina tissues heralds the next generation of generative medicine in retinal degeneration therapeutics and opens up new avenues for the transplantation of artificial retinal tissue sheets, rather than simple cell grafting.



**Fig. 3: An early stage retina floats in a test tube**  
([http://www.perfectwellness.co.in/eye\\_care/corneal-transplantation.html](http://www.perfectwellness.co.in/eye_care/corneal-transplantation.html))

### Heart and stem cell

Artificial hearts the most used device for patients having bi-ventricular heart failure since the number of heart donors is extremely low. Many patients these days leave and actually left hospitals using these devices. Similar to a heart transplant, this device replaces both failing ventricles and the native heart valves, providing blood flow of up to 9.5 liters per minute throughout the body, thus eliminating the symptoms and effects of severe heart failure [21, 22].

The total artificial heart replaces both the left and right heart ventricles and takes over the pumping of blood throughout the whole body., Dr. Robert Jarvik in 2012 transplanted a small artificial heart to a 16-month-old boy who was suffering dilated cardiomyopathy which causes stretched or enlarged fibers of the heart leading the heart to become weaker and unable to pump blood like a healthy heart does. The small

artificial heart was a tiny titanium pump that weighs 11 gram and able to handle a blood flow of 1.5 liters a minute [23]. The artificial heart was successfully working in the baby for 13 days. It is true that in the end an electrical problem occurred, but they found him a donor giving hope that this artificial heart can become a way in helping the patients in the future [24]. A possible new approach is genetic engineering. Today, engineers hope to design a heart completely out of biomaterials. It may be possible that in the near future genetic engineering may lead to develop artificial heart for people. Researchers inject human embryonic stem cells into developed animals to determine if these cells can be properly engineered to produce the tissues and organs that we greatly need. The sheep heart is approximately the same size of a human's.

It would just be a small step more to suggest that with the proper genetic engineering, the heart of sheep can be manipulated so that it is acceptable to the human population at large. Researchers culture and differentiate stem cells in vitro, target the cardiac cells in the body by applying them to an organ built on a 3-D scaffold, and then vascularize the system. Ideally, the man-made scaffold would degrade at the same rate at which new cells are produced. Currently, cultures result in a mix of endothelial and small muscle cells. Researchers are trying to maximize the amount of cells of the type that they want by understanding which growth factors are responsible for shear and stress influences.

### Lungs and stem cell

Modern technologies presented the solutions with great success for problems in normal lung transplantation for example, artificial lungs which are able to sustain the gas exchange requirements of a normal functioning lung. In addition, a successful artificial lung could be used as a support device following transplant or as supplemental support to mechanical

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ventilation. Widespread use of an artificial lung will most likely come first as an extracorporeal device existing outside of the body, also termed paracorporeal and the external ventricular assist devices are currently in use. It might also become a future in rehabilitation for patients with lung injury [25].

### **Kidneys and stem cell**

The number of kidneys available for transplants falls far short of the need. The utmost step in easing the shortage is to create the opportunity for many more people to donate a kidney [26, 27, 28, 29]. However, is that demand still greatly surpasses supply, which is why we still have thousands of people in end stage renal disease (ESRD) who spend their lives on dialysis. Within a decade or two, this may no longer be the case. Researchers have made strides towards developing an artificial, implantable kidney – essentially a self-contained dialysis unit. The first artificial kidney device has been made in India. It is said that it is going to be better than dialysis, even transplants as well. Since patients may not need anti-rejection drugs because there would be no exposed natural tissues for the immune system to attack. The new device is made in two parts: First, is made up of silicon chips that can filter toxins out of the bloodstream. The filtered material is pumped into the second half of the system which is silicon-made chips but coated with human's kidney cells which will help reabsorb useful substances like sugars and salts back into the body. It also produces vitamin D and helps regulate blood pressure.

This technology was tested on animals and showed good result, until 2017, it will be introduced in the field [30]. Another artificial kidney was made at University of California-San Francisco hoping to implant the device right in the body. Thousands of microscopic filters mimic the filtering role of a real kidney. One side filters out toxins while the other re-absorbs salt and water and emits waste. The human

body owns blood pressure performs the filtration without the need for a power supply. However, it is not successfully used yet in the field [31]. Transfer of bone marrow cells from kidney donor to the recipient who will make him avoid taking immunosuppressive drugs is another modern advancement in the field of transplantation. The researchers at the University of Louisville's Institute for Cellular Therapeutics removed stem cells from the bone marrow of the kidney donors, put them through a special process designed to give them a boost, and then inserted them into the organ recipients. Five of eight patients have not required any medications, two of the patients take the medications at a low dose, and one patient experienced many complications related to blood poisoning and a blood clot in an artery to the kidneys [32].

### **Liver and stem cell**

Hepatic transplantation showed to improve health among people having end-stage liver disease. However, many infections including viral, bacterial, and fungal; malignancies and rejections may occur after transplantation some of them would be as a result of taking immunosuppression medications [33, 34]. Shortage of organs is also a problem since there is only one liver in the body making the only source of liver from died donor, cadaveric organ [35]. But many researches appeared to prevent these outcomes include bio-Artificial device, liver support systems utilizing liver tissue preparations were developed in the 1950s, but after knowing the advantages of hepatocyte isolation and culture, better understanding of hepatocyte-matrix interactions, and improved hollow-fiber technology new system devices developed and some of them are currently used in many clinics [36, 37].

HepaPheresis is a Korean-made artificial extracorporeal support device for patients who are suffering from acute liver failure. It is intended to serve as a supportive system so

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that liver patients can wait for a transplant. This device researchers sliced pigs liver and cultured them in special capsules. Right now the device is waiting for an approval [38]. Repairing liver by stem cells is the new treatment developed by Professor Sokal offers the hope of an alternative to liver transplants. The world's first trial using liver stem cells is to take place at London's King's College Hospital and will be headed by paediatric liver consultant Professor Anil Dhawan. They were able supply the liver with new stem cells, which are able to correct the missing functions of the liver in these children. The stem cells are better tolerated than organ transplant and require less immunosuppressant drugs. By using special treated liver cells that are capable of becoming stem cell, the scientists believe they may have found a permanent cure for patients who normally would need a transplant [39].

#### **Pancreas and stem cell**

Pancreas transplant is an acceptable procedure in type 1 diabetic patient undergoing renal transplantation. In addition, the transplantation of pancreas alone considered in the setting of frequent, acute metabolic complications, incapacitating clinical or emotional problems with exogenous insulin or failure of insulin to handle acute complications [40, 41]. The risks that come after pancreas transplant include rejection, graft pancreatitis, peripancreatic abscess or intra-abdominal infection, duodenal stump leak, Cytomegalovirus (CMV) disease, venous or arterial thrombosis requiring graft pancreatectomy and conversion from bladder to enteric drainage.

Risks of islet transplantation include bleeding, peripheral portal vein thrombosis, puncture of the gallbladder, or increased liver function tests and abdominal pain, use of immunosuppressive drugs/skin cancer, retinopathy, neuropathy and hypoglycaemia [42, 43]. Modern technologies came forward to reduce these risks associated with pancreas transplantation. Encapsulating an

organ or making bio-artificial pancreas was an idea many researchers actually found it interesting. The preparation of hybrid organs is based on the isolation of cells and coating them with polymer layers thus forming micro- or macro-capsules.

These polymer layers should be able to protect transplanted structure from recipient's immunological factors and at the same time be permeable for nutrition. The polymer cover should ensure the long-term survival of cell closed inside and should not biodegrade after implantation [44]. In bioartificial pancreas, semi-permeable membranes protect the inner islets from both mechanical stress and the recipient's immune system (both cellular and humoral immunities), while allowing the bidirectional diffusion of glucose, oxygen, nutrients, hormone and wastes [45]. This approach gained success when have human islet cells and the researchers are trying to use animal cells also in order to have more than one source.

#### **Blood and stem cell**

Human body makes 2 000 000 red blood cells every second, all thanks to stem cells. Blood stem cells are also known as haematopoietic stem cells. Like other stem cells, they can self-renew, or copy themselves. They also produce the different types of specialized cells found in the blood: both red blood cells and the many kinds of white blood cells needed by the body's immune system. Red blood cells carry oxygen around the body. Patients who lose a lot of blood need to have it replaced straight away by a blood transfusion. There are not enough blood donors to meet patient needs, so researchers are looking for an alternative solution. Since pluripotent stem cells have the potential to make any cell type of the body, they could potentially provide an unlimited supply of red blood cells. It is already possible to make small numbers of red blood cells from pluripotent stem cells in the lab. Now the

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real challenge is to develop techniques for producing the large numbers of red blood cells that are needed for transfusion. Red blood cells carry oxygen around the body. Patients who lose a lot of blood need to have it replaced straight away by a blood transfusion. There are not enough blood donors to meet patient needs, so researchers are looking for an alternative solution. Since pluripotent stem cells have the potential to make any cell type of the body, they could potentially provide an unlimited supply of red blood cells. It is already possible to make small numbers of red blood cells from pluripotent stem cells in the lab. Now the real challenge is to develop techniques for producing the large numbers of red blood cells that are needed for transfusion. Scientists are working to generate human red blood cells from human pluripotent stem cells at sufficient levels of quality and safety to warrant entry to pre-clinical and clinical studies. These in vitro generated red blood cells (RBCs) offer an alternative to donated blood and may be of particular use for patients receiving repeated red cell transfusions including those with sickle cell disease and thalassaemias. In order to generate RBCs suitable for clinical use, new clinical grade GMP human embryonic stem cell lines were used. The protocol, which lasts 24 days, achieves ~20,000 fold expansion in cell numbers and results in ~95% of the cells in culture expressing erythroid markers (glycophorin A, CD71, CD36) and having the characteristic morphology of haemoglobinised normoblasts.[46]

Scientists face major roadblocks in expanding their use beyond the replacement of blood and immune cells. First, hematopoietic stem cells are unable to proliferate (replicate themselves) and differentiate (become specialized to other cell types) in vitro (in the test tube or culture dish). Second, scientists do not yet have an accurate method to distinguish stem cells from other cells recovered from the blood or bone marrow. Until scientists overcome these

technical barriers, they believe it is unlikely that hematopoietic stem cells will be applied as cell replacement therapy in diseases such as diabetes, Parkinson's Disease, spinal cord injury, and many others.

### **Encouraging development in stem cell technology**

To make a synthetic organ that can function as a normal one without any problem, the same basic premise is taken that is having a source from the patient's own cells then isolate them and making them grow in the right way. These cells, stem cells, can be taken from the patient's own organs; even a small amount of these cells can be expanded to seed an entire scaffold because of the stem cells' ability to continuously grow and divide. After having the cells, controlling their programming and specialization is the important step that is expose these cells to the right balance of temperature, pH, hormones and also give them the forces that they usually face inside the human body. For example, engineering lungs need to feel a regular flow of air to train them to become a suitable organ and as Anthony Atala said "Every cell has the right genetic information to create the organ. You just need to put them in the right environment" and in order to have this environment a suitable scaffold that the patient's cells will be placed in is needed so that new organ would have the same architecture with the flexibility and capability to function like a normal human organ.

### **Decellularization technology for suitable bio artificial scaffold**

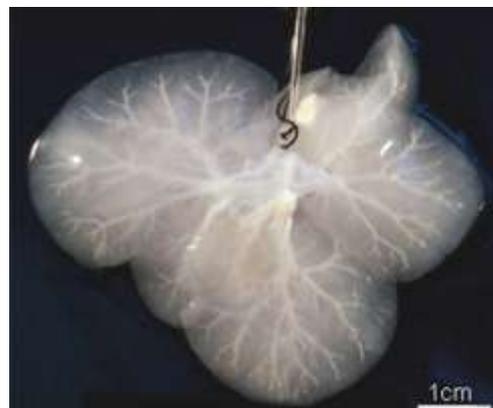
Development of a suitable scaffold to grow the cells on is essential and fabricating it from scratch is possible. However, solid organs have more complicated architecture and it was a challenge for researchers to build one. A new technique that was used on lungs, hearts and liver called decellularization, which was taking an existing organ then add detergents on them

in order to strip away the cells leaving only a scaffold of connective tissues and blood vessels, then it is recellularized by seeding them with the patient's stem cells. A research has been done in University of Minnesota for The world's first beating, retooled "bioartificial heart".

A donor's organ was stripped of cells leaving only the scaffold of extracellular matrix. Then this organ was repopulated, recellularized, with new cells from the recipient's cells. After four days of seeding the decellularized heart scaffolds with cells, contractions were observed. And after eight days, the hearts were pumping; even if it was at only two percent of the efficiency of an adult heart. Because a new heart created by decellularization could be filled with the recipient's own stem cells the researchers believe it's much less likely to be rejected by the body. However, this procedure is not yet used with human [47]. Other researchers are on creating bioartificial lungs that provide gas exchange. It have been generated and transplanted into animal models. Looking ahead, current challenges in bioartificial lung engineering include stripping to their scaffold materials, differentiation and expansion of lung-specific cell populations and full maturation of engineered constructs to provide graft longevity after implantation in vivo [48].

Stem cell scientists have been able to engineer liver using human liver cells. They took animal liver and treated them with a mild detergent to remove all cells which led to the skeleton of collagen. The scientist then replaced the two types of human cells: progenitor liver cells, and endothelial cells the line blood vessels. They were able to introduce the cells through a large vessel that feeds a system of small vessels in the liver, which was due to the network of vessels that remains intact after the decellularization. The liver was then placed into a bioreactor, special equipment that provides a constant flow of nutrients and oxygen throughout the organ, and after a week the

cells spread in the organ successfully (Figure 4) Many approaches was made in decellularization however, they just started to transplant some organs in animals since it is under research and cannot be used clinically yet.



**Fig. 4: Re-cellularized Liver**

(<http://www.gizmag.com/bioengineered-miniature-human-livers/16790/picture/123754/>)

#### **Desktop inkjet tissue printer**

A bioartificial scaffold from scratch was made in Wake Forest University by a desktop inkjet printer that looks like the normal printer but the difference is that they used cells as the printer ink and has the potential in building a three-dimensional organ. A more developed device of it was able to use kidney cells as building blocks along with biomaterials that are used to hold cells together and this machine printed these cells layer by layer and was able to make a kidney structure (Figure 5). This process employs scanner that collect a patient's data which includes a CT scan for the patient's kidney to give a three-dimensional image for an organ that needs to be replaced. After that they create a computer model of the organ to be printed and a small tissue sample seeds the printer. It takes about six or seven hours to replicate the tissues layer by layer to build an organ. The kidney that was printed was not a functional one, but a kidney-shaped mold with no internal structures or vasculature thus it can't be used yet (Figure 6). The device is still experimental and is also being explored for structured tissue [49].



**Fig. 5: Developed Tissue Printer Making Kidney**

(<http://www.wakehealth.edu/Research/WFIRM/Research/Engineering-A-Kidney.htm>)

([http://www.ted.com/talks/anthony\\_atala\\_printing\\_a\\_human\\_kidney.html](http://www.ted.com/talks/anthony_atala_printing_a_human_kidney.html))



**Fig. 6: Kidney made by tissue printer**

(<http://www.wakehealth.edu/Research/WFIRM/Research/Engineering-A-Kidney.htm>)

### **The transplant patient ratio in MESOT Countries**

Middle East Society for Organ transplantation (MESOT) has membership of more than 29 countries and these countries have a population of more than 600 million. These include all Arab countries, Iran, Turkey, Pakistan and countries of central Asia. There are 3 transplantation practices used in MESOT countries

1. Saudi Practice includes a national organ procurement centre as government agency to supervise organ donation and transplantation.
2. Pakistani practice includes a funding agency for management of end stage organ failure in developing countries.
3. Iran provide a renal graft donation from living people. Transplanting in MESOT countries began with renal transplant being performed as early in 1968. The cumulative number of transplants from the beginning of programme until the end of 2012, there was 7990 renal,

1682 liver, 303 pancreatic, 163 hearts, and 59 lung transplant in MESOT countries.

All MESOT countries with the exception of Jordan, Syria and UAE have laws regarding brain death. Transplants have been supported by government and most of them have training programmes [50,51,52,53]. There were total 771 renal transplant from deceased donors and 1508 from live donors in Iran, 118 from deceased donors and 513 from live donors in KSA and 437 from deceased donors and 1979 from live renal donors in Turkey. Total number of renal transplants performed in various MESOT countries was from 6611 live donors and 1379 from deceased donors in year 2012. Turkey, Iran and Kingdom of Saudi Arabia have active programmes for both deceased organ and live liver donors and Egypt with a live donor programme only. The first liver transplant was performed in Qatar in 2011 by deceased donor liver transplant procedure which include a duct to duct biliary anastomosis without a veno-

venous bypass. Cardiac transplant are being performed only in Iran, KSA, Turkey and Lebanon. Among pancreatic transplant there were 33 in Iran Turkey and Kuwait, 19 in KSA and 1 in Lebanon and Qatar. Only 3 MESOT countries Iran, KSA and Turkey are performing lung transplant [54, 55].

In kingdom of Saudi Arabia, the organ transplantation program received a big boost after the beginning of the National Kidney Foundation in 1984 and even more after it was renamed and upgraded to Saudi Centre for Organ Transplantation (SCOT) and that was in 1994. The SCOT's goal was to ease patients suffering and to improve their life expectancy by providing number of organs to all end-stage organ failure patients from both deceased and living organs. Organ Transplantation Centers in the Kingdom of Saudi Arabia for Kidney 17, Cornea 10, Heart 3, Liver 4, Lung 2, and for Pancreas 2 are working. The Men are the most patient who need transplantation than woman. At the end of 2013, a total of 10,021 possible deceased cases have been reported to SCOT and of which, 570 were reported during the year 2013 from 92 intensive care units (ICUs) around the kingdom. An average of 606 cases per was reported in the last 5 years. Male to female ration was 3 to 1 respectively. Ages below 40 years formulated 63.5% of the donors. By the end of year 2013, a total of 5820 living donor and 2563 deceased donor renal transplantation have been performed inside the Kingdom of Saudi Arabia. A total of 558 kidneys have been transplanted during the year 2013, of which 462 were from living donors and 96 from deceased donors. Among the 96 deceased kidneys 14 were used for paediatric recipients and 8 were given for urgent condition recipients. In 1990, liver transplantation program in Saudi Arabia was started. A total of 158 liver transplants have been performed in 2013. There were 109 liver transplants from living and 49 from deceased donors. Between 1986 and 2013, there were 249 whole hearts

and 583 hearts as sources for valves have been transplanted.

Although more than 24,000 corneal transplants have been performed in the Kingdom from 1983 to 2013, the number of locally recovered corneas is dismally low (679 corneas). Lung transplantation activity (started in 1990), has total of 125 lungs transplanted to 78 recipients either as single or bilateral. A total 25 pancreases were transplanted since 1990. Bone transplantation started in the year 2009. This year 20 bones were recovered and 17 musculoskeletal tissues were retrieved. As for the organ sharing program with GCC countries, KSA ( SCOT ) has retrieved and transplanted 55 kidneys, 100 livers, 10 whole hearts, 47 heart for valves, 18 lungs, 4 corneas and 1 pancreas in addition to one kidney shared by KSA ( SCOT ) to UAE. Total Deceased Organs and Tissues Transplanted in KSA (1986 – 2013) are Tissues: (Corneas, Heart for Valves, Bones): 1363; Organs: (Kidneys, Liver, Heart, Pancreas, Lungs): 3673[56].

#### **Regeneration medicine and biobanks in Middle East**

As the transplantation need increasing in Middle East, the problems such as the shortage of organ donors, creating an organ from the patient owns stem cells was a good idea that gave hope to many researchers and encouraged them to know more about the technique. In 2011, The Ramadan Majlis of Shaikh Mohammed bin Zayed Al-Nahyan in Abu Dhabi, United Arab Emirate, had an inspired lecture by Dr. Anthony Atala himself. In there, Anthony Atala introduced the regenerative medicine and its advantages which were very interesting for scientists and researchers to hear. Many scientist and researches from Arab countries are being published about synthetic organs and the decellularization technique. One of these researches was made by Heba Al-Siddiqi, a student in Qatar Foundation's Science Leadership Program, which she discussed in

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Qatar International Conference on Stem Cell Science and Policy 2012 and her research talked about regenerating the human heart by the decellularization process. These successful devices that was made for regenerating organs shown hope for both patients and researchers around the world for growing organs field and maybe one day they will achieves this goal with solid organs.

Over the past decade, the Middle East region has seen a significant increase in HSCT clinical work and research, including programs in Lebanon, Egypt, Algeria, Morocco, Saudi Arabia, Tunisia, and Syria. HSCT are being used to treat patients with blood-related malignancies as well as non-malignant conditions such as aplastic anaemia, thalassaemia and sickle cell anaemia [57, 58]. This activity has been complemented by the establishment, in 2008, of the Eastern Mediterranean blood and marrow transplantation (EMBT) group, a cooperative platform for physicians, scientists and healthcare workers. The use of stem cells to treat other conditions, such as autoimmune, degenerative or congenital diseases, is being evaluated experimentally and in clinical trials- the same type of stem cell clinical trials that have proliferated in the region with 32 registered "open" clinical trials taking place in September 2013. Some bone, skin and corneal diseases or injuries can be treated by the grafting of tissue that depends on stem cells from these organs. This is part of a trend where several countries in the Middle East (ME) are now actively trying to establish a presence in this field through new funding and research facilities.

Qatar Biobank is a large-scale, long term medical research initiative for the population of Qatar, which over the next few years aims to recruit large numbers of participants from the population of Qatar. Qatar Biobank aims to give Qatar's population stronger chances of avoiding serious illnesses and to promote better health for future generations. Qatar Biobank has

recently been certified with two International Organization for Standardization (ISO) certifications by the British Standards Institute Group Middle East (BSI).

King Hussein Cancer Center (KHCCBIO) for Jordan has been first ISO accredited cancer biobank from a diverse ethnic Middle Eastern population. It provides a unique and valuable resource of high-quality human biospecimens and anonymized clinicopathological data to the cancer research communities world-wide.

In Saudi Arabia, the Stem Cell Therapy Program has been established at King Faisal Specialist hospital and research center with the launch of 10 projects. Embryonic stem cell therapy for genetics metabolic disorders is one of the most promising modalities for the therapy and prevention of mentally and physically handicapped in children. The concept of establishing a Cord Blood Bank in Saudi Arabia was raised after the increase in the rate of using cord blood for transplantation due to the inability of finding fully or closely HLA-matched related donors. This Cord Blood Bank is a non-profit public cord blood bank dedicated to making high quality cord blood units available to all patients in need of related and/or unrelated transplantation in the Kingdom of Saudi Arabia and in the neighboring countries through the development and maintenance of a center of excellence for the collection, storage, search and distribution of ethnically and racially diverse cord blood units. Additionally, the mission of the Cord Blood Bank is to educate both the medical community and the public to the value of cord blood donation collection and cryopreservation, and increase the awareness of the importance of cord blood banking. To date, inventory consists of 3,725 units of high quality cord blood with a total of 70 cord blood transplants carried out. In Egypt, Biorepository and Biospecimen Research, Children's Cancer Hospital-Egypt (CCHE) is working on need of having a Biobanking Network. Samples and data are important pillars to having good quality

research. The vision of a biobanking Network is to produce a coalition of researchers and clinicians from different countries looking into research- practice inquiries. This will provide a widespread of ownership of research activity and motivate dissemination of research findings.

In United Arab Emirates, ICLDC Repository is a unique initiative for the storage and management of biological samples linked to clinical data, led by and integrated into Imperial College London Diabetes Centre (ICLDC), Abu Dhabi. The general purpose of the repository is to set up a resource that can support a diverse range of research intended to improve prevention, diagnosis and treatment of illness, and promotion of health throughout the UAE society. The added benefits of the repository are reflected in the collection of samples and data for genetic analysis. In countries with high parental consanguinity such as the UAE, the incidence of monogenic disorders is very high. Thus genomic research has a valuable input to dissect new phenotypes by identifying novel genes. The current reality is that, although extensive researches are ongoing and encouraging partial results are being achieved, there is still much to do in the Middle East to orchestrate the stem cell and regenerative medicine research particularly and also as worldwide.

## CONCLUSION

To find an alternative way to treat patients other than transplantation, many researches and technologies around the world rose up and many of them gave hope for the future. Preparing a synthetic artificial organ is a technology that uses stem cells to build a new organ that is capable to function as normal organ and place it in patients. Urinary bladder and trachea were successfully made and placed in patients who suffer with bladder problems. Decellularizing and tissue printer are two techniques that are still under research and

used to make scaffolds for complicated organs like liver, kidney, heart and lungs. Scientists around the world are now asking whether stem cells might treat or even cure juvenile diabetes with insulin secreting  $\beta$ -islet cells responsive to circulating glucose; cerebral palsy treatments with neuroprogenitors to repair white matter injuries due to premature births; heart muscle repair with cardiomyocytes; spinal cord regeneration with peripheral motor neurones; multiple sclerosis with neuroprogenitor cells or astrocytes for Schwann cell; Parkinson's disease using dopaminergic neurones; amyotrophic lateral sclerosis with neuronal lineages; reduction or replacement of whole organ transplantation by single cell transplantation of hepatocytes for diseased livers; renal cells in place of kidney transplants, and many others. Many researches and conferences are being done in Middle East about stem cell/regeneration medicine/biobanks and they hope that these studies and research would become reality and patients would actually start using them. Until that time would come, scientists are trying to make the synthetic organs work and function properly like a normal organ. It is also required that stem cell research and bio banking communities should be operated internationally in regulation to underpin approaches to the storage, import and export and research with human tissue and cells.

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