# Organogenesis: need of the current world

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*To the Editor*: Regeneration is a common phenomenon among many animals including; starfish, salamander, zebrafish and flatworms. These creatures have a natural ability to regrow their accidentally lost body parts, for example flatworms can regenerate their lost head.[1] But not all organisms can regenerate their whole body organs. However, this natural phenomena is akin with the modern day advancement in stem cell biology and developmental biology, which has enabled scientists to not only study organs *in vitro* but also achieve new frontiers in regenerative medicine.[2]

The possibility of human creation *in vitro* has puzzled scientists for decades now, but its legality and ethical concern limited their endeavour within some parameters determined by social scientists and politicians. However, scientists have been successful in developing certain body parts in their sophisticated labs which are not complete organs but rather a mimicry of organs that will eventually help scientists in exploring anatomy, function and regenerative capacity of organs.[3]

The scope of such experiments paved way for new disciplines in biotechnology, health and medicine. Imagine someone goes through renal failure and can replace his malfunctioning kidney with a new one from biotech lab or an organ manufacturing company! Although it sounds varied, it is actually possible and scientists and doctors have already operated using organoids. For this purpose Rodents and other organisms are a primary research tools for scientists. However, vaginal transplants in humans with lab-grown vaginas has been a success story.[4]

*Fallopian tubes*: Two pairs of fallopian tubes connect the ovaries and uterus, it is responsible for the transport of fertilized egg from ovaries to uterus, hence plays an essential role in reproduction. Their first *in vitro* synthesis was carried out in Berlin by Max Planck Institute for Infection Biology where scientists used fallopian epithelial cells taken from donors. Their findings were published in Nature Communications. Scientists have identified 2 signaling pathways, which allows autonomous development of fallopian tubes like organoids, namely notch and wnt. The synthesized organ was having the features which were similar to original fallopian tubes, particularly their size and shape.[5]

*Mini brain*: A lab-grown brain that resembles human fetus brain, approximately the size of pencil eraser was first grown by scientist at Ohio State University. The brain has same genetics and structure of a 5 weeks fetus. This organoid has functioning neurons with signal carrying extensions like dendrites and exons. The scope of this study covers understanding the anatomy of human brain, studying the abnormal development of human brain, its causes and the possible remedies which was not possible on direct studies with human brain.[6]

Previously, scientists used rodents and other animals to study brain functioning and any development in drugs was first tested on rodents, which was not reliable. Now scientists can study effects of drugs directly on organoids which is far more conducive to develop drugs against diseases such as Parkinson's disease, Alzheimer's disease, Autism and multiple sclerosis.[4]

*Mini heart*: The research results of possible mini heart was first published on March 2015. The tiny organ was measured about half a millimeter in diameter, with the jumpof the ventricle rising up from the dish. It was the first time, that 3-dimensional (3-D) heart-like organ was been created from stem cells alone.[7] Using heart organoids as a

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model, scientists have found that young human heart cells have a natural ability to regenerate after injury, this knowledge sparked a new investigation into heart attacks and if it is possible, then heart tissues can be regenerated after traumas.[8]

*Mini kidney*: Researchers in the University of Queensland, Australia have devised a new method for growing mini kidneys from stem cells mainly for drug screening, disease modeling, and cell therapy. The team has successfully grown an organ which contains all the cell types contained by a mature human kidney, the process of development is same as in humans and resembles kidneys of human fetus. According to kidney models prepared in laboratories can serve to understand normal renal repair and possible regeneration options.[9] Prevalence of kidney diseases is increasing by 8% annually as of 2008 and the end stage treatment of renal failure costs $39 billion per annum, with 88,000 deaths in the US alone.

*Mini lung*: A team from Medical Center of Columbia University created a 3-D mini lung that resembled with mature human lung, with the same appearance, structure and functioning. The lung organoid was grown from pluripotent stem cells. The lung organoid created in Dr. Snoek's lab is similar to human lungs as confirmed by a test. To check functionality of organoid, researchers infected it with Respiratory Syncytial Virus (RSV) and it developed the diseases in a shorter period of time, making it possible for scientists to study the disease and a possible cure of pulmonary diseases in near future and ultimately will save 250,000 children worldwide that die due to end-stage pulmonary disease caused by RSV.[10]

*Mini stomach*: Stomach diseases are common, on average 25% of USA population suffers from stomach related diseases and gastric cancer is ranked third in cancer-related deaths. About 0.1 inches in diameter, a miniature stomach resembling human stomach may help biologists to study how it grows and strike to diseases, particularly caused by bacteria. The research was carried out at Cincinnati Children's Hospital Medical Center, where doctors have shown their concern in studying the early development of stomach in its infancy, it was not previously possible to study during fetal development but now scientists can observe its mimicry in petri dishes, it took scientists 1 month to develop miniature human stomach. The research started with human pluripotent stem cells.[11]

This miniature stomach organoids which resemble human fetal stomach lining and developmental phases was grown in limited size due to lack of nutrients and oxygen supplied in a petri dish, but this model can help scientist to study drug efficiency and diseases like ulcer with a possible application of transplant in individuals.[12]

*Vagina*: Vaginal dysfunction, congenital deformation called Mayer-Rokitansky-Küter-Hauser (MRKH) syndrome, which affects between 1 in 1500 female infants. Scientists have successfully conducted vaginal transplants using vaginas grown in laboratories. Four girls, who were operated in their 13 to 18 years have reported normal function, who are sexually active now. Researchers are optimistic that, by using patients own cells they can grow vaginas and other organs in general, which can then be transplanted to treat cancer and other fatalities. Scientists initially took vulvar tissues from patients, they cultured epithelial and muscle cells on to a biodegradable scaffold and then kept in an incubator to mature. A perineal surgery was performed to implant this organ. Scientists recorded history, vaginoscopy, MRIs, serial tissue biopsies, physical examination, and self-administered Female Sexual Function Index questionnaire results for all patients, with a follow-up of up to 8 year. All the females reported a normal range in all areas tested, such as satisfaction, desire, lubrication, orgasm, painless intercourse, and arousal.[4]

*Penis*: Rabbits were first organisms to get a penile transplant. Scientists at the Wake Forest Institute for Regenerative Medicine took rabbit cells and grew penile erectile tissue after transplants rabbits mated successfully. This research is funded by the U.S. Armed Forces Institute of Regenerative Medicine, as it would help war victims and soldiers to gain there normal sexual abilities. The research on rabbits took almost 20 years with the future prospect of transplants in humans after successful transplants in rabbit's scientists have now shown a new hope for men who have lost their penis through genital defects, traumatic injury, surgery for aggressive penile cancer etc.

Currently, there are 2 options for men with penile dysfunction, one is to construct penis from skin or muscle cells taken from their thigh or forearm. The sexual function can be restored by placing a prosthetic, it can be a malleable rod, with the penis remaining in a semi-erect state. The other option is penis transplant from donors with devastating consequences, both physiological and psychological.[13] The major drawback of surgeries and transplants is tissue rejection, an immunological consequence when a body recognizes what is foreign, resulting in failure to get proper erections. Therefore, scientists are further testing the whole procedure to avoid tissue rejection, it would be possible if penises are grown with patients own cells.[14]

*Esophagus*: The Esophagus is the muscular tube that connects pharynx with stomach, and is the only pathway taken by food to enter stomach. The 18,000 people in the United States are diagnosed with esophageal cancer and other suffer from congenital fatalities, injured by medical procedures or diagnosed after swallowing harmful materials. These patients have to go through surgeries, often tissue taken from other body parts like intestine is used as a replacement for damaged esophageal part, and the consequences are devastating with patients unable to swallow solid material. According to research, scientists have successfully grown an esophagus which was transplanted in rats and have reported normal function with desirable prospects for human surgeries.[15]

Another group of researchers from Karolinska Institutet in Sweden, also reported the same. Swedish scientists were able to implant the organ into lab rats with the same promising results. The exact research was started with allogeneic mesenchymal cells (stem cells) which were allowed to grow onto a scaffold for 3 weeks (the time taken by it to grow). This lab-grown esophagus was then transplanted into a rat, replacing 20% of its esophagus, they repeated the same procedure on 9 rats. The results were indeed fascinating, the transplanted part worked properly showing its flexibility to develop muscle cells, connections to the nervous system and blood vessels, working both voluntarily and involuntarily.[16]

*Ear*: Human ear has 2 main functions, audio detection and body balance. According to a study by WHO in 2012, 5.3% of world population is victim of middle ear injuries, with patients losing either complete audibility or partial. Scientists have grown inner ear human organoids at Indiana University (IU) School of Medicine Study. Starting with human stem cell cultures they grew 3-D structure, this structure was guided through processes involved in the development of human ear, contained sensory and supporting cells as found in human ear. This organiod which resembled human ear was made during the period of 3 months by splashing living cells onto a mold, resulting in a structure which can possibly replace ears of children with congenital deformities. It can also help patients who have lost their ear accidentally or removed due to cancer. This ear was actually fabricated, implanted onto the backs of rats where they grew for 1 to 3 months. The research has prospects for human surgeries in near future and will possibly help millions listen again.[17]

*Liver cells*: Liver is the largest organ inside human body, with diverse functions like detoxification, protein synthesis interconversion of biomolecules and a major source of heat energy for body, which helps to keep normal body temperature in a narrow range, normally 35°C to 37°C. It is capable of regeneration and repair in its proper place, but it is relatively difficult for scientists to grow and keep liver cells alive outside the body. According to a research paper published on 26 October, 2015, scientists from Germany and Israel cultivated hepatocytes in laboratory. These 3-D organoids were used as models to study liver regeneration, stem cell development, function, detoxification, and metabolism. It consists of spherical monolayer epithelium that preserved key physiological features of the liver and is obtained through isolation and expansion of stem and progenitor cells from hepatic stem cell niches. Liver organoids can be obtained from either adult liver cells or human pluripotent cells. The success of this adventure will help scientists towards applications of autologous cell therapy and transplantation.[18]

The progress made in this relatively new field of study, contains vast prospects for developments in human health. It is evident from the above studies that in near future we will overcome many of the fatalities which are considered as incurable and devastating for victims. Moreover, research and investigation using miniature organs might help develop new techniques to treat diseases without a need for replacements or surgery. This change from traditional methods of treatment to advanced methods is in the better interest of humanity and will serve people at large.

Especially, when we are faced by complicated situations of human health devastation; in accidents, war and general decrease in human health standards. With prevalence of bacterial, viral, and infectious diseases, those cannot be cured without grasping to modern methods of treatment. Cancer and organ failures particularly require sophisticated treatment techniques and hence organogenesis contains all the potential as a future endeavor in human health.

## Conflicts of interest

None.

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