Fall 12-16-2016

Combatting the Organ Deficit

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Abstract

Since its beginning in 1954 organ transplantation has become the leading life-saving treatment worldwide for end-stage organ failure. In the past few decades organ transplantation has become so successful that now the number of people in need of a life-saving organ vastly outnumbers the supply of organs available. If this deficit remains unaddressed the number of people that die each day due to organ failure will increase exponentially. Fortunately, this is a problem that can be solved from many angles.

This paper will present possible solutions to the organ crisis by examining the possible positive effects of implementing a mandated choice model for donor registration as well as an incentivized living organ donation program in the United States. Tissue engineering and blastocyst complementation will also be investigated as possible avenues by which the organ deficit can be reduced.

Introduction

Organ transplantation has been one of the great successes of modern medicine. Last year alone, 30,790 people received lifesaving organ transplants [1]. Unfortunately, 22 people also died each day waiting for a life-saving organ that never came [1]. Right now, there are 119,770 people on the national waiting list for organ transplantation and every 10 minutes another person is added to the list but only 80 people nationwide receive a transplant each day [1]. These numbers illustrate clearly that the organ deficit needs to be addressed and possible solutions need to be considered. The solutions suggested in this paper provide four ways in which the number of available organs can be

increased and consequently the number of deaths due to end-stage organ failure can be decreased.

Mandated Choice

Perhaps the easiest way to reduce the organ deficit is by simply changing the way people are asked about their donation preferences. Currently, there are two opposing systems for the designation of organ donor. There is the opt-in system in which countries require their citizens to explicitly express their wish to be an organ donor. This is the system that is used in the United States. The other system is one of presumed consent in which all citizens are considered organ donors upon their death unless they expressly request not to have their organs donated. Upon first glance the opt-out system seems superior but when investigated further neither system provides a valid solution to the organ deficit.

Recently, five before-and-after studies representing three countries were conducted in which the impact of presumed consent was reviewed. According to this study conducted by the British Medical Journal, all countries reported an increase in donation rates after the implementation of presumed consent legislature [2]. However, there was no investigation of other changes like increased publicity for organ donation, or implementation of better infrastructure for organ donation, that could have taken place concurrently with the change in legislature [2]. In fact, the study concluded that the implementation of presumed consent laws was unlikely to explain the differences in organ donation rates between countries because presumed consent legislature is commonly coupled with increased publicity and governmental amelioration of transplant centers [2].

The BMJ is not the only organization that has conducted studies on the effectiveness of presumed consent. A study published in the *International Journal of Surgery* found that organ donation rates in Austria, Belgium, Spain and Singapore all increased after opt out legislation was put in place [3]. This study attributed the success of presumed consent to the fact that decision-makers likely assume the default choice of being a donor is the recommended choice, and consequently the best choice [3]. The study also suggested that many people find decision making difficult and would rather avoid making decisions regarding organ donation, so they agree to the default choice by not choosing [3]. These factors likely contribute to the success of presumed consent laws on increasing the rate of organ donation.

Opponents of presumed consent present valid points about the ethics of harvesting organs from patients that did not want their organs donated but never explicitly expressed that wish. They say that the practice of taking peoples organs who do not actually wish their organs to be used could negatively affect the public perception of organ donation [3]. This claim holds weight when one considers the case of Chile. After the acceptance of opt-out legislature in Chile, organ donation rates actually decreased because citizens were disgruntled by the fact that their family members' wishes were not respected even though their deceased family member never made their wish not to be an organ donor legally known [3].

Another reason that presumed consent may not be the silver bullet in destroying the organ deficit is that its success is not backed by enough evidence. It is true that many opt out countries have very high rates of presumed donors for organ donation but their actual rates of donation are much lower, demonstrating that the majority of citizens in an

opt-out country stay with the default decision but the real choice is left to their next of kin [3]. The country with highest rate of donation is Spain, which implemented its presumed consent laws in 1979, yet the increase of donation rates only became dramatic after the Organización de Nacional de Trasplantes of 1989 brought about the introduction of well-trained transplant coordinators and public health campaigns in support of organ donation [3].

As of right now opt-out and opt-in systems are the only methods for identifying organs donors, neither of which is superior upon review. Fortunately, another model for organ donor designation has recently been developed called the "Mandated Choice" model. Under this model all adults would be asked to make a decision about organ donation [3]. Citizen subject to this model could choose to donate, to not donate or to defer the decision to their next of kin [3]. This model could be easily implemented in the United States as people are already asked about their donation preference when they apply for a driver's license [3]. In using this model donation rates would likely improve because once a decision is made it cannot be contradicted by family members. It would remove the discrepancies between presumed donors and actual donors in presumed consent countries because if a person stated they wished to be a donor their family could not go against their wishes [3]. Citizens would have the ability to change their donor status at any time so changes of heart regarding donation could be accommodated. This model has the potential to change the rate of donation in a way that neither of the other options can, with it the organ deficit could be reduced with little to no change in the current process of donor registration.

Incentivized Living Organ Donation

The idea of providing incentive or flat out payment for organs is not new. There has been a massive, global black market for organs for decades. However, within the last decade, as the organ deficit grows, the idea of providing legal incentives for living organ donors has become more popular. This is not surprising when one considers the expense that comes with being a living organ donor. Currently, in the United States, living donors are treated exactly the same as cadaveric donors, meaning they receive no compensation for their time nor do they receive any government mandated follow-up care according to Dr. Sally Stael of the American Enterprise Institute [4]. In the Elsevier article *Incentives for Organ Donation: Pros and Cons* it is stated that the average living donor's personal cost from providing a lifesaving organ is $3,089 ± $2,354 [5]. Often, a family member provides the lifesaving organ in cases where live donors are an option but cost is still a factor according to a statistic provided by the *Incentives for Organ Donation: Pros and Cons* article, of 133 potential live donors questioned in a study 24% did not donate to *family* members because of the anticipated cost [5]. Living donors cover all their own travel cost and medical bills not to mention the money they lose from being away from their job for the procedure as well as for recovery time.

This is one of the main reason the previously mentioned Dr. Stael, who is herself a recipient of a kidney from a living donor, is an active proponent for incentivized living organ donation. In 2014, she was interviewed by the Washington Post on her opinions regarding living organ donation and in this interview she laid out the basics of her proposed plan for incentivized living organ donation. Her suggested model would include

either a government entity or a designated charity that would offer in-kind rewards to living donors. The rewards could include a contribution to the donor's retirement fund, an income tax credit, a tuition voucher or a donation to the donor's charity of choice [4]. Dr. Stael believes that using a third party ensures that all patients, not just the wealthy ones, will benefit from this program [4]. She also suggests imposing a waiting period of 6 months to ensure that donors are not acting impulsively and that they are giving informed consent when donating their organs [4]. According to her plan donated organs would be allocated to recipients in accordance with rules already in place [4]. This is a well thought out plan that has real potential to decrease the number of people waiting for a lifesaving organ, but it is still in its infancy. In other parts of the world incentives for organ donation have already been implemented.

In 2008 the Israeli Ministry of Health approved the Organ Transplant Act. Under this legislature people who consent to organ donation or who have a first degree relative who consents to organ donation, are given priority if they require a transplant [3]. This act also removes disincentives for donors by allowing living donors to be reimbursed for loss of income, recovery time and transportation expenses [3]. The implementation of this act has yielded a huge increase in living and deceased donors in Israel [3]. Another country in the middle east, Iran, has taken incentives one step further by providing payment for organs donated by living donors. Under this payment system The Dialysis and Transplant Patient Association facilitates the preliminary matching of donors with recipients [3]. Once a match is made the transplant takes place. The donor's hospital expenses are paid by the government and in addition, the donor receives a monetary donation from the government as well as payment from the recipient in an amount which

is agreed upon by both parties prior to the transplant [3]. This system accounts for an increase in transplants of more than 50% [3].

The success found in both of these countries is promising and may provide evidence in support of a plan like the one suggested by Dr. Stael. Despite their success, plans like these are often met with questions, including questions about cost. Many assume that incentivizing living organ donation would be costly, however, quite the opposite appears to be true. American taxpayers bear a substantial burden when it comes to providing Medicare for people with end stage renal disease. This is largely because of the mandate passed by congress in 1972 stating that Medicare would cover the costs of care for people with end stage renal disease regardless of the patients age [4]. In 2011 this mandate resulted in 6% of the entire Medicare budget (34 billion dollars) being allocated to the 500,000 people on dialysis [4]. If incentivized living organ donation was implemented the number of people on dialysis would decrease and consequently so would the amount spent on dialysis through government programs.

Opponents of incentivized living organ donation also find issue with the ethics of the idea, stating that providing in-kind rewards cheapens the gift or is ethically wrong. Dr. Stael makes an excellent opposing point when she states that “Surrogate mothers surely welcome the payment they receive but compensation is hardly the only factor in the decision; almost all of them say they are motivated by a strong desire to help another woman fulfill her maternal dream” [4]. This point goes beyond negating the idea that the donation of one’s body is unethical if payment is received because it also illustrates the fact that payment in return for products rendered from the body is not a new idea. The United States is one of the only countries in which it is legal to receive compensation in

return for a donation of blood plasma, consequently the United States is also the main supplier of blood plasma for the world [4]. Incentivized living organ donation has the potential to save countless lives and has the added benefit of bettering the recipient's life as well as the donor's life. Of the 119,800 people currently waiting for a transplant 99,300 of them are waiting for a lifesaving kidney, it is not presumptuous to say that if living organ donors received incentives for their donation the number of people waiting for a kidney could be cut in half [1]. The current system for organ donation is not meeting the mounting need for organs, in order to rectify this problem new ways of thinking need to be promoted and new ideas need to be tested. Dr. Stael is one of many people with a plan for incentivizing organ donation and it is time these plans are truly considered by congress as a viable way to decrease the organ deficit.

Tissue Engineering

In the mid 1970's scientists began toying with the idea of artificially growing organs, forty years later and the goal is still being targeted but many advancements have been made in the field of tissue engineering. Tissue engineering evolved from the field of biomaterial development [6]. The goal is to combine scaffolds, cells and biologically active molecules to form functional tissue that either restores, maintains or improves damaged tissues or whole organs [6].

In nature cells make and secrete their own support structures also called the extra cellular matrix, this matrix supports the cell and is used as a relay station for a multitude of signaling molecules that are in the local environment of the cell [6]. According to Dr. Bhatia, a professor of Health Science, Technology, Electrical Engineering and Computer Science at MIT, "the challenge is to grow the cells outside the body while maintaining

their function after being removed from their usual microenvironment" [7]. When it comes to tissue engineering it is imperative that cells maintain their functionality outside of the body so that when combined with a scaffold proper tissue development can take place.

Another challenge facing the engineering of functional, implantable organs is that the tissues need to include blood vessels that can connect to the patient's own blood supply. Recently Dr. Bhatia's lab has created 3D liver tissue that does include its own network of blood vessels. She and her research team did this by first printing a 3D network of sugar molecules, then allowing liver tissues to grow around the 3D network [7]. After the tissue develop sufficiently the sugar molecules were dissolved and blood vessels were stimulated to fill in the space left after dissolving the sugar [7]. This recreation of functional liver tissue is huge in the world of medicine because although the tissue is not implantable in a human it does mimic human responses to disease stimulants and drugs. In fact, Dr. Bhatia developed the first stem-cell-derived liver tissue prototype that can be infected with the Hepatitis C Virus [7]. This prototype and the study of how Hepatitis C affects it could lead to a drastic reduction in the number of people waiting for a liver transplant because "liver failure due to hepatitis C is the most common reason for liver transplantation in the United States. But because most infected people don't know about their condition until it's advanced, researchers can provide only rough estimates of the risk and rate of progression to liver failure in chronic hepatitis C" as reported by Dr. Steckleberg of the Mayo Clinic [8].

Tissue engineers have also found an alternative way to develop scaffolds that support cells for tissue growth. Instead of developing a completely artificial scaffold,

cells from a donor organ are stripped away leaving only the remaining collagen, which is then used as the scaffold [6]. This approach allows for a human scaffold from a donor to be combined with the patient's cells which in turn reduces the likelihood of rejection by the patient's immune system as the cells used to create the organ are native to the body. Groundbreaking advancements were recently made by NIDDK researchers who used this approach on a donor kidney. After stripping the organ and using the remaining collagen for the scaffold, the researchers facilitated new cell growth of the organ by seeding the kidney scaffold with epithelial and endothelial cells [6]. This method led to an organ that was able to clear metabolites, reabsorb nutrients and produce urine both in vivo and in vitro in rodents [6]. This technique has also proved useful in the field of drug development as the organs can be used to screen medication candidates, speed up the development of useful medication and provide a tool for the advancement of personalized medicine all of which have the potential to limit the number of people in need of an organ transplant [6].

NIBIB funded researchers have found another way to combat the organ deficit by engineering human liver tissue that can be implanted in a mouse. While this may seem unconnected to the organ deficit the research is actually quite advantageous; the mouse that receives human liver tissue also retains its own liver, this is useful because normal function of the organ is seen in the rodent but the added piece of engineered human liver can metabolize drugs the same way actual human tissue does [6]. With this feature, researchers are able to test the livers susceptibility to toxicity and they can demonstrate species-specific responses to drugs that do not typically appear in clinical trials. This

technique can be used to study drugs that may allow people to be treated for various diseases in a way that does not involve an organ transplant.

Blastocyst Complementation

Though still a relatively new field, blastocyst complementation provides possibly the best scientific solution to the organ deficit. Blastocyst complementation is based on the idea that it is possible to generate an animal fetus that is deficient in a specific organ and then using that empty space in the fetal body as a niche for growth and differentiation of allogenic or xenogeneic pluripotent stem cells (PSCs) to form functional organs [10]. This alternative to tissue engineering is promising because human organs are extremely difficult to grow in an artificial culturing environment. In place of artificial scaffolds human pluripotent stem cells (hPSCs) would be used to develop tissue. There are two characteristics of hPSCs that make them advantageous when trying to grow tissue. Firstly, hPSCs have the ability to proliferate without limitations in cell culture, meaning they survive well outside the body [10]. Secondly, hPSCs are capable of differentiating into any cell type in the adult body [10]. These characteristics and the fact that an animal host provides an environment that is much more similar to the native environment of the tissue cells, make blastocyst complementation the most promising avenue for growing viable human organs outside the human body. While this process is complicated and requires many steps the possibility of creating a functional organ in an animal is quickly becoming a reality.

Blastocyst complementation is dependent on the knowledge that, over millions of years, nature has developed developmental programs many of which are well conserved between species [10]. The idea is to take advantage of these well conserved

developmental programs by differentiating hPSCs in an in vivo environment, namely an animal host. In 2007 Douglas Melton's group successfully generated the first organ via blastocyst complementation. Melton's team developed blastocysts of mice that were deficient in the PdX1 gene, which is a key gene for the development of the pancreas, meaning that if permitted to live to term the fetuses would present without pancreases [10]. They then inserted wild-type mouse embryonic stem cells into the PdX1 deficient blastocyst. The donor mECSs populated the entire pancreatic epithelium in the PdX1 deficient host [10]. These results proved that blastocyst complementation is possible. In 2010 Hiromitus Nakauch's group took blastocyst complementation one step further by using rat PSCs to complement PdX1 deficient mouse blastocysts, further proving that interspecies blastocyst complementation was possible [9].

The next step in blastocyst complementation was to identify and develop large animals that were organ-deficient and capable of developing exogenous PSCs into functional organs. In 2013 Hiromitsu and his associates did just that. To begin, they identified pigs as the best candidate for blastocyst complementation among large mammals because pigs have many similar anatomical and physiological features when compared with humans [9]. After identifying their target animal, they were able to create pancreatogenesis-disabled pigs that could then be used for blastocyst complementation. This feat of genetic manipulation was pivotal for the development of human organs in livestock because until this time organogenesis had only been possible in small rodents, which was not useful when pursuing the long term goal of blastocyst complementation. Once Hiromitsu's had developed the pancreatic deficient pig blastocyst, they wanted to prove that the pig blastocysts were capable of developing into functional and fertile adults

when given exogenous PSCs [9]. In this pursuit they were also successful. Figure one provides a visual explanation of how Hiromitsu's team went about this experiment [9].

Figure 1.

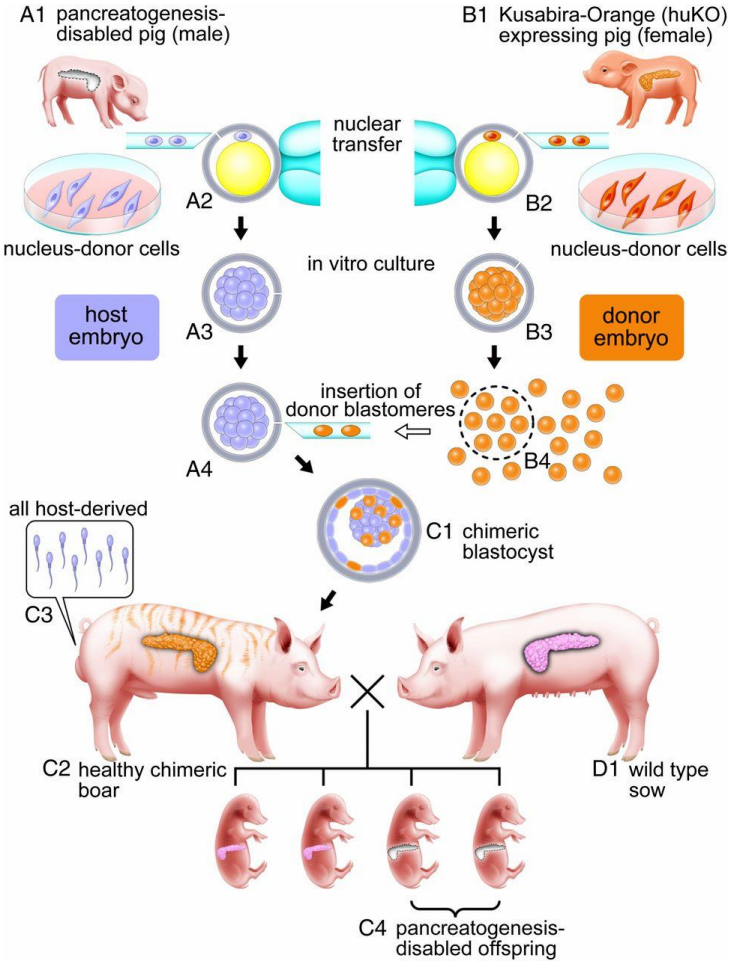

Figure 1. Schematic depiction of complementation for Pdx1-Hes1 cloned pig embryos that are pancreas deficient.

With this study, they were able to "demonstrate generation of a functional organ from exogneous pluripotent cells in a large animal, which is a very important step toward generation of human organs in large animals" [9]. While this accomplishment is huge, Hiromitsu and his associates are already looking ahead to the next obstacle they foresee

which is “overcoming the species barrier to achieve chimerism with pig embryos as hosts” [9]. They will begin by trying to develop a cow or monkey pancreas in a pig with the eventual goal of blastocyst complementation being illustrated clearly in Figure 2.

Figure 2.

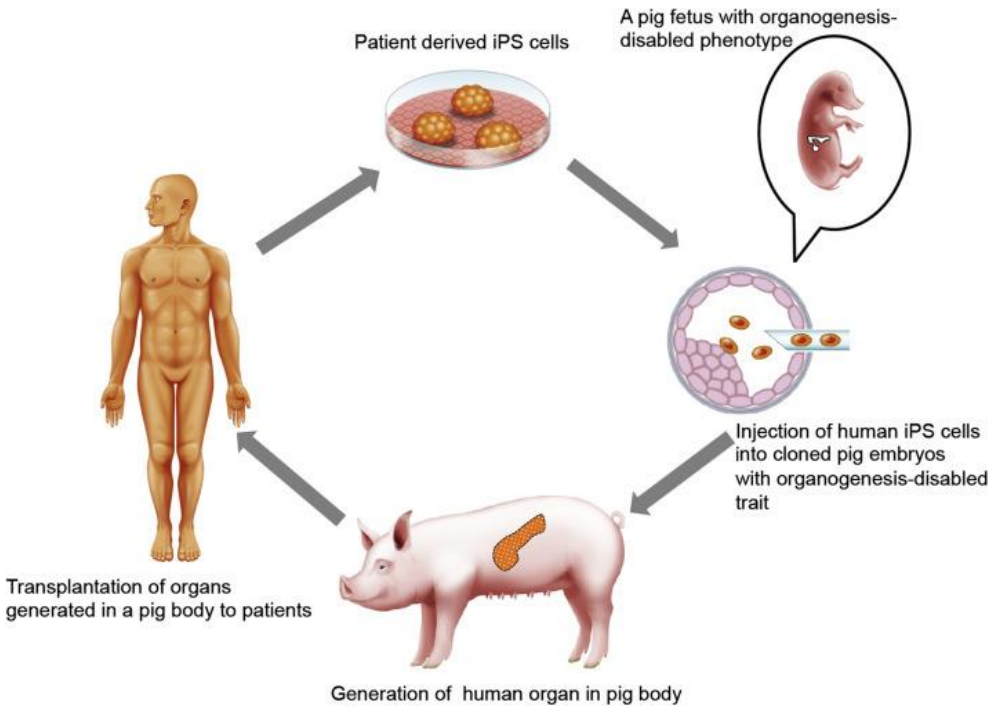

Figure 2. Schematic of the end goal of blastocyst complementation: generation of functional human organs using organogenesis-disabled pigs as the host (iPS cells are induced pluripotent stem cells).

Blastocyst complementation has yet to be proven successful when hPSCs are used but the accomplishments made in this field so far are encouraging. With the impending success of blastocysts complementation inevitably comes the questions of ethics. Firstly, it is important to note that human pluripotent stem cells are drastically different than

embryonic stem cells. A hPCS is a cell extracted from the blood or skin of a child or an adult that is then genetically modified to behave like an embryonic stem cell [11]. These cells then have the capability to form all types of adult cells [11]. If blastocysts complementation were to be used to combat the organ deficit the hPSCs would be collected from consenting patients in need of an organ. Undoubtedly, the use of living animals to grow organs for ailing humans will also be questioned by ethical committees. When asked about this, one need remember that the animals in question will not be harmed in anyway, they will be permitted to grow to adulthood and will assuredly be well taken care of as their overall health is crucial to the health of the lifesaving organs they harbor in their bodies.

Conclusion

The need for solutions to the organ deficit is urgent. Mandated choice, incentivized living organ donation, tissue engineering and blastocyst complementation all provide the best solutions to increasing the number of organs available for transplant. The need for life-saving organs is never going to go away, if we as a society want to decrease the number of people that die each day due to end stage-organ failure initiative needs to be taken. We need to demand new legislature for organ donation and be active in our pursuit of new ways to create transplantable organs, for that is the only way the organ deficit will be abolished.

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