Stem Cells and the Future of Sex Reassignment Surgery

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ABSTRACT

Stem cell technology has the potential to revolutionise many aspects of medicine. This paper will focus on the way that current investigations into the application of stem cells in urology, regenerative medicine and 3D organ printing can be used to improve the treatment of transsexual patients. It is possible that stem cells could be used to treat complications in current sex reassignment surgery procedures, as well as to promote breast development and to create realistic, lab-grown genitalia for transsexual men. However, there are areas where current techniques are not advanced enough to be of use for transsexual patients, such as in the growth of gonads or the growth of genitalia for transsexual women.

INTRODUCTION

Stem cells are unspecialised cells which can reproduce (while remaining unspecialised) and differentiate into specialised cells when required. There are two types of stem cells: adult (tissue) stem cells and embryonic stem cells (ESCs).

ESCs are extracted from a "blastocyst" - an early embryo which contains an inner cell mass of harvestable "pluripotent" cells (cells with the potential to differentiate into any foetal or adult cell type). At the moment, ESCs are used extensively in medical research, for example to study cell development and disease processes, or to determine how cells react to particular drugs. There are also clinical trials looking into therapeutic uses of ESCs, such as combatting macular degeneration to improve sight. The wide range of differentiation of ESCs gives them the potential to be used in a huge variety of eventual therapies, such treating diabetes, neurodegeneration, and spinal cord damage.

However, there are certain ethical issues surrounding the use of ESCs – in particular, many equate the destruction of a human embryo to murder. In order to sidestep these issues, techniques such as the use of Induced Pluripotent Stem Cells (IPS cells) and cloned ESCs can be used. Cloned ESCs still pose ethical difficulties as they involve the creation of an embryo solely for the purpose of extracting cells, but they may be less variable in their results than IPS cells.

Tissue stem cells are also less controversial than ESCs. These have a much narrower differentiation potential, as they can specialise only into some (or all) of the major cell types in an organ or tissue. They are thus considered "multipotent". This limited scope, and the fact that they are more difficult to extract and cultivate than ESCs, hinders their usefulness in medicine. They are, however, involved in certain therapies such as the use of blood stem cells to treat leukaemia via bone marrow transplants.

In general, there are many difficulties that must be overcome before stem-cell therapies achieve their full potential: for example, scientists must be careful to avoid uncontrolled growth that leads to tumorigenesis or the harms of misdirected growth.

Stem cells may also have significant potential to improve the successes of certain surgical procedures. In particular, there is a chance that stem-cell technology could be used to improve the

physical and emotional wellbeing of transsexual individuals through the development of safer and more effective sex reassignment surgery (SRS) procedures.

Definitions

For the purposes of this paper, "transsexual" refers to a person who identifies as a binary (man or woman) gender which is not the binary gender with which they were assigned at birth: for example, a woman who – due to physical characteristics such as her genitalia – was assigned male at birth. This woman can be referred to as an MTF (male-to-female) woman. Men who were assigned female at birth can be referred to as FTM (female-to-male) men. In particular, this paper will focus on those individuals who seek medical treatment for severe gender dysphoria (discomfort or distress due to a transsexual gender identity). "Cisgender" refers to a person who identifies as the binary gender with which they were assigned at birth.

Transsexual Healthcare

The effects of gender dysphoria and discrimination on the mental wellbeing of transsexual individuals are striking. As shown below, transsexual people are roughly 44 times more likely to attempt suicide than those in the general population are to make suicide plans. (Figure 1, average suicide rate = 44%. Figure 2, average rate of suicidal plans = 1%)

Table 4: Lifetime suicide attempts by gender-related characteristics

	Have Attempted Suicide	
	Frequency	Row %
Gender Identity Recode		
Trans Women / MTF	1251	42%
Trans Men / FTM	822	46%

Figure 1 - (USA survey began 2008)

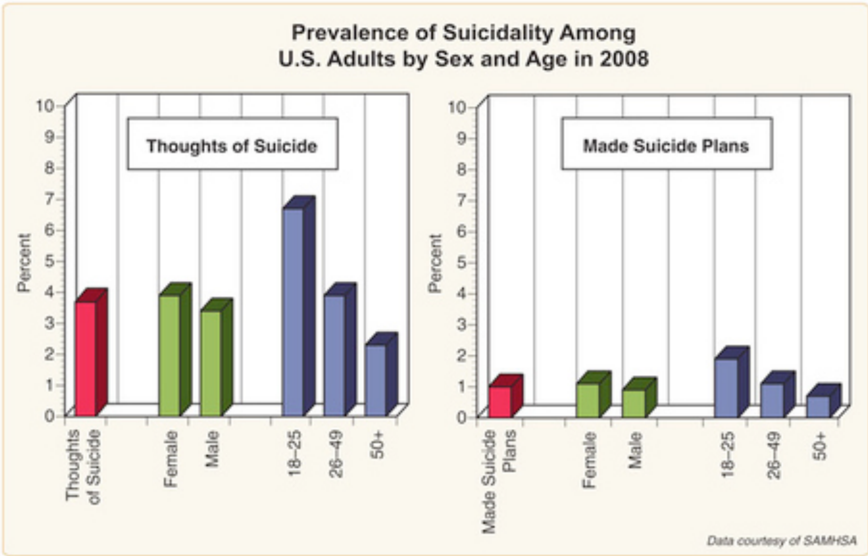

Figure 2

In fact, those with a desire for transition-related healthcare are more likely to attempt suicide than their counterparts (Figure 3): this vulnerability necessitates that high-quality healthcare be provided.

Table 5: Lifetime suicide attempts by responses about transition-related health care

Transition-related Health Care	Do Not Want It	Want It Someday	Have Had It	χ^{2}_{2}*
Counseling	190 (29%)	327 (39%)	1963 (44%)	53.2
Hormone Treatment	272 (31%)	540 (40%)	1608 (45%)	60.6
Top/chest/ breast surgery	500 (34%)	1222 (45%)	563 (44%)	46.3
Male-to-female removal of testes	327 (31%)	800 (43%)	286 (43%)	47.3
Male-to-female genital surgery	340 (31%)	834 (43%)	265 (43%)	49.7
Female-to-male hysterectomy	344 (36%)	564 (49%)	182 (48%)	40.4
Female-to-male genital surgery	570 (40%)	464 (49%)	38 (49%)	21.0
Female-to-male phalloplasty	757 (40%)	268 (56%)	21 (46%)	39.9

Figure 3

SRS "transitions" involve both hormone replacement therapy (HRT) and surgical procedures. SRS surgery combines "removal" procedures such as hysterectomies and mastectomies with reconstructive procedures such as phalloplasties and scrotoplasties for FTM men, and vaginoplasties and breast implants for MTF women. Those who have undergone these techniques consistently report high satisfaction and low regret but there are common complications and areas for improvement which stem cell technology could address.

There is also the concept of creating lab-grown organs for transsexual patients, composed of the same tissue as the genitalia of cisgender men and women. This could lead to improved psychological results, as well as sexual organs of greater functional and aesthetic value.

DISCUSSION

Improvement of SRS techniques through stem cell technology would be very important for transsexual healthcare. Promising areas include FTM genital surgery, MTF breast augmentation and organ growth.

FTM Genital Surgery

For FTM men, genital reassignment surgery can involve either phalloplasties (the creation of a neophallus, using skin grafts to extend the urethra, and the later insertion of an erectile prosthesis) or metoidoplasties (the "releasing" of the clitoris from the clitoral hood following enlargement due to testosterone therapy).

Complications - Often phalloplasties are preferable for patients as they provide larger, more realistic and more functional genitalia than metoidioplasties (which can allow for voiding while standing due to urethral lengthening, but not always penetrative sex), but they also involve longer surgeries which can result in serious complications. Radical forearm flap (RFF) phalloplasties involve using a skin graft from the forearm to create a neophallus, extending the urethra. This is the most common type of phalloplasty due to the lack of fatty tissue on the forearm (making them more suitable for overweight patients) and the ease with which the graft can be manipulated. However, there are common complications, as shown by the work of Mamoon Rashid and Muhammad Sarmad Tamimy (2013):

a) Urethral fistula rates range from 22-68%
b) Urethral stricture rates range from 17-31%

This is problematic both for general health reasons and because the ability to void while standing is one of the primary goals of the phalloplasty – if a healthy, elongated urethra cannot be created, this ultimately fails.

Mesenchymal Stem Cells (MSCs) may be used to treat this. MSCs are stem cells found in the bone marrow which can differentiate into cartilage cells (chondrocytes), bone cells (osteoblasts) and fat cells (adipocytes). They have also been shown to promote neovascularisation (profusion of functional blood vessels in new or abnormal tissues), possibly by stimulating the production of proteins which in turn stimulate the growth of endothelial precursors which develop to form the inner layer of blood vessels.

There have been numerous advancements in the use of MSCs to treat urethral injuries - MSCs with fibrin glue (a sealant made up of thrombonin and fibrinogen, used regularly in many surgical

procedures) can be effective in treating rabbits by promoting the formation of new blood vessel networks and new smooth muscle tissue and thus aiding healing (Wang and others (2012)). Injections of MSCs have also been effective in treating fistulas for human individuals with Crohn's disease, showing "sustained complete closure in a majority of treated patients" (as reported by the Mayo Clinic) and thus showing that MSCs have great potential in urethral treatments and attempts to rectify fistulas. An injection of MSCs mixed with fibrin glue may be able to actively combat some of the most common complications of phalloplasties.

Scarring - One of the major issues with RFF phalloplasties is that the donor site of the skin graft is prominent and visible. As already discussed, gender dysphoria can lead to severe emotional distress, so avoiding excessive scarring which acts as a constant reminder of previous treatments is something to strive towards. Indeed (although it does not appear to lead to patients regretting the procedures), significant levels of dissatisfaction with their scars have been reported amongst those who have received RFF phaloplasties. Grafts from less public sites lend themselves to less successful or more risky procedures.

Wharton's jelly is a tissue in the umbilical cord that contains uncommitted mesenchymal stem cells. The work of Garzón and others (2013) showed that when these stem cells are combined with agarose and fibrin (which aids blood clotting), it is possible to form skin which can be used in skin grafts. These can be used to treat serious burn patients. However, there is controversy over the accuracy of these results, and the role that MSCs actually play. It is certainly the case that epidermal stem cells (EpSCs) have been used clinically to grow skin grafts since the discovery of this application in the 1970s.

There are disadvantages to the general usage of these grafts:

1. A lack of Wharton's jelly: As many umbilical cords are simply discarded following birth, the store of stem cells available to create grafts is small.
2. Time: the cells must be given time and nutrients to divide and grow into a suitable size. Particularly for burn patients who require swift treatment, this can be a major drawback.
3. The skin produced is not a perfect replica of naturally grown skin – it lacks hair follicles and sweat glands.

However, if it were possible to replace the forearm skin grafts currents used in RFF phalloplasties with lab-grown ones, a few things can be noted:

1. SRS is not an emergency procedure. It is easier to take the time required to grow the grafts, and produce optimum results, without the pressure that surrounds the treatment of burn patients.
2. Donor sites for phalloplasties often undergo electrolysis pre-operatively, which would imply that a lack of hair follicles would not be as much of a hindrance.

The expense of stem-cell nutrients (particularly given the high rates of poverty and homelessness amongst transsexuals) and the lack of available stem cells do remain significant drawbacks.

MTF Breast Augmentation

Stem cells also have significant potential in breast construction for MTF transsexual women. While HRT (in this case, the injection of oestrogen by MTF women) induces what is often referred to as a "second puberty" and can cause slight breast development, many women choose to undergo breast augmentation surgery to increase the size of their breasts and achieve a more "realistic" aesthetic appearance.

Currently, MTF breast augmentation is very similar to the procedures undergone by cisgender women, involving saline or silicone implants. There are drawbacks to this technique:

1. In a small number of cases, the skin and tissue size of the MTF woman's chest is not large enough to accommodate implants. More complicated, time-consuming procedures are then required.
2. Implants can rupture with time and then require multiple surgeries over a lifetime.
3. There are the usual risks involved with any surgical procedure and anaesthesia.
4. Some women believe that the look and feel of implants is not "realistic" in comparison to natural breasts. It is important to work towards outcomes for transsexual women that appear to match what is generally experienced by cisgender women in order to promote satisfaction and an improved ability to be read as the gender with which they identify by others.

However, there have been recent developments in the use of stem cells for breast reconstruction. These combine stem cell technology with a technique called lipotransfer which has become increasingly common in reconstructive surgery. This involves increasing the volume of fat in one area of a patient's body by using fat harvested from another area. Cell-assisted lipotransfer (CAL) enriches lipoinjections with adipose derived stem cells (ADSCs). This has been shown to increase the postoperative volume of the breasts, and provide high rates of patient satisfaction. Patients reported a natural shape and feel to their breasts. There is also less of a need for invasive surgical techniques as can be necessary with implants. With this procedure there is less concern about the availability of the stem cells as ADSCs can be derived from fat in the abdomen where they are plentiful.

CAL appears to be a feasible and promising option for transsexual women. However, there has been some controversy over the effectiveness of the use of ADSCs in breast regeneration. The work of Peltoniemi and others (2013) compared the success of stem cell transplants with water assisted lipotransfer in 18 women and found no significant benefit, though the limited numbers compared mean that further studies would be required to prove the reliability of these results.

Organ Growth

One of the most exciting prospects surrounding stem cell technology is that of the growth of new organs. In general, this could lead to a reduced need for organ donation and fewer critically ill patients left indefinitely on transplant lists.

The theoretical process behind organ growth (specifically, organ printing) involves the placement of various cell types into a scaffold (built using a computer-aided 'blueprint') to allow for the development of tissues and organs for a variety of uses.

There are some significant barriers to medical applications of this technology. These include: formulating blueprints which correctly take into account the changes to the shape and size of the organ that occur during printing; developing more advanced and cheaper materials such as "bioink" (self-assembling cell aggregates or single cells in hydrogels) which are suitable for large-scale production; developing biologically effective and economically sound means of accelerating tissue maturation; and developing effective, non-destructive means of monitoring organ growth and maturation. Most researchers agree that the process of vascularisation – which is necessary for cell function as it allows the transportation of nutrients and oxygen, and waste excretion – is vital to organ growth.

However, there have been multiple developments in this field that indicate high hopes for this type of treatment becoming a reality:

1. Scientists have, for years, been able to use 3D printers to print simple sheets of human tissue. However, these were previously unable to survive for any period of time on their own, which provided a significant barrier to the printing of organs.
2. Recently, teams in the US and Australia have made a leap forward for printed tissue vascularisation by printing functional capillaries.
3. Australian scientists have succeeded in using stem cells to grow a "mini-kidney" (a fully functioning kidney, only a few millimetres in diameter) by studying the actions of the genes which were expressed during the differentiation of kidney cells and using a blueprint. A lab-grown kidney has also been successfully transplanted into a rat, where it successfully produced urine at 23% the effectiveness of a natural organ.
4. Lab-grown bladders have been successfully transplanted into adult humans.

In this way it is clear that organ growth is scientifically possible – and in fact has been successfully done on the small-scale – but further, in-depth study of each individual organ and blueprint is still required and there remain significant economic barriers to large-scale production.

FTM Genital Construction - A team lead by Anthony Atala, director of Wake Forest University's Institute of Regenerative Medicine, have successfully grown replacement penises for rabbits. This was done by using a collagen scaffold of a donor penis and seeding the cells – cultured by the team – into the framework.

The technique developed by Atala's team uses cells extracted from the patient's own penis (such as the smooth muscle cells and endothelial cells) when used in reconstructive surgery. This makes it unsuitable for FTM surgery. However, the use of ESCs may provide a suitable method for widening the range of possibilities. If they can be manipulated to divide into the cells that make up the penis, then lab-grown phalluses may be the next step in SRS.

If the ethical issues surrounding ESCs are insurmountable, then transplanted ADSCs may provide a solution. These cells have been shown to undergo neurogenic differentiation, smooth muscle differentiation, and endothelial differentiation – the main differentiation pathways for cells in the penile erectile tissue. For this reason, they are being studied for their potential usefulness in treating erectile dysfunction. The successes of these studies imply that functional erectile tissue could be developed from ADSCs. Seeding these cells into the scaffold may ensure that the techniques derived by Atala's team could be applied to FTM patients. These cells could also reduce the need for erectile prosthesis in FTM patients. These implants are often not ideal as they either require a pump to achieve an erection, or are consistently semi-rigid and difficult to conceal.

Barriers to "complete" stem-cell based SRS

MTF Genital Construction - Research, again carried out by a team lead by Anthony Atala, has succeeded in implanting lab-grown vaginas into women who were born without vaginal canals due to Mayer-Rokitansky-Kuster-Hauser Syndrome. This resulted in fully functioning sexual organs for all participants. Again, a collagen-based scaffold was used, which was then seeded with epithelial cells and smooth muscle cells. This was then shaped and implanted into a cavity created by surgeons, connected to the uterus. After 6 months, the scaffold degraded and the implanted cells matured into normal vaginal wall tissue, resulting in a fully functioning vagina.

These operations took place on cisgender women. The cells used came from a biopsy of the patient's external genitals, which would not be possible with MTF women, and uses of stem cells in vaginal development have not been studied enough to show promise. On top of this, the vaginal canal was connected to the uterus, enabling menstruation. The implanted vaginas were also capable of self-lubrication. These are significant barriers to SRS, as there have been no successful attempts to grow uteri from stem cells and implant them. Current vaginoplasties for MTF women also generally fail to achieve self-lubrication due to factors including:

1. The absence of the correct type of tissue (due to the use of skin grafts instead of vaginal tissue)
2. The absence of the number of different glands and epithelia which contribute to the process.

A final issue here would be the rerouting and shortening of the urethra to place it in a manner appropriate with female anatomy, which isn't necessary in cisgender women. This is currently done during common SRS techniques like the penile inversion vaginoplasty, and would need to be factored into any kind of vaginal implant.

The Gonads – This is an area that could potentially be very beneficial to transsexual patients, but the ability to grow ovaries and testes from stem cells appears to be many years away. Growing fully functioning gonads – with the resulting implications for fertility – is certainly an area that it would be important to develop. Transsexuals who undergo HRT currently have to remain in treatment indefinitely: this is expensive, time consuming and uncomfortable, so organs which could produce hormones such as testosterone and oestrogen would be a great step forward. It should be noted that some genital functions (e.g. the ejaculation of semen by the penis, or menstruation) require these organs. Currently, there is not really enough understanding of how this development could occur – there is even controversy over whether or not female/ovarian germline stem cells exist in mammals. This is not to say that the development of lab-grown genitalia without gonads wouldn't be beneficial for aesthetic and sexual purposes, but mimicking the anatomy of cisgender men and women is a long way away.

CONCLUSION

Stem cell research has great potential to improve multiple aspects of sex reassignment surgery, and therefore improve the health and wellbeing of transsexual patients. For FTM men, mesenchymal stem cells may provide solutions to common urethral complications of RFF Phalloplasties, a particularly popular form of genital construction, and could provide an alternative to visible graft sites. For MTF women, breast augmentation could become a far simpler and less invasive procedure were CAL to be employed. The possibility of growing organs in a lab could lead to the development of stem-cell-produced penises for FTM men, though the technology to make similar advances for MTF women is not as well-developed. Future study into the structure and function of the gonads could lead to insights that would allow implantation of functioning reproductive organs, but is currently beyond our reach and thus remains a significant hurdle in the path towards entirely stem cell based SRS. Technological limits also hinder wide-scale, economically viable organ printing.

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