

# Novel surgical techniques, regenerative medicine, tissue engineering and innovative immunosuppression in kidney transplantation

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## Abstract

On the 60<sup>th</sup> anniversary of the first successfully performed renal transplantation, we summarize the historical, current and potential future status of kidney transplantation. We discuss three different aspects with a potential significant influence on kidney transplantation progress: the development of surgical techniques, the influence of regenerative medicine and tissue engineering, and changes in immunosuppression. We evaluate the standard open surgical procedures with modern techniques and compare them to less invasive videoscopic as well as robotic techniques. The role of tissue engineering and regenerative medicine as a potential method for future kidney regeneration or replacement and the interesting search for novel solutions in the field of immunosuppression will be discussed. After 60 years since the first successfully performed kidney transplantation, we can conclude that the greatest achievements are associated with the development of surgical techniques and with planned systemic immunosuppression.

**Key words:** kidney transplantation, novel surgical techniques, immunosuppression, regenerative medicine, tissue engineering.

## Introduction

The first successful human kidney transplantation was performed by Joseph E. Murray, winner of a Nobel prize (in medicine and physiology, 1990), in 1954 [1, 2]. Dr Murray, who was later a Professor at Harvard and the Peter Bent Brigham Hospital, was not the first person historically to try to transplant a human renal allograft, but his crucial exploit paved the way for many further successes not only in the field of kid-

ney replacement but also transplantation of other solid organs. The first kidney transplant in the 1950s was also a very significant factor in creating the foundations for development of clinical transplantology, after a period of many setbacks and waiting for a great hope of a new unknown therapy form [3–5]. Historically, due to the attitude of knowledge and achievements of Murray, there were other great achievements such as the first liver transplantation performed by Thomas Starzl in 1963 and heart transplantation performed by Christian Barnard in 1967 [6–8]. The field of renal transplantation since 1954 has been significantly changed, especially in the surgical techniques and innovative operations. In addition, the introduction of novel techniques based on regenerative medicine and tissue engineering, as well as in patient care, is leading to elimination of the previously anticipated problems during transplant.

### Objective

In the 60<sup>th</sup> anniversary of the first successfully performed renal transplantation, we will present the historical, current and potential future status of kidney transplantation in selected aspects, based on a systemic overall analysis and literature review. We have previously discussed the following three aspects of kidney transplantation: development of surgical methods (1), the future of tissue engineered treatment procedures and perspectives to obtain a “bio-artificial” kidney (2) as well as analysis of the current status and future perspective of immunosuppression (3).

### The development of surgical methods

#### Background

Historically, the kidney transplantation procedure has been largely performed via open nephrectomy, changing only slightly over the past 60 years [9]. This generally involves: the kidney being placed into the iliac fossa on the contralateral side of its origin; the renal vein anastomosed end-to-side with the external iliac vein; and ureterovesical anastomosis performed without anti-reflux surgery. This type of arterial anastomosis is the only area of dispute concerning the development of open procedures. For whilst most transplant centers carry out the procedure as described, there are some which anastomose the renal artery end-to-end with the internal iliac artery so as to enable easier and safer graftectomy in cases where septic bleeding occurs. Apart from this, the most significant development of surgical techniques and equipment has transpired in the field of living kidney donations, resulting in the implementation of laparoscopic and robot-assisted surgery [10–14].

The main pioneer of laparoscopy was Georg Kelling, who conducted celioscopy research on dogs, publishing his results in 1901. Within this, he outlined the development of a diagnostic procedure for gastrointestinal bleeding whilst studying the potential therapeutic effects of high-pressure insufflations of air into the abdominal cavity, a technique which he called Luffttamponade. Also of significance is Hans Christian Jacobaeus, who reported on his experiences of laparothorascoscopy techniques in 1910, becoming the first to detail how he had performed laparoscopic surgery on humans in Sweden. This did much to popularize laparoscopy in the long term, with subsequent major breakthroughs not taking place until the 1980s. Most significant was the performance of the first laparoscopic appendectomy by the German gynecologist Kurt Semm in 1981, then the world's first cholecystectomy in 1985 by Erich Muhe, who used the same set of instruments as Semm. Following this, the development of laparoscopy accelerated rapidly [15–17].

Living-donor transplantation (LDN) has become the gold standard for the treatment of end-stage renal failure [18]. To minimize the procedure-related risk to a living donor, however, many techniques have been established besides open LDN (OLDN). After successful laparoscopic nephrectomies of kidneys in the early 1990s [19, 20], the first laparoscopic live donor nephrectomy (LLDN) was performed in 1995 by Lloyd Ratner and Louis Kavoussi at Johns Hopkins Bayview Medical Center [21]. From this, several approaches have developed either for OLDN (standard OLDN, mini-OLDN) or for LLDN (pure LDN, hand-assisted LLDN – HALLDN). Such developments have been accompanied by new videoscopic techniques emerging with satisfactory results such as single-port LLDN, natural orifice transluminal endoscopic surgery (NOTES), laparoendoscopic single-site (LESS) and robotic LLDN.

Looking at these in more detail, two meta-analyses comparing OLDN and LLDN by Antcliffe *et al.* [22, 23] concluded that LLDN had no clear benefits over OLDN. For whilst there were shorter operative times using OLDN within random control trials, there were no significant differences in warm ischemia times. It was, however, found that Mini-OLDN (< 15-cm skin incision) had some advantages for the donor vs. standard OLDN with both shorter warm ischemia and operative times. Such measurements took into account the overall complication rate, postoperative analgesia, the total stay in hospital, and time taken off work. Prior to this, a review by Shokeir compared patient morbidity and mortality using OLDN versus LLDN, finding that the latter brought some disadvantages, including a rise in operative and warm

ischemia times as well as an increase in major complications requiring reoperations [24]. Then, when comparing OLDN and HALLDN, laparoscopic techniques were favored with no significant differences found in renal function or allograft survival. For despite longer warm ischemia and operative times, HALLDN methods yielded better results in terms of postoperative donor pain, respiratory function and other recovery parameters [25, 26]. At the same time, though, it was reported that laparoscopic surgery had increased the risk of intraoperative incidents, major complications and significant bleeding [27]. It is, nonetheless, expected that these high-grade complications of LLDN will decrease to the level of OLDN over time as its application is refined [28].

Besides these points, throughout the healing process, LLDN has cosmetic drawbacks, with three or four port incisions required over the single incision of OLDN (especially mini-OLDN) [29]. It is also far more expensive than OLDN, especially when it comes to postoperative complications [19, 30]. Overall, then, it seems that the adoption of laparoscopic techniques is more about shifting public opinion about live donors than replacing OLDN, especially as only a quarter of the general population are in favor of LDN [18, 31]. The availability of LLDN has been credited by the United Network for Organ Sharing (UNOS) as a factor driving a significant increase in LDN [32–34]. This is similar to observations made within the field of urology 10–15 years ago, where laparoscopic and open surgery started being performed in cases of prostate cancer [35]. In the future, it is proposed that these procedures be applied to kidney transplantations via the techniques described in Figure 1.

Ongoing efforts to improve laparoscopy have also benefited from the wider development of surgical robots. The first modern and innovative use of such machines came in 1985 when a robot, PUMA 560, was used by Kwok *et al.* for a precision neurosurgical biopsy. Then in 1988, Davies *et al.* used the same machine to successfully perform a transurethral resection of a prostate. This use of robotics in surgery has continued to evolve since, particularly noticeably in the variety of devices which have been produced, such as PROBOT, ROBODOC, ARTEMIS, PRODOC, AESOP, ZEUS and, most recently, the da VINCI system (Intuitive Surgical, Mountain View, CA). Today, robotic surgery is mostly used for radical hysterectomies, prostatectomies, as well as colorectal and cardiothoracic surgery. Several published articles also describe the use of robotic surgery in gynecology, urology, general surgery and otolaryngology, with varying clinical effects [36–38].

In terms of general laparoscopic surgery, FDA approval for the use of the master-slave robotic

surgical system da VINCI was granted in July 2000 [39]. Since then, numerous studies have correlated several advantages and achievements with the use of this device. Its application applies to two separate stages of the kidney transplantation process:

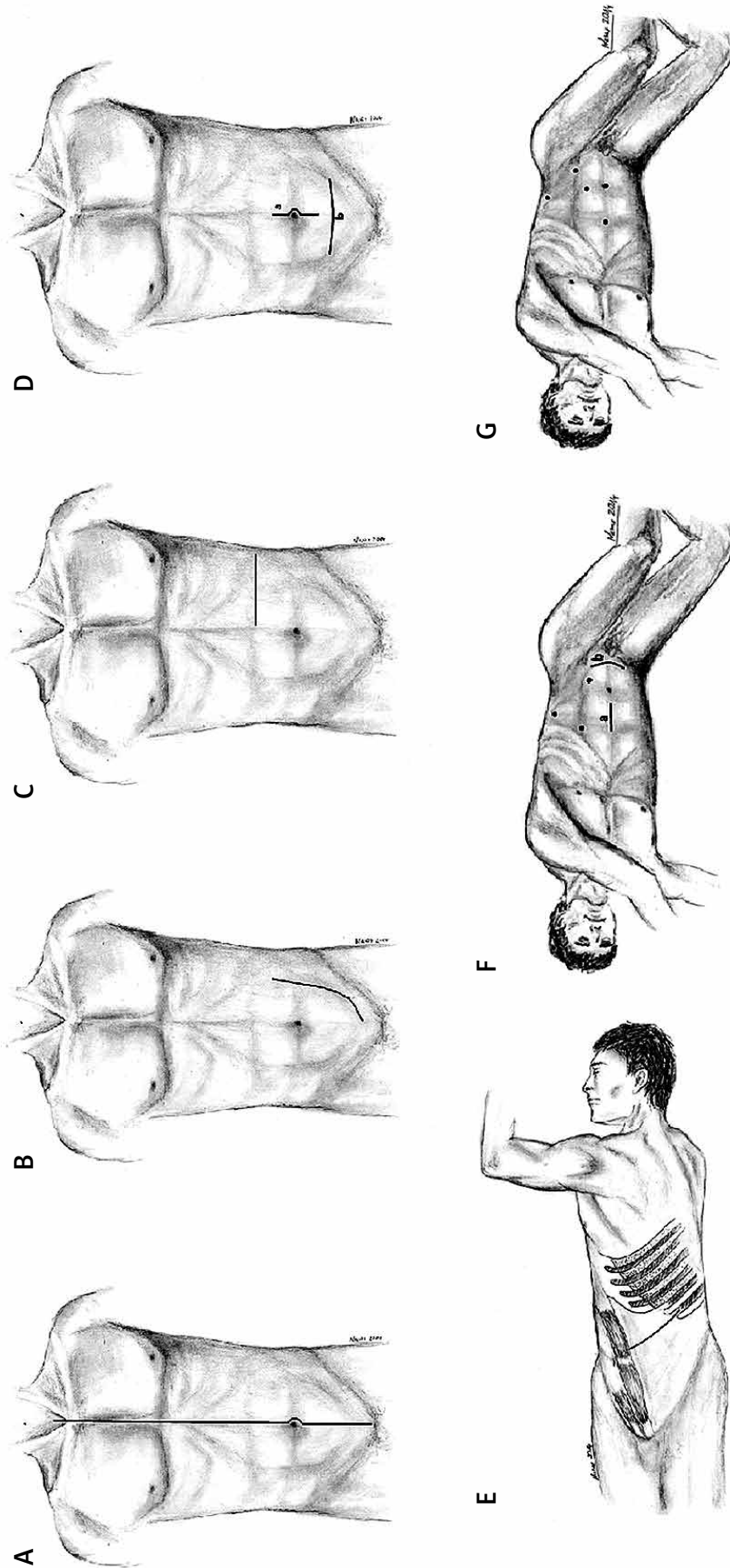
- Robotic donor nephrectomy/procurement (kidney removal from a living donor).
- Complete kidney replacement.

The first successful robot-assisted live-donor nephrectomy (referred to in the literature as RALD or RALDN for short) was performed via the da VINCI system in September 2000 by an operating team led by Professor Santiago Horgan at the Minimally Invasive Surgery Center and Division of Transplantation at the University of Illinois in Chicago. Meanwhile, the first robot-assisted kidney transplant was made using da VINCI again in June 2009 under the guidance of Dr. Stuart R. Gefner from the Division of Renal Transplantation in Livingston, New Jersey. A year later, in June 2010, came the first transplant in Europe, performed by Professor Ugo Boggi from the Division of General Surgery and Transplantation at the University Hospital of Pisa, Italy [40–44].

### The future

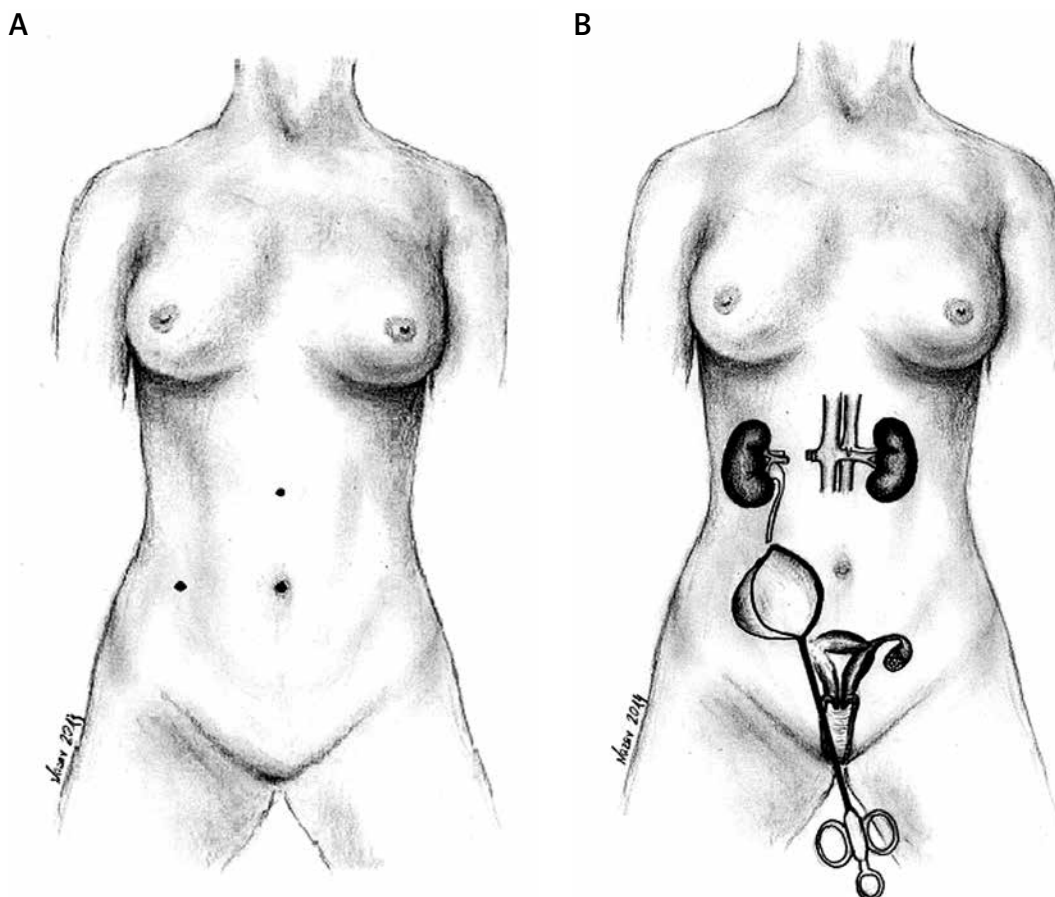
As previously mentioned, the future development of open techniques is likely to focus on refining existing procedures, as has occurred in the last 60 years. The development of laparoscopic procedures correlates in the main with minor technical improvements or general advances in the medical learning curve. This is reflected in the focus of many publications on robotic surgery when discussing future developments in kidney transplantation surgery [45–48].

Robotic transplantation is a fairly recent development, employed in cases where there is a high risk of surgical site infections or when patients are morbidly obese, therapeutic effects being noted. Despite the fact that such innovations have been in use for a relatively short time, it has had a very dynamic effect, with positive results. A notable recent development in kidney transplantation surgery came in 2012 when Galvani *et al.* performed a single-incision robotic-assisted living donor nephrectomy. Another is when Kaouk *et al.* became the first group to perform a transvaginal hybrid natural orifice transluminal surgery robotic donor nephrectomy (Figure 2) [49–52]. More importantly, though, such revolutionary developments are seen by many as key to overcoming the obstacles posed by the small number of donors and organs which exist at present. Minimally invasive and associated with fewer complications, an increasing number of therapy units are offering this method of kidney transplantation, theo-



**Figure 1.** Surgical techniques for kidney harvesting and transplantation. **A** – Standard open approach for abdominal and thoracic organs harvesting from cadaveric donor; **B** – standard approach for kidney transplantation (“hockey stick” incision); **C** – incision for both anterior transperitoneal and anterior retroperitoneal approach for live donor nephrectomy (LDN); **D** – belly-button laparoscopic single-site (LESS) live donor nephrectomy (a) and Pfannenstiel LESS live donor nephrectomy (b); **E** – approach for LDN through lumbotomy incision; **F** – hand-assisted laparoscopic approach. Hand-assisted device is placed in the midline over the umbilicus (a) or through Pfannenstiel incision (b); **G** – totally laparoscopic approach





**Figure 2.** Techniques for living kidney donation in combined laparoscopic surgery. **A** – Proper placement of trocars, **B** – kidney removal in EndoBag through vagina

retically enabling more transplants in general and the possible growth of domino and cross transplants. In turn, a greater volume of living donors may be attracted to this “softer” form of kidney donation, with better cosmetic results and fewer potentially negative consequences compared to standard open and laparoscopic nephrectomies [53–55]. Other factors which indicate the growth of robotic systems in kidney transplantations are that it facilitates access to treatment for morbidly obese patients previously denied it as well as the development of innovative telemedicine procedures, where there is hope that transplants can be performed at distance [56–58].

Overall, though, the prevalence of robotic-assisted kidney transplantations is still low, with not enough fully objective data relating to the effectiveness of such treatments compared to other methods. At present, there are very few medical centers with the necessary equipment to undertake such a procedure, making it difficult to conduct randomized multi-center studies and meta-analyses. In addition, robotic procedures are expensive, at present offered by only one company, with a small number of medical specialists and literate professionals able to perform them [59–

61]. Alongside this, whilst robot-assisted surgery has the potential to decrease the duration of surgery, users who lack experience with such technology are likely to be operating for a substantially longer time than when adopting traditional and laparoscopic techniques. This difference is particularly noticeable when robotic methods are used for the first time [41, 62, 63]. All of this can have a significant impact given that time is a key factor in the success of a donor nephrectomy or kidney replacement, affecting the warm ischemia time and the possibility of reperfusion complications. This is probably the main reason why there is a higher documented number of robot-assisted living donor nephrectomies vs. fully performed replacement procedures.

Nonetheless, numerous examples involving animal models indicate that it is theoretically possible to improve operation times based on this technique. It is also important to stress that such concerns about robotic methods are based on a small number of scientific analyses and are greatly influenced by negative feedback from the US Food and Drug Administration (FDA) and the MAUDE (Manufacturer and User Facility Device Experience) database. These are largely concerned

with the functioning of da VINCI in different surgical specialties and are not backed up by sufficient data [64–67]. In contrast, over 700 successful donor nephrectomies have been performed to date as well as more than 70 renal transplants, which have contributed to a reduced number of infections and other side risk factors correlated with standard open renal replacement. Furthermore, the growing number of robotic-assisted transplants will provide for a more extensive analysis of such procedures, better enabling many of the problems associated with such techniques to be overcome. This, it is hoped, will not only lead to more effective robotic kidney donor nephrectomies and kidney replacements but also have a significant impact on the development of kidney transplantations [53].

### Tissue engineering and regenerative medicine as kidney replacement therapy

#### Background

In the future, tissue engineering and regenerative medicine may offer an alternative method of kidney regeneration and replacement. These two closely overlapping branches of science could provide a lot of new solutions, particularly in helping to meet the needs of organ recipients in a climate where there is a lack of organs and tissues available for transplantations [68]. From the published literature, four different methods of kidney reconstruction and regeneration using tissue engineering can be found: (1) the use of decellularized kidneys, (2) stem cell application, (3) therapeutic cloning and (4) bio-artificial kidney construction. First, there is the utilization of decellularized cadaveric kidneys, whereby scaffolds are seeded with cells to promote the regeneration of kidney tissue [69–71]. Significant progress has recently been made in this area by Song *et al.*, who regenerated functional rat kidneys after decellularization through culturing epithelial and endothelial cells using a specially constructed scaffold within a whole-organ bioreactor [72]. Throughout this process, urine secretion was observed *in vitro* and *in vivo* through a urinary conduit after orthotopic transplantation.

Alternatively, kidneys can also be generated through the use of stem cells derived from another part of living tissue. Among the first innovations here has been the use of embryonic stem cells (ESCs), whose employment presents the advantage of allowing the creation of 3D structures which resemble kidneys without the use of scaffolding, such totipotent cells being able to differentiate into renal cells such as tubules and podocytes [73–75]. Disadvantages, however, center not only around ethical concerns but also the possibility of teratoma formation [76, 77]. As

a result, research has focused more on differentiated autologous stem cells such as bone marrow derived from mesenchymal stem cells (MSCs), adipose derived stem cells (ADSCs), or amniotic fluid stem cells (AFSCs). Such cells offer the benefit that they can be isolated using minimally invasive procedures whilst also having the ability to differentiate into renal cell lines via variant growth factors or conditioned media [78–80]. For instance, cloned metanephroi derived from adult cow fibroblast can be seeded in unwoven polyglycolic acid sheets to successfully create a kidney-like structure which can then be transplanted into the same cow for between 6 and 12 weeks, during which time it is able to discharge a urine-like fluid [81].

Differing from these approaches is the creation of bioartificial kidneys (BAKs), such constructions being able to support or replace the natural filtration process of the kidney. These are formed from material such as hollow fibers and cells (mainly renal) [82–87], clinical studies on an admittedly small number of patients indicating that this is a very promising way of treating acute renal failure. Nonetheless, results so far have yielded insufficient success, with experimental treatment using BAK only being able to be maintained for 24 h [82].

#### The future

Complete kidney regeneration using tissue-engineering methods is still at an experimental stage [84, 88]. Problems remain developing BAK-based treatments which can be used safely on all patients who qualify for renal replacement. Not only are there issues of a technical nature and about “bio-compatibility” but also there is a lack of both knowledge and available bio-technical solutions at present to create a device which can fully replace as physiologically complex an organ as the kidney [89]. All of this means that stem cells, for the restoration of renal function, are likely to feature more prominently in short-term developments as opposed to the implementation of novel BAK systems [90–92]. This is a conclusion borne out by the existing published data, analyses of current studies and general sentiment, not to mention the growing number of stem cell procedures being performed in other medical fields [93–96].

Here, an increasing number of such studies can be observed at ClinicalTrial.gov (Table I). Driving this is a well-established isolation and cultivation technique to extract MSCs from bone marrow as well as adipose tissue. In all registered trials, isolated MSCs are administered intravenously, a procedure which is also simple to perform. Other approaches such as the deployment of a decellularized kidney or constructing a bio-artificial kidney present much greater technical challenges.

**Table I.** Registered studies at ClinicalTrials.gov using mesenchymal stem cell transplantation in patients for kidney regeneration

Type of study and number	Reason	Cell type	Estimated enrollment
An open-label, non-randomized, multi-center study phase 1-2 trial (NCT01453816)	CKD	Autologous ADSC	10
Single-center, open-label phase 1 trial (NCT02195323)	CKD	Autologous BM-MSC	10
Single-center, open-label phase 1-2 trial (NCT00659620)	Chronic allograft nephropathy	MSC	20
Single-center, open-label phase 1 trial (NCT01840540)	Atherosclerotic renal artery stenosis	Autologous ADSC	6
Single-center, open-label phase 1 trial (NCT02166489)	CKD	Autologous BM-MSC	6
Non-randomized, open-label phase 1 trial (NCT00733876)	AKI	Allogenic BM-MSC	15
Single-centre, open-label phase 1 trial (NCT01275612)	AKI	Allogenic BM-MSC	9
Randomized, multicenter, double-blind, placebo-controlled phase 2 trial (NCT01602328)	AKI	Allogenic BM-MSC	156

CKD – chronic kidney disease, AKI – acute kidney injury, MSC – mesenchymal stem cell, ADSC – adipose-derived stem cell, BM-MSC – bone marrow mesenchymal stem cell.

This explains why studies using these latter methods are still at an early stage of development (*in vitro* and animal studies). Similarly, the first clinical study of *de novo* kidney regeneration will require more time [97–102].

## Immunosuppression and patient care

### Background

The immune system can cause significant problems in terms of the acute and chronic rejection of kidney transplantations [103, 104]. These complications have resulted in a constant search for new ways to reduce the likelihood of such outcomes [105, 106]. One of the pioneers of immunosuppression is Jean Hamburger, who used total body irradiation to prevent the rejection of transplants. He discovered this method of preventing rejection after the accidental irradiation of six Yugoslav researchers who survived bone marrow graft surgery. This marked the beginning of scientific attempts to influence the immune system, allowing future successful organ transplants [107, 108]. Hamburger was also the first to note the morphological changes which take place in rejected organs via transplant biopsies. However, whilst total body irradiation produced the desired effect on the immune system, its many adverse effects resulted in attempts to limit the irradiated area, be it to the localized area of the transplant, the thymus or the blood [109, 110].

Attempts were also made in the field of pharmacology to discover a means of chemical immu-

nosuppression to either complement or completely replace irradiation. Experimenting on rabbits, Schwartz and Dameshek concluded that 6-mercaptopurine offered promise as an agent of antibody reduction, the drug subsequently being used as a cytostatic agent in the treatment of neoplastic diseases. Then there was the introduction of azathioprine – a prodrug synthesized by George Hitchings and Gertrude Elion in 1957 which substitutes for normal metabolites through purine synthesis of DNA and RNA – to transplantology by Sir Roy Calne [111–113]. This proved particularly effective when combined with glucocorticoids by Thomas Earl Starzl in 1963, marking the beginning of combined therapy. Since then, though, cyclosporine and mycophenolate mofetil have replaced these drugs in transplant procedures, azathioprine having a number of adverse effects such as hepatotoxicity and myelotoxicity (suppression of bone marrow) as well as biliary and vascular complications [114, 115].

In particular, cyclosporine, a calcineurin inhibitor (CNI) isolated from the Norwegian fungus *Toly-pocladium inflatum*, has become a widely used immunosuppressive agent [116, 117]. Its effect lies in inhibiting the release of interleukins which, in turn, inhibit the differentiation of lymphocytes, significantly improving the results of organ transplantations in general. Among its unwanted side-effects are nephrotoxicity (leading to late allograft loss), thrombotic microangiopathy, anemia and thrombocytopenia. This has led to the development of alternatives, the most recent being

tacrolimus, which, whilst having a stronger effect, is associated with more complications, especially in cases of diabetes, and may lead to posterior reversible encephalopathy syndrome (PRES). This complication, first described in 1996, mainly manifests itself in headaches, confusion, visual loss and seizures, showing the visual characteristics of cerebral edema [118, 119].

Overall, though, CNIs are currently used in 95% of post-transplant immunosuppressive therapy in the US. In the case of cyclosporine, its concentration in the blood needs to be maintained to prevent transplant rejection and to reduce its nephrotoxicity, hepatotoxicity and negative impact on the cardiovascular system [120, 121]. Meanwhile, mycophenolate mofetil, first used in 1995, acts by inhibiting inosine monophosphate dehydrogenase (IMPDH) and purine synthesis whilst preventing the division of lymphocytes. When combined with cyclosporine and steroids, it has also been proven to reduce the occurrence of acute rejection during transplants, increasingly substituting for azathioprine in surgical procedures. Nonetheless, it is not without drawbacks, being linked with complications such as gastrointestinal problems, leucopenia and opportunistic infections [122, 123].

Immunosuppressive drugs also act to inhibit cell proliferation by blocking the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase. One of the agents in this group is sirolimus (rapamycin), a macrolide lactone produced by the actinomycete bacterium *Streptomyces hygroscopicus* [124]. Comparing its side effects to cyclosporine, there are fewer occurrences of wound healing disturbances as well as less adverse effects on lymphocytes and the hematological system. Conversely, it has been found more often to cause nephrotoxicity and hypertension. As a result, sirolimus should not be used in the days immediately following a kidney transplantation, its value coming later in the recovery process as a substitute for calcineurin inhibitors, particularly in allograft nephropathy [125, 126]. At present, immunosuppressive therapy in the aftermath of a kidney transplantation relies on the use of tacrolimus and cyclosporine A to perform the role of calcineurin inhibitors, alongside mycophenolate mofetil and glucocorticoids, which act as maintenance agents [127–129].

Alongside these methods of immunosuppression has been the removal of T lymphocytes using polyclonal antibodies obtained through the immunization of animals. This has proved to be particularly useful in cases of acute kidney rejection whilst minimizing risk levels. Further advances have also been made with the employment of monoclonal antibodies and OKT3 against the lymphocytes of transplant recipients [130, 131]. At

present, though, the application of immunoglobulin is most prevalent as a means of inducing immunosuppression, as well as being used to overcome acute rejection and to reduce the prevalence of alloantibodies as part of the desensitization process. Rituximab, a monoclonal antibody against CD20 which limits the activity of B cells and antibody production, has also been applied during desensitization, and its use in ABO-incompatible transplantations has delivered promising results. Meanwhile, other treatments of acute rejection and induction therapy include daclizumab, a humanized monoclonal antibody, and basiliximab, a chimeric mouse-human monoclonal antibody. Both act as IL-2 receptor antagonists and have the advantage of rarely causing side effects with no increased incidence of infections [132–135].

Such new immunosuppressive regimens have made ABO-incompatible kidney transplantation possible, increasing the pool of potential donors. This is achieved by desensitization in both pre-transplant therapy and as part of treatment in end-stage renal disease [136, 137]. Allied to this, it is important to remember the significant role that post-surgery procedures play in the long-term success of kidney transplants. These require specific problems related to individual patients to be taken into account, whereby it is necessary that medical staff are able to recognize the initial symptoms of complications and to take the necessary preventative measures – all of which requires adherence to international guidelines which have evolved in line with developments in the field of kidney transplantation. One of their major aims is to reduce the risk of death from cardiovascular diseases, malignancy and infection and graft rejection, education having a significant role to play in continuing to improve the lives of those who undergo such treatment [138, 139].

Another important issue to consider is the appropriate matching of donors and recipients. Initially, people were matched only by their blood groups before recipients were also administered with sera and lymphocytes from the donor. Subsequently, bringing developments to the present day, human leukocyte antigens (HLA) have become the core of donor-recipient matching, the most significant being A, B and DR proteins of HLA [140, 141]. With the final assessment made on the basis of a points system, the absolute contraindications for kidney donation include malignancies, the presence of HIV, hepatitis B and C, sepsis and an increase in creatinine. In the case of the recipients, they are: serious liver failure, serious cardiovascular disease and AIDS. Meanwhile, if a patient has suffered from cancer previously, it is necessary to postpone surgery, particularly given that there is a generally greater risk of developing malignan-



cies after kidney transplantation. Among the most common cancers in those who have undergone transplants are Kaposi's sarcoma, vaginal cancer, non-Hodgkin lymphoma, kidney cancer, non-melanoma skin cancer, lip cancer, thyroid cancer and small intestine cancer [142].

Throughout this, the screening process requires that each patient be considered on a case-by-case basis, taking into account family history, tobacco use and other factors which increase the risk of death, for the aftermath of the transplantation treatment may trigger a number of adverse health effects. Though often associated with kidney disease beforehand, hypertension can be brought on by immunosuppressive treatment, prednisone being associated with renal artery stenosis and graft dysfunction. Moreover, increased glucose levels are very common and have a negative impact on patient and graft survival, being defined by the World Health Organization as new-onset diabetes after transplantation (NODAT) [143, 144]. Obesity is another problem which requires patients have their body mass index (BMI) monitored during post-transplant follow-up visits, abnormalities best dealt with via lifestyle modifications which promote greater health more generally [145]. Among other methods to combat hypertension, there is no preferred agent of treatment, though some researchers have suggested that calcium channel blockers could be beneficial in limiting graft channels [146], except for patients with proteinuria, for whom ACE-I and ARB are preferred. Overall, though, combination therapies are considered most effective in spite of administered drugs possibly resulting in hypercalcemia, hyponatremia, hyperuricemia and hyperglycemia. This is especially true among high-risk patients.

### The future

Guiding attempts to improve current immunosuppression methods is a concern to prolong the period in which grafts and patients survive. Calcineurin inhibitors, antiproliferative agents and antibody induction agents have significantly reduced the probability of acute rejection, and patient and graft survival rates in the year after kidney transplantations are presently excellent. Nonetheless, there are various side effects due to the nephrotoxic long-term effect of immunosuppressive therapy in its present form. Therefore, different ways of inhibiting lymphocyte activation need to be explored [147]. In Table II, there is a summary of all the information about the various agents which have been used recently [148–164]. In future, treatments using immunoglobulin may play a greater role in the prevention of transplant rejection, because it allows more precise and effective therapy whilst possessing fewer long-term side effects, welcome

news in attempts to address what is a fundamental problem in renal transplantations.

On the issue of problems, an increasingly common one regards immunosuppression among HIV-positive patients. Nephropathy is one of the complications experienced by this group, and it is a recurring cause of end-stage renal failure. Despite this, kidney transplantation is considered safe at present among correctly selected patients of this type, short-term results proving similar to those observed in cases of uninfected recipients. Moreover, it has been proven that some immunosuppressive drugs benefit from antiretroviral treatment [165–167]. One completely revolutionary way to achieve immunosuppression after surgery is based on a kidney transplant being combined with a simultaneous transplantation of stem cells. This is designed to induce donor-specific tolerance in patients, potentially preventing allograft rejection. Several experiments on animals demonstrate this with drug-free survival possible through a stable mixed chimerism [168]. In such a case, the recipient becomes a chimera after the implantation of stem cells, possessing at least two different populations of genetically distinct cells.

Even so, a study by Seifert and her colleagues revealed increased inflammation in the aftermath of donor-type MSCs being administered [169]. Their study also showed no increase in graft survival or signs of partial tolerance being developed. At the same time, research conducted by Duojiang Wu illustrated a potential method to induce immunologic tolerance, showing that lipoprotein metabolism and plasma levels of fibrinogen play a role in hematopoietic stem cells (HSCs) inducing immunologic tolerance as well as acute rejection [170]. From this it was concluded that the molecular influence of HSC transplants on the immune system is a new area to explore in immunosuppression, given that it could help address adverse effects associated with current techniques. In addition, Tatsuo Kawai also observed that stable graft function may be achieved after the complete withdrawal of immunosuppressive drugs in mismatched HLA grafts where kidney transplantations are combined with bone marrow transplants [171].

More successfully completed clinical trials are detailed in "Science Translational Medicine" by Joseph Leventhal and Suzanne T. Ildstad as part of an article entitled "Chimerism and Tolerance Without GVHD or Engraftment Syndrome in HLA-Mismatched Combined Kidney and Hematopoietic Stem Cell Transplantation". Here, kidney transplantations are preceded by gathering a donor's marrow stem cells and then subjecting them to the appropriate recipient [172]. Positive results were also obtained by Jianming Tan, who noted a lower incidence of acute rejection in

**Table II.** Selected immunosuppressive agents investigated in recent years

Agent	Availability	Influence	Characteristics
Voclosporin	Experimental – not FDA approved [148]	Action against calcineurin – Analog of ciclosporin	– Studies on nonhuman primate model comparing it with cyclosporine showed significantly longer survival of allografts treated with voclosporin though its serum levels were lower and adverse effect fewer
Sotrastaurin	Discontinued investigation [149, 150]	Protein kinase C inhibitor	– Prolongs survival of life-supporting kidney allografts in non-human primate recipients both as a monotherapy and with combination with CsA – Studies showed increased incidence of acute rejection, graft loss and death
Belatacept	Approved by the U.S. Food and Drug Administration in 2011 for use in kidney transplantation [151–153]	Protein consisting of extracellular domain of CTLA-4 linked to the Fc fragment of human Ig	– Incidence of acute rejection is higher in belatacept than in cyclosporine group – Described as “first new agent available in kidney transplantation that achieves the goal of improved long-term renal function” – Lower blood pressure, lower non-HDL lipids, appropriate GFR, may improve long-term graft survival in CNI free immune therapy
Tofacitinib	Approved by Food and Drug Administration in 2012 for treatment of rheumatoid arthritis Tofacitinib development has been discontinued in kidney transplantation [154, 155]	Inhibitor of JAK kinase	– Pre-clinical studies on kidney transplantation which showed the elongation of graft survival clinical trials showed a similar extent of prevention of acute rejection compared to cyclosporine – Compared to cyclosporine renal function was improved and occurrence of post-transplant diabetes was reduced – Increased risk of viral infection, anemia and leukopenia, and lymphoproliferative disorder
Alefacept	Withdrawn from the market in 2011 [156]	Protein consists of LFA3/IgG1– reduces the number of memory T cells	– Incidence of malignancy was higher in alefacept group
Efalizumab	Suspended from the market in 2009 [157–159]	Binds to CD11a – inhibiting lymphocyte activation and cell migration	– Side effect (bacterial sepsis, invasive fungal disease and progressive multifocal leukoencephalopathy (PML))
Eculizumab	Approved by the United States Food and Drug Administration (FDA) in 2007 for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome [160–162]	Recombinant humanized monoclonal IgG2/4 antibody – binds to the complement component 5 and blocks the activation of terminal complement	– Reduces antibodies in highly sensitized patients and in prevention of antibody mediated rejection in a case series – Investigated in an ABO-incompatible kidney transplantation
Bortezomib	Approved for multiple myeloma in the United States in 2010 [163, 164]	Binds proteasome	– Case series confirmed to remove HLA antibodies in live-donor transplant recipients and to treat antibody acute rejection

therapy using autologous MSCs than that found in induction treatment employing an anti-IL-2 receptor antibody [173]. Moreover, during the study, a decreased risk of opportunistic infection was observed along with better renal functionality. In particular, a study of 6 patients assigned to Reinders raised the possibility of treating allograft

rejection after renal transplantation using autologous bone marrow-derived mesenchymal stromal cells. Proceeding from here, the therapy is, on the one hand, considered feasible with high levels of tolerance noted. Yet, on the other hand, attention is drawn to systemic immune suppression demonstrated by the incidence of viral infections [174].

## Conclusions and summary

Overall, reflecting on the development of surgical methods, there is a great deal of innovation present, with modern techniques playing a significant and increasing role in a large number of transplantation centers. This has generally centered around the displacement of standard open-surgery techniques in favor of novel laparoscopic and, to a lesser extent, innovative robotic procedures, particularly in centers with a high level of specialization. Unfortunately though, having studied all the relevant literature, this trend is unevenly spread, failing to reach smaller local centers with less qualified personnel. One of the main factors behind this is that novel treatment procedures such as robotic surgery or modern laparoscopy require a high level of investment. This is not only in terms of the initial capital outlay needed for the necessary operating devices but also in terms of expensive ongoing maintenance costs, the purchase of supporting tools and accessories, as well as expenditure on professional training for all surgeons and their assistants. Nonetheless, in spite of these issues, it is encouraging to see the increasing prevalence of more modern techniques in general, notably those used in the example of obese patients.

Meanwhile, advances in immunosuppression, which historically “opened the door” for successful transplantations to occur, continue to evolve. Not only have techniques become more efficient, they have also become fully “tailored” to each individual patient’s medical requirements. Developments such as the implementation of novel methods to induce immunologic tolerance have made it possible to offer new solutions in the field. Among them, the “most developmental” has been the use of cyclosporine, which has allowed transplantations to be performed on a large scale. To unlock more opportunities, though, further increases in knowledge of the human immune system are needed to be able to influence it in a more targeted way, stem cell therapy and chimerism being possible areas of exploration. Such advances would give hope that immunosuppressive therapy can be performed with fewer complications in future and that transplants will no longer require chronic treatment in this regard.

It is also important to highlight that the development of transplant surgery and immunosuppression medicine has been aided by the birth of two new biomedical disciplines of life science in tissue engineering and regenerative medicine. Analyzing the published materials, it has been observed that a large number of scientists have focused their investigations on new cell-based therapies and ways to construct bio-artificial organs which could be potentially used in clinical transplantology. Within this field, much of the

published data show that there are many obstacles to developing an effective and fully applicable bio-artificial kidney, and it is highly unlikely that a revolutionary discovery will be made in the near future. By contrast, the use of novel stem cell therapies or stem cell based supportive procedures offers far greater cause for optimism, with fewer difficulties associated with their application. Indeed, current *in vitro* and *in vivo* projects indicate that there are some interesting developments on the scientific horizon which are likely, after some modifications and assurances regarding efficiency and safety, to be adopted in future clinical trials.

All of this means that, 60 years on from the first successful kidney transplant, it can be concluded that the greatest achievements in the field have been associated with the development of surgical techniques alongside planned and systemic immunosuppression. It can also be summarized, having observed developments within regenerative medicine and tissue engineering, that there are ongoing innovations which are likely to presage new milestones in the field of transplantology, helping to improve a number of procedures which are presently not as effective as they often promise to be.

## Conflict of interest

The authors declare no conflict of interest.

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