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EDITORIAL

History of kidney transplantation: a journey of progression and evolution for success

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Keywords End-stage kidney disease · Kidney transplantation · Long-term allograft outcomes · Organ procurement · Organ shortage · Personalized precision medicine · Tolerance

Abbreviations
CNI Calcineurin inhibitor
RCT Randomized controlled trial

Human kidney transplantation is a multidisciplinary science. Not unlike other fields of medicine, kidney transplantation was initially perceived as "impossible" but ultimately become an actual routine, life-saving therapy. A unique feature of kidney transplantation arises from the relationship between donors and recipients: donors who give without rewards and recipients who receive without forgetting.

The extraordinary modern epic of transplantation began in 1949 when Sir Frank Macfarlane Burnet, whose research focused on bacteria and viruses, proposed a theory of distinguishability between one's own and foreign tissue that is acquired, but not hereditary, during the fetal stage [1]. This theory raised the interest of Dr. Peter Medawar, who initially studied zoology and became interested in research in areas of biology related to medicine. His pivotal work in the field of transplant immunity started during the Second World War when the Medical Research Council asked him to find the reasons for failure of skin grafts between human donors and recipients. In 1947, in collaboration with Dr. Rupert Everett Billingham, Dr. Medawar used skin grafts to distinguish between monozygotic and dizygotic twins in cattle and concluded that "*actively acquired tolerance*" of homografts could be artificially reproduced. As such, Dr. Medawar defined immunological tolerance as

> "*a state of indifference or non-reactivity towards a substance that would normally be expected to excite an immunological response*."

In 1951, Dr. Medawar successfully transplanted tissue between mouse fetuses [2]. These phenomenal works by Burnet and Medawar demonstrated that human immunity protects against microorganisms and rejects foreign tissues. In 1960, Drs. Burnet and Medawar were awarded the Nobel Prize in Physiology or Medicine for their studies on immunological tolerance.

Transplant science was translated from bench to bedside by Dr. Joseph E. Murray, a plastic surgeon, who had taken care of patients suffering from burns and had observed shorter rejection times than expected in some patients, recipients of skin grafts from unrelated donors. As a result of his interest and work in the transplant field, the first successful human kidney transplantation (a living-related kidney transplant between identical twins) was performed on December 23rd, 1954 at the Peter Bent Brigham Hospital (later Brigham and Women's Hospital) in Boston, Massachusetts [3]. Dr. Murray expressed the unforgettable moment of his

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team's success in providing *Gift-of-Life* to his patient, first describing what is still in the mind of every trainee who sees, for the first time, the change in a kidney allograft, turning pink from almost white, while urine starts flowing after the allograft anastomoses. Dr. Murray was awarded the Nobel Prize in 1990.

A further breakthrough is attributable to Dr. Paul Terazaki, who earned a PhD in zoology in 1950, and started his research in transplantation by studying skin graft transplants in newborn chicks. He later became a research scholar in Dr. Medawar's laboratory in 1957–1958. He first studied the role of antibodies in transplants in chickens, then in mice and rabbits, and eventually extended his studies to humans in 1963. In 1964, he created the microcytotoxicity test, which became the international standard in 1970. In collaboration with other transplant colleagues, Dr. Terasaki started a kidney transplant registry, which became the current United Network for Organ Sharing registry. Dr. Terazaki's discovery of the role of antibodies in transplantation and kidney allograft survival is the basis of modern transplant immunology, now encompassing also post-transplant surveillance of human leukocyte antigen donor-specific antibodies. His works allowed to overcome the first barriers to long-term success in kidney and other organ transplantations [4].

The concomitant development of immunosuppressive medications contributed to the same goal. Dr. Thomas Earl Starzl developed azathioprine and corticosteroid-based immunosuppression and introduced anti-lymphocyte globulin. In 1963, he demonstrated that adding corticosteroids to azathioprine in a timely manner could reverse organ rejection. During the same year, he performed the world's first liver transplant. However, it was after the discovery of cyclosporine by the biologist. Hans Peter Frey, working for the Sandoz corporation in Norway in 1969, and after its introduction in clinical practice in 1979, that the outcomes of kidney transplantation significantly improved. Dr. Starzl was one of the first physicians to use cyclosporine in human transplantation and, again, was one of the promoters of the use of tacrolimus, a newer and more effective calcineurin inhibitor, leading not only to a further improvement in the outcomes, especially in the short term, but also to the further broadening of the indications for kidney transplantation. Because of his work as a surgeon and physician-scientist, Dr. Starzl is acknowledged as the "*Father of Transplantation*" [5].

However, long-term outcomes have improved to a lesser extent. Contributing factors affecting long-term kidney allograft outcomes include chronic allograft dysfunction related to the increased acceptance of kidneys from elderly donors or of suboptimal quality. This choice is necessary because of organ shortage, in the face of an increased number of transplant candidates, including those who are old or at increased risk of graft failure because of re-transplantation. Baseline conditions, including old age, inadequate control of chronic antibody-mediated rejection, and chronic calcineurin inhibitor nephrotoxicity contribute to a shorter lifespan of the grafted kidneys. To mitigate the adverse effect of the CNI, new approaches have been studied over the past two decades, trying to balance the goal of improving long-term kidney allograft function and patient survival, challenged by the iatrogenic increased incidence of cardiovascular diseases, opportunistic infections, and malignancy. The ideal strategy would be to withdraw immunosuppressive medications by tolerance induction, finally achieving the goal of *'One Organ for Life'*.

The best balance between better results and, as a consequence of the better results and fewer side effects, of the increasing pool of potential kidney transplant recipients, is difficult to achieve [6]. The improvements in dialysis therapy are seldom discussed in this context but should probably also be taken into account since demanding schedules, such as daily or extended dialysis, may allow to reach previously unmet goals (including pregnancy).

The increased demands are partially answered by the use of "marginal organs" such as those from elderly donors, and donors after cardiocirculatory death, or with Hepatitis-C and HIV-infection. The technological development for recovering marginal organs that would otherwise be discarded has been outstanding. Hypothermic machine perfusion was a significant improvement and, in the near future, normothermic perfusion may become a "resuscitation tool" that promotes tissue repair and prevents ischemia–reperfusion injury.

The history of transplantation is marked by ingenious solutions, such as the paired exchange programs, whereby patients with incompatible donors simultaneously swap kidneys to receive a compatible kidney, eventually also with the help of non-directed altruistic living donations. For those who cannot exploit those programs, antibody-incompatible transplantation is an increasingly available option, thanks to therapeutic strategies that prevent antibody production by inhibiting germinal center activation, and that cleave circulating antibodies at the time of transplantation [7]. On the other hand, measuring donor immunogenicity as opposed to incompatibility allows to identify feasible transplantations (so-called "acceptable mismatches") [8].

Lifetime anti-rejection therapy, however, increases the risk of infections and cancer. Inducing immunological transplant tolerance would reduce or abolish the need for anti-rejection drugs. Protocols for inducing central tolerance are based on the administration of donor hematopoietic stem cells, whereas those aimed at inducing peripheral tolerance are based on the infusion of T regulatory cells (Tregs). Recent research has focused on the administration of polyclonal Tregs, alloreactive and, most recently, on gene-edited Treg cells (CAR Tregs) [9]. Progress has been

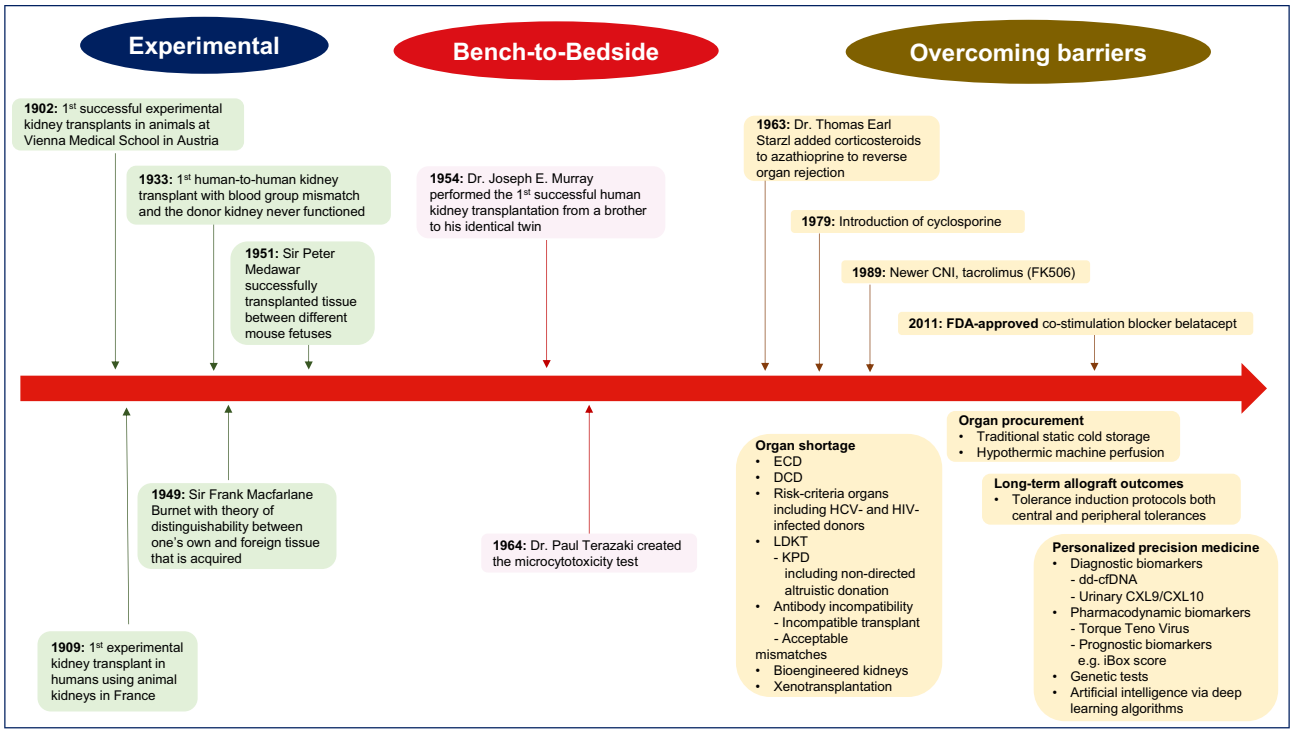

Fig. 1 History of kidney transplantation with three main periods including experimental, bench-to-bedside, and overcoming barrier periods. *CNI* calcineurin inhibitor, *DCD* donation after circulatory death, *dd-cfDNA* donor-derived cell-free DNA, *DNA* deoxyribonucleic acid, *ECD* expanded criteria donor, *HCV* hepatitis C, *KPD* kidney paired donation, *LDKT* living donor kidney transplantation

made in diagnosis, risk-stratification, treatment-response, and pharmacodynamic biomarkers, for fostering precision medicine in the field of kidney transplantation. Diagnostic biomarkers (e.g. donor-derived cell-free DNA, urinary CXL9/CXL10), pharmacodynamic biomarkers (e.g. Torque Teno Virus), and prognostic biomarkers (e.g. iBox score) are presently being proposed. Genetic tests for kidney disease and susceptibility to rejection may be incorporated in the selection of potential donors and recipients. Artificial intelligence may develop algorithms to guide therapeutic drug management.

The final answer may however require further steps forward. Bioengineered kidneys (i.e. cell seeding of a decellularized kidney called "renal scaffold"), thanks to genetic engineering, and xenotransplantation represent the most exciting options. Recently, the first clinical experimental transplants of genetically modified pig kidneys to brain-dead humans, and a pig heart transplant to a non-ischemic cardiomyopathy patient were performed (Fig. 1).

With this fascinating backdrop, in this issue of the *Journal of Nephrology* we invited experts and welcomed researchers to share their expertise and experiences in kidney transplantation in the form of case reports, case series, retrospective observational studies, experimental studies, both clinical trials and reviews, as well as topics of COVID-19-related kidney transplantation.

We hope that our humble effort may contribute to the advancement of knowledge in kidney transplantation thus improving kidney health and our patients' life.

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Declarations

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