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Review Article

Contribution of Large Pig for Renal Ischemia-Reperfusion and Transplantation Studies: The Preclinical Model

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Animal experimentation is necessary to characterize human diseases and design adequate therapeutic interventions. In renal transplantation research, the limited number of *in vitro* models involves a crucial role for *in vivo* models and particularly for the porcine model. Pig and human kidneys are anatomically similar (characterized by multilobular structure in contrast to rodent and dog kidneys unilobular). The human proximity of porcine physiology and immune systems provides a basic knowledge of graft recovery and inflammatory physiopathology through *in vivo* studies. In addition, pig large body size allows surgical procedures similar to humans, repeated collections of peripheral blood or renal biopsies making pigs ideal for medical training and for the assessment of preclinical technologies. However, its size is also its main drawback implying expensive housing. Nevertheless, pig models are relevant alternatives to primate models, offering promising perspectives with developments of transgenic modulation and marginal donor models facilitating data extrapolation to human conditions.

1. Introduction

Experimental models have accelerated our understanding of diseases' pathophysiology and played a major role in the search for adequate therapeutic interventions. Ischemia reperfusion injury (IRI) remains a leading cause of acute kidney injury (AKI) in both native and transplanted kidneys [1]. IRI is a choreographed process leading to delayed graft function (DGF) and reduced long-term organ survival in transplantation. Cold-storage-induced injury is a pivotal contributing factor to early graft dysfunction in organ recipients. The success of organ transplantation is also critically dependent on the quality of the donor organ which, in turn, is determined by a variety of factors, including donor age, donor management prior to organ procurement, hypothermic storage time, and the quality of organ preservation. Organ preservation is a critical link in the chain of donation-transplantation, having a significant effect on posttransplant graft function and graft survival.

Animal experimental models are also crucial in renal IRI research, as there are only a limited number of *in vitro* models. Although animal experimentation is contentious and subject to legal and ethical restrictions, large animal models are still extensively used and are necessary to develop safe preclinical protocols directly transferable to human. Indeed, preclinical studies using pig or nonhuman primate play an important role in the evaluation of new medical devices and pharmacological therapy efficacy before their use in clinical studies. The first renal transplantation was performed by Emerich Ullmann in 1902 in dog, and the first porcine kidney transplantation was published in 1965 [2]. The similarity in size, physiology, and in organ development and disease progression make the swine an ideal model for human disease research [3]. Nowadays, the

porcine model is crucial to adapt surgical procedures and to develop models mimicking for instance deceased after cardiac arrest donors or to test novel preservation solutions in transplantation. This paper provides an overview of porcine models commonly used to evaluate organ transplant protocols and analyzes new surgical models of marginal donors, establishing the pig as a gold standard in renal transplantation research.

2. Renal Transplantation and Ischemia-Reperfusion Injury Models

Different models can be considered for renal transplantation and IRI. The cellular models are interesting to focus on specific pathways or large-scale screening for drug evaluations. It is possible to use different cell lines originating from different organs. However, the absence of integrative studies, which are only possible at the organ or whole-animal levels, limits their interest. In fact, *in vitro* IRI studies cannot mimic the global situation observed *in vivo* because there are many local, systemic, cellular and humoral factors involved during IRI *in vivo*. Such models are more adapted to study cold storage conditions with hypoxia and hypothermia mimicking the cold-preservation stage [4–11]. Other models are also useful such as isolated blood vessel models [12]. Indeed, these models are of interest to evaluate signalling pathways and to test hypotheses with preliminary studies [7, 9]. Perfusion of isolated organs are another group of models interesting for an early evaluation of IRI [13–16]. Animal models are an obvious step needed to confirm the most relevant pathways identified at the *in vitro* in well-controlled systems and to provide a definitive proof of concept [4].

An intermediate step has to be considered with rodent models. There is an extensive literature on renal IRI using rodent models and focusing on the early times of reperfusion with different protocols. A recent paper analysed animal models of chronic allograft injury in kidney, heart, aorta, liver and lung transplantation [17]. This review focused on rodent and nonhuman primate models while the swine model was restricted to lung transplantation. This situation will be changed with the development of mini- or micro-pigs. In addition, transplantation models in rodents are not easy to perform and are not systematically reproducible mainly because they depend on the operator's skills.

Three large animal models have been used extensively in transplantation: dogs, pigs and nonhuman primates. Each species closely approximates human physiology, and the general anatomical similarity has provided a relevant background for preclinical experiments. In renal transplantation, canine models were used for development of blood vessel anastomosis technique and the first autograft and allograft were performed in dogs. The pig has two major advantages: it is generally accepted for human consumption and the public harbours relatively little resentment for porcine research inducing less legal and ethical restrictions conversely to nonhuman primate or dog models [4]. In addition, pigs are easily bred and are now recognized as being genetically modifiable [18]. Pig has also the advantages of large animal model: it is possible, to collect repeated peripheral blood samples or renal tissue biopsy during experiments, to obtain detailed tissue samples at euthanasia and to use technologies adapted to human conditions such as CTscan or NMR [3]. In terms of genomics, it is an asset that the pig genome has high sequence and chromosome structure homology with humans, making possible the use in pigs of human genetic and proteomic tools [3].

In transplantation research, histology of allograft rejection is similar to humans. Immune responses are predicated on a similar network of T cells responding to a similarly organized major histocompatibility complex [18]. Although some issues affect the use of immunosuppressors in non-human primates and dogs inducing ulcerative bowel lesions and diarrhea due to poor absorption. In these conditions, the pig tolerates high doses of calcineurin inhibitors such as cyclosporine without apparent toxicity.

3. Description of the Pig As Biomedical Model

3.1. Anatomy. Many animals have been used in experimental models of renal transplantation but the porcine model is more consistent because of the existence of close analogies between structural features of human and porcine kidneys [19]. Although pig renal and intrarenal anatomy could not be completely transposed to human, many similarities in porcine and human intrarenal arteries have been described [20] as well as anatomical relationships between intrarenal arteries and the kidney collecting system (Figure 1). Using kidney resin perfusions, it was found in 91 pigs that there was only one artery per kidney divided into cranial and caudal branches in 93.4%, or dorsal and ventral branch in 6.6% of cases [20]. The high occurrence of single renal artery in swine is quite different from the human situation, in which multiple renal arteries are reported in 27 to 30% of cases [21]. In addition, in the human single artery condition, the primary division occurs into an anterior and a posterior branch [20]. In the renal superior pole, Pereira-Sampaio et al. described two main arteries in pigs (ventral and dorsal) originating from the cranial branch of the renal artery, similar to the human segmental arteries with an apical artery found in human and absents in 67% of the cases in pigs [20, 22]. In addition, the dorsal artery, always observed in human, is only described in 47% of the pig population [20, 22] in contrast to the horizontal branch in the ventral mid zone of the kidney, which is always described in both species [20, 22]. In the inferior pole, the caudal artery divides into ventral and dorsal branches in 85% of cases in pigs and 62% in human kidneys. In the remaining cases, the ventral branch arises from the caudal artery and the dorsal branch arises from the dorsal artery [20, 22].

As in the human kidney, there are free anastomosis between the intrarenal veins in the pig [23, 24]. The interlobar veins merge to produce large venous trunks which form the renal vein [24]. Bagetti Filho et al. described two major trunks: cranial and caudal and in few cases, three trunks (cranial, middle and caudal). However, only the ventral surfaces of the cranial and caudal poles were drained by large

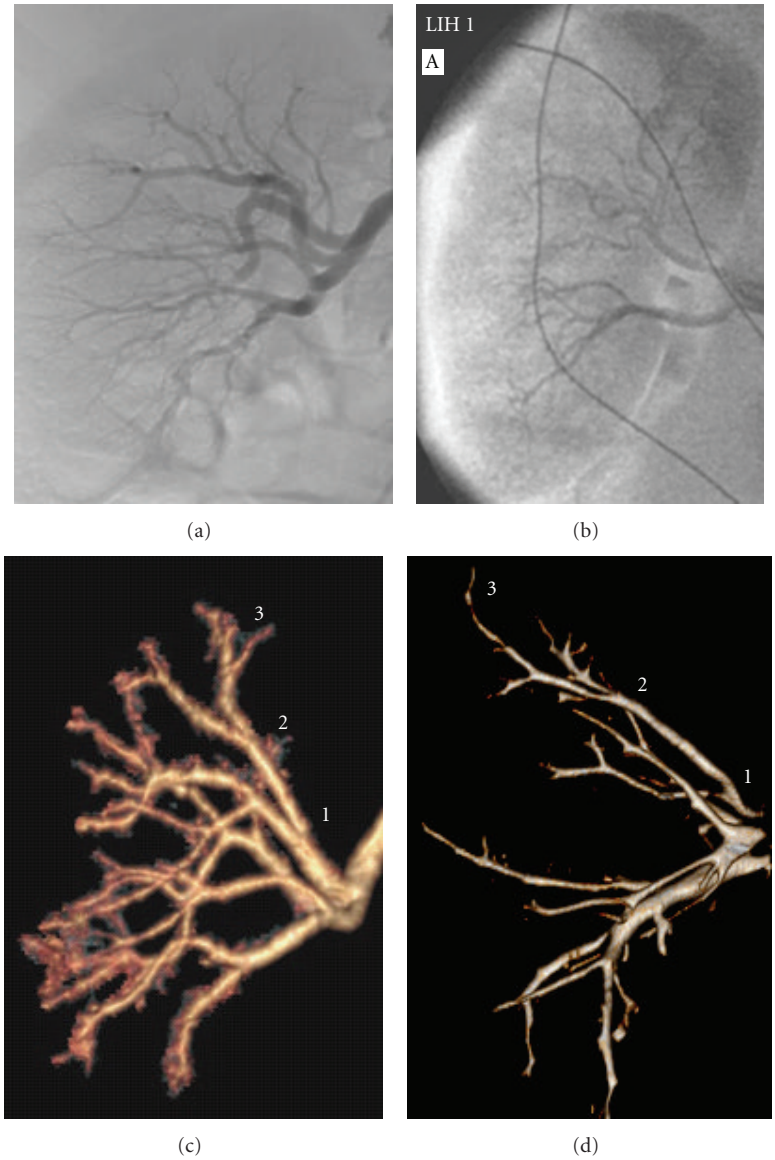

Figure 1: Renal human and pig vasculature. (a, b) are representative angiography pictures, respectively, in human and pig, (c, d) are representative pictures of kidney vasculature obtained with CTscan, respectively, in human and pig. (1) segmental arteries *aera*; (2) interlobar arteries *aera;* (3) arcuate arteries *aera*.

veins while the dorsal surfaces emptied by anastomoses into the ventral interlobar veins [24]. The arterial and venous architectures in each species vary significantly and have evolved to optimise O_2 transport based on each unique anatomical configuration. In dogs and rodents, segmental arteries are bypassed due to the lack of multiple medullary pyramids, while in humans and pigs an elaborate system of interlobar and segmental arteries is present to supply the numerous kidney lobes [25]. There is thus a high degree of proximity between human and pig kidneys [20] (Figure 2), with multilobular, multipapillary architecture, while mice, rats, dogs and rabbits have unilobular, unipapillary kidneys [25].

In term of body size, pig is also close to human, particularly for the mini-pig which reaches body weights of 60–70 kg in adulthood. The large blood volume in pigs allows repeated blood sampling. The use of males greatly facilitates 24h-urine collection in metabolic cages which is a crucial parameter to monitor in renal transplantation.

3.2. Physiology. The mechanisms of IRI, depend on the anatomic and metabolic properties of the kidney [27]. In association with the multilobular, multipapillary kidney and the vascular architecture, renal parenchyma oxygenation is graded with the highest O_2 levels in the cortical zone, medium levels in the outer medulla and the lowest levels in the papillae [25]. Cells in each kidney region are adapted to function optimally at the oxygenation levels in their respective microenvironments [27]. Cortical cells mainly use

Human Pig Rodent

Figure 2: Renal anatomical comparisons between human, pig and rodent [26]. Multilobular and multipapillary kidneys observed in human and pig contrast with unilobular and unipapillary kidney in rodent (http://www.jeremyswan.com/).

O_2-dependent metabolism linked to oxidative phosphorylation. These cells are living in an oxygenated area making them more sensitive to ischemia. Cells in the outer medulla can shift to O_2 independent metabolism, making them less sensitive to an hypoxic environment. Inner medulla and papillae cells predominantly use glucose to generate ATP *via* anaerobic glycolysis. These last regions reside in a permanent hypoxic environment and consequently are less affected by ischemia [25]. Physiological differences among species limit the clinical translation of animal studies. Criteria related to renal embryology, anatomy, architecture and lymphatic pattern, ability to concentrate urine, and sensitivity to ischemia suggest that the pig kidney may be more similar to the human kidney than dog's or rodent's and may be a better model to study human ischemia/reperfusion consequences [25, 28–30].

3.3. Biochemistry. Human reference values for blood biochemical parameters, such as creatinine and Blood Urea Nitrogen (BUN) are identical in pigs [31]. A previous study analysed over 100 physiological variables in pigs in basal conditions, concluded that most porcine values were similar to those collected under comparable conditions in humans [31].

3.4. Genome. Major advances in the understanding of the porcine transcriptome have occurred over the past decade, and especially in the past few years [32]. The pig genome was sequenced and characterised under the auspices of the Swine Genome Sequencing Consortium [33, 34]. Microarray and macroarray from *Sus Scrofa* cDNA have been used since 2005 [35] and chips for immune system are now well established [36–41]. This new technology has been used to characterize a preclinical model of chronic ischemic wound [42] and to study hypoxia effects on stem cells [43]. The important cross-species of gene expression between human and porcine tissue supports the concept of using human GeneChip microarray platform to compare gene expression profiles between pig and human tissues in the absence of a porcine microarray platform [44].

3.5. Immune System. The porcine immune system is better characterized than the canine one, making the pig an interesting alternative model to the nonhuman primate for immunosuppressive therapeutic approaches. The porcine immune system has been studied to elucidate the role of the lymphoid organs during infectious diseases, in order to characterize immune function in transplantation research and to generate a model for various aspects of human immunology [45]. Immunosuppressive drugs have been evaluated in dogs, pigs and nonhuman primates leading to reproducible prolongations of graft survival [4]. The pig is also important to investigate the development of the adaptative immune response in neonates [46, 47]. Studies on laboratory rodents or primates have been ambiguous because neither the effect of environmental nor maternal factors on the newborn can be controlled in mammals such as transmission of potential maternal immunoregulatory factors *in utero*.

Workshop and literature on immune marker identifications report important similarities between human and pig antigens as well as immune response [6, 48–51]. Through these workshops, the available antibodies used in pig studies have increased drastically [6, 50, 52–58].

3.6. Immunosuppressive Therapies in Large Animal Models. A recent review has presented the different aspects and showed that large animal model could be useful for therapeutic protein fused to monoclonal antibodies, depletion strategies, mixed chimerism or donor antigen infusion [4].

4. Limits of the Large Pig Model

Although the porcine model is herein described as a gold standard, it presents several disadvantages. The major inconvenient resides in its fast growth and subsequent large size, complicating handling. In terms of reproduction, a female pig has a gestation period of 114 days, with an average of 2.4 litters per year and 12 piglets per litter, requiring a large kennel. Pigs are often considered noisy and aggressive causing researchers to consider more amenable species to

perform their experiments [59]. In fact, male pigs usually require castration to limit their aggressive behavior at the end of puberty.

Pigs need to be used at a reasonable weight in order to easily perform transplantation surgeries in laboratories under sterile conditions. Therefore the age of the animals used for transplantation is restricted to very young adults rather than adults [4]. Their relatively rapid growth impairs the setting up of long-term studies [60]. In fact, the Large White pigs commonly used in our laboratory, weigh around 1.5 kg at birth, 35 kg at 3 months, 125 kg at 6 months, 200 kg at 1 year and 280 kg at 2 years. At 3 months, the pig needs a large amount (estimated at 1 kg per day) of relatively expensive food: commonly diet prices range from 0.2 euros/kg for standard diet to 3.5 euros/kg for hyperlipidemic diet. Studies in pigs are expensive and consequently include a smaller number of animals. A Large White pig costs around 120 euros at 30 kg and requires important handling, surgical material, such as a pen, a metabolic cage for urine collection (around 2500 euros/unit), a surgical room similar to the ones used for humans, and a large area to stock food. Their large size and the necessity to induce general anesthesia require larger amounts of anesthetics and more human manipulators than for small animal models. A second major limiting point is the adaptation of the material required for biological analysis. In fact, porcine specific antibodies and kits for biological marker detection are rare and expensive; however new tools are emerging due to the expansion of the use of pig as a common experimental model. In addition, human protein analysis kits can be used with porcine samples due to the biological proximity between pig and human. Another point is the limited number of references available in the literature for pig biological data. In summary, the most significant disadvantages of the Large White pig include difficulties in handling, maintenance and high costs.

5. Minipig Model: An Alternative of Large Pig Model

5.1. Rational for Minipig Models. In porcine experimentation, the animal's size is crucial. Indeed, smaller animals are easier to breed and handle than larger ones. The large weight of fully grown farm pigs (up to 250 kg) impairs their routine laboratory use [4]. Thus, several types of miniature pigs also termed "minipigs", have been developed. The predominant breeds are the Yucatan, Hanford, Göttingen and Sinclair. These breeds and dozens of others have been used as experimental models for various clinical situations [61]: (i) the Hanford minipig breed has been used for urological studies [62, 63], (ii) the Yucatan breed, the only natural occurring miniature pig, is one of the predominant models used for cardiovascular physiology and congestive heart failure studies [64, 65], and (iii) the Gottingen minipig is used for comparative drug distribution and pharmacokinetic studies [66–68].

For instance, the Hanford minipig is sociable, trainable, and weighs only 25 to 35 kg at 4 to 6 months old [62]. The average kidney size in a 25 kg Hanford minipig is 120 g and measures 11 × 6 × 3 cm, similar to the kidney of a 70 kg human [62]. The sexual maturity of minipig is reached at around 4-5 months old corresponding to a body weight of 15–20 kg for Sinclair pigs, 20–25 kg for Yucatan pigs and 20–30 kg for the Hanford breed.

The major advantage of using minipigs is their relative low maintenance costs in comparison to large pigs [69]. Indeed, minipigs require less housing surfaces, food (divided by two or more) and less drug amounts. The latter point is particularly appreciated when the drug is under evaluation and only produced on a small expensive scale.

5.2. Minipig Inconveniences. Minipig's smaller body size could be a disadvantage to perform experiments in clinical conditions. Indeed, human surgical protocols or instruments can sometimes not be used in minipigs. Small size makes this type of pigs unsuitable for the modelling of the *normothermic extracorporeal circulation* used for transplantation of kidneys obtained from deceased after cardiac arrest donors [70, 71], mainly because of a smaller vascular size in minipigs in comparison to human, [72–75]. Taken together, the basic knowledge of Large White models acquired during the last twenty years for kidney transplantation studies, contrasts with minipig studies mainly limited to noninvasive surgical experiments. Despite these inconvenients, the use of minipigs as a kidney transplantation model may be one of the few available animal model for the study of extended criteria donors such as older or diabetic donors.

6. Different Models for Renal Transplantation and Ischemia-Reperfusion Injury

6.1. Anaesthesia and Surgical Aspects. Most experiments in the transplantation area are carried out on rodents, but crucial prerequisites for the development of safe preclinical protocols in biomedical research are needed through the use of suitable large animal models needing anaesthesia and surgery similar to human.

6.1.1. Anesthesia Procedure. Pig is a valuable animal for anesthesia experimental studies. This procedure needs to ensure optimal perioperative analgesic control with motor blockade during surgery associated with a rapid postoperative recovery. In our laboratory, we have developed epidural anesthesia techniques in pigs [76] which allow us to conduct pharmacological and pathophysiological studies [77, 78].

6.1.2. Surgical Procedures. Surgical procedures, postoperative course, peri- and postoperative monitoring are necessary in large animal models to provide an optimal tool for surgeon training and resident teaching. Indeed, pigs could be used as preclinical models mimicking true clinical situations which are sometimes complex [79, 80]. Pig models have also been used to develop new surgical aspects [81–84] with a possible rapid translation to the clinical situation mainly because of the pig's body size.

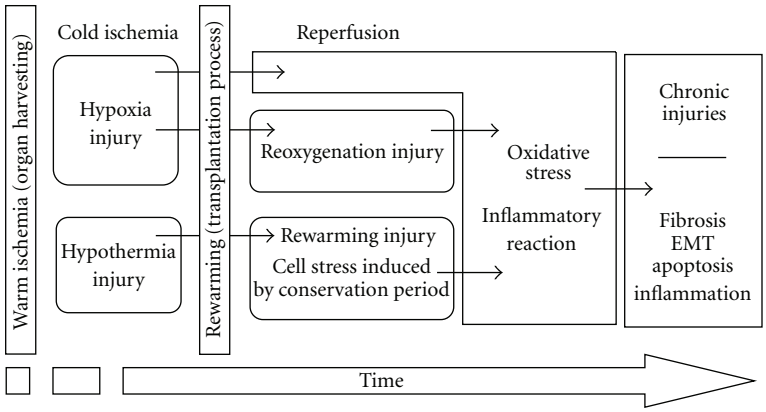

Figure 3: Major processes induced by ischemia-reperfusion injury in renal transplantation.

6.2. Ischemia-Reperfusion Sequences. IRI is known as one of the central nonimmunologic process involved in renal allograft dysfunction implicating vascular and tubular injuries [85]. More than ever, research into the mechanisms of warm ischemia (WI), cold storage (CS), and IRI is needed to maximize the use of the available donor pool and to minimize primary nonfunction (PNF) and delayed graft function (DGF). Although advances in organ preservation solutions and techniques allowed prolongation of hypothermic storage [86], the effects of CS after a period of WI are still incompletely understood. The use of preclinical model in a large animal such as the pig is necessary to adapt transplantation processes closely related to the human condition and clarify the mechanisms involved. Well-known in rodent, renal WI has been scarcely investigated in clinical situations such as transplantation.

Several porcine models have been used to study the mechanisms of WI and the effects of a variety of drugs, and some of them are moving on to clinical evaluation [87–89]. Because the porcine renal anatomy and vascular bed are very similar with human kidneys, these models are very relevant to evaluate the renal response following injury, such as renal tubular inflammation and repair processes [90]. The choice of animal model is crucial to validate proper markers. We and others have validated several precious markers in pigs for pivotal pathways that mediate injury responses and recovery after renal ischemia [75, 88, 89, 91–93].

6.3. Kidney Transplantation. Kidney transplantation and particularly preservation time characterized WI and CS combination leading to IRI (Figure 3). In this setting, translation of experimental findings into effective interventions in human situation requires preclinical studies using an adapted model of large animal. The pig is highly useful to reach this goal because of important similarity between human and pig kidney [19].

6.3.1. Renal Failure and Transplantation. Kidney transplantation is the treatment of choice for end-stage renal failure.

The growing demand of kidney graft for transplantation leads transplantation centres to consider others sources of donor organs. The use of expanded criteria donors, deceased after cardiac arrest donors or donors with acute renal failure has been proposed to limit the organ shortage, especially for kidney [94]. Kidneys from donors with acute renal failure are exposed to additional time of WI followed by the conventional CS period. The grafts from such donors exhibit higher rates of DGF and PNF which are the main barriers to use safely these grafts [95]. The ideal transplant model should replicate these clinical conditions mimicking human surgery, graft rejection, response to immunosuppressors, and functional recovery.

6.3.2. Autotransplantation. Fifteen years ago, we have developed an auto-transplant model using Large White male pigs weighing 30–35 kg, which were prepared as described previously in accordance with the French guidelines of the Ethical Committee for Human and Animal Studies [91, 96, 97]. Briefly, the right kidney is harvested, cold flushed with approximately 400 mL of preservation solution, and preserved for 24 h at 4°C immersed in the solution. The left kidney is removed during the transplantation surgery to mimic the nephron mass in the clinical transplanted situation.

We have validated several markers in the pig model of renal autotransplantation using histological tools, ^{1}H-NMR spectroscopy and different biochemical analyses [98–100]. This model is interesting for relevant evaluations of IRI, inflammation and preservation solution effect [100]. From this preclinical model, we developed a new preservation solution now routinely used in clinic [101]. In addition, different drugs were tested with interesting results and clinical studies will be launched [91, 101–105]. This model was used also to assess the interstitial fibrosis and tubular atrophy development after 3- to 4-month followups and protocol biopsies offer new possibilities to predict kidney graft outcome [106]. For ten years, we have developed this approach to study fibrosis development (using red Sirius staining) and inflammatory cells infiltration [97, 107]. We have outlined, in this autotransplantation model, the role of CD4 positive cells, monocytes/macrophages and the proper effect of cold preservation. Such animal model is

interesting because renal biopsy data bring information on the pathophysiology development. This clinically relevant model of autotransplantation offers the possibility to study various aspects related to kidney preservation without the interference of an allogenic immune response. Several authors have used such model in renal transplantation. Other groups have reported the utility of these models and confirm their interests in preclinical testing of novel surgical procedures that mitigate harmful effect of renal ischemia [74, 93, 108–113].

6.3.3. Allotransplantation. In this model, we have adapted the auto-transplantation condition to allograft matching. Analysis of preoperative blood samples ensure compatibility for swine leucocyte antigen (SLA) class I. The microsatellite technique was used to ensure less than 10 per cent recombination for the class II SLA, permitting graft survival with low-grade acute rejection without immunosuppression [114–116]. For this model, recipients' right kidneys were removed and the donor graft was implanted by end-to-side anastomosis on the aorta and inferior vena cava. The left kidney was removed to mimic the nephron mass in the transplanted situation. Using this model, we have determined the effect of polyethylene glycol polymers on graft recovery [117]. In addition, we have completed inflammatory studies with an evaluation of cell infiltration and tubulo-interstitial fibrosis.

6.3.4. Impact of Immature versus Mature Animals on Kidney Function. Nephrology studies, using human markers of renal function such as 24-h diuresis, creatinemia, or proteinuria, are performed either in young large pigs weighing between 20 to 35 kg [118–122] or in more mature animals: >35 kg [72, 73, 97, 123, 124].

As mentioned before, the large size of pigs implies that young adults are mostly used for kidney transplantation experiments. The use of young animal could impact the results obtained and their extrapolation to the human situation. Indeed, immature kidney could have better regenerative capacities in response to injury. This hypothesis underlines a potential low rate of PNF and DGF in young pigs in contrast to mature animals and supports the young pig model to investigate the renal reparation processes. In term of immunity function, young animals are usually protected from immune challenge [4]. For these reasons the data obtained in young animals have to be confirmed in mature pigs [4]. For instance, in our laboratory, porcine kidney graft is performed in 3-month-old pigs and the followup is around 3 to 6 months. On the other hand, for long-term studies, mature animals allow to investigate the real impact of injury in adult kidneys [4].

The limit of large pig model is mainly due to the large animal size compensated by the use of young animals with immature kidneys. Minipig will be the model of choice to evaluate the influence of kidney maturity.

6.3.5. Renal Chronic Damage and Ischemia-Reperfusion Injury. The majority of research in this field has been performed in small animal models, but extrapolation of data obtained in rodents to humans is difficult [28]. Large animal models are useful for long-term studies of IRI particularly in the context of transplantation. Preferably, the response of the kidney to IRI needs to be also studied in a model closer to humans. The pig is the ideal species to serve this purpose [28]. In different renal ischemic conditions, in pig we have analyzed the role of IRI in tubule interstitial fibrosis development at three months post-transplantation [87, 88, 92, 96, 101, 102, 105, 125–130].

6.4. Marginal Donor Models and Donation after Cardiac Death Models. The demand for kidney transplantation has increased dramatically in the past few years. The critical shortage of organs has led to alternative strategies to expand the donor pool. The use of kidneys from expanded criteria or marginal donors (ECDs) represents an option to reduce the disparity between organ supply and demand. All donors aged over 60, and donors aged 50–59 with at least two of three additional risk factors were considered marginal. The three additional risk factors identified were cerebrovascular accident as a cause of death, history of hypertension, and serum creatinine above 1.5 mg/dL prior to transplantation. This definition of ECD has now been validated by a consensus meeting organized by the American Society of Transplantation in Crystal City which has developed guidelines for the management of marginal kidneys [131]. In addition, to improve the stratification and the identification of deceased donor kidneys with an increased risk of early graft dysfunction and graft loss, Nyberg et al. designed another scoring system, the Deceased Donor Score (DDS) [132]. There are seven donor variables significantly influencing the creatinine clearance of recipients at 6 months: age, creatinine clearance, history of hypertension, Human Leucocyte Antigen (HLA) mismatch, cause of death, ethnicity and cold ischemia time (for review see [133]).

Organ donation after cessation of cardiac pump activity is referred to as nonheart-beating organ donation (NHBOD) or donation after cardiac death (DCD). This condition is one of the strategies that have been implemented in order to face organ shortage. DCD is internationally considered to be an encouraging source of organs for transplantation. However, physicians are reluctant to use such organs because they have a high risk of DGF and PNF.

There is room for experimental studies in these fields and particularly for large animal models. Several recent studies have shown that promising protocols could be used in the clinical situation [92, 102, 103, 120, 126]. More recently, new protocols have been evaluated and the use of normothermic venoarterial extracorporeal membrane oxygenation support seems an interesting alternative [80]. Further experimental studies are warranted to clarify the effect of such protocols.

7. Metabolic Diseases Models

It could be of great interest to develop marginal donor models with experimental situation mimicking human pathologies. Several experimental models have enhanced

understanding of atherothrombosis pathophysiology and have played a major role in the search for adequate therapeutic interventions [134, 135]. Various animal models have been developed to simulate thrombosis and to study *in vivo* parameters related to hemodynamics and rheology changes that lead to thrombogenesis [136–140]. Other models could be also associated with metabolic situations such as reduced nephronic mass model [141]. Disease progression in pigs share similarities with the human aspect such as obesity, diabetes, dyslipidemia or atherosclerosis and hypertension [142–148]. The swine can be used in studies of renal hypertension such as a model of deoxycorticosterone salt-induced hypertension or renin-induced hypertension [149].

8. Other Models

Large animal models have been also used to study the effects of brain death [150, 151]. Such models are of interest to characterize and clarify a major stage before organ collection associated with the inflammatory and cytokines "storm" which has deleterious effects on organ quality.

9. Future Approachs

The swine have served as an important model for human biology [3]. This model requires a greater international interest and new tools are rapidly developing.

9.1. Genetically Modified Pig. Genetically modified pigs are now available in experimentation. Production of transgenic pigs for xenotransplantation started 15 years ago [152]. The first reported transgenic modifications of swine involved introduction of human complement-regulatory proteins (CRPs) as transgenes into outbred swine. The most human CRPs transgenic pig models have been hDAF [153], hCD46 [154] and hCD59 [155].

In addition, another pig model was isolated at the end of the nineties. This model presents a spontaneous mutation of the low density lipoprotein receptor gene associated with recessive familial hypercholesterolemia in swine (FHD pig) [156]. Because anti-Gal antibodies were considered to be the major cause of humoral rejection in pig-to-primate kidney Xenotransplantation, an alpha1,3 galactosyltransferase knockout (GalT-KO) pig was developed [157, 158].

9.2. Xenotransplantation. Xenotransplantation represents an immense potential to solve the critical graft shortage and could be a new source of organs, tissues and cells for clinical transplantation [152, 158–162]. Pigs are considered the ideal donor for kidney transplantation to human recipients [44]. In order to generate the necessary data to allow xenotransplantation to progress towards its initial clinical phase, the European Union has created XENOME, a European Commission-funded multidisciplinary effort. Xenome is an integrated project in the European Sixth Framework Programme (Life Sciences, Genomics and Biotechnology for Health).

9.3. Stem Cells. Embryonic stem cells (ESCs) represent a promising tool for cell therapy, regenerative medicine and tissue repair. Assessment of ESC capacities in species other than the mouse is an ongoing topic of interest and is crucial to allow a rapid transfer to clinical applications. A recent review place the pig among the best models for preclinical development [163]. Pig is a particularly desirable species to create pluripotent cell lines because of its value as a biomedical model in transplantation at a time when the safety of ESC use needs to be evaluated in large animal models before human application [164–166].

10. Conclusion

Although the major part of studies in the field of ischemia-reperfusion has been performed in rodent models, but the pig is becoming the model of choice for preclinical studies [28]. The rodent model is cheaper and easier to manage in the laboratory, however, the studies are limited because of a difficult data extrapolation to human mainly due to kidney anatomical differences between these two species. The large swine model is a valuable model for renal transplantation, with anesthesia and surgical processes very similar to the human conditions offering a good training model for surgery students. In addition, surgery team can evaluate new potential of kidney donor models like DCD and assess new preservation techniques adapted to human like kidney machine perfusion. Pig is one of the rare species which is characterized by a human-like renal anatomic structure with multipapillary and multilobular kidneys. However, the pig size is the main limit of this model, requiring adapted area, expensive food, drugs and surgical materials. Minipigs could be used in parallel for long-term studies with an adult weight around 60 kg. The advantages of rodent models like gene knockout or genetic manipulations is now applicable in pigs offering new perspectives for preclinical studies. Embryonic stem cells therapy already investigated in rodents will soon be tested in pigs to show its clinical interest for kidney graft injuries therapy.

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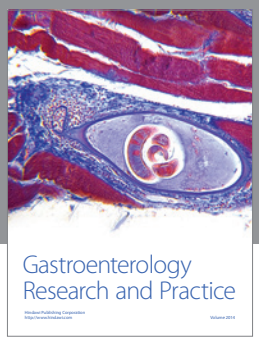

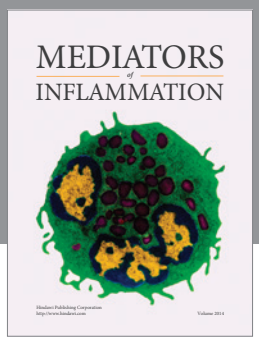

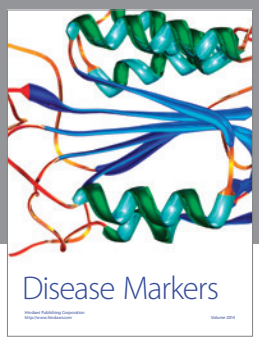

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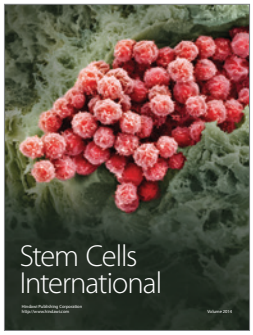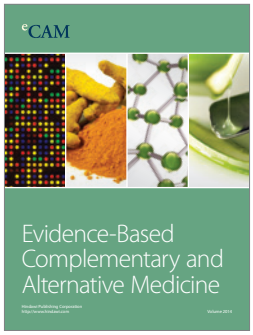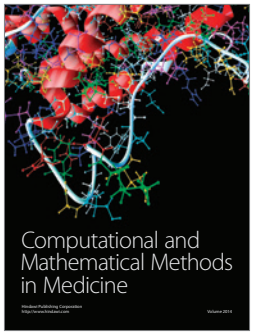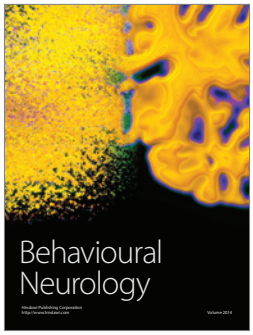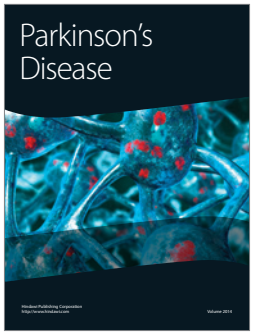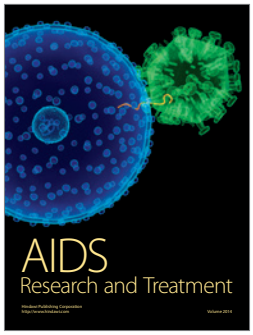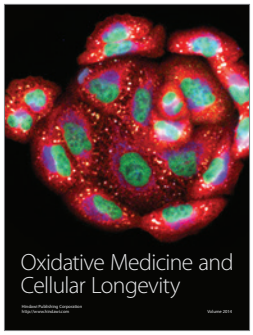
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