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Operational Tolerance after Renal Transplantation in the Regenerative Medicine Era

Giuseppe Orlando¹, Pierpaolo Di Cocco², Lauren Corona³, Tommaso Maria Manzia⁴, Katia Clemente², Antonio Famulari² and Francesco Pisani²

¹*Nuffield Department of Surgery, University of Oxford,*

²*Renal Failure and Transplant Surgery, Department of Surgery, University of L'Aquila*

³*Wayne State University School of Medicine,*

⁴*Transplant Surgery, Tor Vergata University of Rome,*

¹UK

³USA

^{2,4}Italy

1. Introduction

An immunosuppression [IS]-free state is the ultimate goal to achieve in solid organ transplantation [SOT] because IS-related toxicity tremendously impact on overall clinical outcome [Orlando, Hematti et al., 2010]. The IS-free state substantiates into what is referred to as clinical operational tolerance [COT], defined as the condition in which a SOT recipient retains stable graft function and lacks histological signs of rejection, after having been completely off all IS for at least 1 year. The patient in question is an immunocompetent host capable of responding to other immune challenges, including infections or transplantation of organs from third party donors [Orlando, Hematti et al., 2010; Orlando et al., 2008]. However, experimental and clinical information collected so far show that COT is extremely difficult to achieve and is organ-dependent. In fact, the majority of cases of COT reported so far relate to liver graft recipients, in reason of the well known immune-privileged status of the liver determined by factors that remain obscure.

In this chapter, we will provide evidence that the achievement of COT after RT remains exceptional and that tolerogenic strategies are not yet available for daily clinical practice. To do so, we will illustrate and discuss the most relevant cases of COT described so far in the English literature. However, by briefly touching the recent outstanding progress achieved in regenerative medicine, we will bring the attention of the reader on the fact that regenerative medicine may offer a valuable approach to generate immediate, stable and durable COT in SOT recipients.

2. Classification

Several classifications have been proposed to categorize all strategies proposed so far to induce COT in RT recipients [Fehr & Sykes, 2004; Orlando et al, 2008; Orlando, Hematti et

al, 2010]. Nevertheless, given the interest and enthusiasm generated by recent investigations in the field of stem cell biology, we believe that so-called tolerogenic strategies – namely, protocols implemented to induce COT – may be divided into two new groups, cell-based and non-cell-based, according to whether or not stem cell strains showing some immunomodulatory effect *in vitro* are administered in the preoperative period in addition to standard IS.

2.1 Cell-based approach

2.1.1 Metachronous bone-marrow transplant for hematologic disorders

Bone marrow transplantation [BMT], results in the total replacement of the recipient's bone marrow by the donor's bone marrow hematopoietic cells, a condition referred to as full chimerism [Delis et al, 2004]. If the patient receives an organ from the same bone marrow donor late after BMT, then the reconstituted white cell compartment may recognize the new organ as self; theoretically, no response will be mounted by the host immune system and the new graft will be tolerated without need for any IS. However, despite several cases of BMT plus solid organ transplants [RT included] have been reported [Butcher et al, 1999; Chiang & Lazarus, 2003; Helg et al, 1994; Jacobsen et al, 1994; Light et al, 2002; Sayegh et al, 1991; Sellers et al, 2001; Sorof et al, 1995], yet COT has been an exceptional finding. Importantly, according to what reported by all series, COT developed in patients in which the transplant was performed several years after BMT, but never where BMT and RT were performed simultaneously.

2.1.2 Perioperative infusion of HSC

Somehow, the above reported data conflicted with what described in mice by Monaco and Wood, namely that the addition of donor bone marrow to a strong lymphocyte depleting regimen may result in the long-lasting survival of skin allografts from the same donor, without any maintenance IS [Monaco et al, 1970; Monaco et al, 1976; Monaco et al, 1985]. These experimental findings represented the platform for translational investigations aimed to prove that the perioperative infusion of donor-derived bone marrow cells can prolong allograft survival [Sykes, 2009]. The group at Massachusetts General Hospital adopted such strategy in 7 adult patients with renal failure due to multiple myeloma, who received combined human leukocyte antigen [HLA]-matched kidney and bone marrow transplant after a non-myeloablative conditioning regimen consisting of cyclophosphamide, antithymocyte globulin, and pretransplant thymic irradiation [Buhler et al, 2002; Fudaba et al, 2006; Spitzer et al, 1999; Spitzer et al, 2011]. Maintenance IS consisted of cyclosporine which was discontinued as early as day 73 post-transplant. Patients were followed for a mean of 7.4 (range 4-12) years. Two of them died for relapse of the baseline disease and therapy-related acute myeloid leukemia after 7.7 and 4.2 years, respectively; noteworthy, both were IS-free at the time of death. Of the 5 patients who are still alive [4 of whom with no evidence of myeloma recurrence], 3 are IS-free, and show serum creatinine levels of 0.63, 1.14 and 1.7 mg/dL, respectively. The remaining 2 individuals are receiving either prednisone or tacrolimus for graft-versus-host disease [but no rejection!], and present serum creatinine levels of 0.9 and 1.42 mg/dL.

More recently, the same group reported the short-term results of a seminal trial in which non-cancer patients received renal grafts and bone marrow from HLA haploidentical donors following nonmyeloablative conditioning to induce renal allograft tolerance [Kawai et al,

2008; Porcheray et al, 2009]. Even in this case, cyclosporine was the only immunosuppressant used for maintenance therapy. IS could be successfully weaned in 4 out of 5 patients, whereas the remaining patient experienced acute rejection and lost his graft. Cyclosporine could be withdrawn after 294 (range 240-272) days. However, matters of concern are represented by two major findings. First, the reported most recent mean creatinine clearance (67 ml/min, range 60-75) and serum creatinine levels (1.5 mg/dl, range 1.2-1.8) levels in the 4 IS-free patients were slightly abnormal. Second, 2 of these patients have shown evidence of *de novo* antibodies reactive to donor antigens between 1 and 2 years after the transplant [Porcheray et al, 2009]. Overall, this series demonstrates that B-cell immunity can occur in the context of T-cell tolerance to donor antigens through unknown mechanisms, otherwise said T-cell unresponsiveness is not synonymous of tolerance of both arms of the adaptive immune system. This is consistent with information reported by Nantes. Souillou et al. extensively studied IS-free RT recipients [Ashton-Chess et al., 2007; Baeten et al., 2006; Ballet et al., 2006; Brouard et al., 2005; Louis et al., 2006; Roussey-Kesler et al., 2006;] and found that COT may occur in the presence of anti-donor class II antibodies, as well as in patients who have previously experienced acute rejection. Moreover, they showed that IS-free RT recipients are more likely to have received grafts from donors younger than 30 years of age, are low-responders to blood transfusion, may develop graft dysfunction at any time after the weaning of IS, and show an incidence of infectious diseases comparable to that in normal individuals.

The Stanford group has implemented a similar strategy in two distinct small series, where patients received a renal graft followed by the infusion of HSC from the same HLA-mismatched (x4) or -matched (x6) donors, respectively [Millan et al., 2002; Scandling et al., 2008]. IS consisted of induction with total lymphoid irradiation and rabbit anti-thymocyte globulin, followed by cyclosporine and prednisone as maintenance therapy. After steroid discontinuation on day 10, mycophenolate mofetil was introduced and administered for 1 month. Intravenous injection of HSC was repeated during the third postoperative week. Results were poor. In the first trial, only one patient could be weaned off IS, while however showing slightly elevated serum creatinine levels (1.4 mg/dL). In the second trial, one individual could be weaned off IS but renal function tests are not shown. Two further patients rejected, while the remaining 3 were still under weaning at the time of publication.

Overall, based on the reported information, the above series show the lack of safety of hematopoietic stem cell-based regimens. Despite this approach may allow minimization of overall IS, however further studies are required to improve safety and effectiveness. Importantly, most of the IS-free patients reported above do not comply with the stringent criteria for COT adopted in the present chapter.

2.1.3 Perioperative infusion of alternative types of immunomodulatory cells

Transplant-acceptance-inducing cells (TAIC) are immunoregulatory macrophages which have shown some capacity of establishing a state of alloantigen-specific partial tolerance of solid organ transplants in renal transplant recipients [Hutchinson, Brem-Exner et al., 2008; Hutchinson, Riquelme et al., 2008; Riquelme P et al., 2009]. TAIC's presumed tolerogenic properties have been tested in two safety trials differing in the method for TAIC preparation, numbers of cells infused, induction IS, and timing of infusions. None of the 17 patients enrolled in either study could be weaned off IS, most of them rejected, 2 dropped out the study for non-immunological causes, while only 2 individuals did well yet under

tacrolimus monotherapy at the end of the study. Overall, although these trials demonstrated that the infusion of TAIC is feasible, major concerns remain regarding the efficacy and safety of such an approach. It is unclear whether or not this approach confers any benefit in the establishment of minimal IS in RT patients when compared to the protocols currently adopted, as clearly stated by authors in the discussion. Lastly, the optimal dose and timing of cell infusions, as well as the most appropriate concomitant IS regimen, is yet to be determined.

For their ability for tissue repair and immunomodulation, mesenchymal stem cells (MSCs) are currently being evaluated for a wide variety of clinical applications including the treatment of disorders characterized by a dysfunction of immune regulation, such as graft versus host disease after bone marrow transplantation and rejection after cell or organ transplantation [Crop et al., 2009; Ding et al., 2009; Hematti, 2008; Le Blanc et al., 2008; Le Blanc & Ringden, 2007]. As MSCs seem to be able to promote engraftment of allogeneic cells, tissues and organs, as well as to prevent or treat rejection in pre-clinical models, they provide an exciting opportunity for further research in the field of IS minimization and withdrawal in SOT [Hematti, 2008; Hoogduijn MJ et al., 2010].

It is worth to mention that, in addition to stem cells, the therapeutic properties of various other immune cells like regulatory T cells or dendritic cells are currently being explored for SOT purposes [Issa, Hester et al., 2010; Issa, Schiopu et al., 2010; Orlando, Hematti et al., 2010].

2.2 Non cell-based protocols

2.2.1 Non-adherence to IS

The majority of cases of COT described so far after RT is represented by patients who spontaneously decided to stop IS for non-compliance to treatment [Ashton-Chess et al., 2007; Baeten et al., 2006; Ballet et al., 2006; Brouard et al., 2005; Hussey, 1975; Louis et al., 2006; Najarian, 1975; Newell et al., 2010; Owens et al., 1975; Roussey-Kesler et al., 2006; Sagoo et al., 2010; Uehling et al., 1976; Zoller et al., 1980]. These patients have been the object of numerous investigations conducted at different times by diverse authors with methods presenting dissimilar accuracy. However, we believe that it is worth to report the investigations by Burlingham et al. In an attempt to identify patients who may be weaned off IS at no risk, he recurred to the human-to-mouse trans-vivo delayed-type hypersensitivity assay [Geissler et al., 2001; VanBuskirk et al., 2000]. By observing that 2 renal allograft recipients failed to exhibit donor-reactive delayed type hypersensitivity responses, although they frequently develop donor-reactive alloantibodies, the authors demonstrated that this pattern of immune responses is not due to an absence of allosensitization, but to the development of an immune mechanism that actively inhibits anti-donor delayed-type (i.e., cell-mediated) immune responses. In other words, authors provided evidence that COT develops following the onset of regulatory, rather than suppressing mechanisms.

Of interest is the case of spontaneous interruption of IS by a 24-year old woman who had received a deceased donor RT at the age of 13 for membranoproliferative glomerulonephritis. When the woman found out to be pregnant, she stopped all IS to protect the fetus from any possible IS-induced teratogenic effect [Fischer et al., 1996]. Interestingly, she did not resume any IS after delivery, and no immunological response was observed for 9 years after the withdrawal of IS, while the patient was showing perfectly normal renal function tests.

2.2.2 Molecule-based tolerogenic protocols

A molecule-based tolerogenic regimen was implemented by Starzl a decade ago [Starzl et al., 2003]. The working hypothesis was that the need for continual high dose IS could be avoided in most cases with the use of a strong lymphocyte-depleting regimen prior to engraftment, followed by the administration of low dose tacrolimus monotherapy. The rationale was to remove the non-specific clones of immune cells responsible for rejection before contact with foreign donor antigens occurs. Once the donor antigens are in place after implantation of the new organ, repletion of immune cells occurs, favored by the homeostatic expansion triggered by leukocyte depletion. In addition, minimization of maintenance IS was implemented to further reduce the anti-donor response with just enough treatment to prevent irreversible immune damage to the graft, but not with such heavy treatment that the donor-specific clonal exhaustion-deletion process is precluded.

Broadly reacting rabbit antithymocyte globulins were administered preoperatively, followed by tacrolimus monotherapy, to 82 adult kidney, liver, pancreas, and intestinal transplant recipients. After a mean follow-up time of 18-months, 1-year patient and graft survival rates were 95% and 82% overall, respectively, IS-related morbidity was virtually eliminated, and 48/72 surviving patients were receiving spaced doses of tacrolimus monotherapy. Noteworthy, 25/39 (64%) renal, 12/17 (70%) liver, 5/12 (42%) pancreas, as well as 6/11 (54%) intestinal transplant recipients, resulted on tacrolimus spaced doses at the time of publication. However, IS could not be weaned off in any patient. Other protocols based on a similar strategy – i.e., leukocyte depletion followed by the administration of low dose single-drug IS - have been implemented after RT [Agarwal et al., 2008; Calne et al., 2000; Calne et al., 1999; Calne et al., 1998; Ciancio & Burke, 2008; Clatworthy et al., 2009; Kirk et al., 2003; Kirk et al., 2005; Orlando, Hematti et al., 2010; Trzonkowski et al., 2006; Trzonkowski et al., 2008; Watson et al., 2005] and liver, the organ most capable of developing COT, transplantation [Eason et al., 2005]. However, none of these protocols has proved effective or safe in producing COT nor has they shown any convincing impact on overall outcomes.

2.2.3 Total lymphoid irradiation

Three cases of COT have been described in RT recipients subjected to total lymphoid irradiation, a perioperative course of antithymocyte globulin, and maintenance prednisone that was gradually weaned and eventually stopped [Strober et al., 1989; Strober et al., 2000; Strober et al., 2004]. Two patients remained IS-free for 12 years and 69 months, while the third developed severe urinary tract obstruction 10 months after the IS withdrawal, for which he was eventually retransplanted. Importantly, the complete original series comprised 28 RT recipients, 25 of whom did not develop COT.

2.2.4 COT developed after intentional IS withdrawal for lymphoproliferative disorders

Two cases of COT developing after the intentional withdrawal of IS due to the development of post transplant lymphoproliferative disorders (PTLD) have been described, mainly within a larger series [Roussey-Kesler et al., 2006]. A third case relates to a 21-year-old man who received 2 haplo-identical RTs, the first at age 11 from his mother and the second at age 15 from his father [Christensen et al., 1998]. Three years after the second RT, he developed PTLD. IS was promptly interrupted and the PTLD subsequently resolved. At the time of publication, IS had been withdrawn for 3 years with no rejection.

Classification	Subtype	Center	Type of study	Claimed cases of COT	Length of follow up from the time of the withdrawal of the IS
Cell-based	Previous BMT	Boston, Brigham and Women Hospital [Sayegh et al, 1991]	Case report	2*	7 and 3 years
		Geneva [Helg et al, 1994]	Case report	1	2 years
		Copenhagen [Jacobsen et al, 1994]	Case report	1	1 year
		San Francisco [Sorof et al, 1995]	Case report	1	2 year
		Milwaukee [Bucther et al, 1999]	Case report	3	3, 11, 18 years
		Birmingham, US [Sellers et al, 2001]	Case report	1	7
	HSC	Boston, Massachussetts General Hospital [Spitzer et al, 1999; Buhler et al, 2002; Fudaba et al, 2006; Spitzer et al, 2011]	Prospective, non comparative	3/6	12.1, 7.7, 4, 6.8 years
		Boston, Massachussetts General Hospital [Kawai et al, 2008; Porcheray et al, 2009]	Prospective, non comparative	4/5	4.6, 3.4, 2.2 and 1.2 years
		Stanford [Millan et al, 2002]	Prospective, non comparative	1/4	14 years
		Stanford [Scandling et al, 2008]	Prospective, non comparative	1/3	28 months

Classification	Subtype	Center	Type of study	Claimed cases of COT	Length of follow up from the time of the withdrawal of the IS
Non cell-based	TACI	Miami [Ciancio et al, 2004]	Prospective, non randomized, comparative	0/63	-
		Kiel [Hutchinson et al, 2008]	Prospective, non comparative	0/12	-
		Kiel [Hutchinson et al, 2008]	Prospective, non comparative	0/5	-
	Non-adherence to IS	Columbus-Madison [VanBuskirk et al, 2000; Geissler et al, 2001]	Case report	3	3 years
		Madison [Uehling et al, 1976]	Case report	5, but 4 rejected after few months	5 years
		Los Angeles [Owens et al, 1975]	Case report	4, but eventually 1 rejected after 18 months	17, 23, 52 months
		Minneapolis [Najarian, 1975]	Case report	6, but 5 rejected after few months	NA
		Madison [Hussey, 1975]	Case report	8, but 7 rejected after few months	40
	TBI	Stanford [Strober et al, 1989; Strober et al, 2000]	Prospective	3/28, but 1 rejected after 10 months for non-immunological reasons	144 and 69 months
	Pregnancy	Erlangen-Munster [Fischer et al, 1996]	Case report	1	9 years

Classification	Subtype	Center	Type of study	Claimed cases of COT	Length of follow up from the time of the withdrawal of the IS
	PTLD	Aarhus [Christensen et al, 1998]	Case report	1	>3 years
	Molecule-based	Pittsburgh [Starzl et al, 2003]	Prospective, non comparative	0/39	-
		Cambridge [Clatworthy et al, 2009; Watson et al, 2005; Calne et al, 2000; Calne et al, 1999; Calne et al, 1998]	Prospective, comparative, non randomized	0/33	-
		Oxford [Trzonkoski et al, 2008]	Prospective, non comparative	0/13	-
		Bethesda [Kirk et al, 2003]	Prospective, non comparative	0/7	-
		Bethesda [Kirk et al, 2005]	Prospective, non comparative	0/5	-
	Surveys	Boston [Zoller et al, 1980]	Descriptive, observational	13	>1 year
		Nantes [Roussey-Kesler et al, 2006]	Descriptive, investigative	10, but 2 rejected after 7 and 13 years	9 years [mean time, range 1-20]
		Nantes [Braud et al, 2008; Sivozhelezov et al, 2008]	Descriptive, investigative	8	>1 year
		Nantes [Bouard et al, 2007]	Descriptive, investigative	17	>1 year
		Los Angeles [Owens et al, 1975]	Descriptive, observational	24, but 22 rejected after few months	9, 36 months

Classification	Subtype	Center	Type of study	Claimed cases of COT	Length of follow up from the time of the withdrawal of the IS
		European Consortium for tolerance [Sagoo et al, 2010]	Descriptive, investigative	11	>1 year
		American network for immune tolerance [Newell et al, 2010]	Descriptive, investigative	25	>1 year

Table 1. Synoptic view of all successful and unsuccessful cases of COT described after RT. The mismatch between the number of cases claimed by numerous authors and the real effectice number of COT calculated according to the definition of COT adopted in the present manuscript is evident [116 vs. 108, respectively].

3. Immune monitoring

As illustrated above, most cases of COT have developed in individuals who have spontaneously terminated IS. When all clinical trials in which a presumed tolerogenic protocol has been implemented are taken into consideration, it is frustrating to observe that COT could be obtained in only 6 out of 248 patients, accounting for a poor, unacceptable success rate of 2.5% [Orlando, Hematti et al , 2010]. As a corollary, the tolerogenic regimens attempted so far in RT recipients are not efficient and, more importantly, lack safety. Ideally, before implementing any of such regimens, investigators should rely on parameters able to predict with high accuracy whether patients would tolerate the weaning process without any risk to reject. Unfortunately, no parameter as such is available for routine practice, not even renal biopsy. For example, Burlingham reported on a late graft rejection in a patient who received a RT 9.5 years earlier from his mother and who had been IS-free for 7 years; a gradual rise in serum creatinine level to 2.0 mg/dl prompted a biopsy that ruled out rejection, yet 10 months later severe cellular rejection arose [Burlingham et al., 2000]. Investigators have obtained promising results in the field of liver transplantation where this problem has been circumvented by the identification of so-called markers of tolerance [Martinez-Llordella et al., 2008; Martinez-Llordella et al., 2007], defined as functional and molecular correlates of immune reactivity whose purpose is to provide clinically useful information for therapeutic decision-making in view of IS withdrawal [Ashton-Chess et al., 2009]. Investigations in tolerant liver transplant recipients resulted in the discovery and validation of a tolerance-associated transcriptional patterns, consisting of several gene signatures and multiple peripheral blood lymphocyte subsets capable of identifying tolerant and non-tolerant recipients with high accuracy. As these data suggested that transcriptional profiling of peripheral blood can be employed to identify recipients who can discontinue immunosuppressive therapy at no risk for rejection, RT researchers are currently exploring a

signature of COT after RT which may allow the selection of those patients who may be more prone to develop an IS-free state with no or quasi no risk for rejection.

The group in Nantes has pioneered investigations aimed to the identification of specific biological signatures of COT [Braud et al., 2008; Brouard et al., 2007; Sivozhelezov et al., 2008]. Brouard et al. identified a set of 49 genes and differentially expressed gene transcripts using gene-expression profiling of peripheral blood from 17 tolerant RT recipients, with tolerance class prediction scores of >90% [Brouard et al., 2007]. This fingerprint is expected to identify patients who might be eligible for a progressive tapering of their immunosuppressive medications and, more importantly, those who instead need to stay on their current IS regimen. The same group has also exploited the capabilities of high throughput microarray technology to study peripheral blood specific gene expression profiles and corresponding molecular pathways associated with operational tolerance [Braud et al., 2008; Sivozhelezov et al., 2008]. Investigations revealed that tolerant patients display a set of 343 differentially expressed genes, mainly immune and defense genes, in their peripheral blood mononuclear cells (PBMC), of which 223 were also different from healthy volunteers. Using the expression pattern of these 343 genes, they were able to correctly classify >80% of the patients in a cross-validation analysis and correctly identified all of the samples over time. All together, this study identified a unique PBMC gene signature associated with human operational tolerance in kidney transplantation [Orlando, Hematti et al., 2010].

Investigations have been conducted in parallel in Europe and the United States. The European Union Indices of Tolerance Network showed that IS-free RT patients present a distinctive expansion of peripheral blood B lymphocytes and natural killer cells and differential expression of several immune-relevant genes in the absence of donor-specific antibodies [Sagoo et al., 2010]. Similar population expansion of B immune cells and selective expression of B cell-related genes in samples obtained from tolerant individuals were noted by the National Institute of Health's Immune Tolerance Network [Newell et al., 2010].

4. The potential of regenerative medicine

The term regenerative medicine refers to that field in the health sciences which aims to replace or regenerate *human cells, tissues, or organs in order to restore or establish normal function* [Mason & Dunnill, 2008; Orlando, Baptista et al., 2010; Orlando et al., 2011]. The process of regenerating body parts can occur *in vivo* or *ex vivo* and may require cells, natural or artificial scaffolding materials, growth factors, or different combinations of all three elements. Instead, the term tissue engineering refers to a field which is narrower in scope and strictly limited to the production of body parts *ex vivo*, by seeding cells either on or into a supporting scaffold [Orlando et al., 2011].

In the last decade, investigators in the field have been able to produce and implant in patients relatively simple hollow organs like skin [Naughton et al., 1999], vessels [Hibino et al., 2010; L'Heureux N et al., 2007; McAllister et al., 2009; Shinoka et al., 2001; Shinoka et al., 2005;], bladders [Atala et al., 2006], windpipes [Macchiarini et al., 2008] and urethras [Raya-Rivera et al., 2011]. Importantly, all constructs were manufactured by either combining autologous cells with scaffolding material, or through the engineering of autologous cells *per se* [Orlando, Baptista et al., 2010; Orlando et al., 2011]. Importantly, none of the patients did require IS at any time after implantation of the bioengineered body part. Therefore,

regenerative medicine has shown the potential to offer a valuable approach to COT. Importantly, as the above mentioned implanted body parts were bioengineered from autologous cells, recipients never required IS and therefore we can conclude that regenerative medicine offers the only possible approach to immediate, stable and durable COT. In fact, as illustrated throughout the whole chapter, all cases of COT reported so far in the English literature developed at least several weeks after the transplants and always required some IS, the exception being RT between identical twins [Orlando, Hematti et al., 2010]. Moreover, in several circumstances, patients who could be weaned off IS eventually rejected and required resumption of IS.

Bioengineering technology has been implemented to manufacture heart [Ott et al., 2008], liver [Badylak et al., 2011; Baptista et al., 2011; Uydun et al., 2010;] and lung [Ott et al., 2010; Petersen et al., 2010;] organoids from rodent organs [Orlando, Baptista et al., 2010; Orlando et al., 2011]. *In extenso*, rat or ferret organs were decellularized with detergents and repopulated with cells from unrelated species, humans included. In the ideal scenario, when and if this technology will be perfected, the cellular compartment will be reconstituted – even in this case – from patient's autologous cells, whereas the supporting scaffold will be represented by an acellular porcine or non-human primate organ depleted of its native cells.

5. Conclusions

When all the above information is taken together, it is clear that, although a wealth of knowledge exists, little progress has been made in developing a sure-fire strategy towards attaining COT. Despite tolerance has been widely investigated for decades, efforts to understand the mechanisms underlying this phenomenon and how to achieve it have thus far been to no avail. In addition to the failure of all molecule-based strategies, we have learned that stem cells do exert some modulatory effect on the immune system but we do not know why and how this occurs. Therefore, we cannot predict when the opportunities for COT to develop in a patient the greatest.

As it stands, with the technology that is currently available, the withdrawal of IS after RT cannot yet be encouraged because it is neither effective nor safe and must be considered as still in an experimental phase. Efforts to identify a peripheral blood transcriptional biomarker panel associated with COT after RT are certainly laudable but, provided the safety for the withdrawal of IS is not guaranteed, any clinical implementation should be banned outside specialized cutting-edge center. The lack of safety of all tolerogenic strategies implemented so far remains their major weakness. Recent revolutionary progress in regenerative medicine has revealed the immense potential of the field pertinent to COT. In a foreseeable future, regenerative medicine will meet the two major needs of SOT, namely that of a potentially inexhaustible source of organs and COT itself [Orlando, 2011].

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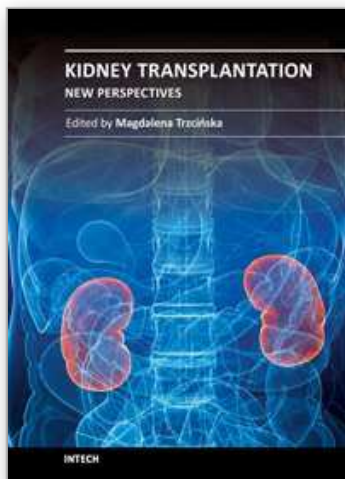
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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and that's why conscious educational efforts are still needed for kidney transplantation, for many people being the only chance for an active lifestyle and improved quality of life, to win common social acceptance and stop triggering negative connotations. Apart from transplantation controversies piling up over years transplantologists also have to face many other medical difficulties. The chapters selected for this book are of high level of content, and the fact that their authors come from many different countries, and sometimes even cultures, has facilitated a comprehensive and interesting approach to the problem of kidney transplantation. The authors cover a wide spectrum of transplant-related topics.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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