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Review

Power to the Tregs in transplantation tolerance in LATAM: From the basics to the bedside☆

Karina Pino-Lagos [a,*], Gloria Soldevila [b,c,**]

[a] Facultad de Medicina, Centro de Investigación e Innovación Biomédica, Universidad de los Andes, Santiago, Chile
[b] Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico
[c] Laboratorio Nacional de Citometría de Flujo, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico

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ABSTRACT

T regulatory cells (Tregs) come in different flavors, but they all share suppressive function and the role in the generation and maintenance of immune tolerance. Due to this essential activity, Tregs are targets for immunotherapy: Tregs promotion is wanted in pathological conditions such as autoimmunity, allergies and transplantation, whereas their elimination is the main goal in the context of cancer. Transplantation is the only treatment available when organ failure is detected but unfortunately transplant rejection has not been fully achieved regardless of all efforts made, such as the identification and use of new immunosuppressant drugs and biological therapies. During the last two decades, Tregs have become a cellular source for therapy to control primarily Graft-versus-Host Disease (GvHD) -in the case of cellular transplantation- and rejection of solid allografts as in liver and kidney transplants. Like in other biomedical disciplines, many advances applying immunological technologies only reach the patients if developed in the north hemisphere, and transplantation is not an exception. Here, we present the contribution of Latin America (LATAM), regarding solid organ transplantation from basic and clinical immunology research, focusing on Tregs as the main topic of study.

1. Introduction

1.1. Transplantation in Latin America and the Caribbean

In 2024, a total of 15,852 transplants were performed considering kidney (11,514), liver (3343), heart (653), lung (161), pancreas (23) and kidney-pancreas (158) as transplanted organs, with Brazil as leading country with the highest numbers of procedures/organ. Regarding donor rates, Uruguay, Argentina and Brazil are the top 3 countries with 19,16; 17,74 and 17,25 donors/per million of inhabitants, respectively [1]. In 2021, a meeting with health authorities/ministers of each country belonging to LATAM and the Caribbean revised several aspects on transplantation, signing agreements to collaborate with access to -updated- information, discussing new laws (for donation and control of organ trafficking) and determining topics to be worked on in the following years. In other scenarios, such as regional and local scientific meetings in Transplantation, the criteria to be considered as organ donor (age, pre-existing medical conditions) is being reevaluated because the general population is aging with no positive numbers on new births; thus, the pool of donors is decreasing without alternative of new sources for the required number of transplants. In addition, the development of new biomedical strategies to monitor the transplant́s status (biomarkers) and others to promote long-lasting transplant acceptance (for the reduction or elimination of immunosuppressive drugs use), such as the implementation of cellular and acellular therapies, are focus of interest since they aim at the growth of personalized medicine, a discipline that seeks the patient's well-being in a controlled way. These advances are the results of research at the basic and applied levels for which LATAM scientists should also be recognized as contributors.

Here, we present advances on the study of T regulatory cells (Tregs),

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* Correspondence to: Facultad de Medicina, Centro de Investigación e Innovación Biomédica, CiiB, Universidad de los Andes, Av. Plaza 2501, Santiago, Las Condes, Chile.
** Correspondence to: Laboratorio Nacional de Citometría de Flujo, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Circuito Escolar S/N, Colonia Copilco, Delegación Coyoacán, Ciudad de México, Mexico.
E-mail addresses: kpino@uandes.cl, karina.p.lagos@gmail.com (K. Pino-Lagos), soldevi@unam.mx, soldevi@iibiomedicas.unam.mx (G. Soldevila).

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a T cell subset that control inflammation and have been described in most -if not all- diseases. Tregs are one the current targets to modulate immunity and control pathological states, including the quest for transplantation tolerance.

1.1.1. Tregs as mediators of immune tolerance

One of the breakthroughs in the understanding of immune tolerance was the contribution of several authors in the identification of a subset of CD4 + T cells as mediators of peripheral T cell tolerance. In 1994, the group of Maria Grazia Roncarolo reported the presence of CD4 + T cells able to produce high levels of IL-10 from a Severe Combined Immunodeficiency (SCID) patient transplanted with fetal liver cells [2]. These cells are currently known as T regulatory cells 1 (Tr1) and have been described in different experimental models and diseases; however, Tr1 cells are less investigated than other Tregs [3]. Sakaguchi and collaborators performed experiments revealing that the transfer of T cells depleted of the CD25 + fraction, and further injected into mice, induced the appearance of autoimmunity signs and even GvHD. In a transplantation setting, the experimental design resulted in enhanced immune response towards the allograft. Importantly, reconstitution with CD4 + CD25 + T cells prevented this heightened immune response [4]. Eight years later, Sakaguchi et al. published the seminal work demonstrating that the transcription factor Forkhead Box Protein 3 (FoxP3) was sufficient to confer regulatory properties to CD4 + T cells as demonstrated *in vivo* in a model of autoimmunity [5]. But the hypothesis of existing cells with suppressive function were proposed much earlier than Sakaguchi's work, from which we can refer to Gershon & Kondo's work from the 70 s [6], and even the transplantation experiments performed by Peter Medawar in the 50 s [7] that were inspired by the findings of Ray D. Owen, who previously reported the lack of immune response -tolerance- between bovine twins from different sires as result of shared circulation during fetal development [8].

1.1.2. Tregs subsets

Central and peripheral tolerance are key to control the immune response towards self and non-self-antigens, thus maintaining immunity in balance and preventing excessive and dangerous immune activity. Central tolerance takes place in the thymus during the ontogeny of T cells and results in the elimination of self-reactive T cells [9]. On the other hand, peripheral tolerance usually controls the reactiveness of the immune responses towards foreign antigens that are not harmful and can be induced and maintained by a variety of mechanisms such as deletion, induction of T cell anergy and differentiation of Tregs [10]. Tregs include different T cell subsets, Fig. 1, capable of inhibiting effector T cell responses through different mechanisms including the production of inhibitory cytokines, cytolysis induction, metabolic disruption, modulation of antigen presenting cells (APC) activity, and the release of small extracellular vesicles. [11–14].

1.2. Thymic or natural Tregs

Thymic or "naturally occurring" Tregs (tTregs) correspond to CD4 + CD25 + T cells that differentiate in the thymus during T cell ontogeny. The acquisition of FoxP3 expression renders high CD25 expression and suppressive functions. The quest for a specific tTregs surface marker that eliminates the necessity to perform intracellular

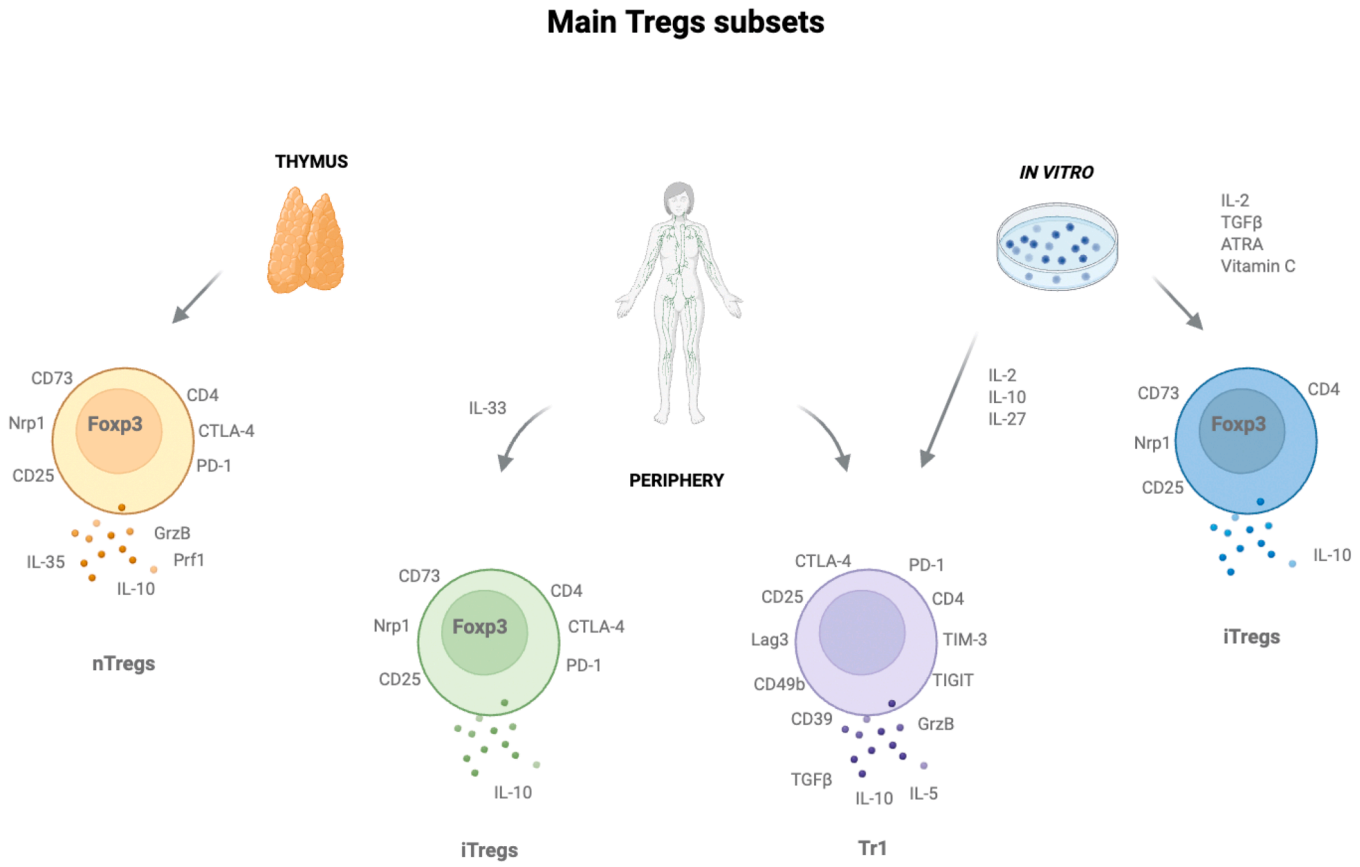


Fig. 1. Main Tregs subsets. Thymic Tregs (tTregs) generate in the thymus and constitutively express FoxP3 and high levels of CD25. Other markers include CD73 and Nrp1, which are also found on iTregs that differentiate in the periphery or *in vitro*. Tr1 cells are CD4 + T cells with suppressive function, they lack FoxP3 but are characterized by high production of IL-10. The main surface markers described for Tr1 cells are LAG-3 and CD49b, although they also express coinhibitor receptors such as CTLA-4, PD-1, CD39, TIM-3 and TIGIT. Tregs can be produced *in vitro* from CD4 + CD25-FoxP3- T cells cultivated in the presence of IL-2 and TGF-β, in addition to other factors that induce Tregs with stable phenotype, such as All-*trans*-Retinoic acid (ATRA) or vitamin C. Created at Biorender.

staining for FoxP3 detection has been active for decades with no good results. This applies to murine and human tTregs. But at least, expression of molecules such as Neuropilin-1 (Nrp1) is linked to tTregs with suppressive function, as demonstrated by the Chilean group led by Dr. Pino-Lagos who has contributed to Tregs biology in the context of Transplantation for more than a decade. This group showed that tTregs expressing Nrp1 can promote skin transplantation acceptance, which was associated with a phenotypic change on conventional CD4 + T cells (Tconv) displaying increased Nrp1 expression only in the presence of Nrp1 + tTregs [15]. These first observations were later investigated using a conditional knock-out approach in which only tTregs lack Nrp1 expression (Nrp1KO tTregs). In this report, Nrp1KO tTregs did not exert suppressive function *in vitro* and *in vivo* they were unable to promote skin transplantation acceptance in mice. Interestingly, Tconv co-cultured with Nrp1 + tTregs gained Nrp1 and Eos expression, and *in vivo* these new Nrp1 + Tconv display suppressive function, suggesting that infectious tolerance may occur in a Nrp1 dependent manner [16]. The role of Nrp1 on tTregs function was then investigated in the production of small extracellular vesicles (sEV), another mechanism that Tregs use to control the immune response. In this context, Dr. Pino-Lagos's team demonstrated that Nrp1 is present on sEV released by tTregs, and that sEV obtained from Nrp1 + tTregs promotes skin transplantation survival [17]. Recent findings indicate that sEV isolated from Tregs cultures are enriched in proteins involved in cell death, supporting other's observation on the cytotoxic function of Tregs [18]. In mice, the availability of transgenic strains permits design *in vivo* experiments to observe whether an increment on Tregs results in tTregs expansion or generation of induced-Tregs (iTregs). This distinction is important because Tregs function stability differs among Tregs subsets. For instance, administration of IL-33 into skin transplanted mice results in graft survival, which associates with higher numbers of Tregs. Using congenic markers and reporter animals, Dr. Pino-Lagos's team demonstrated in a skin transplantation mouse model that IL-33 directly or indirectly- targets CD4 + FoxP3- T cells to become iTregs [17]. They have recently reported that IL-33 causes intestinal dysbiosis and striking changes on intestinal metabolites in mice, highlighting an immune regulatory role for the tryptophan pathway [19, 20]. Apart from the relevance to understand the origin of Tregs found in distinct animal models, the translation of using tTregs as cell therapy to control unwanted inflammatory conditions is indisputable. Several groups have described protocols to isolate and expand human tTregs *in vitro*, identifying factors that could even enhance Tregs function as the inclusion of IL-33 [21]. In fact, some are being used in the US and Europe to obtain Tregs for administration into transplanted patients. In LATAM these efforts are being carried out in Mexico by Dr. Soldevila who leads the development of the first cell therapy using Tregs in the region [22].

1.3. Th3 and induced Tregs

In the early 2000, a population of CD4 + CD25 + T cells that secrete TGF-β and inhibit T cells function and antibody production was described in the context of oral tolerance [23]. Their name was a continuation of the Th0, Th1 and Th2 subsets known at the time, and Th3 was coined as these cells that produced TGF-β as a mechanism of immune regulation. Alternatively, the use of IL-2 and TGF-β was characterized as the main factors required for both human and mouse CD4 + CD25- T cells to become CD4 + CD25 + T cells, upregulating FoxP3 expression and displaying regulatory function in different *in vivo* models including skin transplantation, GvHD, autoimmunity [24–27]. These *in vitro* generated Tregs are referred to as peripheral or iTregs and currently are of great interest because the *in vitro* production for therapeutic purposes yields higher numbers than tTregs expansion. In order to describe iTregs regulatory properties, Dr. Pino-Lagos's team has evaluated the contribution of Nrp1 and the production of sEV, finding that Nrp1 contributes to the expression of FoxP3 and suppressive function of iTregs [18]. Furthermore, a comparison on sEV production by tTregs, iTregs and RATregs (iTregs differentiated in the presence of Retinoic acid or RA) revealed differences on sEV's protein cargo and level of cytotoxicity as potential suppressive mechanism [28]. In addition, it has been reported that tTregs and iTregs differ in their phenotypic stability. In other words, tTregs maintain FoxP3 expression and suppressive activity under activating conditions whereas iTregs are labile and lose the suppressive properties. To overcome this, studies have shown that iTregs cultures supplemented with All-*trans*-Retinoic acid (ATRA) [29] or vitamin C [30, 31] produce iTregs with stable phenotype. Certainly, the search for new molecules that fix Tregs phenotype and function are of current interest. Another limitation is the lack of a marker that permits distinguishing tTregs from iTregs generated in the periphery. Are the tTregs that we isolate from the mouse truly cells that differentiated in the thymus or do they correspond to cells that acquired FoxP3 systemically? The transcription factor Helios was proposed as a marker to differentiate between these two lineages, but its use is controversial [32, 33]. A second proposed molecule was the surface molecule Nrp1, but as Helios, its expression is not exclusive of tTregs; in fact, Nrp1 expression is acquired by Tconv during allograft rejection [14].

1.4. Tr1 cells

Tr1 cells were first described when researchers found the presence of host-reactive CD4 + T cell clones that produced high levels of IL-10, isolated from human SCID chimera successfully transplanted with Human Leukocyte Antigen (HLA)-mismatched hematopoietic stem cells [2]. It was later demonstrated that these cells could be generated *ex vivo* through the activation of human and mouse CD4 + T cells in the presence of high concentrations of IL-10 [34]. These cells showed a unique cytokine production profile distinct from that of Th1 or Th2 cells, and produced significant amounts of IL-10, TGF-β and IL-5, and low levels of IFN-γ and IL-2 [34]. After the FoxP3 protein was proposed as the master regulator of Tregs in 2003, Vieira et al. demonstrated that IL-10-producing CD4 + T cells isolated from mice were able to suppress the proliferation of CD4 + CD25- T cells despite the lack of FoxP3 expression [35]. The absence of a superficial reliable marker for Tr1 cells made their identification rely only on the cell's cytokine production profile and posed a challenge for researchers that wanted to study this subset. In 2013, Gagliani et al. proposed two surface markers for their identification: CD49b, an α2β1 integrin that acts as an extracellular receptor for laminins and collagen, and LAG-3, a cell surface molecule expressed on activated T cells, B cells, NK cells and plasmacytoid DCs [36].

Recently, it was described that among IL-10 producing Tr1 cells, a subtype of those expressing high levels of coinhibitory receptors (CIR) such as TIM-3, TIGIT, PD-1 and CTLA-4, were shown to display a unique transcriptional program, which goes beyond the regulation of IL-10 expression [37]. These CIR + cells were biologically relevant since their absence was associated with the development of bowel inflammation. Furthermore, a recent study suggests that the induction of CD4 + T cells with IL-2 and ATRA generates more stable Tr1 cells with increased co-expression of CD49b, PD-1 and LAG-3, in addition to a greater production of IL-17 and IFN-γ. In this setting, development of Tr1 cells *in vivo* is protected from autoimmune pathologies as shown in the model of experimental autoimmune encephalomyelitis (EAE) and uveitis [38].

2. Molecular determinants of epigenetic/transcriptomic regulation

2.1. Transcriptional regulation of FoxP3

FoxP3 is the master transcription factor that programs and maintains Tregs identity, and is controlled by a network of cytokine signals, transcription factors, and epigenetic mechanisms. FoxP3 gene expression is controlled by several regulatory regions, which include the

promoter sequence and three main conserved non-coding sequences (CNS) [39]. The CNS0 is an enhancer upstream of the FoxP3 promoter, important for Tregs precursor specification. It was shown to bind

STAT5, Smad3, Runx1 and Foxo1/3. CNS1 (TGF-β–responsive enhancer) is crucial for iTregs generation in peripheral tissues. It binds Smad3, NFAT and AP-1. The CNS1 is dispensable for tTregs development but is indispensable for iTregs generation [40]. The CNS2 contains the locus Tregs-specific demethylated region (TSDR), which has been shown to be essential for the stability and heritability of FoxP3 expression. Indeed, many reports have demonstrated that this locus must be demethylated for stable Tregs lineage commitment [41]. Interestingly, this region binds Runx1–CBFβ, STAT5, and FoxP3 itself (positive feedback). Finally, the CNS3 functions as a pioneer enhancer enabling FoxP3 induction. It binds c-Rel (Rel/NF-κB family) and has been shown to be crucial for FoxP3 expression during tTregs generation [42]. Although FoxP3 is mostly expressed on Tregs, its expression is not exclusive for this lineage as activated Tconv can transiently express this transcription factor [43]. In this context, recent data has shown that *cis* and *trans* elements regulate the expression of FoxP3 in specific cell lineages [44] [44].

FoxP3 expression is also regulated by several cytokines. Specifically, signaling through the IL-2 receptor activates the STAT5 pathway, which is relevant for tTregs development and Tregs maintenance [45]. FoxP3 is favored by the binding of STAT5 to the FoxP3 promoter, CNS0 and CNS2. In addition, TGF-β is the main cytokine driving iTregs differentiation, especially through the binding of Smad3 to the CNS1 locus. Although it is not essential to induce *de novo* expression in tTregs, TGF-β has been shown to mediate Tregs precursor survival in the thymus [46]. Another TGF-β superfamily member, Activins have also been shown to induce FoxP3 expression [47] and reviewed in [48].

2.2. Epigenetic regulation of FoxP3

It has been described that demethylation of the TSDR/CNS2 region of FoxP3 is essential for stable FoxP3 expression and resistance to inflammatory cytokines. It was reported that tTregs but no iTregs have fully demethylated TSDR which confers a more stable phenotype. Methylation is induced by DNA methyltransferases (DNMT1, DNMT2 and DNMT3B) whereas demethylation is mediated by the TET1, TET2 and TET3 enzymes, which convert 5-methylcytosine (5mC) into 5-hydroximethylcytosine (5hmC) and other intermediates promoting FoxP3 transcription. Interestingly, Vitamin C has been shown to activate TET enzymes to induce demethylation, which has been proposed as a method to improve the *in vitro* stability of iTregs reviewed in [49]. On the other hand, histone modifications including methylation and acetylation are also key to induce active transcription: for example, H3K4me3 at the promoter and CNS regions activate transcription, whereas H3K27ac at the CNS1 and CNS2 leads to FoxP3 enhancer activation. In contrast, methylation of H3K9me2, H3K9me3, H3K79me2, H3K27me2, and H3K27me inhibits its transcription (reviewed in [49]. Finally, histone/protein acetyl transferases (HATs) and their counterparts, histone/protein deacetylases (HDAC), also regulate FoxP3 [50]. In this context, P300 and CBP facilitate the acetylation of FoxP3, whereas HDAC1 or HDAC2 impairs the functionality of FoxP3 + Tregs through deacetylation [49].

2.3. Transcriptomic and Epigenetic regulation of Tr1 cells

Tr1 cells are induced by interleukin-27 (IL-27). In addition, IL-10 expression is regulated by mechanisms such as chromatin remodeling, 3D loops, histone modification, and DNA methylation [51]. IL-27 induces differentiation of naïve CD4 + T cells into Tr1 cells via STAT1 and STAT3 signaling. Upon T cell activation, IRF1 and BATF are quickly induced via STAT1 and STAT3 signaling, respectively, as pioneer factors for Tr1 cell differentiation.

Recent research has shown that the transcription factors EOMES and IRF4, along with AHR, can drive human Tr1 differentiation [52]. However, Hematopoietic Stem Cell Transplantation (HSCT) donor-derived T-allo10-derived Tr1 products from two Phase I/II trials upregulated IRF4 but not EOMES or AHR. Single-cell analyses revealed a distinct set of transcription factors for antigen-specific Tr1 cells induced *in vitro*, identifying IRF4, BATF, and MAF as central regulators [53].

3. Mechanisms of Tregs suppression

Both FoxP3 + Tregs and Tr1 cells possess a great array of suppressive mechanisms that allow to efficiently regulate several immune cells despite being commonly outnumbered by effector cells. These mechanisms include both soluble and cell-cell contact mediated events (reviewed in [54]). Tregs secrete high levels of immunosuppressive cytokines such as IL-10, TGF-β, and IL-35. Additionally, they can alter APCs through CTLA-4 interaction with CD80 and CD86, which stimulates the expression of indoleamine 2,3-dioxygenase (IDO) by DCs. This enzyme then breaks down tryptophan into kynurenine metabolites, which suppress the proliferation of Tconv. Ectoenzymes CD39 and CD73 on Tregs convert ATP to ADP and then to AMP, which binds to the adenosine A2A receptor on T cells, thereby inhibiting effector T cell activity. Tregs express high levels of CD25 (IL-2R alpha chain), which competes with activated Tconv for IL-2, depleting it from the environment and limiting T cell proliferation. In addition, LAG-3 on Tregs binds to MHC-II on immature DCs, suppressing DC maturation. The production of sEV is another mechanism by which Tregs modulate immunity, including in the context of transplantation [13, 14, 18]. Finally, Tregs can also act as cytotoxic cells as they induce granzyme- and perforin-mediated cell death of effector T cells. Tr1 cells use many of the same mechanisms as FoxP3 + Tregs but are best known for their high IL-10 production [55].

4. Tregs & Transplantation studies in LATAM

With the purpose to assess for current investigation on *Tregs* in the context of *Transplantation* in LATAM, we consulted the abstract book from the 14th Latin American and Caribbean Congress of Immunology (ALACI) held in Argentina (November 4–8, 2024) finding that Argentina (2 groups), Brazil (1 group), Chile (2 groups) and Mexico (2 groups) were represented with investigation on this T cell subset [56]. In addition, a search on Web of Science (WoS) using the terms "Transplantation", "Tregs" and "Country name" delivered 37 original publications on this topic (letter, reviews and meeting abstracts were not considered), which were generated from Mexico (14 studies), Chile (9 studies), Brazil (10 studies), Argentina (2 studies), Colombia (1 study), and Cuba (1 study) (Table I).

Several groups in Mexico have made important contributions on the role of Tregs in transplantation tolerance. Initial work in Mexico examined how immunosuppressants affect peripheral blood immune cells and long-term kidney transplant patients. Furuzawa and colleagues (from National Institute for Medical Sciences and Nutrition in Mexico City) found that Belatacept treatment increased circulating CD10 + CD16 + cells and Tregs, and raised FoxP3 + T cells in the graft [57]. However, a later analysis of circulating Tregs seven years post-transplant performed by Alvarez-Salazar et al. showed that both Belatacept- and Cyclosporine A–treated patients had fewer Tregs with lower CD25 and FoxP3 expression, impaired suppressive function, and increased FoxP3-TSDR methylation [58]. Other studies reported that stable graft function at five years correlated with higher circulating tolerogenic populations (Tregs, DCregs, Bregs) versus patients with chronic graft dysfunction [59]. When directly compared, Belatacept-treated patients exhibited a more tolerogenic profile and higher frequencies of regulatory cells than Cyclosporine A-treated patients. In contrast, cyclosporine was associated with higher levels of inflammatory Th17 and Th22 cells, which may contribute to chronic graft damage and rejection [60]. Importantly, these authors also

Table I
Summary of LATAM studies on the role of Tregs in human and animal transplantation models.

Country	Transplantation model	Main findings	References
Mexico	Human kidney	Belatacept treatment increased circulating CD10 + CD16 + cells and Tregs, and raised FoxP3 + T cells in the graft	[57]
		Belatacept- and Cyclosporine A–treated patients had fewer Tregs plus impaired suppressive function, and increased FoxP3-TSDR methylation	[58]
		Stable graft function at five years correlated with higher circulating tolerogenic populations	[59]
		Belatacept-treated patients exhibited a more tolerogenic profile and higher frequencies of regulatory cells	[60]
		Increased Tregs numbers promote long-term graft survival and function	[61]
		Decrease in circulating Tregs is associated with an unfavorable prognosis	[62]
	Rat kidney	rATG effectively depletes most T cells via apoptosis, it simultaneously promotes the proliferation of donor-specific Tregs	[63]
	Human hematopoietic cells	G-CSF primed bone marrow (G-BM) transplant resulted in lower rates of GvDH, promoting an anti-inflammatory profile with increased Tregs	[64]
Chile	Murine skin	Nrp1 expression on FoxP3 + Tregs favor allograft acceptance	[14–16]
		IL-33 administration into transplanted animals resulted in increased FoxP3 + Tregs frequencies	[17, 19]
		Administration of modulated MSCs….	[83]
		Rapamycin-treated DCs favor allograft survival	[65]
	Murine bone marrow	Administration of RATregs controlled Th1 responses	[67]
Brazil	Pancreatic islets	A novel biomaterial co-seeded with insulin-producing islets and Tregs reverses T1D in NOD mice	[68]
	kidney	Kidney biopsies from patients treated with rapamycin increase the percentage of Foxp3 in standard criteria donors	[69]
		Aging increases the percentage of regulatory T cells (Tregs) as part of an immunoregulatory shift, whereas ESRD actively decreases Treg percentages	[70]
		Use of immunosuppressors affects pathogen-induced regulatory T-cells and correlate with development Type 1 leprosy	[72]
		In acute cellular rejection, a higher density of FOXP3 + cells does not confer a beneficial effect and correlates with worse graft survival	[73]
	Human hematopoietic Stem cell transplantation	Clinical improvement of Systemic sclerosis patients is related to increased newly generated Tregs and Bregs	[76]
	Mouse skin	B cell-induced tolerance to skin transplants associated with the increase in Treg infiltration	[75]
		Skin allograft survival by FTY720 treatment is not dependent in Foxp3 Tregs.	[74]
	Mouse Tumor allograft	Prolonged Survival of Allografts Induced by Mycobacterial Hsp70 Is Dependent on CD4 + CD25 + Regulatory T Cells	[71]
Argentina	Pediatric and rat intestine	Administration of Tacrolimus positively affects Tregs frequencies	[77]
	Rat kidney	Tacrolimus improved renal function and inhibited pro-inflammatory genes	[78]
Colombia	Murine Skin	Both donor- and recipient-derived Tregs contributed to the alloresponse	[79]
Cuba	Human bone marrow	Proposed mathematical model to estimate Tregs/convT cells ratio	[80]

investigated the impact of Tregs in the development of *de novo* donor-specific antibodies (DSAs), demonstrating that increased Tregs numbers promote long-term graft survival and function [61]. In line with these studies, another group from the Universidad Nacional Autónoma de Mexico (UNAM) performed a study in patients with chronic allograft nephropathy demonstrating that a decrease in circulating Tregs is associated with an unfavorable prognosis [62].

Using a rat kidney model of transplantation, Bestard et al. examined the impact of rATG on T cell subsets and its ability to promote Tregs. The study found that while rATG effectively depletes most T cells via apoptosis, it simultaneously promotes the proliferation of donor-specific Tregs [63]. This shift creates a "regulatory environment" that protects the transplanted kidney and improves overall graft function.

A major complication in allogeneic hematopoietic stem cell transplantation (allo HSCT) is the development of GvHD. Experimental models have shown that Tregs transfer can prevent GvHD while preserving the beneficial graft-versus-leukemia (GvL) effect. In this context, an interesting study demonstrated that G-CSF primed bone marrow (G-BM) transplant resulted in lower rates of GvDH, by promoting an anti-inflammatory immunologic profile with an increased presence of Tregs and reduced inflammatory cytokine production [64].

The contribution from Chile comes from the studies of Dr. Pino-Lagos's group evaluating the modulation of DCs (with Rapamycin) or MSC (with IL-33) and its potential regulatory effect on Tregs *in vitro* or *in vivo* in a murine skin transplantation model [64, 65], in addition to the other findings described in other sections. Two additional reports -originated in Dr. Bono's lab- were found. One investigated the impact of allogeneic APCs (DCs or B cells) in the production of RATregs demonstrating that the use of both cell types as APC generates better results in RATregs production than each cell type by itself [66]. The other study described the benefits of administering RATregs in chimerism and controlling Th1 responses using a non-myeloablative bone marrow transplantation model in mice [67].

Brazil was the third LATAM country with most studies including Tregs in Transplantation. The publications range between the use of

biomaterials seeded with Tregs [68], the effect of type of donor's death and immunosuppressant drugs on Tregs [69] and the impact of the patient's age in the immune response (T cell compartment) against the allograft [70].

Over the past two decades, substantial evidence has demonstrated that Tregs play a central role in promoting allograft tolerance in both experimental models and human transplantation. Building on previous findings that *Mycobacterium tuberculosis* heat shock protein 70 (TBHsp70) exerts anti-inflammatory effects in rodent models of autoimmune arthritis, its therapeutic potential was subsequently evaluated in transplantation. These studies showed that TBHsp70 effectively inhibited allograft rejection in murine models of allogeneic melanoma and skin transplantation by promoting the recruitment of Tregs to the graft [71]. In addition, a study of kidney transplant recipients with leprosy reported that a deficiency of Tregs was associated with severe inflammatory reactions, further supporting the importance of Tregs in controlling immune responses after transplantation [72].

Despite the extensive evidence linking Tregs to allograft tolerance, the abundance of FoxP3 + cells alone is not a reliable predictor of graft survival. For example, one study of kidney transplant recipients found that FoxP3 + Tregs were significantly enriched in renal allografts undergoing acute cellular rejection (ACR), suggesting that Tregs accumulation does not necessarily reflect effective immune regulation or favorable graft outcomes [73].

Additional studies have highlighted the importance of Tregs function and localization rather than their absolute numbers. In a murine skin allograft model, treatment with FTY720 significantly prolonged graft survival by suppressing Th17 responses. However, it failed to induce long-term tolerance because it caused a systemic reduction in Tregs, ultimately resulting in graft rejection [74]. Using the same model, another study demonstrated that both the presence of Tregs and the Treg/effector T cell (Teff) ratio within graft infiltrates are critical for accurate histopathological diagnosis and for predicting transplant outcomes [75].

Beyond solid organ transplantation, Tregs have also been implicated in immune reconstitution following HSCT. A collaborative study between Brazilian and French investigators showed that autologous HSCT in patients with systemic sclerosis resulted in significant clinical improvement accompanied by the generation of new Tregs and Bregs, highlighting the contribution of immune regulatory networks to long-term therapeutic benefit [76].

Argentina delivered two results. One study investigated the effect of immunosuppressive treatment (Rapamycin and Tacrolimus) on intestinal transplantation immune response (pediatric patients and rat model) by tracking frequencies of Tregs and amounts of cytokines. The authors found that ACR was linked to a decrease of Tregs and increment of CD8 + T/CD4 + T cells ratio and pro-inflammatory cytokines. Interestingly, Tacrolimus -but no Rapamycin- showed a positive impact on preventing ACR and facilitating the presence of Tregs in blood and graft [77]. The other study also evaluated the effect of these two immunosuppressants but in the graft during the ischemia-reperfusion phase (rat kidney transplantation model). The authors found that Tacrolimus down-regulated creatinine and blood urea nitrogen levels, acute tubular necrosis, and gene expression of pro-inflammatory cytokines such as IL-6, IL-21 and TNF-α [78].

Colombia resulted with 1 study, which was performed in collaboration with a team from the USA, and evaluated the effect of Tregs origin (donor- or recipient-derived) in a murine skin transplantation model revealing that both Tregs types contribute to the alloresponse [79].

Cuba participated in a collaborative work with Norway and Japan. The study reports a mathematical model to estimate Tregs/convT cells ratio in bone marrow transplantation to avoid GvHD, but maintaining a GvL effect [80].

5. Mouse models of transplantation

There are several murine experimental models to study the immune response in transplantation, and their use will depend on the purpose of investigation. For instance, some will be suitable to study early rejection events, others to understand the contribution of antibody-mediated rejection or to validate therapeutic strategies aiming at the induction of long-term graft survival. Importantly, the American Transplantation Society (ATS) created a committee composed by investigators who discuss the limitations and benefits of these models and have raised important points to consider when designing a transplantation study, which can be revised in detail in [81].

5.1. Skin

The skin transplantation model has served as a great tool in deciphering the basics of immune rejection. In fact, it was this model the one used by Peter Medawar to describe the fundamentals of histocompatibility and the properties of cellular immunology (transferable and memory) upon allograft recognition. Due to the high presence of immune cells in the skin graft, and the availability of different mouse strains to evaluate antigen recognition under semi or full mismatch conditions, this model is considered very immunogenic and very adequate to test for interventions of immune tolerance induction [82], as discussed at the end of this section.

In LATAM, this model is used by investigators from Chile, Colombia and Brazil. The Chilean group have reported the role of Nrp1 [14–16] and IL-33 [17, 19] on FoxP3 + Tregs and the establishment of transplantation tolerance, in addition to studies describing the effects of administrating MSCs [83] or Rapamycin-treated DCs [65, 83] into skin transplanted animals. Furthermore, a Colombian group utilized this model to investigate the contribution of donor- and recipient-derived Tregs during the immune response against the allograft [79], whereas Brazilian investigators described the effects of FTY720 on the dynamics of Tregs and Th17 cells and the outcome of the transplant [74], in addition to the predictive use of Tregs and Th cells when infiltrating transplanted skin [75].

5.2. Heart

The heart transplantation model does not mimic the human setting because the graft is implanted in the abdominal cavity by attaching its aorta to the abdominal aorta, and the heart́s pulmonary artery to the recipient́s inferior vena cava, resulting in a heart graft that does not pump blood. Also, it is not appropriate for studying immunosuppressant drugs because graft acceptance is reached with subclinical doses. Technically more challenging than the skin transplantation model, heart transplantation allows for rapid vascularization and easy rejection monitoring, making this model useful to study acute rejection [82, 84].

5.3. Liver

Liver transplantation has been used to understand the mechanisms of suppression since the organ is spontaneously accepted under combination of certain mouse strains (as in kidney transplants). This setting has revealed the role of co-inhibitory molecules, immune cell types with tolerogenic properties and pathways such as IDO-1 [82]. Because liver tolerance is also observed in patients, this model is physiologically relevant albeit its methodological difficulties.

5.4. Kidney

Unlike the heart transplantation model, kidney transplant mimics what occurs in the clinic since the recipient is nephrectomized and the bladder is connected to the donor's ureter. Due to these anatomical aspects, kidney rejection is less convenient to monitor than skin or heart

transplants and relies on kidney function as in transplanted patients. Like liver transplants, some mouse strains combinations also elicit spontaneous graft acceptance, which has been insightful to understand the role of Tregs in transplantation tolerance [82].

5.5. GvHD

Bone marrow transplantation (BMT) is indicated for hematopoietic malignancies, for which the patient is subjected to progenitors and immune cells ablation before BMT to allow reconstitution with donor cells. Unfortunately, in 20–70% of cases (frequencies that depend on sex, age, HLA mismatch, among others) a strong immune response is initiated by donor cells recognizing recipient's antigens as foreign. This response is named Graft-versus-Host Disease (GvHD) and corresponds to a potent inflammatory reaction that usually targets the skin, mucosa and other tissues and, if not treated, causes death. The main treatment for GvHD is the administration of immunosuppressor drugs [84]. In the quest for immune regulatory interventions, such as cellular therapy or administration of other biological products, the model of GvHD in mice has been widely used. As an approximation of a preclinical model, the development of humanized mouse models has served as a first test before therapy production under Good Manufacturing Practices (GMP) conditions and clinical trials [85]. In fact, the *in vivo* suppressive functions of human Tregs were first studied using this approximation (human skin transplant into humanized mouse model) before scaling their production for administration into transplanted patients [86].

With the purpose to assess for current investigation on *Transplantation Immunology* in LATAM, we consulted the abstract book from the 14th Latin American and Caribbean Congress of Immunology (ALACI) [56] finding that:

- Skin Transplantation in mouse was used as model to study the contribution of XPC gene in inflammation and tissue repair (Brazil), the role of IL-33 and Nrp1 on FoxP3 + Tregs (Chile), and the effect of a drug with potential immunosuppressive activity (Uruguay).
- Intestinal Transplantation in rats was used to evaluate the impact of immunosuppressant drugs on intestinal cell populations (Argentina).
- HSCT research was studied in patients with Wiskott-Aldrich syndrome and Chronic granulomatous disease (Argentina) and in patients with Systemic Sclerosis (Brazil).
- Kidney Transplantation was studied in patients by investigating B cell-mediated viral response on PBMC (Brazil).
- Liver Transplantation was studied in patients subjected to SARS-CoV2 immunizations (Argentina).

5.6. Humanized model of human allogeneic skin rejection

Despite all the animal models used for transplantation, and given the evidence indicating that alloantigen specific Tregs are more effective at preventing graft rejection than polyclonally expanded Tregs [87], additional preclinical models have been developed to evaluate Tregs function *in vivo*. One of them is the model of allospecific human skin rejection using humanized mice [88]. This methodology is currently being used in Mexico. Briefly, human skin obtained from surgery patients with informed consent is transplanted onto 8- to 12-week-old NSG (NOD.Cg-Prkdc scid Il2rg tm1Wjl /SzJ) mice and allowed to engraft for 6 weeks after which the recipient mice are injected with 10×10^6 HLA-mismatched CD25-depleted PBMCs. To evaluate Tregs homing and function, PBMC are co-infused with expanded allospecific hTregs (Tr1 or FoxP3 + Tregs) and histologic analysis of the graft is evaluated 6 weeks after PBMC injections. For the total duration of these experiments, 100 μg anti-mouse Gr1 is injected intraperitoneally every 4–5 days to deplete mouse granulocytes.

6. Tregs in the clinic

In the past 15 years, multiple research groups have shown that infusing Tregs is feasible for treating patients with various inflammatory conditions, such as autoimmune diseases (diabetes, intestinal bowel disease) and following transplantation, helping to prevent GvHD and organ rejection [89]. Most clinical trials have utilized tTregs, likely because these cells demonstrate greater stability compared to Tregs generated *in vitro* [90]. Nevertheless, studies in animal models indicate that iTregs transferred *in vivo* also remain stable [91–93]. Additionally, although most research has focused on polyclonal Tregs, several animal models have already shown the potential advantages of using antigen-specific Tregs, both for inducing allograft tolerance [87] and reversing autoimmunity [94]. Due to the low frequency of Tregs in PBMC samples from adult human, as they only comprise around 3–10% of peripheral CD4 + T cells, Tregs isolation and *ex vivo* expansion protocols have been implemented to reach the numbers required for inducing long term tolerance, based on the effective therapeutic dose observed using different animal models [95, 96]. It has been calculated that doses ranging from 5 to 20×10^6 cells per kg may be needed for polyclonal Tregs adoptive transfer into the patients [97]. However, it has been proposed that the use of antigen-specific Tregs [98] may substantially reduce the numbers ($5–20 \times 10^5$ cells per kg) required to induce the same effect of polyclonal Tregs (reviewed in [99]).

To overcome the limitations of peripheral Tregs as a source of cells, umbilical cord blood has the advantage of providing an enriched number of naïve Tregs, although the numbers so far obtained remain limited. Recently, human thymuses that are discarded during pediatric cardiac surgery have been proposed as an alternative source of Tregs and, importantly, GMP protocols have already been implemented, and a Phase I/II clinical trial evaluating the treatment of autologous tTregs in children undergoing cardiac transplantation is currently underway (NCT04924491) [100]. With respect to allogeneic transplantation, several trials have proven the feasibility of avoiding the development of GvDH in allogeneic HSCT patients, showing very promising results [101]. On the other hand, several clinical trials have been developed to induce tolerance towards solid organs using allogeneic donor-specific Tregs and were able to prevent allograft rejection of both kidney and liver (reviewed in [102]).

Several clinical trials are underway to test Tr1 cells for inducing tolerance in transplantation and autoimmune diseases (reviewed in [103]). The ALT-TEN trial used IL-10 anergized donor Tr1 cells to prevent GvHD in HSCT patients [104], while the CATS1 trial evaluated OVA-specific Tr1 cells for refractory Crohn's disease [105]. Finally, T-allo10 cells trial assessed a product with 15% CD49b + LAG-3 + Tr1 cells to prevent GvHD, showing one-year cell persistence without notable side effects. T-allo10 cells are made from donor CD4 + T cells stimulated by host DCs-10 and IL-10 [106]. Initial findings showed good tolerability, although effects on GvHD and long-term tolerance remained under study. Despite these advances, it should be noted that these trials used enriched IL-10 producing T cells—not highly purified "bona fide" Tr1 cells—which contain many memory-like effector T cells with unknown long-term effects. Therefore, it remains a challenge to improve the methodologies to obtain highly purified Tr1 cellular products that may promote specific long-term tolerance in solid organ transplantation.

6.1. The challenges of GMP production: From the lab to the clinic

Despite the growing evidence showing the effectiveness of Tregs therapy in animal models, Tregs cellular products need to be generated under GMP conditions and obtain the regulatory approval for the use in humans. This has been a real challenge for many researchers, specifically in LATAM, as very few laboratories have the necessary conditions to meet GMP standards, and some countries, like Chile, do not have the proper regulatory policies to evaluate, as other important points,

potential risks for patients. Several considerations need to be taken in account when designing Tregs therapies, and one of the main issues is manufacturability (reviewed in [107]) including selection and expansion of Tregs, potency of the expanded cells, analysis of antigen specificity, stability of the expanded cells under inflammatory conditions and persistence in the patient, which may imply the trafficking of Tregs to the inflammatory site to promote and sustain a tolerogenic milieu.

6.2. New approaches in Tregs therapy: engineering antigen-specific Tregs, CAR-Tregs

Given the promising results in the treatment of human malignances through Chimeric Antigen Receptor (CAR)-T cell generation (reviewed in [108]), several CAR-Tregs also were generated (reviewed in [109]) aiming to induce tolerance in animal models of autoimmunity including experimental allergic encephalomyelitis (EAE) [110]) and Dextran Sulfate Sodium (DSS)-induced colitis [111]. In 2009, the first human CAR-Treg was designed directed towards the carcinoembryonic antigen (CEA) using CD3ζ and CD28 intracellular chimeric signaling [112]. CAR-Tregs have been designed for inducing tolerance towards alloantigens. One of the first CAR-Tregs was directed towards the HLA-A2 as this allele is a commonly mismatched antigen in transplantation. In 2022, the first phase I/II trial using CAR-Tregs was carried out (NCT04817774) [113] to evaluate the safety and tolerability of TX200-TR101 (autologous HLA-A2 specific CAR-Tregs) and its effects on the donated kidney in living donor kidney transplant recipients, in the presence of systemic Tacrolimus immunosuppression. A later study using a model of xenogeneic graft-versus-host-disease in NSG mice, demonstrated that although HLA-A2-specific CAR-Tregs were suppressive *in vitro*, they were unable to induce tolerance in a xenogeneic GvHD model [114]. Therefore, one of the current challenges remaining is to prevent exhaustion of CAR-Tregs *in vivo*, as tonic signals lead to expression of inhibitory receptors such as PD-1 and TIM-3, as well as transcription factors related to exhaustion as TIM-3, TOX and BLIMP-1.

Other HLA-A2-CAR-Tregs have been used after deleting the endogenous TCR with CRISPR/Cas9, demonstrating that these TCR deficient human HLA-A2-CAR-Tregs were able to reach the A2- expressing islets in humanized NSG mice and induce tolerance [115]. However, despite the promising results so far obtained, there are still many unanswered questions regarding the stability of CAR-Tregs for inducing long term tolerance *in vivo*, including the dose of Tregs used, the timing, and their homing capacity. In this context, recent reports have indicated that it is possible to genetically modify Tregs to enforce the expression of specific chemokine receptors that were able to reduce the severity of allogeneic acute GvHD [116].

7. First advances in Tregs therapy in LATAM

A significant challenge in kidney transplant recipients is reduced life expectancy, resulting in less than 60% graft and patient survival at ten years post-transplant [117]. This issue primarily arises because patients require intensive immunosuppressive therapy to prevent chronic rejection driven by alloreactive T cell responses. These immunosuppressive agents are associated with adverse effects including toxicity, hypertension, and cardiovascular disease, as well as increased susceptibility to infections and the development of neoplasms due to prolonged immunosuppression.

Dr. Soldevilaś group, at UNAM, have developed different methodologies aiming to obtain highly specific alloreactive Tregs with potential therapeutic use in kidney transplanted patients. This work has been a collaboration with the Transplantation Unit at the Instituto Nacional de Ciencias Médicas y la Nutrición Salvador Zubirán, Mexico City. As mentioned before, many trials had already been successful at preventing GvHD in HSCT patients, both using polyclonal and antigen-specific Tregs, although even fewer studies had been conducted for solid organ transplantation. Most importantly, no clinical trials have yet been performed in LATAM.

7.1. Generation of allospecific Tregs

One of the challenges faced by many research groups when attempting to expand tTregs is the fact that continuous TCR-mediated activation results in T cell exhaustion. Therefore, extensive work has been required to optimize the generation of highly specific-expanded Tregs with functional and phenotypic stability. Three different methodologies have been designed by the group at UNAM in Mexico, consisting in the generation of allospecific iTregs, tTregs [22] and Tr1 cells [118]. Briefly, either tTregs or naïve T cells are FACS-sorted to $>$ 90% purity and co-cultured with monocyte-derived allogeneic DCs. For Tr1 cells, tolerogenic DCs are generated in the presence of IL-10, IL-4 and GM-CSF [119]. Purified T cells are then incubated with allogeneic DCs and after 7 days, proliferating Tregs can be further FACS-sorted to isolate the allospecific tTregs, iTregs and Tr1 cells, respectively. Next, they are polyclonally expanded for 3–4 weeks (4 days of activation followed by 3 days of resting), after which alloTregs are characterized based on their phenotype, suppressive function, stability in the presence of cytokines, epigenetic status, and transcriptomic analysis. In summary, three methodologies were standardized where alloTregs were expanded $>$ 1000x resulting in highly pure tTregs, iTregs and Tr1 cells subpopulations. Most importantly, all three products maintained their phenotype and suppressive function, even in the presence of proinflammatory cytokines (Fig. 2). For FoxP3 + Tregs, epigenetic analysis showed that although expanded Tregs had partially methylated the TSDR locus within the CNS2 region of FoxP3, they were fully functional and displayed a suppressive phenotype (CTLA-4, PD-1, CD39, etc). Recent studies have shown that expansion of allospecific tTregs can be improved by adding IL-15, and the use of CD27 + and CD70- markers during the FACS isolation process, leading to a more stable subpopulation that preserves enhanced TSDR demethylation under inflammatory conditions [120]. In addition, the original protocol to generate allospecific iTregs has also been optimized by adding Vitamin C to the expansion cultures, resulting in enhanced demethylation and suppressive function [121].

Importantly, allo-Tr1 cells displayed the CIR phenotype consisting in the expression of TIGIT, LAG-3, PD-1, CTLA-4 and CCR5. Moreover, preliminary data based on the transcriptomic analysis of these expanded allo-Tr1 cells, but not expanded allo-Tconv, indicate that they express the expected transcription factors relevant to IL-10 producing cells (manuscript in preparation). It is worth mentioning that the alloTr1 protocol is the first successful methodology to ensure a highly purified Tr1 cells population that can be successfully expanded *in vitro,* leading to the generation of clinically relevant numbers of Tr1 cells. One of the main findings of these expanded allo-Tregs is their functional stability in the presence of proinflammatory cytokines and their homing receptor expression pattern. In fact, allo-tTregs and allo-iTregs display chemokine receptors relevant for homing to the graft [122], including CXCR3 and CCR4, whereas CCR7 was less expressed in expanded allo-tTregs and allo-iTregs. Although this chemokine receptor has been shown to be relevant for homing to the lymph node, it was also shown to participate in Tregs-mediated immune suppression through regulating Tregs homing to the graft [123].

While previous studies generated allospecific Tr1 cells to induce transplantation tolerance, their approaches faced limitations. MFarrej et al. [119] generated donor-specific T cells (T10) for kidney transplant patients, but these contained only 6% CD49b + LAG3 + Tr1 cells and were infused without purification or polyclonal expansion. Similarly, Roncarolo's group generated T-allo10 cells with 15% Tr1 cells enrichment; though they prevented GvHD after allo-HSCT without compromising antiviral or antitumor immunity [106], neither study expanded the Tr1 cells as a purified population or evaluated their stability under proinflammatory conditions.

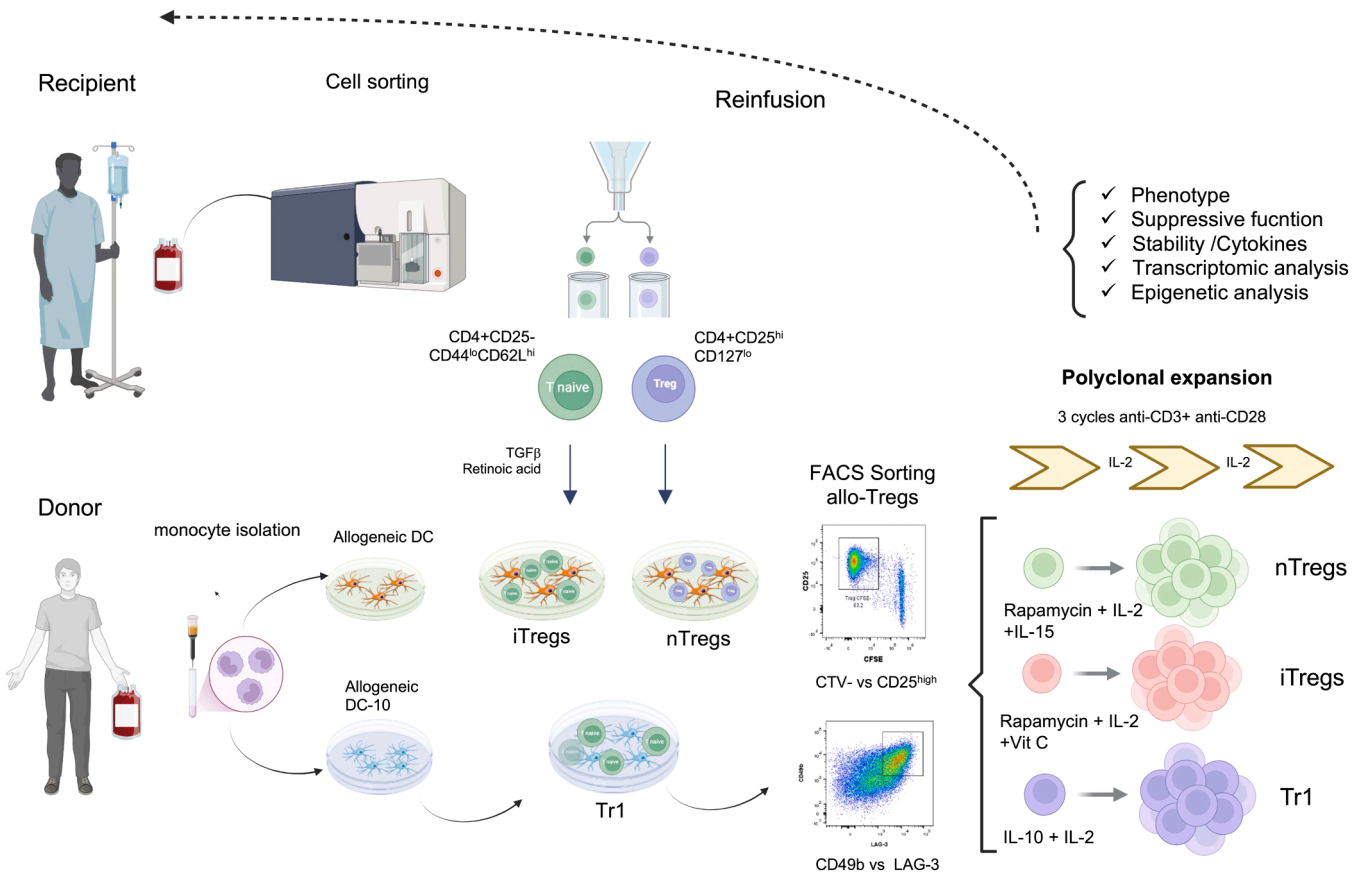


Fig. 2. Schematic representation of the methodologies developed to generate and expand allospecific Tregs. Either tTregs or naïve Tregs can be FACS-purified and co-cultured with allogeneic monocyte-derived DCs (conventional DCs for FoxP3 + Tregs and DC-10 for Tr1 induction) obtained from the donor PBMCs. CTV- or CFSE-labelled responder cells can be then isolated based on dye dilution and polyclonally expanded for several weeks. Each expansion cycle comprises 4 days of anti-CD3 and anti-CD28 stimulation and 3 days of resting in the presence of IL-2 alone. At the end of the expansion cycles, phenotype, function, epigenetic and transcriptomic analysis is performed. Finally, functional stability is performed after the expansion of alloTregs in the presence of pro-inflammatory cytokines for an additional two weeks. Created at Biorender.

8. Current challenges in Tregs and Transplantation Research in LATAM: where do we go from here?

In LATAM, the field of transplantation research faces a highly complex set of hurdles. Despite all the efforts and the important advances achieved by numerous research groups, the advancement in this field is severely "bottlenecked" by a combination of profound infrastructural disparities, restricted funding, collaboration network, and diagnostic limitations (which is tightly linked with the access to novel technologies), all of which are required to strengthen the field in the region.

Perhaps the main obstacle is the funding because is the minimal requisite to: i) access education or training (scholarships, fellowships, international exchange), ii) cover for expenses regarding basic and clinical research, iii) acquire or develop new technologies, iv) invest in adequate infrastructure.

Concerning the socioeconomical and structural disparities, while countries like Brazil and Argentina have highly organized, public national transplant systems, lower-middle-income countries in Central and South America (e.g., Guatemala, Honduras, Bolivia) struggle to maintain basic solid-organ transplant programs. On the other hand, tolerance induction protocols require highly precise long-term monitoring. However, many patients live far from transplant centers, making post-transplant follow-up difficult. As a result, some patients abandon maintenance medication, which can trigger acute rejection episodes.

Finally, due to the critical organ shortage in LATAM countries, compared to Europe or US, centers prefer the use of conventional immunosuppression protocols, rather than tolerance-induction protocols that carry a risk of early graft loss.

Regarding the implementation of novel therapies for transplantation tolerance in LATAM, even in high-resource settings, transitioning Tregs from preclinical discovery to clinical transplantation reality presents massive scientific bottlenecks [124–126]. One of the main constraints is the lack of GMP-compliant manufacturing facilities. In this context culturing, expanding, and purifying autologous or allogeneic Tregs requires rigorous GMP laboratory infrastructure which becomes unaffordable for Latin American institutions [124, 127].

An increase in funding opportunities targeting the training of young scientists, the promotion of local and international collaboration, and the interaction between scientists and clinicians becomes pivotal to foster transplantation research. Technological modernization (including the acquisition of new equipment, implementation of highly sensitive diagnostic techniques and personalized cellular therapies, use of artificial intelligence, and creation/update of data registry among others) pointing out to the incorporation of precision medicine as a practice in the transplantation field may result in a reduction of the rejection rates as donor-recipient matching may improve as well as early stage detection of rejection -or administration of new therapies-may offer a new window for intervention preventing the loss of the transplant.

9. Concluding remarks

The robust existing investigation on tTregs, and its variants iTregs and Tr1, has validated Tregs unquestionable role in immunity homeostasis and their manipulation for therapeutic purposes. The contribution

on this knowledge from the LATAM region has provided information on Tregs cellular immunology in addition to new protocols for Tregs production to use in the clinic. However, to further strengthen this field, the region needs improved funding opportunities, collaborative networks, access to advanced technologies, multicenter studies, training programs, and stronger integration between basic and clinical research.

CRediT authorship contribution statement

Gloria Soldevila: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Karina Pino-Lagos:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition.

Author contribution

GS and KP-L drafted, wrote the article and revised it critically for the scientific content.

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During the preparation of this work GS used an AI assisted technologies (autowrite tool) to improve the clarity and conciseness of the text and Gemini AI for deep research assistance. After using these tools, the author reviewed and edited the content as needed, and took full responsibility for the content of the published article.

Declaration of Competing Interest

GS, is named inventor in patents #421735 and #420864- related to Tregs filed by the National Autonomous University of México. GS is co-founder of InCellTx, a company formed to commercialize the referred patents that may obtain a license for that purpose under conditions to be determined.

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Data availability

No data was used for the research described in the article.

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