Cytokine and Growth Factor Reviews 47 (2019) 62–73

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Role of JAK inhibitors and immune cells in transplantation

Nicolas Sailliet[a,b], Carole Brosseau[a,b], Jean-Michel Robert[c], Sophie Brouard[a,b,*]

[a] Centre de Recherche en Transplantation et Immunologie UMR1064, INSERM, Université de Nantes, Nantes, France
[b] Institut de Transplantation Urologie Néphrologie, CHU Nantes, Nantes, France
[c] Université de Nantes, Nantes Atlantique Universités, Cibles et Médicaments du Cancer et de l'Immunité IICiMed-AE1155, Institut de Recherche en Santé 2, Nantes, France

ARTICLE INFO

Keywords:
Cytokine
JAK inhibitor
JAK
Transplantation
Immunosuppressive treatment

ABSTRACT

Immunosuppressive challenge after transplantation has dual objectives, namely, to efficiently inhibit immune populations involved in acute, chronic, humoral or cellular transplant rejection while minimizing the effect on immune integrity toward pathogens. The current immunosuppressive strategies show limited efficacy and remain associated with strong side effects, and thus, it is essential to develop new strategies. The use of Janus kinase (JAK) inhibitors is one of the new strategies focusing on cytokine pathways. Specifically, the first-generation JAK inhibitors (JAKis) showed low specificity toward the four known JAK molecules and did not exhibit better effects than calcineurin inhibitors, which constitute the standard treatment posttransplantation. However, because the new generation of JAKis present higher specificity, we are gaining further insights on the response of cells to these inhibitions. This review focuses on the impact of JAKis on different immune cell subsets, focusing on their role in transplantation.

1. Drug development in transplantation.

Kidney transplantation is followed by years of immunosuppressive treatments to prevent transplant rejection, but the currently used strategies induce notable toxicity or secondary disorders [1,2]. At present, calcineurin inhibitors are the most common drug used posttransplantation. However, cyclosporine can affect the cardiovascular, renal, endocrine and metabolic systems and increase the risk of developing skin and lymphoproliferative malignancies [3]. The challenge associated with the development of immunosuppressive therapies is thus clear: in addition to the life-long treatments required for the prevention of graft rejection, we need to introduce new immunosuppressive strategies that exhibit improved efficacy with minimal side effects.

Decreased side effects can be achieved by combining different drugs that inhibit different pathways, which would allow us to reduce the dosage of each drug. A second strategy is to focus on new drugs whose effects are strictly limited to immune cells. Over the last decade, new strategies have emerged, and the first commercialized molecules are already available in the market [1]. These strategies focus on cytokine pathways, which are major components of immune cell communication.

2. JAK family and pathways.

Cytokine signal transduction is mediated by different kinase pathways, and the main one is the Janus kinase (JAK)/signal transducer and activators of transcription (STAT) pathway [4]. The JAK family comprises four tyrosine kinases (JAK1, JAK2, JAK3 and TYK2), which are composed of a kinase domain with enzymatic activity, a pseudokinase domain that regulates the kinase activity and two binding domains, namely, SH2-like and 4.1 ezrin radixin moesin (FERM), which associate with the intracellular domains of 60 cytokine or hematopoietic growth factor receptors [5,6] (Fig. 1). In the JAK/STAT pathway, two or three JAKs form a complex, which results in the autophosphorylation of the JAK molecules and in turn the phosphorylation of their substrate; subsequently, the intracellular domain of the receptor undergoes a conformational change to provide access to the docking site for STATs, which are then phosphorylated upon binding [7,8]. Once activated, STATs dimerize and translocate to the nucleus, where they act as transcription factors to shape the immune response [8] (Fig. 2). However, the JAK-STAT pathway is not the only signal transduction pathway downstream of JAK. Through its SH2 domain, a JAK protein also binds to proteins that recruit MAP kinases or PI3K-AKT through pathways that do not interact with JAK/STAT signaling to induce a different transcriptional profile [9,10]. JAK inhibitors (JAKis) are designed as selective ATP competitive inhibitors that prevent the phosphorylation of STAT without altering its binding abilities [11].

Numerous studies have characterized the JAK-STAT pathways. JAK1 is associated with interferons [12], the IL-6 family (IL-6, IL-11,

* Corresponding author at: Centre de Recherche en Transplantation et Immunologie, INSERM UMR1064, 30 bd Jean Monnet, 44093, Nantes Cedex 1, France.
E-mail address: sophie.brouard@univ-nantes.fr (S. Brouard).

https://doi.org/10.1016/j.cytogfr.2019.05.002
Received 16 March 2019; Accepted 9 May 2019
Available online 11 May 2019
1359-6101/

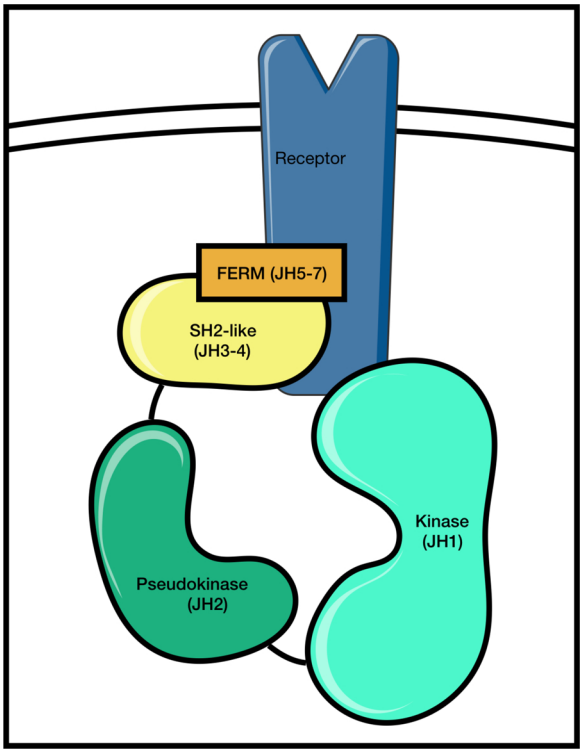

Fig. 1. Structure of the JAK.
Janus kinases are composed of 7 JAK homology domains (JH1-7) associated with the different functions of the molecule: The carboxyl-terminal kinase domain (JH1) carry the enzymatic activity together with the catalytic sites for ATP and substrates. Most JAK inhibitors are competitive inhibitors of ATP. The pseudokinase domain (JH2) has an autoregulatory activity through the phosphorylation of the kinase domain. SH2-like domain (JH3-4) has a similar structure with SH2 domains but does not interact with phosphotyrosines. Associated with the 4.1 Ezrin Radixin Moesin (FERM) domain (JH 5–7), the two N-terminal domains are the receptors binding sites.

ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC), and IL-27) [13], the IL-2 family (IL- 2, IL-4, IL-7, IL-9, IL-15, and IL-21) [14] and the IL-10 family (IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26) [15]. JAK2 is associated with growth factors and hormones (i.e., erythropoietin, thrombopoietin, growth hormone, prolactin, epidermal growth factor, G-CSF, GM-CSF), interferon (IFN) γ, IL-3, IL-5, the IL-6 family and the IL-12 family (IL-12, IL-23, and IL-27) [16–19]. In contrast, JAK3 is only associated with the γc chain in lymphoid cells and is thus specific to the IL-2 family [20], and TYK2 is associated with type I interferons (IFNα and IFNβ) and the IL-6, IL-10 and IL-12 families [19,21–23,15].

3. Clinical relevance of JAK inhibitor development.

JAKis are small molecules marketed or in development for the treatment of bowel or skin autoimmune diseases (Crohn's disease, ulcerative colitis, psoriasis, rheumatoid arthritis), hematological malignancies and graft loss prevention [24]. These molecules are designed to act as ATP competitive inhibitors and show different types of inhibition toward JAKs with more or less stringent specificities. Although treatment with JAKis, such as tofacitinib or baricitinib, has shown efficacy in disease-modifying antirheumatic drug (DMRAD)-unresponsive rheumatoid arthritis [25,26], clinical trials with the low-specificity JAKi tofacitinib have shown a high frequency of infections due to the broad immunosuppressive state [27]. Thus, this JAKi is not superior to cyclosporine in the context of transplantation. After development of the first-generation JAKis, studies have identified new drugs with a more specific profile toward JAKs and a response with the desire to limit the effects to the deficient cells.

JAK1- or JAK2-knockout (KO) mice are perinatally lethal, and JAK3 or TYK2 KO leads to important immune defects [28–30,8]. The role of JAKs in cell signaling makes these kinases important for the biology of several cell types [31]. The administration of therapeutic doses of tofacitinib (approximately 3 μM) to high-fat diet-fed C57BL/6 mice exerts limited effects and does not alter the body weight or composition (muscle mass and body fat mass), whereas the administration of this JAKi to JAK2-KO, high-fat diet-fed mice results in glucose intolerance and insulin resistance [31]. The administration of tofacitinib to patients with rheumatoid arthritis does not affect the muscle mass but significantly increases the body fat mass [32]. The effects of tofacitinib or another JAKi on another nonhematopoietic disorder have not been described [27].

Different transplant dysfunctions do not present the same immune profile, and the immune profile depends on not only the grafted organ but also the initiation of inflammation, which leads to graft loss. In this paper, we review the effects of JAK/STAT inhibition on different immune cells and their involvement in graft loss prevention. All JAKis reviewed in this paper are listed in Fig. 3 (Fig. 3).

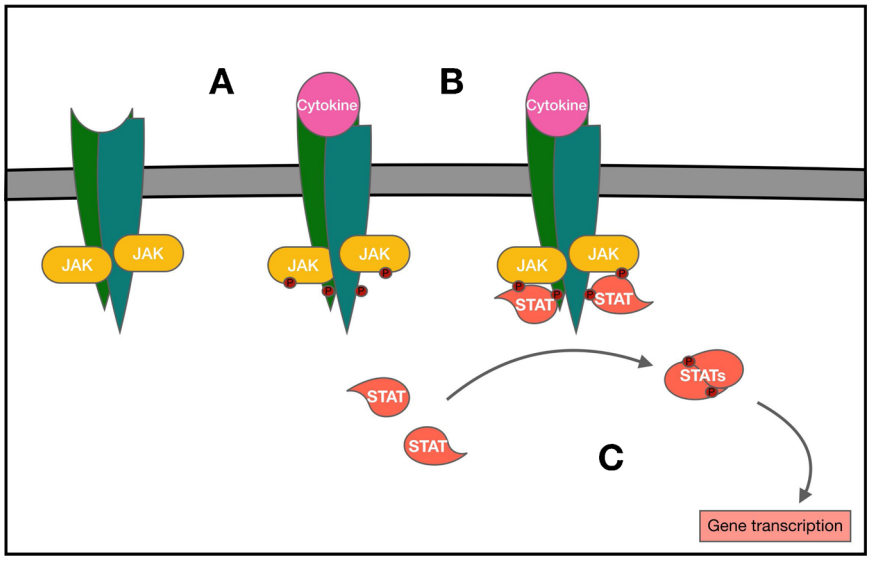

Fig. 2. Cytokine signal transduction through JAK/STAT pathway.
A- Cytokine binding to the receptor results in the autophosphorylation of the Janus Kinases (JAK) which subsequently phosphorylate the intracellular regions of the receptor. B- These phosphorylations reveal docking sites for Signal Transducers and Activators of Transcription (STATs) both on the JAKs and on the receptor subunits. C- STATs are then phosphorylated upon binding. Phosphorylated STATs dimerize and translocate to the nucleus where they act as transcription factors to shape the immune response.

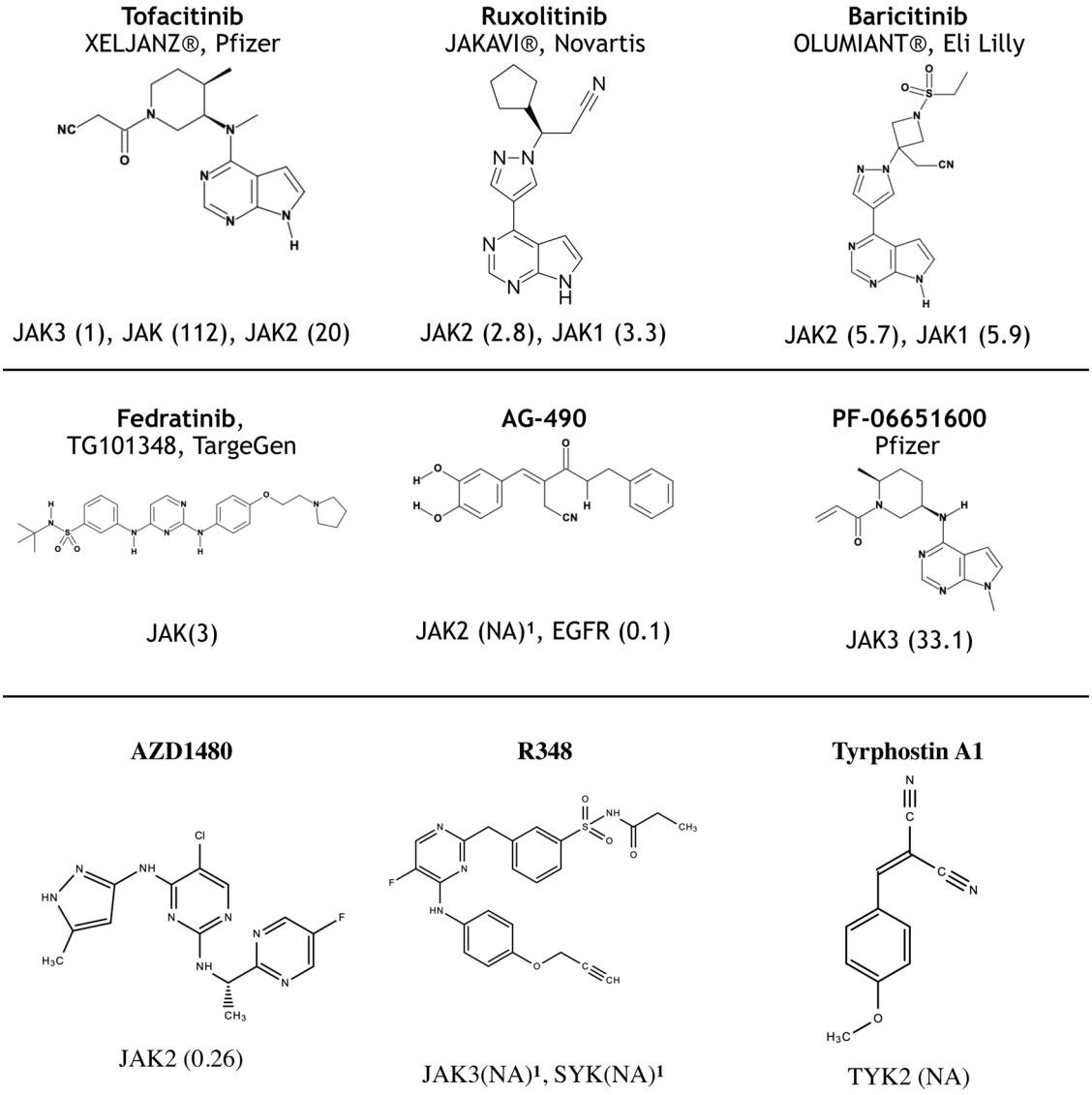

Fig. 3. List of JAK inhibitors reviewed in this paper.
JAK inhibitors as described in the literature (name, commercial name, structure and half max inhibitory concentration (IC_{50}) (nM), IC50 were obtained from selleck.com).([1]): IC_{50} was not assessed (NA) in a cell-free assay.

4. Hematopoietic stem cells.

The differentiation of hematopoietic stem cells (HSCs) to immune cells is a multi-step program, and the fate of the cells at each intermediate state is tightly regulated by the levels of several cytokines in the environment (interferons and colony-stimulating factors), particularly those associated with the JAK2 pathways, which serve as both stimulatory and inhibitory factors. Therefore, the long-term action of JAKis on bone marrow resident cells impacts all immune cells with low specificity.

The JAK1/JAK2 inhibitor ruxolitinib results in 20% inhibition of JAK2 and STAT5 phosphorylation in CD34+ HSCs from chronic myeloid leukemia patients [33], and this inhibition is characterized by a slight increase in cell death and reduced cell proliferation. After 72 h without treatment, CD34+ cells exhibit an increased recovery over the baseline level (140%). In contrast, the administration of ruxolitinib at clinically relevant doses has a low impact on mesenchymal stem cell proliferation and survival in healthy patients and does not affect their clonogenicity [34]. JAKis exert a potent inhibitory effect on HSCs through the inhibition of JAK2. Ruxolitinib has been approved for the treatment of myeloproliferative neoplasms. The inhibition of HSCs or other early-stage hematopoietic progenitors is an effective strategy for inhibiting a broad range of unspecific populations of immune cells as well as erythrocytes and platelets [35]. Thus, the blockage of these early populations is not desirable unless these progenitors are involved in the disease (i.e., myelofibrosis).

5. JAKis efficiently inhibits IFNγ + CD40L-stimulated DCs but not LPS-stimulated DCs.

Dendritic cells (DCs) are the most potent antigen-presenting cells (in addition to B-cells and macrophages) and act as initiators of the adaptive immune response. Pathogen and danger detection through pattern recognition receptors (e.g., Toll-like receptors) or intrinsic activation (e.g., CD40 L and IFNγ) induce DC migration to lymph nodes and their functional maturation (decrease of pathogen detection, increase of costimulatory ability and secretion of inflammatory cytokines) [36]. There are two main subsets of DCs: plasmacytoid DCs (pDCs) and conventional DCs (cDCs). pDCs are involved in antiviral or intracellular bacterial responses and induce abundant secretion of type I IFN and other cytokines, such as IL-12 (Th1 activation) and IL-15 (positive feedback), whereas cDCs play important roles in T-cell activation with

higher antigen-presentation activity [37]. Monocytes can also differentiate into a specific DC subset, namely, moDCs, which can efficiently activate the proliferation, cytotoxicity and cytokine production of natural killer (NK) cells and the proliferation and cytokine secretion of Th1 cells through the secretion of IL-2 and IL-12 [37].

In the context of organ transplantation, ischemia reperfusion injury (IRI) is a leading cause of graft failure that involves the induction of alloimmune-specific responses to the graft. Ischemia upregulates several inflammatory cytokines and chemokines and enhances MCH-II and adhesion molecule expression on DCs and epithelial cells. Moreover, dying cells constitute an important source of danger-associated molecular patterns (DAMPs) [38]. In healthy kidney transplanted patients, donor resident DCs in the graft are replaced within 7 days by host DCs, which are responsible for T-cell activation. Even in healthy tissues, host DCs might present alloantigens through cross dressing with donor DCs (donor CHM-peptide presented by recipient DC) [39]. Thus, the post-transplantation graft environment favors DC activation during both the acute and chronic phases of activation, which is necessary for subsequent T-cell activation, and thus, DCs play a role at the early stage of transplant rejection. DCs also have the potential to delay allograft rejection through the secretion of IL-10 and the inhibition of allogenic T- and B-cell proliferation and effector activity when stimulated with mesenchymal stromal cells [40]. Thus, it is important to block intrinsic DC activation without perturbing the generation of naïve DCs.

In IFNγ + CD40L-stimulated moDCs, JAK1 inhibition (using siRNA or ruxolitinib) leads to the downregulation of IL-12 production, whereas in cells stimulated with LPS (TLR4) + IL-1β, JAK1 inhibition leads to increased expression of IL-12 [41]. On the one hand, JAK1 directly transduces IFNγ signaling through JAK1/JAK2-mediated STAT1 phosphorylation, and this signaling results in the induction of IRF1 and IRF8 transcription and thereby in the induction of IL-12p35 and IL-12p40 transcription. On the other hand, IL-2-stimulated DCs induce STAT3 phosphorylation through the JAK1/JAK3 pathway. STAT3 forms a complex with the transcription factor RELA, and this complex inhibits the transcription of RELA-dependent genes, including IL-12p35 [41] (Fig. 4). Other studies have described tofacitinib as a potent inhibitor of the IFNα pathways because it inhibits its production by single-stranded RNA (TLR7)-stimulated pDCs and the action of IFNα on effector cells [42,43]. These data highlight the potential of JAK1 inhibitors to inhibit DC subsets in the context of transplantation, in which DCs are activated by the release of DAMPs combined with proinflammatory cytokines in the graft environment.

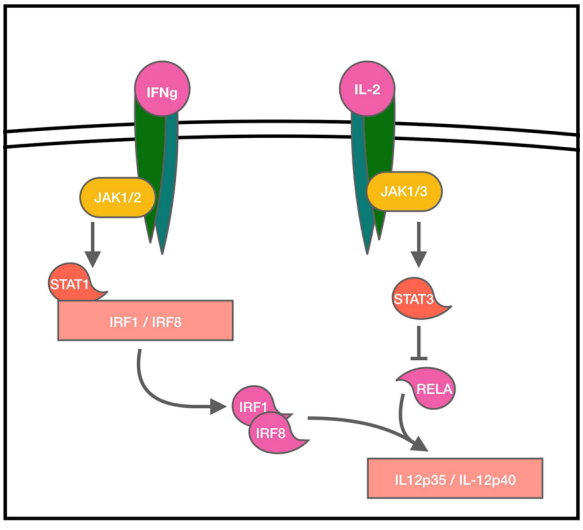

Fig. 4. JAK inhibition may impact opposite pathways.
JAK are overused kinases for cytokine signal transduction. The redundancy between JAK and STAT association led to the implication of the same JAK in both activation and inhibition of a gene transcription. In dendritic cells, JAK1 inhibitors may downregulate IFNg mediated IL-12 transcription and upregulate its transcription in presence of IL-2.

6. JAKis mainly affect T-cells through γC signaling.

T-cells are a wide and heterogeneous population involved in adaptive immunity and play an important role in graft rejection. Moreover, upon activation, T-cells secrete numerous proinflammatory cytokines and chemokines, and these activate other effector cells, thereby amplifying the immune response to the graft.

6.1. Important role of JAK in CD8 + T-cell activation with only minor implications on cell survivability.

CD8 + T-cells are an effector population involved in adaptive cellular immunity. CD8 + T-cell cytotoxicity is mediated through the interaction of FAS with FASL in combination with perforin and granzyme secretion.

The specificity of T-cells is not absolute, and a single TCR can recognize both different peptides and MHC molecules. In the context of transplantation, this cross-reactivity leads to the interaction of TCRs with allogenic cells in a manner similar to that observed with syngeneic cells. EBV- or CMV-specific memory CD8 + T-cells frequently exhibit cross-reactivity toward allogeneic MHC class I complexes [44]. IRI induces a massive infiltration of the graft environment by effector-memory CD8 + T-cells that mediate direct and severe injuries [45]. Thus, memory T-cells are a high-priority target of immunosuppressive treatments after transplantation.

A JAK2 inhibitor (AZD1480) has been shown to prevent the IFNγ-induced upregulation of MHC class I in mice and humans and thus reduces the probability of donor cells stimulating alloreactive CD8 + T-cells. In a murine model of autoimmune insulitis, this inhibition leads to reduced accumulation of CD8 + T-cells in islets [46]. Clinical studies on the effect of tofacitinib in renal allograft recipients observed that this drug has a low impact on the CD8 + cell count and strongly inhibits IL-2 and IL-15 signaling [47,48]. Tofacitinib-induced JAK1/JAK3 inhibition strongly affects γc cytokine-induced STAT5 phosphorylation in CD8 + cells, an effect that is highly reversed after the treatment is stopped, whereas JAK2 inhibition blocks interferon responses. These data suggest an important role for JAK in CD8 + cell activation with only minor implications on cell survivability.

6.2. JAKi efficiently inhibits effector CD4 + T-cells but not regulatory CD4 + T-cells.

CD4 + T-cells are a highly heterogeneous population that includes Th1, Th2, Th9, Th17, Th22 cells, regulatory CD4 + T-cells (Tregs) and follicular helper T-cells (Tfh cells) differentiated from TCR-activated naïve CD4 + T-cells (Th0 cells). The characteristics of the activated cells depend on the cytokine environment after TCR engagement. CD4 + T-cells play a central role in adaptative immunity, leading to the activation of effector cells depending on the recognized pathogens [49].

6.2.1. Implication of all four JAKs in Th1 functions.

Th1 cells are stimulated by IL-12 and IFNγ produced by innate cells (NK cells, DCs and macrophages) [49]. This cytokine stimulation leads to the activation of STAT1, which in turn activates a second transcription factor, T-bet [50]. Th1 cells are a source of IFNγ and IL-2, which serve as diverse mediators of inflammation by increasing IgG production [51] and the proliferation and activation of cytotoxic lymphoid cells [52,53], macrophages [54] and DCs [55]. All four JAKs play important roles in the development of Th1 cells in a nonredundant manner through the IL-2, IL-12 or IFNγ pathways.

The implication of Th1 cells in transplant rejection has been widely assessed [56–58]. Alloreactive Th1 cells produce IL-2 to enhance the proliferation of primed cytotoxic CD8 + T cells, which in turn induce

positive feedback through the production of IFNγ. Different types of JAKis efficiently block CD4+ IFNγ+ (Th1) cell differentiation. Tofacitinib reduces IFNγ mRNA production in human CD4 + T-cells stimulated in vitro with anti-CD3/anti-CD28 antibodies and IL-2 [59]. Tofacitinib also significantly reduces Th1 differentiation in the spleen of arthritis rats [60]. The JAK1/2 inhibitor ruxolitinib reduces the expression of the Th1-related cytokines IFNγ and IL-12 in a rheumatoid arthritis rat model by 55–80% [61]. The more selective JAK3 inhibition obtained with PF-06651600 or R348 has also been shown to block Th1-mediated IFNγ production in healthy human volunteers [62] and in a murine cardiac allograft model [63].

6.2.2. Pan-JAKi, but not JAK3i, inhibits Th2 cell generation.

Th2 cells are stimulated in the presence of IL-2 and IL-4 and are an important source of IL-4, IL-5 and IL- 13, which are mediators of humoral immunity (immunoglobulin (Ig) class switch to IgM, IgA, and IgE, eosinophil activation, and T-cell proliferation) [64]. Th2 stimulation is also dependent on different JAKs: both IL-2R and IL-4R activation engage JAK1 and JAK3, whereas IL-5 activation is dependent on JAK2 [65]. In addition, the IL-13 receptor is associated with JAK1, JAK2 and TYK2, but only JAK1-specific inhibition leads to the downregulation of STAT6 phosphorylation [66]. Clinical studies in kidney transplantation have shown that during acute rejection, only 2% of CD4 + T-cells that invaded the graft show a Th2 secretion profile [67], indicating a minimal role for Th2 cells in acute rejection compared with that of Th1 cells. However, an analysis of mRNA collected from kidney biopsies exhibiting chronic rejection reveals a preference toward a Th2 over a Th1 profile [68]. Because the differentiation to Th2 cells is mediated by IL-2 and IL-4, which requires the γc chain and the JAK1/JAK3 dimer, their inhibition with tofacitinib efficiently modulates the generation of Th2 cells in healthy individuals [69]. However, the specific inhibition of JAK3 by R348 fails to significantly inhibit IL-4 secretion in a murine cardiac allograft model [63]. These data highlight the dominant role of JAK1 over JAK3 in γc cytokine signal transduction, as described by Haan [70].

JAK3is reduce FoxP3 expression, resulting in cells with still a regulatory phenotype and JAK2is enhance regulatory functions.

Tregs are suppressive cells characterized by the transcription factor forkhead box P3 (FoxP3) [71] that act as a negative feedback for immune responses through the production of IL-10 and TGFβ (i.e., FoxP3) [71], an antiproliferative effect, and the downregulation of proinflammatory cytokines, chemokines, MHC II and costimulatory molecules) [72]. Tregs constitute a heterogeneous population. Natural (n) Tregs acquire their regulatory phenotype through thymic development, whereas adaptive Tregs are generated in the periphery from Th0 cells in the presence of TGFβ [73]. IL-2 reinforces this signal through pSTAT5 induction, which in turn enhances FoxP3 production, and IL-10 is known to induce STAT3 phosphorylation and regulate Th17 proinflammatory responses [74,75]. The specific in vitro inhibition of JAK2 achieved with TG101348 increases the ratio of Tregs to effector T-cells in healthy human donors [76]. An in vitro assay of mouse autoimmune arthritis revealed that AG-490, a JAK2 inhibitor, enhances FoxP3 expression under inflammatory conditions (anti-CD3, anti-CD-28, anti-IFNγ, anti-IL-4, TGFβ and IL-6) [77]. JAK2 mediates STAT3 phosphorylation, which negatively regulates STAT5 phosphorylation. JAK2 inhibitors have been shown to eliminate STAT3 activity mediated by inflammatory cytokines (IL-6) [77,78] to potentially increase IL-2 and subsequent Treg activity. In type 1 diabetic NOD mice, specific inhibitors of JAK3 efficiently inhibit IL-2 signaling and significantly reduce the nTreg (CD25+ FoxP3+) population, confirming the essential role of the IL-2/JAK3/STAT5 pathway in Treg activation [79]. However, the cells generated in the absence of IL-2 signaling in pro-Treg conditions (IL-10 and TGFβ) secrete elevated levels of TGFβ and IL-10, which are two common Treg cytokines [79]. Overall, JAKis do not affect the in vivo activity of Tregs, which show active production of their signature cytokines.

6.2.3. JAKi preferentially inhibits pathogenic IL-23, IL-6 and IL-1β-induced Th17.

Th17 cells can be stimulated by TGFβ and IL-6 but can also be produced in the presence of IL-23, IL-6 and IL-1β [80]. The cells can secrete IL-2, IL-17A-F and IL-22, but more than 2000 genes are differentially expressed. This difference shows that IL-23-, IL-6- and IL-1β-generated Th17 cells show increased pathogenicity. In both conditions, IL-23 is required for the secretion of IL-17 and IL-22 by Th17 cells [80]. Th17 cells participate in acute transplant rejection by recruiting neutrophils into the graft through the secretion of IL-17 via a JAK-independent pathway [81]. TGFβ-induced Th17 cells show less dependency on Tregs upon JAK activation. Experimental results from mice administered tofacitinib revealed an increased proliferation of TGFβ- and IL-17-producing cells after stimulation with both TGFβ and IL-6. This increase in Th17 differentiation is explained by the inhibition of the IL-2 pathway, which effects a negative feedback effect on this population. In contrast, tofacitinib suppresses the generation of Th17 cells generated in the presence of IL-23, IL-6 and IL-1β [50]. A high concentration of the Tyk2 inhibitor tyrphostin A1 (50 mg/kg) in a mouse model significantly reduces IL-23 and IL-17 production [82].

6.2.4. IL-22 and IL-9 inhibit JAK dependent proinflammatory cytokines.

Th22 cells are a less-known T-cell population defined as CD4 + T-cells that produce IL-22 and TNFα but not IL-17, IL-4 or IFNγ and exhibit skin-homing properties [83]. Naïve CD4 + T-cells differentiate into Th22 cells in the presence of IL-6 and TNFα [83,84]. There is little information on the importance of Th22 cells compared with other IL-22-producing cells in transplant rejection. Th22 cells are dependent on TNFα, which has been implicated in the pathogenesis of acute and chronic transplant rejection [85,86], but no Th22 cells have been shown to infiltrate transplanted organs. IL-22 is secreted by many cell types, including Th22 cells and other helper T-cells (Th1, Th2, and Th17), innate lymphoid cells (ILCs), monocytes and macrophages. IL-22-knockdown mice show accelerated rejection of heart allografts, revealing the anti-inflammatory role of this cytokine in transplantation [87]. The anti-inflammatory properties of IL-22 have been described in an autoimmune myocarditis rat model [88]. IL-22 inhibits the IL-1-mediated upregulation of prostaglandin synthetases, IL-6, COX2, MIP-2, MCP-1 and CINC-2. The inhibition of IL-22 signaling by JAKis reinforces the action of IL-1 but does not induce direct damage to the graft [89–92]. The information associated with Th9 cells is similar to that associated with Th22 cells. Few studies have focused on Th9 cells in the context of transplantation, and their role is thus uncertain. Th9 cells are one of many IL-9-secreting cells, similarly to Th2 and Th17 cells, Tregs, NKT cells and mast cells [93]. Similar to IL-22, IL-9 inhibition during IRI significantly augments the structural damage in the kidneys of transplanted mice [94]. IL-9 is a member of the IL-2 family of cytokines that share the γc chain and requires JAK1/JAK3 signaling [93]. IL-9 and Il-22 are thus tolerogenic cytokines through the inhibition of several pro-inflammatory factors whose activation is also dependent on JAKs. Thus, the overall activator or inhibitory role of JAKis in these factors should be investigated.

6.2.5. Tfh cells constitute an effective strategy for inhibiting B-cell generation in germinal centers.

Tfh cells are generated from primed naïve T-cells in the presence of IL-6 and IL-21 but are negatively regulated by IL-2 and IL-7 through IL-6Ra downregulation [95]. Other cytokines, such as IL-12 and TGF-β, have been shown to potentiate Tfh differentiation [96,97]. The expression of CXCR5 induces their migration in the germinal centers (GCs) of lymphoid organs [98]. Tfh cell activation in GCs is dependent on TCR engagement and costimulatory signals provided by cognate B-cells [99]. Tfh cells are involved in B-cell-mediated immunity by activating B lymphocyte differentiation into plasmablasts and IgG and IgM production through the secretion of IL-21 and IL-4 [100,101]. Three months after kidney transplantation, the number of peripheral Tfh cells

remains stable in patients with no pre-existing donor-specific antigens (DSAs), whereas the Tfh count in sensitized patients is increased [102]. A previous study showed that B-cells require the direct binding of Tfh cells with donor antigen-presenting cells to efficiently induce IgG and IgM production in B-cells [103]. The inhibition of B-cells by CD20 inhibition does not increase the transplant survival rate of model mice [104], whereas treatments targeting Tfh cells with CD40, IL-21 or IL-21R antagonists efficiently reduce DSA production [100,102,105]. Tfh cells have regulatory equivalents (Tfr cells) derived from Tregs expressing CXCR5 [106]. These results indicate the potential of JAKis for inhibiting B-cell activation in the context of transplantation through the establishment of a tolerogenic background in lymph node GCs.

The blockade of STAT3 significantly reduces both the count and the activity of Tfh cells in vivo, resulting in impaired activation of B-cells and the production of Ig [107]. Thus, JAKis might act on these cells. Tofacitinib downregulates the Tfh cell count and activity without inhibiting the Tfr cell population in a rat model of experimental autoimmune encephalomyelitis (EAE) [108].

Altogether, these data show the importance of JAK-dependent cytokines in the biology of T-cells. All T-cells are dependent on IL-2 to proliferate and express their defining transcription factors. Thus, JAK1 and JAK3 inhibitors efficiently block non-specific T cell activation.

7. JAKis do not affect Naïve B-cell generation.

B-cells comprise the main population of cells involved in adaptive humoral immunity by producing soluble Ig molecules, which are also known as antibodies and specifically target threatening antigens [109]. Their development from a common lymphocyte progenitor in the bone marrow requires the expression of three JAK-dependent cytokines, namely, thymic stromal lymphopoietin (TSLP), IL-7 and stem cell factor (SCF) [110–112]. The main function of B-cells is the release of antigen-specific antibodies that can activate the complement system and antibody-dependent cell cytotoxicity (ADCC) [113,114]. In addition, B-cells can also internalize pathogens recognized by their B-cell receptor (BCR) and then present peptides on MHC II to activate cognate T cells [114,115]. Once generated in the bone marrow, immature B-cells migrate to secondary lymphoid organs to form naïve marginal zone B-cells (MZB) or follicular B-cells. Despite the implication of several IL-2 family cytokines in B-cell development, JAK3 loss-of-function mutations inhibit T-cell development but do not affect B-cell compartments [29].

7.1. T-cell-independent activation is not increased in transplantation.

T-cell independent antigens activate BCR signaling in MZB cells. The signaling downstream of BCRs and TLRs/IL-1 induces strong IgM secretion independent of JAK [116,117]. Thus, JAKis should not target bacterial and viral TLR-dependent responses [118]. These T-cell-independent B-cell stimulations remain minor in allograft transplantation [119].

7.2. Follicular and memory B-cells generate plasma cells in transplantation.

T-cell-dependent antigens activate follicular B-cells [118]. In the context of transplantation, host naïve circulating B-cells recognize DSAs from graft endothelial cells [120]. Primed B-cells internalize DSAs through phagocytosis and present them via MHC class II. These cells re-enter the B-follicle, and through cytokinic crosstalk with Tfh cells (IL-4, IL-5, IL-6, IL-21 and BAFF) and cell-cell interactions, the cells undergo massive proliferation to form long-lived memory cells in GCs and antibody-secreting plasma cells. [121,122]. Plasma cells secrete DSA-specific Ig that cause injury to the endothelium through the complement pathway, antibody-dependent cell cytotoxicity (ADCC) and the recruitment of inflammatory cells (monocytes/macrophages, NK cells and neutrophils) by binding to the Fc portion of DSAs [123,119].

Memory B cells are long-lived quiescent cells that are generated from activated GC cells during the primary immune response and are programmed through epigenetic mechanisms to rapidly differentiate into antibody-secreting plasma cells [118]. Donor-specific memory B-cells can be expressed by recipients after pre-graft sensitization (blood perfusion, during pregnancy or from a previous transplantation) [124,120]. Thus, it is more important to block memory B-cell activation than to block their generation. The differentiation of memory B-cells to plasma cells is restricted to the expression of Blimp1, the absence of the memory subset and the inhibition of BACH2, which repress the transcription of Blimp1 [125].

7.3. Plasma cell-determining genes are downregulated by JAKis.

Plasma cells are terminally differentiated, nondividing B-cells that arise from activated naïve or memory B-cells that produce high amounts of antibodies. The activation of both naïve and memory cells requires BCR, CD40 L and cytokine signals (IL-21) that converge to activate Blimp1 [126]. However, the cytokinic threshold is lower in the memory subset than in the naïve subset. Thus, higher concentrations of the inhibitor are required to efficiently block memory B-cell activation [127,100]. The JAKis baricitinib and tofacitinib efficiently induce dose-dependent inhibition of the transcription of plasmablast-determining genes (Blimp-1, Xbp-1 and IRF-4) downstream of STAT3 in humans and inhibit the production of IL-6 [128,129].

Class switching is an important feature of B-cells, which allows diversification of the effector functions of the generated antibodies (cell surface receptor binding, polymerization, and tissue diffusion). Class switching is initiated by CD40 L and/or TLR stimulation, and the isotype is determined by the cytokine background [130]. In mice, class switching to IgG or IgA is not affected by tofacitinib in vitro [129].

7.4. The JAK2 inhibitor suppresses the secretion of IL-10 from tolerogenic regulatory B-cells (Bregs).

Bregs are a regulatory cell population capable of producing anti-inflammatory cytokines such as IL-10 [131], granzyme B [132], IL-35 [133] and TGF-β [134]. Bregs regulate inflammation through various mechanisms, such as the induction of FoxP3 expression in CD4 + T-cells to promote the T-reg phenotype [135] and the induction of effector T- and B-cell apoptosis [136,137]. Lee et al. showed the role of Bregs in graft tolerance through the adoptive transfer of anti-CD45RB plus anti-TIM-1-treated B-cells exhibiting regulatory activity into B-cell-deficient mice, which resulted in an increased graft survival to more than 100 days, whereas the adoptive transfer of naïve B-cells had no effect [138]. Clinical evidence from human trials associates tolerance with increased frequencies of circulating Bregs [139,140]. The induction of IL-10-producing Bregs requires interaction with CD40 [141]. Among the CD40-induced signals, the JAK3-STAT3 pathway is known to induce IL-10 gene expression [142]. Autocrine IL-10-induced JAK1/JAK2-STAT3 signaling is also important for sending positive feedback signals to Bregs [143]. The JAKi AG490 suppresses the generation of CD40 + hiCD5 + Bregs [143]. TYK2 is phosphorylated in response to IL-10 stimulation, but TYK2-/- mice are responsive to IL-10 [144]. In conclusion, the use of JAKis that inhibit the JAK3-STAT3 or JAK1/JAK2-STAT3 pathways is not a good strategy in the context of transplantation because these pathways induce the generation of both effector plasma cells and tolerogenic Bregs. In contrast, the use of TYK2 inhibitors would be more appropriate to avoid impacting the secretion of IL-10 by Bregs [144].

8. JAKis block innate lymphoid cell (ILC) differentiation from progenitors and ILC1 but not ILC2 and ILC3 function.

ILCs constitute a broad lymphocyte population that can be considered an antigen-independent version of T-cells with similar transcription factors, cytokine activation and secretion profiles. NK cells are

the innate counterpart of CD8 + T-cells and the most studied ILC. Three groups of ILCs called ILC1, ILC2 and ILC3 reproduce the action of Th1, Th2 and Th17 cells because they show similar cytokine activation and secretion profiles [145]. NK cells are a subpopulation of ILC1, the innate counterpart of CD8 + T-cells and the most studied ILCs [146].

NK cells constitute the main cytotoxic population of the innate immune system that has been implicated in malignant and virus-infected cell recognition and death. NK cell cytotoxicity is dependent on the balance between numerous NK receptors (NKR), which dictate NK cell-targeted lysis. Inhibitory receptors allow the avoidance of cytotoxicity toward self-cells such that NK cells can differentiate self from nonself (increased activation of activating receptors) and missing-self (decreased activation of inhibitory receptors). These receptors are independent of JAKs, but the response of NK cells needs to be triggered by interactions with IL-12 and IL-15 from activated macrophages or DCs [147]. In addition to their cytotoxic role, NK cells are important due to their ability to produce cytokines (mainly IFNγ and TNFα) during the early phases of infections that connect innate and adaptive immunity. IFNγ production by NK cells is dependent on both IL-12 and TLR stimulation [148]. NK cells are one of the immune populations that were first associated with transplant rejection in both cell- and antibody-mediated rejection [149]. In rat models of heart transplant rejection, NK cells infiltrate the graft environment within 3 h after reperfusion [150]. In humoral rejection, NK cells are an important source of IFNγ for B-cell differentiation, and NK cell-B-cell interactions trigger Ig class switching and secretion in the absence of any other stimulation [151]. In addition to this B-cell activator role, NK cells directly induce microvascular injuries through ADCC [152].

Tofacitinib significantly reduces the peripheral NK cell number in kidney transplanted patients [153]. JAK3 KO or the use of the JAKis tofacitinib and PF-06651600 is associated with the blockade of pre-NK cell progenitors and ILC progenitor maturation in a mouse model, and this deficiency has been attributed to a loss of IL-15 signaling [154]. Experimental evidence shows that tofacitinib inhibits the ILC1 production of IFNγ and yields better results than the JAK3-specific inhibitor, indicating synergy between JAK3 and JAK1 or JAK2 inhibition. Tofacitinib exerts no effect on ILC2 and ILC3 function (i.e., IL-5 production by ILC2 and IL-22 production by ILC3) [154].

9. JAKis can efficiently block neutrophils and eosinophils but not basophils.

Neutrophils are the first population of cells to infiltrate transplanted organs, and this infiltration occurs within 30 min after reperfusion [155]. These cells are recruited by cytokines (IL-1β and CXCL8 in humans) secreted by resident macrophages, and this recruitment combined with DAMPs induces the expression of reactive oxygen species (ROS) in neutrophils that directly participate in graft damage [155]. In addition to direct damage, neutrophils also participate in T-cell stimulation: they migrate to lymph nodes and express MHC and costimulatory signals to present antigens to CD8+ or CD4 + T-cells [156]. In murine transplantation models, neutrophil depletion induces slower cellular rejection, showing the importance of these cells in promoting alloimmune T-cell responses [157]. Another study using a murine model of transplantation revealed the same role for neutrophils in acute antibody-mediated rejection with prolonged graft survival [158]. In chronic rejection, neutrophilia might be explained by the activation of IL-17-producing cells, which are known to be potent drivers of both neutrophil recruitment and activation. Tofacitinib and ruxolitinib reduce inflammation and the neutrophil percentage in rats and humans with neutrophilic asthma [159,160].

Eosinophils are one of the ADCC effector cells that also participate in plasma cell maintenance through cytokine secretion. In transplantation, eosinophils are recruited by IL-5 secreted from Th2 cells and are associated with graft fibrosis [161], and eosinophilia has been shown to be a poor prognosis factor [162]. However, murine models of eosinophil-depleted heart transplantation show no reduction in DSA secretion [163]. Thus, these data suggest that eosinophils have a more important role in cellular rejection than in antibody-mediated rejection. The activation and survival of eosinophils are dependent on IL-5 and IFNγ, which are JAK2-dependent cytokines that are efficiently inhibited by AG-490 or ruxolitinib in humans and mice with eosinophilic asthma [164,160].

An analysis of murine cardiac allografts revealed that basophils induce fibrosis in the allografts [165]. Fibrosis is associated with two features of basophils: histamine release and IL-4 secretion. Thus, the depletion in basophils induces a reduction in fibrotic organ remodeling [165,166], but a clinical trial of the pan-JAKi tofacitinib did not show a dose-dependent basophil reduction after 12 weeks of psoriasis treatment [167].

10. JAK1/STAT1 inhibition favors pro-regenerative M2 macrophages over inflammatory M1 macrophages.

Macrophages are tissue-infiltrating antigen-presenting cells derived from circulating monocytes whose main function is phagocytosis. Two different activation states have been described: M1 macrophages are induced by IFNγ, LPS and TNFα, which show pro-inflammatory and cytotoxic activity, and M2 macrophage differentiation is induced by IL-4 and IL-13, which show anti-inflammatory activity. Previous studies have implicated macrophages in both acute and chronic rejection [168,169]. Other studies [170–173] have also shown the importance of M2 macrophages in graft regeneration after IRI in both mouse models and humans. In human macrophages, ruxolitinib inhibits 61.4% of LPS-induced genes, including IL-6 and TNFα, but not IL-12B, GM-CSF, CCL20, CXCL2 and IL-1β. This inhibition is not directly associated with LPS signaling, but IFNβ autocrine secretion most likely enhances the expression of LPS-induced genes [174]. The effects of JAKis on M2 macrophages have not been described, but suppressor of cytokine signaling 1 (SOCS1)-mediated JAK1/STAT1 inhibition has been shown to favor the M2 phenotype [175].

11. Ruxolitinib inhibits proinflammatory secretion from mast cells.

Mast cells are epithelium-resident effector cells that have been implicated in bacterial and parasitic infections and allergic reactions. Mast cell activation by IgE through FcεRI or PRR triggers their degranulation in association with a massive release of immune mediators, including histamine. Mast cell responses can be positively modulated by various inflammatory mediators, including hypoxia and cytokines (SCF, IL-3, IL-4, IL-9 and, to a lesser extent, IL-5, IL-6 and GM-CSF) [176]. Mast cells can in turn secrete various cytokines depending on the immunological environment, such as the levels of IL-1β, IL-3–6, IL-10 and IL-13, TNFα, IFNα, GM-CSF, FGF and TGFβ. Thus, through their secretory profile, mast cells participate in both inflammation and regulatory processes. Mast cells show increased activation in lung transplantation than in other solid organ transplantation due to the constant exposure of the lungs to airborne antigens. Several studies have noted a role for mast cells in IRI [177,178]. The treatment of human mast cell lines with ruxolitinib in the presence of substance P or codeine efficiently inhibits their degranulation and production of IL-6, TNFα and CCL2 in a dose-dependent manner [179]; however, the researchers did not assess the impact of ruxolitinib on the anti-inflammatory profile of mast cells.

12. Conclusions

This review summarizes the role of immune cell populations in transplantation and their modulation by JAKis. The literature does not cover the impact of each specific JAK inhibition on all populations, and thus, even if JAKs form part of major signaling pathways in these cells,

it is nearly impossible to predict their role. Indeed, we have to consider the redundancy of the interactions among cytokine receptors, JAK and STAT combined with the massive interplay between all types of immune cells. JAKi-driven immunosuppression is a promising strategy for the treatment of conventional DMRAD-resistant diseases. Thus, the characterization of the immunosuppressive profiles induced by different types of JAKis is an essential step for obtaining a better understanding of the treatments and for proposing the most appropriate immunosuppressive strategies according to each pathology. To the best of our knowledge, although some families of JAK1 inhibitors have been described in the literature, there are no data on the effects of JAK1-specific inhibitors on immune cells [180,181]. JAK2 inhibition, alone or combined with the inhibition of JAK1 by ruxolitinib, mainly interacts with hematopoietic progenitors and myeloid cells (neutrophils, eosinophils, macrophages and mast cells] and mostly affects the Th1 subset and IFN pathways. JAK3 is the only tissue-specific JAK, but the effects of its inhibition are not limited to lymphoid cells. JAK3 inhibitors efficiently block helper T-cell activation through IL-2 and IL-4 and thus inhibit the subsequent production of cytokines, including IFNγ and IL-5, required by myeloid cells. Tyk2 is a less-studied JAK whose action is more limited, particularly to IL-12/IL-23 and type I interferons.

As shown in B-cells, the activation of effector and tolerogenic regulatory cells might be induced through the same JAK/STAT pathways. Under these conditions, it is impossible to select a JAKi that will act on only one subset to favor graft tolerance. Reduced JAKi doses can reduce their impact on regulatory subsets by inducing only partial direct inhibition of B-regs. In effector subsets, reduced JAKi doses combine partial direct inhibition with the inhibition of upstream signaling such as Tfh and Tfr cells.

The ultimate goal in transplantation is to achieve graft tolerance in the most effective way possible, which involves the selection and inhibition of alloimmunity without interrupting the anti-pathogen defense responses. These two mechanisms are mediated by the same cells, and higher sensitivity is associated with reduced specificity to alloimmune responses. In this review, we highlight the implication of nearly all effector subsets in cellular or humoral graft rejection. The inhibition of JAK disrupts cell communication without affecting effector functions, which results in the strong recovery of the latent immune populations after drug elimination [182]. This lack of cell communication induces apoptosis in immune cells. JAKi-mediated apoptosis is inhibited in TLR-stimulated antigen-presenting cells [42], showing that the JAK/STAT pathways and JAKis play less important roles in TLR-mediated bacterial and antiviral responses than in cytokine-stimulated cell activation.

Authorship and conflict-of-interest statements

All authors participated in the writing of this review. This review was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgment

This work was carried out with the support of CENTAURE foundation grant.

References

[1] Philip F. Halloran, Immunosuppressive Drugs for Kidney Transplantation. New England, J. Med. 351 (December (26)) (2004) 2715–2729.
[2] Dominic C. Borie, John J. O'Shea, Paul S. Changelian, JAK3 inhibition, a viable new modality of immunosuppression for solid organ transplants, Trends Mol. Med. 10 (November (11)) (2004) 532–541.
[3] J. Dantal, E. Pohanka, Malignancies in renal transplantation: an unmet medical need, Nephrol. Dial. Transplant. 22 (March (Supplement 1)) (2007) i4–i10.
[4] Alejandro V. Villarino, Yuka Kanno, John J. O'Shea, Mechanisms and consequences of Jak–STAT signaling in the immune system, Nat. Immunol. 18 (April (4)) (2017) 374–384.
[5] Rhiannon Morris, Nadia J. Kershaw, Jeffrey J. Babon, The molecular details of cytokine signaling via the JAK/STAT pathway, Protein Sci. 27 (December (12)) (2018) 1984–2009.
[6] Andrea C. Pfeifer, Jens Timmer, UrsulaKlingmu ller, Systems biology of JAK/STAT signalling, Essays Biochem. 45 (September) (2008) 109–120.
[7] Emira Bousoik, Hamidreza Montazeri Aliabadi, "Do We Know Jack" About JAK? A Closer Look at JAK/STAT Signaling Pathway, Front. Oncol. 8 (July) (2018).
[8] Kamran Ghoreschi, Arian Laurence, John J. O'Shea, Janus kinases in immune cell signaling, Immunol. Rev. 228 (March (1)) (2009) 273–287.
[9] Linda A. Winston, Tony Hunter, JAK2, Ras, and raf are required for activation of extracellular signal-regulated Kinase/Mitogen-activated protein kinase by growth hormone, J. Biol. Chem. 270 (December (52)) (1995) 30837–30840.
[10] Didier Bouscary, Fre deric Pene, Yann-Erick Claessens, Odile Muller, Stany Chre tien, Michaela Fontenay-Roupie, Sylvie Gisselbrecht, Patrick Mayeux, Catherine Lacombe, Critical role for PI 3-kinase in the control of erythropoietin-induced erythroid progenitor proliferation, Blood 101 (May (9)) (2003) 3436–3443.
[11] Robert Roskoski, Classification of small molecule protein kinase inhibitors based upon the structures of their drug-enzyme complexes, Pharmacol. Res. 103 (January) (2016) 26–48.
[12] Olli Silvennoinen, James N. Ihle, Joseph Schlessinger, David E. Levy, Interferon-induced nuclear signalling by Jak protein tyrosine kinases, Nature 366 (December (6455)) (1993) 583–585.
[13] P.C. Heinrich, I. Behrmann, G. Mu¨ller-Newen, F. Schaper, L. Graeve, Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway, Biochem. J. 334 (September (Pt 2) (1998) 297–314.
[14] James A. Johnston, Chris M. Bacon, M.C. Riedy, John J. O'Shea, Signaling by IL-2 and related cytokines: JAKs, STATs, and relationship to immunodeficiency, J. Leukoc. Biol. 60 (October (4)) (1996) 441–452.
[15] Ruud H.P. Wilbers, Debbie R. van Raaij, Lotte B. Westerhof, Jaap Bakker, Geert Smant, Arjen Schots, Re-evaluation of IL-10 signaling reveals novel insights on the contribution of the intracellular domain of the IL-10r2 chain, PLoS One 12 (October (10)) (2017).
[16] K. Igarashi, G. Garotta, L. Ozmen, A. Ziemiecki, A.F. Wilks, A.G. Harpur, A.C. Larner, D.S. Finbloom, Interferon- gamma induces tyrosine phosphorylation of interferon-gamma receptor and regulated association of protein tyrosine kinases, Jak1 and Jak2, with its receptor, J. Biol. Chem. 269 (May (20)) (1994) 14333–14336.
[17] Maria F. Brizzi, Maria G. Aronica, Arturo Rosso, Gian Paolo Bagnara, Yosef Yarden, Luigi Pegoraro, Granulocyte- macrophage colony-stimulating factor stimulates JAK2 signaling pathway and rapidly activates p93, STAT1 p91, and STAT3 p92 in Polymorphonuclear Leukocytes, J. Biol. Chem. 271 (February (7)) (1996) 3562–3567.
[18] Bruce A. Witthuhn, Frederick W. Quelle, Olli Silvennoinen, Taolin Yi, Bo Tang, Osamu Miura, James N. Ihle, JAK2 associates with the erythropoietin receptor and is tyrosine phosphorylated and activated following stimulation with erythropoietin, Cell 74 (July (2)) (1993) 227–236.
[19] C.M. Bacon, D.W. McVicar, J.R. Ortaldo, R.C. Rees, J.J. O'Shea, J.A. Johnston, Interleukin 12 (IL-12) induces tyrosine phosphorylation of JAK2 and TYK2: differential use of Janus family tyrosine kinases by IL-2 and IL-12, J. Exp. Med. 181 (January (1)) (1995) 399–404.
[20] J.A. Johnston, M. Kawamura, R.A. Kirken, Y.Q. Chen, T.B. Blake, K. Shibuya, J.R. Ortaldo, D.W. McVicar, J.J. O'Shea, Phosphorylation and activation of the Jak-3 Janus kinase in response to interleukin-2, *Nature* 370 (July (6485)) (1994) 151–153.
[21] N. Stahl, T.G. Boulton, T. Farruggella, N.Y. Ip, S. Davis, B.A. Witthuhn, F.W. Quelle, O. Silvennoinen, G. Barbieri, S. Pellegrini, Et. Al, Association and activation of Jak-Tyk kinases by CNTF-LIF-OSM-IL-6 beta receptor components, Science 263 (January (5143)) (1994) 92–95.
[22] C. Abramovich, L.M. Shulman, E. Ratovitski, S. Harroch, M. Tovey, P. Eid, M. Revel, Differential tyrosine phosphorylation of the IFNAR chain of the type I interferon receptor and of an associated surface protein in response to IFN-alpha and IFN-beta, EMBO J. 13 (December (24)) (1994) 5871–5877.
[23] Doreen M. Floss, TobiasKlo¨cker, Jutta Schro¨der, Larissa Lamertz, Simone Mrotzek, Birgit Strobl, Heike Hermanns, Jürgen Scheller, Defining the functional binding sites of interleukin 12 receptor b1 and interleukin 23 receptor to Janus kinases, Mol. Biol. Cell 27 (July (14)) (2016) 2301–2316.
[24] Various JAK inhibitor clinical trials (US). avaliable at: https://clinicaltrials.gov/ct2/results?cond=&term=jak+inhibitor&cntry=&state=clinicaltrials.gov, accessed 12.12.2018.
[25] Dafna Gladman, William Rigby, Valderilio F. Azevedo, Frank Behrens, Ricardo Blanco, Andrzej Kaszuba, Elizabeth Kudlacz, Cunshan Wang, Sujatha Menon, Thijs Hendrikx, Keith S. Kanik, Tofacitinib for Psoriatic Arthritis in Patients With an Inadequate Response to TNF Inhibitors, http://dx.doi.org.gate2.inist.fr/10.1056/NEJMoa1615977, October (2017).
[26] Mark C. Genovese, Joel Kremer, Omid Zamani, Charles Ludivico, Marek Krogulec, Li Xie, Scott D. Beattie, Alisa E. Koch, Tracy E. Cardillo, Terence P. Rooney, William L. Macias, Stephanie de Bono, Douglas E. Schlichting, Josef S. Smolen, Baricitinib in Patients With Refractory Rheumatoid Arthritis, (2016), https://doi.org/10.1056/NEJMoa1507247 March.
[27] Kevin L. Winthrop, The emerging safety profile of JAK inhibitors in rheumatic disease, Nat. Rev. Rheumatol. 13 (April (4)) (2017) 234–243.
[28] Evan Parganas, Demin Wang, Dimitrios Stravopodis, David J. Topham, Jean-Christophe Marine, Stephan Teglund, Elio F. Vanin, Sara Bodner, Oscar

R. Colamonici, Jan Mvan Deursen, Gerard Grosveld, James N. Ihle, Jak2 is essential for signaling through a variety of cytokine receptors, Cell 93 (May (3)) (1998) 385–395.
[29] Paolo Macchi, Anna Villa, Silvia Giliani, Maria G. Sacco, Annalisa Frattini, Fulvio Porta, Alberto G. Ugazio, James A. Johnston, Fabio Candotti, John J. O'Sheai, Paolo Vezzoni, Luigi D. Notarangelo, Mutations of Jak-3 gene in patients with autosomal severe combined immune deficiency (SCID), Nature 377 (September (6544)) (1995) 65–68.
[30] Scott J. Rodig, Marco A. Meraz, J.Michael White, Pat A. Lampe, Joan K. Riley, Cora D. Arthur, Kathleen L. King, Kathleen C.F. Sheehan, Yin Li, Diane Pennica, Eugene M. Johnson, Robert D. Schreiber, Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the jaks in cytokine-induced biologic responses, Cell 93 (May (3)) (1998) 373–383.
[31] Sally Yu Shi, Wei Zhang, Cynthia T. Luk, Tharini Sivasubramaniyam, Jara J. Brunt, Stephanie A. Schroer, Harsh R. Desai, Alexandra Majerski, Minna Woo, JAK2 promotes brown adipose tissue function and is required for diet- and cold-induced thermogenesis in mice, Diabetologia 59 (January (1)) (2016) 187–196.
[32] Momoko Chikugo, Mayu Sebe, Rie Tsutsumi, Marina Iuchi, Jun Kishi, Masashi Kuroda, Nagakatsu Harada, Yasuhiko Nishioka, Hiroshi Sakaue, Effect of Janus kinase inhibition by tofacitinib on body composition and glucose metabolism, J. Med. Investig. 65 (2018) 5.
[33] Paolo Gallipoli, Amy Cook, Susan Rhodes, Lisa Hopcroft, Helen Wheadon, Anthony D. Whetton, Heather G. Jørgensen, Ravi Bhatia, Tessa L. Holyoake, JAK2/STAT5 inhibition by nilotinib with ruxolitinib contributes to the elimination of CML CD34+ cells in vitro and in vivo, Blood 124 (August (9)) (2014) 1492–1501.
[34] Dimitra Zacharaki, Roshanak Ghazanfari, Hongzhe Li, Hooi Ching Lim, Stefan Scheding, Effects of JAK1/2 inhibition on bone marrow stromal cells of myeloproliferative neoplasm (MPN) patients and healthy individuals, Eur. J. Haematol. 101 (July (1)) (2018) 57–67.
[35] Sara C. Meyer, Matthew D. Keller, Brittany A. Woods, Lindsay M. LaFave, Lennart Bastian, Maria Kleppe, Neha Bhagwat, Sachie Marubayashi, Ross L. Levine, Genetic studies reveal an unexpected negative regulatory role for Jak2 in thrombopoiesis, Blood 124 (October (14)) (2014) 2280–2284.
[36] Charles A. Janeway, Paul Travers, Mark Walport, Mark J. Shlomchik, Charles A. Janeway Jr., Paul Travers, Mark Walport, Mark J. Shlomchik, Immunobiology, 5th edition, Garland Science, 2001.
[37] C. Munz, Mature myeloid dendritic cell subsets have distinct roles for activation and viability of circulating human natural killer cells, Blood 105 (January (1)) (2005) 266–273.
[38] Aleksandra Kezic, Natasa Stajic, Friedrich Thaiss, Innate immune response in kidney Ischemia/Reperfusion injury: potential target for therapy, J. Immunol. Res. 2017 (2017).
[39] Quan Zhuang, Quan Liu, Sherrie J. Divito, Qiang Zeng, Karim M. Yatim, Andrew D. Hughes, Darling M. Rojas-Canales, A. Nakao, William J. Shufesky, Amanda L. Williams, Rishab Humar, Rosemary A. Hoffman, Warren D. Shlomchik, Martin H. Oberbarnscheidt, Fadi G. Lakkis, Adrian E. Morelli, Graft-infiltrating host dendritic cells play a key role in organ transplant rejection, Nat. Commun. 7 (August) (2016) 12623.
[40] Yanfei Huang, Peter Johnston, Borui Zhang, Asif Zakari, Tayseer Chowdhry, Rachel Ruckdeschel Smith, Eduardo Marba´n, Hamid Rabb, Karl L. Womer, Kidney-derived stromal cells modulate dendritic and t cell responses, J. Am. Soc. Nephrol. 20 (April (4)) (2009) 831–841.
[41] Andreas H. Wagner, Michael Conzelmann, Franziska Fitzer, Thomas Giese, Karsten Gülow, Christine S. Falk, Oliver H. Kra¨mer, Sascha Dietrich, Markus Hecker, Thomas Luft, JAK1/STAT3 activation directly inhibits IL-12 production in dendritic cells by preventing CDK9/P-TEFb recruitment to the p35 promoter, Biochem. Pharmacol. 96 (July (1)) (2015) 52–64.
[42] Patrick P.C. Boor, Petra E. de Ruiter, Patrick S. Asmawidjaja, Erik Lubberts, Luc J.W. van der Laan, Jaap Kwekkeboom, JAK-inhibitor tofacitinib suppresses interferon alfa production by plasmacytoid dendritic cells and inhibits arthrogenic and antiviral effects of interferon alfa, Transl. Res. 188 (October) (2017) 67–79.
[43] Dhifaf Sarhan, Marzia Palma, Yumeng Mao, Lars Adamson, Rolf Kiessling, Hakan Mellstedt, Anders Österborg, Andreas Lundqvist, Dendritic cell regulation of NK-cell responses involves lymphotoxin-a, IL-12, and TGF-b, Eur. J. Immunol. 45 (June (6)) (2015) 1783–1793.
[44] Nicolas Degauque, Sophie Brouard, Jean-Paul Soulillou, Cross-reactivity of TCR repertoire: current concepts, challenges, and implication for allotransplantation, Front. Immunol. 7 (March) (2016).
[45] C.A. Su, S. Iida, T. Abe, R.L. Fairchild, Endogenous memory CD8 t cells directly mediate cardiac allograft rejection: endogenous memory CD8 t cell allograft rejection, Am. J. Transplant. 14 (March (3)) (2014) 568–579.
[46] Prerak M. Trivedi, Kate L. Graham, Nicholas A. Scott, Misty R. Jenkins, Suktilang Majaw, Robyn M. Sutherland, Stacey Fynch, Andrew M. Lew, Christopher J. Burns, Balasubramanian Krishnamurthy, Thomas C. Brodnicki, Stuart I. Mannering, Thomas W. Kay, Helen E. Thomas, Repurposed JAK1/JAK2 inhibitor reverses established autoimmune insulitis in NOD mice, Diabetes 66 (June (6)) (2017) 1650–1660.
[47] E. van Gurp, W. Weimar, R. Gaston, D. Brennan, R. Mendez, J. Pirsch, S. Swan, M.D. Pescovitz, G. Ni, C. Wang, S. Krishnaswami, V. Chow, G. Chan, Phase 1 dose-escalation study of CP-690 550 in stable renal allograft recipients: preliminary findings of safety, tolerability, effects on lymphocyte subsets and pharmacokinetics, Am. J. Transplant. 8 (August (8)) (2008) 1711–1718.
[48] Ramin Vafadari, Monique E. Quaedackers, Marcia M. Kho, Wendy M. Mol, Gary Chan, Willem Weimar, Carla C. Baan, Pharmacodynamic analysis of tofacitinib and basiliximab in kidney allograft recipients, Transplantation 94 (September (5)) (2012) 465.
[49] Bing Sun, Yuan Zhang, Overview of orchestration of CD4+ T cell subsets in immune responses, Adv. Exp. Med. Biol. 841 (2014) 1–13.
[50] Kamran Ghoreschi, Michael I. Jesson, Xiong Li, Jamie L. Lee, Sarbani Ghosh, Jason W. Alsup, James D. Warner, Masao Tanaka, Scott M. Steward-Tharp, Massimo Gadina, Craig J. Thomas, John C. Minnerly, Chad E. Storer, Timothy P. LaBranche, Zaher A. Radi, Martin E. Dowty, Richard D. Head, Debra M. Meyer, Nandini Kishore, John J. O'Shea, Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550), Journal of Immunology (Baltimore, Md.: 1950) 186 (April (7)) (2011) 4234–4243.
[51] H. Kishi, S. Inui, A. Muraguchi, T. Hirano, Y. Yamamura, T. Kishimoto, Induction of IgG secretion in a human B cell clone with recombinant IL 2, J. Immunol. 134 (May (5)) (1985) 3104–3107.
[52] O. Boyman, A.G.A. Kolios, M.E. Raeber, Modulation of T Cell Responses by IL-2 and IL-2 Complexes, (2015), p. 4.
[53] A. Senik, S. Stefanos, J.P. Kolb, M. Lucero, E. Falcoff, Enhancement of mouse natural killer cell activity by type II interferon, Ann. Immunol. (Paris) 131C (June (3)) (1980) 349–361.
[54] Carl F. Nathan, Henry W. Murray, Michael E. Wiebe, Berish Y. Rubin, Identification of interferon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity, J. Exp. Med. 158 (September (3)) (1983) 670–689.
[55] Orr-El Weizman, Nicholas M. Adams, Iona Schuster, Chirag Krishna, Yuri Pritykin, Colleen Lau, Mariapia A. Degli- Esposti, Christina S. Leslie, Joseph C. Sun, Timothy E. O'Sullivan, ILC1 confer early host protection at initial sites of viral infection, Cell 171 (November (4)) (2017) 795–808 e12.
[56] W. Jungraithmayr, L. Ji, L. Yang, W. Weder, S. Korom, M. Hersberger, Increased T-bet to GATA-3 ratio during acute allograft rejection in the rat lung, Transplant. Proc. 41 (December (10)) (2009) 4316–4320.
[57] Xiao-Jing Zuo, Yuji Matsumura, John Prehn, Ryo Saito, Alberto Marchevesky, Jack Matloff, Stanley C. Jordan, Cytokine gene expression in rejecting and tolerant rat lung allograft models: analysis by RT-PCR, Transpl. Immunol. 3 (June (2)) (1995) 151–161.
[58] Zhongmin Liu, Huimin Fan, Shuiping Jiang, CD4+ T-cell subsets in transplantation, Immunol. Rev. 252 (1) (2013) 183–191.
[59] Keisuke Maeshima, Kunihiro Yamaoka, Satoshi Kubo, Kazuhisa Nakano, Shigeru Iwata, Kazuyoshi Saito, Masanobu Ohishi, Hisaaki Miyahara, Shinya Tanaka, Koji Ishii, Hironobu Yoshimatsu, Yoshiya Tanaka, The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-g and interleukin-17 production by human CD4+ T cells, Arthritis Rheum. 64 (6) (2012).
[60] Smadar Gertel, Hussein Mahagna, Gidi Karmon, Abdulla Watad, Howard Amital, Tofacitinib attenuates arthritis manifestations and reduces the pathogenic CD4 T cells in adjuvant arthritis rats, Clin. Immunol. 184 (November) (2017) 77–81.
[61] J.S. Fridman, P.A. Scherle, R. Collins, T.C. Burn, Y. Li, J. Li, M.B. Covington, B. Thomas, P. Collier, M.F. Favata, X. Wen, J. Shi, R. McGee, P.J. Haley, S. Shepard, J.D. Rodgers, S. Yeleswaram, G. Hollis, R.C. Newton, B. Metcalf, S.M. Friedman, K. Vaddi, Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050, J. Immunol. 184 (May (9)) (2010) 5298–5307.
[62] Jean-Baptiste Telliez, Martin E. Dowty, Lu Wang, Jason Jussif, Tsung Lin, Li Li, Erick Moy, Paul Balbo, Wei Li, Yajuan Zhao, Kimberly Crouse, Caitlyn Dickinson, Peter Symanowicz, Martin Hegen, Mary Ellen Banker, Fabien Vincent, Ray Unwalla, Sidney Liang, Adam M. Gilbert, Matthew F. Brown, Matthew Hayward, Justin Montgomery, Xin Yang, Jonathan Bauman, John I. Trujillo, Agustin Casimiro-Garcia, Felix F. Vajdos, Louis Leung, Kieran F. Geoghegan, Amira Quazi, Dejun Xuan, Lyn Jones, Erik Hett, Katherine Wright, James D. Clark, Atli Thorarensen, Discovery of a JAK3- Selective Inhibitor: Functional Differentiation of JAK3-Selective Inhibition over pan-JAK or JAK1-Selective Inhibition, ACS Chem. Biol. 11 (December (12)) (2016) 3442–3451.
[63] Tobias Deuse, Jeffrey B. Velotta, Grant Hoyt, Johannes A. Govaert, Vanessa Taylor, Esteban Masuda, Ellen Herlaar, Gary Park, David Carroll, Marc P. Pelletier, Robert C. Robbins, Sonja Schrepfer, Novel immunosuppression: R348, a JAK3- and syk-inhibitor attenuates acute cardiac allograft rejection, Transplantation 85 (March (6)) (2008) 885–892.
[64] Masato Kubo, Innate and adaptive type 2 immunity in lung allergic inflammation, Immunol. Rev. 278 (1) (2017) 162–172.
[65] T. Kouro, Y. Kikuchi, H. Kanazawa, K. Hirokawa, N. Harada, M. Shiiba, H. Wakao, S. Takaki, K. Takatsu, Critical proline residues of the cytoplasmic domain of the IL-5 receptor alpha chain and its function in IL-5-mediated activation of JAK kinase and STAT5, Int. Immunol. 8 (February (2)) (1996) 237–245.
[66] Yoshihiko Chiba, Kumiko Goto, Miwa Misawa, Interleukin-13-induced activation of signal transducer and activator of transcription 6 is mediated by an activation of Janus kinase 1 in cultured human bronchial smooth muscle cells, Pharmacological reports: PR 64 (2) (2012) 454–458.
[67] Mario M. D'elios, Regis Josien, Marta Manghetti, Amedeo Amedei, Marco de Carli, Maria Cristina Cuturi, Gilles Blancho, Francoise Buzelin, Gianfranco Del Prete, Jean-Paul Soulillou, Predominant Th1 cell infiltration in acute rejection episodes of human kidney grafts, Kidney Int. 51 (June (6)) (1997) 1876–1884.
[68] Arcangelo Nocera, Augusto Tagliamacco, Raffaele De Palma, Francesco Del Galdo, Andrea Ferrante, Iris Fontana, Sergio Barocci, Fabrizio Ginevri, Davide Rolla, Jean Louis Ravetti, Umberto Valente, Cytokine mRNA expression in chronically rejected human renal allografts, Clin. Transplant. 18 (October (5)) (2004) 564–570.
[69] Kamran Ghoreschi, Michael I. Jesson, Xiong Li, Jamie L. Lee, Sarbani Ghosh, Jason W. Alsup, James D. Warner, Masao Tanaka, Scott M. Steward-Tharp, Massimo Gadina, Craig Thomas, John C. Minnerly, Chad E. Storer, Timothy P. LaBranche, Zaher A. Radi, Martin E. Dowty, Richard D. Head, Debra M. Meyer,

Nandini Kishore, John J. O'Shea, Modulation of Innate and Adaptive Immune Responses by Tofacitinib (CP-690,550), J. immune. (Baltimore, Md.: 1950) 186 (April (7)) (2011) 4234–4243.
[70] Claude Haan, Catherine Rolvering, Friedrich Raulf, Manuela Kapp, Peter Druckes, Gebhard Thoma, Iris Behrmann, Hans-Gunter Zerwes, Jak1 Has a Dominant Role over Jak3 in Signal Transduction through gc-Containing Cytokine Receptors, Chem. Biol. 18 (March (3)) (2011) 314–323.
[71] Eli M. Eisenstein, Calvin B. Williams, The Treg/Th17 cell balance: a new paradigm for autoimmunity, Pediatr. Res. 65 (May (5 Part 2)) (2009).
[72] O. Palomares, M. Marťın-Fontecha, R. Lauener, C. Traidl-Hoffmann, O. Cavkaytar, M. Akdis, C.A. Akdis, Regulatory T cells and immune regulation of allergic diseases: roles of IL-10 and TGF-b, Genes Immun. 15 (December (8)) (2014) 511–520.
[73] Shuang Fu, Nan Zhang, Adam C. Yopp, Dongmei Chen, Minwei Mao, Dan Chen, Haojiang Zhang, Yaozhong Ding, S. Jonathan, Bromberg. TGF-b induces Foxp3 + T-Regulatory cells from CD4 + CD25 - precursors, Am. J. Transplant. 4 (October (10)) (2004) 1614–1627.
[74] Ashutosh Chaudhry, Dipayan Rudra, Piper Treuting, Robert M. Samstein, Yuqiong Liang, Arnold Kas, Alexander Y. Rudensky, CD4+ regulatory T cells control Th17 responses in a Stat3-dependent manner, Science 326 (November (5955)) (2009) 986–991.
[75] Thomas C. Mangodt, Mikhaıl A. Van Herck, Sara Nullens, Jose Ramet, Jozef J. De Dooy, Philippe G. Jorens, Benedicte Y.De Winter, The role of Th17 and Treg responses in the pathogenesis of RSV infection, Pediatr. Res. 78 (November (5)) (2015) 483–491.
[76] Brian C. Betts, Omar Abdel-Wahab, Shane A. Curran, Erin T. St Angelo, Priya Koppikar, Glenn Heller, Ross L. Levine, James W. Young, Janus kinase-2 inhibition induces durable tolerance to alloantigen by human dendritic cell–stimulated T cells yet preserves immunity to recall antigen, Blood 118 (November (19)) (2011) 5330–5339.
[77] Jin-Sil Park, Jennifer Lee, Mi-Ae Lim, Eun-Kyung Kim, Sung-Min Kim, Jun-Geol Ryu, Jae Ho Lee, Seung-Ki Kwok, Kyung-Su Park, Ho-Youn Kim, Sung-Hwan Park, Mi-La Cho, JAK2-STAT3 blockade by AG490 suppresses autoimmune arthritis in mice via reciprocal regulation of regulatory t cells and Th17 cells, J. Immunol. 192 (May (9)) (2014) 4417–4424.
[78] Brian C. Betts, David Bastian, Hung Nguyen, Jessica Lauren Heinrichs, Wu Yongxia, Anandharaman Veerapathran, Marie C. Lee, Jack Singer, Claudio Anasetti, Yu Xue-Zhong, Targeting JAK2 by Gene Knockout or pacritinib treatment reduces gvhd and xenograft rejection by promoting induced treg differentiation, Blood 126 (December (23)) (2015) 1874–1874.
[79] Marina Cetkovic-Cvrlje, Marin Olson, Ketaki Ghate, Targeting Janus tyrosine kinase 3 (JAK3) with an inhibitor induces secretion of TGF-b by CD4+ T cells, Cell. Mol. Immunol. 9 (July (4)) (2012) 350–360.
[80] Kamran Ghoreschi, Arian Laurence, Xiang-Ping Yang, CristinaM. Tato, Mandy J. McGeachy, Joanne Konkel, HaydeeL. Ramos, Lai Wei, Todd Davidson, Nicolas Bouladoux, John Grainger, Qian Chen, Yuka Kanno, Wendy T. Watford, Hong- Wei Sun, Gerard Eberl, Ethan Shevach, Yasmine Belkaid, Daniel J. Cua, Wanjun Chen, John J. O'Shea, Generation of pathogenic Th17 cells in the absence of TGF-b signaling, Nature 467 (October (7318)) (2010) 967–971.
[81] M. Laan, Z.H. Cui, H. Hoshino, J. Lötvall, M. Sjöstrand, D.C. Gruenert, B.E. Skoogh, A. Lindén, Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways, J. Immun. (Baltimore, Md.: 1950) 162 (February (4)) (1999) 2347–2352.
[82] M. Ishizaki, R. Muromoto, T. Akimoto, Y. Sekine, S. Kon, M. Diwan, H. Maeda, S. Togi, K. Shimoda, K. Oritani, T. Matsuda, Tyk2 is a therapeutic target for psoriasis-like skin inflammation, Int. Immunol. 26 (May (5)) (2014) 257–267.
[83] Thomas Duhen, Rebekka Geiger, David Jarrossay, Antonio Lanzavecchia, Federica Sallusto, Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells, Nat. Immunol. 10 (August (8)) (2009) 857–863.
[84] Ting Wang, Zhiwei Zhang, Huaixin Xing, Li Wang, Guoxiang Zhang, Na Yu, Junzhi Wang, Wei Guo, Jie Jiang, Elevated Th22 cells and related cytokines in patients with epithelial ovarian cancer, Medicine 96 (October (43)) (2017).
[85] P.J. McLaughlin, A. Aikawa, H.M. Davies, R.G. Ward, A. Bakran, R.A. Sells, P.M. Johnson, Evaluation of sequential plasma and urinary tumor necrosis factor alpha levels in renal allograft recipients, Transplantation 51 (June (6)) (1991) 1225–1229.
[86] S. Heidenreich, D. Lang, M. Tepel, K.H. Rahn, Monocyte activation for enhanced tumour necrosis factor-alpha and interleukin 6 production during chronic renal allograft rejection, Transpl. Immunol. 2 (1) (1994) 35–40.
[87] P. Kapessidou, L. Poulin, L. Dumoutier, M. Goldman, J.-C. Renauld, M.Y. Braun, Interleukin-22 deficiency accelerates the rejection of full major histocompatibility complex-disparate heart allografts, Transplant. Proc. 40 (June (5)) (2008) 1593–1597.
[88] He Chang, Haruo Hanawa, Hui Liu, Tsuyoshi Yoshida, Manabu Hayashi, Ritsuo Watanabe, Satoru Abe, Ken Toba, Kaori Yoshida, Raafat Elnaggar, Shiro Minagawa, Yuji Okura, Kiminori Kato, Makoto Kodama, Hiroki Maruyama, Junichi Miyazaki, Yoshifusa Aizawa, Hydrodynamic-based delivery of an Interleukin-22-Ig fusion gene ameliorates experimental autoimmune myocarditis in rats, J. Immunol. 177 (September (6)) (2006) 3635–3643.
[89] I. Gomez, N. Foudi, D. Longrois, X. Norel, The role of prostaglandin E2 in human vascular inflammation, Prostaglandins Leukot. Essent. Fatty Acids 89 (August (2-3)) (2013) 55–63.
[90] Chao-Chao Qin, Yan-Ning Liu, Ying Hu, Ying Yang, Zhi Chen, Macrophage inflammatory protein-2 as mediator of inflammation in acute liver injury, World J. Gastroenterol. 23 (May (17)) (2017) 3043–3052.
[91] Satish L. Deshmane, Sergey Kremlev, Shohreh Amini, Bassel E. Sawaya, Monocyte chemoattractant Protein-1 (MCP-1): an overview, J. Interferon Cytokine Res. 29 (June (6)) (2009) 313–326.
[92] Futoshi Shibata, [The role of rat cytokine-induced neutrophil chemoattractants (CINCs) in inflammation]. Yakugaku Zasshi, J. Pharma. Soc. Japan 122 (April (4)) (2002) 263–268.
[93] Randolph J. Noelle, Elizabeth C. Nowak, Cellular sources and immune functions of interleukin-9, Nat. Rev. Immunol. 10 (October (10)) (2010) 683–687.
[94] Kirsten A. Kortekaas, Dorottya K. de Vries, Marlies E.J. Reinders, Ellen Lievers, Jan Ringers, Jan H.N. Lindeman, Alexander F.M. Schaapherder, Interleukin-9 release from human kidney grafts and its potential protective role in renal ischemia/reperfusion injury, Inflamm. Res. 62 (January (1)) (2013) 53–59.
[95] Gajendra M. Jogdand, Suchitra Mohanty, Satish Devadas, Regulators of tfh cell differentiation, Front. Immunol. 7 (November) (2016).
[96] Nathalie Schmitt, Rimpei Morita, Laure Bourdery, Salah Eddine Bentebibel, Sandra M. Zurawski, Jacques Banchereau, Hideki Ueno, Human dendritic cells induce the differentiation of Interleukin-21-producing t follicular helper-like cells through Interleukin-12, Immunity 31 (July (1)) (2009) 158–169.
[97] Sau K. Lee, Diego G. Silva, Jaime L. Martin, Alvin Pratama, Xin Hu, Pheh-Ping Chang, Giles Walters, Carola G. Vinuesa, Interferon-g excess leads to pathogenic accumulation of follicular helper t cells and germinal centers, Immunity 37 (November (5)) (2012) 880–892.
[98] ChristopherD.C. Allen, K. Mark Ansel, Caroline Low, Robin Lesley, Hirokazu Tamamura, obutaka Fujii, Jason G. Cyster, Germinal center dark and light zone organization is mediated by CXCR4 and CXCR5, Nat. Immunol. 5 (September (9)) (2004) 943–952.
[99] Anne Kolenbrander, Bastian Grewe, David Nemazee, Klaus Überla, Vladimir Temchura, Generation of T follicular helper cells in vitro: requirement for B-cell receptor cross-linking and cognate B- and T-cell interaction, Immunology 153 (February (2)) (2018) 214–224.
[100] Kitty de Leur, Frank J.M.F. Dor, Marjolein Dieterich, Luc J.W. van der Laan, RudiW. Hendriks, Carla C. Baan, IL- 21 receptor antagonist inhibits differentiation of B cells toward plasmablasts upon alloantigen stimulation, Front. Immunol. 8 (March) (2017).
[101] T. Defrance, B. Vanbervliet, J. Pène, J. Banchereau, Human recombinant IL-4 induces activated B lymphocytes to produce IgG and IgM, J. Immunol. 141 (September (6)) (1988) 2000–2005.
[102] G. N de Graav, M. Dieterich, D.A. Hesselink, K. Boer, M.C. Clahsen-van Groningen, R. Kraaijeveld, N.H.R. Litjens, R. Bouamar, J. Vanderlocht, M. Tilanus, I. Houba, A. Boonstra, D.L. Roelen, F.H.J. Claas, M.G.H. Betjes, W. Weimar, C.C. Baan, Follicular T helper cells and humoral reactivity in kidney transplant patients, Clin. Exp. Immunol. 180 (May (2)) (2015) 329–340.
[103] Thomas M. Conlon, Kourosh Saeb-Parsy, Jennifer L. Cole, Reza Motallebzadeh, M. Saeed Qureshi, Sylvia Rehakova, Margaret C. Negus, Chris J. Callaghan, Eleanor M. Bolton, J. Andrew Bradley, Gavin J. Pettigrew, Germinal centre alloantibody responses are mediated exclusively by indirect-pathway CD4 T follicular helper cells, J. Immunol. 188 (March (6)) (2012) 2643–2652.
[104] J. Marino, J.T. Paster, A. Trowell, L. Maxwell, K.H. Briggs, P. Crosby Bertorini, G. Benichou, B cell depletion with an Anti-CD20 antibody enhances alloreactive memory t cell responses after transplantation, Am. J. Transplant. 16 (February (2)) (2016) 672–678.
[105] Eugenia J. Kim, Jean Kwun, Adriana C. Gibby, Jung Joo Hong, Alton B. Farris, Neal N. Iwakoshi, Francois Villinger, Allan D. Kirk, Stuart J. Knechtle, Costimulation blockade alters germinal center responses and prevents antibody-mediated rejection, Am. J. Transplant. 14 (January (1)) (2014) 59–69.
[106] Brodie Miles, Elizabeth Connick, Control of the germinal center by follicular regulatory t cells during infection, Front. Immunol. 9 (November) (2018).
[107] Cindy S. Ma, Danielle T. Avery, Anna Chan, Marcel Batten, Jacinta Bustamante, Stephanie Boisson-Dupuis, Peter D. Arkwright, Alexandra Y. Kreins, Diana Averbuch, Dan Engelhard, Klaus Magdorf, Sara S. Kilic, Yoshiyuki Minegishi, Shigeaki Nonoyama, Martyn A. French, Sharon Choo, Joanne M. Smart, Jane Peake, Melanie Wong, Paul Gray, Matthew C. Cook, David A. Fulcher, Jean-Laurent Casanova, Elissa K. Deenick, Stuart G. Tangye, Functional STAT3 deficiency compromises the generation of human T follicular helper cells, Blood 119 (April (17)) (2012) 3997–4008.
[108] Ling Li, Zuoxiao Li, Effects of tofacitinib on Tfr/Tfh balance and expression of CXCL13 and TGF-b1 in experimental autoimmune encephalomyelitis rats, Cns Neurol. Disord. - Drug Targets (September) (2018).
[109] J. Punnonen, G. Aversa, J.E. de Vries, Human pre-B cells differentiate into Ig-secreting plasma cells in the presence of interleukin-4 and activated CD4+ T cells or their membranes, Blood 82 (November (9)) (1993) 2781–2789.
[110] Terry-Ann M. Milford, Ruijun J. Su, Olivia L. Francis, Ineavely Baez, Shannalee R. Martinez, Jacqueline S. Coats, Abby J. Weldon, Milcris N. Calderon, Michael C. Nwosu, Allen R. Botimer, Batul T. Suterwala, Xiao-Bing Zhang, Christopher L. Morris, David J. Weldon, Sinisa Dovat, Kimberly J. Payne, TSLP or IL-7 provide an IL-7ra signal that is critical for human B lymphopoiesis, Eur. J. Immunol. 46 (September (9)) (2016) 2155–2161.
[111] I.K. McNiece, K.E. Langley, K.M. Zsebo, The role of recombinant stem cell factor in early B cell development. Synergistic interaction with IL-7, J. Immun. (Baltimore, Md.: 1950) 146 (June (11)) (1991) 3785–3790.
[112] Sheryl M. Gough, Liat Goldberg, Marbin Pineda, Robert L. Walker, Yuelin J. Zhu, Sven Bilke, Yang Jo Chung, Joseph Dufraine, Subhadip Kundu, Elad Jacoby, Terry J. Fry, Susanna Fischer, Renate Panzer-Grümayer, Paul S. Meltzer, Peter D. Aplan, Progenitor B-1 B-cell acute lymphoblastic leukemia is associated with collaborative mutations in 3 critical pathways, Blood Adv. 1 (September (20)) (2017) 1749–1759.
[113] Ekkehard Mössner, Peter Brünker, Samuel Moser, Ursula Püntener, Carla Schmidt,

Sylvia Herter, Roger Grau, Christian Gerdes, Adam Nopora, Erwinvan Puijenbroek, Claudia Ferrara, Peter Sondermann, Christiane Jäger, Pamela Strein, Georg Fertig, Thomas Friess, Christine Schüll, Sabine Bauer, Joseph Dal Porto, Christopher Del Nagro, Karim Dabbagh, Martin J.S. Dyer, Sibrand Poppema, Christian Klein, Pablo Umana, Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell–mediated B-cell cytotoxicity, Blood 115 (June (22)) (2010) 4393–4402.
[114] Tucker W. LeBien, F. Thomas, Tedder. B lymphocytes: how they develop and function, Blood 112 (September (5)) (2008) 1570–1580.
[115] Vaclav Seda, Marek Mraz, B-cell receptor signalling and its crosstalk with other pathways in normal and malignant cells, Eur. J. Haematol. 94 (March (3)) (2015) 193–205.
[116] Kathryn E. Gunn, Joseph W. Brewer, Evidence that marginal zone B cells possess an enhanced secretory apparatus and exhibit superior secretory activity, J. Immunol. 177 (September (6) (2006) 3791–3798.
[117] Thierry Defrance, Morgan Taillardet, Laurent Genestier, T cell-independent B cell memory, Curr. Opin. Immunol. 23 (June (3)) (2011) 330–336.
[118] Stephen L. Nutt, Philip D. Hodgkin, David M. Tarlinton, Lynn M. Corcoran, The generation of antibody-secreting plasma cells, Nat. Rev. Immunol. 15 (March (3)) (2015) 160–171.
[119] Alice Koenig, Christophe Mariat, Christiane Mousson, Kathryn J. Wood, Gérard Rifle, Olivier Thaunat, B cells and antibodies in transplantation, Transplantation 100 (July (7)) (2016) 1460.
[120] Olivier Aubert, Alexandre Loupy, Luis Hidalgo, Jean-Paul Duongvan Huyen, Sarah Higgins, Denis Viglietti, Xavier Jouven, Denis Glotz, Christophe Legendre, Carmen Lefaucheur, Philip F. Halloran, Antibody-mediated rejection due to pre-existing versus de novo donor-specific antibodies in kidney allograft recipients, J. Am. Soc. Nephrol. 28 (June (6)) (2017) 1912–1923.
[121] Jean Kwun, Miriam Manook, Eugenia Page, Christopher Burghuber, Jungjoo Hong, Stuart J. Knechtle, Cross-talk between T and B cells in the Germinal Center following transplantation, Transplantation 101 (April (4)) (2017) 704–712.
[122] Yang Zhang, Laura Garcia-Ibanez, Kai-Michael Toellner, Regulation of germinal center B-cell differentiation, Immunol. Rev. 270 (March (1)) (2016) 8–19.
[123] Maria Carmen Ochoa, Luna Minute, Inmaculada Rodriguez, Saray Garasa, Elisabeth Perez-Ruiz, Susana Inoge´s, Ignacio Melero, Pedro Berraondo, Antibody-dependent cell cytotoxicity: immunotherapy strategies enhancing effector NK cells, Immunol. Cell Biol. 95 (4) (2017) 347–355.
[124] C. Wehmeier, G. Hönger, H. Cun, P. Amico, P. Hirt-Minkowski, A. Georgalis, H. Hopfer, M. Dickenmann, J. Steiger, S. Schaub, Donor specificity but not broadness of sensitization is associated with antibody-mediated rejection and graft loss in renal allograft recipients, Am. J. Transplant. 17 (8) (2017) 2092–2102.
[125] Gislâine Martins, Kathryn Calame, Regulation and functions of Blimp-1 in t and B lymphocytes, Annu. Rev. Immunol. 26 (April (1)) (2008) 133–169.
[126] B. Belinda Ding, Enguang Bi, Hongshan Chen, J. Jessica Yu, B. Hilda Ye, IL-21 and CD40l synergistically promote plasma cell differentiation through upregulation of Blimp-1 in human B cells, J. Immunol. 190 (February (4)) (2013) 1827–1836.
[127] Elissa K. Deenick, Danielle T. Avery, Anna Chan, Lucinda J. Berglund, Megan L. Ives, Leen Moens, Jennifer L. Stoddard, Jacinta Bustamante, Stephanie Boisson-Dupuis, Miyuki Tsumura, Masao Kobayashi, Peter D. Arkwright, Diana Averbuch, Dan Engelhard, Joachim Roesler, Jane Peake, Melanie Wong, Stephen Adelstein, Sharon Choo, Joanne M. Smart, Martyn A. French, David A. Fulcher, Matthew C. Cook, Capucine Picard, Anne Durandy, Christoph Klein, Steven M. Holland, Gulbu Uzel, Jean-Laurent Casanova, Cindy S. Ma, Stuart G. Tangye, Naive and memory human B cells have distinct requirements for STAT3 activation to differentiate into antibody-secreting plasma cells, J. Exp. Med. 210 (November (12)) (2013) 2739–2753.
[128] Satoshi Kubo, Shingo Nakayamada, Kei Sakata, Yukihiro Kitanaga, Xiaoxue Ma, Seunghyun Lee, Akina Ishii, Kaoru Yamagata, Kazuhisa Nakano, Yoshiya Tanaka, Janus kinase inhibitor baricitinib modulates human innate and adaptive immune system, Front. Immunol. 9 (June) (2018).
[129] Marta Rizzi, Raquel Lorenzetti, Kathleen Fischer, Julian Staniek, Iga Janowska, Arianna Troilo, Valentina Strohmeier, Miriam Erlacher, Mirjam Kunze, Bettina Bannert, Diego Kyburz, Reinhard E. Voll, Nils Venhoff, Jens Thiel, Impact of tofacitinib treatment on human B-cells in vitro and in vivo, J. Autoimmun. 77 (February) (2017) 55–66.
[130] Janet Stavnezer, Jeroen E.J. Guikema, Carol E. Schrader, Mechanism and regulation of class switch recombination, Annu. Rev. Immunol. 26 (2008) 261–292.
[131] Thomas F. Tedder, B10 cells: a functionally defined regulatory B cell subset, J. Immunol. 194 (February (4)) (2015) 1395–1401.
[132] Mélanie Chesneau, Laure Michel, Emilie Dugast, Alexis Chenouard, Daniel Baron, Annaïck Pallier, Justine Durand, Faouzi Braza, Pierrick Guerif, David-Axel Laplaud, Jean-Paul Soulillou, Magali Giral, Nicolas Degauque, Elise Chiffoleau, Sophie Brouard, Tolerant kidney transplant patients produce B cells with regulatory properties, J. Am. Soc. Nephrol. 26 (October (10)) (2015) 2588–2598.
[133] Simon Fillatreau, Claire H. Sweenie, Mandy J. McGeachy, David Gray, Stephen M. Anderton, B cells regulate autoimmunity by provision of IL-10, Nat. Immunol. 3 (October (10)) (2002) 944–950.
[134] Avijit Ray, Luman Wang, Bonnie N. Dittel, IL-10-independent regulatory B-cell subsets and mechanisms of action, Int. Immunol. 27 (October (10)) (2015) 531–536.
[135] Xi Zhou, Yu-Xiong Su, Xiao-Mei Lao, Yu-Jie Liang, Gui-Qing Liao, CD19(+)IL-10(+) regulatory B cells affect survival of tongue squamous cell carcinoma patients and induce resting CD4(+) T cells to CD4(+)Foxp3(+) regulatory T cells, Oral Oncol. 53 (February) (2016) 27–35.
[136] Carole Brosseau, Maxim Durand, Luc Colas, Eugenie Durand, Aurore Foureau, Marie Aude Cheminant, Gregory Bouchaud, Laure Castan, Martin Klein, Antoine Magnan, Sophie Brouard, CD9+ regulatory B cells induce t cell apoptosis via IL-10 and are reduced in severe asthmatic patients, Front. Immunol. 9 (2018).
[137] Ren-Xi Wang, Cheng-Rong Yu, Ivy M. Dambuza, Rashid M. Mahdi, Monika Dolinska, Yuri V. Sergeey, Paul T. Wingfield, Sung-Hye Kim, Charles E. Egwuagu, Interleukin-35 induces regulatory B cells that suppress CNS autoimmune disease, Nat. Med. 20 (June (6)) (2014) 633–641.
[138] Kang Mi Lee, Ryan T. Stott, Gaoping Zhao, Julie SooHoo, Wei Xiong, Moh Moh Lian, Lindsey Fitzgerald, Shuai Shi, Elsie Akrawi, Lei Ji, Shaoping Deng, Heidi Yeh, James F. Markmann, James I. Kim, TGF-b-producing regulatory B cells induce regulatory T cells and promote transplantation tolerance: immunomodulation, Eur. J. Immunol. 44 (June (6)) (2014) 1728–1736.
[139] Kenneth A. Newell, Adam Asare, Allan D. Kirk, Trang D. Gisler, Kasia Bourcier, Manikkam Suthanthiran, William J. Burlingham, William H. Marks, Ignacio Sanz, Robert I. Lechler, Maria P. Hernandez-Fuentes, Laurence A. Turka, Vicki L. Seyfert-Margolis, Identification of a B cell signature associated with renal transplant tolerance in humans, J. Clin. Invest. 120 (June (6)) (2010) 1836–1847.
[140] M. Chesneau, A. Pallier, F. Braza, G. Lacombe, S. Le Gallou, D. Baron, M. Giral, R. Danger, P. Guerif, H. Aubert- Wastiaux, A. Ne´el, L. Michel, D.-A. Laplaud, N. Degauque, J.-P. Soulillou, K. Tarte, S. Brouard, Unique B cell differentiation profile in tolerant kidney transplant patients, Am. J. Transplant. 14 (January (1)) (2014) 144–155.
[141] Claudia Mauri, David Gray, Naseem Mushtaq, Marco Londei, Prevention of arthritis by interleukin 10–producing B cells, J. Exp. Med. 197 (February (4)) (2003) 489–501.
[142] Paul A. Blair, Lina Yassin Noren˜a, Fabian Flores-Borja, David J. Rawlings, David A. Isenberg, Michael R. Ehrenstein, Claudia Mauri, CD19+CD24hi CD38hi B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic lupus erythematosus patients, Immunity 32 (January (1)) (2010) 129–140.
[143] Hyuk Soon Kim, Jun Ho Lee, Hee Dong Han, A.-Ram Kim, Seung Taek Nam, Hyun Woo Kim, Young Hwan Park, Dajeong Lee, Min Bum Lee, Yeong Min Park, Hyung Sik Kim, Young Mi Kim, Chang You Ji, Wahn Soo Choi, Autocrine stimulation of IL-10 is critical to the enrichment of IL-10-producing CD40hi CD5+ regulatory B cells in vitro and in vivo, BMB Rep. 48 (January (1)) (2015) 54–59.
[144] Marina Karaghiosoff, Hans Neubauer, Caroline Lassnig, Pavel Kovarik, Heike Schindler, Hanspeter Pircher, Barbara McCoy, Christian Bogdan, Thomas Decker, Gottfried Brem, Klaus Pfeffer, Mathias Mu ller, Partial impairment of cytokine responses in Tyk2-Deficient mice, Immunity 13 (October (4)) (2000) 549–560.
[145] Elisa Montaldo, Paola Vacca, Chiara Vitale, Francesca Moretta, Franco Locatelli, Maria Cristina Mingari, Lorenzo Moretta, Human innate lymphoid cells, Immunol. Lett. 179 (November) (2016) 2–8.
[146] Elisa Montaldo, Genny Del Zotto, Mariella Della Chiesa, Maria Cristina Mingari, Alessandro Moretta, Andrea De Maria, Lorenzo Moretta, Human NK cell receptors/markers: a tool to analyze NK cell development, subsets and function, Cytom. Part A 83A (8) (2013) 702–713.
[147] Obinna Chijioke, Christian Munz, Dendritic cell derived cytokines in human natural killer cell differentiation and activation, Front. Immunol. 4 (November) (2013).
[148] Asa Lindgren, Voja Pavlovic, Carl-Fredrik Flach, Asa Sjöling, Samuel Lundin, Interferon-gamma secretion is induced in IL-12 stimulated human NK cells by recognition of Helicobacter pylori or TLR2 ligands, Innate Immun. 17 (April (2)) (2011) 191–203.
[149] Diane Cosner, Michelle Rooney, Dilip Samarpungavan, Wei Li, Steven Cohn, Vijay Mudunuri, Gampala Reddy, Leslie Rocher, Francis Dumler, Alan Koffron, Ping Zhang, Natural killer cells are involved in both acute antibody mediated rejection and acute cellular rejection, Am. J. Clin. Pathol. 142 (October (suppl 1)) (2014) A220–A220.
[150] B. Dreßke, X. Zhu, C. Herwartz, K. Brötzmann, F. Fändrich, The time pattern of organ infiltration and distribution of natural killer cells and macrophages in the course of acute graft rejection after allogeneic heart transplantation in the rat, Transplant. Proc. 29 (May (3)) (1997) 1715–1716.
[151] Ning Gao, Tam Dang, Dorothy Yuan, IFN-g-Dependent and -Independent initiation of switch recombination by NK cells, J. Immunol. 167 (August (4)) (2001) 2011–2018.
[152] Thomas Resch, Cornelia Fabritius, Susanne Ebner, Paul Ritschl, Katja Kotsch, The role of natural killer cells in humoral rejection, Transplantation 99 (July (7)) (2015) 1335–1340.
[153] Evelien A.F.J. van Gurp, Wenda Schoordijk-Verschoor, Mariska Klepper, Sander S. Korevaar, Gary Chan, Willem Weimar, Carla C. Baan, The effect of the JAK inhibitor CP-690,550 on peripheral immune parameters in stable kidney allograft patients, Transplantation 87 (January (1)) (2009) 79–86.
[154] M.L. Robinette, M. Cella, J.B. Telliez, T.K. Ulland, A.D. Barrow, K. Capuder, S. Gilfillan, L.-L. Lin, L.D. Notarangelo, M. Colonna, Jak3 deficiency blocks innate lymphoid cell development, Mucosal Immunol. 11 (January (1)) (2018) 50–60.
[155] B. McDonald, K. Pittman, G.B. Menezes, S.A. Hirota, I. Slaba, C.C.M. Waterhouse, P.L. Beck, D.A. Muruve, P. Kubes, Intravascular danger signals guide neutrophils to sites of sterile inflammation, Science 330 (October (6002)) (2010) 362–366.
[156] Taku Kambayashi, Terri M. Laufer, Atypical MHC class II-expressing antigen-presenting cells: can anything replace a dendritic cell? Nat. Rev. Immunol. 14 (November (11)) (2014) 719–730.
[157] Nick D. Jones, Matthew O. Brook, Manuela Carvalho-Gaspar, Shiqao Luo, Kathryn J. Wood, Regulatory T cells can prevent memory CD8+ T-cell-mediated rejection following polymorphonuclear cell depletion, Eur. J. Immunol. 40 (November (11))

(2010) 3107–3116.
[158] M.J. Bogman, I.M. Cornelissen, R.A. Koene, Absence of requirement for polymorphonuclear granulocytes in the acute antibody-mediated rejection of murine skin allografts, Transplantation 37 (April (4)) (1984) 402–405.
[159] Elena Calama, Isabel Ramis, Anna Dome`nech, Cristina Carren˜o, Jorge De Alba, Neus Prats, Montserrat Miralpeix, Tofacitinib ameliorates inflammation in a rat model of airway neutrophilia induced by inhaled LPS, Pulm. Pharmacol. Ther. 43 (April) (2017) 60–67.
[160] R.-F. Li, G.-F. Wang, . JAK/STAT5 Signaling Pathway Inhibitor Ruxolitinib Reduces Airway Inflammation of Neutrophilic Asthma in Mice Model. *European Review*, February (2018).
[161] Alain Le Moine, Véronique Flamand, François-Xavier Demoor, Jean-Christophe Noe¨l, Murielle Surquin, Robert Kiss, Marie-Anne Nahori, Marina Pretolani, Michel Goldman, Daniel Abramowicz, Critical roles for IL-4, IL-5, and eosinophils in chronic skin allograft rejection, J. Clin. Invest. 103 (June (12)) (1999) 1659–1667.
[162] Wang Hongwei, Ranjit S. Nanra, Anne Stein, Leanne Avis, Anna Price, Adrian D. Hibberd, Eosinophils in acute renal allograft rejection, Transpl. Immunol. 2 (March (1)) (1994) 41–46.
[163] P. Cravedi, D.A. Lessman, P.S. Heeger, Eosinophils are not required for the induction and maintenance of an alloantibody response: eosinophils in the alloantibody response, Am. J. Transplant. 13 (October (10)) (2013) 2696–2702.
[164] K. Ochiai, E. Tanabe, C. Ishihara, M. Kagami, T. Sugiyama, M. Sueishi, N. Koya, H. Tomioka, Role of JAK2 signal transductional pathway in activation and survival of human peripheral eosinophils by interferon-gamma (IFN-g), Clin. Exp. Immunol. 118 (December (3)) (1999) 340–343.
[165] G. Schiechl, F.J. Hermann, M. Rodriguez Gomez, S. Kutzi, K. Schmidbauer, Y. Talke, S. Neumayer, N. Goebel, K. Renner, H. Bru¨hl, H. Karasuyama, K. Obata-Ninomiya, K. Utpatel, M. Evert, S.W. Hirt, E.K. Geissler, S. Fichtner- Feigl, M. Mack, Basophils trigger fibroblast activation in cardiac allograft fibrosis development, Am. J. Transplant. 16 (September (9)) (2016) 2574–2588.
[166] W. Schonfeld, A. Saak, G. Steinkamp, Histamine release from basophils in cystic fibrosis, Clin. Exp. Immunol. 76 (1989) 434–439.
[167] B. Strober, M. Buonanno, J.D. Clark, T. Kawabata, H. Tan, R. Wolk, H. Valdez, R.G. Langley, J. Harness, A. Menter, K. Papp, Effect of tofacitinib, a Janus kinase inhibitor, on haematological parameters during 12 weeks of psoriasis treatment, Br. J. Dermatol. 169 (November (5)) (2013) 992–999.
[168] D.K. Nayak, F. Zhou, M. Xu, J. Huang, M. Tsuji, R. Hachem, T. Mohanakumar, Long-term persistence of donor alveolar macrophages in human lung transplant recipients that influences donor-specific immune responses, Am. J. Transplant. 16 (August (8)) (2016) 2300–2311.
[169] Ajda Tahereh Rowshani, Elly Johanna Francisca Vereyken, The role of macrophage lineage cells in kidney graft rejection and survival, Transplantation 94 (August (4)) (2012) 309.
[170] E. Vinuesa, G. Hotter, M. Jung, I. Herrero-Fresneda, J. Torras, A. Sola, Macrophage involvement in the kidney repair phase after ischaemia/reperfusion injury, J. Pathol. 214 (January (1)) (2008) 104–113.
[171] Y. Wang, Y.P. Wang, G. Zheng, V.W.S. Lee, L. Ouyang, D.H.H. Chang, D. Mahajan, J. Coombs, Y.M. Wang, S.I. Alexander, D.C.H. Harris, Ex vivo programmed macrophages ameliorate experimental chronic inflammatory renal disease, Kidney Int. 72 (August (3)) (2007) 290–299.
[172] James A. Hutchinson, Paloma Riquelme, Beate G. Brem-Exner, Maren Schulze, Martina Matthi, Lutz Renders, Ulrich Kunzendorf, Edward K. Geissler, Fred Fndrich, Transplant acceptance-inducing cells as an immune-conditioning therapy in renal transplantation, Transpl. Int. 21 (August (8)) (2008) 728–741.
[173] J.A. Hutchinson, P. Riquelme, B. Sawitzki, S. Tomiuk, P. Miqueu, M. Zuhayra, H.H. Oberg, A. Pascher, U. Lutzen, U. Janssen, C. Broichhausen, L. Renders, F. Thaiss, E. Scheuermann, E. Henze, H.-D. Volk, L. Chatenoud, R.I. Lechler, K.J. Wood, D. Kabelitz, H.J. Schlitt, E.K. Geissler, F. Fandrich, Cutting edge: immunological consequences and trafficking of human regulatory macrophages administered to renal transplant recipients, J. Immunol. 187 (September (5)) (2011) 2072–2078.
[174] Marie Febvre-James, Valérie Lecureur, Yu Augagneur, Abdullah Mayati, Olivier Fardel, Repression of interferon b-regulated cytokines by the JAK1/2 inhibitor ruxolitinib in inflammatory human macrophages, Int. Immunopharmacol. 54 (January) (2018) 354–365.
[175] Yan-Bing Liang, Hao Tang, Zhi-Bin Chen, Li-Jin Zeng, Jing-Guo Wu, Wen Yang, Zhen-Yu Li, Ma. Zhong-Fu, Downregulated SOCS1 expression activates the JAK1/STAT1 pathway and promotes polarization of macrophages into M1 type, Mol. Med. Rep. 16 (November (5)) (2017) 6405–6411.
[176] Yingxin Yu, Bart R. Blokhuis, Johan Garssen, Frank A. Redegeld, Non-IgE mediated mast cell activation, Eur. J. Pharmacol. 778 (May) (2016) 33–43.
[177] Christopher J. Wingard, Dianne M. Walters, Brook L. Cathey, Susana C. Hilderbrand, Pranita Katwa, Sijie Lin, Pu Chun Ke, Ramakrishna Podila, Apparao Rao, Robert M. Lust, Jared M. Brown, Mast cells contribute to altered vascular reactivity and ischemia-reperfusion injury following cerium oxide nanoparticle instillation, Nanotoxicology 5 (December (4)) (2011) 531–545.
[178] M. Su, E.Y. Chi, M.J. Bishop, W.R. Henderson, Lung mast cells increase in number and degranulate during pulmonary artery occlusion/reperfusion injury in dogs, Am. Rev. Respir. Dis. 147 (February (2)) (1993) 448–456.
[179] Maud A.W. Hermans, Benjamin Schrijver, Conny C.P.A. van Holten-Neelen, Roy Gerthvan Wijk, P. Martin van Hagen, Paul L.Avan Daele, Willem A. Dik, The JAK1/JAK2- inhibitor ruxolitinib inhibits mast cell degranulation and cytokine release, Clin. Exp. Allergy 48 (November (11)) (2018).
[180] Janusz J. Kulagowski, Wade Blair, Richard J. Bull, Christine Chang, Gauri Deshmukh, Hazel J. Dyke, Charles Eigenbrot, Nico Ghilardi, Paul Gibbons, Trevor K. Harrison, Peter R. Hewitt, Marya Liimatta, Christopher A. Hurley, Adam Johnson, Tony Johnson, Jane R. Kenny, Pawan Bir Kohli, Robert J. Maxey, Rohan Mendonca, Kyle Mortara, Jeremy Murray, Raman Narukulla, Steven Shia, Micah Steffek, Savita Ubhayakar, Mark Ultsch, Annevan Abbema, Stuart I. Ward, Bohdan Waszkowycz, Mark Zak, Identification of imidazo-pyrrolopyridines as novel and potent JAK1 inhibitors, J. Med. Chem. 55 (June (12)) (2012) 5901–5921.
[181] Mi Kyoung Kim, Heerim Shin, Kwang-su Park, Hyungmi Kim, Jiseon Park, Kangjeon Kim, Joonwoo Nam, Hyunah Choo, Youhoon Chong, Benzimidazole derivatives as potent JAK1-Selective inhibitors, J. Med. Chem. 58 (September (18)) (2015) 7596–7602.
[182] Kent J. Weinhold, Jack F. Bukowski, Todd V. Brennan, Robert J. Noveck, Janet S. Staats, Liwen Lin, Linda Stempora, Constance Hammond, Ann Wouters, Christopher F. Mojcik, John Cheng, Mark Collinge, Michael I. Jesson, Anasuya Hazra, Pinaki Biswas, Shuping Lan, James D. Clark, Jennifer A. Hodge, Reversibility of peripheral blood leukocyte phenotypic and functional changes after exposure to and withdrawal from tofacitinib, a Janus kinase inhibitor, in healthy volunteers, Clin. Immunol. 191 (June) (2018) 10–20.

Nicolas Sailliet (PhD student): started a thesis supervised by Sophie Brouard and Jean-Michel Robert on the development of new kinase inhibitors to specifically target JAK1.

Sophie Brouard (VMD, PhD): leads a team of 32 researchers at the ITUN. After completing her PhD in Immunology and transplantation at INSERM U437, she undertook a Post-doctoral study in the Department of Immunobiology at Harvard Medical School (Boston, USA). She joined ITUN in 2000 as Director of research (CNRS). Since 2011, she is Director and Coordinator of the CENTAURE national RTRS network. She is co-author of 10 patents, 121 original articles, 42 reviews/books and importantly she discovered with her team IL7R as a potential target in transplantation and auto-immune diseases.

Jean-Michel Robert: is professor in medicinal chemistry and drug discovery. He leads researches based on the development of PI3K and JAK inhibitors and pro-apoptosis molecules for cancer therapy.

Carole Brosseau (PhD): joined Sophie Brouard's team to characterize B lymphocyte signature in chronic lung allograft dysfunction and to characterize CD9+ regulatory B cells induction of effector T cell apoptosis as a new therapeutic strategy for severe asthma.