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JAK inhibition as a therapeutic strategy for immune and inflammatory diseases

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Abstract

Proof provided by biological therapies that cytokines are truly key drivers of immune-mediated diseases has spurred effort in targeting their associated signaling pathways. Small-molecule drugs that inhibit Janus kinases (jakinibs), which are essential signaling mediators downstream of many pro-inflammatory cytokines, have gained traction as safe and efficacious options for the treatment of inflammation-driven pathologies like rheumatoid arthritis, psoriasis and inflammatory bowel disease. Building on the clinical success of first-generation jakinibs, second-generation compounds which claim greater selectivity are currently undergoing development and proceeding to clinical trials. However, important questions remain about the advantages and limitations of improved JAK selectivity, optimal routes and dosing regimens, and how best to identify patients that will benefit from jakinibs. This review will discuss the biology of jakinibs from a translational perspective, focusing on recent insights from clinical trials, the development of novel agents, and the use of jakinibs in a spectrum of immune and inflammatory diseases.

Introduction

The discovery of the numerous cytokines underlying the pathogenesis of allergic, inflammatory and autoimmune disorders has provided a basis for the development of highly successful therapeutic monoclonal antibodies and recombinant proteins that target several such cytokines and their receptors[1]. Such therapies have dramatically altered outcomes for a range of diseases, including rheumatoid arthritis (RA), psoriasis and Inflammatory Bowel Disease (IBD)[1]. However, even for a disorder like rheumatoid arthritis (RA) in which much progress has been made, most patients do not respond completely to currently available therapies, and there are relatively few examples of long-term remissions after cessation of therapy [2]. For other disorders, there has been even less progress, especially diseases in which fibrosis and tissue destruction are major features, such as systemic sclerosis.

Thus, despite substantial advances, there is still a major need for novel therapeutic strategies for immune and inflammatory diseases. If targeting specific cytokines outside the cell is

inadequate, an obvious alternative strategy is to target the action of multiple cytokines inside the cell. However, given the complex molecular basis of cytokine action, this can be a daunting task. In this review, we will discuss one class of drugs, Janus kinase (JAK) inhibitors (jakinibs), briefly discussing the role of JAKs in cytokine signaling, the rationale for targeting these kinases, the status of current jakinibs, and future directions in this field including their potential utility in a wide variety of immune-mediated diseases.

The rationale for targeting JAKs

The term “cytokine” encompasses many structurally unrelated proteins that are grouped based on their binding to distinct receptor superfamilies. These cytokine receptor superfamilies include: the tumour necrosis factor (TNF) receptor family, the interleukin (IL)-1 receptor superfamily, the IL–17 receptor superfamily, the transforming growth factor (TGF) receptor superfamily, the receptor tyrosine kinase superfamily and the seven-transmembrane receptor superfamily. These cytokines have critical roles in the pathogenesis of immune-related diseases, but do not depend upon JAKs for signal transduction. Although drugs that target several such cytokines (e.g. “biologics”), particularly TNF, are widely used in the treatment of immune-mediated disorders such as rheumatoid arthritis, psoriasis and inflammatory bowel disease, these have been well-described elsewhere[3–6].

This review instead focuses on the signalling pathways for Type I and Type II cytokine receptors, a family of receptors employed by over 50 cytokines, interleukins, interferons, colony stimulating factors, and hormones. Like other receptor superfamilies, Type I and Type II cytokine receptors are related by their mode of intracellular signaling: they all employ JAKs (Figure 1), a small family of kinases — JAK1, JAK2, JAK3 and Tyrosine Kinase 2 (TYK2) — that bind directly to the intracellular domains of Type I/II cytokine receptors and not to other classes of cytokine receptors (Figure 2).

There are several reasons why targeting JAKs might be a reasonable therapeutic strategy for immune-mediated diseases. An overwhelming body of evidence has established that JAK-dependent cytokines are major contributors to immunopathology and that blocking such cytokines with biologics can be beneficial in immune-mediated diseases. For instance, IL-6 is a prototypic proinflammatory cytokine commonly overexpressed in many autoimmune and inflammatory diseases [7], and is a driver of acute phase responses including induction of C-reactive protein (CRP) and Serum Amyloid A [8]. The efficacy of monoclonal antibodies that target IL-6 or its receptor in rheumatological diseases confirms the criticality of this cytokine in immunopathogenesis [7]. Similarly, there is extensive data to support the pathogenic role of IL-12 and IL-23 in inflammatory bowel disease (IBD) and psoriasis; the efficacy of ustekinumab, a monoclonal antibody targeting the p40 subunit of both cytokines, strongly supports this conclusion [9]. The overexpression of IL-4, IL-5, and IL-13 in allergic disease and the success of drugs that target these cytokines [10–12] provide yet another compelling argument for the potential utility of interfering with Type I/II cytokine signaling in disorders such as asthma and atopic dermatitis. Many other JAK-dependent cytokines have been shown in various settings to contribute to inflammatory diseases. These include but are not limited to: interferons, IL-15, IL-21, granulocyte colony stimulating factor (G-CSF), and granulocyte-macrophage (GM)-CSF[1].

It is well-established that Type I/II cytokine receptors require JAKs to exert their effects, and that other receptor superfamilies do not. The dependence of Type I and Type II cytokines on JAKs was established in a variety of genetic models from mutagenized cell lines and knockout mice to humans with mutations – these approaches all confirmed that JAKs are essential for signaling by cytokines that use Type I and Type II receptors [1,13,14]. Polymorphisms in *JAK* and *STAT* genes are associated with autoimmunity, and loss-of-function mutations cause immunodeficiency due to the inability of Type I/II cytokines to transmit signals through their receptors [1,13,14]. More recent phosphoproteomic analysis established that for the IL-2 receptor, at least 90% of signaling is JAK dependent [15]. The criticality of this straightforward pathway to Type I/II cytokine signaling was compelling evidence that interfering with the activity of JAKs could lead to a new class of immunomodulatory drugs [16,17], and also indicated some potential adverse effects of JAK blockade.

Can JAKs be successfully, specifically, and safely targeted?

JAKs are tyrosine kinases, meaning that they transfer phosphate from ATP to tyrosine residues on other proteins, including cytokine receptors, JAKs themselves and downstream signaling molecules. Tyrosine phosphorylation of kinases, including JAKs, triggers their enzymatic activity. Additionally, tyrosine phosphorylation of receptors causes the recruitment of signaling molecules that bind to the phosphorylated tyrosines of the ligand-engaged receptor. One critical class of signaling molecules for Type I/II cytokine receptors is the STAT (signal transducer and activator of transcription) family of DNA binding proteins (Figure 1). Phosphorylated STATs translocate to the nucleus, bind DNA, and drive gene transcription. This simple pathway is essential for the effects of cytokines that bind Type I/II receptors, but it is not used by TNF, IL-1, IL-17 or other cytokines.

In the early 2000s, the success of the tyrosine kinase inhibitor imatinib for the treatment of chronic myelogenous leukemia provided startling evidence that targeting kinases was not only feasible, but could be game-changing [18]. The oncology field moved ahead quickly and now 31 kinase inhibitors have been approved by the FDA for the treatment of various cancers [19,20]. Not surprisingly, the first jakinib to gain FDA approval was designed for neoplastic rather than immune-mediated diseases. A V617F mutation in *JAK2* is strongly associated with myeloproliferative neoplasms, including myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET), occurring in nearly 100% of PV patients and over 75% of ET patients [21]. The JAK pseudokinase domain attenuates kinase activity, and mutations in this domain can result in constitutive activation of JAK2, which signals downstream of erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), and thrombopoietin (TPO). V617F is an acquired mutation, so proliferation is restricted to the lineage expressing the mutant allele. These observations were a strong rationale for the development of the JAK1/JAK2 inhibitor ruxolitinib (Figure 3), and the clinical trials that led to its approval by the FDA in 2011 showed that JAK inhibition was not only possible, but safe and effective for these indications [22,23]. Indeed, the JAK-STAT pathway is constitutively activated in many cancers[1324], which has led to the initiation of multiple trials using jakinibs in hematological and solid tumours, including trials in which multiple kinase inhibitors are used in combination (e.g. NCT02912754).

While targeting kinases may be sufficiently safe and effective in the setting of neoplastic disorders, it is a very different question as to whether such drugs can be used long term in patients with immune-mediated disease, particularly given the greater need for a 'clean' safety profile outside of life-threatening diseases such as cancer. A large body of evidence leading to the acceptance of jakinibs as a therapy for RA has started to answer this question and will now be reviewed briefly.

Rheumatoid arthritis

Tofacitinib (Figure 3), a first-generation jakinib that inhibits JAK3, JAK1, and to a lesser degree JAK2, is the first jakinib developed for the treatment of autoimmune disease. It has been studied in a variety of preclinical models from transplant rejection to arthritis [25–27]. More importantly, multiple clinical trials including six Phase 3 trials studying tofacitinib in RA have been completed, encompassing more than 6000 subjects followed for as long as 8 years [28–32]. These trials have shown that tofacitinib is efficacious for new and established disease[33], as monotherapy[34] or in combination with methotrexate (MTX) [32], and in treatment-naive[31] or treatment refractory patients[29,30]. Patients achieved significant amelioration of disease activity, as measured by the American College of Rheumatology 20%, 50%, and 70% (ACR20, 50, 70) response criteria. Patients also reported improvements in functional status measured by the HAQ-DI (health assessment questionnaire - disability index) and SF-36 (short form 36). Tofacitinib was proven superior to methotrexate [28,31,35], noninferior to adalimumab [30], and effective in patients who had failed multiple biologics[36,37]. Moreover, tofacitinib was shown to prevent the progression of structural joint disease using conventional radiography and magnetic resonance imaging[28,35,38]. The largest radiographic treatment effect was seen in patients with the most baseline structural damage, but improvement was also noted in other groups [39]. Based on these and other findings, tofacitinib 5 mg twice daily was approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis in 2012 for patients intolerant of or unresponsive to MTX [40]. Since then, its effectiveness has been borne out in long-term extension studies tracking disease activity in >4000 patients [2,4142–44]. This is particularly true for disease activity measures that incorporate the CRP [45], which may reflect blockade of IL-6 signaling [8,46]. Tofacitinib has also been effective in improving patient-reported outcomes [36,4748] and other disease measures that do not incorporate CRP [45]. After reviewing long-term safety and efficacy data, the European Medical Agency (EMA) also recommended approving tofacitinib for RA in January 2017. In addition, an extended release version of that uses osmotic delivery to allow once daily dosing was recently FDA-approved for the treatment of RA[49].

Baricitinib is a first-generation jakinib with activity against JAK1 and JAK2 (Figure 3) that is structurally related to ruxolitinib. Baricitinib is cleared by the kidney, and is not metabolized via the cytochrome P450 (CYP) system, which sets it apart from tofacitinib and ruxolitinib [50]. It has been studied extensively in the treatment of RA, with extensive phase 3 trial data demonstrating safety and efficacy. Patients with RA refractory to conventional DMARDs (cDMARDs) displayed clinically significant improvements in disease activity, in radiographically assessed structural damage, and in patient-reported outcomes [51]. Baricitinib was also effective in patients who failed standard-of-care treatment with TNF inhibitors and

in treatment-naive patients, where it outperformed methotrexate [52,53]. Baricitinib was superior to the TNF inhibitor adalimumab in methotrexate-refractory patients, a previously unseen milestone [54]. Baricitinib has been approved by the European Medicines Agency (EMA) for the treatment of RA. The FDA issued a Complete Response Letter, indicating that it was unable to approve the application for baracitinib, citing the need for additional clinical data to determine the most appropriate doses and clarify safety concerns [55].

Peficitinib blocks all four JAK isoforms but has slight JAK3 selectivity (Figure 3) [56]. RA patients treated with peficitinib as monotherapy or in combination with MTX achieved clinical responses similar to those seen with other jakinibs[5657].

Other forms of arthritis

TNF inhibitors have been effective in the treatment of other forms of arthritis, but like RA, are often not completely effective, and our understanding of the role of various cytokines in other arthritides is very incomplete. Nonetheless, tofacitinib was shown to be effective in psoriatic arthritis [58], where it reduces inflammatory cytokine production by synoviocytes [59]. There was a trend toward higher response rates with tofacitinib than with the standard-of-care TNF inhibitor adalimumab, but the trial was not adequately powered to assess superiority. If this finding is replicated in larger studies, it would be an exciting advance in the treatment of psoriatic joint disease. Tofacitinib also demonstrated efficacy in ankylosing spondylitis, another seronegative spondyloarthropathy, although results were difficult to interpret due to a high placebo response rate [60,61]. The efficacy of tofacitinib in seronegative spondyloarthropathy represents a potentially important advance, since the therapeutic armamentarium for this group of diseases comprises only three FDA-approved classes of drugs: TNF inhibitors, the IL12/23 blocking agent ustekinumab, and the IL-17 blocking agent secukinumab. Tofacitinib is also being evaluated in the treatment of juvenile idiopathic arthritis (JIA) (NCT01500551, NCT02592434), as it was reported effective in an adult patient with longstanding treatment-refractory polyarticular disease [62].

IBD

IBD is a term that encompasses two diseases, ulcerative colitis (UC) and Crohn’s disease (CD), but more likely represents a broad constellation of inflammatory disorders of the gastrointestinal tract driven by multiple diverse mechanisms that affect tissues beyond the gut, including joints. UC is typically restricted to the colon and primarily affects the mucosa, whereas CD is characterized by transmural inflammation, skip lesions, and inflammation throughout the gastrointestinal tract; however, there can be considerable overlap between the two diseases. Despite the success of biologics including TNF blockers, ustekinumab, and vedolizumab (an $\alpha_4\beta_7$ integrin inhibitor), current IBD therapies are ineffective for many patients. Tofacitinib 10 mg twice daily has proven an effective induction treatment for both moderate and severe UC, inducing remission and mucosal healing in a significant proportion of patients[63]. A subsequent UC trial has demonstrated that both 5 mg and 10 mg doses of tofacitinib are effective in maintaining remission for up to 1 year[63]. Results in CD have been less consistent [64], with the most recent data suggesting a very modest treatment effect for both induction and maintenance therapy [65]. The basis for differences in efficacy is unknown,

but it could relate to the basic mechanism of disease and differential contribution of various JAK-dependent cytokines to immunopathogenesis. JAK-dependent cytokines like IL-6 are generally implicated in IBD pathogenesis; however, IL-9 is thought to be involved the pathogenesis of UC but not in that of CD [66]. Moreover, the JAK-dependent cytokine IL-10 has critical anti-inflammatory effects in the gut, therefore blockade with jakinibs has the potential for being detrimental. Impaired barrier function with dysbiosis and bacterial overgrowth are integral to the pathogenesis of IBD. The type I/II cytokines IL-22 and IL-9 are important for maintaining barrier integrity [67,68], underlying another potential mechanism by which jakinibs could be detrimental in IBD. IL-17, also important for gut barrier function, does not signal via JAKs but is regulated by IL-6 and IL-23, which are JAK-dependent. In the case of IL-17, clinical trials using IL-17A blocking antibodies to treat IBD showed unexpected disease exacerbations, possibly due to loss of mucosal protection [69,70]. It is also possible that immunodeficiency underlies some forms of IBD and thus disease could be exacerbated by jakinibs. [71] Further data from late-phase clinical trials, and a more sophisticated understanding of disease pathogenesis should help to clarify these concerns and identify the best candidates for treatment with jakinibs.

Psoriasis

Psoriasis is an autoimmune skin disorder, which is responsive to targeting multiple cytokines including TNF, IL-17, IL-12/23 and IL-23 alone. Given the JAK-dependence of multiple cytokines involved in psoriasis pathogenesis, tofacitinib has been tested extensively in late-phase clinical trials for the treatment of this disease. Patients treated with tofacitinib experienced clinically significant improvements in the PASI 50/75/90 (Psoriasis Activity and Severity Index 50%/75%/90% improvement) at both 5 mg and 10 mg twice daily doses [72,73]. Tofacitinib rapidly blocked STAT phosphorylation in keratinocytes from psoriasis patients and abrogated keratinocyte-induced pathogenic cytokine signaling – both of which may underlie its efficacy [74]. However, in a trial directly comparing tofacitinib to standard-of-care treatment with etanercept (a TNF inhibitor) only the 10 mg twice daily (BID) dose of tofacitinib showed noninferiority[75]. The FDA issued a Complete Response Letter indicating that it would not be able to approve tofacitinib for psoriasis without additional information [76]. Likely this relates to the need to establish that the 10 mg BID dose provides an appropriate safety/benefit ratio, which was the reason why only the 5 mg dose was approved for RA.

Baricitinib was also found to be efficacious in a phase 2 study testing its effect in patients with moderate-to-severe psoriasis with over 50% of patients achieving a sustained response as measured by the PASI75[77]. These responses were also seen predominantly at the higher, 8 mg and 10 mg, daily doses and baricitinib has not been compared with TNF inhibitors. Additional safety data that has emerged over the last 2 years may influence future decisions regarding FDA or EMA approval, as may the adoption of IL-17 blocking agents secukinumab and ixekizumab as a new and more effective standard-of-care in psoriatic skin disease.

Peficitinib also appeared effective for psoriasis in a Phase 2 trial [78], although no Phase 3 trials are currently recruiting patients.

Considering the risks associated with systemic JAK inhibition, topical formulations are an attractive alternative for cutaneous disease. Topical formulations of tofacitinib and ruxolitinib have been developed and tested in Phase II studies in psoriasis. Treatment with topical tofacitinib demonstrated significantly higher response rate at 8 weeks compared with placebo, but the efficacy was transient [79]. Trials with topical ruxolitinib demonstrated improvement in psoriasis compared to treatment with placebo or other topical approved therapies, but as with tofacitinib, it was not a sustained improvement after discontinuation. [80,81]. Importantly, systemic absorption was minimal and there was no evidence of systemic toxicity [81].

Alopecia areata

Alopecia areata (AA) is an autoimmune disorder in which hair follicles overexpress a variety of proinflammatory cytokines. Several case reports have been published using jakinibs to treat AA, alopecia totalis (affecting the entire scalp), and alopecia universalis, (affecting the entire body). Moreover, AA is characterized by tissue upregulation of genes induced by IFN-γ, which signals through JAK1 and JAK2 [1,82]. Early phase clinical trials and large retrospective studies indicate that tofacitinib[83–86] ruxolitinib and baricitinib[87,88] are effective for the spectrum of autoimmune forms of alopecia. However, symptoms recur upon drug discontinuation [89], and tofacitinib may lose efficacy in some patients [90]. Topical ruxolitinib has also demonstrated efficacy in treatment of alopecia areata [91] and there is an ongoing clinical trial evaluating the efficacy of topical tofacitinib (NCT02812342). Of considerable interest, it also appears that JAK inhibition can promotes hair regrowth; this is an area that clear will attract more investigation[84].

Atopic dermatitis

Atopic dermatitis or atopic eczema is a common disorder in which cytokines associated with allergic disease frequently dominate (e.g. IL-4, IL-5 and IL-13). The pathogenic role of cytokines is evidenced by the utility of biologics targeting these cytokines. Oclacitinib (Figure 3) is the first jakinib to be FDA-approved for allergic and atopic canine dermatitis [92,93]. However, this provides a strong precedent for the use of jakinibs to treat atopic dermatitis in humans, and preclinical studies indicate that this would likely be an effective strategy [94,95]. Inflammation in atopic dermatitis is often complicated by concomitant irritant contact disease, a disease in which JAK-dependent cytokines like IL-6 and IL-31 play an important role [96], and in which JAK2 inhibitors appear to reduce pathology [97]. A clinical trial using baricitinib to treat atopic dermatitis is ongoing (NCT02576938). Balancing efficacy and safety is always a priority, especially in this disease where morbidity may be high but mortality is low, so topical formulations of jakinibs are desirable if efficacious[98]. Tofacitinib ointment is efficacious in the treatment of atopic dermatitis, with an 80% improvement in EASI Eczema Area and Severity Index (EASI) score after 4 weeks of treatment [99]. One prominent feature of AD is pruritus, which results in an itch-scratch cycle. Cytokines have also been linked to the molecular pathogenesis of pruritus, such that treating with jakinibs might break the scratch-itch cycle[100].

Other dermatologic conditions

Tofacitinib has been reported efficacious in the treatment of vitiligo [101], and a clinical trial using topical ruxolitinib for this indication is ongoing (NCT02809976). Palmoplantar pustulosis [102], a refractory form of psoriatic skin disease that can be associated with arthritis, has also been treated successfully with tofacitinib. Finally, a case of the mucocutaneous disease idiopathic erythema multiforme (EM) associated with mutation of the *TRPS1* gene and JAK-STAT activation was treated successfully with tofacitinib [103]. It would be intriguing to see whether other dermatologic diseases might be similarly responsive to jakinibs: candidates would include mycosis fungoides, graft-versus-host-disease (GVHD), cutaneous lupus, and others.

Other autoimmune and autoinflammatory diseases

Tofacitinib was first studied in the prevention of transplant rejection [104,105], where it was efficacious but was also associated with an unacceptable risk of adverse events due to over-immunosuppression. Foremost among these were BK viremia, nephropathy, and post-transplant lymphoproliferative disease (PTLD). This may be due to the relatively high doses of tofacitinib used in the transplant trials (10–15 mg BID) and because the transplant patients were also treated with other potent immunomodulatory drugs (basiliximab, mycophenolate, sirolimus). Measuring post-dose serum concentrations to prevent overexposure may prevent such outcomes and lead jakinibs to be reevaluated in the prevention of transplant rejection [106].

Baricitinib has been used in the treatment of autoinflammatory diseases, particularly those characterized by an interferon signature, or activation of interferon signaling genes [107]. Doses required have been high (mean dose 8.5 mg/day), and treatment has been associated with BK viremia [107,108], possibly due to over-immunosuppression required to control symptoms.

Jakinibs are also being used to treat other diseases associated with an interferon signature, namely systemic lupus erythematosus (SLE), dermatomyositis, and Sjogren's syndrome. For SLE, preclinical studies have been encouraging [109]. A Phase 1 tofacitinib trial (NCT02535689) and a Phase 2 baricitinib study (NCT02708095) are currently recruiting patients. Several cases of jakinib-responsive myositis [110–112] have also been reported, and a clinical trial is planned (NCT03002649), although recruitment has not yet started.

Topical ophthalmic tofacitinib has also been tested in the treatment of dry eye disease, where results showed a trend towards improvement but were not significantly different from placebo [113]. It should be noted that patient selection may have contributed to lack of efficacy: dry eye is not always Sjogren's syndrome, or even immune-mediated [114] and patient responses to topical cyclosporine, which is FDA-approved for keratoconjunctivitis sicca, were also poor [113].

Given the number of immune-mediated diseases linked to activation of JAK-dependent cytokines, jakinibs are also being investigated for a host of other indications. Secondary hypereosinophilic syndrome (HES) [98] is a group of disorders characterized by elevation of

JAK-dependent cytokines including IL-4, IL-5, and IL-13. The IL-5 blocking agent mepolizumab is extremely effective in the treatment of HES [115] and other eosinophilic diseases including allergic asthma [10], although some subjects fail to respond completely, raising the possibility that blockade of multiple JAK-dependent cytokines might increase therapeutic efficacy. Preliminary reports support the efficacy of jakinibs in treating hypereosinophilic syndrome[98], indicating that jakinibs might be useful in other diseases driven by the same cytokines, such as eosinophilic esophagitis allergy, and allergic asthma.

Tofacitinib has been reported as a treatment for vasculitis [116] and has shown promising results in preclinical models [117] of GVHD: a clinical trial using baricitinib is ongoing for this indication (NCT02759731). Another potential use could be multiple sclerosis (MS), a disease driven by pathogenic Th1 and Th17 subsets of CD4 T cells [118]. Tofacitinib can antagonize signaling downstream of IL-23, a pathogenic cytokine produced by Th17 cells. However, MS is a disease where the blockade of multiple cytokines could worsen pathogenesis: IFN-β is used to treat patients; although its mechanism of action in this disease is still poorly understood. The IL-12/23 blocking agent ustekinumab, which is also thought to inhibit pathogenic Th17 cells, is not efficacious in MS, although preliminary results from a Phase 2a using the IL-17 blocking antibody secukinumab were encouraging [119]. Further results will potentially clarify the role of pathogenic Th17 cells in MS pathogenesis [118].

Other diseases

The role of JAK-dependent cytokines is increasingly being appreciated in several common diseases traditionally seen as driven by non-immunologic mechanisms. For example, preliminary data suggest that tofacitinib may be a potential treatment for diabetic nephropathy, where it appears to reduce albuminuria through blockade of renal inflammation [120]. Another such example is cardiovascular (CV) disease, which is increasingly seen as an inflammatory process [121]. Among other cytokines, IL-6 is associated with the pathogenesis of CV disease [122], and the JAK-STAT pathway has been proposed as a potential therapeutic target in atherosclerosis [123].

The downside of JAK inhibition

The adverse effects of jakinibs are largely predictable based on their biological functions as signal transducers for Type I and Type II cytokines. Because tofacitinib is the most widely used drug, its safety profile is the best characterized. However, the side effects of baricitinib and other nonselective jakinibs are similar, which is expected given the similar cytokine inhibition of the two drugs [124].

Infection

It is not surprising that the most significant concerns regarding adverse effects have focused on the increased risk of infection. Indeed, review of the RA trials revealed that infections were commonly reported side effects [28–30,38,42,125]. Although most infections did not necessitate treatment discontinuation, severe and opportunistic infections such as tuberculosis and osteomyelitis were also reported. However, the risk of serious infections for

jakinibs appear to be similar to that seen with biological agents[42]. A recent pooled meta-analysis confirms that tofacitinib may actually be less likely to increase infection risk than biological DMARDs[125]. Tofacitinib, baricitinib and peficitinib are associated with increased risk of *Herpes zoster*. Other serious viral infections have been associated with jakinibs, including a case of progressive multifocal leukoencephalopathy (PML) secondary to JC virus associated with ruxolitinib [126]. BK nephropathy was also reported in trials using tofacitinib to prevent rejection after kidney transplantation, in combination with mycophenolate mofetil or cyclosporine[104,105]. Inhibition of IFN signaling and effects on natural killer (NK) cells may underlie the increased risk of viral infections: NK cells are critical for antiviral defense, and their development and function both depend on JAK3-dependent cytokines. Tofacitinib causes a dose-dependent decrease in NK cell counts although this effect may be temporary [127128]; careful studies probing tofacitinib-mediated alterations in NK cell function might better address these questions. Tofacitinib may also affect the development and function of plasmablasts [129], also important in host defense against viral infection [130]. Tofacitinib does not affect response to influenza vaccine but decreases response to pneumococcal vaccination, particularly in combination with methotrexate, and temporary withdrawal does not restore responsiveness [131]. Thus, patients should be vaccinated against Herpes zoster and pneumococcal infections prior to starting tofacitinib, as with other biological DMARDs [132].

Anemia, leukopenia

Because hematopoietic growth factors including erythropoietin signal through JAK2, cytopenias are commonly seen in patients treated with first generation pan-jakinibs. Neutropenia and anemia have been observed in many of the RA trials, particularly at higher doses of tofacitinib[28–30,43,104]. These alterations were typically well-tolerated and did not require treatment discontinuation. Baricitinib trials have shown similar results, with mild anemia and neutropenia in baricitinib-treated patients [51,53,133,134]. Subjects treated with peficitinib developed neutropenia but did not develop anemia; instead increases in hemoglobin were noted at higher doses of peficitinib, which may reflect resolution of inflammation-driven anemia of chronic disease. Unexpectedly, mild thrombocytosis has also been noted in baricitinib-treated patients, although not in those on tofacitinib. Because JAK2 blockade is an FDA-approved treatment for essential thrombocytosis [14], one would rather expect thrombocytopenia as an adverse effect, and the reasons underlying treatment-associated thrombocytosis are not clear.

Lipids and cardiovascular disease

Patients with autoimmune diseases, including RA and SLE, are at increased risk of cardiovascular (CV) disease, a major cause of mortality [135–136]. Psoriasis patients are also at risk for CV disease [137] and metabolic syndrome, even compared to other inflammatory diseases [135,129, 138]. The reasons for this are likely multifactorial: patients with autoimmune disease have a high prevalence of CV risk factors, yet autoimmune disease activity also increases CV disease risk[126,139,137, 135,138,140]. JAK-dependent cytokines are thought to contribute to CV disease in autoimmunity, implying that JAK inhibition may actually reduce risk. Type I IFN promotes endothelial dysfunction[141], while IL-6 affects lipid metabolism, drives insulin resistance, and promotes redistribution of serum lipids to peripheral tissues.

This causes a lowering of serum lipid levels, which may paradoxically raise CV risk [142,143]. Indeed, patients treated with the IL-6 receptor inhibitor tocilizumab have increases in their serum lipid concentrations, but do not appear to have increased CV risk [144].

Potentially related to blockade of signaling downstream of IL-6, treatment with nonselective jakinibs also increases serum low density lipoprotein (LDL) and high density lipoprotein (HDL) concentrations but does not alter the LDL:HDL ratio [145]. Review of pooled data from late-phase clinical trials indicates that tofacitinib, like tocilizumab, does not increase the risk of major cardiovascular events [146,147]. Yet patients with CV disease were excluded from the late-phase clinical trials, limiting the generalizability of this finding[146]. Moreover, tofacitinib reduces cholesterol ester catabolism, which is elevated in RA patients [148]. Tofacitinib also reduces arterial stiffness [149] and lupus-associated vascular dysfunction [109]. Long-term data from Phase IV clinical trials is needed to determine whether JAK inhibition ultimately prevents, ameliorates, or exacerbates CV risk. Clearly, additional work in this area is warranted.

GI perforation

Patients treated with IL-6 receptor blockade also have a higher risk of lower gastrointestinal tract perforation than those treated with other biological DMARDs [150], raising the concern that jakinibs may cause similar complications. Lower GI tract perforation was reported in several RA clinical trials, but thus far a significantly increased risk has not been seen in analysis of the late-phase clinical trial data nor has it been seen in the Phase 3 baricitinib trials [69]. The mechanisms by which jakinibs might increase risk of GI perforation are poorly defined but may be tied to the role of cytokines in gut barrier immunity. As detailed previously, IL-6 is critical to the differentiation of Th17 cells, and other type I/II cytokines including IL-22, IL-10 and IL-9 all have a protective role in intestinal barrier function[151,152]. The association of jakinibs with GI perforation once again highlights the multifaceted role of JAK-dependent cytokines in immune homeostasis and the importance of long-term monitoring for unexpected complications.

Malignancy

Aside from infection, a concern with immunosuppression is the potential for increased risk of malignancy. The possible mechanisms through which jakinibs might negatively impact immune responses to cancer include interference with T and NK cell function in immunosurveillance and the antineoplastic role of interferons. In patients receiving tofacitinib after kidney transplantation, the risk of post-transplant lymphoproliferative disease is indeed elevated in tofacitinib-treated patients[105]. Thus far, data from clinical trials and long-term extension studies in RA patients have not revealed an increased risk of hematologic or solid organ malignancy [153]. Further monitoring of tofacitinib-treated patients will be needed to determine whether long-term therapy confers any malignancy risk.

Other side effects of jakinibs

Other laboratory abnormalities in jakinib-treated patients included sporadic elevations in serum creatinine[154], but this usually returned to baseline upon drug discontination[42,43,154]. Acute renal failure was infrequent and associated with concurrent serious illness, primarily

infection[155]; chronic renal dysfunction has not been reported as an adverse effect of jakinibs[42,43,154]. Some jakinibs have also been reported to cause elevations in transaminases [127]. This is more common in patients being treated with tofacitinib and methotrexate in combination, and may necessitate dose adjustment or discontinuation [35]. In tofacitinib-treated rats, prolonged blockade of JAK2 downstream of prolactin caused testicular Leydig cell hyperplasia and adenoma[156]. Because human Leydig cells are not prolactin-dependent[156], tofacitinib is not likely to cause testicular adenomas in patients. However, other long-term risks of hormone-like receptor blockade may become apparent from long-term extension studies.

Next-generation jakinibs

First-generation jakinibs block multiple JAKs and therefore inhibit the actions of a large variety of cytokines and several pan-JAK inhibitors continue to be developed (Table 3, Table 4). The rationale for this is that nonselective JAK inhibitors have already been proven safe, and that blockade of multiple JAKs might increase therapeutic efficacy. However, to minimize adverse effects, especially those arising from JAK2 inhibition, the generation of selective jakinibs could in principle maintain efficacy and improve safety. Moreover, novel mechanisms of achieving exquisite selectivity are emerging. All current jakinibs act through non-covalent interactions with the kinase domain, which is relatively conserved between JAK isoforms, but several novel compounds have been reported to bind covalently to non-conserved amino acid residues, leading to irreversible inhibition and reportedly high selectivity across the kinome. It is important, however, to appreciate that specificity as defined by doses used *in vitro* and in cell-based assays may lead to different conclusions compared to specificity as measured in patients treated with doses required for clinical efficacy.

JAK1-selective inhibitors

Filgotinib (Figure 3) is a JAK1 selective inhibitor with reduced activity against JAK2 [157]. Filgotinib was discovered after a kinase-focused high throughput library screen identified triazolopyridines as JAK1-selective catalytic inhibitors; this strategy has since been exploited to develop most other patented JAK1-selective drugs [158],[159,160]. Further structure-activity relationships and structure-based design culminated in the development of filgotinib, which was effective in preclinical disease models [158]. Filgotinib was subsequently investigated in RA as monotherapy and in combination with MTX for patients with inadequate responses to MTX. In both settings, filgotinib displayed comparable efficacy to tofacitinib. Importantly, with respect to the purported lack of effect on JAK2, patients did not develop anemia; rather, a mild increase in hemoglobin was observed. However, patients did develop neutropenia, possibly due to inhibition of cytokines like G-CSF and IL-11 which signal through JAK1 and support myelopoiesis[161]. Other laboratory abnormalities were similar to those seen with tofacitinib, with dose-dependent increases in serum transaminases and lipids. Unlike tofacitinib, however, filgotinib increased the HDL:LDL ratio. Filgotinib is also the first jakinib to display clinically significant efficacy in Crohn's disease [162], with a 2-fold increase in clinical remission compared with placebo and rates similar to those seen

with the standard-of-care therapy infliximab. Phase 3 trials are currently ongoing for both ulcerative colitis and Crohn's disease (NCT02914561, NCT02914522).

Upadacitinib (Figure 3) was developed using structural predictions that indicated potential for differential binding interactions outside the ATP-binding of JAK1 compared to JAK2, which is believed to provide JAK selectivity via an allosteric mechanism [163,164]. Upadacitinib is metabolized by CYP enzymes including CYP3A but can be taken with other CYP3A-metabolized drugs, including statins [165]. The efficacy of upadacitinib in RA was evaluated in the BALANCE1 and 2 Phase II clinical trials [166,167], where patients who had failed either MTX or TNF inhibitors were treated with upadacitinib in combination with MTX. ACR20 responses were similar to those seen with nonselective drugs, and results were seen as early as 2 weeks after starting treatment. Adverse effects included infections, transient elevations in serum transaminases, and dose-dependent increases in serum lipids. Dose-dependent decreases in hemoglobin were noted in upadacitinib-treated patients, raising the possibility that at the higher doses needed to control autoimmune disease, the drug does inhibit JAK2 [166,167], or that JAK1-dependent cytokines are necessary for normal erythropoiesis. Preliminary results from the phase 3 SELECT program have been encouraging in cDMARD-refractory RA patients; further trials are evaluating the drug in MTX-refractory, bDMARD-refractory, and treatment-naïve subjects [168]. Positive top-line results have also emerged from the CELEST trial in Crohn's disease, and trials are ongoing for atopic dermatitis (ClinicalTrials.gov NCT02782663, NCT02925117, NCT02819635).

Solcitinib (GLPG-0778, GSK-2586184, Figure 3) is a JAK1-selective inhibitor with a triazolopyridine scaffold and a acyclopropylamide in position 2 derived from GLPG0634 (which was originally discovered using high-throughput screening). Solcitinib was found to be efficacious for the treatment of plaque psoriasis [169]. However, during a phase II trial evaluating solcitinib as a treatment for SLE, six patients developed elevated liver enzymes, two of whom were diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS) [170]. These severe adverse events necessitated early termination of the trial and, in combination with the subsequent discovery of a statin drug-drug interaction, led to discontinuation of further development for the drug. PF-04965842 is another recently developed JAK1-selective drug; although clinical trials for lupus and plaque psoriasis were discontinued due to changes in the drug development portfolio, a Phase 2 trial for the treatment of atopic dermatitis is currently underway (NCT02780167).

JAK3-selective inhibitors

Decernotinib (Figure 3) is reported to be a JAK3-selective inhibitor developed to preserve JAK1 and JAK2 signaling, which, in principle, would eliminate non-immunologic adverse effects. This is because JAK3 transmits signals via common γ-chain associated cytokines, which prinicipally affect immune cells (Figure 2) [16,17]. In vitro assays indicate that decernotinib may have some activity against JAK1, however, and the drug has been reported to cause neutropenia in clinical trials [171172,173]. Thus, the degree of JAK3 selectivity has yet to be fully determined.

Decernotinib was discovered using high-throughput screening of a compound library [174]. It has comparable efficacy to tofacitinib for RA, both as monotherapy and in combination with

methotrexate[172,173,175]. These results were encouraging, but the development of neutropenia in decernotinib-treated patients was puzzling. Another major concern arises from the fact that decernotinib alone amongst the JAK inhibitors is a potent inhibitor of CYP3A4[176]. Because CYP3A4 is the predominant hepatic CYP, it metabolizes over half of the medications currently used to treat human disease, including high-potency statins. This drug-drug interaction could present a limitation to decernotinib use.

Several novel compounds are reported to bind covalently to nonconserved amino acid residues, leading to irreversible inhibition and reportedly high selectivity across the kinome [177]. Because these are both new features, it will be critical to carefully assess the risks and benefits of each as such compounds proceed to clinical development and to assess whether the reported in vitro selectivity translates to in vivo efficacy and selectivity. PF-06651600 is the only irreversible covalent JAK3 inhibitor being used in clinical trials: it was developed by modifying the structure of tofacitinib to optimize selectivity and allow covalent binding (Figure 3). PF-06651600 is being tested for the treatment of RA and alopecia areata, and a trial is planned for ulcerative colitis [178] (NCT02969044, NCT02974868, NCT02958865).

TYK2-selective inhibitors

TYK2-selective inhibitors have been developed [179180] with the goal of blocking signaling downstream of the cytokines IL-6, IL-12, and IL-23, all of which are implicated in the pathogenesis of various autoimmune diseases [1]. Investigational TYK2 inhibitors have shown exciting preclinical efficacy in models of psoriasis, lupus, and inflammatory bowel disease [179,181]. BMS986165 is a TYK2 inhibitor that was discovered using a phenotypic screen of kinase inhibitors to identify ligands of the TYK2 pseudokinase domain. The pseudokinase domain was then targeted based on crystallographic structural information, resulting in allosteric inhibition [182181]. BMS986165 ameliorates disease in preclinical models of SLE and IBD, and a phase 2 trial is currently ongoing for the treatment of psoriasis [181] (NCT02931838). Other TYK2 inhibitors, such as NDI-031232 and NDI-031407, were developed using structure-based design and are being tested in preclinical models [179,180]. Finally, several new inhibitors in phase 1 trials inhibit both JAK1 and TYK2. PF-06700841 was developed using a structurally enabled program in combination with high-throughput screening, and is being tested in psoriasis, and alopecia areata, with plans for a trial in IBD. [183] (NCT02969018, 02974868, 02958865). SAR-20347 was discovered using high-throughput computational screening followed by secondary screening against a panel of 291 kinases, and is effective in mouse models of inflammatory skin disease [184]. Given differences between *in vitro* and *in vivo* selectivity of other jakinibs, this and other trials will determine whether TYK2-blockers are selective in clinical practice, and how selectivity might affect outcomes.

JAK inhibitors that also inhibit other kinases

Several JAK inhibitors that have been tested for immune-mediated disease also inhibit non-JAK kinases, most notably SYK (spleen tyrosine kinase). SYK is a critical kinase used by a number of multichain immune recognition receptors [185]. In principle, targeting SYK along with JAKs could enhance efficacy by broadening the signaling pathways that are blocked; however, this could also be associated with exaggerated adverse events. The SYK inhibitor

fostamitinib was effective in the treatment of RA but was associated with hypertension. Fostamitinib is currently being evaluated for the immune-mediated diseases Autoimmune Hemolytic Anemia (AIHA), Immune-mediated Thrombocytopenic Purpura (ITP), and IgA Nephropathy (NCT 02076412, 02612558, 02077192, 02112838)[186]. The topical JAK/SYK inhibitor R348 did not meet its primary endpoints for the treatment of dry eye disease and is no longer being pursued.. R333, a topical drug that is the active metabolite of R348, was tested for the treatment of discoid lupus erythematosus but also failed to meet its primary endpoint. Another JAK/SYK inhibitor, cerdulatinib, was discovered using extensive structure-activity relationship studies and has demonstrated efficacy in an animal arthritis model[187].

SB-1578 is an inhibitor of JAK2, CSF-1 (colony stimulating factor 1, c-Fms) receptor, and FLT3 (Fms Related Tyrosine Kinase 3). CSF-1 receptor is a tyrosine kinase that promotes the proliferation and differentiation of myeloid cells, and FLT3 is essential for hematopoiesis [188,189]. FLT3 and CSF-1 receptor mutations cause hematopoietic malignancy, and both kinases are also implicated in RA pathogenesis. As for combinations JAK/SYK inhibitors, simultaneous blockade of three discrete signaling pathways with agents like SB-1578 might increase efficacy but could also worsen adverse effects[190]. SB-1578 was developed by modifying the structure of pacritinib, a multikinase inhibitor under investigation for myelofibrosis and various malignancies, to achieve an improved therapeutic window [191]. SB-1578 was effective in the preclinical model of collagen-induced arthritis[190]. A Phase I trial in healthy subjects was completed in 2012, but results were not made available and further development has not taken place (NCT01235871).

Future directions

The last decade has witnessed an explosion of data regarding the efficacy of selective and nonselective jakinibs in the treatment of autoimmunity. In many respects, the success of jakinibs based on genetic models was predictable. What was less predictable was their relative safety (Table 5). Jakinibs therefore serve as an interesting model for other drugs designed to target key intracellular signaling pathways.

Still critical questions with immediate clinical relevance remain unanswered, providing several areas of research for future investigators. Among the most exciting of these is the possibility that tofacitinib may be efficacious for debilitating, treatment-refractory autoimmune diseases. Immune-mediated diseases such as SLE, IBD, and dermatomyositis have fewer treatment choices than RA and psoriasis. With multiple early-phase clinical trials in such diseases underway, the next few years should begin to establish the efficacy and safety of various JAK inhibitors in such diseases (NCT 03159936, 02535689 02708095, 03002649, 03026504).

Next, the benefits, risks, and optimal mechanisms for achieving *in vivo* selectivity remain elusive. While many next-generation Jakinibs are reasonably selective *in vitro*, their selectivity in the clinical arena is not as fully characterized and remains to be proven. Moreover, while current studies indicate that selective and pan-jakinibs are equally effective for RA, this may not be true for other immune-mediated diseases. For example, the JAK1-

selective filgotinib significantly ameliorates CD, whereas tofacitinib does not. This raises the question as to which cytokines are being differentially inhibited by filgotinib and tofacitinib, and how various JAK isoforms contribute to CD pathophysiology. It also raises the prospect that selective blockade of one JAK isoform over another may be sufficient or even advantageous in certain immune-mediated diseases [192], while blockade of multiple JAKs may be necessary in other settings [193]. Moreover, other kinase inhibitors have activity against JAKs [194], raising the prospect that wider blockade of multiple signaling pathways may provide additional therapeutic benefit – although the risks must be carefully balanced. As the spectrum of jakinib-responsive disease expands, perhaps even including IL-13 driven fibrotic diseases such as berylliosis [195], the risks and benefits of JAK isoform selectivity in different rheumatic diseases will become increasingly clear and will perhaps contribute to our understanding of disease pathogenesis.

For jakinib-responsive diseases, it is still unknown which patients would derive the most benefit from JAK blockade: the current ACR guidelines recommend tofacitinib for the treatment of cDMARD-refractory established RA but do not distinguish between tofacitinib and bDMARDs. Clearly, the field needs more rational treatment selection: in clinical trials 30–40% of RA patients invariably fail to respond to therapy. While most RA patients can be successfully treated with an FDA-approved agent, we are currently unable to predict which therapy will be most effective for a particular patient. This may be because most polygenic autoimmune diseases are heterogeneous [1], such that JAK-dependent cytokines might drive disease in a large subset of patients, while other cytokines could be more important for different subgroups. A vigorous search is currently underway to identify biomarkers that could predict response to various immunomodulatory agents, including jakinibs. With improved success in treating diseases like RA, the prospect emerges of cure or long term remission. Many believe that this will require more aggressive, early treatment of patients. One might expect that trials employing jakinibs in early RA will be considered. In addition, one can imagine tapering patients off methotrexate when disease comes under control; this too should be investigated in clinical trials.

Another area that remains to be established is the optimal dosing regimen for jakinibs. Currently, all clinical trials use an identical dose for induction of remission and for maintenance therapy. However, preclinical data suggests that chronically treated cells become less responsive to JAK-dependent cytokines, or chronically “inhibited”, even after a washout period[196] when they are not being treated with Jakinibs. This raises the possibility that jakinibs could be dosed aggressively to induce remission, then tapered to a much lower dose for maintenance therapy [196]. This is already the regimen used in canines, where oclacitinib is dosed twice daily for up to 14 days and once daily thereafter.

Moreover, some autoimmune diseases present with limited cutaneous, mucosal, or ocular involvement. Clearly, the possibility of treating such diseases with topical formulations and sparing systemic adverse effects is very exciting. While some topical formulations of tofacitinib and ruxolitinib have been investigated in preliminary studies, these studies are still in their infancy.

Similarly, the risks and benefits of jakinibs as monotherapy vs. combination therapy with other immunomodulators such as MTX or even biologics [197] remain incompletely characterized. As the renal transplant studies have shown, this strategy is not without risk, but could potentially be managed using a serum concentration-based dose escalation protocol or immunological functional studies to gauge early response to therapy. As with corticosteroids, there might be a role for bDMARDs with long half-lives as maintenance therapy, whereas potent tsDMARDs with short half-lives could be used for breakthrough activity. This strategy could be particularly relevant to catastrophic flares of systemic autoimmune diseases, where current standard of care is to profoundly immunosuppress patients and induce remission, then follow up with less toxic consolidation and maintenance therapy.

Along these lines, our understanding of immunopathology is increasingly becoming more refined as we begin to incorporate recent discoveries about the role of noncoding, regulatory DNA elements[198]. Such elements may be relatively close to genes but can also be far away. Moreover, some key genes are surrounded by dense regions of regulatory elements termed “superenhancers”. In T cells, genes with superenhancer structure seem preferentially affected by jakinibs [198]. As our understanding of the immense numbers of regulatory elements becomes clearer, physicians may be able to fine-tune the expression of critical disease regulators, rather than simply turning them on or off; much like an acoustic editor in a recording studio “adjusts the gain” of faders on a mixing console. In this way, the effect of immunomodulation might be optimized and adverse effects minimized. In this way, the effect of immunomodulation might be optimized and adverse effects minimized.

Finally, a host of novel jakinibs are being developed (Table 4), with at least 95 patented candidates [159,160]. Many are analogs of FDA-approved compounds, but some have achieved unprecedented selectivity by covalently targeting nonconserved residues at the kinase domain. As the field evolves, jakinibs thus continue demonstrating clinical efficacy as immunomodulators, while also providing critical insights into the mechanisms driving immune-mediated disease.

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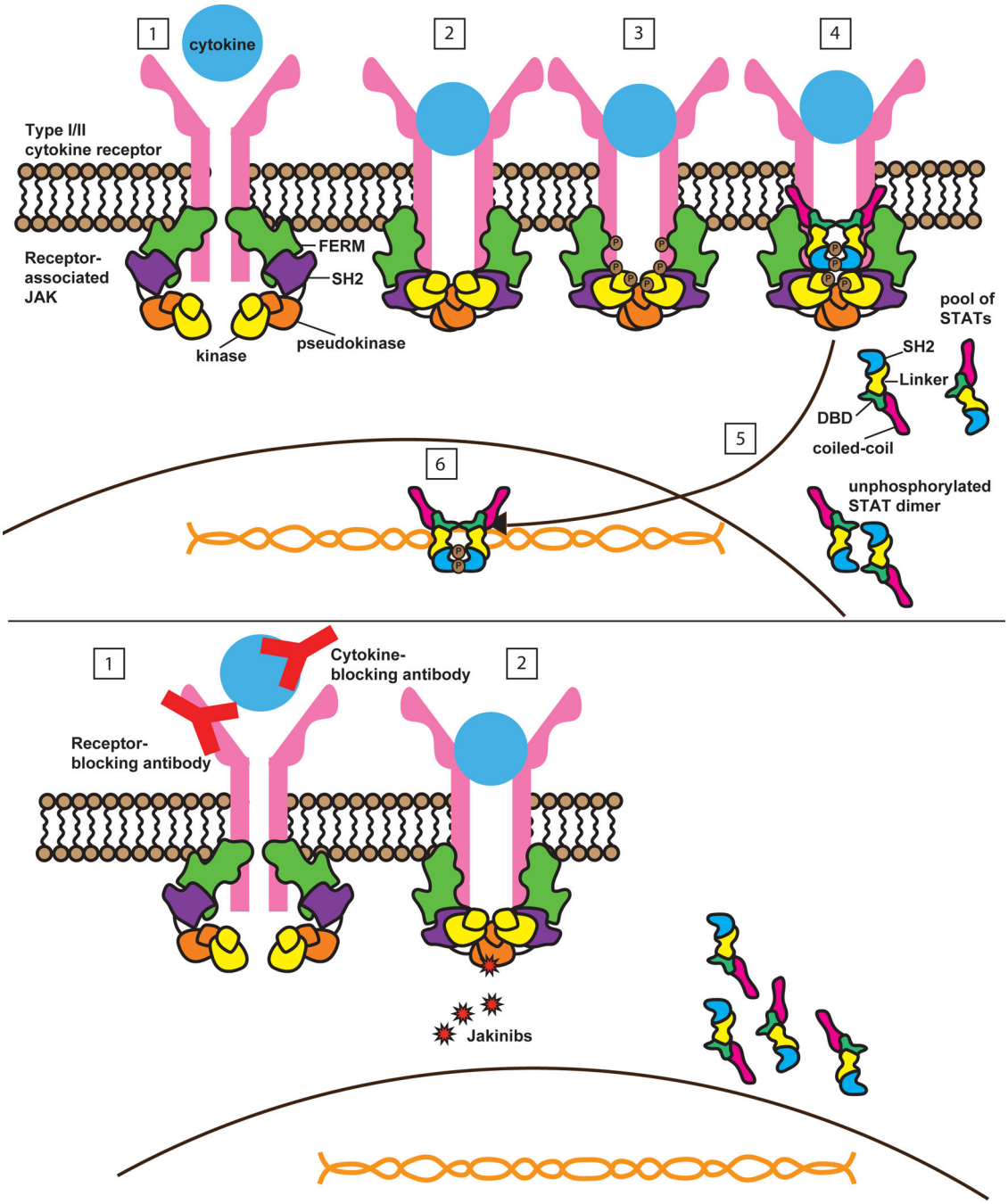

Figure 1: Signalling by type I and II cytokine receptors.

(A) Type I and II cytokine receptors comprise subunits that physically associate with Janus kinases (JAKs). Type I/II cytokine receptors do not have any enzymatic activity but instead depend upon JAKs to transduce intracellular signals. JAK proteins share 4 components: the kinase domain, the pseudokinase domain, the FERM (Four-point-one protein, Ezrin, Radixin, Moesin) domain, and the SH2-like domain. The canonical JAK/STAT pathway is initiated by extracellular association of cytokines with their cognate receptors (1). This activates the receptor, resulting in apposition of receptor-associated JAKs (2). JAKs are

tyrosine kinases, so upon activation they transfer phosphate from ATP to tyrosine residues on other proteins, including cytokine receptors and JAKs themselves. This is an important event, as tyrosine phosphorylation of kinases, including JAKs, triggers their enzymatic activity. Tyrosine phosphorylation of receptors (3) creates docking sites for signaling molecules including signal transducers and activators of transcription (STATs), which also undergo JAK-mediated phosphorylation of their tyrosine residues (4), leading to STAT dimerization, nuclear translocation (5), DNA binding and target gene induction (6). **(B)**. Monoclonal antibodies can block Type I/II cytokines and their receptors. In contrast, jakinibs block cytokine signaling by inhibiting kinase activity. This prevents JAKs from phosphorylating STATs and other substrates, so that intracellular signals cannot be transduced. Because JAKs are critical for multiple different cytokines, jakinibs block the action of a range of cytokines, unlike biologics. First generation jakinibs block multiple JAKs whereas second generation jakinibs may have more selectivity for JAKs and so may inhibit a narrow range of cytokines. Cytokine receptors, JAK and STATs are drawn based on structural information [199,200].

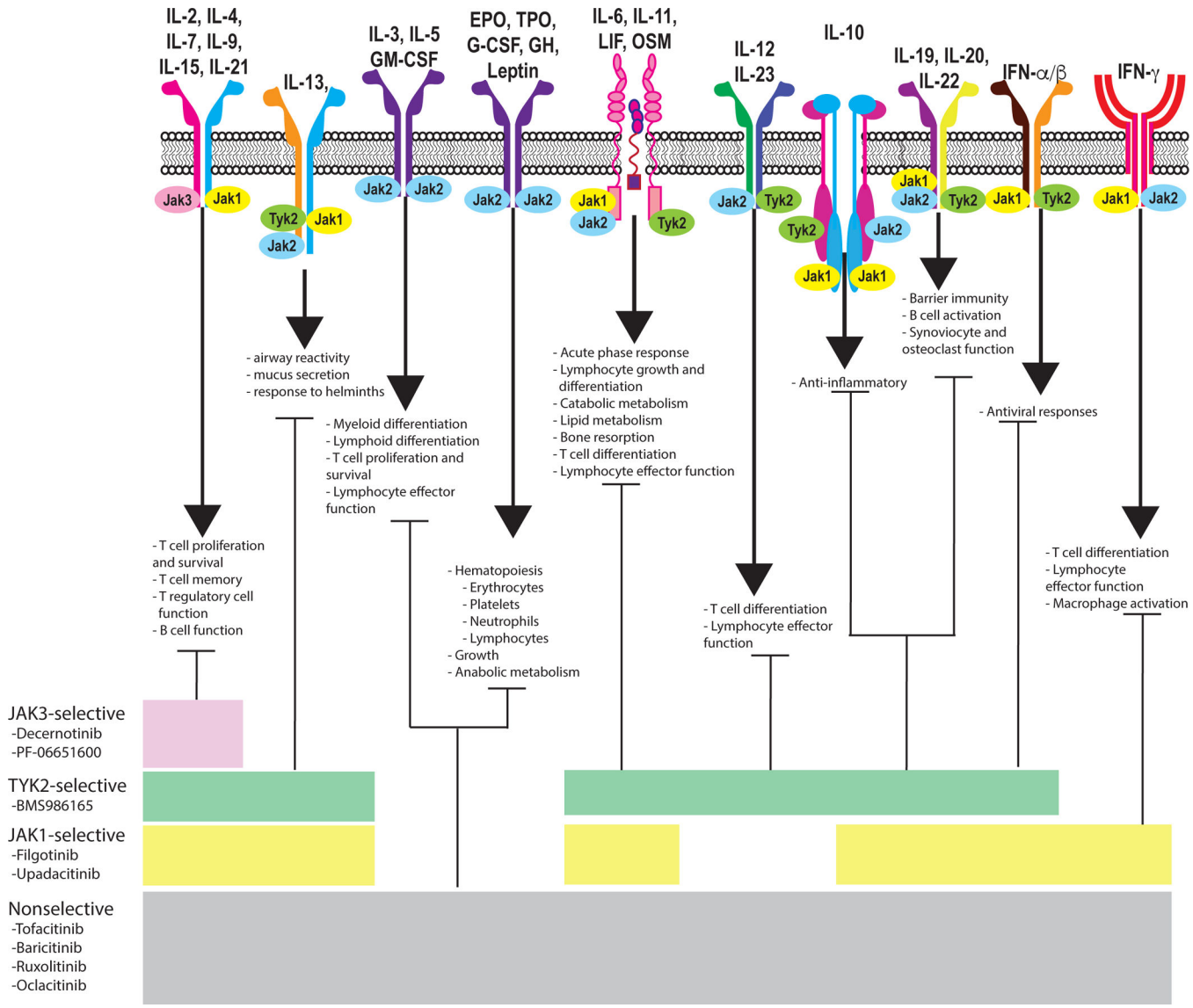

Figure 2: Effects of targeting different JAKs.

Type I and II cytokine receptors physically associate with JAKs, which transduce downstream intracellular signals. Different receptors associate with different JAKs, so that selective blockade of one JAK can inhibit a specific biologic function while allowing other JAK-dependent cytokines to signal normally. For example, selective blockade of JAK3, which is associated exclusively with the common gamma chain receptor, should inhibit T cell, NK cell, and B cell function while leaving hematopoietic and metabolic pathways unaffected. IL, interleukin; IFN, interferon; Jak, Janus kinase; NK, natural killer

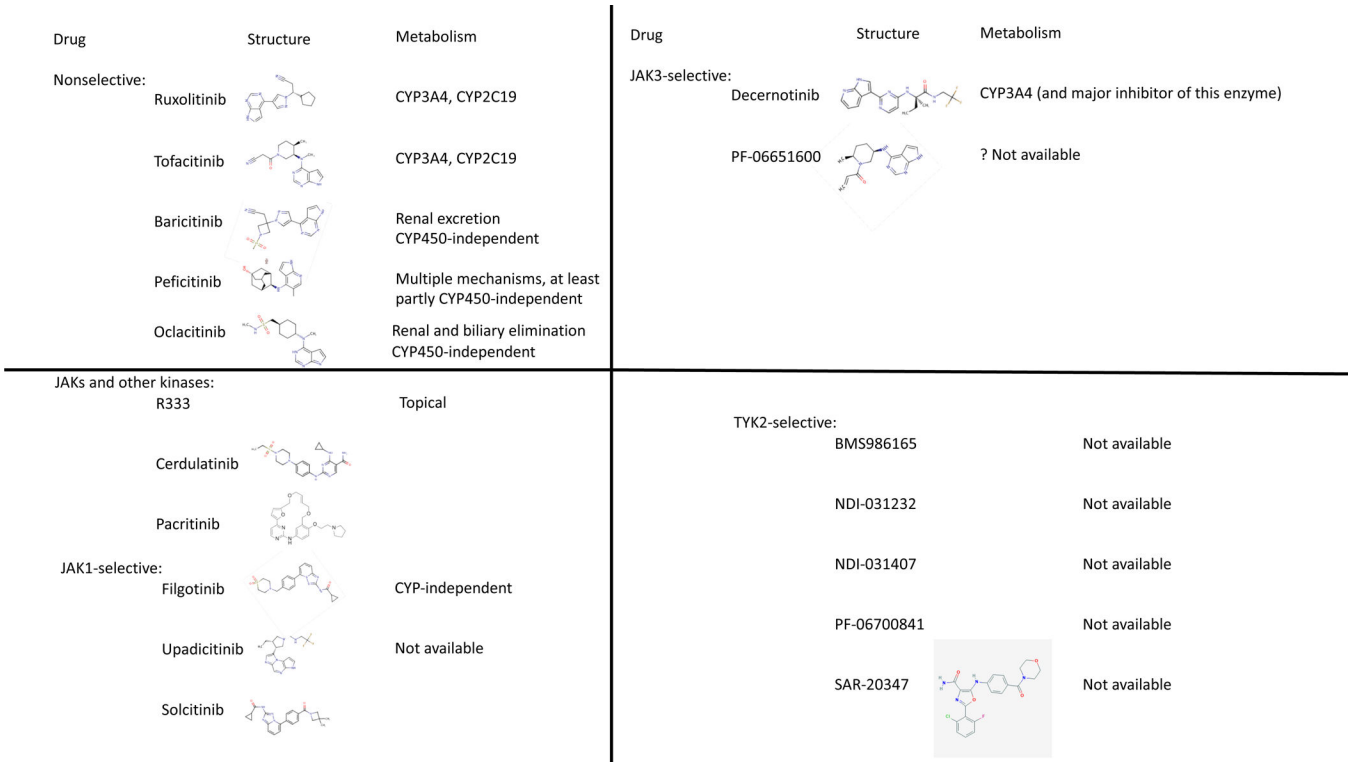

Figure 3: Chemical structure and attributes of various jakinibs

The first-generation JAK inhibitors ruxolitinib, tofacitinib, and baricitinib block multiple JAKs. The newer pan-jakinib peficitinib has IC_{50} of 3.9, 5.0, 0.71 and 4.8 nmol/L for JAK1, JAK2, JAK3 and TYK2 enzymatic activity respectively. A variety of next-gen JAK inhibitors are emerging. Several block JAKs and other kinases (R333, cerdulatinib, SB-1578), while many are selective for one particular JAK isoform. Filgotinib, Upadacitinib, and Solcitinib block JAK1; Decernotinib and PF-06651600 block JAK3; and BMS986165, NDI-021232, NDI=031407, PF-06700841, and SAR-20347 all block TYK2. Chemical structures and data regarding metabolism/clearance are shown where available. (IC_{50}, inhibitory concentration 50%; CYP, cytochrome P; JAK, Janus kinase)

Table 1:

Clinical trials involving Tofacitinib

RA TRIALS								
Study Name	**# subjects**	**Participants**	**Intervention**	**Concomitant DMARDs**	**Study Duration**	**Efficacy (ACR20)**	**Other outcome measures**	**Reference number**
ORAL solo	611	Active RA refractory to bDMARD or cDMARD	Tofacitinib 5 mg BID	Allowed: antimalarials, prednisone<10mg daily, NSAIDs	6 months, results reported at 3 months	Placebo: 26.7%	ACR 50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, FACIT	34
			Tofacitinib 10 mg BID			Tofacitinib 5mg: 59%		
			Placebo × 3 mo. --> tofacitinib 5mg BID × 3 mo.			Tofacitinib 10mg: 65.7%		
			Placebo × 3 mo. --> tofacitinib 10mg BID × 3 mo.					
ORAL step	399	Moderate-to-severe RA, refractory to TNF inhibitors	Tofacitinib 5 mg BID	Required: MTX	6 months	Placebo: 24.4%	ACR 50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, FACIT, SDAI	29
			Tofacitinib 10 mg BID	Allowed: prednisone≤10mg daily, NSAIDs		Tofacitinib 5mg: 41.7%		
			Placebo × 3 mo. --> tofacitinib 5mg BID × 3 mo.			Tofacitinib 10mg: 48·1%		
			Placebo × 3 mo. --> tofacitinib 10mg BID × 3 mo.					
ORAL-standard	717	Active RA refractory to MTX	Tofacitinib 5 mg BID	Required: MTX	12 months, results reported at 6 months	Placebo: 28.3%	ACR 50, ACR70, HAQ-DI, DAS28-ESR<2.6 Other patient-reported outcomes are described in a separate study	30
			Tofacitinib 10 mg BID			Tofacitinib 5mg: 51.5%		
			Adalimumab 40mg biweekly			Tofacitinib 10mg: 52.6%		
			Placebo × 3 mo. --> tofacitinib 5mg BID (nonresponders) or placebo × 3 mo. --> tofacitinib 5mg BID × 6 mo. (all)	Allowed: prednisone≤10mg daily, NSAIDs		Adalimumab 47.2%		
			Placebo × 3 mo. --> tofacitinib 10mg BID (nonresponders) or placebo × 3 mo. --> tofacitinib 10mg BID × 6 mo. (all)					
ORAL sync	792	Active RA, refractory to cDMARD or bDMARD	Tofacitinib 5mg BID × 12 mo.	Required: one cDMARD (no potent immunosuppressives, e.g. AZA, CSA)	12 months	Placebo: 30.8% (month 6)	ACR50, ACR70, HAQ-DI DAS28-ESR, DAS28-CRP	201201
			Tofacitinib 10mg BID × 12 mo.			Tofacitinib 5mg: 52.1%		
			Placebo × 6mo --> tofacitinib 5mg BID × 6 mo.	Allowed: prednisone<10mg daily, NSAIDs		Tofacitinib 10mg: 56.6%		
			Placebo × 6 mo. --> tofacitinib 10mg BID × 6 mo.					

RA TRIALS								
Study Name	**# subjects**	**Participants**	**Intervention**	**Concomitant DMARDs**	**Study Duration**	**Efficacy (ACR20)**	**Other outcome measures**	**Reference number**
ORAL scan	797	Active RA, prior use of bDMARDs or cDMARDs permitted	Tofacitinib 5mg BID × 12 mo.	Required: MTX	24 months, results reported at 6 months	Placebo: 25.3%	ACR50/70, HAQ-DI DAS28-ESR, DAS28-CRP, vdH-mTSS, FACIT	38
			Tofacitinib 10mg BID × 12 mo.			Tofacitinib 5mg: 51.5%		
			Placebo × 3 mo. --> tofacitinib 5mg BID (nonresponders) or placebo × 3 mo. --> tofacitinib 5mg BID × 6 mo.	Allowed: prednisone≤10mg daily, NSAIDs		Tofacitinib 10mg: 61.8%		
			Placebo × 3 mo. --> tofacitinib 10mg BID (nonresponders) or placebo × 3 mo. --> tofacitinib 10mg BID × 6 mo.					
ORAL start	958	Treatment-naïve active RA	Tofacitinib 5mg BID × 6 mo.	Allowed: antimalarials, prednisone<10mg daily, NSAIDs	6 months	MTX:50.5%	ACR50/70, HAQ-DI DAS28-ESR, DAS28-CRP, vdH-mTSS, FACIT	28
			Tofacitinib 10mg BID × 6 mo.			Tofacitinib 5mg: 71.3%		
			MTX up to 20mg weekly			Tofacitinib 10mg: 76.1%		

PSORIATIC ARTHRITIS TRIALS								
Study Name	**# subjects**	**Participants**	**Intervention**	**Concomitant DMARDs**	**Study Duration**	**Efficacy (PASI75)**	**Other outcome measures**	**Reference number**
OPAL Beyond	395	Active psoriatic arthritis refractory to TNF inhibitors	Tofacitinib 5 mg BID	Required: one cDMARD	6 months, results reported at 3 mints	Placebo: 23.7%	ACR50/70, HAQ-DI, PASI75, DLEI, DDSS; 6 month outcomes	202
			Tofacitinib 10 mg BID			Tofacitinib 5mg: 49.6%		
			Placebo × 3 mo. --> tofacitinib 5mg BID × 3 mo.			Tofacitinib 10mg: 47%		
			Placebo × 3 mo. --> tofacitinib 10mg BID × 3 mo.					
OPAL Broaden	422	Psoriatic arthritis	Tofacitinib 5 mg BID	Required: one cDMARD	12 months, results reported at 3 and 12 months	Placebo: 33.3%	ACR50/70, HAQ-DI, PASI75, DLQI, DSS; 12 month outcomes	58
			Tofacitinib 10 mg BID			Adalimumab: 51.9%		
			Adalimumab 40mg biweekly			Tofacitinib 5mg: 50.5%		
			Placebo × 3 mo. --> tofacitinib 5mg BID			Tofacitinib 10mg: 60.6%		
			Placebo × 3 mo. --> tofacitinib 10mg BID					
OPAL Balance	817	Psoriatic arthritis	see above	see above	LTE study	N/A	see above	N/A

PSORIASIS TRIALS								
Study Name	**# subjects**	**Participants**	**Intervention**	**Concomitant DMARDs**	**Study Duration**	**Efficacy (PASI75)**	**Other outcome measures**	**Authors**
OPT Pivotal 1/2 (Two identically designed studies)	1859	Active plaque psoriasis	Placebo × 16 weeks --> tofacitinib 5mg or 10mg BID	None	12 months (16-week outcomes reported)	Placebo: 6.2% (Pivotal 1), 11.4% (Pivotal 2)	PGA “clear” or “almost clear”, PASI 50/90, DLQI, BSA, NAPSI; results at 28 weeks are reported in separate study	203
			Tofacitinib 5mg BID			Tofacitinib 5mg: 39.9% (Pivotal 1), 46% (Pivotal 2)		
			Tofacitinib 10mg BID			Tofacitinib 10mg: 59.2% (Pivotal 1), 59.6% (Pivotal 2)		
OPT Compare	1106	Chronic stable active plaque psoriasis	Placebo	None	12 weeks	Placebo: 5.6%	PGA “clear” or “almost clear”, PASI50/90, BSA, patient-reported itch severity	75
			Etanercept 50mg twice weekly			Etanercept: 58.8%		
			Tofacitinib 5mg BID			Tofacitinib 5mg: 39.5%		
			Tofacitinib 10mg BID			Tofacitinib 10mg: 63.6%		
OPT Retreatment	666	Chronic active plaque psoriasis	Tofacitinib 5mg BID	None	40 weeks	Tofacitinib 5mg: 49.9%	PGA “clear” or “almost clear”, DLQI, PASI 50/90	72
			Tofacitinib 10mg BID			Tofacitinib 10mg: 63.9%		
			Tofacitinib 5mg BID × 24 weeks --> withdrawal × 16 weeks			Tofacitinib 10mg --> placebo: 18%		
			Tofacitinib 10mg BID × 24 weeks --> withdrawal × 16 weeks			Tofacitinib 5mg --> placebo: 22.9%		
OPT Extend		Psoriasis	see above	None	LTE study	N/A	see above	N/A

ULCERATIVE COLITIS TRIALS								
Study Name	**# subjects**	**Participants**	**Intervention**	**Concomitant DMARDs**	**Study Duration**	**Disease Remission**	**Other outcome measures**	**Authors**
OCTAVE Induction 1/2 (Two identically designed studies)	1139	Moderately to severely active ulcerative colitis refractory to corticosteroids, cDMARDs, or TNF inhibitors	Placebo	None	8 weeks	Placebo: 6.2% (Induction 1), 3.6% (Induction 2)	Mucosal healing, clinical response	63
			Tofacitinib 10mg BID			Tofacitinib 10mg: 18.5% (Induction 1), 16.6% (Induction 2)		
OCTAVE Sustain	593	Placebo or tofacitinib-treated patients with clinical response in OCTAVE Induction 1 or 2	Placebo	None	52 weeks	Placebo: 11.1%	Mucosal healing, clinical response, sustained clinical responses, sustained steroid-free remission	204
			Tofacitinib 5mg BID			Tofacitinib 5mg: 34.3%		
			Tofacitinib 10mg BID			Tofacitinib 10mg: 40.6%		
OCTAVE Open	1732	All patients in OCTAVE Induction and Sustain trials	See above	N/A	long-term extension	see above	see above	N/A

RA, rheumatoid arthritis; cDMARD, conventional disease modifying antirheumatic drug; bDMARD, biological disease modifying antirheumatic drug; MTX, methotrexate; BID, twice daily; NSAID, nonsteroidal anti-inflammatory drug; ACR20 (50, 70), American College of Rheumatology Criteria 20% (50%, 70%) improvement; HAQ-DI, Health Assessment Questionnaire Disability Index; DAS-28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FACIT, functional assessment of chronic illness therapy; SDAI, Simple Disease Activity Index; vdH-

Nat Rev Drug Discov. Author manuscript; available in PMC 2018 October 02.

mTSS = van der Heijde modified total Sharp score; PASI75 (50, 90), 75% (50%, 90%) reduction in Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; DSS, dactylitis severity score; PGA Physician's Global Assessment; NAPSI, nail psoriasis severity index; BSA, body surface area involvement.

Table 2:

Clinical trials involving baricitinib

RA TRIALS								
Study Name	**# subjects**	**Participants**	**Intervention**	**Concomitant DMARDs**	**Study Duration**	**Efficacy (ACR20)**	**Other outcome measures**	**Reference number**
RA-BEACON	527	Active RA refractory to bDMARDs	Baricitinib 2mg daily	Allowed: cDMARDs, NSAIDs, prednisone ≥ 10mg daily	24 weeks (outcomes reported at 12 weeks)	Placebo: 27%	ACR 50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI	53
			Baricitinib 4 mg daily			Baricitinib 2mg: 49%		
			Placebo			Baricitinib 4mg: 55%		
RA-BUILD	684	Active RA and refractory to cDMARDs (prior bDMARDs not allowed)	Baricitinib 2mg daily	Allowed: up to 2 cDMARDs, NSAIDs, prednisone ≥ 10mg daily	24 weeks	Placebo: 39%	ACR 50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, MJS duration and severity, vdH-mTSS	51
			Baricitinib 4 mg daily			Baricitinib 2mg: 66%		
			Placebo			Baricitinib 4mg: 62%		
RA-BEGIN	584	Active RA, DMARD-naïve (≤3 doses of MTX allowed)	Baricitinib 4 mg daily	Required; MTX (if assigned	52 weeks (outcomes reported at 24 weeks)	MTX: 62%	ACR 50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, vdH-mTSS	52
			Baricitinib 4mg daily + MTX			Baricitinib 4mg: 77%		
			MTX	Allowed: NSAIDs, prednisone > 10mg daily		Baricitinib + MTX: 78%		
RA-BEAM	1305	Active RA on stable background MTX	Placebo	Required; MTX	24 weeks (outcomes reported at 12 weeks)	Placebo: 40%	ACR 50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, MJS duration and severity, vdH-mTSS	54
			Baricitinib 4 mg daily			Adalimumab: 61%		
			Adalimumab 40mg biweekly	Allowed: NSAIDs, prednisone > 10mg daily		Baricitinib 4mg: 70%		

RA, rheumatoid arthritis; cDMARD, conventional disease modifying antirheumatic drug; bDMARD, biological disease modifying antirheumatic drug; MTX, methotrexate; BID, twice daily; NSAID, nonsteroidal anti-inflammatory drug; ACR20 (50, 70), American College of Rheumatology Criteria 20% (50%, 70%) improvement; HAQ-DI, Health Assessment Questionnaire Disability Index; DAS-28, disease activity score based on 28 joints; ESR, erythrocyte 1 sedimentation rate; CRP, C-reactive protein; CDAI, clinical disease activity index; SDAI, Simple Disease Activity Index; MJS, morning joint stiffness; vdH-mTSS = van der Heijde modified total Sharp score

Table 3:

Jakinibs that are FDA-approved or in late phase (> Phase 2) clinical trials

Drug	Target	Status	Diseases	Clinical Trial Identifier
Ruxolitinib (INC424)	JAK1, JAK2	*FDA and EMA approved*	Myeloproliferative neoplasms	N/A
		Phase II, III	Various cancers	NCT02117479, NCT00638378, NCT01562873, NCT00639002, NCT02723994, NCT02119676, NCT02876302, NCT01712659, others
		Phase II, III	GVHD	NCT02913261, NCT02953678, NCT02396628
		Phase II	RA	NCT00550043
		Phase II	AA	NCT01950780
		Phase II	vitiligo, AA, psoriasis, AD (topical)	NCT02809976, NCT00617994, NCT02553330, NCT03011892
Tofacitinib (CP690550)	JAK3>JAK1>> (JAK2)	*FDA approved, EMA approval recommended*	RA	N/A
		Phase III	Psoriasis/psoriatic arthritis, UC, JIA	NCT02592434, NCT01500551, NCT01976364, NCT03000439, NCT01470612, NCT01882439, NCT01877668
		Phase II	AA, Crohn's disease, AS, kidney transplant	NCT01786668, NCT01393899, NCT01393626, NCT01470599, NCT00615199, NCT02299297, NCT02197455, NCT02312882, NCT01375127, NCT00106639, NCT00263328, NCT00483756, NCT00658359
		Phase II	Psoriasis, AA, AD (topical)	NCT02001181, NCT02812342, NCT02193815, NCT00678561, NCT01831466, NCT01246583
Oclacitinib	JAK1	*FDA approved*	Canine allergic dermatitis	N/A
Baricitinib (INCB28050, LY3009104)	JAK1, JAK2	*EMA approved*	RA	N/A
		Phase II	GVHD, giant cell arteritis, diabetic nephropathy	NCT02759731, NCT03026504, NCT01683409
Decernotinib (VX509)	JAK3	Phase II, III	RA	NCT01830985, NCT01590459, NCT01052194
Upadacitinib (ABT494)	JAK1	Phase III	RA	NCT02955212, NCT02706847, NCT02720523, NCT02629159, NCT02706873, NCT02675426, NCT02706951, NCT02049138
		Phase II, III	UC, Crohn's disease	NCT03006068, NCT02782663, NCT02819635, NCT02365649
		Phase II	AD	NCT02925117
Filgotinib (GLPG0634)	JAK1	Phase III	RA	NCT02873936, NCT03025308, NCT02886728, NCT02889796, NCT02885181
		Phase II, III	UC, Crohn's disease	NCT02048618, NCT02914600, NCT02914535, NCT03077412, NCT03046056, NCT02914561, NCT02914522
Itacitinib (INCB039110)	JAK1, JAK2	Phase II	Psoriasis, RA, pruritis	NCT01634087, NCT01626573, NCT02909569
Peficitnib (ASP015K)	pan-JAK	Phase III	RA	NCT01638013
R333 *	JAK, SYK	Phase II	DLE	NCT01597050
PF-06651600	JAK3	Phase II	RA, AA, UC	NCT02969044, NCT02974868, NCT02958865
PF-06700841	JAK1, TYK2	Phase II	AA, UC, psoriasis	NCT02969018, NCT02974868, NCT02958865

Drug	Target	Status	Diseases	Clinical Trial Identifier
BMS-986165	TYK2	Phase II	Psoriasis	NCT02534636, NCT02931838
Solcitinib (GSK2586184, GLG0778) *	JAK1	Phase II	Psoriasis, SLE	NCT02000453, NCT01782664, NCT01687309, NCT01777256, NCT01953835
PF-04965842 *	JAK1	Phase II	Psoriasis, AD	NCT02201524, NCT02780167

JAK, Janus kinase; TYK, tyrosine kinase; RA, rheumatoid arthritis; GVHD, graft-versus-host disease; SLE, systemic lupus erythematosus, FDA, Food and Drug administration; UC, ulcerative colitis

* Further development has been discontinued

Table 4:

Jakinibs under early investigation (discontinued compounds are excluded)

Drug	Target	Status	Diseases	Clinical Trial Identifier
SAR-20347	Jak1/Tyk2	preclinical	psoriasis	N/A
Cerdulatinib (PRT-062070)	Jak/Syk	preclinical	collagen-induced arthritis	N/A
NDI-031407	Tyk2	preclinical	IBD, psoriasis	N/A
NDI-031232	Tyk2	preclinical	Response to IL-12	N/A
SHR-0302	pan-jakinib	Phase 1	RA	NCT02892370, NCT02665910
VR588	pan-jakinib	Early phase 1	Severe asthma	NCT02740049
SB-1578	Jak2, Flt3, c-Fms	Phase 1	Healthy subjects	NCT01235871
JTE-052	nonselective	Phase 1	Atopic dermatitis	JapicCTI-152887, JapicCTI-142494

JAK, Janus kinase; TYK, tyrosine kinase; RA, rheumatoid arthritis

Table 5:

Lesson learned from jakinibs

Concept	Predicted	Not Predicted	Unknown
Target broad spectrum of cytokines	X		
Efficacious for autoimmune adaptive immunity-mediated disease Useful for autoinflammatory innate-mediated disease	X	X	
Efficacious for autoinflammatory innate-mediated disease		X	
Selectivity achievable			X
Selectivity unnecessary		X	
Selectivity advantageous			X
Pan jakinib viable		X X	
JAK1 inhibitor viable			X
JAK2 inhibitor viable		X	
adverse effects-infection	X		
adverse effects-anemia, cytopenia	X		
Adverse effects Hyperlipidemia		X	

JAK, Janus kinase