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MINI-REVIEW

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The Promise of JAK Inhibitors for Treatment of Sarcoidosis and Other Inflammatory Disorders with Macrophage Activation: A Review of the Literature

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Certain inflammatory disorders are characterized by macrophage activation and accumulation in tissue; sometimes leading to the formation of granulomas, as in sarcoidosis. These disorders are often difficult to treat and more effective, molecularly targeted therapies are needed. Recent work has shown that overproduction of inflammatory cytokines, such as interferon gamma (IFN-γ) leading to constitutive activation of the JAK-STAT pathway may be a conserved feature of these disorders. Use of JAK inhibitors, which can block these signals, has resulted in dramatic improvement in several patients with sarcoidosis. JAK inhibitors also appear to have activity in other inflammatory disorders with macrophage activation including hemophagocytic lymphohistiocystosis, Crohn's disease, granuloma annulare, and necrobiosis lipoidica. Here, we review the role of JAK dependent cytokines in macrophage activation and granuloma formation and the clinical evidence supporting the use of JAK inhibition in these disorders. Ongoing efforts to evaluate role of JAK inhibitors in these disorders is also discussed.

INTRODUCTION

Macrophages play a key role in many functions including immunity and tissue homeostasis/repair. Macrophages can also become activated inappropriately leading to tissue damage during auto-inflammation and auto-immunity. While macrophages are likely important in the pathogenesis of many auto-immune diseases, in a subset of these disorders, macrophage activation and accumulation in tissue is a central pathogenic feature. This latter group will be the focus of this review. Some macrophage activation disorders affect specific organs. Granuloma

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Abbreviations: CD, Crohn's disease; GA, granuloma annulare; HLH, hemophagocytic lymphohistiocytosis; IFN, interferon; IL, interleukin; JAK, Janus kinase; NL, necrobiosis lipoidica; PD-L1, Programmed death ligand 1; STAT, Signal transducer and activator of transcription.

Keywords: sarcoidosis, granuloma annulare, necrobiosis lipoidica, Crohn's disease, hemophagocytic lymphohistiocytosis, Janus kinase, JAK inhibitor, tofacitinib, ruxolitinib

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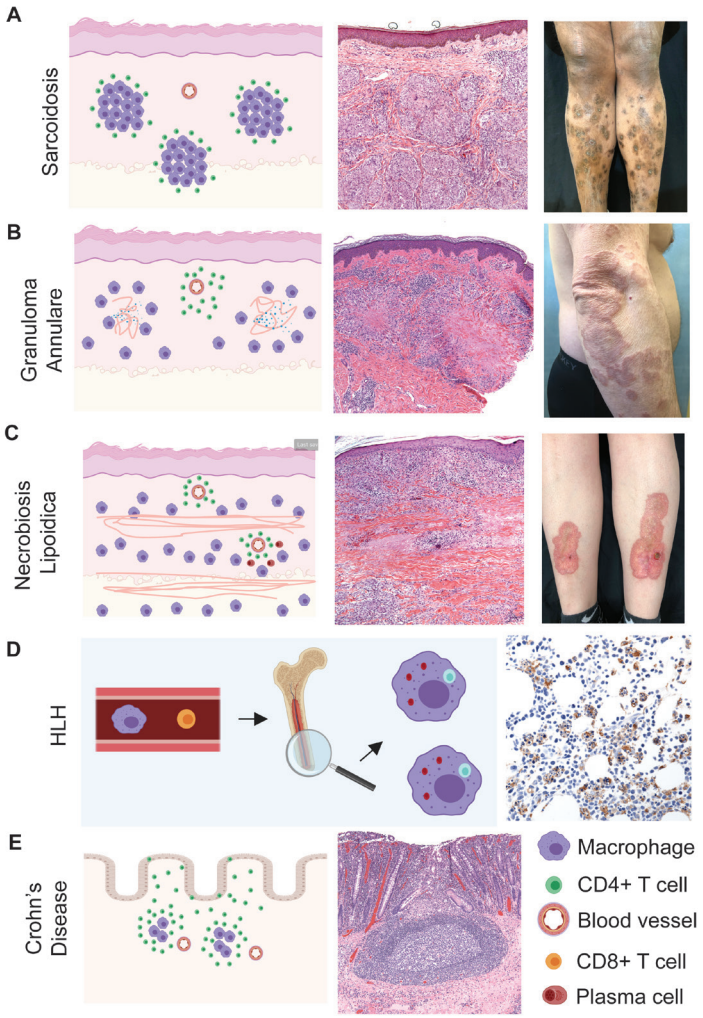

Figure 1. Clinical and histopathologic features of inflammatory diseases with macrophage activation. A. In sarcoidosis, well-formed granulomas are present in affected tissues (skin or other). Granuloma macrophages have epithelioid morphology and are tightly aggregated. A relative paucity of CD4+ T cells are present at the edges of the granulomas (cartoon: left panel, hematoxylin and eosin stained skin biopsy (H&E)). Clinically, there are annular papules and plaques (right panel). **B.** In granuloma annulare, macrophages palisade around round areas of altered collagen; mucin is often present. Lymphocytes are present around blood vessels (cartoon: left panel, H&E: middle panel). Clinically, there are annular papules and plaques. **C.** In necrobiosis lipoidica, macrophages palisade around areas of altered collagen in a horizontal fashion, resulting in a "layer cake" appearance affecting the entire dermis. Lymphocytes and plasma cells are present, particularly around blood vessels (cartoon: left panel, H&E: middle panel). Clinically, there are yellow-pink plaques on the shins which can ulcerate (right panel). **D.** In hemophagocytic lymphohistiocytosis (HLH), CD8+ T cells activate macrophages leading to engulfment of other cell types (hemophagocytosis), most commonly in the bone marrow (cartoon: left panel). Right panel: HLH in the skin, CD68 staining highlights macrophages which are phagocytosing other cell types. **E.** In Crohn's disease, the lymphocytic component of the infiltrate is prominent, ulceration is often present, and poorly formed granulomas can be found in approximately 50% of cases (cartoon: left panel, H&E: middle panel).

annulare (GA) and necrobiosis lipoidica (NL) affect the skin. Crohn's disease (CD) affects the gastrointestinal tract. In contrast, sarcoidosis can affect nearly any organ system and is often present in multiple organ systems simultaneously (most commonly the lungs, lymph nodes, and/or skin). Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by systemic macrophage activation.

These disorders have both overlapping and distinct pathogenic features and as a group can be challenging to treat. Historically broadly acting immunosuppressants such as prednisone have been used. In HLH, etoposide,

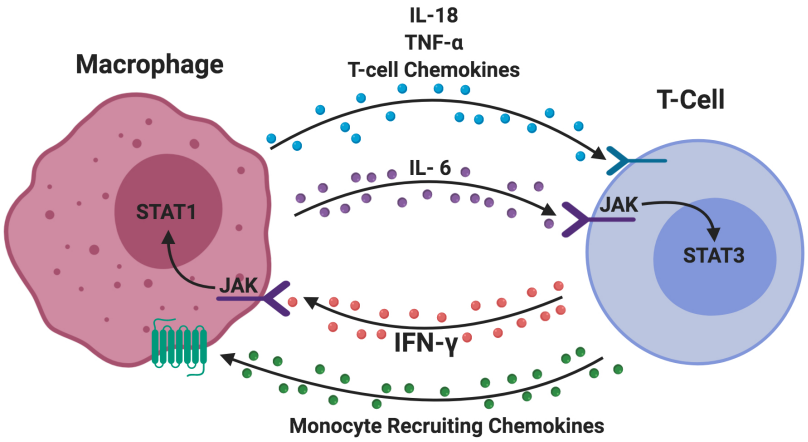

Figure 2. Molecular mechanism of macrophage – T cell cross talk leading to macrophage activation. CD4+ T cells secrete IFN-γ and monocyte recruiting chemokines, leading to monocyte recruitment and activation. IFN-γ signaling leads to STAT1 activation in macrophages (for HLH, CD8+ T cells are the source of IFN-γ). Following activation, macrophages produce IL-6, IL-18, TNF-α, and T cell chemokines. CD40-CD40L interactions may also be important (not pictured). IL-6 is a JAK-STAT dependent cytokine and activates STAT3 in T cells. IL-18, TNF-α, CD40, and chemokines do not signal via JAK-STAT.

a chemotherapy is often used. With the exception of CD, there are not well-established molecularly targeted therapies for these disorders. Here, we will focus on the role of Janus kinase – signal transducer and activator of transcription (JAK-STAT) signaling in the pathogenesis of these disorders and review emerging evidence that JAK inhibition is a promising molecularly targeted treatment approach.

MACROPHAGES, GRANULOMAS, AND GRANULOMATOUS INFLAMMATION

Granulomatous, or macrophage-predominant, inflammation is an evolutionarily conserved immune reaction pattern that occurs in the setting of both infections and non-infectious processes [1]. Granuloma is a more specific term and refers to tightly associated clusters of macrophages with epithelioid morphology. Granulomas are common in mycobacterial infections and are thought to create a physical barrier to prevent dissemination of organisms [2]. Multinucleate macrophage giant cells are often also present, but their role in host defense is less-well understood [3]. Granulomatous inflammation and granulomas are also common in reactions to foreign bodies in tissue [4] as well as particular idiopathic inflammatory disorders; the latter will be the focus of the remainder of the manuscript.

In inflammatory disorders with macrophage activation granulomatous inflammation is triggered for unclear reasons. In general, these diseases are thought to be driven by auto-reactive T cells. The specific clinical and histologic features vary by disorder (Figure 1). The biological explanation for the varying clinical presentations in these disorders is still poorly understood; however, from a treatment perspective, there are commonalities in the signals that lead to macrophage activation and will be the focus of the following section.

MOLECULAR MECHANISMS OF MACROPHAGE ACTIVATION AND GRANULOMA FORMATION

Cytokines are small secreted proteins which allow immune cells to communicate amongst themselves and with other cell types. In granulomatous inflammation, cytokines are produced by both macrophages and lymphocytes and reinforce inflammation. CD4+ helper T cells are the predominant lymphocyte population associated with both infectious and non-infectious granulomatous inflammation and secrete high levels of interferon gamma (IFN-γ), other cytokines such as IL (Interleukin)-2 and IL-17, and monocyte recruiting chemokines [5] (Figure 2). IFN-γ along with CD40 ligand (CD40L) appear to play a prominent functional role in inflammatory polarization of macrophages and granuloma formation *in vivo* in mouse models [6-8]. In turn, macrophages have been shown to produce IL-6, IL-12, IL-18, IL-23, TNF-α, and T cell chemokines [9,10]. These mutually-reinforcing cytokine programs likely create a self-sustaining loop perpetuating granulomatous inflammation in the presence of pathogenic antigens. Medications that disrupt these cytokine-based communication networks between T cells and macrophages might be an effective treatment approach in these disorders.

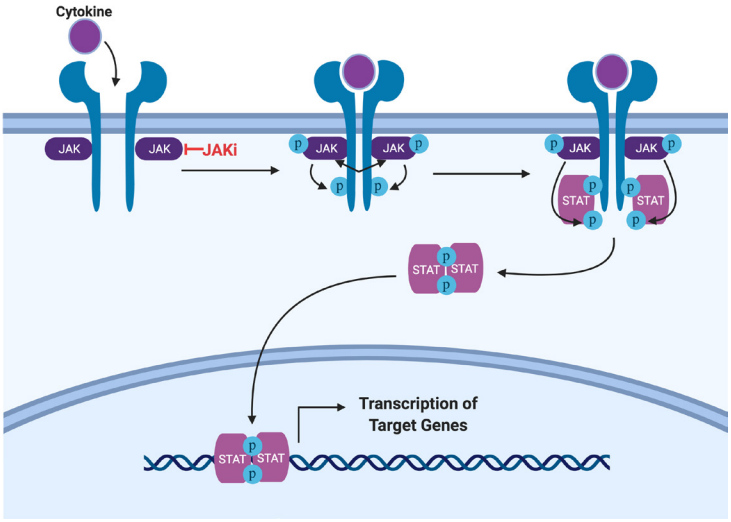

Figure 3. Overview of the JAK-STAT pathway. Cytokine binding at the cell surface leads to recruitment and activation (phosphorylation) of JAK proteins. This in turn leads to recruitment and activation of STAT proteins (phosphorylation) leading to dimerization and nuclear translocation of STATs where they affect gene transcription. JAK inhibitors block the pathway at the level of JAKs, preventing activation of STATs.

JAK-STAT SIGNALING

Cytokines bind to specific receptors on target cells. While many cytokine receptors can directly activate downstream signaling, others lack intrinsic kinase activity and rely on the JAK-STAT pathway to transmit their signal. In fact, >50 cytokines including IFN-γ, IL-2, IL-6, IL-12, and IL-23 rely on the JAK-STAT pathway [11]. Medications which inhibit JAK proteins, thus can block the activity of these cytokines simultaneously. TNF-α, CD40L, IL-17, and IL-18 do not directly signal via the JAK-STAT pathway.

Activation of the JAK-STAT pathway is induced by cytokine binding to surface receptors and culminates in regulation of transcription by STATs (Figure 3). There are four JAK proteins: JAK1, JAK2, JAK3, and TYK2 and 7 STAT proteins: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 [12,13]. There is both specificity and redundancy in JAK-STAT usage. For example, IFN-γ signals via JAK1 and JAK2 which in turn activate STAT1; whereas IL-6 can signal via JAK1, JAK2, and/or TYK2 and activates STAT3 [14]. Thus, medications which variably inhibit individual JAKs will have varying activity against individual cytokines.

JAK INHIBITORS

There are presently four FDA approved JAK inhibitors; myriad other JAK inhibitors are at various stages of preclinical and clinical development [15]. The FDA approved JAK inhibitors are summarized in Table 1. In addition to their FDA approved indications, JAK inhibitors are being widely evaluated for the treatment of multiple auto-immune and auto-inflammatory disorders [16,17]. These medications are orally bioavailable and are administered once or twice daily. Not all patients are candidates for JAK inhibitors; practical considerations regarding usage, safety, and laboratory monitoring have been reviewed elsewhere [18]. The potential risks of these drugs, which includes infection and thrombosis, must be reviewed carefully with patients prior to administration.

INFLAMMATORY DISORDERS WITH MACROPHAGE ACTIVATION: IMPLICATING JAK-STAT

Sarcoidosis

Background and Disease Pathogenesis

Sarcoidosis is an idiopathic disorder characterized by the presence of well-formed, non-caseating granulomas composed of epithelioid macrophages in affected tissues. Granuloma formation in sarcoidosis is most common in lymph nodes, lung, and skin, but can affect nearly any organ including the heart, where it causes significant morbidity [19]. At a microscopic level, there is relatively conspicuous infiltration of lymphocytes, primarily CD4+ T cells. Clonally expanded T cell populations have been detected [10], suggesting antigen dependency. Multiple other observations, including association with certain MHC class II alleles and triggering of sarcoidosis by PD-1 inhibitors [20], also suggest T cell dependency.

Table 1. FDA approved JAK inhibitors. IC50 values for each JAK protein (*in vitro*) are shown in nanomolar (nM) concentration [69,70], package inserts). Those in bold and italics are thought to be the most clinically relevant targets of each drug.

	JAK1	JAK2	JAK3	TYK2	FDA approved indications
Ruxolitinib	***2.8***	***4.5***	322	30	Polycythemia vera Myelofibrosis Acute graft-versus-host disease
Tofacitinib	***15.1***	77.4	***55.0***	489	Rheumatoid arthritis Psoriatic Arthritis Ulcerative Colitis
Baracitinib	***4.0***	***6.6***	787	61	Rheumatoid Arthritis
Upadacitinib	***8***	600	139	NA	Rheumatoid Arthritis

Although some cases of sarcoidosis remit spontaneously, many are chronic and require ongoing therapy. Corticosteroids are the only FDA approved treatment for sarcoidosis, but due to their myriad adverse effects, are not ideal for therapy in chronic disease. Other corticosteroid-sparing therapies are used off label in sarcoidosis, and include TNF-α inhibitors; however, the evidence for such therapies is variable and many cases are recalcitrant to these and other approaches [21].

Analysis of tissue and circulating mononuclear cells from patients with sarcoidosis by multiple groups has consistently revealed a signature of constitutive JAK-STAT activation [22-27]. In particular, a STAT1 molecular signature, consistent with the effect of IFN-γ, is prominent [28] and is consistent with high levels of IFN-γ production by T cells and PD-L1 expression by macrophages in sarcoidosis [5,29]. Other JAK-STAT dependent cytokines including IL-2, IL-6, and IL-12 have also been implicated in sarcoidosis [30-32]. We have used immunohistochemistry on tissues from patients with sarcoidosis to show constitutive activation of STAT1 in granuloma macrophages and STAT3 in surrounding lymphocytes, likely reflecting the effect of IFN-γ and IL-6, respectively [27,33] (Figure 2).

Clinical Experience with JAK Inhibitors

Based on this rationale, we first described the efficacy of tofacitinib in a single patient with long-standing, recalcitrant cutaneous sarcoidosis. Tofacitinib treatment in this patient induced clinical remission of cutaneous disease and biopsy of previously affected skin showed histologic resolution of granulomas with treatment. IFN-γ/STAT1 and IL-6/STAT3 gene signatures present in the skin prior to treatment normalized with tofacitinib [27]. Subsequently, we showed that two additional consecutive patients with long-standing, recalcitrant cutaneous sarcoidosis also had clinical, histologic, and molecular remission of their cutaneous sarcoidosis activity with tofacitinib [33]. Most recently, we showed a similar effect in a fourth patient with multi-organ sarcoidosis. In this patient, serial PET-CT imaging showed that tofacitinib also resulted in dramatic improvement of in internal organ (pulmonary, lymph node, bone) sarcoidosis activity and reduction in disease biomarkers on therapy [34].

In parallel, three other groups each published case reports of individual patients showing dramatic improvement in their cutaneous and/or internal organ sarcoidosis with ruxolitinib, including improvement in lung function in patients with pulmonary involvement [35-37]. Although very promising, the findings in these reports need to be validated in larger studies, which are underway (NCT03793439 and NCT03910543). Confirmation/identification of the critical targets of tofacitinib/ruxolitinib in sarcoidosis may allow further refinement of therapy.

Granuloma Annulare and Necrobiosis Lipoidica

Background and Disease Pathogenesis

Granuloma annulare (GA) and necrobiosis lipoidica (NL) are granulomatous diseases that only affect the skin (Figure 1). They cause skin lesions with characteristic clinical and histologic features reflecting macrophage accumulation and associated alterations involved tissue. GA is often limited in its distribution and can remit spontaneously, but in a subset of patients it is widespread in distribution or otherwise severe and chronic [38]. NL presents as plaques on the skin of the lower legs and is chronic; recurrent/persistent ulceration is not uncommon. NL sometimes occurs in diabetic patients (both type I and type II) [39]. Almost nothing is known about the pathogenesis of these two disorders; IFN-γ has been proposed to be expressed by CD4+ T cells in GA, but this finding has not been well-validated [40-42]. We have found low level activation of JAK-STAT signaling in GA and NL [33,43].

Clinical Experience with JAK Inhibitors

We recently reported successful treatment of a single

patient with longstanding, recalcitrant, generalized GA with tofacitinib resulting in complete clinical remission of disease. A skin biopsy on therapy showed resolution of granulomatous inflammation and normalization of JAK-STAT signaling [33]. In another patient with localized GA, we have shown that tofacitinib 2% ointment is very effective [43]. We are now performing an open label trial using tofacitinib in additional patients with GA (NCT03910543).

In 2018, Lee *et al*. reported that ruxolitinib led to marked improvement in a patient ulcerative NL [44]. In this patient, ruxolitinib did not remit the NL, but decreased ulceration. We have also recently reported that tofacitinib led to improvement in ulcerative NL in a single patient. In this patient, a combination of tofacitinib plus intralesional corticosteroids was superior to either therapy alone [45]. Based on this limited experience, NL appears to be less responsive to JAK inhibition compared with GA and sarcoidosis, but still potentially helpful in this otherwise recalcitrant disease; clearly more work is needed.

Crohn's Disease

Background and Disease Pathogenesis

Crohn's disease (CD) is a chronic inflammatory disease of the GI tract that in contrast to other forms of inflammatory bowel disease, often contains granulomas histologically. Approximately 50% of CD resections have granulomas [46,47], the significance of granuloma presence or absence in CD is unresolved. Compared to sarcoidosis, granulomas in CD are generally more poorly developed and typically have a more prominent lymphocytic component (Figure 1). In CD granulomas can also be found in gastrointestinal lymph nodes and rarely can involve the skin.

In CD, CD4+ T cells predominate and are also thought to have a T helper phenotype and secrete IFN-γ, IL-2, and possibly IL-17 [48]. Additional cytokines derived from macrophages and/or stromal cells include IL-1β, IL-6, IL-12, IL-18, IL-23, TNF-α and likely also contribute to CD pathogenesis. Of these, IFN-γ, IL-2, IL-6, and IL-12/23 signal via JAK-STAT. Constitutive STAT3 activation has been reported in T cells in patients with CD [49,50]. STAT1 activation has been reported as well [51]. Several targeted therapies are already approved in CD including TNF-α, IL-12/23, and integrin blocking antibodies; however, the role of JAK inhibitors is considered here.

Clinical Experience with JAK Inhibitors

JAK inhibitors have and are being studied extensively in both CD and ulcerative colitis. In fact, tofacitinib is FDA approved for ulcerative colitis. The first large trials with tofacitinib in CD were halted due to lack of efficacy, however, some authors have postulated that the initial failure of these trials may have been related to trial design [52]. Subsequently, other JAK inhibitors are being evaluated in CD including figotinib and upadacitinib, both JAK1-specific inhibitors, with more promising results [53]. Phase III trials with these agents are ongoing (NCT02914561, NCT03345849).

Despite some immunologic commonalities, CD and sarcoidosis are clearly distinct disorders and are rarely both present in the same patient. Elucidation of differences in the molecular immunology and response to JAK inhibition in these two disorders will be very useful moving forward.

Hemophagocytic Lymphohistiocytosis

Background and Disease Pathogenesis

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by macrophage activation in blood and tissue and often leads to critical illness with multiorgan failure (Figure 1). HLH can be either primary (due to genetic defects in the cytotoxic granules of lymphocytes) or secondary (occurring in the setting of infection, malignancy, or autoimmune disease) [54]. Macrophage activation syndrome refers to secondary HLH that occurs in the setting of autoimmune disease. At a microscopic level, affected tissue (particularly the bone marrow) from patients with HLH shows an increased number of macrophages which characteristically exhibit hemophagocytosis, that is engulfment of erythrocytes, platelets, and/or other leukocytes [55]. In contrast to other disorders discussed above, CD8+ T cells predominate in HLH and appear to be a major source of IFN-γ [56]. Historically, these disorders have been treated with high dose corticosteroids and/or cytotoxic therapies such as etoposide. In primary HLH, bone marrow transplantation is often pursued.

Murine models of primary HLH have been used to show that disease pathogenesis is dependent on IFN-γ production by CD8+ T cells [57]. Other cytokines including IL-2, IL-6, IL-10, IL-12, IL-18, and TNF-α have also been implicated [58]; of these IL-2, IL-6, IL-10, and IL-12 signal via JAK-STAT. Preclinical data generated with murine models of HLH has shown that JAK inhibition is effective [59-61].

Clinical Experience with JAK Inhibitors

JAK inhibitors have now moved into the clinic in HLH, where they have shown benefit. For example, in a small open label trial of five patients with secondary HLH, ruxolitinib was effective [62]. Other individual case reports describing the successful use of ruxolitinib in HLH have been published [63-68]. Trials are underway

(NCT02400463 and NCT04120090).

CONCLUSIONS

The use of JAK inhibitors to treatment inflammatory disorders with macrophage activation appears very promising, consistent with their broad activity in several other auto-immune spectrum disorders. Clear scientific priorities moving forward include better defining why disorders with so many overlapping pathogenic cytokines manifest so differently in patients. Better defining which cytokine(s) are essential for each disorder will allow more rationale selection of the most appropriate JAK inhibitor for each disease. Clinically, better defining efficacy of JAK inhibitors in these disorders with larger studies is paramount and ongoing. This work foreshadows improved treatment options for patients with inflammatory disorders with macrophage activation, including those that have historically been difficult to manage.

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