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Emerging Therapies for Systemic Lupus Erythematosus - Focus on Targeting Interferon-alpha

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Abstract

Current therapies for systemic lupus erythematosus (SLE), a debilitating, potentially lethal, multifactorial systemic autoimmune disease, are limited to suppressing disease activity and are associated with multiple adverse effects. Recent advances in basic and translational sciences have elucidated a crucial role for the interferon-alpha (IFN α) pathway in the pathogenesis of this enigmatic disease. The so-called “type I interferon signature” has emerged as a major risk factor for disease activity of SLE. Multiple genes encoding for molecules within the type I interferon pathway have been associated with SLE in genome wide association studies. In addition, innate immune receptors are thought to be triggered by either endogenous and/or exogenous stimuli that lead to hypersecretion of IFN α . We review the multiple emerging treatment strategies targeting IFN α -related pathways. These include monoclonal antibodies against IFN α , anti-IFN α antibody-inducing vaccines, and inhibitors of toll-like receptors. We also summarize the current status of these pharmaceutical agents in early clinical trials.

Keywords

pDC; TLR; IRF; JAK/STAT; Pin1; interferonopathies; virome; proteasome

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with a wide range of clinical manifestations and a pathogenesis whose details have remained relatively elusive. Dysregulation of adaptive immune responses in SLE leads to autoantibody production and immune complex deposition in various tissues [1–2]. Clinical manifestations commonly appear in the skin, kidney, musculoskeletal, and hematologic systems, but SLE can also affect the lungs, central nervous system, serous membranes and virtually every other organ system of the body [1, 3]. The disease is responsible for significant morbidity and mortality, with most recent studies showing a 10-year survival of approximately 70–90% [4–5]. Both genetic and environmental factors have been linked to

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SLE [2, 6]. The genetic risk of developing SLE is generally thought to result from the aggregate effects of multiple polymorphisms (although rare single gene mutations also cause SLE-like disease) [7]. Environmental triggers include smoking [8], UV light [9], various medications [10], and possibly certain viruses [2].

Current therapies for SLE are generally lacking in effectiveness and/or safety, and include primarily nonspecific immunomodulatory, immunosuppressive or cytotoxic agents. These therapies inhibit broadly inflammatory mediators or pathways, including those that are not particularly relevant to SLE pathogenesis. Antimalarial agents and nonsteroidal anti-inflammatory drugs (NSAIDs) remain the first-line drugs for mild disease. Corticosteroids are the primary therapy for more serious disease or one that is resistant to first-line agents, as well as during a lupus flare. Other systemic treatments targeting inflammation include cyclophosphamide, mycophenolate mofetil, and azathioprine. Less commonly used immunosuppressive agents include methotrexate, cyclosporine, tacrolimus, and leflunomide [11–12]. All of these therapies have a broad range of nonspecific effects, and are associated with considerable toxicities [11–12]. More recently developed biologic therapies have been studied in SLE patients and B cell targeted therapy appears to provide some benefit. Belimumab (an inhibitor of the molecule “B Lymphocyte Stimulator,” or BLyS) was recently given FDA-approval for use in treating SLE, the first drug in over 40 years to achieve this status [13]. The original FDA-approved disease-modifying drug for SLE, hydroxychloroquine, an antimalarial agent, has a lengthy track record in the treatment of lupus and has been shown to have an impact on survival [14]. Antimalarial agents have a variety of effects that may be relevant to their therapeutic benefit in SLE, including interference with Toll-like receptor (TLR) signaling pathways that induce interferon-alpha (IFN α) production [15]. Additional evidence has also implicated IFN α in SLE pathogenesis, heightening interest in development of novel pharmaceutical agents that specifically target the IFN α pathway. The role of IFN α in disease pathogenesis, and the current state of development of therapies targeting IFN α are discussed below.

2. PATHOGENESIS OF SLE

A poor understanding of the pathogenesis of SLE has hampered the development of new therapies directed at the underlying disease process. SLE involves immune dysregulation at the interface between the innate and adaptive immune systems with both endogenous and exogenous triggers contributing to evolution of disease and induction of disease flares, e.g. viral infections, UV light exposure and certain drugs. Basic research has led to the widely held view that defective clearance of apoptotic cellular debris in SLE patients causes a loss of self-tolerance, autoantibody generation, and the formation of immune complexes [16–19]. Several clinical manifestations of SLE are thought to be the result of autoantibody and immune-complex deposition in tissues leading to a secondary inflammatory response [20]. In addition, direct damage of tissues by T cells and maladaptive mechanisms of tissue injury might also be at play.

2.1 PHYSIOLOGIC ROLE OF INTERFERON-ALPHA

Interferon-alpha is a pleiotropic cytokine belonging to the type I cytokine family, and numerous studies over the past several years have provided increasing evidence for a central role of IFN α in the pathogenesis of SLE [21–26]. Type I interferons are normally produced by the innate immune system in response to viral infections [27–29]. They act via type I interferon receptors (INFARs) to trigger the JAK/STAT signaling cascade, leading to induction of interferon-stimulated genes (ISGs) that amplify interferon signaling, activate the adaptive immune system, and produce factors that directly inhibit viral replication [27–29]. IFN α can influence the function and activation of most types of adaptive immune cells [28, 29] after its secretion is stimulated via RNA or DNA sensing receptors [30, 31]. Its

effects range from upregulation of major histocompatibility complex (MHC) and costimulatory molecules to increased survival and activation of dendritic cells, B cells, and T cells [27, 30, 33]. Plasmacytoid dendritic cells (pDCs) are the main source of serum IFN α [34]. They are normally present in lymphoid tissues, but have been found in large numbers in the skin of patients with SLE [35].

Viruses and their nucleic acids induce type I interferon expression specifically via activation of endosomal Toll-like receptors [30] and cytosolic nucleic acid sensors [30–32]. Ligand binding induces a conformational change in the receptors that permits association of an adaptor protein, which in TLR signaling is most commonly MyD88 [36]. After binding to the cytosolic domain of the TLR, MyD88 recruits interleukin-1 receptor-associated kinase (IRAK) 4 and IRAK1, which in turn form a complex with tumor necrosis factor receptor-associated factor (TRAF) 6 [37]. Transcription factors known as Interferon Regulatory Factors (IRF) 5 and 7 subsequently interact directly with the MyD88/IRAK/TRAF6 complex and are activated via phosphorylation and ubiquitination [38–42]. Activated IRFs translocate to the nucleus, bind to specific regulatory sequences in IFN α genes, and promote their transcription, leading to the broad range of effects described above [40, 42–46].

2.2 ASSOCIATIONS OF INTERFERON-ALPHA WITH SLE

While early studies demonstrated high levels of interferons in the sera of patients with SLE [21], the first convincing evidence linking IFN α to SLE came in 2003 when global gene expression profiling of peripheral blood mononuclear cells from SLE patients showed that a high number of IFN α -responsive genes were abnormally expressed [22–23]. Subsequent reports have shown that IFN α therapy for neoplasias or chronic viral infection can induce SLE with features almost identical to those seen in idiopathic disease [47–50]. High serum levels of IFN α have also been identified as a heritable risk factor for SLE, with clustering of high IFN α levels among family members of patients with the disease [24]. An increasing body of evidence suggests that the elevated levels of IFN α seen in SLE are likely to result from primary genetic variations in the type I interferon signaling pathway and that such variations could be central to the pathogenesis of SLE. Along these lines, rare genetic disorders with complex autoimmune phenotypes have been discovered and linked to the type I interferon pathway [51]. An example would be a disorder caused by mutations in Trex1, a 3' repair exonuclease that was elegantly shown to negatively regulate the response to IFN-stimulatory endogenous retroelements [52]. These syndromes have recently been termed appropriately “type I interferonopathies”. Importantly, many patients affected by them develop lupus-like features which are most likely due to excess IFN α or dysregulation of the type I interferon pathway ([51] and references herein).

While genetic alterations contribute clearly to classic SLE pathogenesis, the possibility that chronic viral infections or particular viruses within the endogenous virome add to elevations and/or fluctuations of type I interferons in lupus patients is intriguing and not mutually exclusive [53–54]. Interestingly, virus-like tubuloreticular inclusions within lymphocytes from SLE patients have been observed decades ago and correlated with higher IFN α [55]. Their relationship, however, to both an infectious agent and the pathogenesis of SLE remain unproven to date ([55] and references herein). On the other hand, the associations of IFN α with SLE in general have also been mechanistically supported by multiple murine studies, e.g. with the New Zealand Black (NZB) mouse model of systemic lupus; genetic deficiency of the type I interferon receptor in NZB mice led to significantly reduced disease activity [56]. A comprehensive summary of the various in vivo models that functionally link the type I interferon pathway with systemic autoimmunity and lupus goes beyond the scope of this review. The effects of elevated IFN α on the immune system in SLE patients is briefly reviewed in the next paragraph.

2.3 INTERFERON-ALPHA IN SLE IMMUNOPATHOGENESIS

High levels of IFN α have been shown to contribute directly to immune dysregulation in a number of ways. IFN α , for example, causes dendritic cells to mature and become more likely to activate T cells. In lupus patients, myeloid dendritic cells are more likely to present self-antigens to T cells in a stimulatory manner, likely as a result of high IFN α levels [25]. IFN α has also been shown to decrease regulatory T cell activity in patients with lupus, further contributing to autoimmunity [25–26]. IFN α increases TLR7 signaling in dendritic cells, which in turn leads more IFN α production, forming a positive feedback loop [25, 57–58]. Figure 1 shows a simplified overview of the mechanism of IFN α production in SLE patients as well as emerging therapeutic targets as discussed in the next section.

2.4 INTERFERON REGULATORY FACTORS

Recent genome-wide association studies (GWAS) and genetic studies using a candidate-gene approach have identified more than 25 SLE susceptibility genes involved in adaptive immunity, autoantibody production, innate immunity, and interferon signaling [59–75], including STAT4 variants sensitizing to increased IFN α production [62, 76–79] and polymorphisms in TNFAIP3, the gene encoding for the ubiquitin-modifying enzyme A20 that is required for termination of TLR responses [67, 69, 80–82]. An association of SLE-risk with polymorphisms of the transcription factor interferon regulatory factor (IRF) 5 was initially discovered by linkage analysis of genes in the type I interferon pathway [59–60], and was subsequently confirmed in several GWAS [65–67]. The major association of IRF5 with SLE risk has also been demonstrated across multiple populations [46, 60–61, 83–87]. Recent studies have identified up to five major haplotypes of IRF5, and have shown that certain haplotypes are associated with increased SLE risk while others may be protective [60–61, 88–89]. IRF5 haplotypes conferring SLE risk are also associated with increased serum IFN α activity [88–89]. For each of these haplotypes, however, increased IFN α activity was only seen in a subset of the patients who had specific autoantibodies [88–89]. For example, anti-double-stranded DNA and anti-Ro autoantibodies were each associated with a different IRF5 haplotype, and each haplotype-auto-antibody pair strongly predicted elevated serum IFN α in patients with SLE [89]. In addition to inducing several proinflammatory cytokines [90–91], IRF5 has been shown to promote transcription of IFN α in specific cell types, including precursor dendritic cells [40, 43–45]. Similar to IRF5, IRF7 variants have also been linked to SLE risk [92]. Furthermore, several studies have shown correlations between specific IRF7 variants and elevated IFN α levels only in a subset of the patients who had certain autoantibodies [46, 93]. IRF7 has also been shown to play a critical role in IFN α production [42]. Taken together, the above studies suggest that IRF gene polymorphisms combined with autoantibody activation of TLR receptors leads to higher IFN α levels in SLE patients [94–96].

3. THERAPEUTIC TARGETS FOR SLE

Evidence for the IFN α pathway in the pathogenesis of lupus has highlighted IFN α and many related signaling molecules as attractive therapeutic targets. Several clinical trials are now underway investigating monoclonal antibodies against IFN α (discussed below) [97–99]. Other therapeutic approaches under investigation include vaccination against IFN α using an IFN α -kinoid [100–101], inhibition of TLRs [102], blockade of INFARs [103], and inhibition of JAK/STAT signaling [104]. IFN α pathway-targeting approaches for SLE patients that are currently in development or early clinical trials are discussed in more detail below and are summarized in table I.

3.1 BIOMARKERS FOR INTERFERON-ALPHA ACTIVITY

In order to evaluate the efficacy of IFN α -targeted therapies and to select suitable candidates for treatment, it has been necessary to identify appropriate biomarkers for disease-related IFN α -activity. Attempts to directly measure type I interferon proteins by enzyme-linked immunosorbent assays (ELISA) have yielded low reproducibility and poor correlation with functional assays [24, 105–107]. Traditional methods of measuring IFN α are generally indirect, and rely on the effects of IFN α on the survival or proliferation of cultured cells. These include the Daudi cell proliferation assay, which quantifies the antiproliferative effect of IFN α [108–109], and bioassays measuring the growth of virally infected cell cultures to quantify the antiviral effects of IFN α [105]. Initial reports of interferon-inducible genes [110] were followed by large-scale gene expression analyses that first characterized the “type I interferon signature” in SLE [22–23]. The identification of genes specifically induced by IFN α provided a proxy for directly measuring IFN α levels. In one functional assay, quantitative RT-PCR analysis of representative IFN α -induced genes in reporter cells is used to detect IFN α in patient sera [24, 106]. A more recent study used microarrays to identify a set of 21 genes that would serve as pharmacodynamic and diagnostic biomarkers in the evaluation of anti-IFN α monoclonal antibody therapies [107, 111]. These genes were selected because they met the study's predefined requirements of being IFN α / β -inducible, over-expressed in whole blood from SLE patients, induced by ex-vivo stimulation with SLE patient sera, and neutralized by an anti-IFN- α / β monoclonal antibody [111]. Interestingly, application of this assay to a population of 202 SLE patients yielded a bimodal distribution between patients that were negative and those that were positive for the type I interferon signature [107]. While the significance of this is unclear, it suggests that biomarkers are likely to become increasingly important in identifying subgroups of patients who may benefit from IFN α -targeted therapies under development [107]. Other possible biomarkers for IFN α -related lupus activity include IFN α -inducible cytokines. Recent studies demonstrated that serum levels of interferon-regulated chemokines correlate well with disease activity, in particular the Th1-related chemokine CXCL10 (IP-10), whose gene expression has been shown to be induced by type I IFNs in human peripheral blood mononuclear cells [112–114].

3.2 MONOCLONAL ANTIBODIES DIRECTED AT INTERFERON-ALPHA

Sifalimumab (MedImmune LLC, Gaithersburg, MD), also known as Medi-545, is a fully human anti-IFN α monoclonal antibody studied in a phase I randomized, double-blind, dose-escalation study in adults with moderately active SLE [109]. By quantifying the type I interferon signature as described above, the authors identified a dose dependent inhibition of the IFN α pathway by sifalimumab. Exploratory data from the phase I trial showed that sifalimumab-treated subjects required fewer new or increased immunosuppressive treatments and had fewer SLE Disease Activity Index flares [109]. Rontalizumab (Genentech, Inc., South San Francisco, CA), a recombinant humanized monoclonal anti-IFN α antibody, was also shown to inhibit the IFN α / β -inducible gene signature in a phase I clinical trial [115]. Both sifalimumab and rontalizumab are currently being tested in phase II clinical trials [97–98, 116–117]. AGS-009, under development by Argos Therapeutics Inc. (Durham, NC), is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that recently completed a phase 1 clinical [99, 118].

3.3 INTERFERON-ALPHA VACCINE

Further evidence for the potential benefit of anti-IFN α -antibodies in SLE comes from a recent study of SLE patients with endogenous anti-IFN α autoantibodies (AIAAs) [119]. The study reported that endogenous AIAAs were found in the serum of approximately 25% of the SLE patients studied, and that the presence of these autoantibodies was associated with lower levels of serum type I IFN bioactivity, reduced downstream IFN-pathway activity, and

lower disease activity. They also showed that sera from AIAA-positive patients were able to neutralize the activity of type I IFN α in vitro [119]. These studies suggest that an IFN α vaccine designed to induce AIAAs could potentially benefit SLE patients. Neovacs S.A. (Paris, France) is currently developing an IFN α kinoid vaccine for this purpose. This vaccine was recently shown to induce polyclonal antibodies in mice, which neutralize all subtypes of human IFN α as well as IFN α in sera from patients with SLE [100–101]. Results were recently reported of a phase I–II double-blind, placebo-controlled, dose-escalation study on twenty-eight patients with mild to moderate seropositive lupus [120–121]. The authors demonstrated a dose-related anti-IFN α response in all immunized patients. This was associated with a significant down-regulation of SLE over-expressed genes among a subset of patients who were found to have a positive IFN α signature at baseline.

3.4 TOLL-LIKE RECEPTOR INHIBITORS

TLR inhibition is another intriguing possibility for treatment of lupus, and could reduce the production of IFN α by pDCs in SLE patients. There is also evidence that TLR inhibitors could improve glucocorticoid activity in patients with SLE. A recent study demonstrated that chronic stimulation of pDCs via activation of TLR receptors by self nucleic acid-containing immune complexes contributes to the decreased activity of glucocorticoids in SLE [122]. Antimalarials (e.g. hydroxychloroquine), long used for treatment of lupus, are thought to work at least partially via inhibition of intracellular TLRs as mentioned above [123]. Idera Pharmaceuticals (Cambridge, MA) has recently developed a synthetic oligonucleotide-based inhibitor of TLR7 and TLR9 referred to as IMO-3100. Although there are currently no peer-reviewed studies, Idera reports that the drug inhibited disease development in lupus prone mice [124]. They also report that the drug suppressed TLR7- and TLR9-mediated induction of cytokines, including IFN α , in a recent four-week placebo-controlled multiple-dose phase I clinical trial [125]. Dynavax Technologies Corp. (Berkeley, CA) has also been developing oligonucleotide-based TLR inhibitors for use in autoimmune diseases such as SLE [126]. They reported that such inhibitors prevented and reversed disease in a mouse model of cutaneous lupus [127] and that phase I clinical trials of a bifunctional TLR7- and TLR9-inhibitor called DV1179 have begun [102, 128]. Pfizer Inc. (New York, NY) has also developed a TLR inhibitor that is in phase I clinical trials [129]. Known as CpG-52364, this inhibitor has activity against TLR7/8/9 and was previously reported to be effective in a murine model of lupus [130].

3.5 OTHER POTENTIAL TARGETS

Other potential therapeutic targets along the IFN α pathway include the type I interferon receptors (INFRs) and the JAK/STAT pathway. Medi-546 (MedImmune LLC, Gaithersburg, MD), formerly known as MDX-1333, is a fully human monoclonal antibody directed against subunit 1 of the type I interferon receptor, and is currently in clinical trials for treatment of lupus [103]. Recent research has suggested that inhibitors of JAK1 or JAK2 may also provide potential benefit in SLE [131–132] and a Jak1/Jak2 inhibitor, INCBO18424, recently underwent clinical trials for myeloproliferative disease [104].

Several studies have shown that proteasome inhibitors, such as bortezomib, carfilzomib, and the immunoproteasome-specific inhibitor ONX 0914 are effective therapies in murine models of lupus [133–135]. While proteasome inhibitors have previously been shown to block plasma cell proliferation and reduce autoantibody formation, a recent study indicates these drugs also efficiently suppress IFN α production by TLR-activated pDCs [135]. Other work has shown that bortezomib inhibits pDCs by targeting intracellular trafficking of TLRs [136]. While proteasome inhibition is a decidedly less targeted approach than those described above, the combined effects on both plasma cells and pDCs could prove beneficial in some patients.

Finally, the molecular biology of the IFN- and TLR-related pathways is rapidly progressing and more rational targeting approaches could emerge quickly from discoveries in the basic sciences. Based on a recent publication, it would be, for instance, a logical approach to modify an isopropyl isomerase called Pin1 [137–138]. Pin1 specifically facilitates IRAK1 activation and release from the TLR receptor complex (in particular TLR7/9) [138]. Importantly, deletion of Pin1 completely abrogated the production of type I interferon by pDCs while affecting only relatively little the production of proinflammatory cytokines [138]. Targeting specifically Pin1 or IRAK1 might lead to novel selective inhibitors for SLE patients that potentially leave a broader proinflammatory response intact in vivo. Broad inhibition of the type I interferon pathway might be associated with unacceptable risks that are discussed in the last section below.

3.5 POTENTIAL RISKS OF INHIBITING THE INTERFERON-ALPHA PATHWAY

Inhibiting the IFN α pathway theoretically has the potential to significantly increase risk of new or reactivated infections, particularly with viruses. In phase I clinical trials of sifalimumab (discussed above), placebo and treatment groups had similar rates of infection. One case of sinusitis and one upper respiratory tract infection were the only infections that were considered treatment-related among the patients receiving sifalimumab during the blinded phase of the study. Rates of conversion to positive viral surveillance test results were similar among placebo- and sifalimumab-treated subjects [109]. The IFN α vaccine also had an apparently favorable safety profile, with reports of only minor and transient infections. Concerns about the potential for irreversible long-term effects of the vaccine were eased by reports that serum antibody concentrations declined after the last vaccine dose [120]. For most of the drugs discussed above, we must wait until larger phase III clinical trials have been completed before we will know what the side effect profile of IFN α -pathway inhibition will be, and whether viral or other infections will pose a serious problem. Finally, in light of the fact that at least 20% of human cancers are linked to infectious agents including viruses [139–140], a word of caution should also be said about the theoretical potential of inducing malignancies that are otherwise prevented by an intact type I interferon pathway.

4. SUMMARY

In summary, evidence from gene expression profiling in SLE patients, as well as from animal and in vitro models, has stimulated the development of anti-cytokine therapy for this disease. Given the remarkable success of targeting cytokines with biologic drugs to treat other autoimmune disease, especially TNF in rheumatoid arthritis, this approach seems reasonable, and we may soon see the emergence of a new class of effective drugs for SLE. Limited early data using sifalimumab has shown reduced SLE disease activity and a decreased need for immunosuppressive agents among patients receiving the drug. Most of the preliminary data however has focused on IFN α / β -inducible gene signatures as a measurement of treatment effectiveness, and it is still unclear how well this will correlate with clinical improvement in SLE symptoms. It is also unclear how significant the increased risk of infections and malignancies will be in patients receiving drugs targeting the IFN α pathway. Despite these potential roadblocks, it seems likely that we will see the emergence of additional SLE therapies in the near future, and inhibition of the “IFN α signature” appears to be a promising approach.

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Highlights

1. Several anti-IFN α monoclonal antibodies are being tested in early clinical trials.
2. Active immunotherapy with a kinoid leads to a sustained anti-IFN α immune response.
3. Novel TLR7/TLR9 inhibitors are expected to attenuate stimulation of IFN α secretion.
4. Here we summarize these novel approaches to target the IFN α pathway in SLE patients.

Figure 1. Mechanism of IFN α production in SLE patients and potential targeting approaches
 Shown is a simplified model of how aberrant IFN α production can occur in SLE patients. Inherently abnormal T and B lymphocyte signaling in conjunction with innate immune stimulation via endogenous and/or exogenous triggers leads to a vicious cycle of autoantibody-immune complex signaling. The putative autoantigens in SLE form complexes with a myriad of autoantibodies produced in SLE. These complexes have been shown to trigger TLR signaling in antigen-presenting cells, in particular TLR7 and TLR9 in plasmacytoid dendritic cells (pDC). These endosomal ligands can also physiologically be triggered by viral or bacterial nucleic acids. The DNA/RNA molecules could be released from either pathogens or commensals which then amplify the IFN α circuit in SLE patients. Endosomal TLR7/9 signaling leads to interferon regulator factor (IRF) 5/7 activation and induction of IFN α gene production. Translated and secreted IFN α can in turn stimulate T and B cells as well as augment TLR signaling, closing the cycle that leads to ongoing IFN α pathway activation. Shown in red are some of the current approaches described in the main text that attenuate this vicious cycle. A, blockade of TLR signaling (at various levels) via novel TLR7/9 inhibitors; B, endosomal inhibition of TLR7/9 with antimalarials like hydroxychloroquine (which is only one of many modes of action of antimalarials); C, direct targeting of IFN α via monoclonal antibodies; D, indirect targeting of IFN α using a kinoid that leads to an endogenous T- and B-cell mediated anti-IFN α response after vaccination.

Table ISLE therapies in development targeting the IFN α pathway*.

Therapeutic Approaches	Pharmaceutical Agents in Early Clinical Development
Anti-IFNα monoclonal antibodies	Sifalimumab (Medi-545, Medimmune, Inc.); fully human anti-IFN α monoclonal antibody Rontalizumab (Genentech); recombinant humanized anti-IFN α monoclonal antibody AGS-009 (Argos Therapeutics); humanized IgG4 anti-IFN α monoclonal antibody
Anti-IFNα Vaccination	IFN α -Kinoid (NeoVacs); active immunotherapy inducing an anti-IFN α response
TLR inhibitors	IMO-3100 (Idera Pharmaceuticals); oligonucleotide-based inhibitor of TLR7 and TLR9 DV1179 (Dynavax); oligonucleotide-based inhibitor of TLR7 and TLR9

* Therapeutic approaches targeting the IFN α and TLR pathways are shown in the left column. Monoclonal antibodies, kinoid, or oligonucleotide-based inhibitors are listed on the right column. Companies involved in developing these agents are listed in parentheses.