Published in final edited form as:

Expert Opin Investig Drugs. 2008 November ; 17(11): 1685–1692. doi:10.1517/13543784.17.11.1685.

FLT3 inhibitors for the treatment of autoimmune disease

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Abstract

Background—Autoimmune diseases encompass a broad range of illnesses with a variety of underlying causes, some of which are known and some of which remain elusive.

Objective—The focus of this review will be on describing the development of a new type of therapy that could potentially treat T cell-mediated autoimmune diseases. Unlike traditional therapies, which have primarily focused on suppressing T cells directly, targeting the step of antigen presentation may allow a less toxic therapy in which autoimmunity is lessened without compromising the entire immune system. This review will outline the science behind the development of the therapy, the roles of dendritic cells in generating autoimmune disease, and the function of the FLT3 receptor in this process.

Keywords

autoimmune disease; dendritic cell; FLT3; signal transduction

1. Role of dendritic cells in autoimmunity

Dendritic cells (DCs) are a specialized cell of the immune system that serve as a link between the innate and adaptive immune system and have an extremely potent capacity to activate naive T cells [1]. While T cells are generally thought to be the mediators of many autoimmune diseases (Table 1), they receive instruction on when to become activated by DCs. Thus, targeting the step of DC activation of T cells is an upstream step at which potential intervention may take place. In addition, the interaction between DCs and T cells not only instructs the T cells on activation but also on the characteristics and differentiation of T cells; interaction with DCs and the cytokines produced by DCs can drive T cells towards these phenotypes. Targeting the differentiation of T cells such that they are skewed away from a particular phenotype would be one possibly selective way of downregulating an autoimmune response while keeping helpful immune responses intact. While the exact nature of DCs responsible for generating autoreactive responses remains controversial, more data have been generated that implicate the potential for DCs to contribute to pathology. DCs provide an attractive alternative target in that the specific antigen does not need to be

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identified, issues such as epitope spreading are avoided, and it may be possible to bias the response away from an autoimmune response but leave beneficial immune responses intact.

Initially, the inflammatory profile of T_H1 cells (those that secrete IFN-γ) implicated these cells in the pathogenesis of autoimmune disease and they became a major target for therapy development. Many T-cell autoimmune diseases, including psoriasis [2–4], EAE (experimental allergic encephalomyelitis) and MS (multiple sclerosis) [5–7], arthritis [8,9], Crohn's disease [10,11] and type 1 diabetes [12–14] have been shown to have an increase in T_H 1 cells and IL-12, which were both associated with both the generation and severity of disease. IL-12 and IFN-γ are necessary for the generation of T_H 1 responses. On a molecular level, T-bet was shown to be necessary for the generation of IFN-γ and considered to be a 'master regulator' of T_H1 generation [15,16], and thus became a new type of target for inhibition.

IL-12 is a heterodimer, made up of two components, known as p40 and p35 subsets. It was later discovered that the p40 subset is shared with another cytokine, IL-23, which is made up of p40 and a second component, p19 [17]. IL-23, which is produced by DCs, is important for driving T cells to differentiate along the T_H17 pathway, which derived their name from their secretion of IL-17. Interestingly, although ROR-α and ROR-γ have been identified as transcription factors that drive cells towards T_H17 [18,19], T-bet may also be involved in the generation of the autoimmune responses of the T_H17 subset [20]. Additional studies showed that this more recently defined subset of T cells was necessary for either onset or maintenance of a number of disease models [21]. In addition, in several case studies, these cells have been identified in patients with autoimmune diseases [22–24]. For the future, targeting this cell type selectively may lead to the generation of less toxic and more specific therapies.

As mentioned, DCs are thought to stimulate the differentiation of T cells into T_H17 in part because of their secretion of cytokines, notably IL-23, TGF-β, and IL-6 [25]. Thus, preventing the differentiation into T_H17 cells by blocking this step may be one avenue by which such a goal could be achieved (Figure 1).

Another important barrier to successful autoimmune disease therapy is the issue of antigen identification and specificity. As T cells are specific for an antigen, targeting the T cells requires not only that the antigen be identified but also that the antigen remain stable. In a disease model for MS and EAE, as well as other autoimmune diseases, a number of reports have identified the occurrence of epitope spreading [26,27], which is the process by which T cells that have a different specificity from the original antigenic epitope become mediators of disease. Thus, in effect, T cells with the original specificity could be eliminated, but disease would not be improved, because of the emergence of T cells with specificity for new epitopes. In addition, tolerance to the newly-identified epitopes has been shown to improve disease outcome, further indicating the relevance of this event in disease progression.

2. FLT3 signaling

FLT3 is a receptor tyrosine kinase that was originally reported in 1991 as a murine gene with similarities to fms, kit, and pdgfr. It was thus named as fms-like tyrosine kinase [28]. It was shown to have a relatively restricted expression in hematopoietic stem and progenitor cells [29,30]. This restricted expression led to the study of this gene as an important contributor to stem cell survival, and the human form of FLT3 was cloned shortly thereafter and was shown to be important for bone marrow stem cell survival [31]. Its relevance in disease was investigated in 1992, with the report that 92% of human acute myelogenous leukemia cells expressed high levels of FLT3 message [32]; and further in 1996, with the finding of high-level protein expression in AML and B-lineage leukemias [33]. Its function as a strong growth stimulus thus had the potential for a significantly negative outcome, which was found to be the case with acute myeloid leukaemia (AML).

The role of FLT3 in DC development was first reported in 1996, with both *in vivo* and *in vitro* studies showing that treatment of progenitor cells or mice with FLT3L led to the generation of DCs [34,35] and that mice that are deficient in FLT3L have a profound defect in the generation of DCs [36]. With the notion that stimulation through FLT3 could generate DCs, studies were undertaken in which FLT3L was investigated as an immunostimulatory antitumor agent and found to produce significant anticancer effects [37]. This initial report was followed by multiple others showing that FLT3L, either alone or in combination with other agents, elicited antitumor effects [38–40]. Thus, the immunostimulatory capacity of stimulation through FLT3 was fairly clearly demonstrated; although, in some models, limitations were observed [41,42].

3. Development of FLT3 inhibitors

The findings described above that demonstrated a high level of expression of FLT3 in leukemias led to further discoveries that constitutive activation of FLT3 was occurring through mutation in some forms of leukemia. As a form of molecular targeted therapy, a number of small-molecule FLT3 tyrosine kinase inhibitors (TKI) were developed, and continue to be developed, for the treatment of AML in particular [43–46]. These molecules include CEP-701/lestaurtinib, MLN 518/CT53518/tandutinib [47,48], PKC412 [49,50], SU11248/sunitinib [51,52], BAY43-9006/sorafenib [53,54] and SU5614 [55], among others. As signaling through the receptor leads to kinase activation, these small compounds prevent signal transduction by competitively inhibiting the binding of ATP to the receptor’s active site. These types of drugs are potentially appealing for the treatment of autoimmune disease, since they are often administered orally, which would provide a significant advantage over currently available treatments; in addition, several of them have already been tested in clinical trials. Thus, much of the pharmacokinetic and toxicology information is already available.

As inhibitors of signal transduction pathways have varying degrees of specificity, many agents are multi-kinase inhibitors, and the targeting of these additional pathways should also be considered. In some instances, this may contribute to a therapeutic effect, if an additional target also contributes to pathology.

4. FLT3 inhibition as an approach to autoimmunity

The role of FLT3 in generating DCs has been shown through results of studies demonstrating that mice deficient in FLT3L have markedly reduced numbers of DCs and that mice that have been administered FLT3L have dramatically increased numbers of DCs. While some currently used therapies have effects on DCs, the rational targeting of DCs as opposed to T cells is a relatively recent concept.

While these and other studies indicated that FLT3 expression on progenitor cells was necessary for the development of DCs, receptor expression on mature DCs had not been reported until two studies have showed that mature steady-state DCs retained expression of FLT3 [56,57] and, importantly, that the receptor was activated upon exposure to ligand [57]. The activation of FLT3 on mature cells was an important consideration, since inhibition of signaling would only produce an effect if the mature cells maintained signaling through this receptor. Of note, expression was maintained on DCs derived from common myeloid progenitors as well as from common lymphoid progenitors [56], indicating that most, if not all, DC subsets would be potential targets for this class of agents.

While treatment with FLT3 inhibitors is likely to lower the number of DCs through its actions on progenitors, DCs also appear to rely on ongoing signaling through FLT3, since inhibition produced apoptosis in a significant fraction of the more mature DCs. These findings are significant in that in order for FLT3 inhibition to have an effect on ongoing disease, presumably mature DCs would need to be somewhat dependent on this pathway (Figure 2).

Two separate studies have now reported results that suggest the possibility of developing FLT3 inhibition for the treatment of autoimmunity. In one study, development of type I interferon producing DCs (classically plasmacytoid DCs, pDCs) was inhibited in culture by treatment with SU11657 [58]. Further, *in vivo* treatment of mice produced a phenotype that was strikingly similar to that reported for the FLT3-deficient mice. In consideration for clinical use, there were additional implications of some of the results. First, the effect was reversible *in vivo* in that numbers of DCs returned to normal after discontinuation of therapy. Second, the effect of FLT3 inhibition on repopulation of bone marrow stem/progenitor cells was not affected. The second parameter was measured both *in vitro* for colony-forming capacity, and *in vivo* for hematopoietic reconstitution ability. Neither of these was dramatically reduced after treatment, indicating that no serious toxicities should be expected from usage of this class of agents [58].

In another study, the FLT3 inhibitor CEP-701 was used with similar results in terms of decreasing the *in vivo* populations of DCs and, further, decreasing an autoimmune response. Both pDCs and cDCs were decreased after *in vivo* administration of CEP-701, as well as NK cells; but no changes in mature B- and total T-cell number were observed. However, a decrease in expansion of autoreactive T cells was observed, and further, in the model system for multiple sclerosis and EAE, mice that had established disease showed a significant improvement in the course of disease after treatment with CEP-701. No major toxicity was observed, and the mice were able to ward off a *Listeria* infection in a manner similar to

control counterparts, indicating that no severe gross immunosuppresion was present [57]. One possible mechanism for the downregulation in the effector response is that even activated T cells rely on continued co-stimulation to varying degrees; thus, it may be that inhibiting an ongoing T-cell response via inhibition of DCs will prove to be effective. Since DCs are also important to maintaining tolerance, it is possible that the reverse effect might have occurred, i.e., worse autoimmune disease; however, this was not the case in these experiments. Two significant advantages to this approach are that, in theory, it would be applicable to all T cell-mediated autoimmune diseases, since there is no antigen specificity required; and oral bioavailability and Phase II data in humans would make it easy to rapidly begin clinical testing once appropriate preclinical data are obtained.

5. Alternative approaches

Traditional approaches to treating autoimmune disease have primarily focused on downregulating immune responses nonspecifically. Drugs and biologics may act by decreasing the numbers of lymphocytes or subsets of lymphocytes, decreasing the activity of lymphocytes, altering traffic patterns of T cells, or shifting the phenotype of T cells. In the early 1980s, ciclosporin A was shown to suppress both organ rejection and autoimmunity. While this approach has had some degree of efficacy, it carries with it significant toxicity, due in a large part to its high degree of nonspecificity.

Cyclophosphamide is an alkylating agent that must be metabolized *in vivo* by the cytochrome P450 family in order to generate an active metabolite. Methotrexate (*N*-10-methylaminopterin) was developed in the 1940s as an antagonist for folic acid. Its mechanism of action is probably due to its competitive inhibition of dihydrofolate reductase, which leads to defects in the synthesis of DNA. It has been shown to have a number of toxic effects on the immune system, including inhibition of T-cell proliferation and activity as well as several off-target toxicities, including liver, gut, and brain.

The notion of using a B cell-targeted therapy in auto-immune disease was lent some support by a case report showing improvement in a patient with psoriasis who was being treated with an anti-CD20 antibody (rituximab) [59]. Since that time, trials have been undertaken to assess the efficacy of this approach; and in rheumatoid arthritis and systemic lupus erythematosus (SLE), it has shown some positive effects. It is currently under evaluation for MS, but no human trial data are yet available. Possible mechanisms of action of this agent include decreasing antigen presentation and decreased production of cytokines that drive inflammation and/or autoimmunity (e.g., IL-6), as well as eventual depletion of Ig.

Etanercept, a soluble tumor necrosis family receptor, has been tested in a number of autoimmune diseases, including psoriasis [60]. As TNF is a hallmark inflammatory cytokine and its upregulation has been noted in many autoimmune/inflammatory conditions, it might be expected that this approach would be applicable to most autoimmune diseases. However, while treatment of patients with psoriasis yielded positive clinical outcomes [61], there were reports of new-onset MS in at least one patient, and a trial testing this agent in MS was stopped prematurely due to worsening of disease. Thus, it can be difficult to predict the results that agents will generate under different circumstances.

Another cytokine that has been directly targeted is IL-12, which is required for driving T_H1 responses and is necessary for generating T-cell responses against infectious agents; thus it is possible that inhibiting its function may lead to an undesirable level of immunosuppression, potentially resulting in infections. However, there are preclinical data that strongly support its role in T_H1-mediated diseases. In addition, since it shares the p40 chain with IL-23, which has been strongly implicated in the generation of T_H-IL-17 cells found in autoimmunity, this approach does have significant potential. Again, a limitation may be found in that T_H1 cells may be required to fight off infection, which leads to the concern of an unacceptably high level of nonspecific immunosuppression. Encouragingly, one trial in plaque psoriasis reports an improvement of symptoms as well as a high level of tolerability [62].

Early reports of effects of statins on autoimmune disease were mixed, with an induction of SLE [63] and an improvement of symptoms in EAE [64–66], as well as in other diseases such as inflammatory arthritis [67] and others [68,69]. These drugs appear to have anti-inflammatory properties as well as effects on T-cell tolerance [70], modulating T_H1:T_H2 ratios [71] and cell migration [69].

Blocking migration of cells into inflamed tissue via targeting alpha 4 integrin is currently an approved therapy for MS and Crohn's disease, and is being investigated as a therapy for other autoimmune diseases [72,73]; but fatal side effects related to JC viral infection in MS have limited its widespread application.

Another approach to blocking lymphocyte migration by limiting egress from the lymph node has been tested using FTY720, a sphingosine receptor agonist that is currently in Phase III trials for MS [74].

6. Expert opinion

Autoimmune diseases are absolutely in need of new types of therapies. The toxicities and lack of effectiveness for many of the currently available therapies produce significant limitations on their use. As most autoimmune diseases are chronic, developing therapies that could be used intermittently for long-term therapy is one goal. Targeting antigen presentation of self components is a new avenue that is being developed.

One challenge of decreasing autoimmune responses is discovering methods to selectively inhibit autoreactivity without generally suppressing the immune system. Targeting FLT3 is a potentially advantageous approach, in that it targets a signaling pathway that is expressed in antigen-presenting cells but not in mature B or T cells. This selectivity provides a theoretical advantage in two distinct considerations. First, the cells that are specific for an autoantigen are difficult to target specifically, as the antigen may either be unknown or may mutate over time. By targeting the antigen presentation, this limitation is bypassed. Second, since mature B and T cells are not direct targets, it may be possible to eliminate an auto-immune response without destroying existing B and T cells, which may help to decrease the common side effect of gross immunosuppression as a result of auto-immune therapy. In addition, the

ability to administer some of these agents orally would present a distinct advantage for patients.

Acknowledgments

KA Whartenby is supported by NCI 111989. D Small is supported by NCI-CA70970 and the Kyle Haydock Professorship. PA Calabresi is supported by RO1-NS41435 and the National MS Society TR 3760-A-3.

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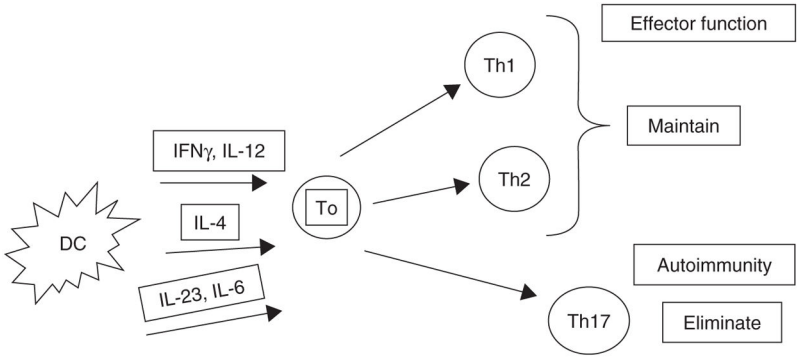

Figure 1.
Manipulating DC function as a means to maintain beneficial immune responses while eliminating harmful ones.

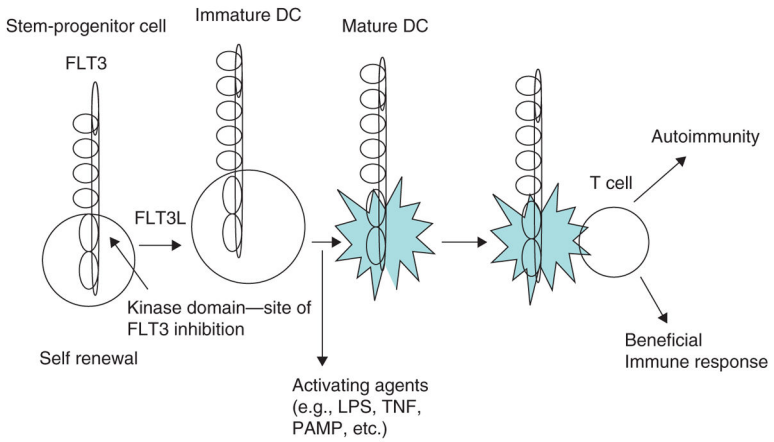

Figure 2.
FLT3 signaling as a target for DCs.

Table 1

Known or suspected T cell-mediated autoimmune diseases.

Multiple sclerosis
Type 1 diabetes
Psoriasis
Systemic lupus erythematosus
Rheumatoid arthritis
Sjögren's syndrome
Crohn's disease
Myasthenia gravis
Dermatomyositis
Addison's disease
Grave's disease
Pernicious anemia
Primary biliary cirrhosis
Scleroderma
Hashimoto's thyroiditis
Uveitis
Vitiligo