Brief Reviews

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Cytokines in Graft-versus-Host Disease

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Graft-versus-host disease (GVHD) is a complication of allogeneic bone marrow transplantation whereby transplanted naive and marrow-derived T cells damage recipient tissue through similar mechanisms to those that allow destruction of malignant cells, the therapeutic intent of bone marrow transplantation. The manifestations and severity of GVHD are highly variable and are influenced by the proportions of naive cells maturing along regulatory T cell, Th1, Th2, or Th17 phenotypes. This maturation is largely influenced by local cytokines, which, in turn, activate transcription factors and drive development toward a dominant phenotype. In addition, proinflammatory cytokines exert direct effects on GVHD target tissues. Our knowledge of the role that cytokines play in orchestrating GVHD is expanding rapidly and parallels other infective and inflammatory conditions in which a predominant T cell signature is causative of pathology. Because a broad spectrum of cytokine therapies is now routinely used in clinical practice, they are increasingly relevant to transplant medicine. ***The Journal of Immunology*****, 2015, 194: 4604–4612.**

Graft-versus-host disease (GVHD) is a phenomenon almost unique to allogeneic bone marrow transplantation (BMT) whereby lymphocytes are introduced and permitted to engraft and proliferate within an immunocompromised host. In this setting, naive (i.e., those that have not previously encountered Ag) donor T cells are able to recognize host or recipient Ags as foreign, an effect that constitutes the therapeutic intent of BMT, allowing destruction of leukemic or other malignant cells through activation of pathways of the adaptive immune response. This beneficial effect is termed "graft-versus-leukemia" (GVL). The relative contributions of memory T cells to GVHD and GVL were discussed elsewhere (1). However, the effect is not specific to malignant cells, and simultaneous damage and destruction of healthy cells and tissues via the same or similar mechanisms give rise to GVHD. The morbidity and mortality of GVHD limit the clinical scenarios in which allogeneic hematopoietic stem cell transplantation may otherwise offer therapeutic benefit. Therefore, much research has focused on the separation of GVL and GVHD, although success has been limited because of the use of the same immune effector mechanisms. An example of this is T cell depletion of transplants: a reduction in GVHD is offset by attendant increases in the rates of relapse of primary malignancy (2, 3), in addition to more delayed immune reconstitution with increased morbidity and mortality due to opportunistic infection. An alternate focus has been to examine the influences on emerging innate and adaptive immune responses in an attempt to preserve beneficial GVL effects while eliminating the harmful "off-target" GVHD effects. In this setting, understanding the cytokine orchestration of the maturing immune response within allogeneic transplantation offers the opportunity to improve outcomes of this treatment through identification of rapidly translatable clinical therapeutic targets. Our understanding of events within the allogeneic transplantation landscape also informs our understanding of emerging innate and adaptive immune responses in scenarios other than BMT.

Cytokines and acute GVHD

The initiation of GVHD is necessarily influenced by the cytokine milieu in which it arises, and three distinct phases have been described (4, 5). The initial phase is triggered by tissue damage and associated loss of mucosal barrier function, primarily in the gastrointestinal (GI) tract, which is caused by the conditioning regimens needed to bring malignant disease to a minimal residual level suitable for subsequent immune control and to ablate existing immune function, allowing engraftment of the naive donor inoculum. Myeloablative stem cell transplantation typically uses total body irradiation or busulphan-based chemotherapy to achieve these dual aims; however, they also result in damage to the GI tract mucosa and other cells contributing to the "cytokine storm," which is characterized by the release of proinflammatory cytokines: classically TNF, IL-1, and IL-6 (4, 6). Although less well defined, there is an appreciation that a similar process occurs with reduced intensity–conditioning transplantation, although the dominant cytokines and temporal relationships may differ (7).

In addition to chemotherapy and radiation-induced tissue damage and inflammation, recognition of pathogen-associated molecular patterns, such as LPS, and danger-associated molecular patterns arising from GI microbiota have significant bearing on GVHD pathophysiology. The inflammatory signals generated in the emerging adaptive immune response are added to by recognition of molecular motifs from both pathogenic and commensal organisms and subsequent acti-

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Abbreviations used in this article: aGVHD, acute GVHD; BMT, bone marrow transplantation; cGVHD, chronic GVHD; GI, gastrointestinal; GVHD, graft-versus-host disease; GVL, graft-versus-leukemia; T_{FH}, T follicular helper; Treg, regulatory T cell.

vation of innate lymphoid pathways. The diversity of the resident organisms can be affected by conditioning-associated inflammation and by GVHD itself; conversely, the microbiota present can influence the severity of GVHD (8). The quantitative and qualitative contributions of this microbiota-driven inflammatory signal are influenced by the variety and pathogenicity of organisms present, and has been demonstrated to affect the severity of GVHD (8–10). A reduction in the bacterial burden by use of antimicrobial decontamination in the posttransplant period also can reduce GVHD severity (10). Although our mechanistic understanding of this effect is not complete, it is apparent that GVHD mediates a loss of Paneth cell–derived antimicrobial peptides that play an important role in shaping the diversity of microbiota (11), in addition to the use of pharmaceutical antimicrobials (9). Understanding these mechanisms may offer manipulable targets to alter this primary, inflammation-mediated, initiation phase of GVHD.

Recognition of the range of triggers to the cytokine storm complements our knowledge of subsequent T cell and APC interactions that define the second phase of acute GVHD (aGVHD) pathophysiology and during which cytokines play a key role in driving naive T cell differentiation and expansion toward one maturation program or another. Type 1 or Tc1/Th1 maturation is recognized as the dominant pattern in aGVHD (12, 13), and is linked to severe GI tract pathology (14). Indeed, in animal models of aGVHD, Th2 and regulatory T cells (Tregs) are rare (15). T cells expressing IL-17 are also rare, although this may reflect the plasticity of this lineage (16). Increased quantities of Th1-associated cytokines, TNF and IFN-γ, in aGVHD are associated with earlier onset and more severe disease in preclinical models and clinical BMT (4, 14, 17–19). Although the dominance of Th1 subsets is well established, Th2 and Th17 subsets are also involved in pathology, and the balance between subsets determines aGVHD severity (20), in addition to organ specificity (15, 20), and the pathogenic or protective effects of any subset cannot be viewed in isolation. Implicit in the known reciprocal regulation of T cell differentiation by these cytokines is the concept that inhibition of any one lineage may provoke unwanted and exaggerated differentiation down alternative differentiation pathways.

Th2 differentiation is often seen as opposing Th1 differentiation; however, this subset is also recognized to cause aGVHD but with predominant pathology in pulmonary, hepatic, and cutaneous tissues (21), in contrast to the strong GI association with Th1. Cutaneous pathology also may be generated by Th17 cells; although they are more commonly associated with chronic GVHD (cGVHD), they also have been associated with acute pathology (22–24). Th17 differentiation is initiated by IL-6 (25), and RORγt is the defining transcription factor (26), whereas maintenance and amplification relies on IL-23 and IL-21, respectively (27). The use of RORC-deficient donor T cells results in attenuated aGVHD severity and lethality (26). Further studies are needed to better define the role of this subset in late aGVHD versus early cGVHD, as well as the relative contribution of IL-17 from CD4 and CD8 T cells to end-organ pathology.

The third and final effector phase of aGVHD is characterized by target tissue damage, with the hallmark histological finding being apoptosis, most commonly in the GI tract, liver, and skin. This tissue damage is mediated by more than one immunological mechanism. First, cognate T cell–MHC interactions are required for effector, usually CD8, T cells that are able to evoke cytolytic machinery, including perforins and granzymes that induce target cell death via apoptosis (5, 6, 28). Interestingly, granzyme B–deficient donor T cells mediate less severe GVHD but may still generate GVL (29), via reduced activation-induced death of CD8 T cells (30). In a complementary pathway in which cognate T cell–MHC interactions are not required, myeloid cells, in addition to lymphoid cells, are primed during aGVHD to release cytopathic quantities of inflammatory cytokines (e.g., TNF, IL-6) that directly invoke apoptosis (31). Importantly, TNF is also involved in GVL effects, and inhibition can compromise antitumor immunity (32). Damage to the primary target organs of GVHD is driven by chemokine expression that results in tissue homing of lymphocyte populations. LPAM-1 ($\alpha_4\beta_7$ integrin) and L-selectin (CD62L) are associated with homing to GI and GALTs and cutaneous lymphoid Ag to skin (33) and are necessary for induction of GVHD tissue damage at these sites (34). Cytokines, including IFN-γ, are known to induce upregulation of chemokines and receptors (35), and these mechanisms were shown to be important in determining the severity of GVHD within an inflammatory environment (36–38). The expression of molecules associated with lymphocyte exhaustion (e.g., PD1) and their ligands (e.g., PD-L1) on nonlymphoid tissue also was shown to be cytokine (IFN) dependent and contribute to the constraint of lymphocyte-mediated tissue damage late in the aGVHD setting (39, 40). Therefore, the inflammatory cytokines present in this setting participate in positive- and negative-feedback loops in both lymphocyte and nonlymphocyte populations.

Cytokines and cGVHD

cGVHD represents a distinct pathophysiological entity from aGVHD that traditionally is separated by time of onset; however, it is now recognized by its distinct end-organ pathology. Although the cardinal feature of aGVHD is apoptosis, fibrosis is the predominant mechanism of tissue damage in cGVHD. Additionally, primary target organs also differ, with lung and skin being the primary target organs in cGVHD, manifesting as bronchiolitis obliterans and scleroderma (41, 42). Sicca symptoms secondary to salivary and lacrimal gland destruction and oral lichenoid GVHD are also prominent. Despite these disparate pathophysiological manifestations, clear roles for cytokine control of this phase of disease also were demonstrated, unaccompanied by large-scale conditioning-related tissue damage and the "cytokine storm" that initiates aGVHD. IL-17 and subsequent T cell differentiation along the Th17 pathway are becoming more strongly associated with cGVHD. Initially identified with the use of G-CSF in stem cell mobilization of donors and prominent Th17 differentiation (43), IL-17 was shown more recently to result in CSF1-dependent macrophage accumulation in skin and lung, which drives tissue fibrosis (44). We demonstrated recently that, consistent with this, systemic IL-17 levels increase late after clinical BMT, at a time when cGVHD develops (45). It is also clear that T follicular helper (T_{FH}) cells and IL-21 play important roles in the development of cGVHD via the stimulation of germinal center B cells and alloantibody generation (46).

This is particularly relevant to bronchiolitis obliterans, because preliminary evidence suggests that Th17 differentiation and CSF1 dysregulation are also involved in this aberrant immunological pathway (44). Thus, inhibition of Th17 differentiation and CSF1 appear highly relevant to the prevention and treatment of cGVHD. Inhibition of terminal cytokines involved in fibrosis, such as TGF-β and IL-13, represent additional targets; however, TGF-β inhibition is problematic given its important role in Treg homeostasis (47).

Cytokines and T cell–differentiation programs

The ability of cytokines to drive cellular differentiation is recognized in situations other than GVHD, with the acceptance that derivation of phenotypically distinct erythroid, myeloid, and lymphoid populations from a common long-term hematopoietic stem cell is dependent upon binding of cytokines to their cognate receptors (48, 49). Similarly, the maturation of the naive T cell population in the context of BMT and GVHD is also driven by cytokines and subsequent transcriptional pathways elicited thereafter (50). A summary of these effects is shown in Fig. 1 and outlined further below.

Cytokines and Th1 differentiation. IFN-γ, IL-2, and TNF are the key cytokines generated during Th1 differentiation (14), and phenotypic differentiation is initiated by IL-12 and controlled by the transcription factor T-bet (25, 48). IFN-γ in this setting participates in positive feedback to reinforce Th1 responses, in addition to exerting effects on nonlymphocytes, as well as on nonhematopoietic cells (18). Initial attempts to define the role of IFN-γ in determining aGVHD severity were hampered by conflicting data supporting the exacerbation and amelioration of pathology; however, subsequent work demonstrated this to be related to differing effects on donor and host tissues, in addition to tissue-specific effects on nonhematopoietic tissues. Donor lymphocyte IFN-γ signaling enhanced GVHD via the promotion of Th1 differentiation, and it also is directly cytotoxic to gut mucosa (18). Tissue-specific effects are also seen in pulmonary parenchyma in which a protective role for IFN-γ was demonstrated and these effects have also been described by other groups (15). IFN-γ provides evidence for a paradigm where cytokines may exert effects in nonhematopoietic tissue, in addition to specific effects on lymphocytes and other hematopoietic cells. Evidence of similar patterns for other cytokines is continually being defined and allows selection of appropriate targets for inhibition in the clinic.

With regard to other Th1-associated cytokines, a similarly complex effect is seen for IL-2, both mechanistically and in therapeutic outcomes (51). Initially used at a high dose in an attempt to augment proliferation of lymphocytes as "immunotherapy" for solid malignancies (52, 53), it was subsequently found, paradoxically, to have a critical role in supporting Treg populations and in controlling GVHD (51, 54). The promotion of regulatory pathways in GVHD was demonstrated in small numbers of patients when used in a "low dose" (55). These apparently dose-dependent effects are likely explained by competition for consumption of this cytokine by maturing Treg and T effector cell populations (56); in the clinical transplantation scenario, they are further complicated by the use of calcineurin inhibitors, which also target this pathway, when used as GVHD prophylaxis post-transplant.

Cytokines and Th2 differentiation. The presence of IL-25 and, subsequently, IL-4 supports the development of T cells of the Th2 lineage that traditionally have been described as being involved in allergy and host defense against parasites and helminths. Th2 cells produce IL-4, IL-5, IL-10, and IL-13, with transcriptional control exerted by GATA3 (57).

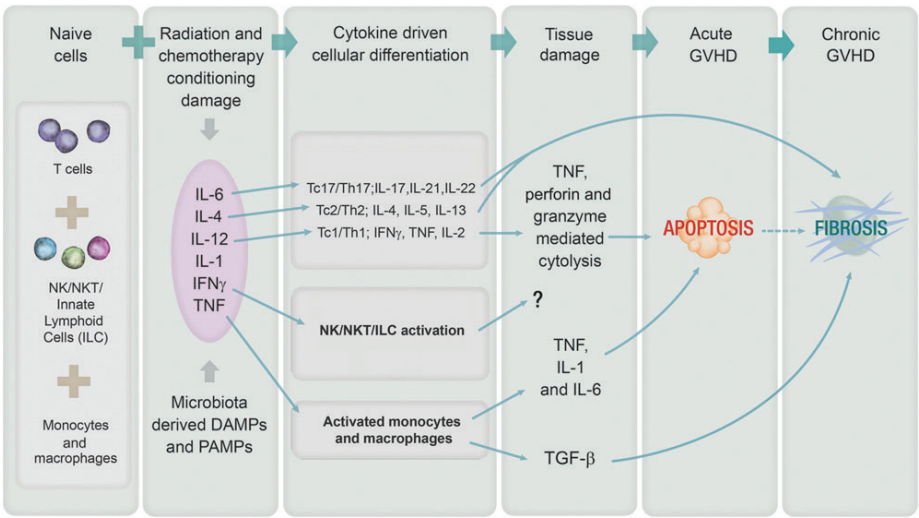

FIGURE 1. Cytokine drivers in the three phases of aGVHD initiation and end-organ pathology. Initial inflammatory signals are elicited by cellular damage from chemo- and radiotherapy, in addition to those derived from gut microbiota following GI tract damage and loss of integrity. Cytokines act on naive T cell, ILC, and myeloid cell populations, resulting in differentiation to Th1, Th2, and Th17 cell subsets, activated ILC subsets, and activated myeloid cells. End-organ tissue damage in aGVHD is caused by apoptosis elicited by Th1/Tc1 cytokines and cytolytic machinery, including perforin and granzyme, following cognate TCR–MHC interactions. Additional inflammatory pathways that are not dependent on cognate T cell pathways, including IL-6– and TNF–mediated apoptosis, following release of these cytokines from activated monocyte and macrophage populations. End-organ damage in cGVHD classically follows aGVHD and is mediated by Th2/Th17 cells and monocyte/macrophage populations secreting TGF-β that result in tissue fibrosis. The influence of ILCs on GVHD requires further delineation but they may be regulatory, at least early after BMT.

In aGVHD, the Th2 program appears to mediate skin and lung pathology (15, 18), as opposed to the strong association of Th1 cells with gut and liver damage. Recent work demonstrated a role for an IL-25–dependent immature non-B non-T cell innate immune effector cell population that is responsible for propagation of Th2 responses and production of IL-4, IL-5, and IL-13; where lacking, this results in an impaired ability to expel helminths (58–60). This cytokine may be seen as having protective effects on GI tissues, an outcome that is clearly attractive in the context of aGVHD pathology.

Other Th2 cytokines were shown to have protective roles in GVHD, including IL-10. Despite mixed results when initially given as therapy to patients, its production by B lymphocytes in animal models of transplantation reduces the severity of GVHD (61). These outcomes were mediated by effects on donor T cell expansion; similarly, reductions in IL-4 and IL-10 were demonstrated in patients with cGVHD (62, 63).

Cytokines and Th17 differentiation. Th17 cells are a more recent addition to the Th1/Th2 paradigm (25), and roles for IL-17–producing cells of both Th17 and Tc17 varieties are still being defined in the GVHD setting and in other immune pathologies (64). Initiation of Th17 development is triggered by IL-6 and TGF-β and is associated with transcriptional activation of RORγt after phosphorylation of STAT3, as well as with the secretion of IL-17, IL-21, and IL-22. There is an increasing appreciation for the role that Th17 cells play in determining the severity of GVHD (65), with a particular role for IL-6 becoming apparent (66, 67). Recently, our group demonstrated the importance of this effect in cohorts in which IL-6 inhibition represents a potentially effective therapeutic strategy to reduce the severity of aGVHD in clinical stem cell transplantation (45). IL-22 may be secreted by Th17 cells and, in this setting, it appears to be pathogenic (68); conversely, it may be secreted by innate lymphoid cells where, in the GI tract at least, it appears to be an important protective cytokine (69). IL-21 can be produced by both Th17 and T_{FH} cells, and it promotes aGVHD by impairing Treg homeostasis (70). Given that it also has an important role in inducing aberrant, allospecific germinal center B cell responses and cGVHD, inhibition of this Th17-associated cytokine represents another attractive therapeutic target for GVHD control after BMT.

Heterogeneity of effect conferred by cellular target

Increasingly, the effects mediated by a particular cytokine are being defined as dependent on the cells in which it transduces a signal and may be considered to regulate effector cell populations, as well as to confer susceptibility or protection to other inflammatory signals in target organs and tissues. Modes of signaling also influence these responses, with a recent appreciation for the differential pathology induced by the binding of cytokines by membrane-bound receptors as opposed to soluble receptors.

Hematopoietic and nonhematopoietic cells. Cytokines may exert effects on cells of hematopoietic origin, in addition to nonhematopoietic target tissues directly. IFN-γ (18) and IL-22 (68, 69) are clear examples that were already discussed. Further examples are seen in cGVHD: IL-2, IL-10, and TGF-β may act directly on tissue fibroblasts in affected organs to mediate pathology (71), in addition to known effects of IL-2 in supporting Treg populations (51, 55) and B cell–derived IL-10 being protective in the initiation of aGVHD (61). A role for innate lymphoid cells as cytokine-responsive mediators of protection from GVHD is emerging (72), with ILC1, ILC2, and ILC3 subtypes demonstrating similar transcriptional control and cytokine profiles to Th1, Th2, and Th17 cells (73).

Donor and host cells. The effect of a single cytokine can be dependent upon its roles in hematopoietic and nonhematopoietic tissue; however, in BMT, donor or host origin of the cell transducing the signal is as an additional factor influencing outcomes. Type I IFN is an example of a cytokine for which signaling through recipient APCs results in less severe class II–dependent GVHD in the colon, whereas signaling through donor APCs may amplify GVHD responses. The former is mediated through decreased donor CD4 proliferation, and the latter is mediated through more effective cross-presentation of alloantigens to CD8 T cells (19). IL-4 is another example. A subpopulation of recipient NKT cells secretes high levels of IL-4 and indirectly expands donor Treg populations to promote tolerance after BMT (74). In contrast, IL-4 may drive donor Th2 differentiation directly and enhance GVHD that likely usually represents chronic disease. Appreciation of these mechanisms is important, because treatment of a recipient or graft can be temporally separated and offers the opportunity to select desirable effects while avoiding potentially deleterious outcomes.

Receptor disposition. Additional complicating factors exist when considering cytokine-mediated effects in immune-mediated and inflammatory conditions. IL-6 is an example of a cytokine for which signaling via "classical" or membrane-bound receptor–ligand interactions produces differing pathology than does signaling mediated through soluble or *trans* receptor binding. These effects were described originally in mouse models of rheumatoid arthritis, in which *trans* signaling (by the IL-6–soluble IL-6R complex) recapitulated inflammatory joint disease in IL-6–deficient mice, whereas injection of the native IL-6 cytokine itself did not (75). Subsequently, IL-6 signaling through the *trans* pathway has been thought to be more inflammatory in nature than classical signaling, in part relating to the ability of IL-6 to signal through cells that express the gp130 receptor complex but do not basally express IL-6R (76). A similar paradigm was demonstrated in allergic asthma: Th2 expansion appears to be driven by *trans* signaling whereby expansion of Tregs was limited by classical IL-6 signaling, and inhibition with anti–IL-6R mAb resulted in increased numbers of Tregs (77), and an increase in asthma risk was associated with a single nucleotide polymorphism that results in an increase in soluble IL-6R and *trans* signaling (78). Appreciation of the mechanisms by which a cytokine can mediate differential effects is critical to understanding both disease pathophysiology and effective clinical translation of therapeutics. The availability of mAbs to cytokine receptors, such as tocilizumab for IL-6R, which inhibits all IL-6 signaling, in addition to more specific inhibitors of signalling pathway components, such as soluble gp130:Fc, which inhibits IL-6 *trans* signaling only, is a clear example.

Translational application

Accepted murine models of transplantation and rapid and reproducible multiplexed techniques to measure cytokines in serum or cell culture supernatants or intracellular cytokine

production by flow cytometry have allowed identification of, and will continue to define, the key cytokines in aGVHD (45, 79), as well as facilitate clinical translation of findings. However, a number of factors must be considered when extrapolating laboratory observations into clinical cohorts. Variation exists in transplantation protocols, patient populations, modes of conditioning, and posttransplant immunesuppression strategies. The last factor is of particular importance when considering the translation of observations made in animal models to the clinical setting, where immune suppression with cyclosporin or tacrolimus, combined with methotrexate or mycophenolate, is considered standard of care to avoid life-threatening acute and severe GVHD. However, most animal models of transplantation rely solely on radiation-based conditioning. Therefore, effective translation will require validation of observations made in animal models with clinical cohorts, because standard immunesuppressing agents were shown to affect cytokine levels produced by T cells and NK cells, and profiles vary with stem cell source (80, 81). Importantly, IFN-γ, TNF, and IL-1 are not systemically dysregulated in clinical subjects after BMT who receive immune suppression in the same way as seen in rodent models (45). With this in mind, it should be noted that no cytokine-inhibition strategy or cytokine administration has proved efficacious in randomized studies. In general, encouraging results seen in preclinical studies and early-phase clinical trials have either not progressed into phase III studies, or effects have not been robust within this context [e.g., IL-1 (82) and TNF inhibition (83, 84)]. Table I provides a summary of cytokines and inhibitors that have been explored for

Table I. Summary of relevant cytokine-targeted therapeutic studies

Cytokine Inhibitors	Phase I and/or II Clinical Trial Data	Randomized, Double-Blind Controlled and/or Phase III Clinical Trial Data
TNF-αR2 (etanercept)		
Prophylaxis	+ (83)	•
Treatment	+ (102–105)	•
TNF-α binding mAb (infliximab)		
Prophylaxis	− (84)	•
Treatment	+ (99, 100)	− (101)
IL-1Ra (anakinra)		
Prophylaxis		− (82)
Treatment	+ (106)	•
IL-2Ra/anti-CD25 (basiliximab/daclizumab[a])		
Prophylaxis	+ (107)	•
Treatment	+ (108–110)	− (111, 112)
IL-6R (tocilizumab)		
Prophylaxis	+ (45)	•
Treatment	+ (113, 114)	•
Keratinocyte growth factor (palifermin)		
Prophylaxis	− (115–119)	− (120)
Cytokines		
IL-2 (aldesleukin)		
Prophylaxis	+ (55)	•
Treatment	+ (51)	•
IL-11 (oprelvekin)		
Prophylaxis	− (121)	•
Cytokines with Non-GVHD Benefits		
IFN-α (INTRON A, Roferon-A)—promotion of GVL with concomitant promotion of GVHD		
Prophylaxis	+ (122–126)	•
Treatment	+ (127, 128)	•
Keratinocyte growth factor (palifermin)—for reduction of oral mucositis		
Prophylaxis	+ (116–118)	+ (120)
Potential GVHD Therapies	**Phase I and/or II Clinical Data Outside GVHD**	**Phase III Clinical Trial Data Outside GVHD**
IL-17		
IL-17A mAb (secukinumab, ixekizumab, perakizumab)	+ Ixekizumab (129)	+ Secukinumab (131)
IL-17RA mAb (brodalumab)	+ (130)	•
IL-17A/TNF (ABT122)	Ongoing	•
IL-22 (fezakinumab)	Ongoing	•
IL-12p40/23 mAb (ustekinumab)	+ (97, 132)	•
IL-23p19 (guselkumab, tildrakizumab)	+ Guselkumab (133)	
	+ Tildrakizumab (134)	Tildrakizumab (ongoing)
IL-13 (lebrikizumab, tralokinumab)	+ Tralokinumab (135)	+ Lebrikizumab (136)
		Tralokinumab (ongoing)

Cytokines and their antagonists are included that have been tested within a trial setting to prevent or treat GVHD or other complications of allogeneic BMT. Also included is a list of newer therapeutics with potential application to GVHD that are undergoing testing in other disease settings.

+, positive data; •, lack of data in this setting; −, negative data.

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