GvHDHub

aGvHD, cGvHD, GvHD Prophylaxis

Editorial theme | Novel targets for the treatment of GvHD

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This month's educational theme on the GvHD Hub is focusing on novel targets in the treatment of chronic graft-*versus*-host disease (GvHD). GvHD remains major complications after hematopoietic stem cell transplantation (HSCT), and a leading cause of non-relapse mortality and morbidity.[1] Therefore, developing new therapeutic options has been a focus for many research groups, which using pre-clinical models are searching for new ways to target pathological processes involved in GvHD. Over the next few weeks, we will present some of those promising targets, starting with this article recapping some of the relevant articles and video interviews on the topic that were covered on the GvHD Hub earlier this year (**Table 1**).

Table 1. An overview of novel targets articles currently available on GvHD Hub

Drug target	Drug candidate	GvHD type	GvL effect	Link to article
Gut homeostasis				
IL-22	F-652	Lower GI GvHD	Not studied	https://gvhdhub.com/medical-information/f-652-for-agvhd-of-the-lower-gi-tract
	Defibrotide	aGvHD	Preserved	https://gvhdhub.com/medical-information/effects-of-defibrotide-preventive-treatment-on-acute-graft-versus-host-disease-after-allogeneic-hematopoietic-stem-cell-transplantation
Nutrition	Lactose-free diet	aGvHD	Not studied	https://gvhdhub.com/medical-information/lactose-driven-enterococcus-expansion-linked-to-unfavorable-prognosis-in-gvhd

NLRP6	–	GI GvHD	Preserved	https://gvhdhub.com/medical-information/nlrp6-aggravates-graft-versus-host-disease-gvhd-regardless-of-gut-microbial-composition
T-cell function				
TAK1	–	CNS GvHD	Not studied	https://gvhdhub.com/medical-information/the-role-of-microglia-in-cns-gvhd
ROCK2	KD025	cGvHD	Not studied	https://gvhdhub.com/medical-information/is-sustained-treatment-with-kd025-required-for-cgvhd-control
Mesenchymal stem cells	remestemcel-L	Pediatric SR-aGvHD	Not studied	https://gvhdhub.com/medical-information/prospective-study-investigating-a-mesenchymal-stem-cells-infusion-remestemcel-l-in-pediatric-patients-with-steroid-refractory-acute-gvhd
	–	bone marrow aplasia in aGvHD	Not studied	https://gvhdhub.com/medical-information/adipose-tissue-derived-mesenchymal-stem-cells-protect-against-bone-marrow-gvhd
Trx1	–	GvHD	Preserved	https://gvhdhub.com/medical-information/pathogenicity-and-alloresponse-of-t-cells-confined-by-thioredoxin-1
MyD88	PF-06650833	GvHD	Preserved	https://gvhdhub.com/medical-information/myd88-signaling-in-donor-t-cells-accelerates-graft-versus-host-disease

S1PR	KRP203	GvHD	Slight impairment	https://gvhdhub.com/medical-information/gvhd-prophylaxis-krp203-plus-post-transplant-cyclophosphamide
CCR7	–	aGvHD	Preserved	https://gvhdhub.com/medical-information/ccr7-as-a-potential-therapeutic-target-for-gvhd-results-from-preclinical-models
CD25 (IL-2 α) and TNFRSF25	–	GI GvHD	Not studied	https://gvhdhub.com/medical-information/could-dual-targeting-of-tnfrsf25-and-cd25-minimize-gastrointestinal-graft-versus-host-disease

aGvHD, acute GvHD; CCR7, C-C Motif Chemokine Receptor 7; cGvHD, chronic GvHD; CNS, central nervous system; GI, gastrointestinal; GvHD, graft-*versus*-host disease; IL, interleukin; MyD88, myeloid differentiation factor 88; NLRP6, NOD-like receptor family pyrin domain containing 6; ROCK2, Rho-associated coiled-coil containing protein kinase 2; S1PR, sphingosine-1-phosphate receptor; TAK1, transforming growth factor beta-activated kinase 1; TNFRSF25, tumor necrosis factor receptor superfamily member 25; Trx1, thioredoxin-1

Targeting gut homeostasis

The gastrointestinal tract is the main target organ in GvHD, and the severity of gastrointestinal GvHD (GI GvHD) is in part mediated by the host's innate immunity and microbiome. Researchers are investigating several approaches to reduce the burden of GI GvHD disease.

1. Endothelial protection

Endothelial damage as a consequence of GvHD is induced by an inflammatory T-cell response, leading to organ damage and contributing to poorer outcomes. The protection from endothelial damage may, therefore, improve the outcomes of patients with GvHD. We have recently covered two different ways to protect the endothelium from the damage.

***IL-22 activation for endothelium protection and treatment of lower GI GvHD*[2]**

Interleukin (IL)-22, produced by T cells, is up-regulated during inflammation and has a key role in controlling bacterial infection, homeostasis, and tissue repair. IL-22 is involved in the response to the intestinal mucosa damage and promotes epithelial survival and regeneration, as well as induces innate antimicrobial molecules, like REG3.

In murine models, the induction of GvHD led to the elimination of host-derived IL-22-producing cells that correlated with increased mortality and GI pathology. Conversely, treatment with exogenous IL-22 reduced GI pathology and improved survival in mice with GvHD.

Doris M. Ponce and colleagues conducted a phase II study of F-652, a novel tissue-targeted recombinant human IL-22 dimer for the treatment of newly diagnosed acute GvHD (aGvHD), specifically affecting the lower GI tract. F-652 plus corticosteroids led to a 70% response rate in patients with lower GI aGvHD, meeting the primary efficacy endpoint of the study. Combining standard immunosuppression with tissue-supportive strategies was well tolerated and may provide a way to improve treatment response in GvHD.

Endothelium protection with defibrotide[3]

Defibrotide is a mixture of predominantly single-stranded nucleotides with endothelial protective properties. Senthilnathan Palaniyandi, presented a study in mice, investigating the role of defibrotide as a preventive treatment of aGvHD after allogeneic (allo-) HSCT, during the 2020 Transplantation & Cellular Therapy meeting.[3] The results of this study, conducted in mice, demonstrated that the anti-inflammatory and endothelial protective properties of defibrotide can be useful in preventing aGVHD after allo-HSCT. Furthermore, treatment with defibrotide after allo-HSCT appears to preserve graft-*versus*-leukemia (GvL) effect.

2. Other approaches

Nutritional approaches[4]

Patients undergoing allo-HSCT have been shown to display a reduced diversity and marked shift in their intestinal microbiota. In particular, commensal *Enterococcus* species are suggested to dominate the fecal microbiota of patients following allo-HSCT. Pre-clinical mouse studies have uncovered that *Enterococcus* species are involved in the initiation of antigen-presenting cell (APC) and $CD4^+/ROR\gamma^+$ T-cell infiltration that results in the establishment of colitis.

A study by Stein-Thoeringer and colleagues investigated the role of enterococci in the establishment of aGvHD in both allo-HSCT recipients and pre-clinical allo-HSCT mouse models. The study also explores the theory that *Enterococcus* vitality is reliant on lactose metabolism.

The results demonstrated that fecal *Enterococcus* species domination following allo-HSCT is a risk factor for aGvHD development and increased GvHD-associated mortalities. The expansion of enterococci is fueled by lactose and could be targeted to prevent intestinal and systemic T-cell activation with subsequent development of GvHD. The authors suggest restricting the intake of lactose especially following the administration of broad-spectrum antibiotics. Observations from the study provide rationale for a lactose-free diet, to improve patient outcome following allo-HSCT.

Targeting NLRP6[5]

NOD-like receptor family pyrin domain-containing 6 (NLRP6) has been shown to regulate innate immune responses and GI homeostasis by providing protective resistance against enteric infections in synergy with the host microbiome.

Tomomi Toubai et al., studied the role of NLRP6 in GI GvHD, and showed that the absence of NLRP6 reduces the severity of GvHD and the pathogenic role for NLRP6 in GI GvHD is independent of the intestinal microbiome and immunity. Importantly, the GvL effect was intact with this approach, which provides a potentially novel target for therapeutic intervention.

Targeting T cells

1. Inhibiting the inflammatory response and T cell activation

***TAK1 inhibition for CNS GvHD*[6]**

GvHD was primarily believed to be restricted to the skin, GI tract and liver, preclinical and clinical observations have since revealed that the central nervous system (CNS) can also be affected.

Microglia are a tissue macrophage population found in the CNS and stand as the main major histocompatibility complex class II (MHC-II)-expressing APC in the CNS. Although microglia are important in mediating CNS immune responses, they have also been linked to the pathogenesis of a number of neurodegenerative diseases.

A team led by Mathew R Nimitha and Vinnakota M Janaki investigated microglial activation in CNS GvHD mouse models and patient samples. They found that microglia play a crucial role in the establishment of CNS GvHD by augmenting T-cell stimulation and migration into the CNS. The microglial transforming growth factor beta (TGF-β)-activated kinase 1 (TAK1)/ tumour necrosis factor (TNF)/MHC-II axis was found to be imperative in the initiation and maintenance of CNS GvHD. The data from this study provides the grounds for investigating TAK1 inhibition in phase I clinical trials for the treatment of CNS GvHD.

ROCK inhibition

***Mesenchymal stem cells*[7,8]**

In vitro studies and results from animal models demonstrated immunosuppressive and immunomodulatory function of bone marrow-derived mesenchymal stem cells (MSCs). A phase III study (NCT02336230) by Joanne Kurtzberg evaluated the efficacy and safety of remestemcel-L, an ex-vivo cultured adult human MSCs infusion, in pediatric patients with high-risk steroid-refractory (SR) -aGvHD.[7] The study demonstrated the efficacy of remestemcel-L in pediatric patients with SR-aGVHD, inducing a durable overall response rate of 70.4% with rates for complete responses improving over time. The safety profile was manageable.

aGvHD is associated with cytopenia and bone marrow suppression, which can cause life-threatening infections. In order to study bone marrow aplasia related to GvHD, Yukiko Nishi and Akikazu Murakami *et al*., conducted a study to investigate the prophylactic potential of adipose-derived-multipotent cells (AD-MSCs) in GvHD, with a focus on bone marrow aplasia related to aGvHD.[8] AD-MSCs can be collected via a minimally invasive liposuction procedure, offering a unique advantage over other MSCs. The study results demonstrated that AD-MSCs are effective against bone marrow aplasia in aGvHD. Administering MHC-mismatched AD-MSCs inhibited the proliferation of donor $CD4^+$ and $CD8^+$ T-cells and increased peripheral blood cell counts. The results support the rationale of using AD-MSCs for ameliorating bone marrow suppression and susceptibility to infections after allo-HSCT in humans.

***Targeting thioreduxin-1*[9]**

Hanief Sofi and colleagues explored the role of the human redox-sensing molecule thioredoxin-1, (Trx1) on the development of GvHD in murine and xenograft models. Xenograft models of allogeneic bone marrow transplantation (allo-BMT) and transgenic models of Trx1 were used for their potential to modify GvHD and GvL effects. The results of the study demonstrated that Trx1 exerts anti-oxidative and anti-inflammatory effects and down-regulates T cell allo-responses,

alleviating GvHD development in both murine and xenograft models while still maintaining a GvL response. The research team anticipate that the effects of human recombinant Trx1 treatment can be extended to human T cells and could potentially treat GvHD in patients with hematological malignancies undergoing allo-HSCT.

Targeting MyD88[10]

Myeloid differentiation factor 88 (MyD88) signaling is vital in the activation of both innate and adaptive immunity. While the role of MyD88 for immunity has been well studied, its role in the development of GvHD pathophysiology remains unknown.

Satomi Matsuoka and colleagues evaluated the role of MyD88 signaling in donor T cells by using a well-established mouse model of allo-BMT, where lethally irradiated recipient mice were transplanted with MyD88-deficient T cells ($MyD88^{-/-}$ T cells), and T cell depleted bone marrow cells from wild-type mice.

The authors found that the deficiency of MyD88 signaling in the donor T cells directly modulated the adaptive T-cell response thereby reducing the severity of GvHD in relation with the impaired donor Th1, Tc2, and Th17 responses. Administrating a pharmacological IRAK4 inhibitor (PF-06650833) ameliorated the effects of GvHD while sparing GvL effects.

2. Inhibiting T cell migration

S1P receptor modulator in combination with PTCy[11, 12]

Sphingosine-1-phosphate receptor (S1PR) signaling plays an important role in the migration of lymphocytes from the lymph nodes to the circulation and internal organs. S1PR modulators upon binding to S1P receptor on the surface of T lymphocytes, lead to the internalization of the receptor and prevent the migration.[10]

Emi Yokoyama and colleagues recently published a study investigating the use of short-term KRP203, a S1PR modulator, in combination with post-transplant cyclophosphamide (PTCy) as a novel GvHD prophylaxis regimen in murine models.[11] They found that KRP203 plus PTCy reduced donor T cell infiltration and pathological GvHD scores in the gut, enhanced Regulatory T cells (Treg) reconstitution in the spleen, ameliorated GvHD, and improved survival after allo-HSCT compared to PTCy alone. However, a slight impaired GvL effect was noted.

CCR7 inhibition for targeting intestinal T-cell migration[13]

The GvHD disease process is initiated by the migration of donor T cells to the host secondary lymphoid organs and their activation by alloantigens on host APC. CCR7, a chemokine receptor, is critically important for lymph node specific homing and activation of T cells by APCs. Previous reports demonstrated that a high proportion of $CCR7^{+}$ donor T-cell subsets in the graft was an independent risk factors for aGvHD and correlated with poorer outcome.

A study published by Carlos Cuesta-Mateos and colleagues demonstrated that selective targeting of CCR7 with antibodies is a feasible and promising way to prevent donor T-cell migration to secondary lymphoid organs and to reduce the severity of aGvHD. Importantly, CCR7+ T cells seem not to be involved in the GvL effect or cytomegalovirus reactivation.

The most profound anti-aGvHD effect was observed in transplanted mice, when an anti-hCCR7 mAb was administrated within the first five days after transplantation. This novel prophylactic approach could offer a benefit to patients in haploidentical settings, who have a particularly large unmet need for safe and effective therapies preventing GvHD. Importantly, the approach does not compromise the benefit of GvL.

3. Expanding Treg cells

CD25 and TNFRSF25 activation for gut GvHD [14]

Innate lymphoid cells (ILCs) and Tregs are both found in abundance in the GI tract and are imperative for the development of immune homeostasis and tolerance. Growing evidence highlights the role of Treg and ILC signaling in modulating GI-associated GvHD. Two membrane-bound proteins are associated with the modulatory activity of Tregs and ILCs, CD25 and the tumor necrosis factor receptor superfamily member 25 (TNFRSF25).

Sabrina N Copsel, and colleagues found that the activation of Treg and ILC cells by TL1A-fusion protein (FP) and IL-2 is dependent on compartmental location, with significantly higher levels obtained in the GI compartments compared to other lymphohematopoietic compartments, like spleen and cervical lymph nodes. The selective activation of Treg cells was achieved with TL1A-FP only, while ILCs required both TL1A-FP and IL-2.

These preliminary data, alongside existing evidence that the TNFRSF25 and CD25 pathways are implicated in other GI inflammatory disorders, provide scope for further investigation into their regulatory role in GI-GvHD.

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