UTILITY PATENT APPLICATION

METHODS OF TREATING AND PREVENTING GRAFT VERSUS HOST DISEASE

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Filed Electronically on: October 24, 2014

METHODS OF TREATING AND PREVENTING GRAFT VERSUS HOST DISEASE

CROSS-REFERENCE

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 61/895,981, filed October 25, 2013; U.S. Provisional Application No. 61/910,945, filed December 2, 2013; U.S. Provisional Application No. 61/973,173, filed March 31, 2014; and U.S. Provisional Application No. 61/973,176 filed March 31, 2014, each of which is incorporated herein by reference.

SEQUENCE LISTING

[0001.1] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 20, 2014, is named 25922-885-201SEQ.txt and is 633 bytes in size.

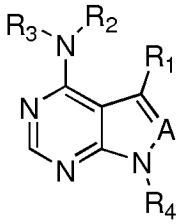
BACKGROUND OF THE INVENTION

[0002] Chronic graft versus host disease (cGVHD) is the most common long-term complication following allogeneic stem cell transplant (SCT), affecting 30-70% of patients who survive beyond the first 100 days. cGVHD and its associated immune deficiency have been identified as a leading cause of non-relapse mortality (NRM) in allogeneic SCT survivors. SCT survivors with cGVHD are 4.7 times as likely to develop severe or life-threatening health conditions compared with healthy siblings, and patients with active cGVHD are more likely to report adverse general health, mental health, functional impairments, activity limitation, and pain than allo-SCT survivors with no history of cGVHD. Any organ system can be affected, and further morbidity is frequently caused by long-term exposure to the corticosteroids and calcineurin inhibitors required to treat the condition.

SUMMARY OF THE INVENTION

[0003] Disclosed herein, in some embodiments, are methods of preventing the occurrence of graft versus host disease (GVHD) or reducing the severity of GVHD occurrence in a patient requiring cell transplantation comprising administration of a therapeutically effective amount of an ACK inhibitor (e.g., an ITK or BTK inhibitor). In some embodiments, disclosed herein are methods of reducing the severity of GVHD occurrence in a patient requiring cell transplantation comprising administration of a therapeutically effective amount of an ACK inhibitor (e.g., an ITK or BTK inhibitor). In some embodiments the ACK inhibitor is a compound of Formula (A). In some embodiments, disclosed herein are methods of preventing the occurrence of graft versus host disease (GVHD) or reducing

the severity of GVHD occurrence in a patient requiring cell transplantation, comprising administration of a therapeutically effective amount of a compound of Formula (A) having the structure:



Formula (A);

wherein:

A is N;

R_1 is phenyl-O-phenyl or phenyl-S-phenyl;

R_2 and R_3 are independently H;

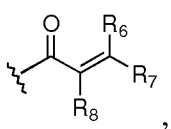
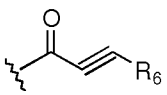
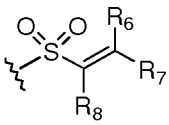
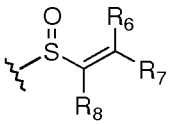
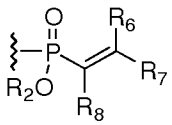
R_4 is L_3-X-L_4-G, wherein,

L_3 is optional, and when present is a bond, optionally substituted or unsubstituted alkyl, optionally substituted or unsubstituted cycloalkyl, optionally substituted or unsubstituted alkenyl, optionally substituted or unsubstituted alkynyl;

X is optional, and when present is a bond, -O-, -C(=O)-, -S-, -S(=O)-, -S(=O)$_2$-, -NH-, -NR_9-, -NHC(O)-, -C(O)NH-, -NR_9C(O)-, -C(O)NR_9-, -S(=O)$_2$NH-, -NHS(=O)$_2$-, -S(=O)$_2$$NR_9$-, -$NR_9$S(=O)$_2$-, -OC(O)NH-, -NHC(O)O-, -OC(O)NR_9-, -NR_9C(O)O-, -CH=NO-, -ON=CH-, -NR_{10}C(O)NR_{10}-, heteroaryl-, aryl-, -NR_{10}C(=NR_{11})NR_{10}-, -NR_{10}C(=NR_{11})-, -C(=NR_{11})NR_{10}-, -OC(=NR_{11})-, or -C(=NR_{11})O-;

L_4 is optional, and when present is a bond, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycle;

or L_3, X and L_4 taken together form a nitrogen containing heterocyclic ring;

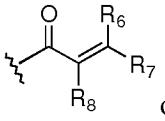
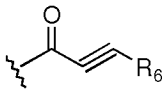
G is  ,  ,  ,  , or  , wherein,

R_6, R_7 and R_8 are independently selected from among H, halogen, CN, OH, substituted or unsubstituted alkyl or substituted or unsubstituted heteroalkyl or substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

each R_9 is independently selected from among H, substituted or unsubstituted lower alkyl, and substituted or unsubstituted lower cycloalkyl;

each R_{10} is independently H, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower cycloalkyl; or

two R_{10} groups can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or

R_{10} and R_{11} can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or each R_{11} is independently selected from H or substituted or unsubstituted alkyl; or a pharmaceutically acceptable salt thereof. In some embodiments, L_3, X and L_4 taken together form a nitrogen containing heterocyclic ring. In some embodiments, the nitrogen containing heterocyclic ring is a piperidine group. In some embodiments, G is  or  . In some embodiments, the compound of Formula (A) is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one. In some embodiments, the patient has cancer. In some embodiments, the patient has a hematological malignancy. In some embodiments, the patient has a relapsed or refractory hematological malignancy. In some embodiments, the patient has a B-cell malignancy. In some embodiments, the patient has a T-cell malignancy. In some embodiments, the patient has a leukemia, a lymphoma, or a myeloma. In some embodiments, the B-cell malignancy is a non-Hodgkin's lymphoma. In some embodiments, the B-cell malignancy is chronic lymphocytic leukemia (CLL). In some embodiments, the B-cell malignancy is a relapsed or refractory B-cell malignancy. In some embodiments, the B-cell malignancy is a relapsed or refractory non-Hodgkin's lymphoma. In some embodiments, the B-cell malignancy is a relapsed or refractory CLL. In some embodiments, the patient has high risk CLL. In some embodiments, the patient has a 17p chromosomal deletion. In some embodiments, the patient has 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater CLL as determined by bone marrow biopsy. In some embodiments, the patient has received one or more prior anticancer agents. In some embodiments, the anticancer agent is selected from among alemtuzumab, bendamustine, bortezomib, CAL-101, chlorambucil,

cyclophosphamide, dexamethasone, docetaxel, doxorubicin, endostatineverolimus, etoposide, fludarabine, fostamatinib, hydroxydaunorubicin, ibritumomab, ifosphamide, lenalidomide, mesalazine, ofatumumab, paclitaxel, pentostatin, prednisone, rituximab, temsirolimus, thalidomide, tositumomab, vincristine, or a combination thereof. In some embodiments, the anticancer agent is rituximab. In some embodiments, the anticancer agent is alemtuzumab. In some embodiments, the anticancer agent is fludarabine, cyclophosphamide, and rituximab (FCR). In some embodiments, the anticancer agent is oxaliplatin, fludarabine, cytarabine, rituximab (OFAR). In some embodiments, the amount of the ACK inhibitor compound (e.g., a compound of Formula (A)) prevents or reduces GVHD while maintaining a graft-versus-leukemia (GVL) reaction effective to reduce or eliminate the number of cancerous cells in the blood of the patient. In some embodiments, the cell transplantation is a hematopoietic cell transplantation. In some embodiments, the GVHD is acute GVHD. In some embodiments, the GVHD is chronic GVHD. In some embodiments, the GVHD is sclerodermatous GVHD. In some embodiments, the GVHD is steroid resistant GVHD. In some embodiments, the GVHD is cyclosporin-resistant GVHD. In some embodiments, the GVHD is refractory GVHD. In some embodiments, the GHVD is oral GVHD. In some embodiments, the oral GVHD is reticular oral GVHD. In some embodiments, the oral GVHD is erosive oral GVHD. In some embodiments, the oral GVHD is ulcerative oral GVHD. In some embodiments, the oral GVHD is GVHD of the oral cavity. In some embodiments, the oral GVHD is GVHD of the oropharyngeal region. In some embodiments, the oral GVHD is GVHD of the pharyngeal region. In some embodiments, the oral GVHD is GVHD of the esophageal region. In some embodiments, the oral GVHD is acute oral GVHD. In some embodiments, the oral GVHD is chronic oral GVHD. In some embodiments, the patient exhibits one or more symptoms of GVHD. In some embodiments, the patient has or will receive an allogeneic bone marrow or hematopoietic stem cell transplant. In some embodiments, the ACK inhibitor compound (e.g., a compound of Formula (A)) is administered concurrently with an allogeneic bone marrow or hematopoietic stem cell transplant. In some embodiments, the ACK inhibitor compound (e.g., a compound of Formula (A)) is administered prior to an allogeneic bone marrow or hematopoietic stem cell transplant. In some embodiments, the ACK inhibitor compound (e.g., a compound of Formula (A)) is administered subsequent to an allogeneic bone marrow or hematopoietic stem cell transplant. In some embodiments, the patient is a candidate for receiving HLA-mismatched hematopoietic stem cells. In some embodiments, the patient is a

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