

Materials And Methods Of Treating MHC-I-Opathy Risk Haplotypes

Reference To Sequence Listing

This application includes a Sequence Listing filed electronically as a text file named
5 18923810702SEQ, created on April 6, 2022, with a size of 1027 kilobytes. The Sequence Listing
is incorporated herein by reference.

Field

The present disclosure is directed, in part, to methods of treating subjects having an
10 immune disorder by administering to the subject a therapeutically effective amount of an
Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor in combination with an HLA-A29 or
HLA-B27 inhibitory nucleic acid molecule.

Background

15 The cellular immune response in humans relies at least partly on the presentation of
small peptides that are 8 to 10 amino acids long, which are bound proteins of the major
histocompatibility complex (MHC) (i.e., class I MHC molecules). These small peptides are
derived from the proteolytic degradation of proteins (foreign antigens and self-antigens). One
source of these antigens come from infected or malignantly transformed cells that express
20 particular protein molecules that, upon degradation, yield distinct antigenic peptides that are
presented on the cell surface complexed with MHC class I molecules (MHCI). Cytotoxic T cells
can recognize these complexes of MHC molecules with degraded protein antigens and induce
apoptotic cell death. Aberrant generation of antigenic peptides can lead to immune system
evasion or to autoimmune reactions.

25 Although most antigenic peptides are initially produced by the proteasome, many of
them are larger than the final antigenic epitope and contain one or more additional amino acids
at their N-termini. These antigenic peptide precursors are transported
into the endoplasmic reticulum (ER), where they are further degraded by at least two different
aminopeptidases, ERAP1 and ERAP2, to generate the mature antigenic peptides for complexing
30 with MHC class I molecules. Thus, the activity of ERAP1 and ERAP2 can directly affect the
presentation of antigenic peptides complexed with particular MHC molecules in a beneficial or
adverse manner, thus altering the immune response. Accordingly, there continues to be a need

for identifying subjects that have particular MHC-I-opathies related to ERAP2 activity and treatment of the same.

Birdshot Chorioretinopathy (BSCR) is a rare autoimmune uveitis predominately affecting individuals over the age of 50 of European descent and treated with

5 immunomodulatory therapies. The disease presents with vitritis and gradual decline in vision due to choroidal and retinal inflammatory lesions and atrophy. T cells have been identified in the retinal and choroidal tissues as well as the vitreous of affected BSCR eyes.

Summary

10 The present disclosure provides methods of treating a subject having an immune disorder, the methods comprising administering to the subject an ERAP2 inhibitor and: i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor.

Disclosed herein is the use of an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor in the manufacture of a medicament for treating a subject having an immune disorder,
15 wherein the medicament is to be administered with: i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor to the subject.

Disclosed herein is the use of i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor in the manufacture of a medicament for treating a subject having an immune disorder, wherein the medicament is to be administered with an Endoplasmic Reticulum Aminopeptidase 2
20 (ERAP2) inhibitor.

Disclosed herein is the use of an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor and i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor in the manufacture of a medicament for treating a subject having an immune disorder.

The present disclosure provides methods of treating a subject having an MHC-I-opathy,
25 the methods comprising: performing or having performed an assay on a biological sample from the subject to determine whether the subject comprises: i) an HLA-A29 allele and/or an HLA-B27 allele; and ii) a functional ERAP2 protein or a nucleic acid molecule encoding a functional ERAP2 protein; and administering to the subject a therapeutically effective amount of an ERAP2 inhibitor and an HLA-A29 inhibitor to the subject having the functional ERAP2 protein or the
30 nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-A29 allele; or administering to the subject a therapeutically effective amount of an ERAP2 inhibitor and an HLA-B27 inhibitor to the subject having the functional ERAP2 protein or the nucleic acid

molecule encoding a functional ERAP2 protein, and having the HLA-B27 allele; wherein the presence of both: i) the HLA-A29 allele and/or the HLA-B27 allele, and ii) the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.

5 Disclosed herein is the use of an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor in the manufacture of a medicament for treating a subject having an MHC-I-opathy, wherein the subject has been determined to comprise: i) an HLA-A29 allele and/or an HLA-B27 allele; and ii) a functional Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) protein or a nucleic acid molecule encoding a functional ERAP2 protein by performing or having performed
10 an assay on a biological sample from the subject; and wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-A29 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-A29 allele; or wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-B27 inhibitor are to be administered to the subject having the
15 functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-B27 allele; wherein the presence of both: i) the HLA-A29 allele and/or the HLA-B27 allele, and ii) the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.

20 Disclosed herein is the use of i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor in the manufacture of a medicament for treating a subject having an MHC-I-opathy, wherein the subject has been determined to comprise: i) an HLA-A29 allele and/or an HLA-B27 allele; and ii) a functional Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) protein or a nucleic acid molecule encoding a functional ERAP2 protein by performing or having performed an assay on
25 a biological sample from the subject; and wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-A29 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-A29 allele; or wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-B27 inhibitor are to be administered to the subject having the functional ERAP2
30 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-B27 allele; wherein the presence of both: i) the HLA-A29 allele and/or the HLA-B27 allele, and ii)

the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.

Disclosed herein is the use of an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor and i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor in the manufacture of a medicament for treating a subject having an MHC-I-opathy, wherein the subject has been determined to comprise: i) an HLA-A29 allele and/or an HLA-B27 allele; and ii) a functional Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) protein or a nucleic acid molecule encoding a functional ERAP2 protein by performing or having performed an assay on a biological sample from the subject; and wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-A29 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-A29 allele; or wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-B27 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-B27 allele; wherein the presence of both: i) the HLA-A29 allele and/or the HLA-B27 allele, and ii) the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.

The present disclosure provides combinations of an ERAP2 inhibitor and an HLA-A29 inhibitor for use in the treatment of an immune disorder.

The present disclosure provides combinations of an ERAP2 inhibitor and an HLA-B27 inhibitor for use in the treatment of an immune disorder.

Brief Description Of The Drawings

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Figure 1 shows a table of HLA-A 2nd allele frequencies in the French cohort compared to UKB and GHS EUR A29 carriers. Alleles belonging to the Aw19 broad antigen group that increase risk are A29, A30, A31 and A33 (red) and A32 exhibits protection (green). A Fisher's exact test combining all Aw19 risk alleles presents the strongest enrichment in all comparisons. Only alleles that have three or more case carriers are presented. Table is sorted by p-values when comparing case frequencies against A29 controls in UKB.

Figure 2 shows Aw19 enrichment in Birdshot cases. Odds-ratio for BSCR, comparing frequencies of 14 HLA-A alleles that are present in three or more cases (>1%, x-axis) in 286 UParis cases compared with 108 UParis controls (Blue), GHS control cohort #1 (n= 4,014, dark green), GHS control cohort #2 (n= 2,829, bright green) and UKB controls (n= 38,543, yellow).

- 5 Aw19 alleles show the highest ORs (red box) that replicates with large A29 control cohorts, with the exception of A32 that is depleted in cases (green box). * $p < 0.01$

Figure 3 shows a table of HLA-A 2nd allele frequencies in the French cohort compared to UKB and GHS EUR A29 carriers. Alleles belonging to the Aw19 broad antigen group that increase risk are A29, A30, A31 and A33 (red) and A32 exhibits protection (green). A logistic regression test with covariates included for sex and six principal components, calculated based on genetic array data for each analytic set. Results are presented for all HLA-A alleles that have three or more case carriers. Alleles are sorted as in Figure 1. *Three principal components.

Figure 4 shows a table of top SNPs in ERAP2 regions. Variants in ERAP2 are genome-wide significant when analyzed together with previous results (125 cases and 670 controls (Kuiper 2014). Rs10044354 is the top association in the ERAP1-ERAP2 locus in the previous GWAS of Dutch and Spanish cohorts, while rs27432 is the top association in the region in the current French cohort. The LD between the two loci is also presented. *The reference A-allele is the minor allele, risk is the G-allele.

Figure 5 shows ERAP2 splice region variant is protective for BSCR. The common ERAP2 splice region variant rs2248374 that disrupts ERAP2 expression is protective in the current BSCR cohort and the previous Spanish and Dutch cohorts.

Figure 6 shows the combined risk of ERAP2 and two copies of Aw19. Utilizing 286 Birdshot cases and 4,014 controls from GHS cohort #1 to calculate additive risk while combining risk factors in ERAP2 and Aw19. An additive genotype model of ERAP2 risk signal tagged by rs10044354 and single (A29/-) or double (A29/Aw19) Aw19 copies relative to lowest risk combination of rs10044354-CC and one copy of Aw19 allele (A29).

Figure 7 shows a table of the combined risk of ERAP2 and Aw19. Utilizing 286 Birdshot cases and 4,014 controls from GHS cohort #1 to calculate additive risk while combining risk factors in ERAP2 and Aw19. An additive genotype model of ERAP2 risk signal tagged by rs10044354 and single (A29/-) or double (A29/Aw19) Aw19 copies relative to lowest risk combination of rs10044354-CC and one copy of Aw19 allele (A29).

Figure 8 shows differences between risk Aw19 alleles and A32. Panel A) Sequence differences between risk Aw19 alleles (red) and protective A32 allele (green). A32 exhibits F at position 9 as is the reference A:01:01 allele, while risk alleles are either T or S at that position. The Bw4 epitope sequence is apparent at positions 79-83 or A32 only.

5

Description Of Embodiments

Various terms relating to aspects of the present disclosure are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art, unless otherwise indicated. Other specifically defined terms are to be construed in a manner

10 consistent with the definitions provided herein.

Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended that an order be inferred,

15 in any respect. This holds for any possible non-expressed basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

As used herein, the singular forms “a,” “an” and “the” include plural referents unless

20 the context clearly dictates otherwise.

As used herein, the term “about” means that the recited numerical value is approximate and small variations would not significantly affect the practice of the disclosed embodiments. Where a numerical value is used, unless indicated otherwise by the context, the term “about” means the numerical value can vary by $\pm 10\%$ and remain within the scope of the

25 disclosed embodiments.

As used herein, the term “comprising” may be replaced with “consisting” or “consisting essentially of” in particular embodiments as desired.

As used herein, the terms “nucleic acid”, “nucleic acid molecule”, “nucleic acid sequence”, “polynucleotide”, or “oligonucleotide” can comprise a polymeric form of

30 nucleotides of any length, can comprise DNA and/or RNA, and can be single-stranded, double-stranded, or multiple stranded. One strand of a nucleic acid also refers to its complement.

As used herein, the term “subject” includes any animal, including mammals. Mammals include, but are not limited to, farm animals (such as, for example, horse, cow, pig), companion animals (such as, for example, dog, cat), laboratory animals (such as, for example, mouse, rat, rabbits), and non-human primates (such as, for example, apes and monkeys). In some
5 embodiments, the subject is a human. In some embodiments, the subject is a patient under the care of a physician.

The present disclosure provides methods of treating a subject having an immune disorder, the methods comprising administering to the subject an ERAP2 inhibitor. In some embodiments, the immune disorder is an MHC-I-opathy. In some embodiments, the immune
10 disorder is an MHC-II-opathy. In some embodiments, the MHC-I-opathy is Birdshot Chorioretinopathy (BSCR), Ankylosing Spondylitis (AS), psoriasis in combination with uveitis, or Juvenile Idiopathic Arthritis (JIA). In some embodiments, the MHC-I-opathy is BSCR. In some embodiments, the MHC-I-opathy is AS. In some embodiments, the MHC-I-opathy is psoriasis in combination with uveitis. In some embodiments, the MHC-I-opathy is JIA.

15 In some embodiments, the MHC-I-opathy is BSCR. In some embodiments, the method further comprises detecting the presence or absence of an HLA-Aw19 allele in a biological sample obtained from the subject. In some embodiments, the subject is HLA-Aw19⁺. In some embodiments, the subject is or is suspected of being HLA-A29⁺, HLA-A30⁺, HLA-A31⁺, or HLA-A33⁺, or any combination thereof. In some embodiments, the method further comprises
20 determining whether the subject has one or two copies of an HLA-Aw19 allele. In some embodiments, the subject has a single copy of HLA-Aw19. In some embodiments, the subject has two copies of HLA-Aw19. In some embodiments, the subject is HLA-A29⁺/HLA-A30⁺. In some embodiments, the subject is HLA-A29⁺/HLA-A31⁺. In some embodiments, the subject is HLA-A29⁺/HLA-A33⁺.

25 In some embodiments, the subject having BSCR is not HLA-A29⁺.

In some embodiments, the subject having BSCR has a copy of at least any two of HLA-A29, HLA-A30, HLA-A31, or HLA-A33. In some embodiments, the subject having BSCR has a copy of at least any three of HLA-A29, HLA-A30, HLA-A31, or HLA-A33. In some embodiments, the subject having BSCR has a copy of all of HLA-A29, HLA-A30, HLA-A31, or HLA-A33.

30 In some embodiments, the subject having BSCR has one copy of each HLA-A29 and HLA-A30. In some embodiments, the subject having BSCR has one copy of each HLA-A29 and HLA-A31. In some embodiments, the subject having BSCR has one copy of each HLA-A29 and

HLA-A33. In some embodiments, the subject having BSCR has one copy of each HLA-A30 and HLA-A31. In some embodiments, the subject having BSCR has one copy of each HLA-A30 and HLA-A33. In some embodiments, the subject having BSCR has one copy of each HLA-A31 and HLA-A33.

5 In some embodiments, the subject having BSCR has one copy of HLA-A29 and two copies of HLA-A30. In some embodiments, the subject having BSCR has one copy of HLA-A29 and two copies of HLA-A31. In some embodiments, the subject having BSCR has one copy of HLA-A29 and two copies of HLA-A33. In some embodiments, the subject having BSCR has one copy of HLA-A30 and two copies of HLA-A31. In some embodiments, the subject having BSCR
10 has one copy of HLA-A30 and two copies HLA-A33. In some embodiments, the subject having BSCR has one copy of HLA-A31 and two copies of HLA-A33.

 In some embodiments, the subject having BSCR has two copies of HLA-A29 and one copy of HLA-A30. In some embodiments, the subject having BSCR has two copies of HLA-A29 and one copy of HLA-A31. In some embodiments, the subject having BSCR has two copies of
15 HLA-A29 and one copy of HLA-A33. In some embodiments, the subject having BSCR has two copies of HLA-A30 and one copy of HLA-A31. In some embodiments, the subject having BSCR has two copies of HLA-A30 and one copy of HLA-A33. In some embodiments, the subject having BSCR has two copies of HLA-A31 and one copy of HLA-A33.

 In some embodiments, the subject having BSCR or suspected of having BSCR has two
20 copies of HLA-A29 and two copies of HLA-A30. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A29 and two copies of HLA-A31. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A29 and two copies of HLA-A33. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A30 and two copies of HLA-A31. In some embodiments, the
25 subject having BSCR or suspected of having BSCR has two copies of HLA-A30 and two copies of HLA-A33. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A31 and two copies of HLA-A33.

 In some embodiments, the method further comprises administering to the subject an HLA-Aw19 inhibitor. In some embodiments, the HLA-Aw19 inhibitor comprises an antibody. In
30 some embodiments, the antibody comprises an anti-HLA-A29 antibody. In some embodiments, the HLA-Aw19 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense

nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to an HLA-Aw19. In some embodiments, the HLA-Aw19 is HLA-A29.

In some embodiments, the MHC-I-opathy is AS. In some embodiments, the method further comprises detecting the presence or absence of HLA-B27 or HLA-B40 in a biological sample obtained from the subject. In some embodiments, the subject is or is suspected of being HLA-B27⁺. In some embodiments, the subject is or is suspected of being HLA-B40⁺. In some embodiments, the method further comprises determining whether the subject has one or two copies of HLA-B27 or HLA-B40. In some embodiments, the subject has a single copy of HLA-B27 or HLA-B40. In some embodiments, the subject has two copies of HLA-B27 or HLA-B40. In some embodiments, the method further comprises administering to the subject an HLA-B27 inhibitor or an HLA-B40 inhibitor. In some embodiments, the HLA-B27 inhibitor or HLA-B40 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody or an anti-HLA-B40 antibody. In some embodiments, the HLA-B27 inhibitor or HLA-B40 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27 or an HLA-B40.

In some embodiments, the MHC-I-opathy is psoriasis in combination with uveitis. In some embodiments, the uveitis is anterior uveitis. In some embodiments, the method further comprises detecting the presence or absence of HLA-B27 in a biological sample obtained from the subject. In some embodiments, the subject is or is suspected of being HLA-B27⁺. In some embodiments, the method further comprises determining whether the subject has one or two copies of HLA-B27. In some embodiments, the subject has a single copy of HLA-B27. In some embodiments, the subject has two copies of HLA-B27. In some embodiments, the method further comprises administering to the subject an HLA-B27 inhibitor. In some embodiments, the HLA-B27 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody. In some embodiments, the HLA-B27 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27.

In some embodiments, the MHC-I-opathy is JIA. In some embodiments, the method further comprises detecting the presence or absence of HLA-B27 and/or DRB1 in a biological sample obtained from the subject. In some embodiments, the subject is or is suspected of

being HLA-B27⁺ and/or DRB1⁺. In some embodiments, the method further comprises determining whether the subject has one or two copies of HLA-B27 and/or DRB1. In some embodiments, the subject has a single copy of HLA-B27 and/or DRB1. In some embodiments, the subject has two copies of HLA-B27 and/or DRB1. In some embodiments, the method further
5 comprises administering to the subject an HLA-B27 inhibitor and/or a DRB1 inhibitor. In some embodiments, the HLA-B27 inhibitor and/or DRB1 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody or an anti-DRB1 antibody. In some embodiments, the HLA-B27 inhibitor and/or DRB1 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic
10 acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27 and/or an DRB1.

In some embodiments, the ERAP2 inhibitor comprises a small molecule degrader, a proteolysis-targeting chimera, an immunomodulatory drug, or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense
15 nucleic acid molecule, an siRNA, or an shRNA that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an siRNA that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an shRNA that hybridizes to ERAP2 mRNA. In some
20 embodiments, the ERAP2 inhibitor comprises an anti-ERAP2 antibody. In some embodiments, the ERAP2 inhibitor comprises a pseudopeptide. In some embodiments, the pseudopeptide is a phosphinic pseudopeptide. In some embodiments, the phosphinic pseudopeptide is DG002 or DG013 (see, for example, Zervoudi et al., Proc. Natl. Acad. Sci. USA, 2013, 110, 19890-19895). In some embodiments, the phosphinic pseudopeptide is DG002. In some embodiments, the
25 phosphinic pseudopeptide is DG013. In some embodiments, the ERAP2 inhibitor comprises a small molecule. In some embodiments, the ERAP2 inhibitor is compound 4, compound 15, compound 16, compound 5, or analogues of compound 5, which are drug-like carboxylic acids and bioisosters screened for enhanced selectivity for ERAP2 over ERAP1 (see, Medve et al., European Journal of Medicinal Chemistry, 2021, 211, 113053). In some embodiments, the
30 ERAP2 inhibitor is a phosphonic or phosphinic acid compound with higher affinity for ERAP2 than ERAP1 (see, Weglarz-Tomczak et al., Bioorg. Med. Chem. Lett., 2016, 26, 4122-4126).

Additional ERAP2 inhibitors are described in, for example, Georgiadis et al., Curr. Medic. Chem., 2019, 26, 2715-2729.

In any of the embodiments described herein, any of the inhibitors or other agents described herein can form a component of an antibody-drug-conjugate (ADC). For example, an ERAP2 inhibitor can be conjugated to an antibody, or antigen-binding fragment thereof. The inhibitor can comprise a small molecule degrader, a proteolysis-targeting chimera, an immunomodulatory drug, or an inhibitory nucleic acid molecule.

The present disclosure also provides methods of treating a subject having an MHC-I-opathy. In some embodiments, the method comprises performing or having performed an assay on a biological sample from the subject to determine whether the subject comprises: i) an MHC-I-opathy-related HLA genotype; and ii) a functional ERAP2 protein or a nucleic acid molecule encoding a functional ERAP2 protein. In some embodiments, the method comprises administering to the subject a therapeutically effective amount of an ERAP2 inhibitor, wherein the subject comprises both an MHC-I-opathy-related HLA genotype and a functional ERAP2 protein or a nucleic acid molecule encoding a functional ERAP2 protein. The presence of both the MHC-I-opathy-related HLA genotype and the functional ERAP2 protein or a nucleic acid molecule encoding a functional ERAP2 protein indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.

In some embodiments, the MHC-I-opathy is BSCR and the MHC-I-opathy-related HLA genotype comprises an HLA-Aw19 allele. In some embodiments, the HLA-Aw19 allele comprises an HLA-A29 allele, an HLA-A30 allele, an HLA-A31 allele, or an HLA-A33 allele, or any combination thereof. In some embodiments, the subject has a single copy of the HLA-Aw19 allele. In some embodiments, the HLA-Aw19 allele comprises an HLA-A29 allele. In some embodiments, the HLA-Aw19 allele comprises an HLA-A30 allele. In some embodiments, the HLA-Aw19 allele comprises an HLA-A31 allele. In some embodiments, the HLA-Aw19 allele comprises an HLA-A33 allele. In some embodiments, the subject has two copies of the HLA-Aw19 allele. In some embodiments, the subject is or is suspected of being HLA-A29⁺/HLA-A30⁺. In some embodiments, the subject is or is suspected of being HLA-A29⁺/HLA-A31⁺. In some embodiments, the subject is or is suspected of being HLA-A29⁺/HLA-A33⁺.

In some embodiments, the subject having BSCR is not HLA-A29⁺.

In some embodiments, the subject having BSCR has a copy of at least any two of HLA-A29, HLA-A30, HLA-A31, or HLA-A33. In some embodiments, the subject having BSCR has a copy

of at least any three of HLA-A29, HLA-A30, HLA-A31, or HLA-A33. In some embodiments, the subject having BSCR has a copy of all of HLA-A29, HLA-A30, HLA-A31, or HLA-A33.

In some embodiments, the subject having BSCR has one copy of each HLA-A29 and HLA-A30. In some embodiments, the subject having BSCR has one copy of each HLA-A29 and HLA-A31. In some embodiments, the subject having BSCR has one copy of each HLA-A29 and HLA-A33. In some embodiments, the subject having BSCR has one copy of each HLA-A30 and HLA-A31. In some embodiments, the subject having BSCR has one copy of each HLA-A30 and HLA-A33. In some embodiments, the subject having BSCR has one copy of each HLA-A31 and HLA-A33.

In some embodiments, the subject having BSCR has one copy of HLA-A29 and two copies of HLA-A30. In some embodiments, the subject having BSCR has one copy of HLA-A29 and two copies of HLA-A31. In some embodiments, the subject having BSCR has one copy of HLA-A29 and two copies of HLA-A33. In some embodiments, the subject having BSCR has one copy of HLA-A30 and two copies of HLA-A31. In some embodiments, the subject having BSCR has one copy of HLA-A30 and two copies HLA-A33. In some embodiments, the subject having BSCR has one copy of HLA-A31 and two copies of HLA-A33.

In some embodiments, the subject having BSCR has two copies of HLA-A29 and one copy of HLA-A30. In some embodiments, the subject having BSCR has two copies of HLA-A29 and one copy of HLA-A31. In some embodiments, the subject having BSCR has two copies of HLA-A29 and one copy of HLA-A33. In some embodiments, the subject having BSCR has two copies of HLA-A30 and one copy of HLA-A31. In some embodiments, the subject having BSCR has two copies of HLA-A30 and one copy of HLA-A33. In some embodiments, the subject having BSCR has two copies of HLA-A31 and one copy of HLA-A33.

In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A29 and two copies of HLA-A30. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A29 and two copies of HLA-A31. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A29 and two copies of HLA-A33. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A30 and two copies of HLA-A31. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A30 and two copies of HLA-A33. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A31 and two copies of HLA-A33.

In some embodiments, the method further comprises administering to the subject an HLA-Aw19 inhibitor. In some embodiments, the HLA-Aw19 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-A29 antibody. In some embodiments, the HLA-Aw19 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-Aw19. In some embodiments, the HLA-Aw19 is HLA-A29.

In some embodiments, the MHC-I-opathy is AS and the MHC-I-opathy-related HLA genotype comprises an HLA-B27 allele or an HLA-B40 allele. In some embodiments, the subject has a single copy of HLA-B27 or HLA-B40. In some embodiments, the subject has two copies of HLA-B27 or HLA-B40. In some embodiments, the method further comprises administering to the subject an HLA-B27 inhibitor or an HLA-B40 inhibitor. In some embodiments, the HLA-B27 inhibitor or HLA-B40 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody or an anti-HLA-B40 antibody. In some embodiments, the HLA-B27 inhibitor or HLA-B40 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27 or an HLA-B40.

In some embodiments, the MHC-I-opathy is psoriasis in combination with uveitis and the MHC-I-opathy-related HLA genotype comprises an HLA-B27 allele. In some embodiments, the uveitis is anterior uveitis. In some embodiments, the subject has a single copy of HLA-B27. In some embodiments, the subject has two copies of HLA-B27. In some embodiments, the method further comprises administering to the subject an HLA-B27 inhibitor. In some embodiments, the HLA-B27 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody. In some embodiments, the HLA-B27 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27.

In some embodiments, the MHC-I-opathy is JIA and the MHC-I-opathy-related HLA genotype comprises an HLA-B27 and/or DRB1. In some embodiments, the subject has a single copy of HLA-B27 and/or DRB1. In some embodiments, the subject has two copies of HLA-B27 and/or. In some embodiments, the method further comprises administering to the subject an

HLA-B27 inhibitor and/or a DRB1 inhibitor. In some embodiments, the HLA-B27 inhibitor and/or DRB1 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody and/or a DRB1 antibody. In some embodiments, the HLA-B27 inhibitor and/or DRB1 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27 or DRB1.

In any of the embodiments described herein, the nucleic acid molecule comprises genomic DNA, mRNA, or cDNA obtained from mRNA. In some embodiments, the nucleic acid molecule comprises genomic DNA. In some embodiments, the nucleic acid molecule comprises mRNA. In some embodiments, the nucleic acid molecule comprises cDNA obtained from mRNA.

In any of the embodiments described herein, the ERAP2 inhibitor comprises a small molecule degrader, a proteolysis-targeting chimera, an immunomodulatory drug, or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an siRNA that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an shRNA that hybridizes to ERAP2 mRNA. In some embodiments, the ERAP2 inhibitor comprises an anti-ERAP2 antibody. In some embodiments, the ERAP2 inhibitor comprises a pseudopeptide. In some embodiments, the pseudopeptide is a phosphinic pseudopeptide. In some embodiments, the phosphinic pseudopeptide is DG002 or DG013. In some embodiments, the ERAP2 inhibitor comprises a small molecule.

HLA-class-I antibodies can be generated by numerous methodologies with different degrees of antigen/allele specificity attained and are reported to be used for *in vitro* assays. HLA-B27 antibodies can be generated by numerous methodologies. In addition, three commercially available antibodies for HLA-B27 flow cytometric screening include the monoclonal mouse anti-human ABC-m3, FD705, and GS145.2 which have been shown to each have differing levels of cross-reactivity to other HLA-B antigens/alleles (Levering et al., Cytometry B Clin. Cytom., 2003, 54, 28-38).

In some embodiments, the assay for determining whether the subject comprises an MHC-I-opathy-related and/or MHC-II-opathy-related HLA genotype and a functional ERAP2

protein, or a nucleic acid molecule encoding a functional ERAP2 protein, is a genotyping assay or sequencing assay. In some embodiments, the nucleic acid molecule encoding a functional ERAP2 protein comprises genomic DNA, mRNA, or cDNA obtained from mRNA. By comparing the nucleotide or protein sequence of the ERAP2 protein in the sample from a subject to the
5 wild type sequence for ERAP2 protein or nucleic acid molecule, or to published sequences of variant ERAP2 proteins or nucleic acid molecules having reduced or no activity, a determination can be made whether the subject comprises a functional ERAP2 protein, or a nucleic acid molecule encoding a functional ERAP2 protein. In addition, although an individual ERAP2 protein may have biological activity, the overall function of the ERAP2 protein may not be
10 functional due to reduced levels of expression. Thus, as used herein, an ERAP2 protein can be determined not to be functional because the ERAP2 protein lacks or had reduced biological activity or because the expression level is reduced.

Determining whether a subject has an MHC-I-opathy-related and/or MHC-II-opathy-related HLA genotype and/or a functional ERAP2 protein, or a nucleic acid molecule encoding a
15 functional ERAP2 protein, in a biological sample from a subject can be carried out by any of the methods described herein. In some embodiments, these methods can be carried out *in vitro*. In some embodiments, these methods can be carried out *in situ*. In some embodiments, these methods can be carried out *in vivo*. In any of these embodiments, the nucleic acid molecule can be present within a biological sample obtained from the subject.

20 The biological sample can be derived from any cell, tissue, or biological fluid from the subject. The biological sample may comprise any clinically relevant tissue, such as a bone marrow sample, a tumor biopsy, a fine needle aspirate, or a sample of bodily fluid, such as blood, gingival crevicular fluid, plasma, serum, lymph, ascitic fluid, cystic fluid, or urine. In some cases, the sample comprises a buccal swab. The biological sample used in the methods
25 disclosed herein can vary based on the assay format, nature of the detection method, and the tissues, cells, or extracts that are used as the sample. A biological sample can be processed differently depending on the assay being employed. For example, when detecting any particular nucleic acid molecule, preliminary processing designed to isolate or enrich the biological sample for the particular nucleic acid molecule can be employed. A variety of techniques may
30 be used for this purpose. Various methods to detect the presence or level of an mRNA molecule or the presence of a particular genomic DNA locus can be used.

In some embodiments, the biological sample comprises a cell or cell lysate. Such methods can further comprise, for example, obtaining a biological sample from the subject comprising genomic nucleic acid molecules or mRNA molecules, and if mRNA, optionally reverse transcribing the mRNA into cDNA. In some embodiments, the method is an *in vitro* method. In some embodiments, the assay comprises RNA sequencing (RNA-Seq). In some
5 embodiments, the assays also comprise reverse transcribing mRNA into cDNA, such as by the reverse transcriptase polymerase chain reaction (RT-PCR).

Illustrative examples of nucleic acid sequencing techniques include, but are not limited to, chain terminator (Sanger) sequencing and dye terminator sequencing. Other methods
10 involve nucleic acid hybridization methods other than sequencing, including using labeled primers or probes directed against purified DNA, amplified DNA, and fixed cell preparations (fluorescence in situ hybridization (FISH)). In some methods, a target nucleic acid molecule may be amplified prior to or simultaneous with detection. Illustrative examples of nucleic acid amplification techniques include, but are not limited to, polymerase chain reaction (PCR), ligase
15 chain reaction (LCR), strand displacement amplification (SDA), and nucleic acid sequence based amplification (NASBA). Other methods include, but are not limited to, ligase chain reaction, strand displacement amplification, and thermophilic SDA (tSDA).

Administration of any of the therapeutic agents described herein (including the ERAP2 inhibitor, and/or the HLA inhibitor) can be in a therapeutically effective amount to be
20 determined by a health care professional. Administration of any of the therapeutic agents can be repeated, for example, after one day, two days, three days, five days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, eight weeks, two months, or three months. The repeated administration can be at the same dose or at a different dose. The administration can be repeated once, twice, three times, four times, five times, six times, seven
25 times, eight times, nine times, ten times, or more. For example, according to certain dosage regimens a subject can receive therapy for a prolonged period of time such as, for example, 6 months, 1 year, or more.

Administration of any of the therapeutic agents can occur by any suitable route including, but not limited to, parenteral, intravenous, oral, subcutaneous, intra-arterial,
30 intracranial, intrathecal, intraperitoneal, topical, intranasal, intra-articular, intravitreal, intracameral, subretinal, suprachoroidal, or intramuscular.

Pharmaceutical compositions for administration are desirably sterile and substantially isotonic and manufactured under GMP conditions. Pharmaceutical compositions can be provided in unit dosage form (i.e., the dosage for a single administration). Pharmaceutical compositions can be formulated using one or more physiologically and pharmaceutically acceptable carriers, diluents, excipients or auxiliaries. The formulation depends on the route of administration chosen. The term "pharmaceutically acceptable" means that the carrier, diluent, excipient, or auxiliary is compatible with the other ingredients of the formulation and not substantially deleterious to the recipient thereof.

The terms "treat", "treating", and "treatment" and "prevent", "preventing", and "prevention" as used herein, refer to eliciting the desired biological response, such as a therapeutic and prophylactic effect, respectively. In some embodiments, a therapeutic effect comprises one or more of a decrease/reduction in an MHC-I-opathy and/or MHC-II-opathy, a decrease/reduction in the severity of an MHC-I-opathy and/or MHC-II-opathy (such as, for example, a reduction or inhibition of development of an MHC-I-opathy and/or MHC-II-opathy), a decrease/reduction in symptoms and MHC-I-opathy-related effects and/or MHC-II-opathy-related effects, delaying the onset of symptoms and MHC-I-opathy-related effects and/or MHC-II-opathy-related effects, reducing the severity of symptoms of MHC-I-opathy-related effects and/or MHC-II-opathy-related effects, reducing the severity of an acute episode, reducing the number of symptoms and MHC-I-opathy-related effects and/or MHC-II-opathy-related effects, reducing the latency of symptoms and MHC-I-opathy-related effects and/or MHC-II-opathy-related effects, an amelioration of symptoms and MHC-I-opathy-related effects and/or MHC-II-opathy-related effects, reducing secondary symptoms, reducing secondary infections, preventing relapse to an MHC-I-opathy and/or MHC-II-opathy, decreasing the number or frequency of relapse episodes, increasing latency between symptomatic episodes, increasing time to sustained progression, speeding recovery, or increasing efficacy of or decreasing resistance to alternative therapeutics, and/or an increased survival time of the subject, following administration of the agent or composition comprising the agent. A prophylactic effect may comprise a complete or partial avoidance/inhibition or a delay of an MHC-I-opathy and/or MHC-II-opathy development/progression (such as, for example, a complete or partial avoidance/inhibition or a delay), and an increased survival time of the affected subject, following administration of a therapeutic protocol. Treatment of an MHC-I-opathy and/or MHC-II-opathy encompasses the treatment of subjects already diagnosed as having any form of the

MHC-I-opathy and/or MHC-II-opathy at any clinical stage or manifestation, the delay of the onset or evolution or aggravation or deterioration of the symptoms or signs of an MHC-I-opathy and/or MHC-II-opathy, and/or preventing and/or reducing the severity of an MHC-I-opathy and/or MHC-II-opathy.

5 In some embodiments, the ERAP2 antisense nucleic acid molecules comprise or consist of any of the nucleotide sequences represented by SEQ ID NOs: 1-858. In some embodiments, the ERAP2 siRNA molecules comprise or consist of any of the nucleotide sequences (sense and antisense strands presented one after the other) represented by SEQ ID NOs: 859-2748 (e.g., the sense strand is, for example, SEQ ID NO: 859 and the corresponding antisense strand is SEQ
10 ID NO: 860; the sense strand is, for example, SEQ ID NO: 861 and the corresponding antisense strand is SEQ ID NO: 862; the sense strand is, for example, SEQ ID NO: 2747 and the corresponding antisense strand is SEQ ID NO: 2748; etc.).

 In some embodiments, the HLA-A antisense nucleic acid molecules comprise or consist of any of the nucleotide sequences represented by SEQ ID NOs: 2749-2763. In some
15 embodiments, the HLA-A siRNA molecules comprise or consist of any of the nucleotide sequences (sense and antisense strands presented one after the other) represented by SEQ ID NOs: 2764-2777 (e.g., the sense strand is, for example, SEQ ID NO: 2764 and the corresponding antisense strand is SEQ ID NO: 2765; the sense strand is, for example, SEQ ID NO: 2766 and the corresponding antisense strand is SEQ ID NO: 2767; the sense strand is, for example, SEQ ID
20 NO: 2776 and the corresponding antisense strand is SEQ ID NO: 2777; etc.).

 In some embodiments, the HLA-B antisense nucleic acid molecules comprise or consist of any of the nucleotide sequences represented by SEQ ID NO: 2778 and SEQ ID NO: 2779. In some embodiments, the HLA-B siRNA molecules comprise or consist of any of the nucleotide sequences (sense and antisense strands presented one after the other) represented by SEQ ID
25 NOs: 2780-2783 (e.g., the sense strand is, for example, SEQ ID NO: 2780 and the corresponding antisense strand is SEQ ID NO: 2781; the sense strand is, for example, SEQ ID NO: 2783 and the corresponding antisense strand is SEQ ID NO: 2783).

 In some embodiments, the HLA-C antisense nucleic acid molecules comprise or consist of any of the nucleotide sequences represented by SEQ ID NO: 2784 and SEQ ID NO: 2785. In
30 some embodiments, the HLA-C siRNA molecules comprise or consist of any of the nucleotide sequences (sense and antisense strands presented one after the other) represented by SEQ ID NO: 2786 and SEQ ID NO: 2787.

In some embodiments, the B27 antisense nucleic acid molecules comprise or consist of any of the nucleotide sequences represented by SEQ ID NOs: 2788-3132. In some embodiments, the B27 siRNA molecules comprise or consist of any of the nucleotide sequences (sense and antisense strands presented one after the other) represented by SEQ ID NOs: 3133-3870 (e.g., the sense strand is, for example, SEQ ID NO: 3133 and the corresponding antisense strand is SEQ ID NO: 3134; the sense strand is, for example, SEQ ID NO: 3135 and the corresponding antisense strand is SEQ ID NO: 3136; the sense strand is, for example, SEQ ID NO: 3869 and the corresponding antisense strand is SEQ ID NO: 3870; etc.).

In some embodiments, the A29 antisense nucleic acid molecules comprise or consist of any of the nucleotide sequences represented by SEQ ID NOs: 3871-4145. In some embodiments, the A29 siRNA molecules comprise or consist of any of the nucleotide sequences (sense and antisense strands presented one after the other) represented by SEQ ID NOs: 4146-4755 (e.g., the sense strand is, for example, SEQ ID NO: 4146 and the corresponding antisense strand is SEQ ID NO: 4147; the sense strand is, for example, SEQ ID NO: 4148 and the corresponding antisense strand is SEQ ID NO: 4149; the sense strand is, for example, SEQ ID NO: 4754 and the corresponding antisense strand is SEQ ID NO: 4755; etc.).

The inhibitory nucleic acid molecules disclosed herein can comprise RNA, DNA, or both RNA and DNA. The inhibitory nucleic acid molecules can also be linked or fused to a heterologous nucleic acid sequence, such as in a vector, or a heterologous label. For example, the inhibitory nucleic acid molecules disclosed herein can be within a vector or as an exogenous donor sequence comprising the inhibitory nucleic acid molecule and a heterologous nucleic acid sequence. The inhibitory nucleic acid molecules can also be linked or fused to a heterologous label. The label can be directly detectable (such as, for example, fluorophore) or indirectly detectable (such as, for example, hapten, enzyme, or fluorophore quencher). Such labels can be detectable by spectroscopic, photochemical, biochemical, immunochemical, or chemical means. Such labels include, for example, radiolabels, pigments, dyes, chromogens, spin labels, and fluorescent labels. The label can also be, for example, a chemiluminescent substance; a metal-containing substance; or an enzyme, where there occurs an enzyme-dependent secondary generation of signal. The term "label" can also refer to a "tag" or hapten that can bind selectively to a conjugated molecule such that the conjugated molecule, when added subsequently along with a substrate, is used to generate a detectable signal. For example, biotin can be used as a tag along with an avidin or streptavidin conjugate of horseradish

peroxidase (HRP) to bind to the tag, and examined using a calorimetric substrate (such as, for example, tetramethylbenzidine (TMB)) or a fluorogenic substrate to detect the presence of HRP. Exemplary labels that can be used as tags to facilitate purification include, but are not limited to, myc, HA, FLAG or 3XFLAG, 6XHis or polyhistidine, glutathione-S-transferase (GST),
5 maltose binding protein, an epitope tag, or the Fc portion of immunoglobulin. Numerous labels include, for example, particles, fluorophores, haptens, enzymes and their calorimetric, fluorogenic and chemiluminescent substrates and other labels.

The disclosed inhibitory nucleic acid molecules can comprise, for example, nucleotides or non-natural or modified nucleotides, such as nucleotide analogs or nucleotide substitutes.

10 Such nucleotides include a nucleotide that contains a modified base, sugar, or phosphate group, or that incorporates a non-natural moiety in its structure. Examples of non-natural nucleotides include, but are not limited to, dideoxynucleotides, biotinylated, aminated, deaminated, alkylated, benzylated, and fluorophore-labeled nucleotides.

The inhibitory nucleic acid molecules disclosed herein can also comprise one or more
15 nucleotide analogs or substitutions. A nucleotide analog is a nucleotide which contains a modification to either the base, sugar, or phosphate moieties. Modifications to the base moiety include, but are not limited to, natural and synthetic modifications of A, C, G, and T/U, as well as different purine or pyrimidine bases such as, for example, pseudouridine, uracil-5-yl, hypoxanthin-9-yl (I), and 2-aminoadenin-9-yl. Modified bases include, but are not limited to,
20 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other
25 8-substituted adenines and guanines, 5-halo (such as, for example, 5-bromo), 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, and 3-deazaadenine.

Nucleotide analogs can also include modifications of the sugar moiety. Modifications
30 to the sugar moiety include, but are not limited to, natural modifications of the ribose and deoxy ribose as well as synthetic modifications. Sugar modifications include, but are not limited to, the following modifications at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl;

O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl, and alkynyl may be substituted or unsubstituted C₁₋₁₀alkyl or C₂₋₁₀alkenyl, and C₂₋₁₀alkynyl. Exemplary 2' sugar modifications also include, but are not limited to, -O[(CH₂)_nO]_mCH₃, -O(CH₂)_nOCH₃, -O(CH₂)_nNH₂, -O(CH₂)_nCH₃, -O(CH₂)_n-ONH₂, and -O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m, independently, are from 1 to about 10. Other modifications at the 2' position include, but are not limited to, C₁₋₁₀alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. Similar modifications may also be made at other positions on the sugar, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Modified sugars can also include those that contain modifications at the bridging ring oxygen, such as CH₂ and S.

Nucleotide sugar analogs can also have sugar mimetics, such as cyclobutyl moieties in place of the pentofuranosyl sugar.

Nucleotide analogs can also be modified at the phosphate moiety. Modified phosphate moieties include, but are not limited to, those that can be modified so that the linkage between two nucleotides contains a phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl and other alkyl phosphonates including 3'-alkylene phosphonate and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates. These phosphate or modified phosphate linkage between two nucleotides can be through a 3'-5' linkage or a 2'-5' linkage, and the linkage can contain inverted polarity such as 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts, and free acid forms are also included. Nucleotide substitutes also include peptide nucleic acids (PNAs).

In some embodiments, the antisense nucleic acid molecules are gapmers, whereby the first one to seven nucleotides at the 5' and 3' ends each have 2'-methoxyethyl (2'-MOE) modifications. In some embodiments, the first five nucleotides at the 5' and 3' ends each have 2'-MOE modifications. In some embodiments, the first one to seven nucleotides at the 5' and 3' ends are RNA nucleotides. In some embodiments, the first five nucleotides at the 5' and 3' ends

are RNA nucleotides. In some embodiments, each of the backbone linkages between the nucleotides is a phosphorothioate linkage.

In some embodiments, the siRNA molecules have termini modifications. In some embodiments, the 5' end of the antisense strand is phosphorylated. In some embodiments, 5' 5'-phosphate analogs that cannot be hydrolyzed, such as 5'-(E)-vinyl-phosphonate are used.

In some embodiments, the siRNA molecules have backbone modifications. In some embodiments, the modified phosphodiester groups that link consecutive ribose nucleosides have been shown to enhance the stability and *in vivo* bioavailability of siRNAs. The non-ester groups (-OH, =O) of the phosphodiester linkage can be replaced with sulfur, boron, or acetate to give phosphorothioate, boranophosphate, and phosphonoacetate linkages. In addition, substituting the phosphodiester group with a phosphotriester can facilitate cellular uptake of siRNAs and retention on serum components by eliminating their negative charge. In some embodiments, the siRNA molecules have sugar modifications. In some embodiments, the sugars are deprotonated (reaction catalyzed by exo- and endonucleases) whereby the 2'-hydroxyl can act as a nucleophile and attack the adjacent phosphorous in the phosphodiester bond. Such alternatives include 2'-O-methyl, 2'-O-methoxyethyl, and 2'-fluoro modifications.

In some embodiments, the siRNA molecules have base modifications. In some embodiments, the bases can be substituted with modified bases such as pseudouridine, 5'-methylcytidine, N6-methyladenosine, inosine, and N7-methylguanosine.

In some embodiments, the siRNA molecules are conjugated to lipids. Lipids can be conjugated to the 5' or 3' termini of siRNA to improve their *in vivo* bioavailability by allowing them to associate with serum lipoproteins. Representative lipids include, but are not limited to, cholesterol and vitamin E, and fatty acids, such as palmitate and tocopherol.

In some embodiments, a representative siRNA has the following formula:

25 Sense: mN*mN*/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/
i2FN/*mN*/32FN/
Antisense: /52FN*/i2FN/*mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/
i2FN/mN/i2FN/mN*N*N

wherein: "N" is the base; "2F" is a 2'-F modification; "m" is a 2'-O-methyl modification, "I" is an internal base; and "*" is a phosphorothioate backbone linkage.

The present disclosure also provides vectors comprising any one or more of the inhibitory nucleic acid molecules disclosed herein. In some embodiments, the vectors comprise

any one or more of the inhibitory nucleic acid molecules disclosed herein and a heterologous nucleic acid. The vectors can be viral or nonviral vectors capable of transporting a nucleic acid molecule. In some embodiments, the vector is a plasmid or cosmid (such as, for example, a circular double-stranded DNA into which additional DNA segments can be ligated). In some
5 embodiments, the vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Expression vectors include, but are not limited to, plasmids, cosmids, retroviruses, adenoviruses, adeno-associated viruses (AAV), plant viruses such as cauliflower mosaic virus and tobacco mosaic virus, yeast artificial chromosomes (YACs), Epstein-Barr (EBV)-derived episomes, and other expression vectors known in the art.

10 The present disclosure also provides compositions comprising any one or more of the inhibitory nucleic acid molecules disclosed herein. In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the compositions comprise a carrier and/or excipient. Examples of carriers include, but are not limited to, poly(lactic acid) (PLA) microspheres, poly(D,L-lactic-co-glycolic-acid) (PLGA) microspheres, liposomes, micelles, inverse
15 micelles, lipid cochleates, and lipid microtubules. A carrier may comprise a buffered salt solution such as PBS, HBSS, etc.

 The present disclosure also provides methods of identifying a subject having an increased risk for developing an MHC-I-opathy and/or an MHC-II-opathy. The methods comprise performing or having performed an assay on a biological sample from the subject to
20 determine whether the subject comprises: i) an MHC-I-opathy-related HLA genotype and/or an MHC-II-opathy-related HLA genotype; and ii) a functional ERAP2 protein or a nucleic acid molecule encoding a functional ERAP2 protein. When the subject has both the MHC-I-opathy-related HLA genotype and/or an MHC-II-opathy-related HLA genotype and the functional ERAP2 protein or the nucleic acid molecule encoding the functional ERAP2 protein, then the subject
25 has an increased risk of developing the MHC-I-opathy and/or an MHC-II-opathy. When the subject lacks the MHC-I-opathy-related HLA genotype and/or an MHC-II-opathy-related HLA genotype, or lacks the functional ERAP2 protein or the nucleic acid molecule encoding the functional ERAP2 protein, or lacks both, then the subject has a decreased risk of developing the MHC-I-opathy and/or an MHC-II-opathy. In some embodiments, the method further comprises
30 determining whether the subject has a single copy of the MHC-I-opathy-related HLA genotype and/or an MHC-II-opathy-related HLA genotype or two copies of the MHC-I-opathy-related HLA genotype and/or an MHC-II-opathy-related HLA genotype. When the subject comprises two

copies of the MHC-I-opathy-related HLA genotype and/or an MHC-II-opathy-related HLA genotype, then the subject has an increased risk of developing the MHC-I-opathy and/or an MHC-II-opathy compared to comprising a single copy of the MHC-I-opathy-related HLA genotype and/or an MHC-II-opathy-related HLA genotype.

5 In some embodiments, the MHC-I-opathy is BSCR. In some embodiments, the subject is HLA-Aw19⁺. In some embodiments, the subject is or is suspected of being HLA-A29⁺, HLA-A30⁺, HLA-A31⁺, or HLA-A33⁺, or any combination thereof. In some embodiments, the subject has a single copy of HLA-Aw19. In some embodiments, the subject has two copies of HLA-Aw19. In some embodiments, the subject is HLA-A29⁺/HLA-A30⁺. In some embodiments, the subject is
10 HLA-A29⁺/HLA-A31⁺. In some embodiments, the subject is HLA-A29⁺/HLA-A33⁺.

 In some embodiments, the subject having BSCR is not HLA-A29⁺.

 In some embodiments, the subject having BSCR has a copy of at least any two of HLA-A29, HLA-A30, HLA-A31, or HLA-A33. In some embodiments, the subject having BSCR has a copy of at least any three of HLA-A29, HLA-A30, HLA-A31, or HLA-A33. In some embodiments, the
15 subject having BSCR has a copy of all of HLA-A29, HLA-A30, HLA-A31, or HLA-A33.

 In some embodiments, the subject having BSCR has one copy of each HLA-A29 and HLA-A30. In some embodiments, the subject having BSCR has one copy of each HLA-A29 and HLA-A31. In some embodiments, the subject having BSCR has one copy of each HLA-A29 and HLA-A33. In some embodiments, the subject having BSCR has one copy of each HLA-A30 and
20 HLA-A31. In some embodiments, the subject having BSCR has one copy of each HLA-A30 and HLA-A33. In some embodiments, the subject having BSCR has one copy of each HLA-A31 and HLA-A33.

 In some embodiments, the subject having BSCR has one copy of HLA-A29 and two copies of HLA-A30. In some embodiments, the subject having BSCR has one copy of HLA-A29
25 and two copies of HLA-A31. In some embodiments, the subject having BSCR has one copy of HLA-A29 and two copies of HLA-A33. In some embodiments, the subject having BSCR has one copy of HLA-A30 and two copies of HLA-A31. In some embodiments, the subject having BSCR has one copy of HLA-A30 and two copies HLA-A33. In some embodiments, the subject having BSCR has one copy of HLA-A31 and two copies of HLA-A33.

30 In some embodiments, the subject having BSCR has two copies of HLA-A29 and one copy of HLA-A30. In some embodiments, the subject having BSCR has two copies of HLA-A29 and one copy of HLA-A31. In some embodiments, the subject having BSCR has two copies of

HLA-A29 and one copy of HLA-A33. In some embodiments, the subject having BSCR has two copies of HLA-A30 and one copy of HLA-A31. In some embodiments, the subject having BSCR has two copies of HLA-A30 and one copy of HLA-A33. In some embodiments, the subject having BSCR has two copies of HLA-A31 and one copy of HLA-A33.

5 In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A29 and two copies of HLA-A30. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A29 and two copies of HLA-A31. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A29 and two copies of HLA-A33. In some embodiments, the subject having BSCR or suspected of
10 having BSCR has two copies of HLA-A30 and two copies of HLA-A31. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A30 and two copies of HLA-A33. In some embodiments, the subject having BSCR or suspected of having BSCR has two copies of HLA-A31 and two copies of HLA-A33.

In some embodiments, the method further comprises administering to the subject an
15 HLA-Aw19 inhibitor. In some embodiments, the HLA-Aw19 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-A29 antibody. In some embodiments, the HLA-Aw19 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that
20 hybridizes to an HLA-Aw19. In some embodiments, the HLA-Aw19 is HLA-A29.

In some embodiments, the MHC-I-opathy is AS. In some embodiments, the subject is or is suspected of being HLA-B27⁺ or HLA-B40⁺. In some embodiments, the subject has a single copy of HLA-B27 or HLA-B40. In some embodiments, the subject has two copies of HLA-B27 or HLA-B40. In some embodiments, the method further comprises administering to the subject an
25 HLA-B27 inhibitor or an HLA-B40 inhibitor. In some embodiments, the HLA-B27 inhibitor or HLA-B40 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody or an anti-HLA-B40 antibody. In some embodiments, the HLA-B27 inhibitor or HLA-B40 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense
30 nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27 or HLA-B40.

In some embodiments, the MHC-I-opathy is psoriasis in combination with uveitis. In some embodiments, the uveitis is anterior uveitis. In some embodiments, the subject is or is

suspected of being HLA-B27⁺. In some embodiments, the subject has a single copy of HLA-B27. In some embodiments, the subject has two copies of HLA-B27. In some embodiments, the method further comprises administering to the subject an HLA-B27 inhibitor. In some embodiments, the HLA-B27 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody. In some embodiments, the HLA-B27 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27.

In some embodiments, the MHC-I-opathy is JIA. In some embodiments, the subject is or is suspected of being HLA-B27⁺ and/or DRB1⁺. In some embodiments, the subject has a single copy of HLA-B27 and/or DRB1. In some embodiments, the subject has two copies of HLA-B27 and/or DRB1. In some embodiments, the method further comprises administering to the subject an HLA-B27 inhibitor and/or a DRB1 inhibitor. In some embodiments, the HLA-B27 inhibitor and/or DRB1 inhibitor comprises an antibody. In some embodiments, the antibody comprises an anti-HLA-B27 antibody or an anti-DRB1 antibody. In some embodiments, the HLA-B27 inhibitor and/or DRB1 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to an HLA-B27 and/or an DRB1.

In any of the embodiments described herein, the methods can further comprise administering to the subject having an increased risk of developing the MHC-I-opathy-related HLA genotype and/or an MHC-II-opathy an ERAP2 inhibitor. In some embodiments, the ERAP2 inhibitor comprises a small molecule degrader, a proteolysis-targeting chimera, an immunomodulatory drug, or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or an shRNA that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an siRNA that hybridizes to ERAP2 mRNA. In some embodiments, the inhibitory nucleic acid molecule comprises an shRNA that hybridizes to ERAP2 mRNA. In some embodiments, the ERAP2 inhibitor comprises an anti-ERAP2 antibody. In some embodiments, the ERAP2 inhibitor comprises a pseudopeptide. In some embodiments, the pseudopeptide is a phosphinic pseudopeptide. In some embodiments,

the phosphinic pseudopeptide is DG002 or DG013. In some embodiments, the phosphinic pseudopeptide is DG002. In some embodiments, the phosphinic pseudopeptide is DG013. In some embodiments, the ERAP2 inhibitor comprises a small molecule.

In some embodiments, the assay for determining whether the subject comprises an MHC-I-opathy-related and/or MHC-II-opathy-related HLA genotype and a functional ERAP2 protein, or a nucleic acid molecule encoding a functional ERAP2 protein, is a genotyping assay or sequencing assay. In some embodiments, the nucleic acid molecule encoding a functional ERAP2 protein comprises genomic DNA, mRNA, or cDNA obtained from mRNA. By comparing the nucleotide or protein sequence of the ERAP2 protein in the sample from a subject to the wild type sequence for ERAP2 protein or nucleic acid molecule, or to published sequences of variant ERAP2 proteins or nucleic acid molecules having reduced or no activity, a determination can be made whether the subject comprises a functional ERAP2 protein, or a nucleic acid molecule encoding a functional ERAP2 protein. In addition, although an individual ERAP2 protein may have biological activity, the overall function of the ERAP2 protein may not be functional due to reduced levels of expression. Thus, as used herein, an ERAP2 protein can be determined not to be functional because the ERAP2 protein lacks or had reduced biological activity or because the expression level is reduced.

Determining whether a subject has an MHC-I-opathy-related and/or MHC-II-opathy-related HLA genotype and/or a functional ERAP2 protein, or a nucleic acid molecule encoding a functional ERAP2 protein, in a biological sample from a subject can be carried out by any of the methods described herein. In some embodiments, these methods can be carried out *in vitro*. In some embodiments, these methods can be carried out *in situ*. In some embodiments, these methods can be carried out *in vivo*. In any of these embodiments, the nucleic acid molecule can be present within a biological sample obtained from the subject.

The biological sample can be derived from any cell, tissue, or biological fluid from the subject. The biological sample may comprise any clinically relevant tissue, such as a bone marrow sample, a tumor biopsy, a fine needle aspirate, or a sample of bodily fluid, such as blood, gingival crevicular fluid, plasma, serum, lymph, ascitic fluid, cystic fluid, or urine. In some cases, the sample comprises a buccal swab. The biological sample used in the methods disclosed herein can vary based on the assay format, nature of the detection method, and the tissues, cells, or extracts that are used as the sample. A biological sample can be processed differently depending on the assay being employed. For example, when detecting any particular

nucleic acid molecule, preliminary processing designed to isolate or enrich the biological sample for the particular nucleic acid molecule can be employed. A variety of techniques may be used for this purpose. Various methods to detect the presence or level of an mRNA molecule or the presence of a particular genomic DNA locus can be used.

5 In some embodiments, the biological sample comprises a cell or cell lysate. Such methods can further comprise, for example, obtaining a biological sample from the subject comprising genomic nucleic acid molecules or mRNA molecules, and if mRNA, optionally reverse transcribing the mRNA into cDNA. In some embodiments, the method is an *in vitro* method. In some embodiments, the assay comprises RNA sequencing (RNA-Seq). In some
10 embodiments, the assays also comprise reverse transcribing mRNA into cDNA, such as by the reverse transcriptase polymerase chain reaction (RT-PCR).

 Detecting the presence or absence of any particular HLA allele can be carried out by numerous techniques. Detection of HLA-A alleles on a 2-digit and 4-digit resolution can be carried out. For example, an assay that targets the HLA region in high resolution (all class-I and
15 class-II genes) can be used. In some embodiments, the assay amplifies the full HLA gene (in this case HLA-A) from the 5'UTR to the 3'UTR and provides genetic variants across the full amplicon (the DNA that is the product of this amplification of the gene). A method can then be used to call the HLA-A alleles with high accuracy (e.g., PHLAT2; Bai et al., Methods Mol. Biol., 2018, 1802, 193-201). The output of PHLAT2 provides the HLA-A 4-digits allele data for each sample,
20 which can be used for the analysis that identified other Aw19 alleles as enriched in Birdshot cases. In addition, commercial sources of HLA typing are available.

 Detecting the presence or absence a functional ERAP2 protein, or a nucleic acid molecule encoding a functional ERAP2 protein, can be carried out by numerous techniques. For example, detection of presence or absence of ERAP2 protein and the relevant nucleotide
25 sequence can be carried out as described in Andres et al., PLoS Genetics, 2010, 6, 1-13. For example, a subject having an ERAP2 intronic variant designated rs2248374-A has a functional ERAP2 protein, or a nucleic acid molecule encoding a functional ERAP2 protein, and has an increased risk of developing the MHC-I-opathy. A subject having an ERAP2 variant designated rs10044354, HapA has a functional ERAP2 protein, or a nucleic acid molecule encoding a
30 functional ERAP2 protein, and has an increased risk of developing the MHC-I-opathy. A subject having an ERAP2 splice variant designated rs2248374-G does not have a functional ERAP2

protein, or a nucleic acid molecule encoding a functional ERAP2 protein, and has a decreased risk of developing the MHC-I-opathy.

Representative embodiments of the present disclosure include but are not limited to the following.

5 The present disclosure provides methods of treating a subject having an immune disorder, the methods comprising administering to the subject an ERAP2 inhibitor and: i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor. In some embodiments, the immune disorder is an MHC-I-opathy.

10 The present disclosure also provides methods of treating a subject having an MHC-I-opathy, the methods comprising: performing or having performed an assay on a biological sample from the subject to determine whether the subject comprises: i) an HLA-A29 allele and/or an HLA-B27 allele; and ii) a functional ERAP2 protein or a nucleic acid molecule encoding a functional ERAP2 protein; and administering to the subject a therapeutically effective amount of an ERAP2 inhibitor and an HLA-A29 inhibitor to the subject having the functional ERAP2
15 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-A29 allele; or administering to the subject a therapeutically effective amount of an ERAP2 inhibitor and an HLA-B27 inhibitor to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-B27 allele; wherein the presence of both: i) the HLA-A29 allele and/or the HLA-B27 allele, and ii) the
20 functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.

25 The present disclosure also provides a combination of an ERAP2 inhibitor and an HLA-A29 inhibitor for use in the treatment of an immune disorder. The present disclosure also provides a combination of an ERAP2 inhibitor and an HLA-A29 inhibitor for use in the
30 preparation of a medicament for treating an immune disorder. In some embodiments, the immune disorder is an MHC-I-opathy.

 In some embodiments, the MHC-I-opathy is BSCR, and the method comprises administering the ERAP2 inhibitor and the HLA-A29 inhibitor to the subject. In some embodiments, the methods further comprise detecting the presence or absence of an HLA-A29
30 allele in a biological sample obtained from the subject. In some embodiments, the methods further comprise determining whether the subject has one or two copies of an HLA-A29 allele. In some embodiments, the HLA-29 inhibitor comprises an antibody. In some embodiments, the

HLA-A29 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or a short hairpin RNA that hybridizes to an HLA-A29. In some embodiments, the antisense nucleic acid molecule comprises a nucleotide sequence selected
5 from the group consisting of SEQ ID NOs: 3871-4145. In some embodiments, the siRNA molecule comprises a sense strand and a corresponding antisense strand selected from the group consisting of SEQ ID NOs: 4146-4755.

In some embodiments, the MHC-I-opathy is AS, and the methods comprise administering the ERAP2 inhibitor and the HLA-B27 inhibitor to the subject. In some
10 embodiments, the methods further comprise detecting the presence or absence of an HLA-B27 allele in a biological sample obtained from the subject. In some embodiments, the methods further comprise determining whether the subject has one or two copies of an HLA-B27 allele. In some embodiments, the HLA-B27 inhibitor comprises an antibody. In some embodiments, the HLA-B27 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid
15 molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, an siRNA, or a short hairpin RNA that hybridizes to an HLA-B27. In some embodiments, the antisense nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 2788-3132. In some embodiments, the siRNA molecule comprises a sense strand and a corresponding antisense strand selected from the
20 group consisting of SEQ ID NOs: 3133-3870.

In some embodiments, the MHC-I-opathy is psoriasis and the subject also has uveitis, and the methods comprise administering the ERAP2 inhibitor and the HLA-B27 inhibitor to the subject. In some embodiments, the uveitis is anterior uveitis. In some embodiments, the methods further comprise detecting the presence or absence of an HLA-B27 allele in a
25 biological sample obtained from the subject. In some embodiments, the methods further comprise determining whether the subject has one or two copies of an HLA-B27 allele. In some embodiments, the HLA-B27 inhibitor comprises an antibody. In some embodiments, the HLA-B27 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense nucleic acid
30 molecule, an siRNA, or a short hairpin RNA that hybridizes to an HLA-B27. In some embodiments, the antisense nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 2788-3132. In some embodiments, the siRNA

molecule comprises a sense strand and a corresponding antisense strand selected from the group consisting of SEQ ID NOs: 3133-3870.

In some embodiments, the MHC-Iopathy is JIA, and the methods comprise administering the ERAP2 inhibitor and the HLA-B27 inhibitor to the subject. In some
5 embodiments, the methods further comprise detecting the presence or absence of an HLA-B27
allele in a biological sample obtained from the subject. In some embodiments, the methods
further comprise determining whether the subject has one or two copies of an HLA-B27 allele.
In some embodiments, the HLA-B27 inhibitor comprises an antibody. In some embodiments,
the HLA-B27 inhibitor comprises a small molecule degrader or an inhibitory nucleic acid
10 molecule. In some embodiments, the inhibitory nucleic acid molecule comprises an antisense
nucleic acid molecule, an siRNA, or a short hairpin RNA that hybridizes to an HLA-B27. In some
embodiments, the antisense nucleic acid molecule comprises a nucleotide sequence selected
from the group consisting of SEQ ID NOs: 2788-3132. In some embodiments, the siRNA
molecule comprises a sense strand and a corresponding antisense strand selected from the
15 group consisting of SEQ ID NOs: 3133-3870.

In some embodiments, the ERAP2 inhibitor comprises a small molecule degrader or an
inhibitory nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule
comprises an antisense nucleic acid molecule, an siRNA, or a short hairpin RNA that hybridizes
to ERAP2 mRNA. In some embodiments, the antisense nucleic acid molecule comprises a
20 nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-858. In some
embodiments, the siRNA molecule comprises a sense strand and a corresponding antisense
strand selected from the group consisting of SEQ ID NOs: 859-2748. In some embodiments, the
ERAP2 inhibitor comprises an anti-ERAP2 antibody. In some embodiments, the ERAP2 inhibitor
comprises a pseudopeptide. In some embodiments, the pseudopeptide is a phosphinic
25 pseudopeptide. In some embodiments, the phosphinic pseudopeptide is DG002 or DG013. In
some embodiments, the ERAP2 inhibitor comprises a small molecule.

The present disclosure also provides pharmaceutical compositions comprising one or
more ERAP2 inhibitors in combination with one or more HLA-A29 inhibitors. The present
disclosure also provides pharmaceutical compositions comprising one or more ERAP2 inhibitors
30 in combination with one or more HLA-B27 inhibitors. The present disclosure also provides
pharmaceutical compositions comprising one or more ERAP2 inhibitors in combination with
one or more HLA-A29 inhibitors and one or more HLA-B27 inhibitors.

In order that the subject matter disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the claimed subject matter in any manner. Throughout these examples, molecular cloning reactions, and other standard
5 recombinant DNA techniques, were carried out according to methods described in Maniatis et al., *Molecular Cloning - A Laboratory Manual*, 2nd ed., Cold Spring Harbor Press (1989), using commercially available reagents, except where otherwise noted.

Examples

10 **Example 1: Methods**

Study subjects and samples

The genomic DNA samples from 286 patients with BSCR and 108 unrelated healthy local French volunteers that exhibited HLA tissue typing common in the French population were included in this study. The patients were recruited at Hôpital Cochin, Paris, France. All patients
15 met the criteria for diagnosis of BSCR as defined both by an international consensus conference held in 2002 and by the Standardization of Uveitis Nomenclature (SUN) Working Group. In brief, all patients had a posterior bilateral uveitis with multifocal cream-colored or yellow-orange, oval or round choroidal lesions ("birdshot spots"). Although the presence of the HLA-A29 allele was not a requirement for the diagnosis of BSCR according to the international criteria, all
20 patients included in the current study carried the HLA-A29 allele. The control DNA samples were collected from volunteer donors recruited by the hematopoietic stem cell donor center of Rheims for France Greffe de Moelle Registry, and local control healthy individuals of the Registry. The DNA samples were isolated from peripheral blood samples using a standard salting out method or QIAamp Blood Kit (Qiagen, Chatsworth, CA, USA). Quality and quantity of
25 DNA was determined by UV spectrophotometry and the concentration was adjusted to 100 ng/ml. Signed informed consent documentation was obtained from all participants, and all research adhered to the tenets set forth in the Declaration of Helsinki. All study-related data acquisitions were approved by the Paris Cochin institutional review board.

Genetic data

30 A comprehensive approach was taken to both sequence the exomes and genotype all samples, to allow for identification of common and rare variants filtered based on high quality calls. DNA from participants was genotyped on the Illumina Global Screening Array (GSA) and

imputed to the HRC reference panel. Prior to imputation, the variants that had a MAF $\geq 0.1\%$, missingness $< 1\%$ and HWE p-value $> 10^{-15}$ were retained. Imputation using the HRC reference panel yielded 8,385,561 variants with imputation INFO >0.3 and MAF $>0.5\%$.

Exome sequencing was performed to a mean depth of 31X, followed by variant calling
5 and quality control as reported previously (Van Hout et al., Nature, 2020, 586, 749-756),
resulting in 238,942 variants. When integrated, this produced an overall dataset with 8,459,907
variants: 65.5% common (MAF $> 5\%$), 34.5% low-frequency ($0.5\% < \text{MAF} < 5\%$) and 0.01% rare
(MAF $< 0.5\%$).

HLA genotyping

10 HLA Class I genes (HLA-A, -B, and -C) were amplified in a multiplex PCR reaction with
primers encompassing the full genomic loci for each target. The resulting amplicons were
enzymatically fragmented to an average size of 250 base pairs and prepared for Illumina
sequencing (New England Biolabs, Ipswich, MA). The libraries were sequenced on the Illumina
HiSeq 2500 platform on a rapid run flow cell using paired-end 125 base pair reads with dual 10
15 base pair indexes. Upon completion of sequencing, raw data from each Illumina HiSeq run was
gathered in local buffer storage and uploaded to the DNAnexus platform (Reid et al., BMC
Bioinformatics, 2014, 15, 30) for automated analysis. The FASTQ-formatted reads were
converted from the BCL files and assigned to samples identified by specific barcodes using the
bcl2fastq conversion software (Illumina Inc., San Diego, CA). All the reads in sample-specific
20 FASTQ files were subject to HLA typing analysis using an updated version of PHLAT program (Bai
et al., BMC Genomics, 2014, 15, 325) with the reference sequences consisting of GRCh38
genomic sequences and HLA type reference sequences in the IPD-IMGT/HLA database v3.30.0
(Robinson et al., Hum. Immunol., 2016, 77, 233-237).

In addition, HLA allele imputation was performed following SNP2HLA (Jia et al., PLoS
25 One, 2013, 8, e64683) with the T1DGC HLA allele reference panel (Rich et al., Ann. N.Y. Acad.
Sci., 2006, 1079, 1-8). HRC-imputed genotypes in the extended Major Histocompatibility
Complex (MHC) region (chr6:25-35Mb) were filtered for high INFO score (>0.9) and certainty
(maximum GP >0.8 for all genotyped), in order to increase overlap with the T1DGC reference
panel, were re-phased along with chromosome 6 array genotypes using SHAPEIT4 (Delaneau et
30 al., Nat. Commun., 2019, 10, 5436), and were imputed using Minimac4 (Das et al., Nat. Genet.,
2016, 48, 1284-1287). HLA allele imputation quality was assessed by examining INFO score vs
MAF, and imputed vs reference panel MAF.

Genetic association analyses

Association analyses in each study were performed using the genome-wide Firth logistic regression test implemented in SAIGE (Mbatchou et al., bioRxiv, 2020, 2020.2006.2019.162354, doi:10.1101/2020.06.19.162354; and Zhou et al., Nat. Genet., 2018, 50, 1335-1341). In this implementation, Firth's approach is applied when the p-value from standard logistic regression score test is below 0.05. The directly genotyped variants with a minor allele frequency (MAF) >1%, <10% missingness, Hardy-Weinberg equilibrium test P -value > 10^{-15} and linkage-disequilibrium (LD) pruning (1000 variant windows, 100 variant sliding windows and $r^2 < 0.1$) were included for GRM for SAIGE. The association model included as

10 covariates sex and the first 10 ancestry-informative principal components (PCs) derived from the GRM dataset. Haplotype analyses were performed using PLINK 1.0 (Purcell et al., Am. J. Hum. Genet., 2007, 81, 559-575) *--chap* and *--hap-assoc* and *--hap-logistic*, and in R. High haplotype imputation and phasing quality was indicated by PLINK *--hap-phase* maximum likelihood haplotype genotypes' posterior probabilities all equal to one.

15 *HLA-A allele association analyses*

Association of HLA-A alleles was performed as follows: for each sample, both HLA-A alleles were typed as described above. Following HLA allele typing, related samples were removed. For the remaining cohort of 282 cases and 106 controls, one HLA-A allele that is not A29 (the "second" allele) was obtained next. Samples carrying two copies of A29, were

20 considered having A29 as the second allele. The cohort was then subjected to a Fisher's exact test, which tested the association of each allele that was identified in three or more BSCR cases, with the case-control status. To answer the question of whether the A19 allele group is also associated with the case-control status, the samples were combined, and tested together in two different ways: carrying all Aw19 alleles (A29, A30, A31, A32 and A33). Since A32 is

25 biologically different than the other Aw19 alleles in its peptide binding domain, a group that is made of samples carrying all Aw19 alleles excluding A32 was also constructed and tested. The final odds-ratios and p-values are presented in the table in Figure 1.

Example 2: HLA-Aw19 Broad Antigen Serotype Alleles and BSCR Risk

30 The HLA-A29-controlled cohort allowed for examination of the HLA region while controlling for the strong association of HLA-A29 with BSCR, and therefore to detect possible additional association signals in the HLA region.

First, it was asked whether rare variants on the HLA-A29 background were enriched in BSCR cases. No significant enrichments of rare single or aggregated variants were identified either within or outside the MHC region.

Second, the question was whether other HLA-A alleles in addition to the HLA-A29 allele increased BSCR risk. An assay to type HLA-A alleles in this cohort (see Methods) was constructed, and tested the second HLA-A allele (other than the known first HLA-A29) was tested for association with BSCR. Additional HLA-A alleles were found to be associated with BSCR, and those with the largest effects belonged to the same HLA-Aw19 broad antigen serotype group: HLA-A29:02, A30:02, A31:01 and A33:01 (Figure 1). As a group, HLA-Aw19 alleles were significantly enriched in the second allele of BSCR patients (OR=4.44, $p=2.2e-03$, Figure 2, blue bars). This result suggests, for example, that individuals carrying two copies of HLA-A29 would be at a greater risk of developing BSCR compared to those carrying one copy. It also suggests that other Aw19 allele may play a role in BSCR co-susceptibility or pathogenesis in concert with A29. The sole exception within the HLA-Aw19 serotype group is HLA-A32, which has been reported not to share the defining Aw19 binding domain (McKenzie et al., *Genes Immun.*, 1999, 1, 120-129); HLA-A32 appears to be depleted in BSCR cases and thus protective against BSCR (OR=0.28, $p=0.1$).

The above results presented two issues due to the small numbers of controls in UParis ($n=108$): 1) The frequency of alleles might not represent the frequency of HLA-A alleles in general EUR population. 2) While the high ORs replicate in several HLA-Aw19 alleles, the numbers are not sufficient to support significant associations. To tackle these concerns, the frequency of HLA-A alleles in three other large European (EUR) ancestry control populations, two cohorts from the Geisinger Health System (GHS cohort #1, $n=77,198$ and GHS cohort #2, $n=59,072$) and the UK Biobank (UKB, $n=463,315$) were examined. In all three datasets, the EUR samples carrying at least one HLA-A29 allele were selected, matching the BSCR cohort: 4,014 A29 carriers from GHS cohort #1 (5.2% of all EUR subjects), 2,829 A29 carriers from GHS cohort #2 (4.8% of all EUR), and 38,543 A29 carriers from UKB (8.3% of all EUR). The frequencies of the second HLA-A alleles in these cohorts were compared to those observed in the BSCR cohort (Figure 2, Figure 1). The results support the enrichment of four of the five HLA-Aw19 alleles in BSCR cases, with highest increased risk for HLA-A30:02 (GHS cohort #1 OR=4.31, GHS cohort #2 OR=6.6, UKB OR= 4.6) and HLA-A33 (GHS cohort #1 OR=3.4, GHS cohort #2 OR=2.8, UKB OR= 4.9). When combining samples carrying the four co-susceptibility alleles A29, A30, A31 and A33,

was found a highly significant enrichment in BSCR cases was found a when compared with the larger control cohorts (GHS cohort #1 p-val= 1.29E-06, GHS cohort #2 p-val= 1.07E-06, UKB p-val= 9.62E-07, Figure 1 top row). This analysis excludes A32 because of its biological difference in the sequence of the peptide binding domain as previously reported. The additional analyses with all Aw19 alleles including A32 showed that the enrichment in cases is reduced when it is included (Figure 1 bottom row).

In order to test whether these associations are affected by measurable confounders, logistic regression tests were conducted to evaluate the effects of the second HLA-A allele in HLA-A29 carriers, in UParis BSCR cases compared with each control cohort, with covariates included for sex and principal components, calculated based on genetic array data for each analytic set (Figure 3). The results were consistent with increased risk for the HLA-Aw19 co-susceptibility alleles, A29, A30, A31, and A33.

Example 3: HLA-A32 Exhibits Protection from BSCR in an HLA-A29 Positive Cohort

HLA-A32 is underrepresented in BSCR cases (3/286, ~1%) versus A29 carrier controls (4/108, 3.7%), corresponding to a nominally significant protection from risk (OR=0.28, p=0.1; Figure 1). When compared with the larger control cohorts, the trend protection is maintained with both UKB controls (3.4%, OR=0.3, p=0.02) and GHS controls (cohort #1: 3.8%, OR=0.27, p=0.01; cohort #2: 3.7%, OR=0.27, p=0.02). While nominally significant, this result does not pass the threshold of multiple test correction (p=3.57e-03) and will need to be further validated with additional case cohorts.

Example 4: ERAP2 is Independently Associated with BSCR

All variants and gene burdens were tested for association with case-control status, while controlling for sex and ten principal components, using a generalized linear mixed model (SAIGE). Due to the fact that both cases and controls were A29 allele carriers, the expected strong HLA-A signal was at least partially controlled, as evidenced by the strongest HLA p-value = 8.98E-07, compared with p=6.6e-74 with 125 cases in the previous BSCR report (Kuiper et al., Hum. Mol. Genet., 2014, 23, 6081-6087). Overall, no locus passed the genome wide significance threshold (p< 5e-8). Other than the remnant signal at HLA-A, only the *ERAP1/ERAP2-LNPEP* locus on chromosome 5 showed an association with disease at p<1e-6 (Figure 2).

The previously reported top association for BSCR at this locus tags a common variant near ERAP2/LNPEP, rs10044354. This reported risk allele is in a strong linkage disequilibrium ($D'=0.99$, $R^2=0.76$), with a strong eQTL increasing *ERAP2* expression. The results show a nominal association of rs10044354 with increased risk for Birdshot (OR (95% CI) = 1.55 (1.13 - 2.11), $p=$ 5 5.8e-3). Furthermore, no significant evidence was found for an interaction of rs10044354 with rs27432-rs2287987 haplotypes (conditional haplotype test $p=0.46$).

Next, a meta-analysis of the results with the published results from Kuiper et al. was carried out, which yielded genome-wide significant associations for ERAP2 (rs10044354, OR (95% CI)=1.95 (1.55-2.44), $p=6.2e-09$) loci with BSCR (Figure 1). Both previous and current 10 studies showed consistent directionality for ERAP2, which, separated by over 201,222 bp, show low linkage disequilibrium (LD) in the present cohort ($R^2=0.18$, $D'=0.79$).

The expression of *ERAP2* has been previously reported to be disrupted by a common splice region variant (rs2248374, AF=0.53) that causes mis-splicing of intron 10 and eventual transcript degradation via nonsense-mediated decay (Andres et al., PLoS Genet., 2010, 6, 15 e1001157; and Coulombe-Huntington et al., PLoS Genet., 2009, 5, e1000766), and which is in high LD with rs10044354 ($R^2=0.8$, $D'=1$). Thus, about 25% of the population of most ancestries (including European, AF=0.53; African, AF=0.57 and South Asian, AF=0.58) is estimated to be lacking an active ERAP2 protein. Both datasets were examined for rs2248374 associations and found that it is protective for BSCR with nominal significance in both datasets (Figure 4). 20 Furthermore, ERAP2-rs2248374 that disrupts ERAP2 expression is protective (OR 0.56; 95% CI [0.45-0.70]; $p=2.39e-07$; Figure 5). In summary, higher expression of ERAP2 protein increases risk for BSCR and a lower expression is protective.

Example 5: Cumulative Effect of HLA-Aw19 Alleles and *ERAP2* Haplotypes on BSCR Risk

25 The potential interactions between the *ERAP2* association signals and between HLA-Aw19 and *ERAP2* signals was examined by calculating the cumulative effects of HLA-Aw19, and ERAP2 genotypes on BSCR risk using the 286 cases and the 4,014 A29 carriers from the GHS cohort #1. First, an analysis of ERAP2-rs10044354 risk haplotype, the top non-MHC signal in Kuiper et al. was performed, stratified by single (A29/-) versus double (A29/AW19) Aw19 30 background, which yielded a trend of increased risk with additional ERAP2-rs10044354-T variant alleles, particularly on the double A29/AW19 background (Figure 6). The combination of

rs10044354-TT and two copies of Aw19 with 12 cases and 34 controls was found to have the highest risk (OR=9.9 [4.4-21.2], $p=1.66e-07$, Figure 7).

Example 6: Discussion

5 The sequencing of a new large BSCR patient cohort and HLA-A29 controls has confirmed the importance of the ERAP2 polymorphisms in increasing risk for developing BSCR. The association of the ERAP2 haplotype is consistent with a mechanism in which increased ERAP2 expression contribute to disease risk. Several studies have reported that ERAP2 haplotypes affect their expression as well as the resulting peptidome (Kuiper et al., Hum. Mol. Genet., 2018, 27, 4333-4343; Paladini et al., Sci. Rep., 2018, 8, 10398; and Sanz-Bravo et al., Mol. Cell Proteomics, 2018, 17, 1564-1577).

 The present study found that several other HLA-Aw19 family alleles (HLA- A29, A30, A31, A33) contribute additional risk as the second HLA-A allele, in addition to HLA-A29 risk allele. HLA-Aw19 family alleles have a similar antigen-binding sequence and therefore would
15 bind similar peptide motifs. Hence, the enrichment of Aw19 alleles in cases supports the inferred mechanism underlying activation of the immune response in BSCR: having two copies of these alleles may increase the cell-surface presentation of specific types of peptides in BSCR cases compared to HLA-A29 positive controls. Furthermore, it was found that the HLA-A32 allele within the Aw19 family is potentially protective.

20 HLA-A32 is the only HLA-Aw19 member that is found at lower rates in BSCR patients compared to controls, suggesting that it could be protective. The HLA-Aw19 serotype was initially identified by antibody binding to related family members; however, this identifies the HLA-A proteins based on structure outside of the peptide-binding groove. Serofamilies have since been re-analyzed by overall and peptide binding region sequences (McKenzie et al., Genes
25 Immun. 1999, 1, 120-129). Comparison of the sequences in the peptide binding region reveals that HLA-A32 is more distantly related than the other Aw19 alleles which are identified as novel risk factors in this present study: HLA-A29, A30, A31, A33. When examining the differences in sequence between these Aw19 alleles, two main differences are evident: at position 9, which is part of the peptide binding domain, and a stretch of amino-acids at positions 79-83 that is only
30 found in HLA-A32 and not the other Aw19 alleles (Figure 8). Theoretically, the peptide pool bound by HLA-A32 would differ from the remaining members of the Aw19 family and would not activate the same subset of responding CD8 T cells. This adds further evidence supporting

the hypothesis of the threshold requirement of an increased concentration of the driving autoantigenic peptide pool presented on high-risk HLA-A proteins as a driving component for development of BSCR uveitis.

5 Various modifications of the described subject matter, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference (including, but not limited to, journal articles, U.S. and non-U.S. patents, patent application publications, international patent application publications, gene bank accession numbers, and
10 the like) cited in the present application is incorporated herein by reference in its entirety.

What Is Claimed Is:

1. Use of an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor in the manufacture of a medicament for treating a subject having an immune disorder, wherein the medicament is to be administered with: i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor
5 to the subject.
2. The use according to claim 1, wherein the immune disorder is an MHC-I-opathy.
3. The use according to claim 2, wherein the MHC-I-opathy is Birdshot Chorioretinopathy (BSCR), and wherein the medicament and the HLA-A29 inhibitor are to be administered to the subject.
- 10 4. The use according to claim 3, wherein the presence or absence of an HLA-A29 allele has been detected in a biological sample obtained from the subject.
5. The use according to claim 3, wherein the HLA-29 inhibitor comprises an antibody, a small molecule degrader or an inhibitory nucleic acid molecule.
6. The use according to claim 5, wherein the inhibitory nucleic acid molecule comprises
15 an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA that hybridizes to an HLA-A29.
7. The use according to claim 6, wherein the antisense nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 3871-4145, or wherein the siRNA molecule comprises a sense strand and a corresponding antisense strand selected
20 from the group consisting of SEQ ID NOs: 4146-4755.
8. The use according to claim 2, wherein the MHC-I-opathy is Ankylosing Spondylitis (AS), and the medicament and the HLA-B27 inhibitor are to be administered to the subject.
9. The use according to claim 8, wherein the presence or absence of an HLA-B27 allele has been detected in a biological sample obtained from the subject.
- 25 10. The use according to claim 8, wherein the HLA-B27 inhibitor comprises an antibody, a small molecule degrader or an inhibitory nucleic acid molecule.
11. The use according to claim 10, wherein the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA that hybridizes to an HLA-B27.
- 30 12. The use according to claim 11, wherein the antisense nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 2788-3132, or

wherein the siRNA molecule comprises a sense strand and a corresponding antisense strand selected from the group consisting of SEQ ID NOs: 3133-3870.

13. The use according to claim 2, wherein the MHC-I-opathy is psoriasis and the subject also has uveitis, and wherein the medicament and the HLA-B27 inhibitor are to be administered
5 to the subject.
14. The use according to claim 13, wherein the presence or absence of an HLA-B27 allele has been detected in a biological sample obtained from the subject.
15. The use according claim 13, wherein the HLA-B27 inhibitor comprises an antibody, a small molecule degrader, or an inhibitory nucleic acid molecule.
- 10 16. The use according to claim 15, wherein the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA that hybridizes to an HLA-B27.
17. The use according to claim 16, wherein the antisense nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 2788-3132 or wherein
15 the siRNA molecule comprises a sense strand and a corresponding antisense strand selected from the group consisting of SEQ ID NOs: 3133-3870.
18. The use according to claim 2, wherein the MHC-I-opathy is Juvenile Idiopathic Arthritis (JIA), and wherein the medicament and the HLA-B27 inhibitor are to be administered to the subject.
- 20 19. The use according to claim 18, wherein the presence or absence of an HLA-B27 allele has been detected in a biological sample obtained from the subject.
20. The use according to claim 18, wherein the HLA-B27 inhibitor comprises an antibody, a small molecule degrader or an inhibitory nucleic acid molecule.
21. The use according to claim 20, wherein the inhibitory nucleic acid molecule comprises
25 an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA that hybridizes to an HLA-B27.
22. The use according to claim 21, wherein the antisense nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 2788-3132 or wherein the siRNA molecule comprises a sense strand and a corresponding antisense strand selected
30 from the group consisting of SEQ ID NOs: 3133-3870.

23. The use according to claim 1, wherein the ERAP2 inhibitor comprises a small molecule degrader, an inhibitory nucleic acid molecule, an anti-ERAP2 antibody, or a pseudopeptide.

24. The use according to claim 23, wherein the inhibitory nucleic acid molecule comprises an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA that
5 hybridizes to ERAP2 mRNA.

25. The use according to claim 24, wherein the antisense nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-858 or wherein the siRNA molecule comprises a sense strand and a corresponding antisense strand selected from the group consisting of SEQ ID NOs: 859-2748.

10 26. Use of i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor in the manufacture of a medicament for treating a subject having an immune disorder, wherein the medicament is to be administered with an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor.

27. Use of an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor and i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor in the manufacture of a medicament for treating a
15 subject having an immune disorder.

28. Use of an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor in the manufacture of a medicament for treating a subject having an MHC-I-opathy,
wherein the subject has been determined to comprise:

i) an HLA-A29 allele and/or an HLA-B27 allele; and
20 ii) a functional Endoplasmic Reticulum Aminopeptidase 2 (ERAP2)
protein or a nucleic acid molecule encoding a functional ERAP2 protein by
performing or having performed an assay on a biological sample from the subject; and

wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-A29 inhibitor are to be administered to the subject having the functional ERAP2 protein or the
25 nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-A29 allele; or

wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-B27 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-B27 allele;

wherein the presence of both: i) the HLA-A29 allele and/or the HLA-B27 allele, and ii)
30 the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein,
indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.

29. Use of i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor in the manufacture of a medicament for treating a subject having an MHC-I-opathy,

wherein the subject has been determined to comprise:

- 5 i) an HLA-A29 allele and/or an HLA-B27 allele; and
 ii) a functional Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) protein or a nucleic acid molecule encoding a functional ERAP2 protein by performing or having performed an assay on a biological sample from the subject; and

 wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-A29
10 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-A29 allele; or

 wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-B27 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-B27 allele;

15 wherein the presence of both: i) the HLA-A29 allele and/or the HLA-B27 allele, and ii) the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.

30. Use of an Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) inhibitor and i) an HLA-A29 inhibitor and/or ii) an HLA-B27 inhibitor in the manufacture of a medicament for treating a

20 subject having an MHC-I-opathy,

wherein the subject has been determined to comprise:

- i) an HLA-A29 allele and/or an HLA-B27 allele; and
 ii) a functional Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) protein or a nucleic acid molecule encoding a functional ERAP2 protein by performing or having
25 performed an assay on a biological sample from the subject; and

 wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-A29 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-A29 allele; or

 wherein a therapeutically effective amount of the ERAP2 inhibitor and an HLA-B27
30 inhibitor are to be administered to the subject having the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, and having the HLA-B27 allele;

 wherein the presence of both: i) the HLA-A29 allele and/or the HLA-B27 allele, and ii)

the functional ERAP2 protein or the nucleic acid molecule encoding a functional ERAP2 protein, indicates that the subject is a candidate for treating the MHC-I-opathy by inhibiting ERAP2.