conventionally-defined pDC population is heterogeneous, incorporating an independent pre-DC sub-population. This makes it difficult to target specific populations of cells within the heterogeneous population to treat specific diseases. In addition, there is limited understanding of the pre-DC sub-population functions, especially the role of pre-DC in eliciting and increasing immune responses. Also, there has been no development of pre-DC specific therapeutic interventions, for example, in vaccines or treatment of diseases.

[0005] There is a need to provide means for stimulating pre-DC to increase the immune response for treating or preventing certain diseases in a subject in need thereof, that overcomes, or at least ameliorates, one or more of the disadvantages described above.

[0006] There is also a need to provide molecules which are capable of effectively stimulating pre-DC to activate or increase a subject's immune response, and molecules which are capable of being effective indicators of pre-DC stimulation and activation.

[0007] There is further a need to provide an immunogenic composition for treating or preventing diseases or improving immunization by targeting pre-DC for an increased immune response.

SUMMARY

[0008] According to one example, there is provided a method of treating or preventing an infection, a neoplastic disease or an immune-related disease in a subject in need thereof, the method comprising contacting a therapeutically effective or immuno-effective amount of an TLR9 agonist with a precursor dendritic cell (pre-DC), wherein the TLR9 agonist stimulates the pre-DC to secrete one or more cytokines, to thereby activate or increase the subject's immune response for treating or preventing the infection, the neoplastic disease or the immune-related disease.

[0008a] In one aspect, the present disclosure refers to use of a ~~one or more~~ TLR9 agonist~~s~~ contacted precursor of conventional dendritic cell (cDC) in the manufacture of a medicament for treating ~~or preventing~~ an infection, or a neoplastic disease in a human in need thereof, wherein the TLR9 agonist contacted precursor of cDC has been obtained by an *ex vivo* contact of one or more TLR9 agonists ~~is to be contacted~~ with a ~~human~~ precursor of cDC~~dendritic cell (pre-DC), *ex vivo*~~, wherein the TLR9 agonist stimulates the TLR9 agonist-contacted precursor of cDC~~pre-DC~~ to secrete one or more cytokines, to thereby activate or increase the human~~subject~~'s immune response for treating ~~or preventing~~ the infection, or the neoplastic disease, ~~and~~ wherein the ~~pre-DC~~precursor of cDC is a human precursor of cDC characterized by the expression of CD45RA, CD327 and CD5, and wherein the human precursor of cDC further comprises one or more markers selected from the group consisting of CD123, CD303, CD304, ~~CD327, CD45RA,~~ CD85j, ~~CD5 and~~ BTLA, CD33, CX3CR1 and CD2.

[0009] According to one example, there is provided use of one or more TLR9 agonists in the manufacture of a medicament for treating or preventing an infection, a neoplastic disease or an immune-related disease in a subject in need thereof, wherein the TLR9 agonist stimulates pre-DC to secrete one or more cytokines to thereby activate or increase the subject's immune response for treating or preventing the infection, the neoplastic disease or the immune-related disease.

[0010] In one example, the present disclosure refers to an immunogenic composition comprising one or more TLR9 agonists capable of stimulating pre-DC to secrete one or more cytokines.

[0011] According to one example, there is provided an adjuvant composition comprising a TLR9 agonist that is capable of stimulating pre-DC to secrete one or more cytokines for increasing a subject's immune response to treat or prevent an infection, a neoplastic disease or an immune-related disease.

[0011a] In one example, the present disclosure refers to an adjuvant composition comprising a TLR9 agonist that is capable of stimulating pre-DC to secrete one or more cytokines for activating or increasing a subject's immune response to treat or prevent an infection, a neoplastic disease or an immune-related disease.

[0012] According to one example, there is provided a method of diagnosing a deficient immune system in a subject, said method comprising:
(a) obtaining a sample comprising pre-DC from the subject;
(b) contacting the sample with one or more TLR9 agonists;
(c) detecting the presence or absence of one or more cytokines in the sample; and
(d) diagnosing the subject as one having a deficient immune system when the one or more cytokines in the sample is absent (or not detected) or is present in a lower level when compared to a control sample.

[0012a] In one aspect, the present disclosure refers to an *in vitro* method of diagnosing a deficient immune system in a human~~subject~~, said method comprising:

(a) contacting a precursor of cDC~~pre-DC~~ that has been obtained from the human~~subject~~ with one or more TLR9 agonists;

(b) detecting the presence or absence of one or more cytokines selected from the group consisting of TNF-α and IL-12p40; and

(c) diagnosing the human~~subject~~ as one having a deficient immune system when the one or more cytokines is absent or not detected or is present in a lower level when compared to a control sample;

wherein the precursor of cDC is characterized by the expression of CD45RA, CD327 and CD5, and wherein the precursor of cDC further comprises one or more markers selected from the group consisting of CD123, CD303, CD304, CD85j, BTLA, CD33, CX3CR1 and CD2.

[0012b] In one aspect, the present disclosure refers to use of a~~one or more~~ TLR9 agonist~~s~~-contacted precursor of cDC in the manufacture of a medicament for diagnosing a deficient immune system in a human~~subject~~, wherein the TLR9 agonist-contacted precursor of cDC has been obtained by a contact of one or more TLR9 agonists ~~is to be contacted~~ with a ~~pre-DC~~precursor of cDC in a sample that has been obtained from the human~~subject~~, wherein the precursor of cDC is characterized by the expression of CD45RA, CD327 and CD5, wherein the precursor of cDC further comprises one or more markers selected from the group consisting of CD123, CD303, CD304, CD85j, BTLA, CD33, CX3CR1 and CD2, wherein the presence or absence of one or more cytokines selected from the group consisting of TNF-α and IL-12p40 is to be detected, and wherein the human~~subject~~ is to be diagnosed as one having a deficient immune

system when the one or more cytokines is absent or not detected or is present in a lower level when compared to a control humansubject.

[0013] According one example, there is provided a method of eliciting an immune response against an infection, a neoplastic disease or an immune-related disease in a subject in need thereof, the method comprising contacting an immuno-effective amount of an TLR9 agonist with pre-DC, wherein the TLR9 agonist stimulates the pre-DC to secrete one or more cytokines, to thereby elicit an immune response against the infection, the neoplastic disease or the immune-related disease.

[0013a] In one aspect, the present disclosure refers to an *in vitro* method of eliciting an immune response against an infection, or a neoplastic disease, the method comprising contacting an immuno-effective amount of an TLR9 agonist with a precursor of cDCpre-DC, wherein the TLR9 agonist stimulates the precursor of cDCpre-DC to secrete one or more cytokines, to thereby elicit an immune response against the infection, or the neoplastic disease, wherein the precursor of cDCpre-DC is a human precursor of cDCpre-DC characterized by the expression of CD45RA, CD327 and CD5, and wherein the precursor of cDCpre-DC further comprises one or more markers selected from the group consisting of CD123, CD303, CD304, CD327, CD45RA, CD85j, CD5 and BTLA, CD33, CX3CR1 and CD2.

[0013b] In one aspect, the present disclosure refers to use of an immune-effective amount of an TLR9 agonist-contacted precursor of cDC in the manufacture of a medicament for eliciting an immune response against an infection, or a neoplastic disease in a human in need thereof, wherein the TLR9-agonist contacted precursor of cDC has been obtained by an *ex vivo* contact of a TLR9 agonist is to be contacted with a precursor of cDChuman pre-DC *ex vivo*, wherein the TLR9 agonist stimulates the precursor of cDCpre-DC to secrete one or more cytokines, to thereby elicit an immune response against the infection, or the neoplastic disease, and wherein the precursor of cDC is a human precursor of cDC characterized by the expression of CD45RA, CD327 and CD5, and wherein the precursor of cDC furtherpre-DC comprises one or more markers selected from the group consisting of CD123, CD303, CD304, CD327, CD45RA, CD85j, CD5 and BTLA, CD33, CXCR1 and CD2.

[0014] According to one example, there is provided a kit for diagnosing a deficient immune system in a subject according to the method as described herein.

[0014a] In one example, the present disclosure refers to a kit for diagnosing a deficient immune system in a subject according to the method as described herein or the use as described herein.

DEFINITION OF TERMS

[0015] The following words and terms used herein shall have the meaning indicated:

[0016] The term “marker” refers to any biological compound, such as a protein and a fragment thereof, a peptide, a polypeptide, or other biological material whose presence, absence, level or activity is correlative of or predictive of a characteristic such as a cell type. Such specific markers may be detectable by using methods known in the art, such as but are not limited to, flow cytometry, fluorescent microscopy, immunoblotting, RNA sequencing,

CLAIMS

1. Use of a ~~one or more~~ TLR9 agonist~~s~~-contacted precursor of conventional dendritic cell (cDC) in the manufacture of a medicament for treating ~~or preventing~~ an infection, or a neoplastic disease in a human in need thereof, wherein the TLR9 agonist-contacted precursor of cDC has been obtained by an *ex vivo* contact of one or more TLR9 agonists ~~is to be contacted~~ with a ~~human~~ precursor of cDC ~~dendritic cell (pre-DC), *ex vivo*~~, wherein the TLR9 agonist stimulates the TLR9 agonist-contacted precursor of cDC~~pre-DC~~ to secrete one or more cytokines, to thereby activate or increase the human~~subject~~'s immune response for treating ~~or preventing~~ the infection, or the neoplastic disease, ~~and~~ wherein the ~~pre-DC~~precursor of cDC is a human precursor of cDC characterized by the expression of CD45RA, CD327 and CD5, and wherein the human precursor of cDC further comprises one or more markers selected from the group consisting of CD123, CD303, CD304, ~~CD327, CD45RA,~~ CD85j, ~~CD5 and~~ BTLA, CD33, CX3CR1 and CD2.

~~2. The use of claim 1, wherein the pre-DC is further characterized by the expression of any one of CD33, CX3CR1, CD2, CD5 and CD327.~~

~~3.~~2. The use of claim 1 ~~or 2~~, wherein the precursor of cDC~~pre-DC~~ is one that presents an antigen or a fragment thereof associated with the infection, or the neoplastic disease.~~;~~

~~wherein optionally the infection is selected from the group consisting of a bacterial infection and a viral infection; and~~

~~wherein optionally the pre-DC is selected from the group consisting of early pre-DC, pre-conventional dendritic cells 1 (pre-cDC1), and pre-conventional dendritic cells 2 (pre-cDC2).~~

3. The use of claim 1 or 2, wherein the infection is selected from the group consisting of a bacterial infection and a viral infection.

4. The use of any one of claims 1 to 3, wherein the precursor of cDC is selected from the group consisting of early precursor of cDC, pre-conventional dendritic cells 1 (pre-cDC1), and pre-conventional dendritic cells 2 (pre-cDC2).

~~4.~~5. The use of any one of claims 1 to ~~4~~3, wherein an antigen delivery system that specifically targets precursor of cDC~~pre-DC~~ and committed precursor of cDC~~pre-DC~~ is to be used~~, and wherein optionally the antigen delivery system comprises an antibody that specifically targets pre-DC and committed pre-DC~~.

6. The use of claim 5, wherein the antigen delivery system comprises an antibody that specifically targets precursor of cDC and committed precursor of cDC.

5.7.An *in vitro* method of diagnosing a deficient immune system in a humansubject, said method comprising:

(a)contacting a precursor of cDCpre-DC that has been obtained from the humansubject with one or more TLR9 agonists;

(b)detecting the presence or absence of one or more cytokines selected from the group consisting of TNF-α and IL-12p40; and

(c)diagnosing the humansubject as one having a deficient immune system when the one or more cytokines is absent or not detected or is present in a lower level when compared to a control sample;

wherein the precursor of cDC is characterized by the expression of CD45RA, CD327 and CD5, and wherein the precursor of cDC further comprises one or more markers selected from the group consisting of CD123, CD303, CD304, CD85j, BTLA, CD33, CX3CR1 and CD2.

6.8.Use of a one or more TLR9 agonists-contacted precursor of cDC in the manufacture of a medicament for diagnosing a deficient immune system in a humansubject, wherein the TLR9 agonist-contacted precursor of cDC has been obtained by a contact of one or more TLR9 agonists is to be contacted with a pre-DCprecursor of cDC in a sample that has been obtained from the humansubject, wherein the precursor of cDC is characterized by the expression of CD45RA, CD327 and CD5, wherein the precursor of cDC further comprises one or more markers selected from the group consisting of CD123, CD303, CD304, CD85j, BTLA, CD33, CX3CR1 and CD2, wherein the presence or absence of one or more cytokines selected from the group consisting of TNF-α and IL-12p40 is to be detected, and wherein the humansubject is to be diagnosed as one having a deficient immune system when the one or more cytokines is absent or not detected or is present in a lower level when compared to a control humansubject.

7.9.The method of claim 75 or the use of claim 86, wherein the precursor of cDCpre-DC is to be further contacted with an antigen or a fragment thereof associated with an infection, or a neoplastic disease, before or at the same time as the contact of the precursor of cDCpre-DC with the one or more TLR9 agonists.

8.10. The method of claim 75, the use of claim 86, or the method or use of claim 97, wherein an antigen delivery system that specifically targets precursor of cDCpre-DC and committed precursor of cDCpre-DC is to be used, and optionally wherein the antigen delivery system comprises an antibody that specifically targets pre-DC and committed pre-DC.

11. The method or use of claim 10, wherein the antigen delivery system comprises an antibody that specifically targets precursor of cDC and committed precursor of cDC.

~~9.~~12. The method of claim ~~7~~5, the use of claim ~~8~~6, or the method or use of any one of claims 9 to 11~~7 or 8~~, wherein the human~~subject~~ diagnosed with a deficient immune system is one that is to be treated by an immunogenic composition comprising one or more TLR9 agonists capable of stimulating, to thereby increase the human~~subject~~'s immune response.

~~10.~~13. The method or use of claim 12~~9~~, wherein the immunogenic composition further comprises an antigen or a fragment thereof associated with an infection, or a neoplastic disease.

~~11.~~14. An *in vitro* method of eliciting an immune response against an infection, or a neoplastic disease, the method comprising contacting an immuno-effective amount of an TLR9 agonist with a precursor of cDC~~pre-DC~~, wherein the TLR9 agonist stimulates the precursor of cDC~~pre-DC~~ to secrete one or more cytokines, to thereby elicit an immune response against the infection, or the neoplastic disease, wherein the precursor of cDC~~pre-DC~~ is a human precursor of cDC~~pre-DC~~ characterized by the expression of CD45RA, CD327 and CD5, and wherein the precursor of cDC~~pre-DC~~ further comprises one or more markers selected from the group consisting of CD123, CD303, CD304, ~~CD327, CD45RA,~~ CD85j, ~~CD5 and~~ BTLA, CD33, CX3CR1 and CD2.

~~12.~~15. Use of an immune-effective amount of a~~n~~ TLR9 agonist-contacted precursor of cDC in the manufacture of a medicament for eliciting an immune response against an infection, or a neoplastic disease in a human in need thereof, wherein the TLR9-agonist contacted precursor of cDC has been obtained by an *ex vivo* contact of a TLR9 agonist ~~is to be contacted~~ with a precursor of cDC~~human pre-DC *ex vivo*~~, wherein the TLR9 agonist stimulates the precursor of cDC~~pre-DC~~ to secrete one or more cytokines, to thereby elicit an immune response against the infection, or the neoplastic disease, ~~and~~ wherein the precursor of cDC is a human precursor of cDC characterized by the expression of CD45RA, CD327 and CD5, and wherein the precursor of cDC further~~pre-DC~~ comprises one or more markers selected from the group consisting of CD123, CD303, CD304, ~~CD327, CD45RA,~~ CD85j, ~~CD5 and~~ BTLA, CD33, CXCR1 and CD2.

~~13.~~16. The method of claim 14~~11~~ or the use of claim 15~~12~~, wherein the precursor of cDC~~pre-DC~~ is one that presents an antigen or a fragment thereof associated with the infection, or the neoplastic disease ~~or immune related disease~~.

~~14~~17. The method or the use of claim 16~~13~~, wherein an antigen delivery system that specifically targets precursor of cDC~~pre-DC~~ and committed precursor of cDC~~pre-DC~~ is to be used~~, and wherein optionally the antigen delivery system comprises an antibody that specifically targets pre-DC and committed pre-DC~~.

18. The method or use of claim 17, wherein the antigen delivery system comprises an antibody that specifically targets precursor of cDC and committed precursor of cDC.