

CDR2 region comprises an amino acid sequence with at least 60 % sequence identity with the amino acid sequence of SEQ ID NO. 32 AISWSGGSTYYADSVKG; wherein preferably the immunoglobulin molecule is a single domain antibody.

Furthermore, such immunoglobulins comprise a CDR3 region, wherein the CDR3
5 region contributes to V γ 9V δ 2 T cell receptor binding and may have an effect on the action of the immunoglobulin molecule. This may, without being bound by theory, implicate the CDR3 sequence in the functionality of the immunoglobulin molecule, i.e. type of modulation such as blocking activation of V γ 9V δ 2 T cells, inducing activation of V γ 9V δ 2 T cells or neither blocking activation nor inducing activation of V γ 9V δ 2 T cells. The immunoglobulins of the
10 invention are in particular for use in medical treatments and for use in assays involving V γ 9V δ 2 T cells.

Preferably, the immunoglobulin molecules according to the invention comprise a CDR3 region, wherein the CDR3 region comprises an amino acid sequence selected from the group consisting of amino acid sequences SEQ ID NO. 3, 6, 9, 11, 14, 17, 20, 22, 25, 27, 29,
15 30, 33, 35, 37, 40, 43, and 46. These CDR3 regions combined with the CDR1 and CDR2 sequences provided for binding and functions, as discussed in detail below.

In another aspect, there is provided a nucleotide sequence that encodes an immunoglobulin molecule as described herein.

In yet another aspect, there is provided a host cell comprising a nucleotide sequence
20 as described herein.

In yet another aspect, there is provided a method for preparing an immunoglobulin molecule as described herein, comprising:

- culturing a host cell as described herein;
- allowing the host cell to express the immunoglobulin;
- 25 - obtaining the immunoglobulin.

In yet another aspect, there is provided an immunoglobulin molecule as described herein for use in a medical treatment.

In yet another aspect, there is provided a human V γ 9V δ 2 T cell receptor binding immunoglobulin molecule, wherein the immunoglobulin molecule is an immunoglobulin
30 molecule that blocks activation of human V γ 9V δ 2 T cells

In yet another aspect, there is provided an immunoglobulin molecule as described herein for use in a medical treatment, wherein the medical treatment preferably comprises the use of inhibitors of the mevalonate pathway or wherein the medical treatment comprises the treatment of cancer or an infectious disease.

35 In yet another aspect, there is provided an immunoglobulin molecule as described herein for blocking activation of human V γ 9V δ 2 T cells.

In yet another aspect, there is provided immunoglobulin molecule as described herein, wherein the immunoglobulin molecule is an immunoglobulin molecule that activates human V γ 9V δ 2 T cells.

In yet another aspect, there is provided an immunoglobulin molecule as described
5 herein for use in a medical treatment, wherein preferably the medical treatment is a treatment of cancer.

In yet another aspect, there is provided an immunoglobulin molecule as described herein for activating human V γ 9V δ 2 T cells.

In yet another aspect, there is provided an immunoglobulin molecule as described
10 herein,

wherein the immunoglobulin molecule is an immunoglobulin molecule that
does not block activation of human V γ 9V δ 2 T cells; and
does not activate human V γ 9V δ 2 T cells.

In yet another aspect, there is provided the use of an immunoglobulin molecule as
15 described herein for labelling or for selecting human V γ 9V δ 2 T cells.

Figures:

Figure 1: Alignment of the VHH sequences wherein the framework regions (1, 2, 3 and 4) are indicated as well as CDR1, CDR2 and CDR3. The code for each of the VHHs is
20 indicated as well (i.e. 5C7 is the sequence of VHH 5C7).

Figure 2: VHH 5E7 and VHH 6F6 do not activate V γ 9V δ 2 T cells. Data indicate relative expression of the activation marker CD25, the pro-inflammatory cytokine IFN- γ , and the cytotoxic molecule granzyme B by healthy donor-derived V γ 9V δ 2 T cells in comparison with the positive control (phosphoantigen (pAg+) expressing HeLa cells)

25 Figure 3: VHH 5E7 neutralizes phosphoantigen induced activation of healthy donor-derived V γ 9V δ 2 T cells. A representative example demonstrates the dose dependent neutralization of phosphoAg-induced V γ 9V δ 2 T cell activation using VHH 5E7 while a non-specific VHH (negative control) cannot neutralize phosphoAg-induced V γ 9V δ 2 T cell activation. Vertical axis indicates activation of V γ 9V δ 2 T cells as assessed by CD25
30 expression, horizontal axis indicates different VHH concentrations. V γ 9V δ 2 T cell stimulations were performed using phosphoantigen expressing HeLa cells, generated by pretreating HeLa cells with increasing doses of the aminobisphosphonate pamidronate (which results in increasing levels of phosphoantigen expression by HeLa cells).

Figure 4: V γ 9V δ 2 TCR specific VHH are capable of inducing activation and cytokine
35 production in healthy donor-derived V γ 9V δ 2 T cells. Data indicate relative expression of the activation marker CD25 and the pro-inflammatory cytokine IFN- γ by healthy donor-derived V γ 9V δ 2 T cells in comparison with the positive control (phosphoantigen (pAg+) expressing

8. The immunoglobulin molecule according to any one of claims 1-7, wherein the immunoglobulin molecule has an amino acid sequence selected from the group of amino acid sequences consisting of SEQ ID NO. 47-66.

5 9. A nucleotide sequence that encodes an immunoglobulin molecule according to any one of claims 1-8.

10. A host cell comprising a nucleotide sequence according to claim 9.

10 11. Method for preparing an immunoglobulin molecule according to any one of claims 1-8, comprising:
- culturing a host cell according claim 10;
- allowing the host cell to express the immunoglobulin;
- obtaining the immunoglobulin.

15 12. An immunoglobulin molecule according to any one of claims 1-8 for use in a medical treatment.

20 13. A human V γ 9V δ 2 T cell receptor binding immunoglobulin molecule, wherein the immunoglobulin molecule is an immunoglobulin molecule that blocks activation of human V γ 9V δ 2 T cells.

14. The immunoglobulin molecule according to claim 13, wherein the immunoglobulin molecule is an immunoglobulin molecule according to any one of claims 1-6.

25 15. The immunoglobulin molecule according to claim 13-14, wherein the immunoglobulin molecule comprises a CDR3 region, wherein the CDR3 region comprises an amino acid sequence selected from the group consisting of amino acid sequences SEQ ID NO. 27 and 30.

30 16. An immunoglobulin molecule according to any one of claims 13-15 for use in a medical treatment, wherein the medical treatment preferably comprises the use of inhibitors of the mevalonate pathway or wherein the medical treatment comprises the treatment of cancer or an infectious disease.

35 17. An immunoglobulin molecule according to any one of claims 13-15 for blocking activation of human V γ 9V δ 2 T cells.

18. An immunoglobulin molecule according to any one of claims 1-5, wherein the immunoglobulin molecule is an immunoglobulin molecule that activates human V γ 9V δ 2 T cells.
- 5 19. The immunoglobulin molecule according to claim 18, wherein the immunoglobulin molecule comprises a CDR3 region, wherein the CDR3 region comprises an amino acid sequence selected from the group consisting of amino acid sequences SEQ ID NO. 6, 9, 11, 14, 17, 20, 22, 25, 29, 33, 35, and 46.
- 10 20. The immunoglobulin molecule according to claim 18 or claim 19, wherein the immunoglobulin molecule is linked to an agent.
- 15 21. An immunoglobulin molecule according to any one of claims 18-20 for use in a medical treatment, wherein preferably the medical treatment is a treatment of cancer.
22. An immunoglobulin molecule according to any one of claims 18-20 for activating human V γ 9V δ 2 T cells.
- 20 23. An immunoglobulin molecule according to any one of claims 1-5, wherein the immunoglobulin molecule is an immunoglobulin molecule that does not block activation of human V γ 9V δ 2 T cells; and does not activate human V γ 9V δ 2 T cells.
- 25 24. The immunoglobulin molecule according to claim 23 wherein the immunoglobulin molecule comprises a CDR3 region wherein the CDR3 region comprises an amino acid sequence selected from the group consisting of SEQ ID NO. 3, 37, 40 and 43.
- 30 25. The immunoglobulin molecule according to claim 23 or claim 24 wherein the immunoglobulin molecule or the antigen-binding part thereof comprises a label.
26. Use of an immunoglobulin molecule according to any one of claims 23-25 for labelling or for selecting human V γ 9V δ 2 T cells.