immunized with cancer cells of a patient, where after cancer-specific B cells are harvested from the animal and used for *ex vivo* antibody production. Since such antibodies are a tailor-made medicine for the individual patient, they should be produced as fast as possible so that the patient can start his/her Ab therapy as soon as possible. Such antibodies that are specific for an individual's tumor cannot be produced beforehand.

It is one of the objects of the present invention to provide means and methods for producing improved *ex vivo* B cell cultures with a shorter doubling time.

The present invention provides the insight that B cell cultures with a shorter doubling time, as compared to the B cell cultures disclosed in WO 2007/067046, are obtained when rabbit B cells are used. Whereas commonly used B cells such as human B cells, murine B cells and llama B cells typically have a doubling time of 25-36 hours, the present inventors have surprisingly found that rabbit B cell cultures can be obtained with a doubling time of 20 hours or less. This insight allows significant faster production of antibodies of interest, resulting in a higher yield within a given time frame, which is particularly valuable for commercial antibody production and therapeutic applications.

Summary

In one aspect, the present invention refers to use of a rabbit B cell and a nucleic acid molecule encoding Bcl-6 or a rabbit homologue thereof, and an anti-apoptotic nucleic acid molecule of the Bcl-2 family, for obtaining an ex vivo B cell culture with a mean doubling time of 20 hours or less. In another aspect, the present invention refers to a method for obtaining an ex vivo B cell culture with a mean doubling time of 20 hours or less, the method comprising inducing, enhancing and/or maintaining expression of Bcl-6, or a rabbit homologue thereof, in a B cell and inducing, enhancing and/or maintaining expression of at least one anti-apoptotic nucleic acid molecule of the Bcl-2 family in said B cell, characterized in that said B cell is a rabbit B cell. In yet another aspect, the present invention refers to a method for increasing the replicative life span of a rabbit B cell, the

method comprising inducing, enhancing and/or maintaining expression of Bcl-6, or a rabbit homologue thereof, in a rabbit B-cell and inducing, enhancing and/or maintaining expression of at least one anti-apoptotic nucleic acid of the Bcl-2 family in said B-cell, characterized in that said rabbit B cell is provided with a nucleic acid molecule encoding Bcl-6, or a rabbit homologue thereof, and with at least one anti-apoptotic nucleic acid molecule of the Bcl-2 family, via transduction with a gene delivery vehicle that comprises at least the extracellular domain of a gibbon ape leukemia virus (GALV) envelope protein or a protein that has at least 70% sequence identity with at least the extracellular domain of a GALV envelope protein. In a further aspect, the present invention refers to use of at least the extracellular domain of a gibbon ape leukemia virus (GALV) envelope protein, or a protein that has at least 70% sequence identity with at least the extracellular domain of a GALV envelope protein, for introducing a nucleic acid molecule encoding Bcl-6 or a rabbit homologue thereof, and/or an anti-apoptotic nucleic acid molecule of the Bcl-2 family, into a rabbit B cell. In yet another aspect, the present invention refers to a method for obtaining antibodies, comprising inducing, enhancing and/or maintaining expression of Bcl-6, or a rabbit homologue thereof, in a rabbit B-cell; inducing, enhancing and/or maintaining expression of at least one anti-apoptotic nucleic acid molecule of the Bcl-2 family in said B-cell; culturing said B cell *ex vivo*; and harvesting antibodies produced by said B cell within 7-14 days, preferably within 9-12 days. In yet another aspect, the present invention refers to an isolated or recombinant rabbit B cell comprising:

- a non-rabbit anti-apoptotic nucleic acid molecule of the Bcl-2 family, preferably encoding Bcl-xL or Mcl-1 or Bcl-2 or A1 or Bcl-w or Bcl2L10 , and a non-rabbit nucleic acid molecule encoding Bcl-6. In a further aspect, the present invention refers to an *ex vivo* rabbit B cell culture which has a mean doubling time of 20 hours or less. In another aspect, there is provided an *ex vivo* rabbit B cell culture comprising rabbit B cells as described herein.. In one aspect, the present invention refers to use of a gene delivery vehicle comprising at least the extracellular domain of a gibbon ape leukemia virus (GALV) envelope protein, or a protein that has at least 70% sequence identity with at least the extracellular domain of a GALV envelope protein, and a nucleic acid sequence encoding Bcl-6, or a rabbit homologue

thereof, and at least one anti-apoptotic nucleic acid sequence of the Bcl-2 family, for increasing the replicative life span of a rabbit B cell.

Accordingly, the disclosure describes a use of a rabbit B cell for obtaining an *ex vivo* B cell culture with a mean doubling time of 20 hours or less. *Ex vivo* rabbit B cell cultures according to the present invention are typically obtained by expression of Bcl-6, or a rabbit homologue thereof, and an anti-apoptotic nucleic acid molecule in a rabbit B-cell. Further described is therefore a method for obtaining an *ex vivo* B cell culture with a mean doubling time of 20 hours or less, the method comprising:

- inducing, enhancing and/or maintaining expression of Bcl-6, or a rabbit homologue thereof, in a B-cell and
- inducing, enhancing and/or maintaining expression of an anti-apoptotic nucleic acid molecule in said B-cell,

characterized in that said B cell is a rabbit B cell.

Claims

1. Use of a rabbit B cell and a nucleic acid molecule encoding Bcl-6 or a rabbit homologue thereof, and an anti-apoptotic nucleic acid molecule of the Bcl-2 family, for obtaining an *ex vivo* B cell culture with a mean doubling time of 20 hours or less.

2. A method for obtaining an *ex vivo* B cell culture with a mean doubling time of 20 hours or less, the method comprising:
- inducing, enhancing and/or maintaining expression of Bcl-6, or a rabbit homologue thereof, in a B-cell and
- inducing, enhancing and/or maintaining expression of at least one anti-apoptotic nucleic acid molecule of the Bcl-2 family in said B-cell,
characterized in that said B cell is a rabbit B cell.

3. A method for increasing the replicative life span of a rabbit B cell, the method comprising:
- inducing, enhancing and/or maintaining expression of Bcl-6, or a rabbit homologue thereof, in a rabbit B-cell and
- inducing, enhancing and/or maintaining expression of at least one anti-apoptotic nucleic acid of the Bcl-2 family in said B-cell,
characterized in that said rabbit B cell is provided with a nucleic acid molecule encoding Bcl-6, or a rabbit homologue thereof, and with at least one anti-apoptotic nucleic acid molecule of the Bcl-2 family, via transduction with a gene delivery vehicle that comprises at least the extracellular domain of a gibbon ape leukemia virus (GALV) envelope protein or a protein that has at least 70% sequence identity with at least the extracellular domain of a GALV envelope protein.

4. Use of at least the extracellular domain of a gibbon ape leukemia virus (GALV) envelope protein, or a protein that has at least 70% sequence identity with at least the extracellular domain of a GALV envelope protein, for introducing a nucleic acid molecule encoding Bcl-6 or a rabbit homologue thereof, and/or an anti-apoptotic nucleic acid molecule of the Bcl-2 family, into a rabbit B cell.

5. A method for obtaining antibodies, comprising:
- inducing, enhancing and/or maintaining expression of Bcl-6, or a rabbit homologue

thereof, in a rabbit B-cell;
- inducing, enhancing and/or maintaining expression of at least one anti-apoptotic nucleic acid molecule of the Bcl-2 family in said B-cell;
- culturing said B cell *ex vivo*; and
- harvesting antibodies produced by said B cell within 7-14 days, preferably within 9-12 days.

6. A method according to any one of claims 2, 3 or 5, characterized in that said rabbit B cell is provided with:

* a nucleic acid molecule encoding a non-rabbit Bcl-6, and
* at least one non-rabbit anti-apoptotic nucleic acid molecule of the Bcl-2 family.

7. A method according to claim 6, wherein said non-rabbit nucleic acid molecule is a human nucleic acid molecule.

8. A method according to any one of claims 2-3 or 5-7, wherein said at least one anti-apoptotic nucleic acid molecule is selected from the group consisting of Bcl-xL, Mcl-1, Bcl-2, A1, Bcl-w, Bcl2L10, and rabbit homologues thereof.

9. A method according to any one of claims 2-3 or 5-8, wherein the method also comprises inducing, enhancing and/or maintaining expression of Blimp-1, or a rabbit homologue thereof, in said rabbit B-cell.

10. A method according to any one of claims 2-3 or 5-9, further comprising providing said rabbit B cell with IL21 and CD40L.

11. A method according to claim 10, wherein said IL21 is mouse or human IL21 and/or wherein said CD40L is mouse or human CD40L.

12. A method according to any one of claims 2-3 or 5-11, comprising:
- providing said rabbit B cell with a compound capable of directly or indirectly enhancing expression of Bcl-6, or expression of a rabbit homologue thereof; and/or
- culturing said rabbit B cell in the presence of a compound capable of directly or indirectly enhancing expression of Bcl-6, or expression of a rabbit homologue thereof.

13. A method according to any one of claims 2-3 or 5-12, comprising:
- providing said rabbit B cell with at least one compound capable of directly or indirectly enhancing expression of Bcl-xL and/or Mcl-1 and/or Bcl-2 and/or A1 and/or Bcl-w and/or Bcl2L10 and/or or a rabbit homologue thereof; and/or
- culturing said rabbit B cell in the presence of at least one compound capable of directly or indirectly enhancing expression of Bcl-xL and/or Mcl-1 and/or Bcl-2 and/or A1 and/or Bcl-w and/or Bcl2L10 and/or or a rabbit homologue thereof.

14. A method according to any one of claims 2-3 or 5-13, further comprising:
- providing said rabbit B cell with at least one compound capable of directly or indirectly increasing expression of Blimp-1, or expression of a rabbit homologue of Blimp-1; and/or
- culturing said rabbit B cell in the presence of at least one compound capable of directly or indirectly increasing expression of Blimp-1, or expression of a rabbit homologue of Blimp-1.

15. An isolated or recombinant rabbit B cell, which is bound via at least the extracellular domain of a GALV envelope protein, or via a protein that has at least 70% sequence identity with at least the extracellular domain of a GALV envelope protein, to a gene delivery vehicle that comprises a nucleic acid sequence encoding Bcl-6, or a rabbit homologue thereof, and/or an anti-apoptotic nucleic acid sequence of the Bcl-2 family.

16. A rabbit B cell according to claim 15, wherein said anti-apoptotic nucleic acid sequence is a nucleic acid sequence encoding a protein selected from the group consisting of Bcl-6, Bcl-xL, Mcl-1, Bcl-2, A1, Bcl-w, Bcl2L10, a rabbit homologue thereof, and any combination thereof.

17. An isolated or recombinant rabbit B cell comprising:
- a non-rabbit anti-apoptotic nucleic acid molecule of the Bcl-2 family, preferably encoding Bcl-xL or Mcl-1 or Bcl-2 or A1 or Bcl-w or Bcl2L10, and
- a non-rabbit nucleic acid molecule encoding Bcl-6.

18. A rabbit B cell according to claim 17, wherein said non-rabbit nucleic acid sequence is a human nucleic acid sequence.

19. An *ex vivo* rabbit B cell culture which has a mean doubling time of 20 hours or less.

20. An *ex vivo* rabbit B cell culture comprising rabbit B cells according to claim 17 or 18.

21. An *ex vivo* rabbit B cell culture when obtained by a method according to any one of claims 2-3 or 5-14.

22. Use of a gene delivery vehicle comprising at least the extracellular domain of a gibbon ape leukemia virus (GALV) envelope protein, or a protein that has at least 70% sequence identity with at least the extracellular domain of a GALV envelope protein, and a nucleic acid sequence encoding Bcl-6, or a rabbit homologue thereof, and at least one anti-apoptotic nucleic acid sequence of the Bcl-2 family, for increasing the replicative life span of a rabbit B cell.

23. A method according to claim 3, or a use according to claim 4, or a rabbit B cell according to claim 15, or a use according to claim 22, wherein said extracellular domain is of an envelope protein of GALV strain SEATO.

24. A method according to claim 3 or a rabbit B cell according to claim 15 or a use according to claim 22, wherein said gene delivery vehicle comprises a chimeric envelope protein as depicted in Figure 9, or a protein comprising a chimeric envelope protein as depicted in Figure 9, or a protein that has at least 70% sequence identity with a chimeric envelope protein as depicted in Figure 9.