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 expressing an exogenous nucleic acid molecule encoding Bcl-6 or a rabbit homologue thereof, and expressing an exogenous 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 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, 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 an anti-apoptotic nucleic acid sequence of the Bcl-2 family. 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

Claims

1. Use of a rabbit B cell expressing an exogenous nucleic acid molecule encoding Bcl-6 or a rabbit homologue thereof, and expressing an exogenous 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 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

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 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.