CLAIMS

1. A cell line comprising an endogenous dehydroorotate dehydrogenase (DHODH) gene which is partially or fully inactivated, wherein the cell line is chosen among Chinese Hamster Ovary (CHO) cell lines, HEK293, HKB11, PER-C6, HT1080, Jurkat, Daudi, Raji and CAP cell lines.

2. The cell line according to claim 1, which is a Chinese Hamster Ovary (CHO) cell line.

3. The cell line according to claim 1 or 2, wherein the cell line is produced by

a) inactivating the endogenous DHODH gene in a cell, and

b) culturing the cell in a culture medium comprising uridine under conditions suitable for generating a cell line in which the endogenous DHODH gene is partially or fully inactivated.

4. The cell line according to claim 3, wherein the endogenous DHODH gene is inactivated by a gene-editing method.

5. The cell line according to claim 4, wherein the endogenous DHODH gene is inactivated by the CRISPR-Cas9 method.

6. The cell line according to any one of claims 1 to 5, wherein one or more or all the alleles of the endogenous DHODH gene are partially or fully inactivated.

7. The cell line according to any one of claims 1 to 6, wherein the cell line further comprises an expression vector comprising a nucleotide sequence encoding an exogenous mammalian DHODH and at least one expression cassette for expressing recombinant protein, wherein said exogenous DHODH comprises a sequence at least 60% identical to the sequence SEQ ID NO: 2 or to the sequence SEQ ID NO: 4, and has DHODH activity.

8. An expression system comprising:

(i) the cell line according to any one of claims 1 to 6, and

(ii) an expression vector comprising a nucleotide sequence encoding a mammalian DHODH and at least one expression cassette for expressing a recombinant protein, wherein said DHODH comprises a sequence at least 60% identical to the sequence SEQ ID NO: 2 or to the sequence SEQ ID NO: 4, and wherein said DHODH has DHODH activity.

9. The cell line according to claim 7 or the expression system according to claim 8, wherein said nucleotide sequence comprises the sequence of SEQ ID NO: 1 or the sequence of SEQ ID NO: 3.

10. The cell line according to claim 7 or 9 or the expression system according to claim 8 or 9, wherein said recombinant protein is a monoclonal antibody.

11. The cell line according to any one of claims 7, 9 and 10 or the expression system according to any one of claims 8 to 10, wherein said vector comprises a first expression cassette suitable for cloning of an antibody light chain, and a second expression cassette suitable for cloning of an antibody heavy chain.

12. A kit comprising (i) the cell line according to any one of claims 7 and 9-11, or the expression system according to any one of claims 8 to 11, and (ii) a culture medium devoid of uridine, in particular further devoid of DHODH inhibitor.

13. An *in vitro* method of producing a recombinant protein comprising the steps of:

A) a1) providing a cell line according to any one of claims 7 and 9-11;

or

a2) providing a cell line according to any one of claim 1 to 6, and
a2') introducing an expression vector as defined in any one of claims 9 to 11 into the cell line provided in step a2);

or

a3) providing a cell line comprising an endogenous DHODH gene,
a3') partially or fully inactivating the endogenous DHODH gene in the cell line provided in step a3), and
a3") introducing an expression vector as defined in any one of claims 9 to 11 into the cell line comprising a partially or fully inactivated endogenous DHODH gene obtained in step a3');

B) culturing said cell line under conditions suitable for production of the recombinant protein; and

C) isolating and/or purifying said recombinant protein.

14. The method according to claim 13, wherein step B) is conducted in a culture medium devoid of uridine, in particular further devoid of DHODH inhibitor.

15. The method according to claim 13 or 14, further comprising a step D) of formulating said recombinant protein into a pharmaceutical composition.

16. Use of a cell line according to any one of claims 7 and 9-11, an expression system according to any one of claims 9-11 or a kit according to claim 12 for producing a recombinant protein.

17. The use according to claim 16, wherein the cell line, the expression system or the kit is used in combination with a culture medium devoid of uridine, in particular in the absence of DHODH inhibitor.