[0008] In certain examples, disclosed herein isa vector comprising a) a first nucleic acid encoding a first polypeptide, b) a second nucleic acid encoding a first fragment of glutamine synthetase, wherein the transcription of the first nucleic acid is operably linked to the transcription of the second nucleic acid, c) a third nucleic acid encoding a third polypeptide, the third polypeptide is capable of associating with the first polypeptide to form a heteromeric complex, and d) a fourth nucleic acid encoding a second fragment of glutamine synthetase, wherein the transcription of the third nucleic acid is operably linked to the transcription of the fourth nucleic acid, and wherein the first fragment and the second fragment of glutamine synthetase associate to provide a selectable activity, and wherein the vector is capable of being transfected into mammalian cells and improving selection of the transfected cells.

[0009] In certain examples, disclosed herein is an expression system comprising: a) a first vector comprising a first nucleic acid encoding a first polypeptide, wherein the transcription of the first nucleic acid is operably linked to the transcription of a second nucleic acid encoding a first fragment of glutamine synthetase, and b) a second vector comprising a third nucleic acid encoding a third polypeptide, wherein the transcription of the third nucleic acid is operably linked to the transcription of a fourth nucleic acid encoding a second fragment of glutamine synthetase, wherein the first polypeptide is capable of associating with the third polypeptide to form a heteromeric complex, wherein the first and second fragments of glutamine synthetase associate to provide a selectable activity, and wherein the expression system is capable of being transfected into mammalian cells and improving selection of the transfected cells.

[0009a] In one aspect, the present disclosure refers to a vector comprising a) a first nucleic acid encoding a first polypeptide, b) a second nucleic acid encoding a first fragment of glutamine synthetase fused to a first interaction domain, wherein the transcription of the first nucleic acid is operably linked to the transcription of the second nucleic acid, c) a third nucleic acid encoding a third polypeptide, the third polypeptide is capable of associating with the first polypeptide to form a heteromeric complex, and d) a fourth nucleic acid encoding a second fragment of glutamine synthetase fused to a first interaction domain, wherein the transcription of the third nucleic acid is operably linked to the transcription of the fourth nucleic acid, and wherein the first fragment and the second fragment of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position equivalent to an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ

ID NO: 1 according to sequence alignment, the first fragment and second fragment associate via the first and second interaction domains to provide a selectable activity, and wherein the vector is capable of being transfected into mammalian cells and improving selection of the transfected cells.

[0009b] In another aspect, the present disclosure refers to an expression system comprising: a) a first vector comprising a first nucleic acid encoding a first polypeptide, wherein the transcription of the first nucleic acid is operably linked to the transcription of a second nucleic acid encoding a first fragment of glutamine synthetase fused to a first interaction domain, and b) a second vector comprising a third nucleic acid encoding a third polypeptide, wherein the transcription of the third nucleic acid is operably linked to the transcription of a fourth nucleic acid encoding a second fragment of glutamine synthetase fused to a second interaction domain, wherein the first polypeptide is capable of associating with the third polypeptide to form a heteromeric complex, wherein the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ ID NO: 1 according to sequence alignment, the first fragment and second fragment associate via the first and second interaction domains to provide a selectable activity, and wherein the expression system is capable of being transfected into mammalian cells and improving selection of the cells.

[0010] In certain examples, the first fragment of glutamine synthetase is an N-terminal fragment of glutamine synthetase and the second fragment of glutamine synthetase is a C-terminal fragment of glutamine synthetase, or the first fragment of glutamine synthetase is a C-terminal fragment of glutamine synthetase and the second fragment of glutamine synthetase is an N-terminal fragment of glutamine synthetase.

[0011] In certain examples of the vector or the expression system disclosed herein, the glutamine synthetase comprising the amino acid sequence of SEQ ID NO: 1, and the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ ID NO: 1. In certain examples, the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position selected from K52, E55, D92, G187, and G245 of SEQ ID NO: 1, and in

host cell is CHO cells. In certain examples, the host cell lacks endogenous glutamine synthetase.

[0021] In yet another aspect, the present disclosure refers to a method of producing an antibody heavy chain or a fragment thereof and an antibody light chain or a fragment thereof comprising culturing the host cell under conditions wherein the heteromeric complex is expressed by the host cell. In certain examples, the method further comprises isolating the heteromeric complex.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] Figure 1 shows sequence alignment of glutamine synthetase from difference species using Geneious Aligner.

[0023] Figure 2 shows the plasmid map of the vectors used in the Examples.

[0024] Figure 3 shows cell recovery data of various control cell lines (CS9, pGS) and cells transfected with plasmids comprising glutamine synthetase fragments generated by splitting the polypeptide at sites 1-55, 1-92, 1-187, and 1-244 of SEQ ID NO:1 in both linear (L1, L2) and circular format (C1, C2). Cells carrying split site 1-187 recovered in both the linear and circular format while the site 1-92 recovered in the linear format.

[0025] Figure 4 shows cells recovery data of cells carrying split site 1-186 in the linear format.

DETAILED DESCRIPTION

[0026] Disclosed herein are vectors, expression systems and methods for producing heteromeric complexes (e.g., monoclonal antibodies). The invention disclosed herein is advantageous in that they are robust, express each component of a heteromeric complex in proportion and to high levels. In addition, it reduces the time required to select for cells expressing high levels of proteins.

[0027] The invention disclosed herein utilizes that the selectable marker glutamine synthetase can be divided into two fragments at selected amino acid positions of the glutamine synthetase polypeptide, and the two fragments interact and form a functional glutamine synthetase protein when expressed together, thereby providing a selectable activity. The individual fragment does not have significant selectable activity when expressed alone, but they provide selectable activity when co-expressed. Polynucleotide encoding each glutamine

CLAIMS

What is claimed:

1. A vector comprising:

a) a first nucleic acid encoding a first polypeptide,

b) a second nucleic acid encoding a first fragment of glutamine synthetase fused to a first interaction domain,

wherein the transcription of the first nucleic acid is operably linked to the transcription of the second nucleic acid,

c) a third nucleic acid encoding a third polypeptide, the third polypeptide is capable of associating with the first polypeptide to form a heteromeric complex, and

d) a fourth nucleic acid encoding a second fragment of glutamine synthetase fused to a second interaction domain,

wherein the transcription of the third nucleic acid is operably linked to the transcription of the fourth nucleic acid, and

wherein the first fragment and the second fragment of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position equivalent to an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ ID NO: 1 according to sequence alignment, the first fragment and second fragment associate via the first and second interaction domains to provide a selectable activity, and wherein the vector is capable of being transfected into mammalian cells and improving selection of transfected cells.

2. The vector of claim 1, wherein

a) the first fragment of glutamine synthetase is an N-terminal fragment of glutamine synthetase and the second fragment of glutamine synthetase is a C-terminal fragment of glutamine synthetase, or

b) the first fragment of glutamine synthetase is a C-terminal fragment of glutamine synthetase and the second fragment of glutamine synthetase is an N-terminal fragment of glutamine synthetase.

3. The vector of claim 1 or claim 2, wherein the glutamine synthetase comprises the amino acid sequence of SEQ ID NO: 1, and the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ ID NO: 1.

4. The vector of claim 3, wherein the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position selected from K52, E55, D92, G187, and G245 of SEQ ID NO: 1.

5. The vector of claim 4, wherein the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at the amino acid position D92 or G187 of SEQ ID NO: 1.

6. The vector of claim 1 or claim 2, wherein the glutamine synthetase is a mammalian glutamine synthetase having an amino acid sequence different from SEQ ID NO:1, and the first and second fragments of glutamine synthetase are generated by splitting the mammalian glutamine synthetase polypeptide at an amino acid position equivalent to an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ ID NO: 1 according to sequence alignment.

7. The vector of claim 3, wherein:

a) the first glutamine synthetase fragment comprises amino acid residues 1 to 51 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 52 to 373 of SEQ ID NO: 1;

b) the first glutamine synthetase fragment comprises amino acid residues 1 to 52 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 53 to 373 of SEQ ID NO: 1;

c) the first glutamine synthetase fragment comprises amino acid residues 1 to 54 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 55 to 373 of SEQ ID NO: 1;

d) the first glutamine synthetase fragment comprises amino acid residues 1 to 55 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 56 to 373 of SEQ ID NO: 1;

e) the first glutamine synthetase fragment comprises amino acid residues 1 to 91 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 92 to 373 of SEQ ID NO: 1;

f) the first glutamine synthetase fragment comprises amino acid residues 1 to 92 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 93 to 373 of SEQ ID NO: 1;

g) the first glutamine synthetase fragment comprises amino acid residues 1 to 186 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 187 to 373 of SEQ ID NO: 1;

h) the first glutamine synthetase fragment comprises amino acid residues 1 to 187 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 188 to 373 of SEQ ID NO: 1;

i) the first glutamine synthetase fragment comprises amino acid residues 1 to 244 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 245 to 373 of SEQ ID NO: 1;

j) the first glutamine synthetase fragment comprises amino acid residues 1 to 245 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 246 to 373 of SEQ ID NO: 1**;**

k) the first glutamine synthetase fragment comprises amino acid residues 1 to 261 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 262 to 373 of SEQ ID NO: 1;

l) the first glutamine synthetase fragment comprises amino acid residues 1 to 262 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 263 to 373 of SEQ ID NO: 1;

m) the first glutamine synthetase fragment comprises amino acid residues 1 to 301 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 302 to 373 of SEQ ID NO: 1;

n) the first glutamine synthetase fragment comprises amino acid residues 1 to 302 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 303 to 373 of SEQ ID NO: 1;

o) the first glutamine synthetase fragment comprises amino acid residues 1 to 310 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 311 to 373 of SEQ ID NO: 1; or

p) the first glutamine synthetase fragment comprises amino acid residues 1 to 311 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 312 to 373 of SEQ ID NO: 1.

8. The vector of claim 7, wherein

a) the first fragment of glutamine synthetase comprises amino acid residues 1 to 91 of SEQ ID NO: 1 and the second fragment of glutamine synthetase comprises amino acid residues 92 to 373 of SEQ ID NO:1;

b) the first fragment of glutamine synthetase comprises amino acid residues 1 to 92 of SEQ ID NO: 1 and the second fragment of glutamine synthetase comprises amino acid residues 93 to 373 of SEQ ID NO:1;

c) the first fragment of glutamine synthetase comprises amino acid residues 1 to 186 SEQ ID NO: 1 and the second fragment of glutamine synthetase comprises amino acid residues 187 to 373 of SEQ ID NO:1; or

d) the first fragment of glutamine synthetase comprises amino acid residues 1 to 187 SEQ ID NO: 1 and the second fragment of glutamine synthetase comprises amino acid residues 188 to 373 of SEQ ID NO:1.

9. The vector of any one of claims 1-8, wherein the heteromeric complex is an antibody, an antigen binding fragment of an antibody or a bispecific antigen binding molecule.

10. The vector of any one of claims 1-9, wherein:

a) the first nucleic acid encodes an antibody heavy chain or a fragment thereof and the third nucleic acid encodes an antibody light chain or a fragment thereof; or

b) the first nucleic acid encodes an antibody light chain or a fragment thereof and the third nucleic acid encodes an antibody heavy chain or a fragment thereof.

11. The vector of any one of claims 1-10, wherein the vector further comprises an internal ribosomal entry site (IRES) and/or expression augmenting sequence element (EASE).

12. The vector of claim 11, wherein the IRES occurs at a site selected from:

a) a site between the first nucleic acid and the second nucleic acid;

b) a site between the third nucleic acid and the fourth nucleic acid, and

c) at sites between both first and second, and third and fourth nucleic acids.

13. The vector of any one of claims 1-12, wherein the IRES comprises the sequence of GATGATAATACCCTCGAGATCCGTGCCATCATG.

14. The vector of any one of claims 1 to 13, wherein each of the first and second interaction domains is a leucine zipper or an anti-parallel leucine zipper polypeptide.

15. The vector of any one of claims 1 to 13, wherein each of the first and second interaction domains comprise the amino acid sequence of ALKKELQANKKELAQLKWELQALKKELAQ or EQLEKKLQALEKKLAQLEWKNQALEKKLAQ**.**

16. The vector of any one of claims 1-15, wherein each of the first and second interaction domains further comprises a linker.

17. The vector of claim 16, wherein the linker comprises a sequence selected from GGPGG, GPGGG, GGGGSGGGGGS, GGGGS and GGGGSGGGGS.

18. The vector of claim 17, wherein the linker comprises the sequence of GGGGSGGGGS.

19. The vector of claim 16 or 17, wherein

a) the first interaction domain is fused to the N-terminal of the first glutamine synthetase fragment and has the amino acid sequence of

EQLEKKLQALEKKLAQLEWKNQALEKKLAQGGGGSGGGGS and the second interaction domain is fused to the C-terminal of the second glutamine synthetase fragment and has the amino acid sequence of GGGGSGGGGSALKKELQANKKELAQLKWELQALKKELAQ; or

b) the first interaction domain is fused to the C-terminal of the first glutamine synthetase fragment and has the amino acid sequence of GGGGSGGGGSALKKELQANKKELAQLKWELQALKKELAQ and the second interaction domain is fused to the N-terminal of the second glutamine synthetase fragment and has the amino acid sequence of EQLEKKLQALEKKLAQLEWKNQALEKKLAQGGGGSGGGGS.

20. The vector of any one of claims 1-19, wherein the vector further comprises a fifth nucleic acid encoding a selectable marker selected from Zeomycin, neomycin, puromycin, Blasticidin S, and GPT.

21. A host cell comprising the vector of any one of claims 1-20.

22. The host cell of claim 21, wherein the host cell is CHO, VERO, BHK, HeLa, Cos, MDCK, 293, 3T3, WI338, or NSO cells.

23. The host cell of claim 21 or 22, wherein the host cell lacks endogenous glutamine synthetase.

24. A method of producing an antibody heavy chain or a fragment thereof and an antibody light chain or a fragment thereof comprising culturing the host cell of any one of claims 21-23 under conditions wherein the heteromeric complex is expressed by the host cell.

25. The method of claim 24, wherein the heteromeric complex is an antibody.

26. The method of claim 25, further comprising isolating the heteromeric complex.

27. An expression system comprising:

a) a first vector comprising a first nucleic acid encoding a first polypeptide, wherein the transcription of the first nucleic acid is operably linked to the transcription of a second nucleic acid encoding a first fragment of glutamine synthetase fused to a first interaction domain, and

b) a second vector comprising a third nucleic acid encoding a third polypeptide, wherein the transcription of the third nucleic acid is operably linked to the transcription of a fourth nucleic acid encoding a second fragment of glutamine synthetase fused to a second interaction domain,

wherein the first polypeptide is capable of associating with the third polypeptide to form a heteromeric complex,

wherein the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ ID NO: 1 according to sequence alignment,

the first fragment and second fragment associate via the first and second interaction domains to provide a selectable activity, and

wherein the expression system is capable of being transfected into mammalian cells and improving selection of the cells.

28. The expression system of claim 27, wherein

a) the first fragment of glutamine synthetase is an N-terminal fragment of glutamine synthetase and the second fragment of glutamine synthetase is a C-terminal fragment of glutamine synthetase, or

b) the first fragment of glutamine synthetase is a C-terminal fragment of glutamine synthetase and the second fragment of glutamine synthetase is an N-terminal fragment of glutamine synthetase.

29. The expression system of claim 27 or 28, wherein the glutamine synthetase comprises the amino acid sequence of SEQ ID NO: 1, and the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ ID NO: 1.

30. The expression system of claim 29, wherein the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position selected from K52, E55, D92, G187 and G245 of SEQ ID NO: 1.

31. The expression system of claim 29, wherein the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at the amino acid position D92 or G187 of SEQ ID NO: 1.

32. The expression system of claim 27 or 28, wherein the glutamine synthetase is a mammalian glutamine synthetase having an amino acid sequence different from SEQ ID NO:1, and the first and second fragments of glutamine synthetase are generated by splitting the glutamine synthetase polypeptide at an amino acid position equivalent to an amino acid position selected from K52, E55, D92, G187, G245, R262, K291, G302 and D311 of SEQ ID NO:1 according to sequence alignment.

33. The expression system of claim 29, wherein

a) the first glutamine synthetase fragment comprises amino acid residues 1 to 51 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 52 to 373 of SEQ ID NO: 1;

b) the first glutamine synthetase fragment comprises amino acid residues 1 to 52 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 53 to 373 of SEQ ID NO: 1;

c) the first glutamine synthetase fragment comprises amino acid residues 1 to 54 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 55 to 373 of SEQ ID NO: 1;

d) the first glutamine synthetase fragment comprises amino acid residues 1 to 55 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 56 to 373 of SEQ ID NO: 1;

e) the first glutamine synthetase fragment comprises amino acid residues 1 to 91 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 92 to 373 of SEQ ID NO: 1;

f) the first glutamine synthetase fragment comprises amino acid residues 1 to 92 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 93 to 373 of SEQ ID NO: 1;

g) the first glutamine synthetase fragment comprises amino acid residues 1 to 186 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 187 to 373 of SEQ ID NO: 1;

h) the first glutamine synthetase fragment comprises amino acid residues 1 to 187 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 188 to 373 of SEQ ID NO: 1;

i) the first glutamine synthetase fragment comprises amino acid residues 1 to 244 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 245 to 373 of SEQ ID NO: 1;

j) the first glutamine synthetase fragment comprises amino acid residues 1 to 245 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 246 to 373 of SEQ ID NO: 1**;**

k) the first glutamine synthetase fragment comprises amino acid residues 1 to 262 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 263 to 373 of SEQ ID NO: 1;

l) the first glutamine synthetase fragment comprises amino acid residues 1 to 263 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 264 to 373 of SEQ ID NO: 1;

m) the first glutamine synthetase fragment comprises amino acid residues 1 to 301 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 302 to 373 of SEQ ID NO: 1;

n) the first glutamine synthetase fragment comprises amino acid residues 1 to 302 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 303 to 373 of SEQ ID NO: 1;

o) the first glutamine synthetase fragment comprises amino acid residues 1 to 310 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 311 to 373 of SEQ ID NO: 1; or

p) the first glutamine synthetase fragment comprises amino acid residues 1 to 311 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 312 to 373 of SEQ ID NO: 1.

34. The expression system of claim 33, wherein

a) the first glutamine synthetase fragment comprises amino acid residues 1 to 91 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 92 to 373 of SEQ ID NO: 1;

b) the first glutamine synthetase fragment comprises amino acid residues 1 to 92 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 93 to 373 of SEQ ID NO: 1;

c) the first glutamine synthetase fragment comprises amino acid residues 1 to 186 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 187 to 373 of SEQ ID NO: 1; or

d) the first glutamine synthetase fragment comprises amino acid residues 1 to 187 of SEQ ID NO: 1 and the second glutamine synthetase fragment comprises amino acid residues 188 to 373 of SEQ ID NO: 1.

35. The expression system of any one of claims 27-34, wherein one or both the first and second vectors further comprise an IRES and/or an EASE.

36. The expression system of any one of claims 27 to 35, wherein each of the first and second interaction domains is a leucine zipper or an anti-parallel leucine zipper polypeptide.

37. The expression system of any one of claims 27 to 36, wherein each of the first and second interaction domains further comprises a linker having a sequence selected from GGPGG, GPGGG, GGGGSGGGGGS, GGGGS and GGGGSGGGGS.

38. The expression system of claim 37, wherein

a) The first interaction domain is fused to the N-terminal of the first glutamine synthetase fragment and has the amino acid sequence of GGGGSGGGGSALKKELQANKKELAQLKWELQALKKELAQ and the second interaction domain is fused to the C-terminal of the second glutamine synthetase fragment and has the amino acid sequence of EQLEKKLQALEKKLAQLEWKNQALEKKLAQGGGGSGGGGS; or

b) The first interaction domain is fused to the C-terminal of the first glutamine synthetase fragment and has the amino acid sequence of EQLEKKLQALEKKLAQLEWKNQALEKKLAQGGGGSGGGGS and the second interaction domain is fused to the N-terminal of the second glutamine synthetase fragment and has the amino acid sequence of EQLEKKLQALEKKLAQLEWKNQALEKKLAQGGGGSGGGGS.

39. The expression system of any one of claims 27-38, wherein the heteromeric complex is an antibody, an antigen binding fragment of an antibody or a bispecific antigen binding molecule.

40. The expression system of any one of claims 27-39, wherein

a) the first polypeptide is a heavy chain of an antibody or a fragment thereof and the third polypeptide is a light chain of an antibody or a fragment thereof; or

b) the first polypeptide is a light chain of an antibody or a fragment thereof and the third polypeptide is a heavy chain of an antibody or a fragment thereof.

41. The expression system of any one of claims 27-40, wherein one or both the first and second vector further comprises an additional nucleic acid encoding a selectable marker selected from Zeomycin, neomycin, puromycin, Blasticidin S, and GPT.

42. A host cell comprising the expression system of any one of claims 27-41.

43. The host cell of claim 42, wherein the host cell is CHO, VERO, BHK, HeLa, Cos, MDCK, 293, 3T3, NSO, or WI38 cells.

44. The host cell of claim 42 or 43 wherein the host cell lacks endogenous glutamine synthetase.

45. A method of producing an antibody heavy chain or a fragment thereof and an antibody light chain or a fragment thereof comprising culturing the host cell of any one of claims 42-44 under conditions wherein the heteromeric complex is expressed by the host cell.

46. The method of claim 45, further comprising isolating the heteromeric complex.