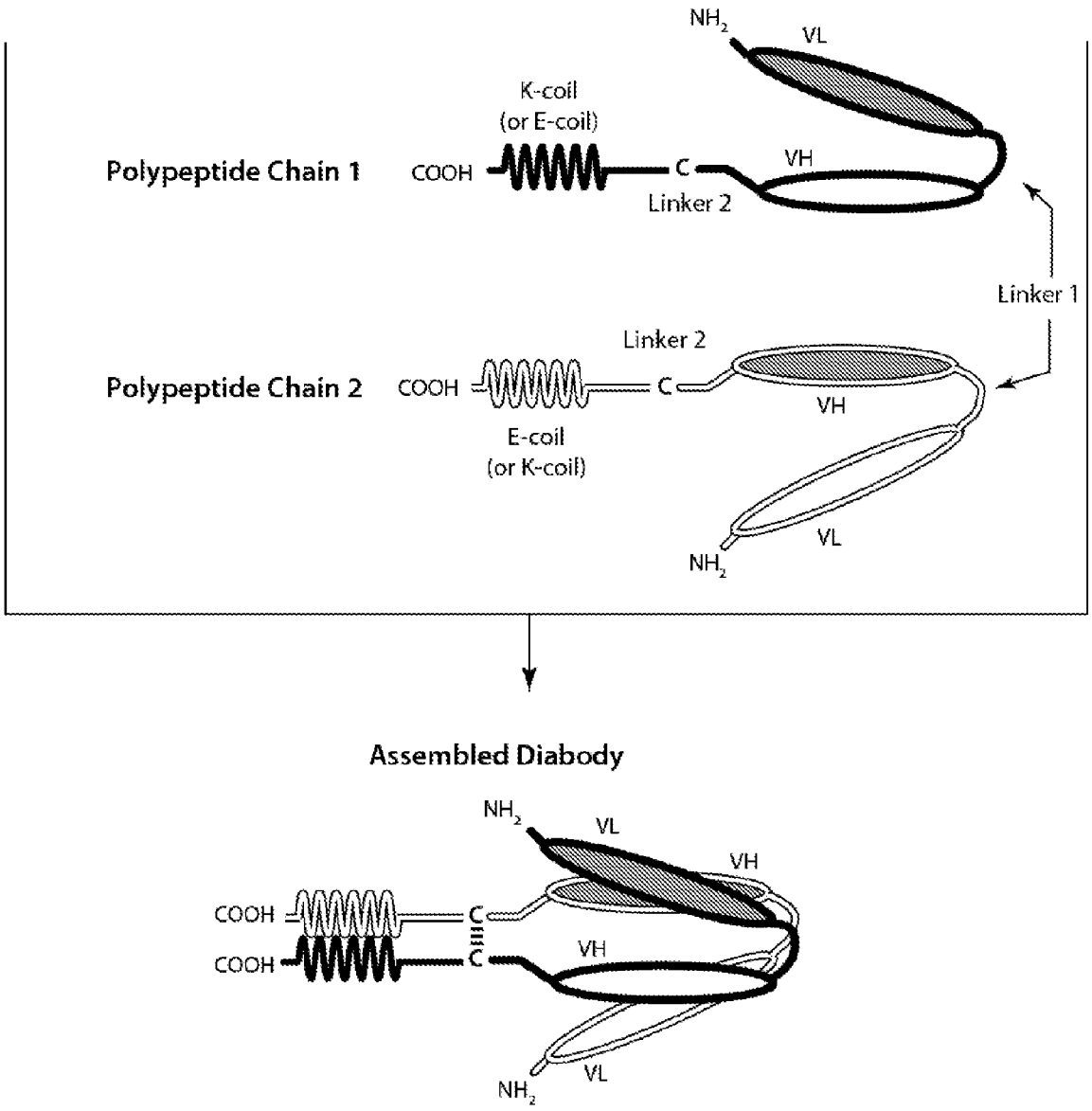
NH2
VL
K-coil
(or E-coil)
Polypeptide Chain 1
COOH
C
VH
Linker 2
Linker 1
Linker 2
Polypeptide Chain 2
COOH
C
VH
E-coil
(or K-coil)
VL
NH2
Assembled Diabody
NH2
VL
VH
COOH
C
COOH
C
VH
VL
NH2

Figure 1

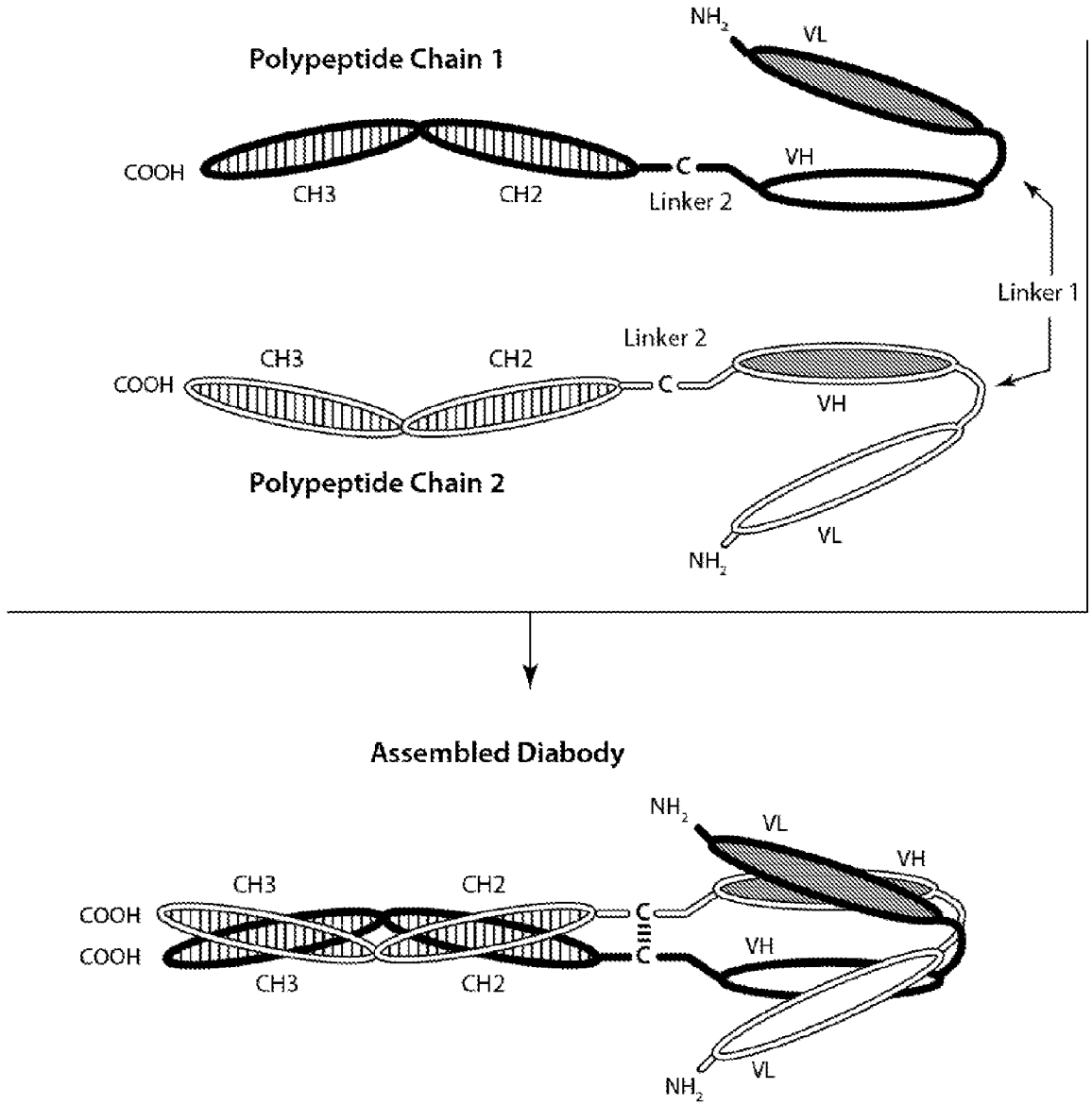
Polypeptide Chain 1
NH2
VL
COOH
CH3
CH2
C
VH
Linker 2
Linker 1
Linker 2
CH3
CH2
COOH
C
VH
Polypeptide Chain 2
VL
NH2
Assembled Diabody
NH2
VL
VH
CH3
CH2
COOH
COOH
C
C
VH
CH3
CH2
VL
NH2

Figure 2

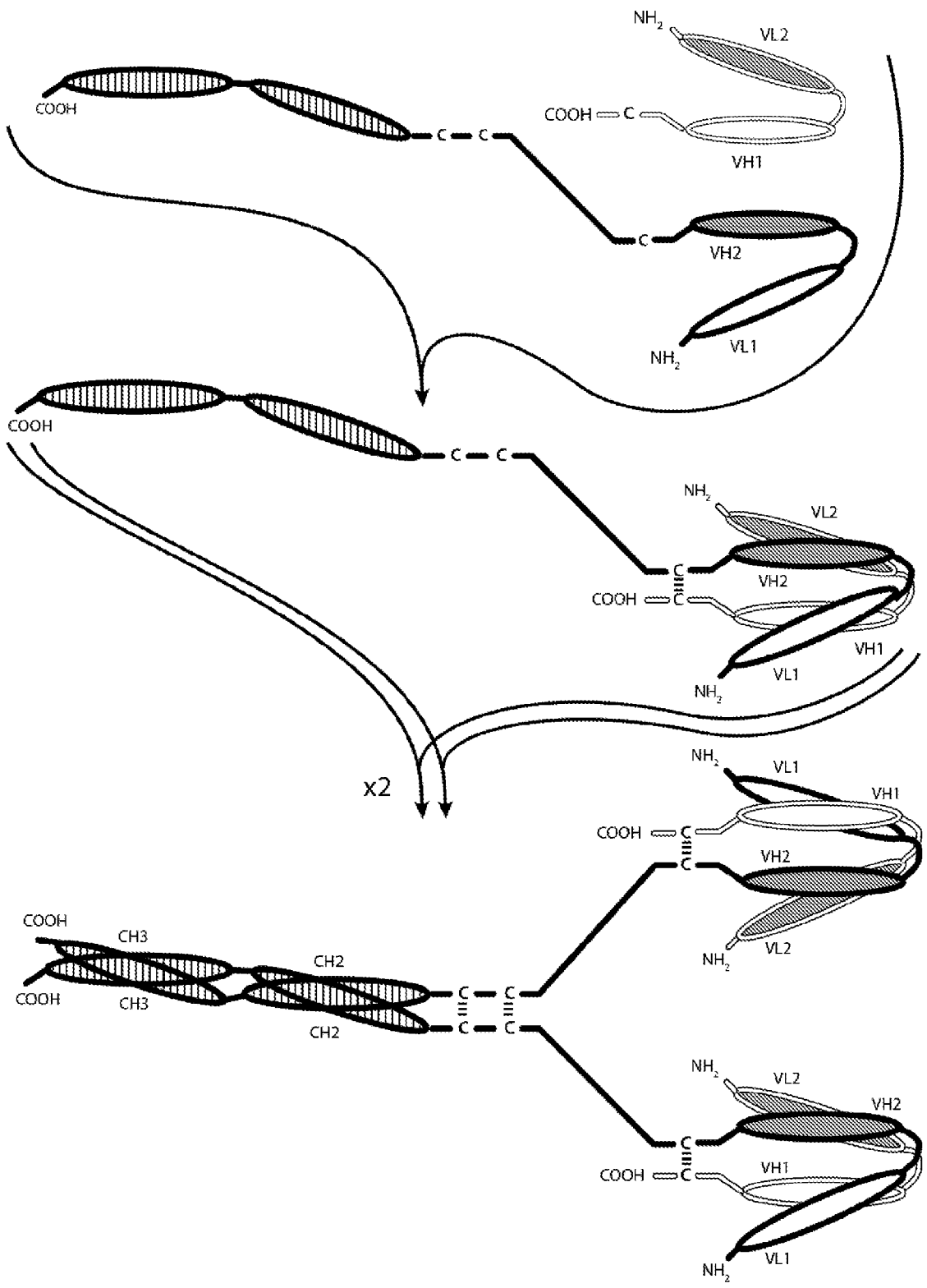
NH2
VL2
COOH
C
C
C
VH1
C
VH2
NH2
VL1
COOH
C
C
NH2
VL2
VH2
COOH
C
C
VH1
VL1
NH2
x2
NH2
VL1
VH1
COOH
C
C
VH2
NH2
VL2
COOH
CH3
CH2
C
C
COOH
CH3
CH2
C
C
NH2
VL2
VH2
COOH
C
C
VH1
NH2
VL1

Figure 3A

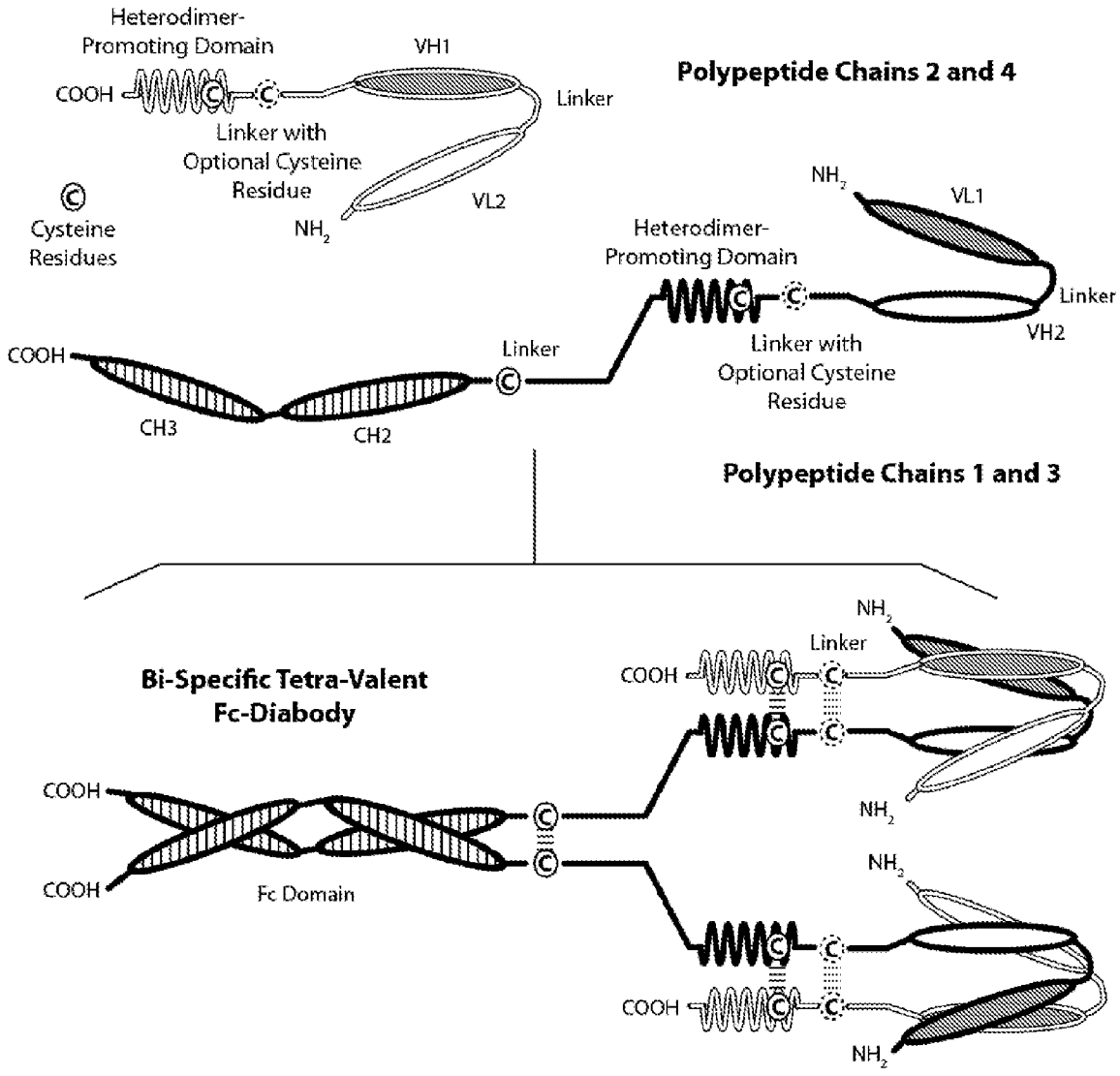
Heterodimer-
Promoting Domain
VH1
COOH
Linker
Linker with
Optional Cysteine
Residue
VL2
NH2
Cysteine
Residues
Polypeptide Chains 2 and 4
NH2
VL1
Heterodimer-
Promoting Domain
Linker
VH2
Linker with
Optional Cysteine
Residue
COOH
Linker
CH3
CH2
Polypeptide Chains 1 and 3
Bi-Specific Tetra-Valent
Fc-Diabody
NH2
Linker
COOH
COOH
Fc Domain
NH2
NH2
COOH
NH2

Figure 3B

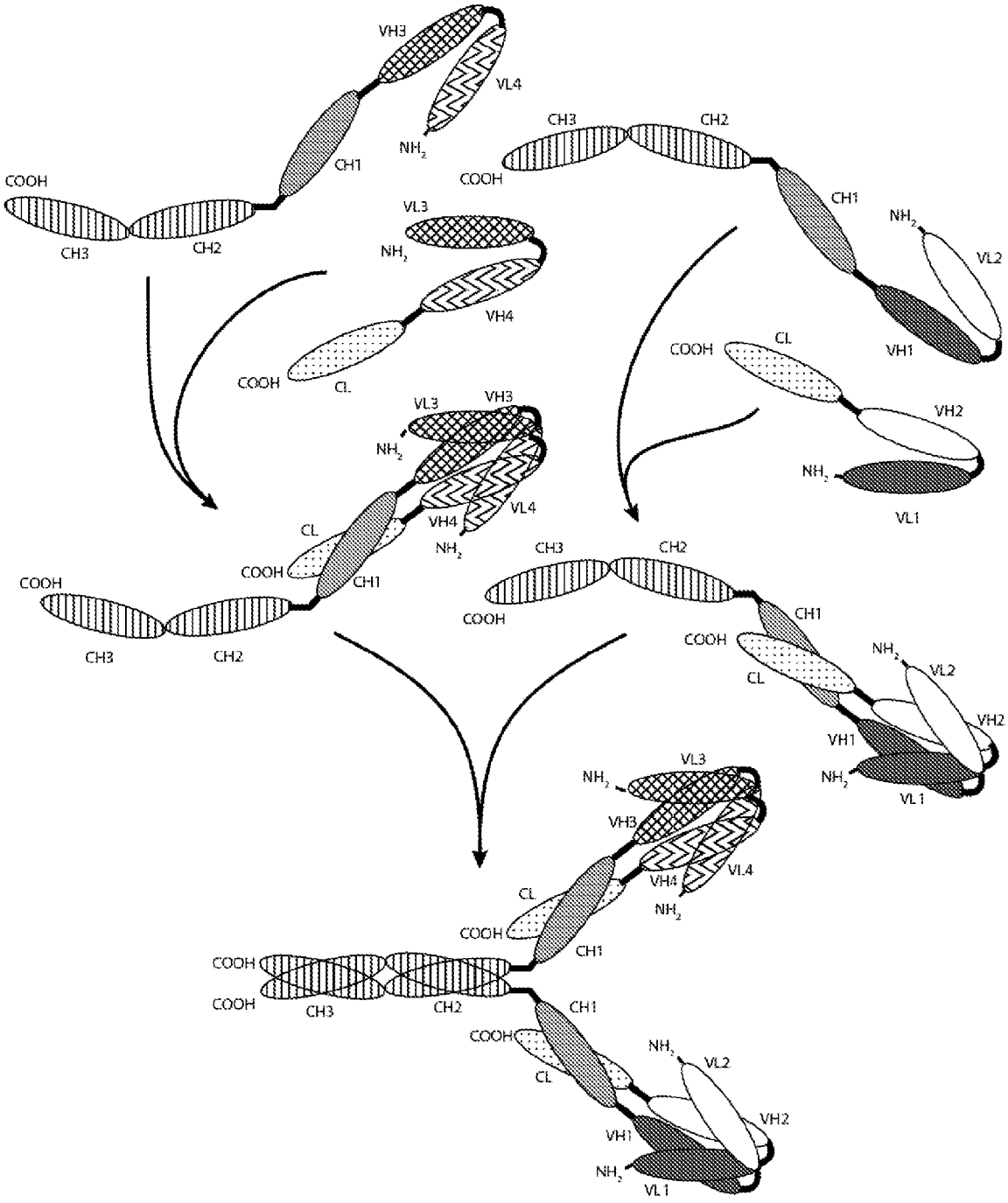
VH3
VL4
NH2
CH1
COOH
CH3
CH2
VL3
NH2
VH4
COOH
CL
CH3
CH2
COOH
CH1
NH2
VL2
VH1
COOH
CL
VH2
NH2
VL1
VL3
VH3
NH2
VH4
VL4
NH2
CL
COOH
CH1
COOH
CH3
CH2
CH3
CH2
COOH
CH1
COOH
CL
NH2
VL2
VH2
VH1
NH2
VL1
VL3
NH2
VH3
VH4
VL4
NH2
CL
COOH
CH1
COOH
COOH
CH3
CH2
CH1
COOH
CL
NH2
VL2
VH2
VH1
NH2
VL1

Figure 3C

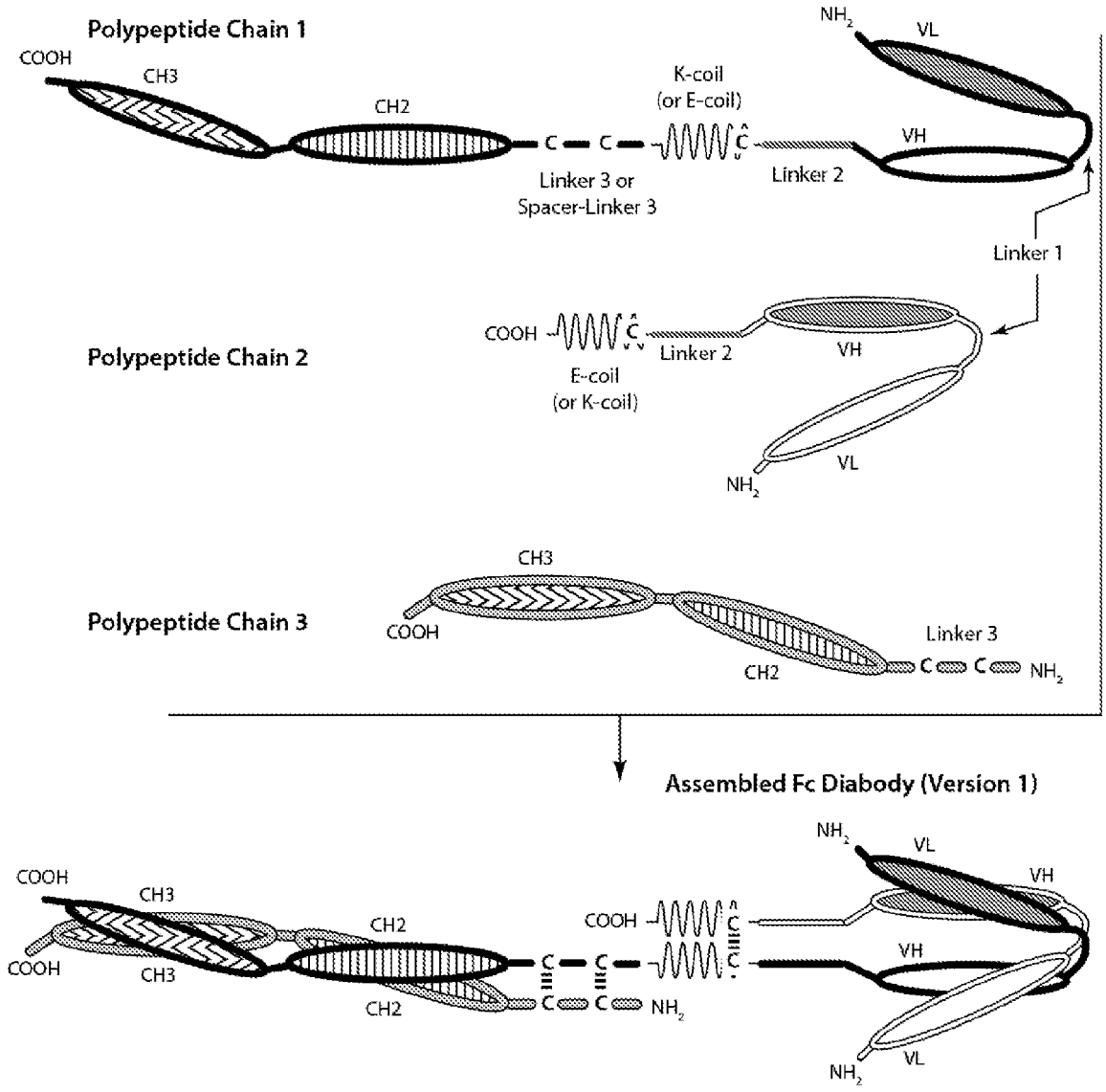
Polypeptide Chain 1
COOH
CH3
CH2
K-coil
(or E-coil)
NH2
VL
VH
Linker 3 or
Spacer-Linker 3
Linker 2
Linker 1
Polypeptide Chain 2
COOH
E-coil
(or K-coil)
Linker 2
VH
VL
NH2
Polypeptide Chain 3
CH3
COOH
CH2
Linker 3
NH2
Assembled Fc Diabody (Version 1)
COOH
CH3
CH3
COOH
CH2
CH2
NH2
NH2
VL
VH
VH
NH2
VL

Figure 4A

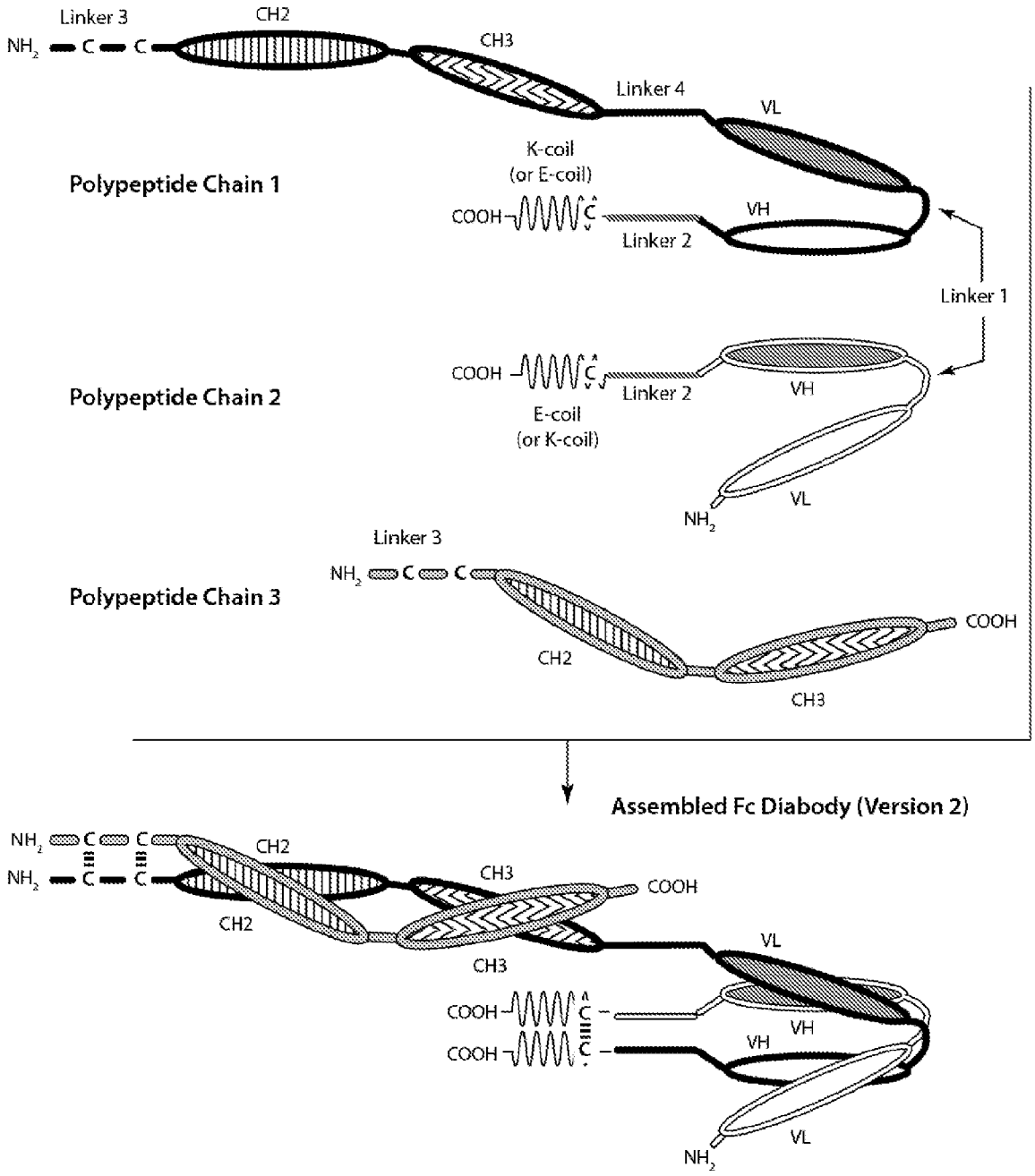
Linker 3
CH2
CH3
Linker 4
VL
K-coil
(or E-coil)
Polypeptide Chain 1
COOH
VH
Linker 2
Linker 1
Polypeptide Chain 2
COOH
Linker 2
VH
E-coil
(or K-coil)
VL
Linker 3
Polypeptide Chain 3
CH2
COOH
CH3
Assembled Fc Diabody (Version 2)
CH2
CH3
COOH
CH2
CH3
VL
COOH
VH
COOH
VH
VL

Figure 4B

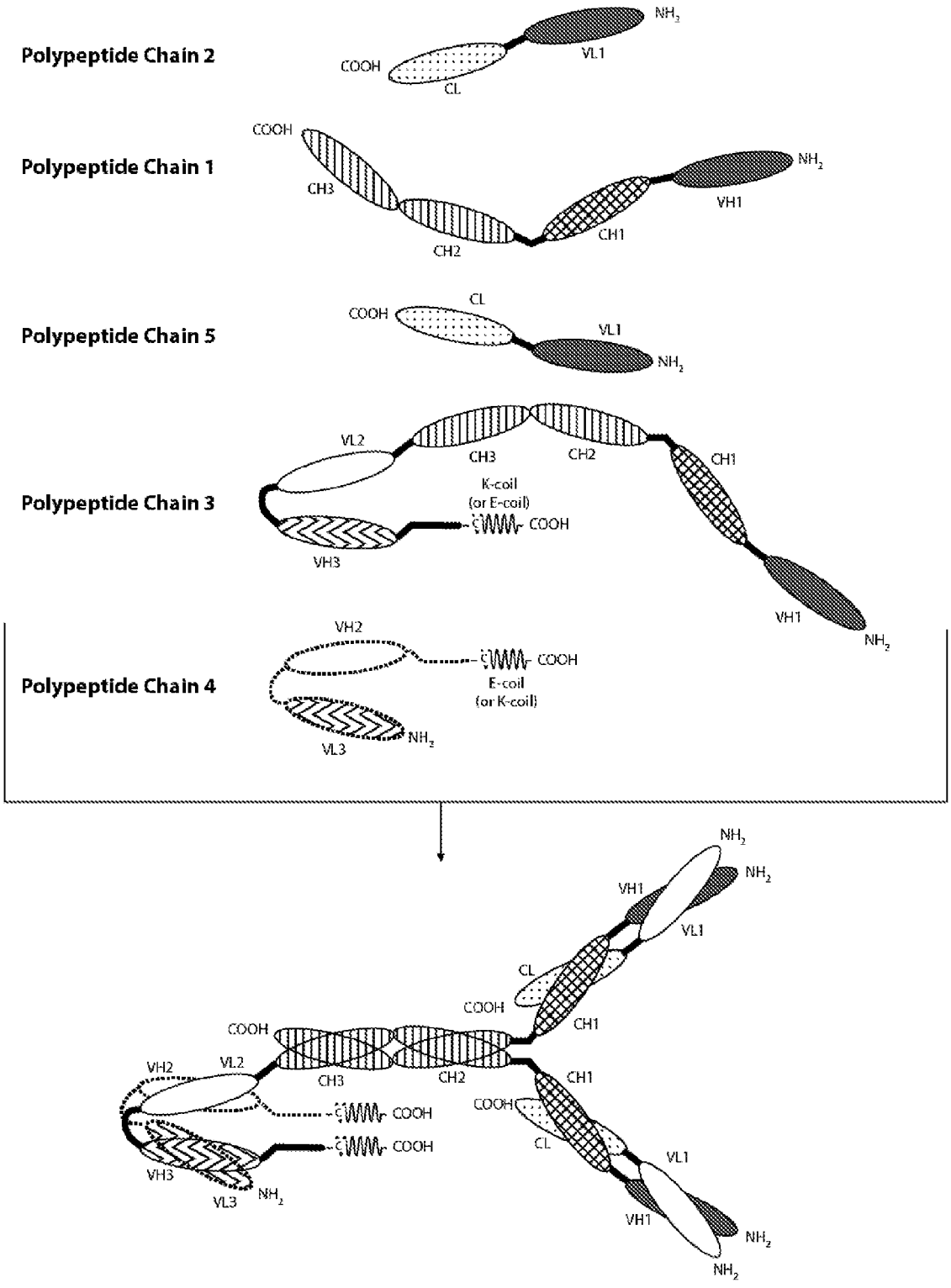
Polypeptide Chain 2
NH2
VL1
COOH
CL
Polypeptide Chain 1
COOH
CH3
NH2
VH1
CH2
CH1
Polypeptide Chain 5
CL
COOH
VL1
NH2
Polypeptide Chain 3
VL2
CH3
CH2
CH1
K-coil
(or E-coil)
COOH
VH3
VH1
NH2
Polypeptide Chain 4
VH2
COOH
E-coil
(or K-coil)
NH2
VL3
NH2
NH2
VH1
VL1
CL
COOH
CH1
COOH
VH2
VL2
CH3
CH2
CH1
COOH
COOH
CL
VL1
VH3
NH2
VL3
VH1
NH2
NH2

Figure 5

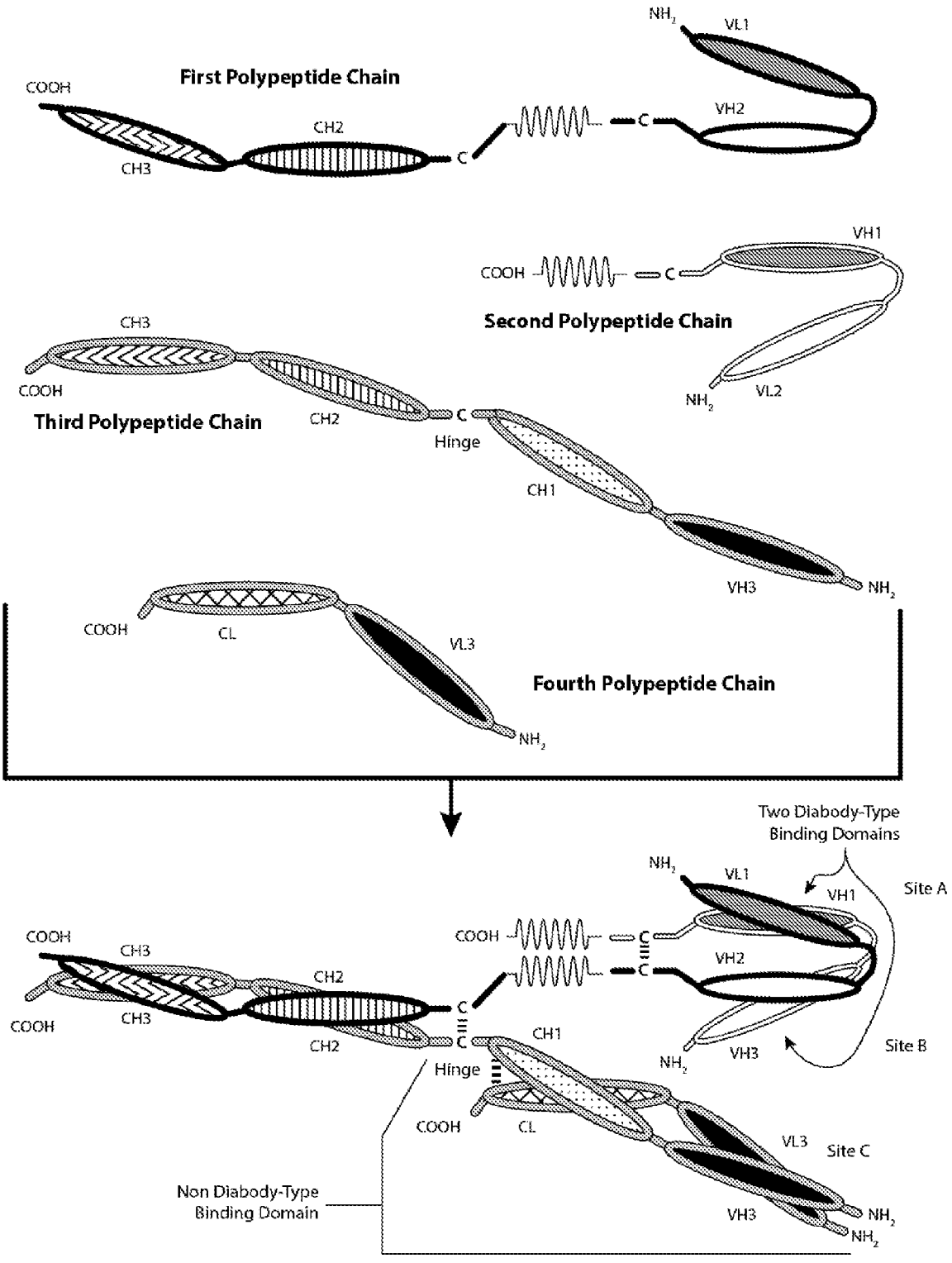
First Polypeptide Chain
COOH
CH2
CH3
C
NH2
VL1
VH2
Second Polypeptide Chain
VH1
COOH
C
NH2
VL2
Third Polypeptide Chain
CH3
COOH
CH2
C
Hinge
CH1
VH3
NH2
Fourth Polypeptide Chain
COOH
CL
VL3
NH2
Two Diabody-Type
Binding Domains
Site A
Site B
Site C
Non Diabody-Type
Binding Domain

Figure 6A

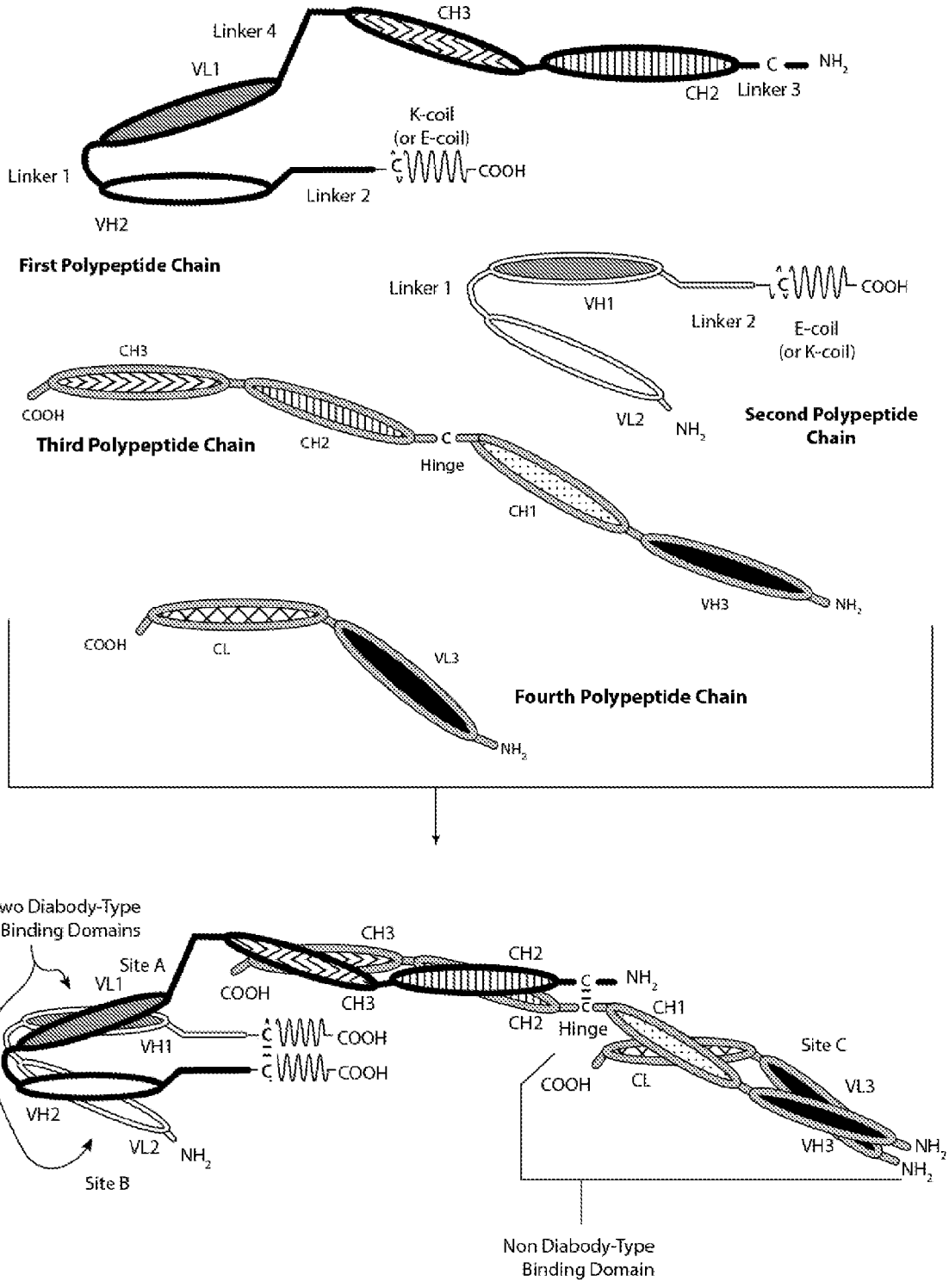
CH3
Linker 4
VL1
C
NH2
CH2
Linker 3
K-coil
(or E-coil)
Linker 1
COOH
Linker 2
VH2
First Polypeptide Chain
Linker 1
VH1
COOH
Linker 2
E-coil
(or K-coil)
CH3
VL2
NH2
Second Polypeptide Chain
COOH
Third Polypeptide Chain
CH2
C
Hinge
CH1
VH3
NH2
COOH
CL
VL3
Fourth Polypeptide Chain
NH2
Two Diabody-Type
Binding Domains
Site A
VL1
CH3
CH2
COOH
C
NH2
CH3
CH1
CH2
Hinge
VH1
COOH
COOH
Site C
COOH
CL
VL3
VH2
VH3
NH2
VL2
NH2
NH2
Site B
Non Diabody-Type
Binding Domain

Figure 6B

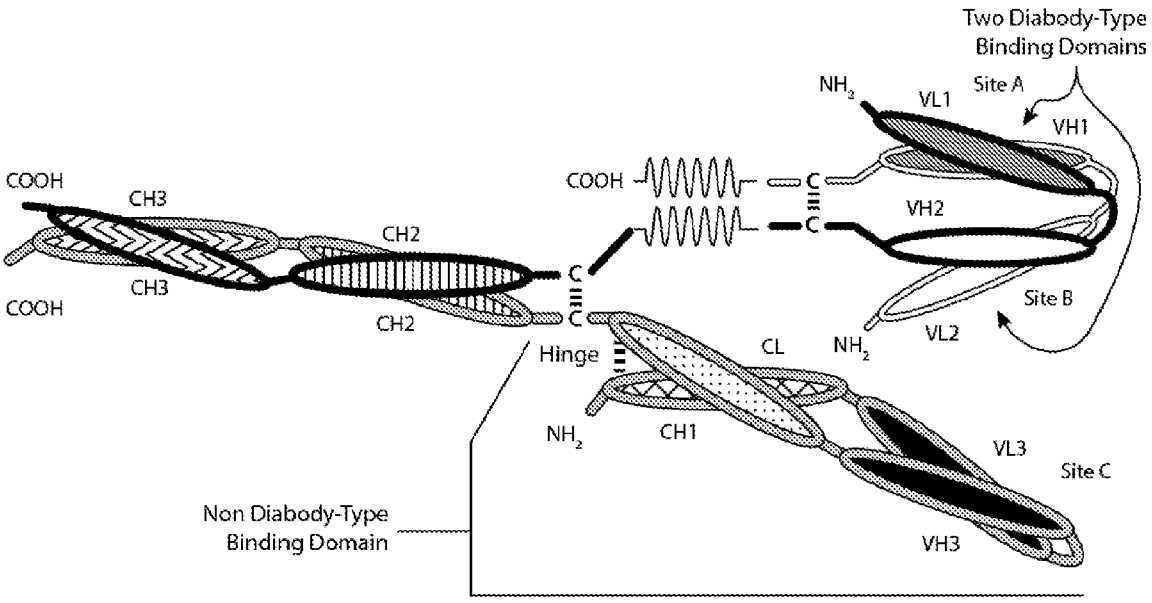

Figure 6C

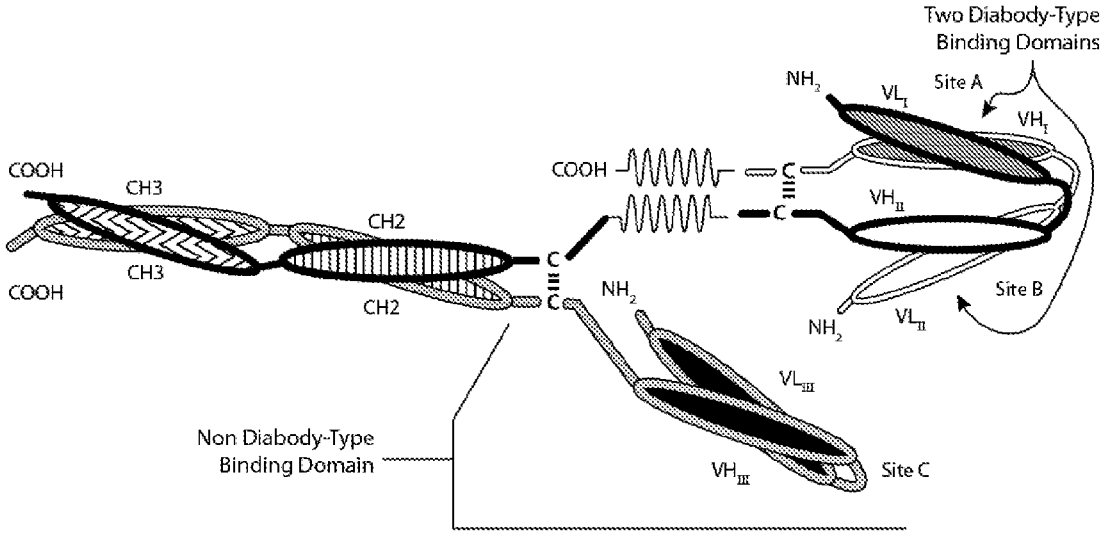

Figure 6D

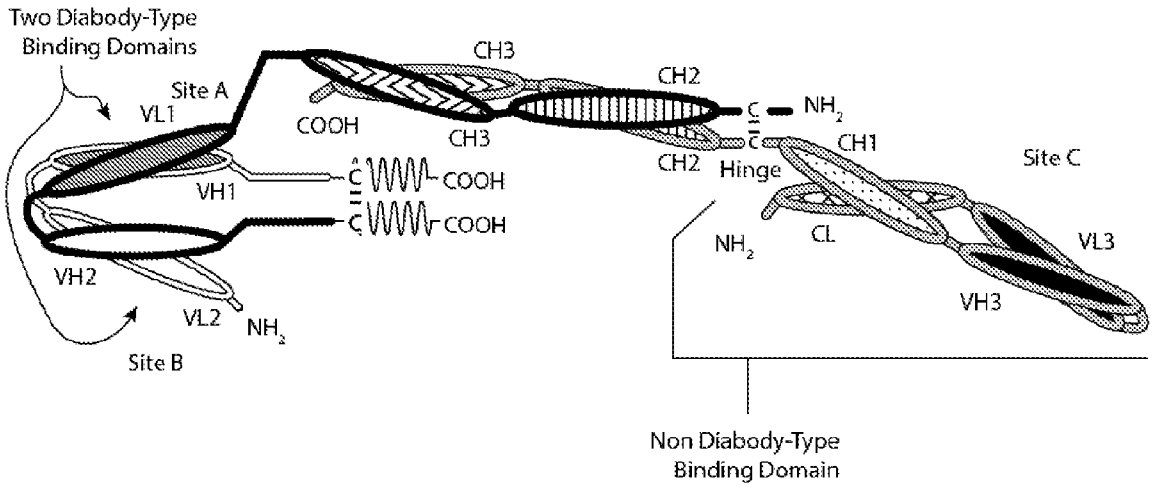

Figure 6E

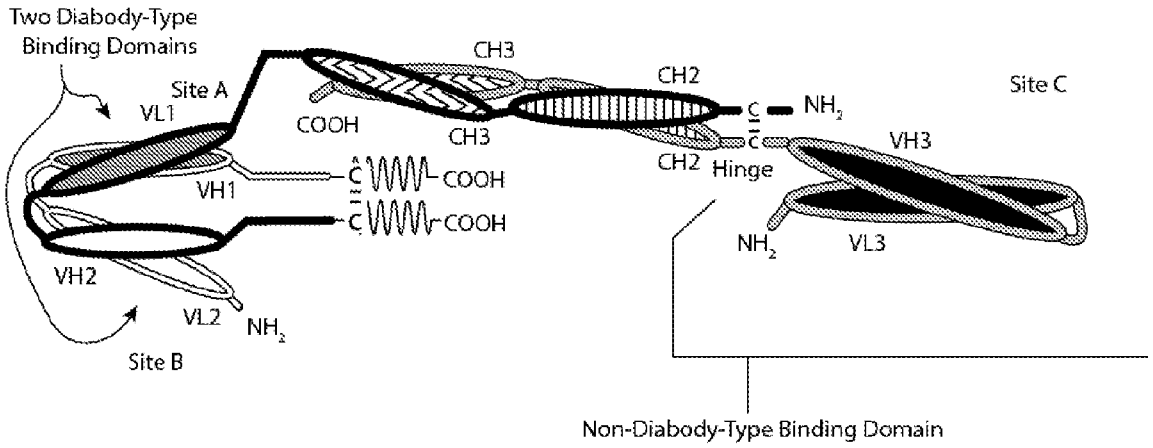

Figure 6F

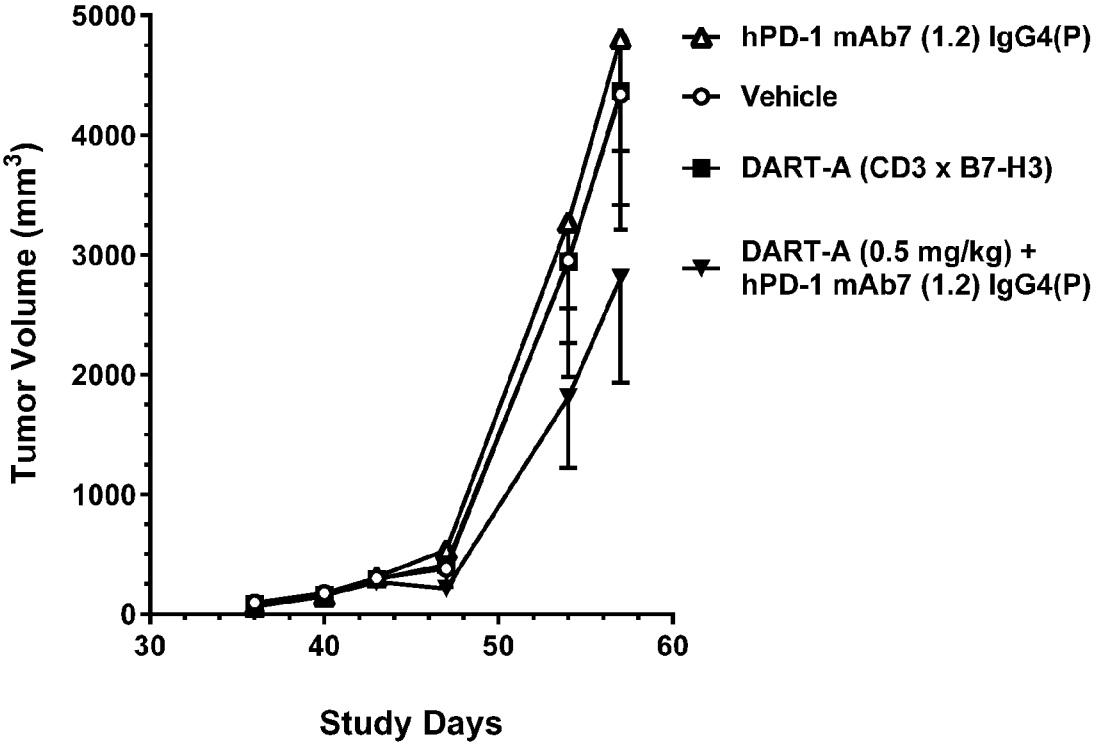
5000
4000
3000
2000
1000
0
Tumor Volume (mm3)
30
40
50
60
Study Days
hPD-1 mAb7 (1.2) IgG4(P)
Vehicle
DART-A (CD3 x B7-H3)
DART-A (0.5 mg/kg) +
hPD-1 mAb7 (1.2) IgG4(P)

Figure 7

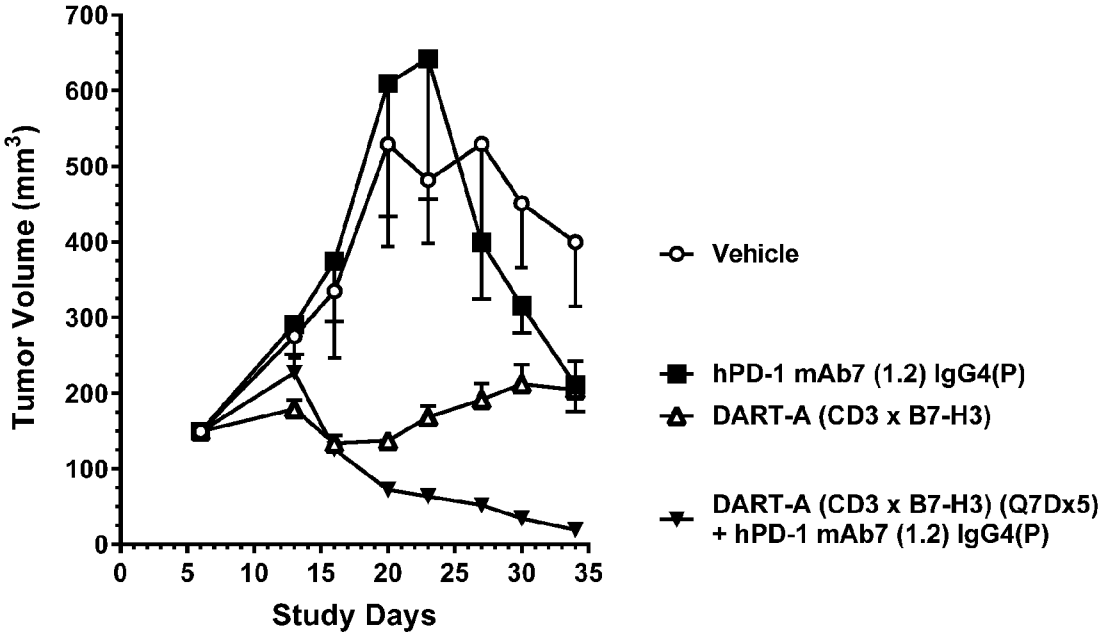
Tumor Volume (mm3)
700
600
500
400
300
200
100
0
0
5
10
15
20
25
30
35
Study Days
Vehicle
hPD-1 mAb7 (1.2) lgG4(P)
DART-A (CD3 x B7-H3)
DART-A (CD3 x B7-H3) (Q7Dx5)
+ hPD-1 mAb7 (1.2) lgG4(P)

Figure 8A

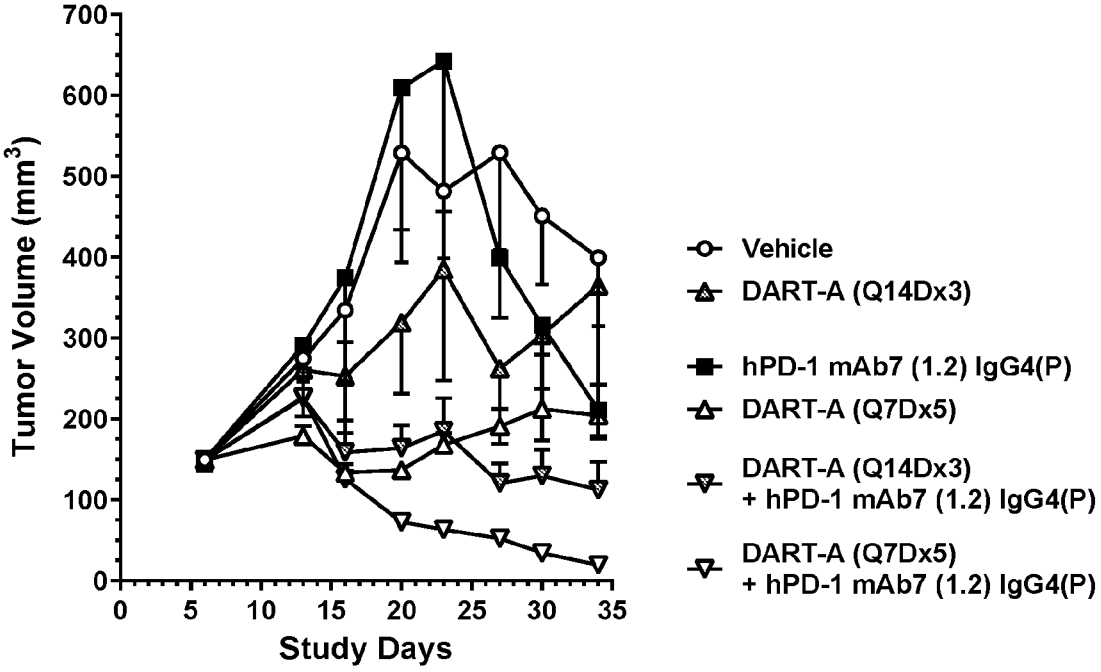
700
600
500
400
300
200
100
0
Tumor Volume (mm3)
0
5
10
15
20
25
30
35
Study Days
Vehicle
DART-A (Q14Dx3)
hPD-1 mAb7 (1.2) IgG4(P)
DART-A (Q7Dx5)
DART-A (Q14Dx3)
+ hPD-1 mAb7 (1.2) IgG4(P)
DART-A (Q7Dx5)
+ hPD-1 mAb7 (1.2) IgG4(P)

Figure 8B

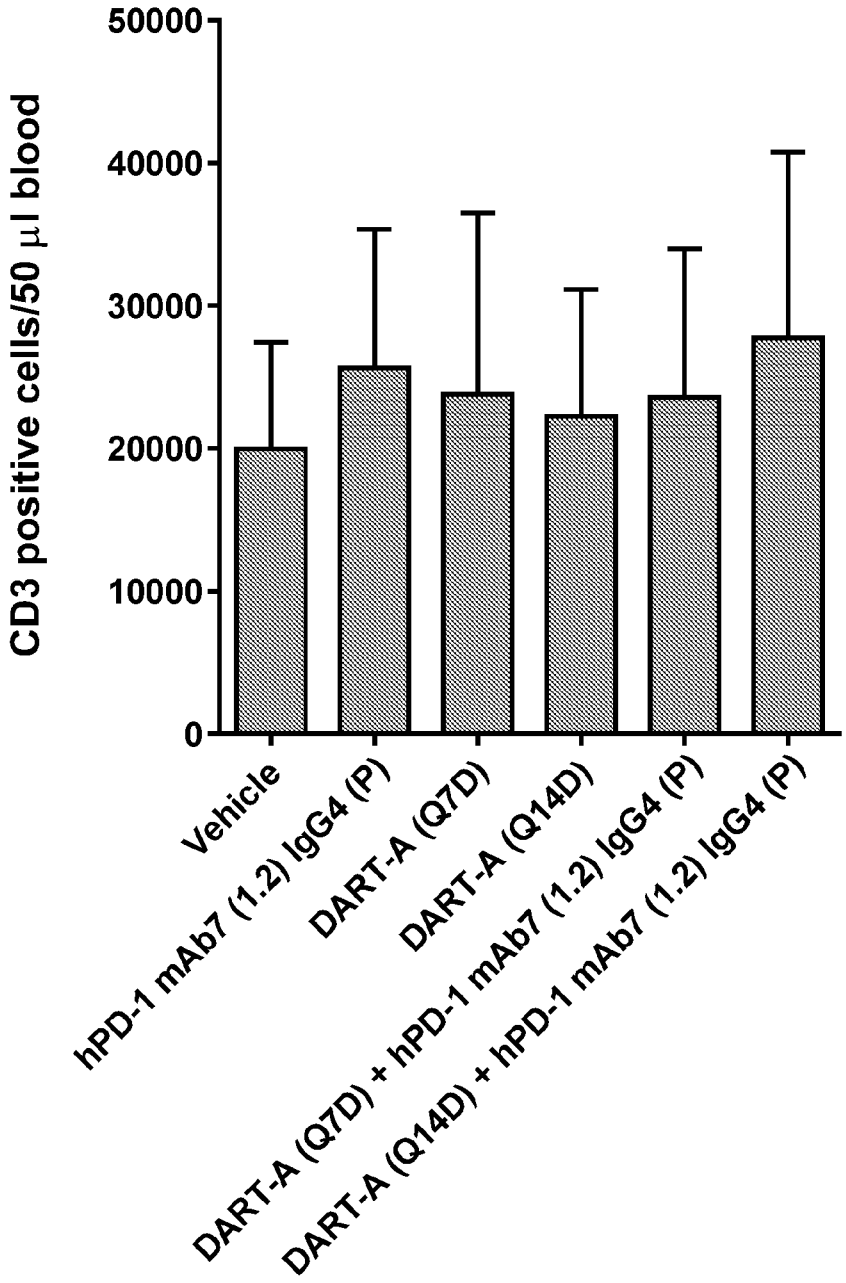
CD3 positive cells/50 µl blood
50000
40000
30000
20000
10000
0
Vehicle
hPD-1 mAb7 (1.2) IgG4 (P)
DART-A (Q7D)
DART-A (Q14D)
DART-A (Q7D) + hPD-1 mAb7 (1.2) IgG4 (P)
DART-A (Q14D) + hPD-1 mAb7 (1.2) IgG4 (P)

Figure 9

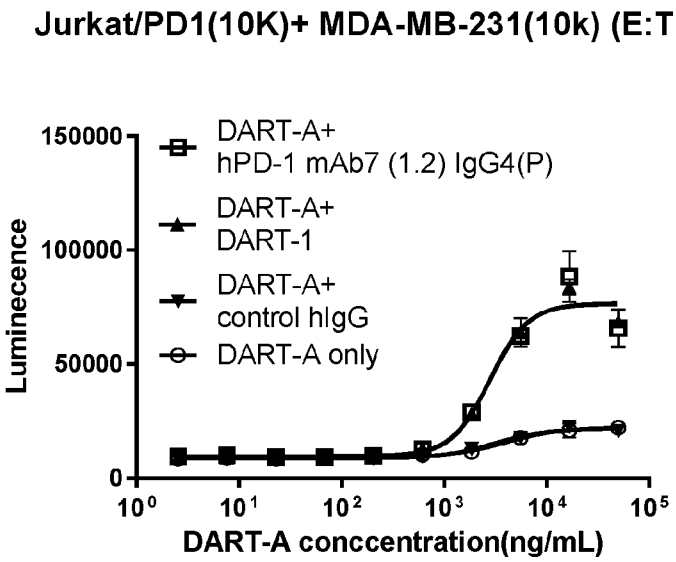

Figure 10A

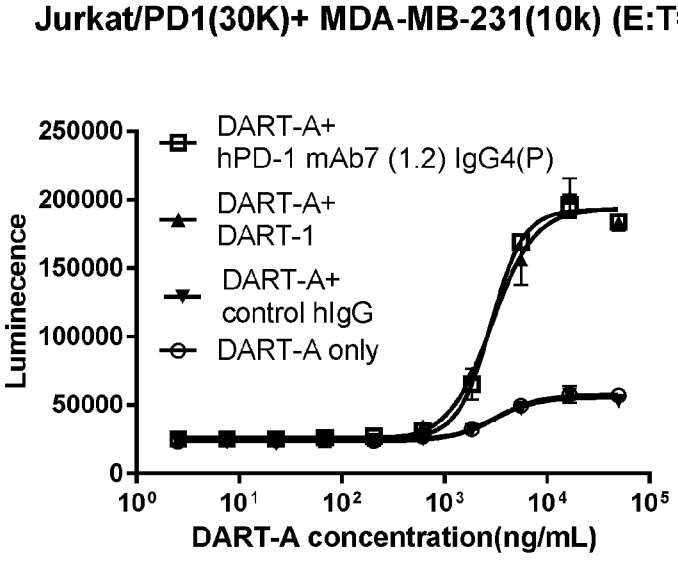

Figure 10B

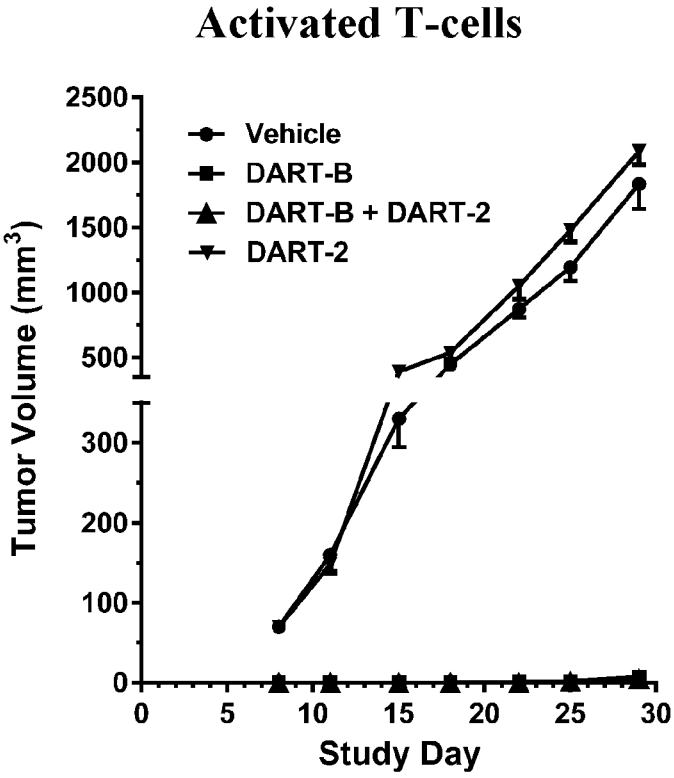

Figure 11A

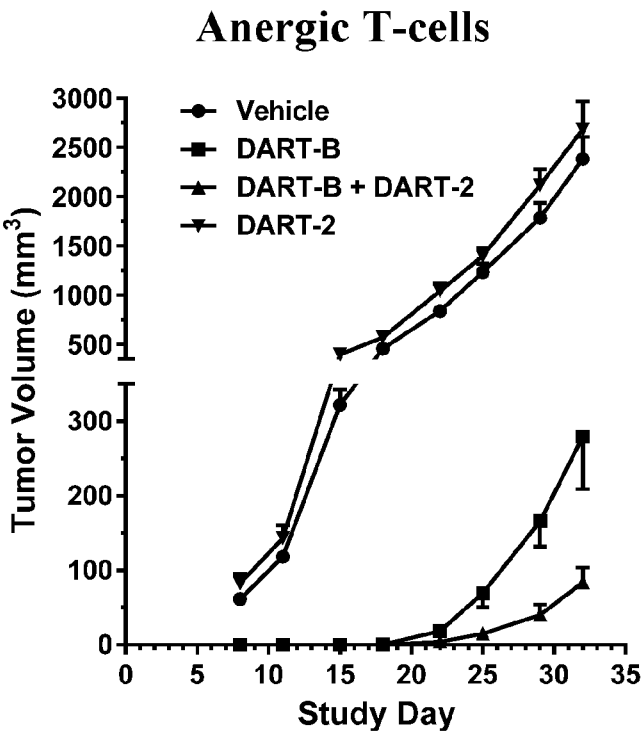

Figure 11B

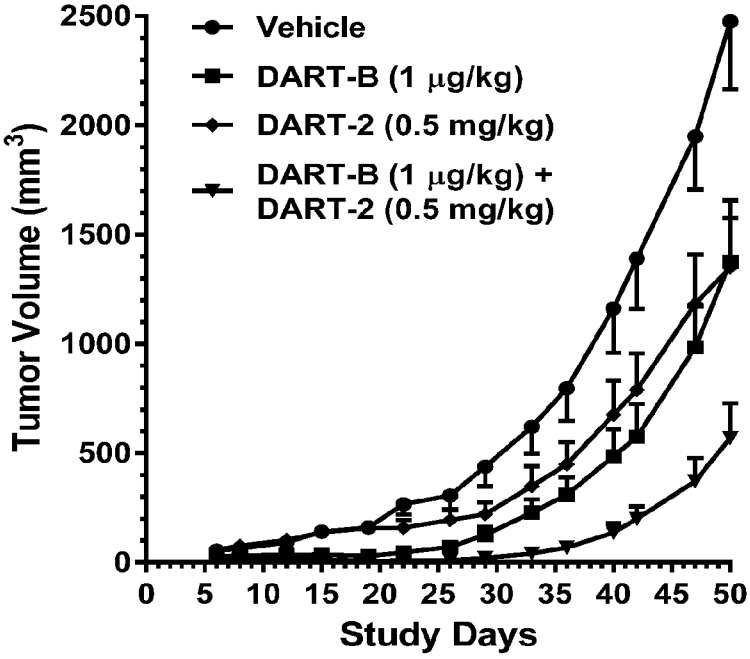

Figure 12A

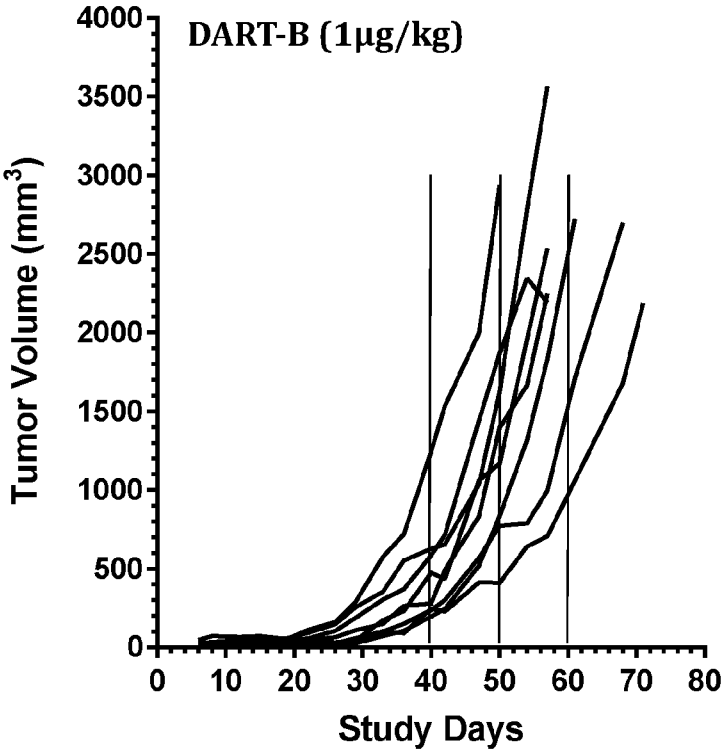

Figure 12B

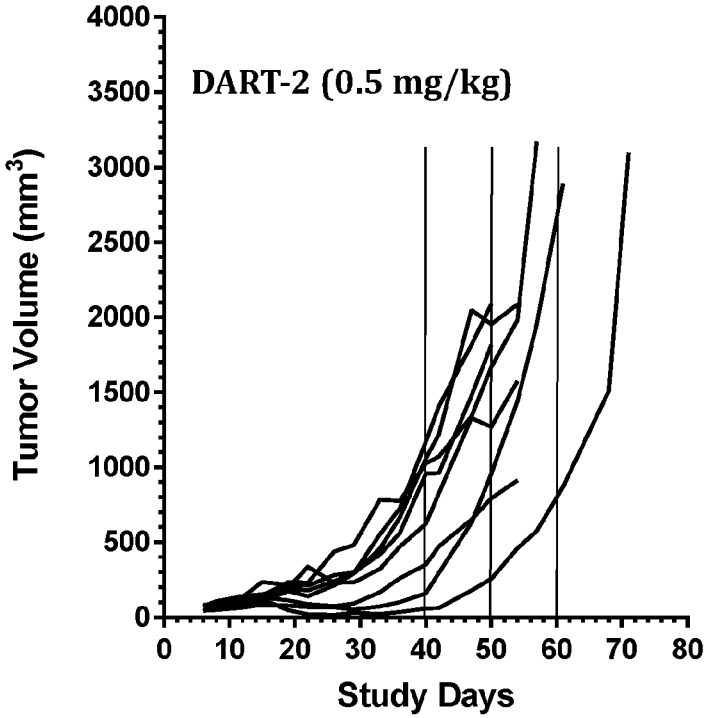

Figure 12C

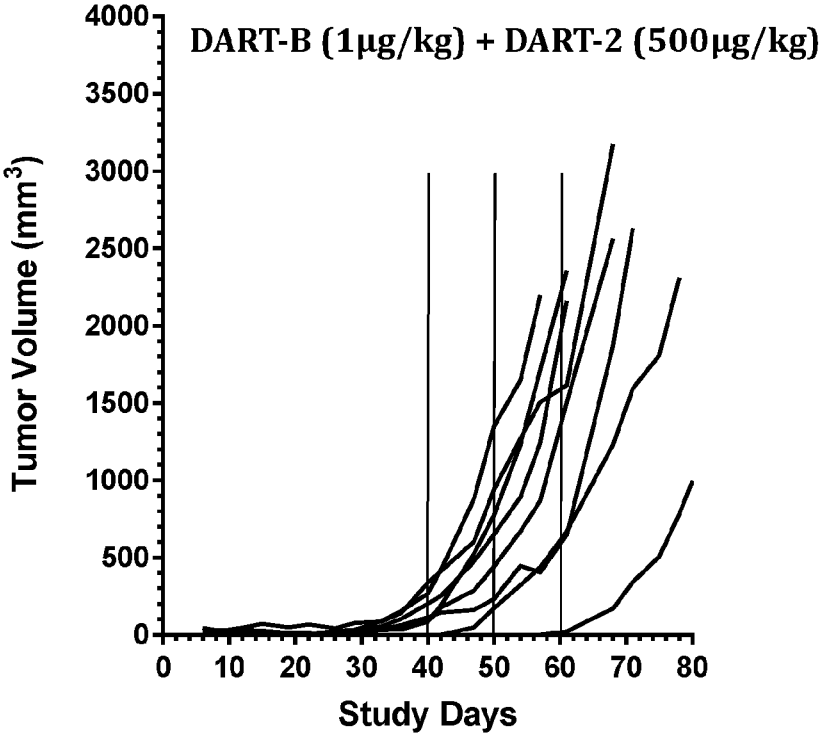

Figure 12D

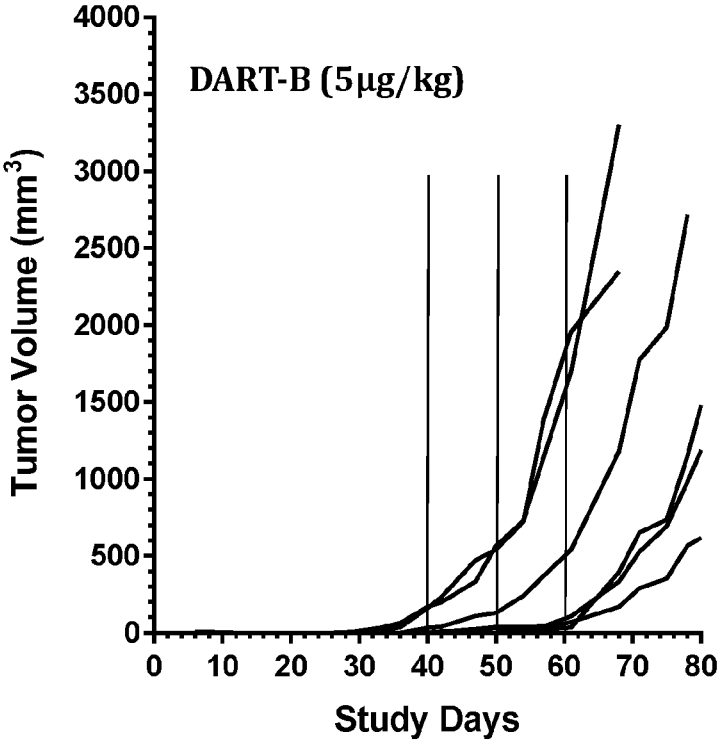

Figure 12E

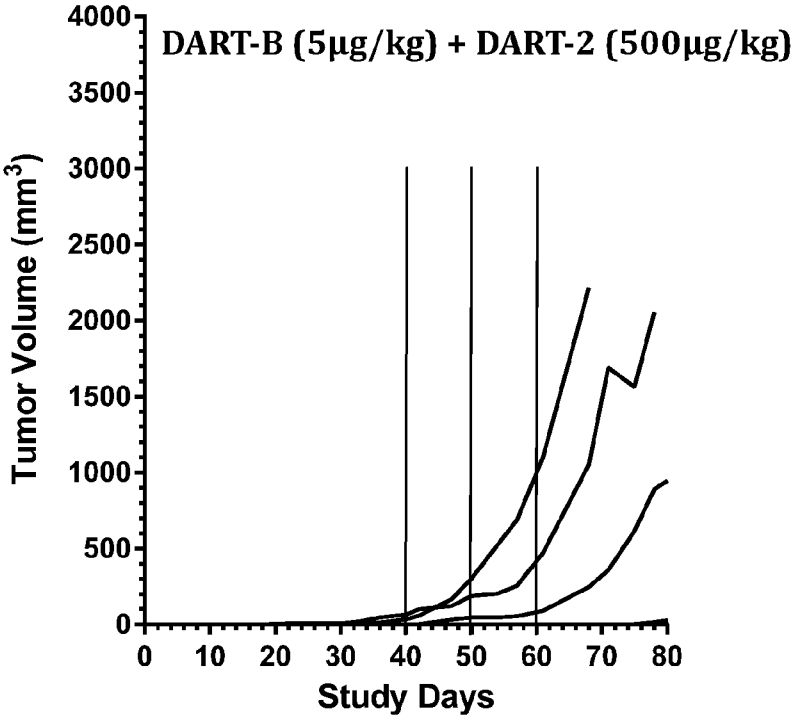

Figure 12F

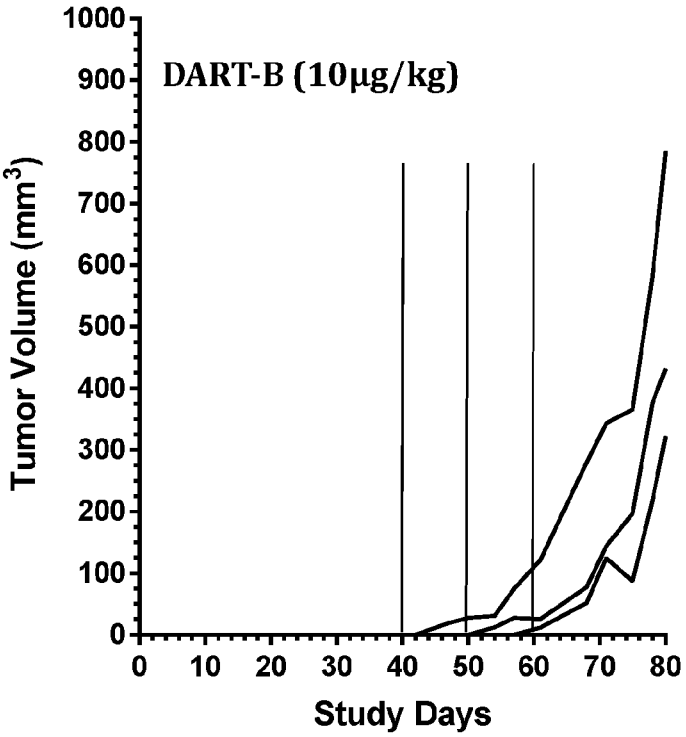

Figure 12G

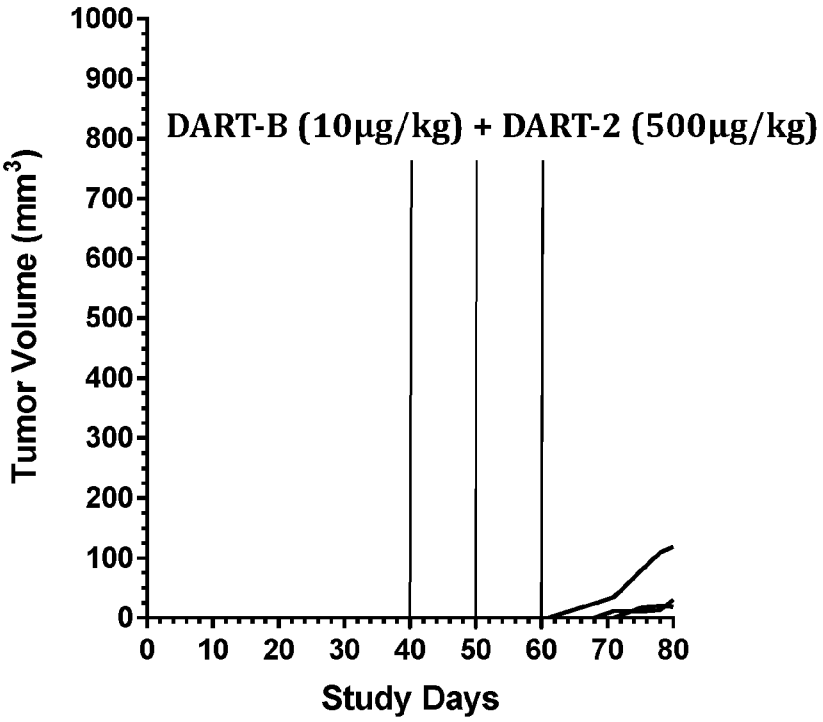

Figure 12H