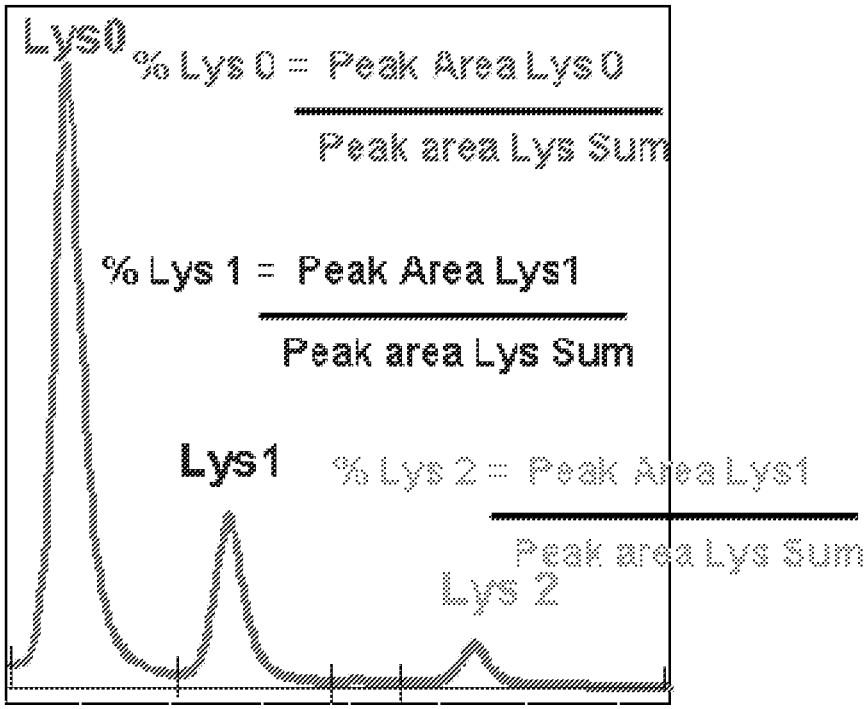


Figure 1) Representation of the lysine variants in a sample WCX-10 chromatogram and quantification scheme of each of the variants

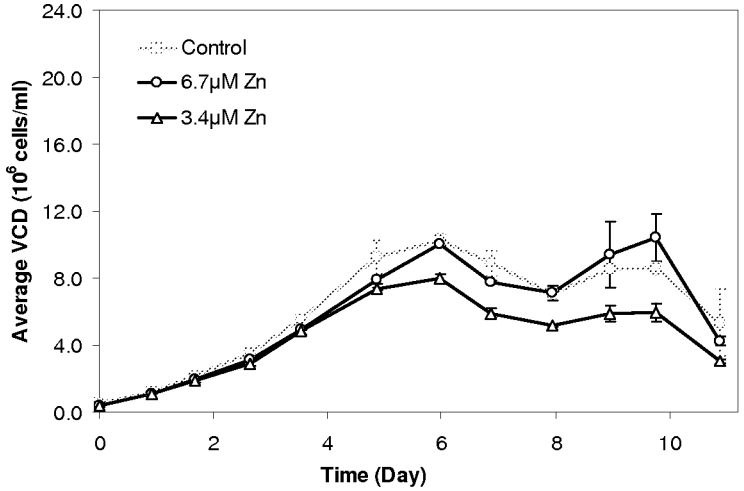


Figure 2) Effect of zinc modulation in adalimumab producing cell line 1, media 1 on viable cell density (n=2)

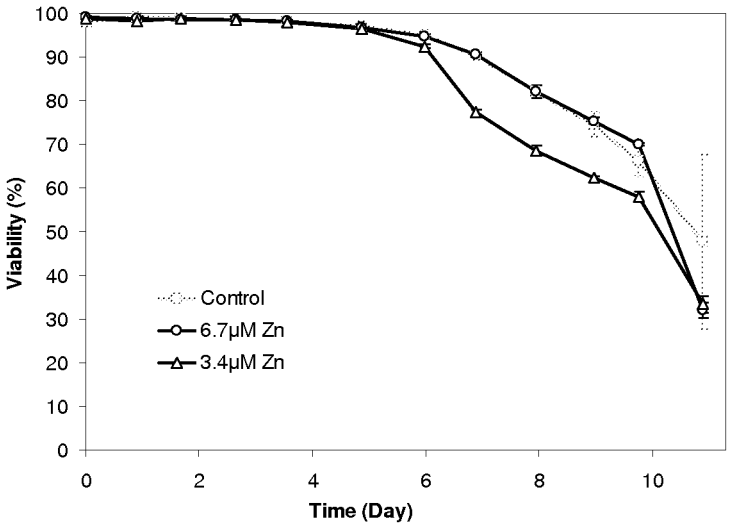


Figure 3) Effect of zinc modulation in adalimumab producing cell line 1, media 1 on viability (n=2)

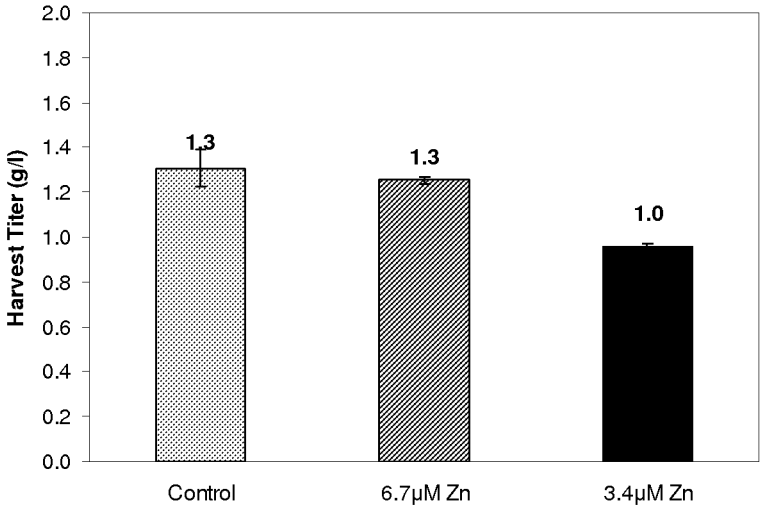


Figure 4) Effect of zinc modulation in adalimumab producing cell line 1, media 1 on harvest titer (n=2)

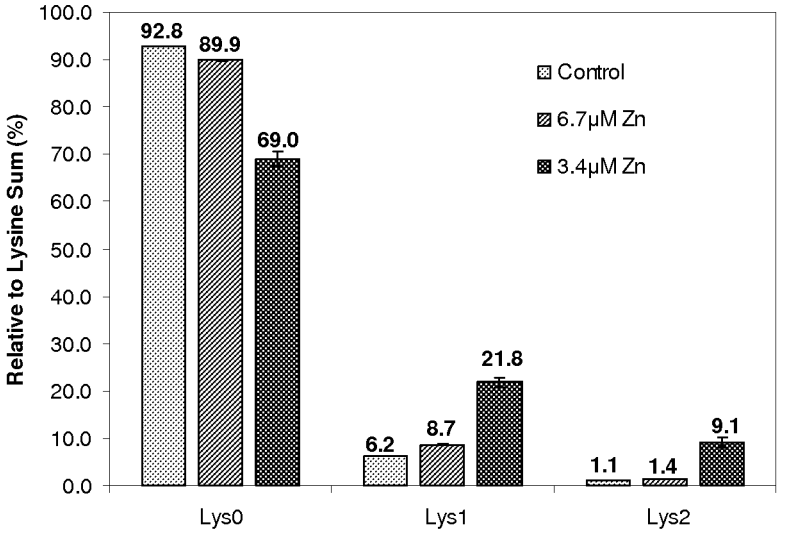


Figure 5) Effect of zinc modulation in adalimumab producing cell line 1, media 1 on day 10 WCX-10 profile relative lysine distribution (n=2)

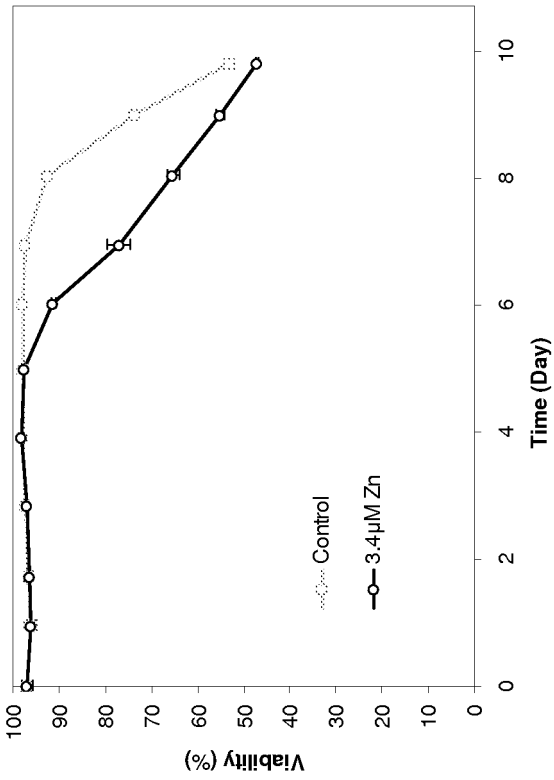


Figure 7) Effect of zinc modulation in adalimumab producing cell line 1, media 1 on viability (n=2)

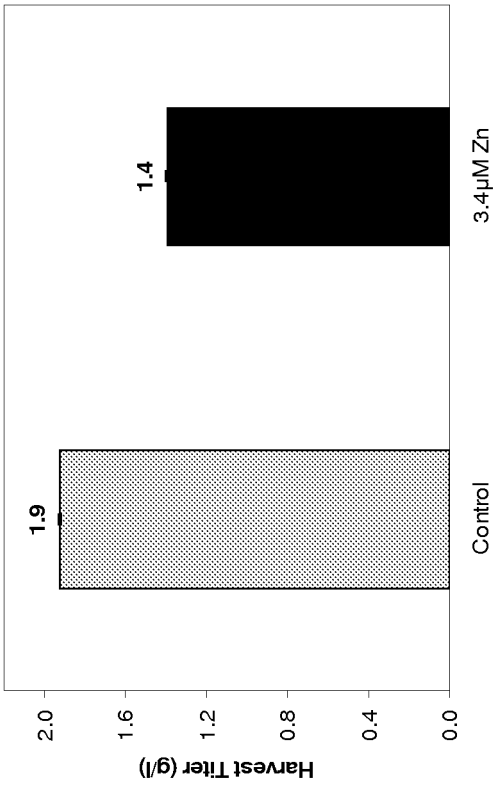


Figure 8) Effect of zinc modulation in adalimumab producing cell line 1, media 1 on harvest titer (n=2)

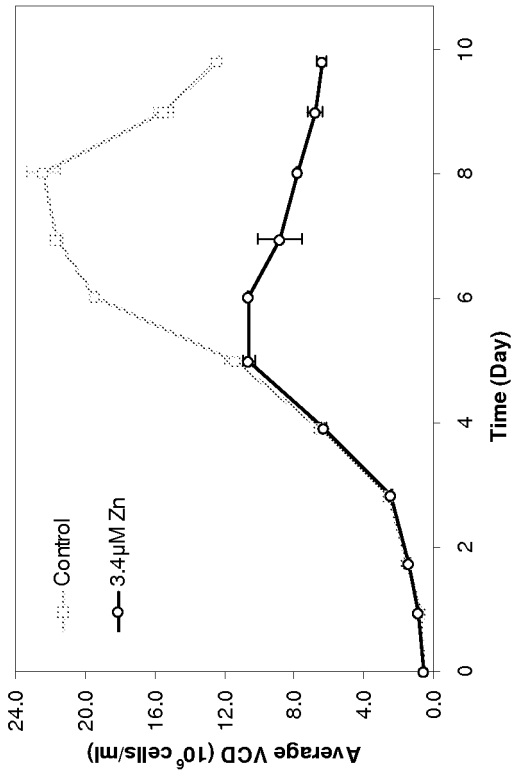


Figure 6) Effect of zinc modulation in adalimumab producing cell line 1, media 1 on viable cell density (n=2)

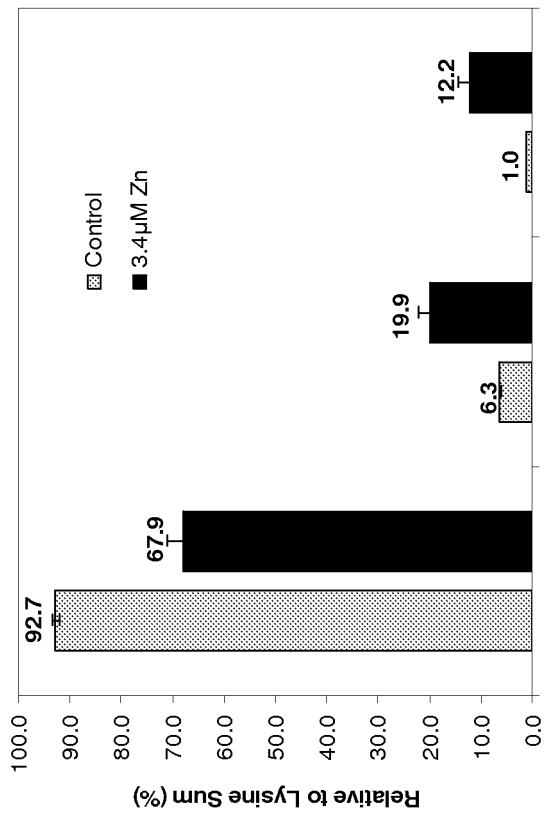


Figure 9) Effect of zinc modulation in adalimumab producing cell line 1, media 1 on day 10 WCX-10 profile relative lysine distribution (n=2)

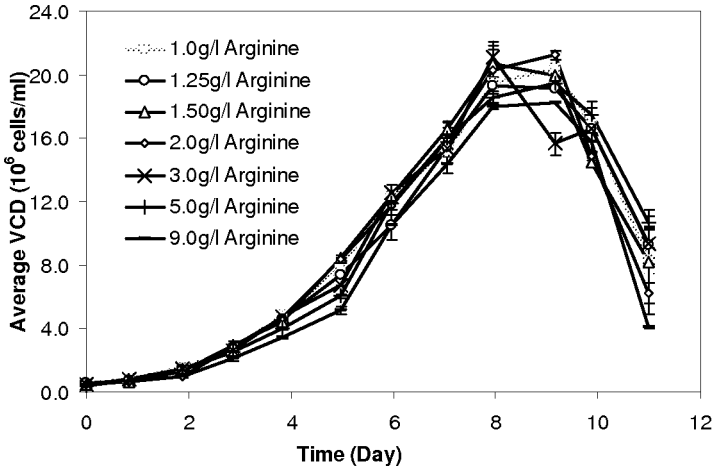


Figure 10) Effect of total arginine concentration in adalimumab producing cell line 2, media 1 on viable cell density (n=2)

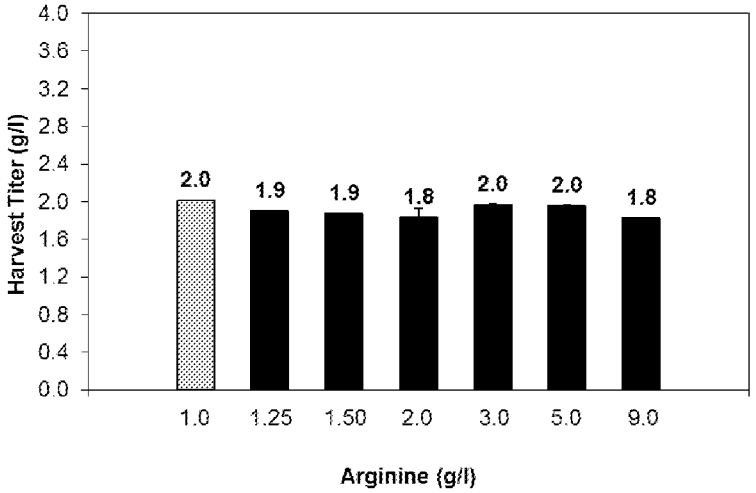


Figure 12) Effect of total arginine concentration in adalimumab producing cell line 2, media 1 on harvest titer (n=2)

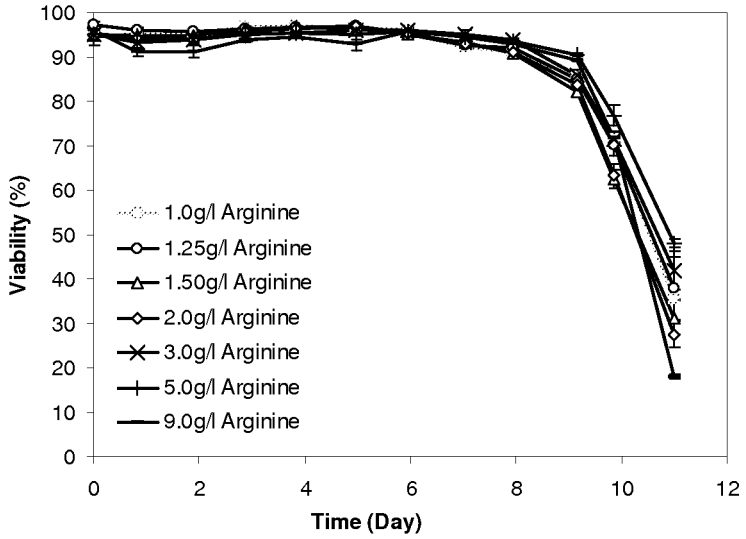


Figure 11) Effect of total arginine concentration in adalimumab producing cell line 2, media 1 on viability (n=2)

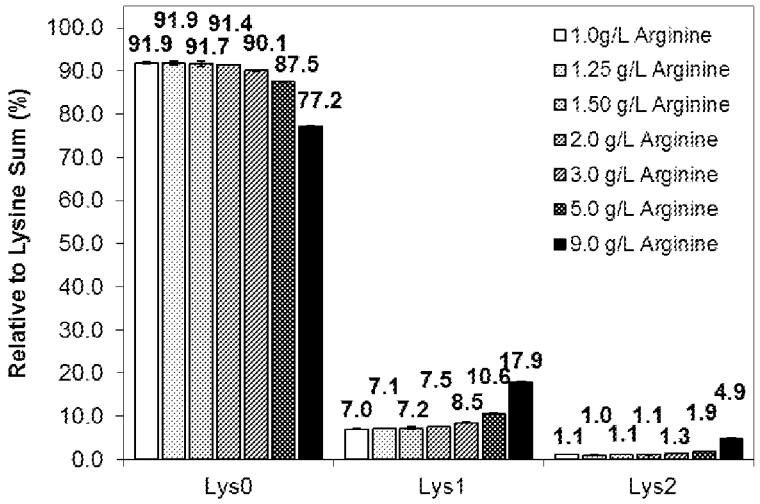


Figure 13) Effect of total arginine concentration in adalimumab producing cell line 2, media 1 on day 10 on WCX-10 profile relative lysine distribution (n=2)

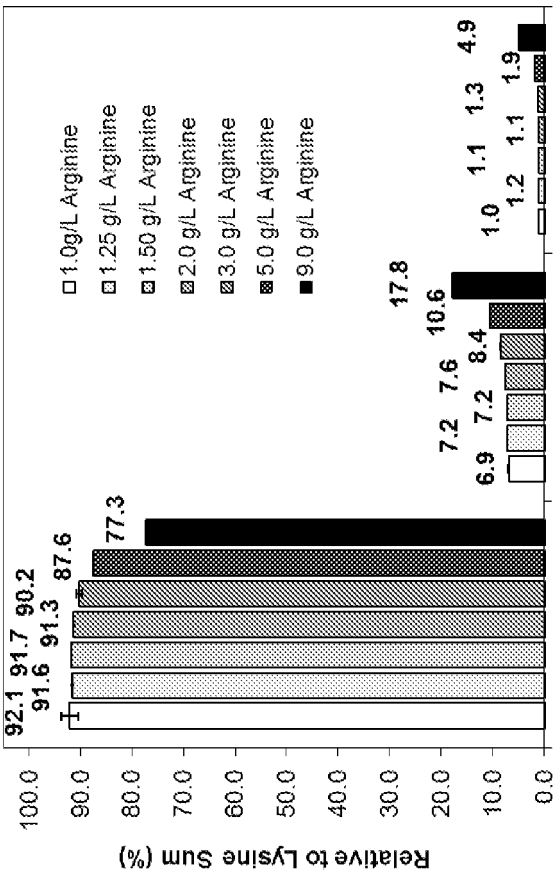


Figure 14) Effect of total arginine concentration in adalimumab producing cell line 2, media 1 on day 12 on WCX-10 profile relative lysine distribution (n=2)

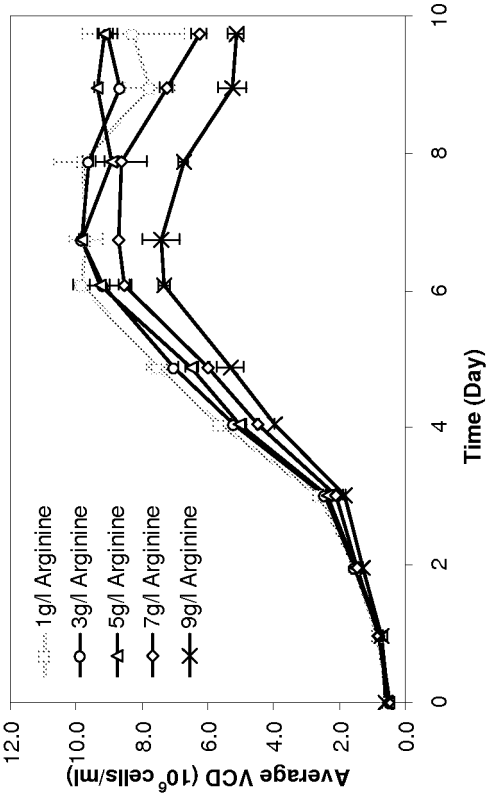


Figure 15)Effect of total arginine concentration in adalimumab producing cell line 3, media 1 on viable cell density (n=2)

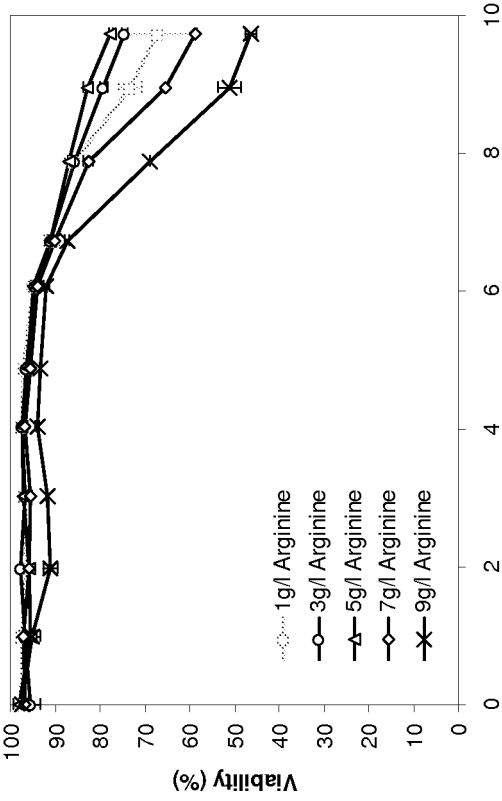


Figure 16) Effect of total arginine concentration in adalimumab producing cell line 3, media 1 on viability (n=2)

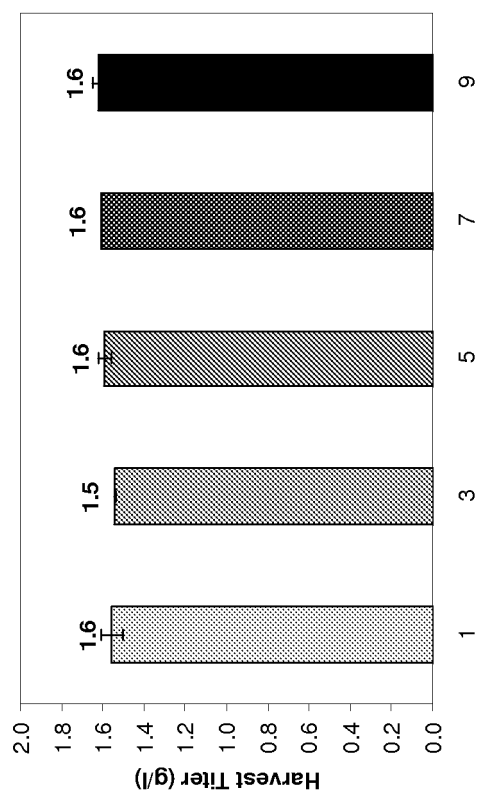


Figure 17) Effect of total arginine concentration in adalimumab producing cell line 3, media 1 on harvest titer (n=2)

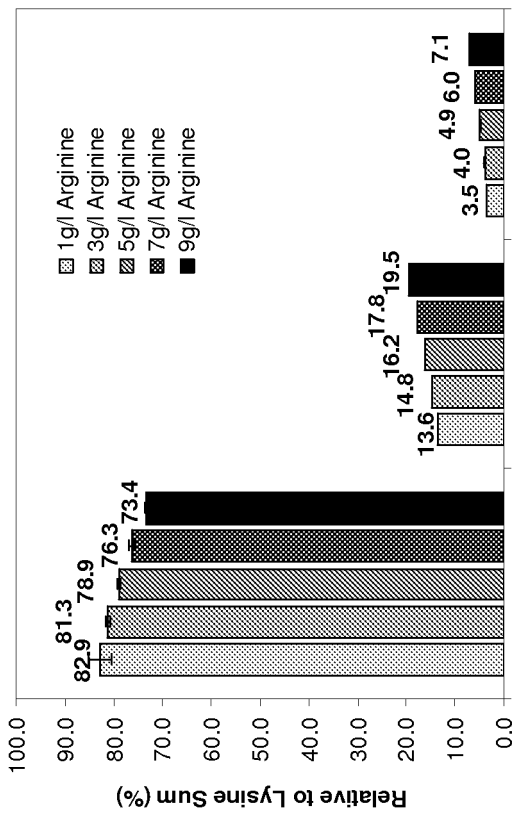


Figure 18) Effect of total arginine concentration in adalimumab producing cell line 3, media 1 on WCX-10 profile relative lysine distribution (n=2)

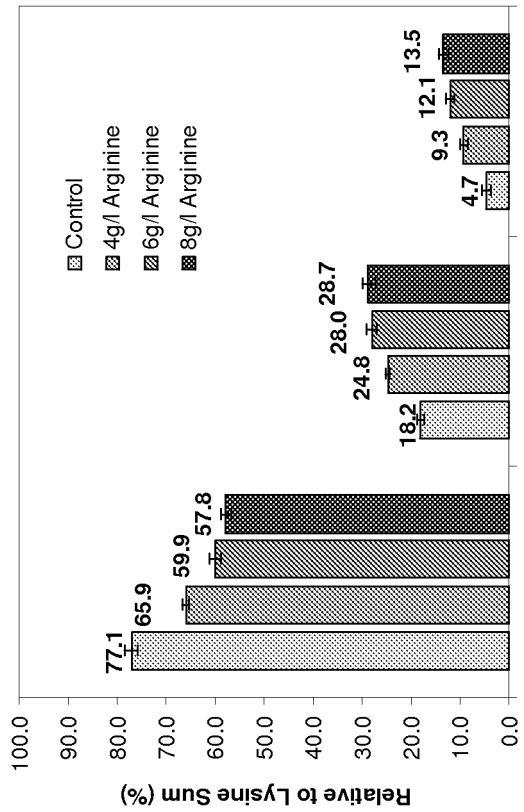


Figure 20) Effect of arginine addition to adalimumab producing cell line 1, media 2 on day 11 on WCX-10 profile relative lysine distribution (n=2)

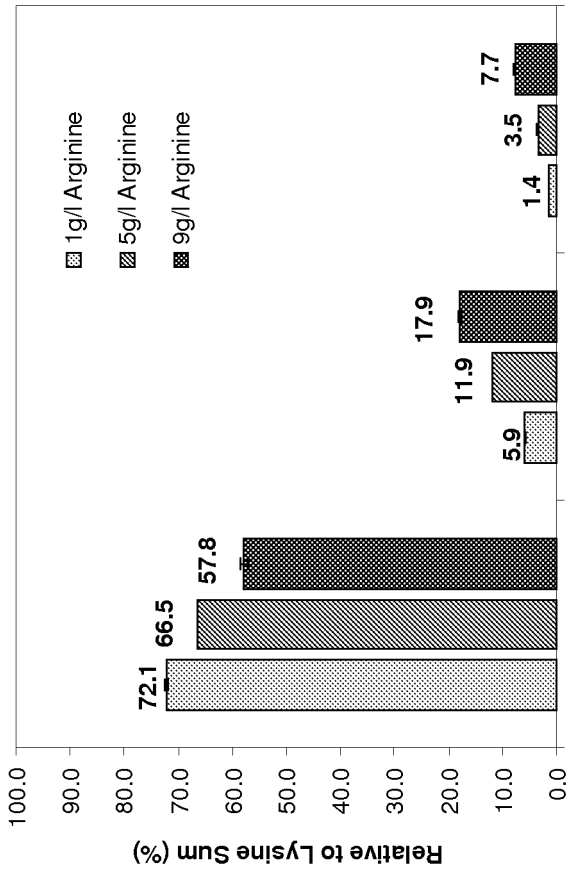


Figure 19) Effect of total arginine concentration in adalimumab producing cell line 1, media 1 on WCX-10 profile relative lysine distribution (n=2)

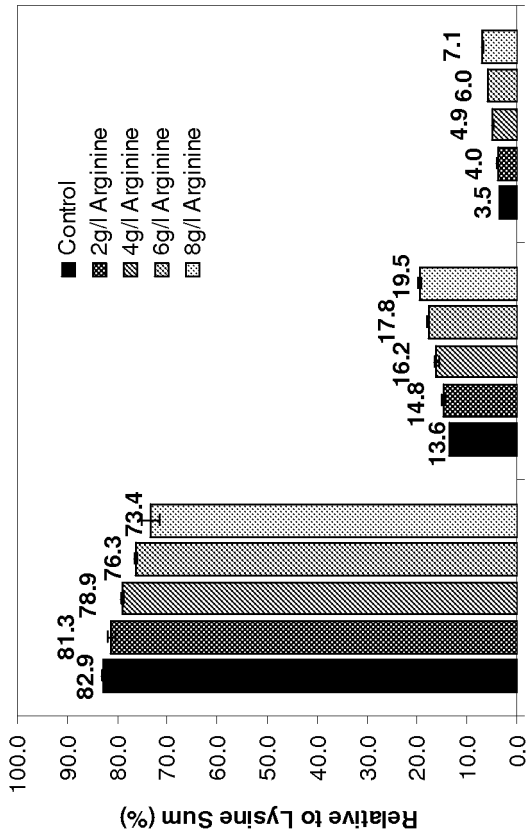


Figure 21) Effect of arginine addition to adalimumab producing cell line 2, media 3 on WCX-10 profile relative lysine distribution (n=2)

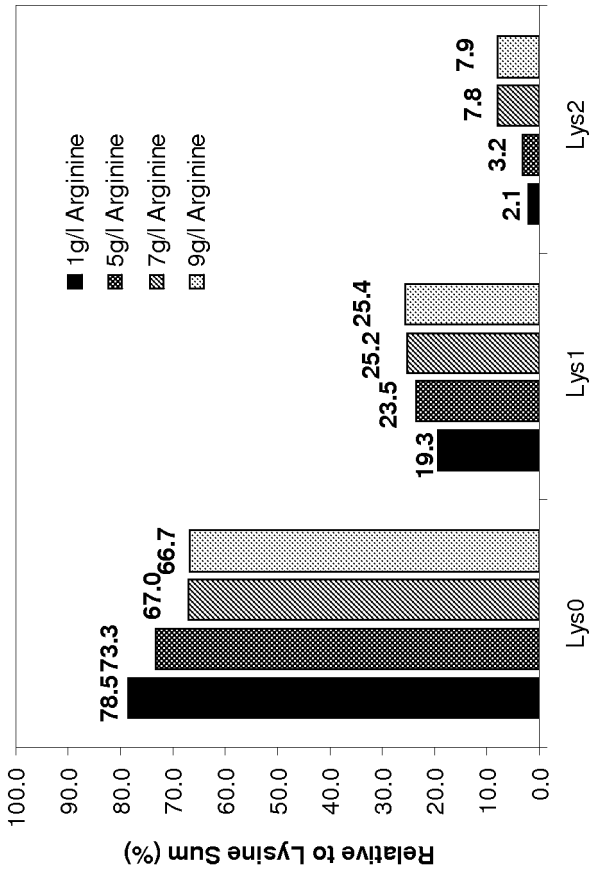


Figure 22) Effect of total arginine concentration in mAb1 producing cell line on WCX-10 profile relative lysine distribution (nn=1)

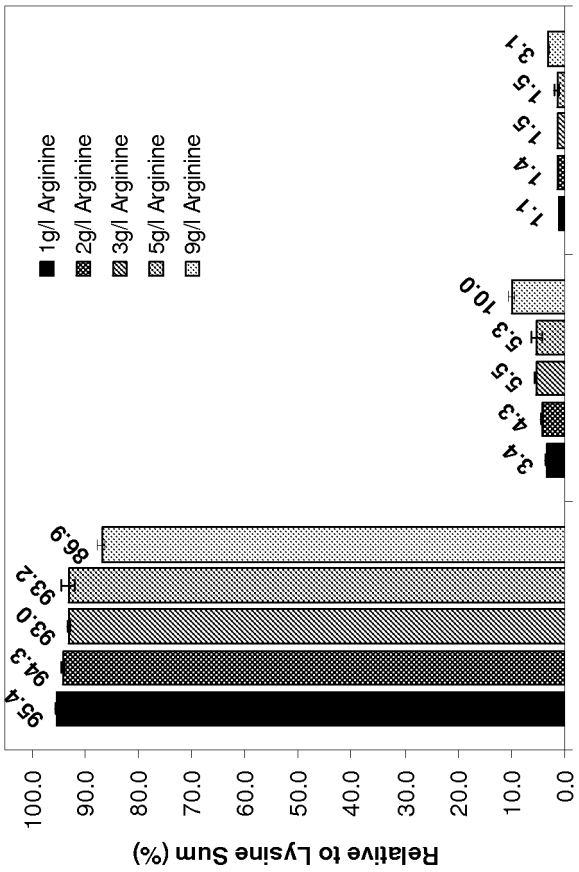


Figure 23) Effect of total arginine concentration in mAb2 producing cell line on WCX-10 profile relative lysine distribution (n=2)

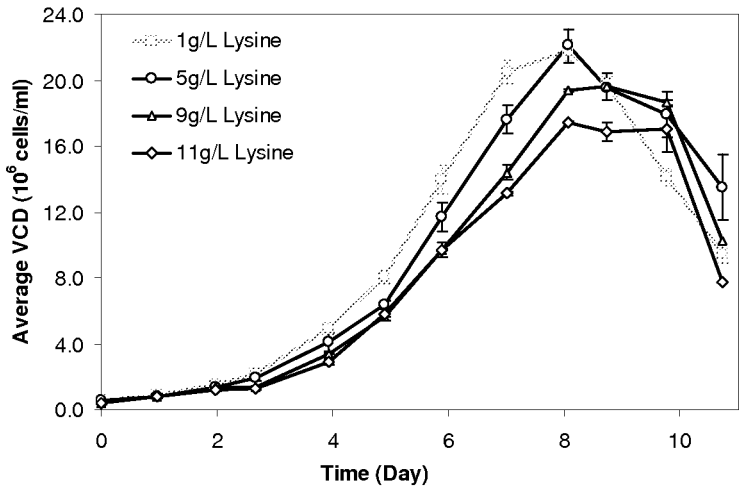


Figure 24) Effect total lysine concentration in adalimumab producing cell line 2, media 1 on viable cell density (n=2)

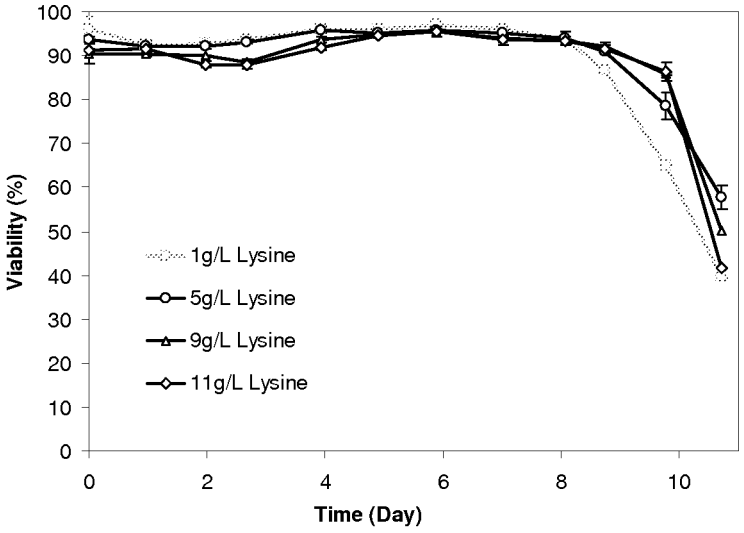


Figure 25) Effect of total lysine concentration in adalimumab producing cell line 2, media 1 on viability (n=2)

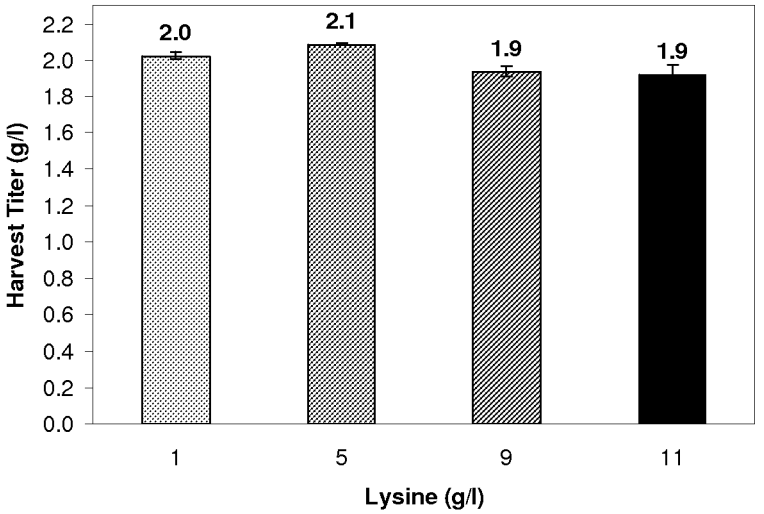


Figure 26) Effect of total lysine concentration in adalimumab producing cell line 2, media 1 on harvest titer (n=2)

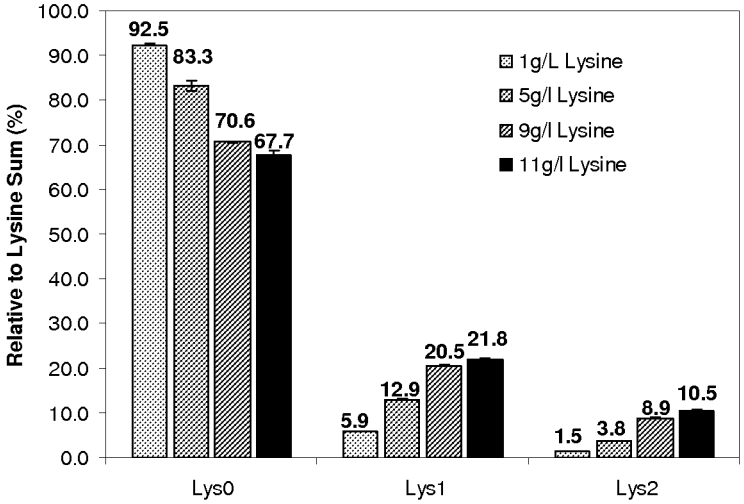


Figure 27) Effect of total lysine concentration in adalimumab producing cell line 2, media 1 on WCX-10 profile relative lysine distribution (n=2)

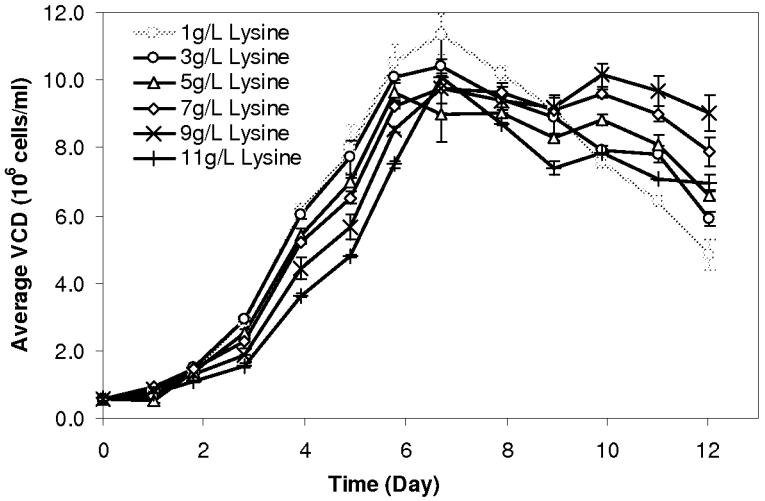


Figure 28) Effect of total lysine concentration in adalimumab producing cell line 3, media 1 on viable cell density (n=2)

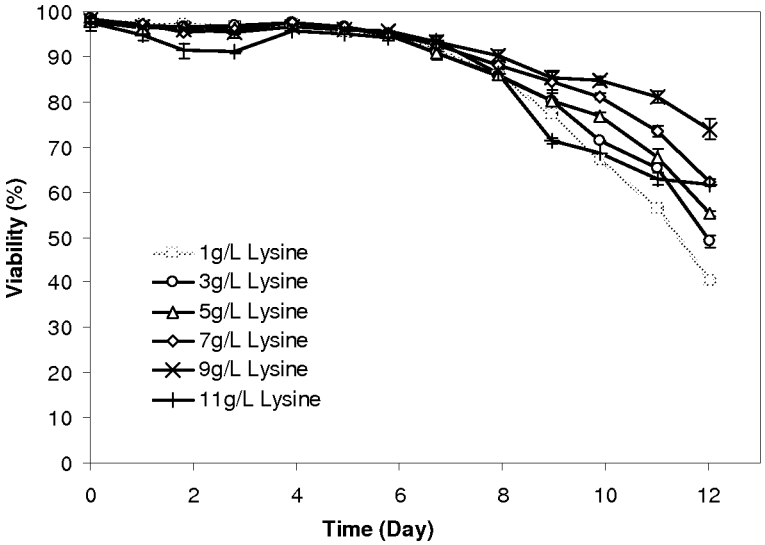


Figure 29) Effect of total lysine concentration in adalimumab producing cell line 3, media 1 on viability (n=2)

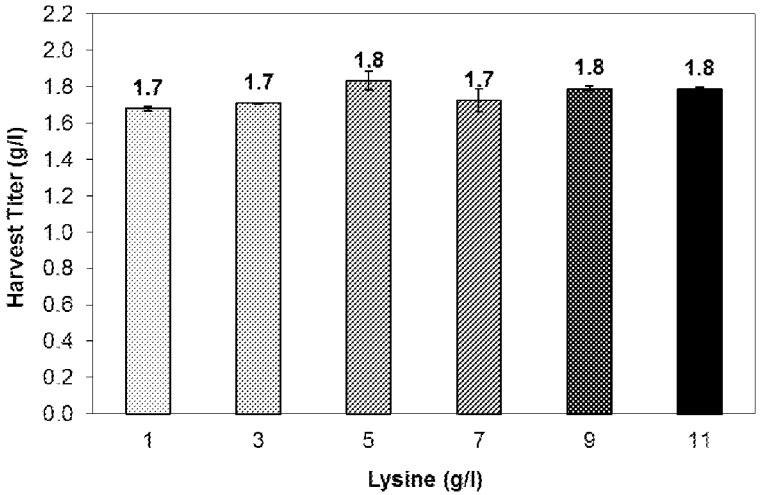


Figure 30) Effect of total lysine concentration in adalimumab producing cell line 3, media 1 on harvest titer (n=2)

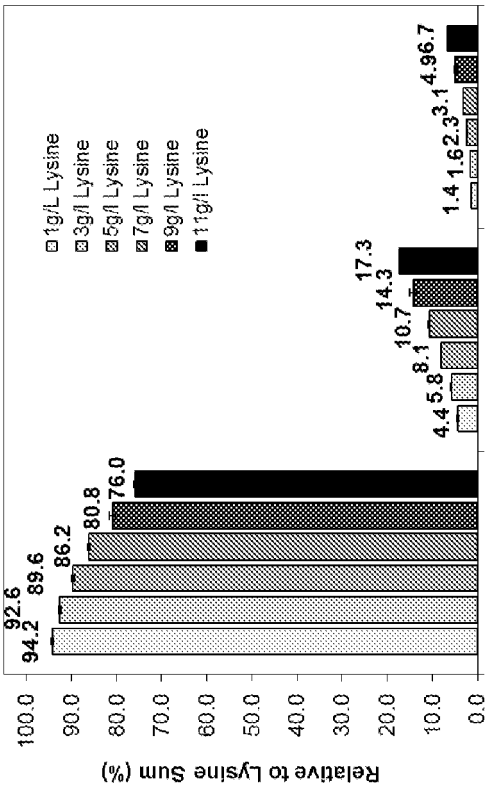


Figure 31) Effect of total lysine concentration in adalimumab producing cell line 3, media 1 on WCX-10 profile relative lysine distribution (n=2)

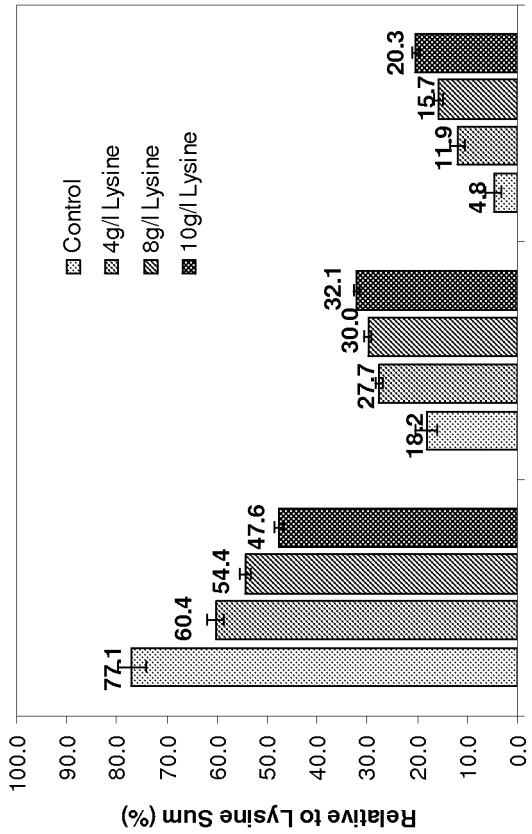


Figure 33) Effect of lysine addition to adalimumab producing cell line 1, media 2 on WCX-10 profile relative lysine distribution (n=2)

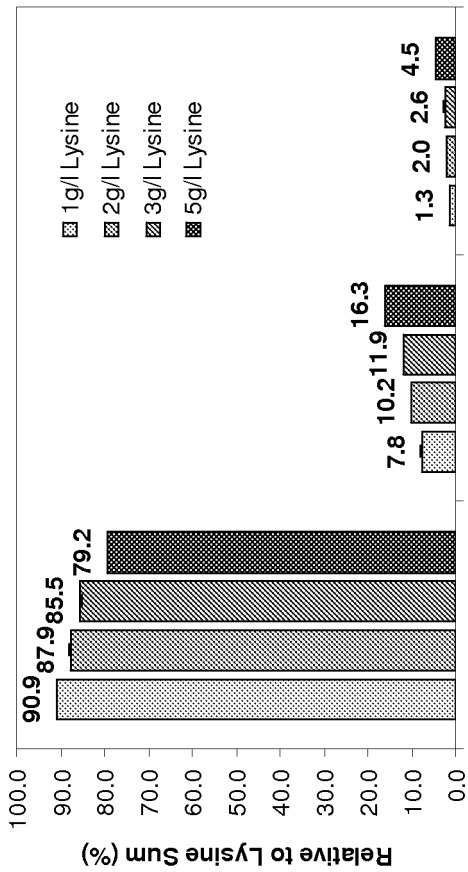


Figure 32) Effect of total lysine concentration in adalimumab producing cell line 1, media 1 on WCX-10 profile relative lysine distribution (n=2)

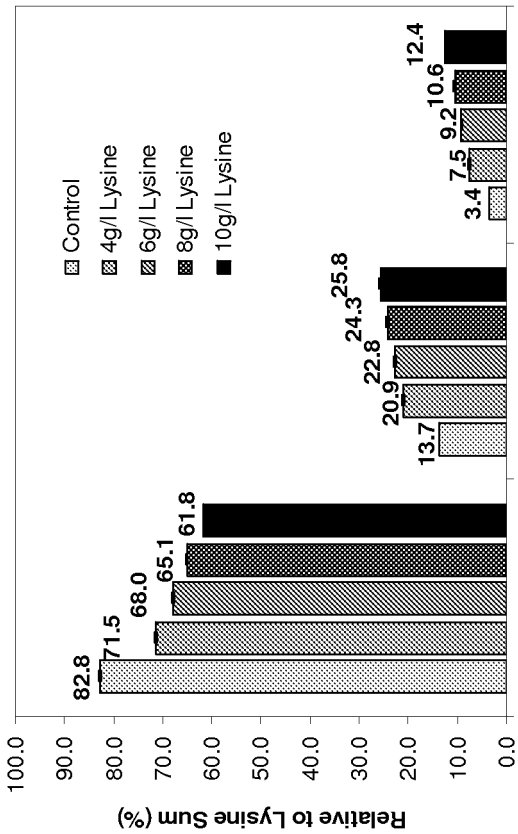


Figure 34) Effect of lysine addition to adalimumab producing cell line 2, media 3 on WCX-10 profile relative lysine distribution (n=2)

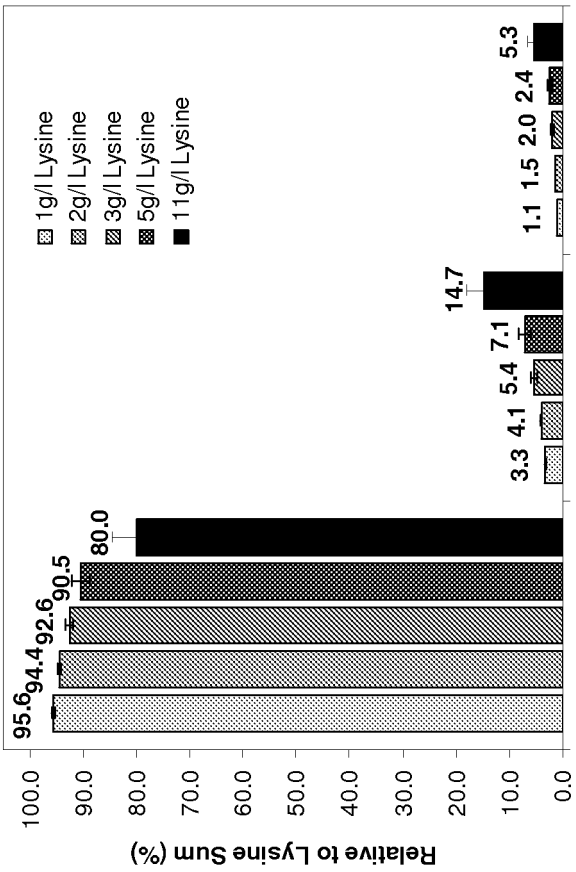


Figure 36) Effect of total lysine concentration in mAb2 producing cell line on WCX-10 profile relative lysine distribution (n=2)

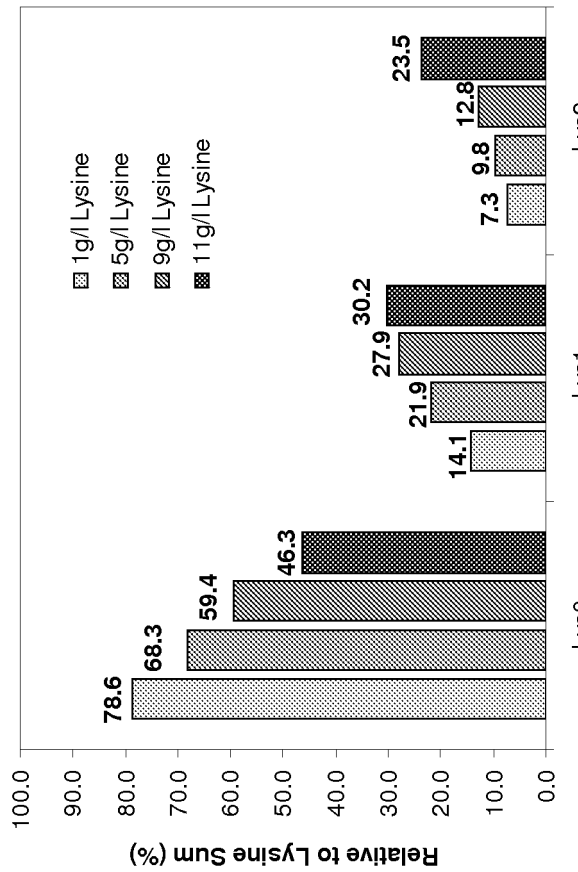


Figure 35) Effect of total lysine concentration in mAb1 producing cell line on WCX-10 profile relative lysine distribution (n=1)

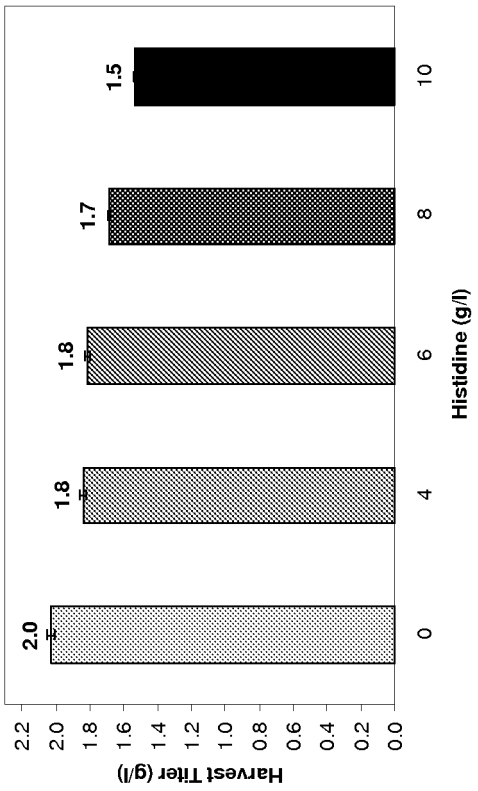


Figure 39) Effect of total histidine concentration in adalimumab producing cell line 2, media 1 on harvest titer (n=2)

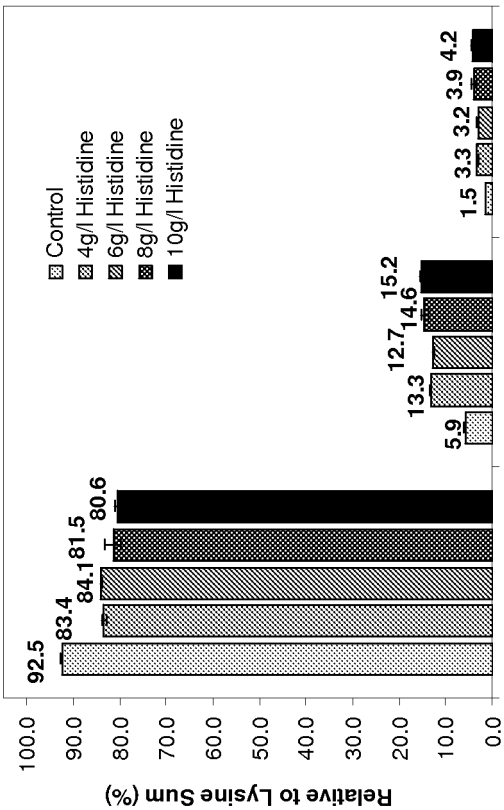


Figure 40) Effect of total histidine concentration in adalimumab producing cell line 2, media 1 on WCX-10 profile relative lysine distribution (n=2)

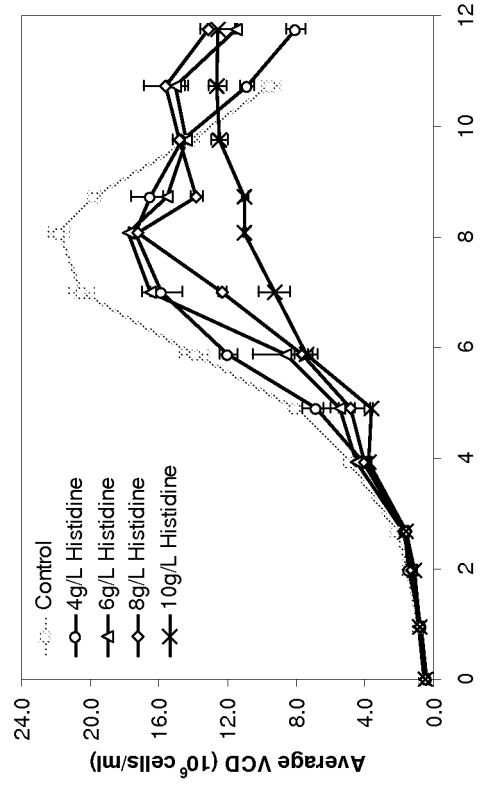


Figure 37) Effect of total histidine concentration in adalimumab producing cell line 2, media 1 on viable cell density (n=2)

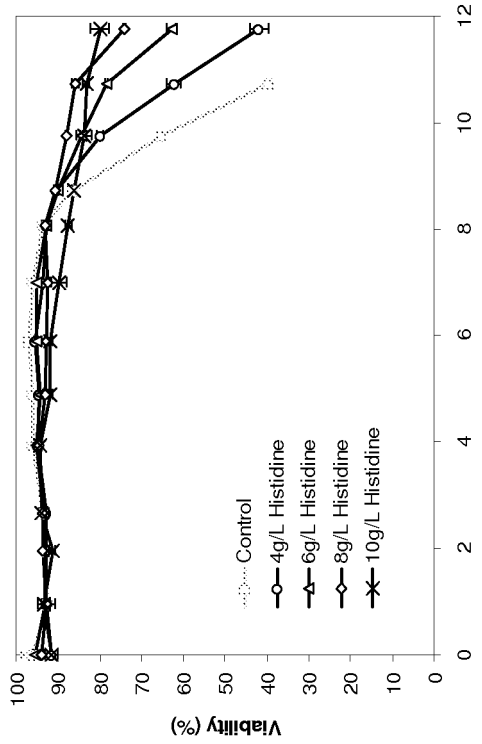


Figure 38) Effect of total histidine concentration in adalimumab producing cell line 2, media 1 on viability (n=2)

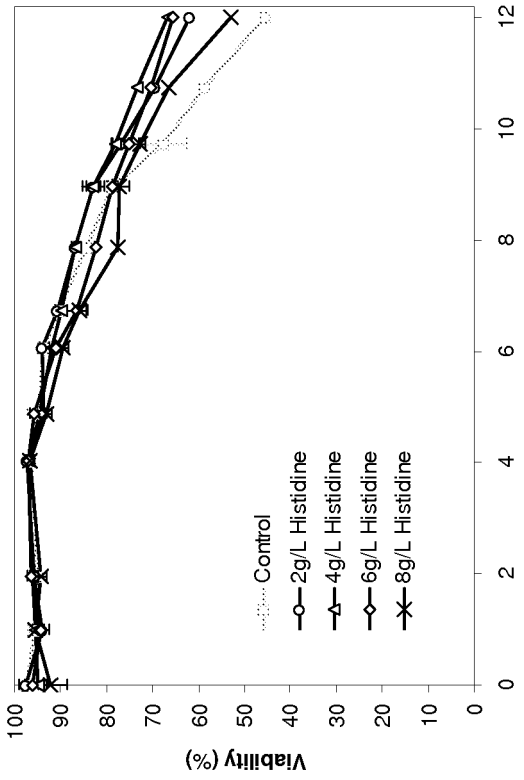


Figure 42) Effect of total histidine concentration in adalimumab producing cell line 3, media 1 on viability (n=2)

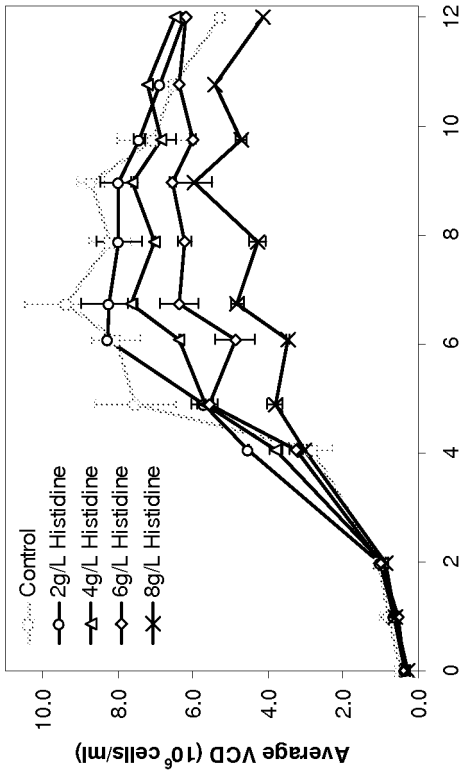


Figure 41)Effect of total histidine concentration in adalimumab producing cell line 3, media 1 on viable cell density (n=2)

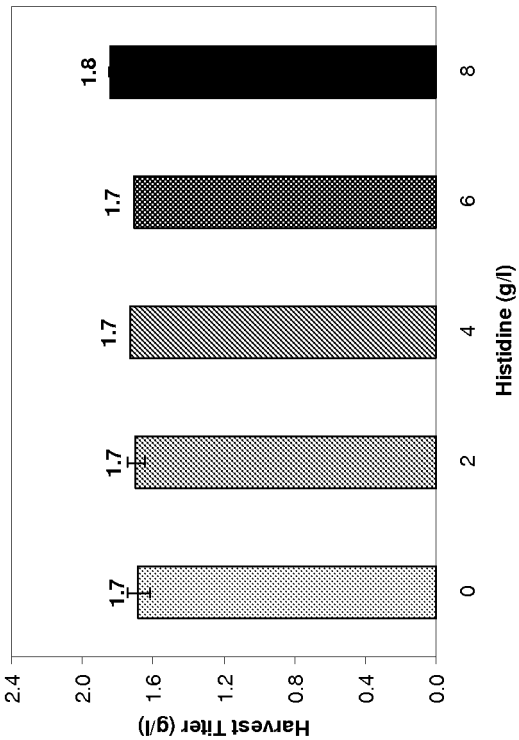


Figure 43) Effect of total histidine concentration in adalimumab producing cell line 3, media 1 on harvest titer (n=2)

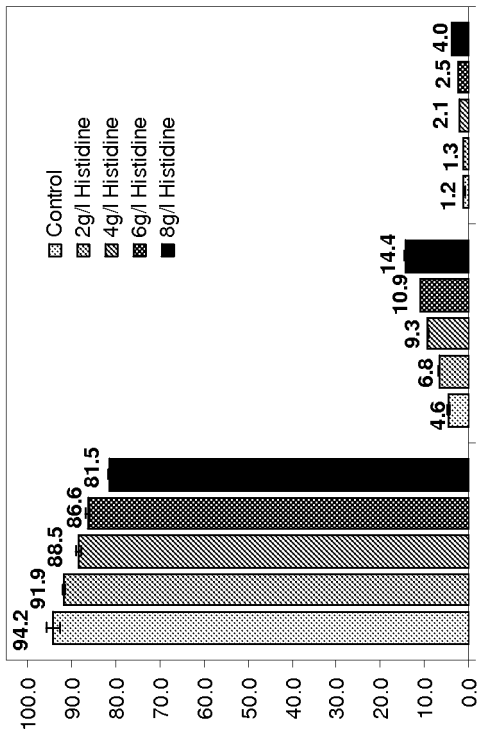


Figure 44) Effect of total histidine concentration in adalimumab producing cell line 3, media 1 on WCX-10 profile relative lysine distribution (n=2)

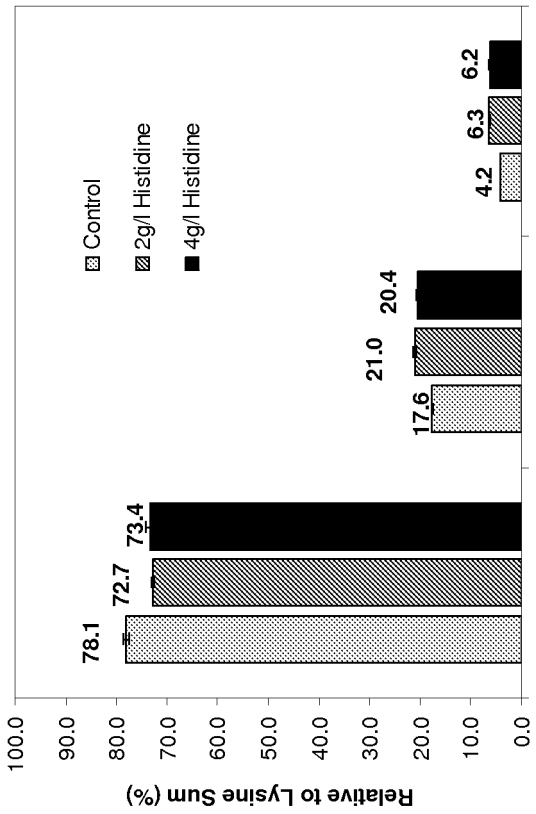


Figure 46) Effect of histidine addition to adalimumab producing cell line 1, media 2 on WCX-10 profile relative lysine distribution (n=2)

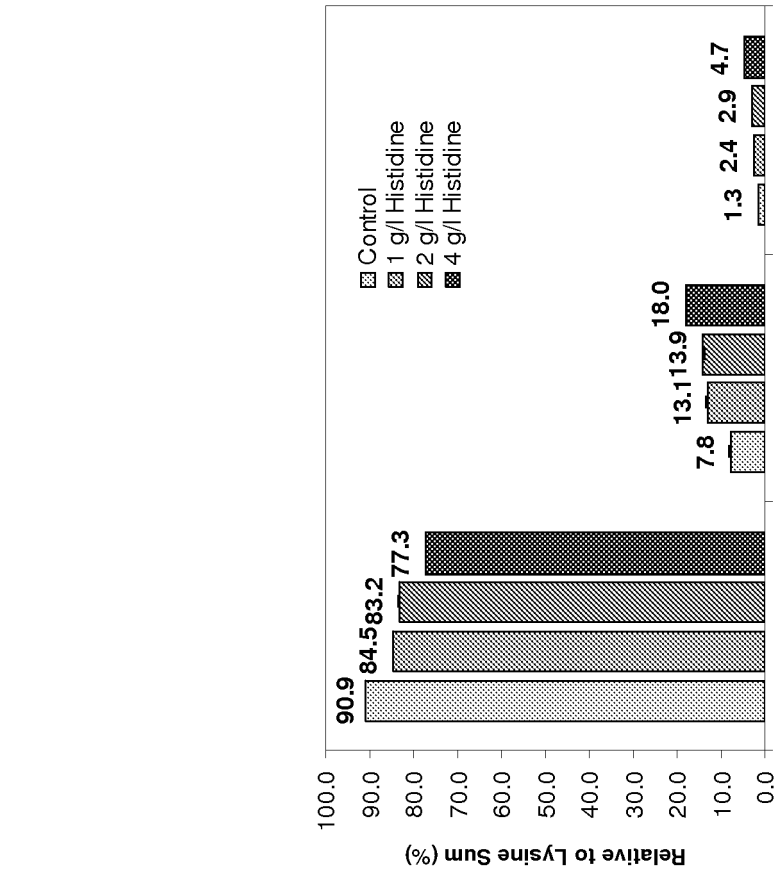


Figure 45) Effect total histidine concentration in adalimumab producing cell line 1, media 1 on WCX-10 profile relative lysine distribution (n=2)

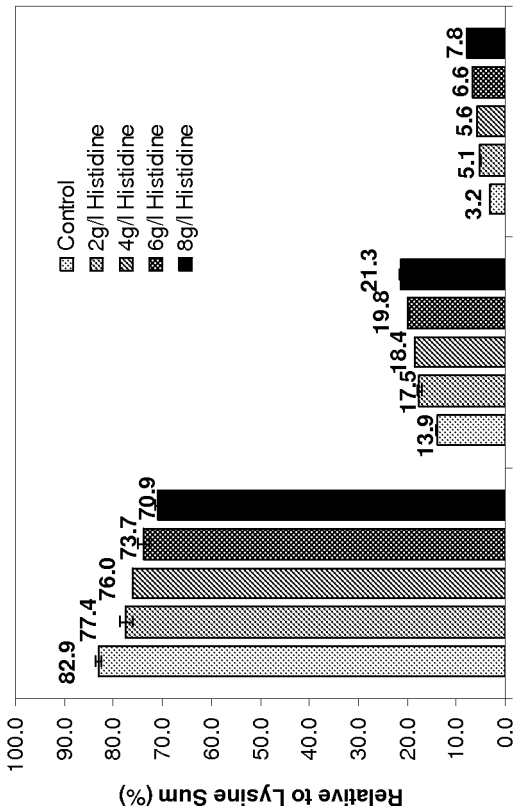


Figure 47) Effect of histidine addition to adalimumab producing cell line 2, media 3 on WCX-10 profile relative lysine distribution (n=2)

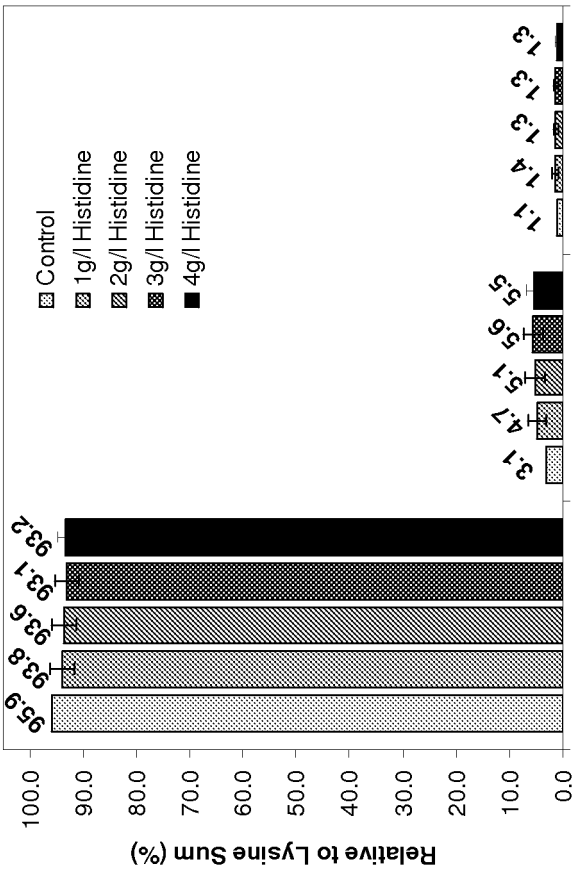


Figure 49) Effect of total histidine concentration in mAb2 producing cell line on WCX-10 profile relative lysine distribution (n=2)

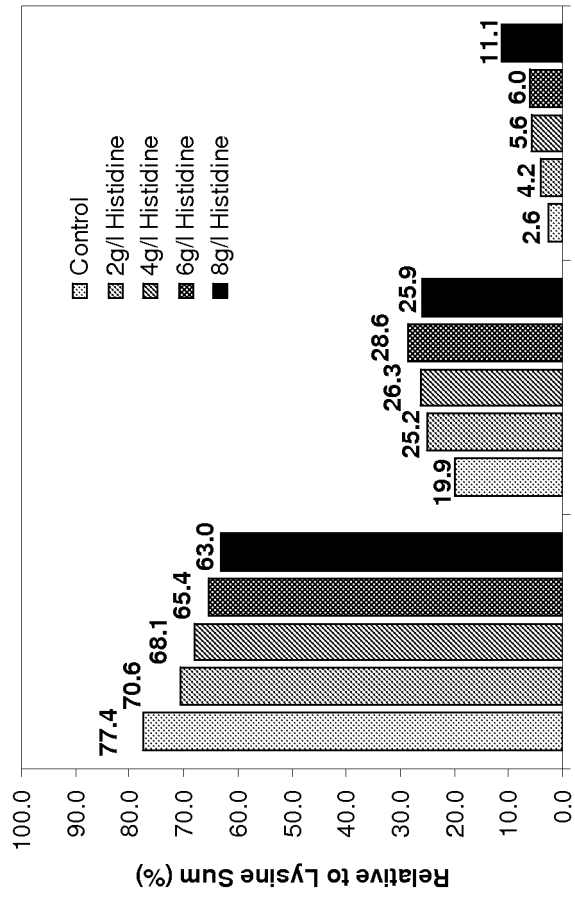


Figure 48) Effect of total histidine concentration in mAb1 producing cell line on WCX-10 profile relative lysine distribution (n=1)

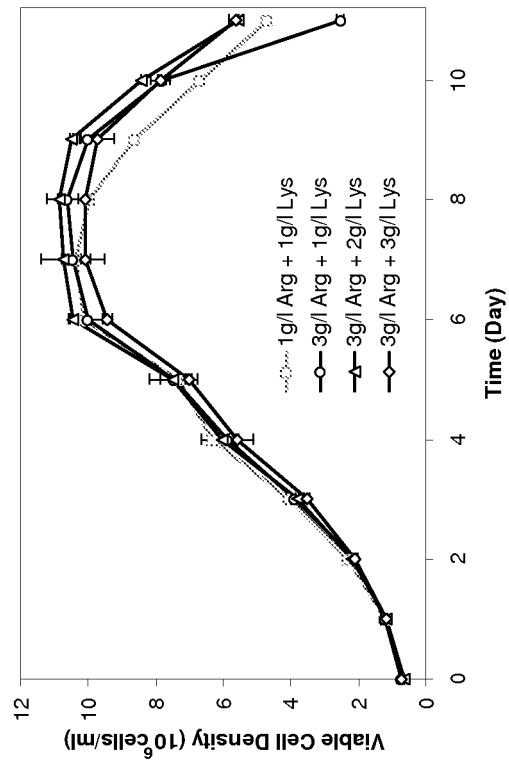


Figure 50)Effect of increase in multiple amino acids to adalimumab producing cell line 1, media 1 on viable cell density (n=2)

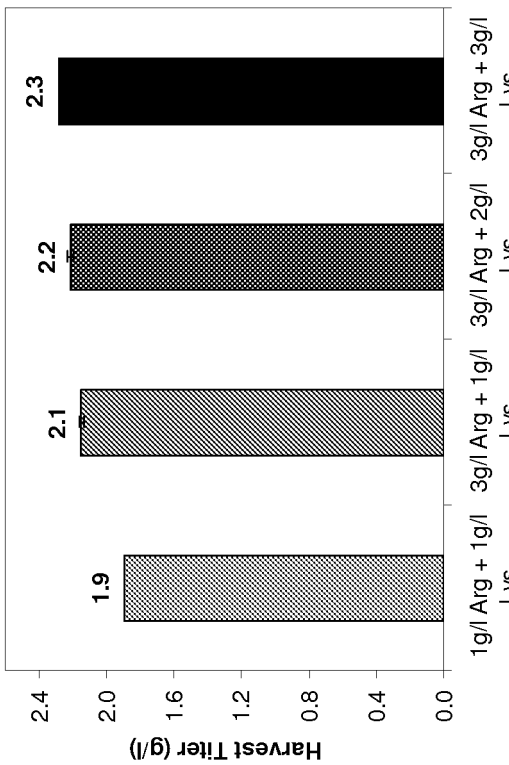


Figure 52) Effect of increase in multiple amino acids to adalimumab producing cell line 1, media 1 on harvest titer

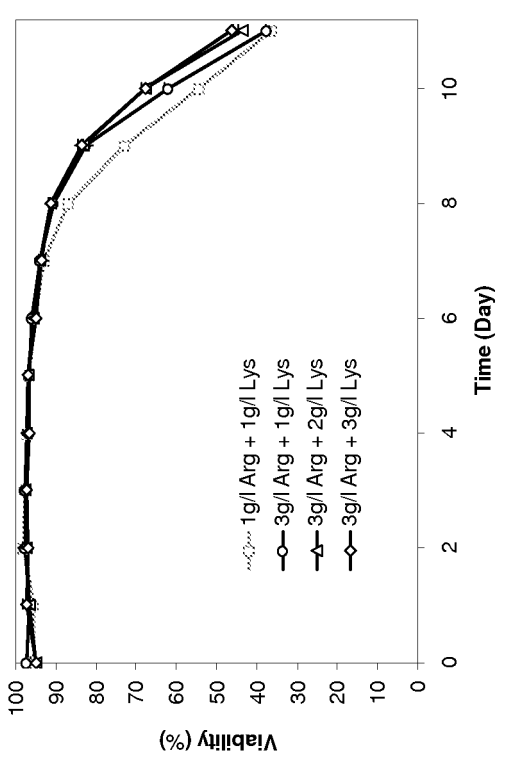


Figure 51) Effect of increase in multiple amino acids to adalimumab producing cell line 1, media 1 on viability

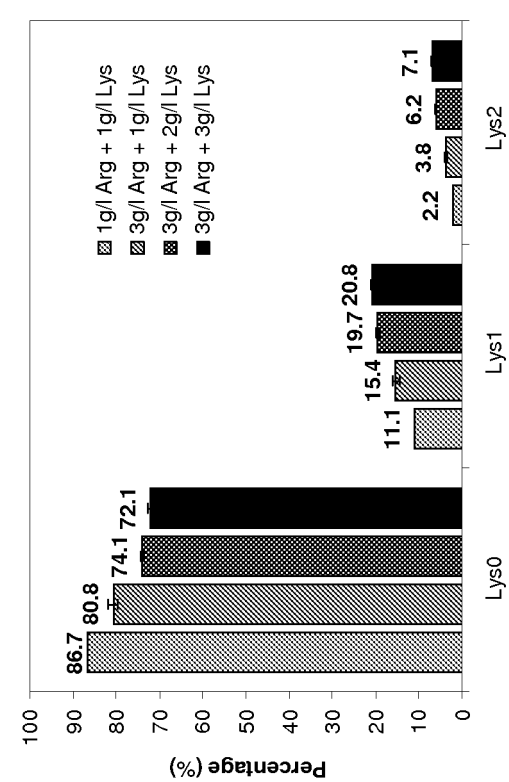


Figure 53) Effect of increase in multiple amino acids to adalimumab producing cell line 1, media 1 on WCX-10 profile relative lysine distribution

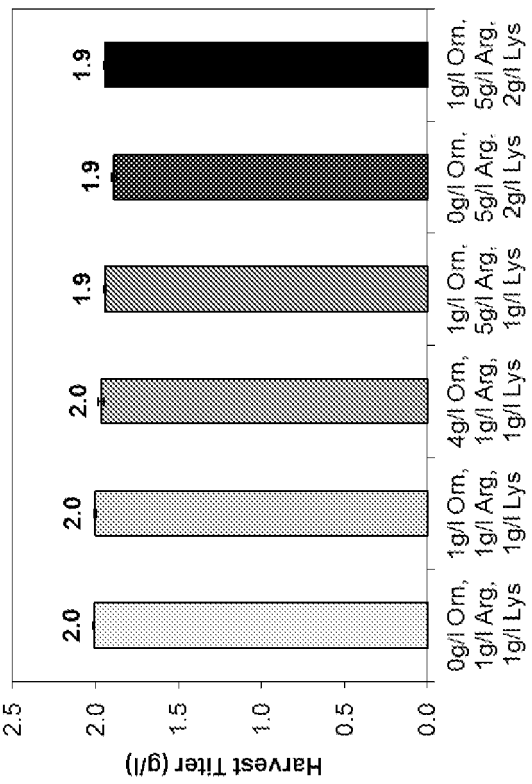


Figure 56) Effect of increase in multiple amino acids to adalimumab producing cell line 3, media 1 on harvest titer

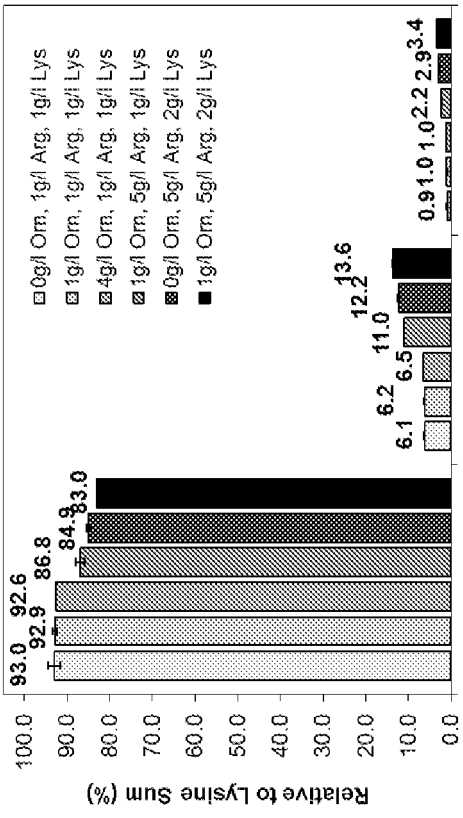


Figure 57) Effect of increase in multiple amino acids to adalimumab producing cell line 3, media 1 on WCX-10 profile relative lysine distribution

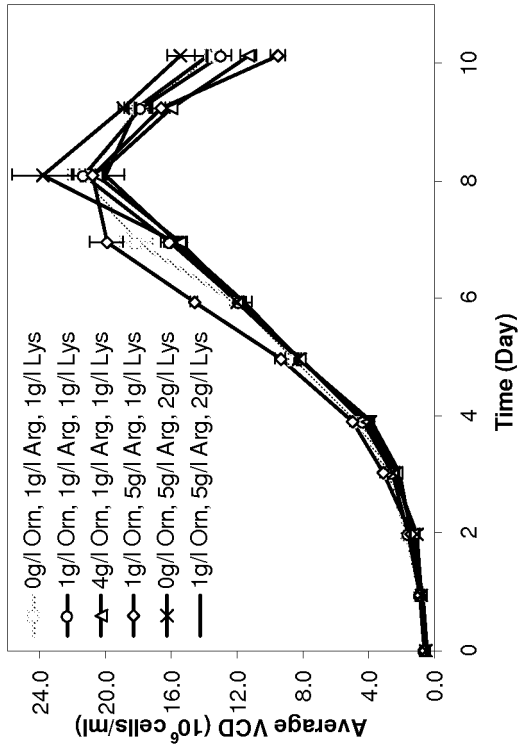


Figure 54)Effect of increase in multiple amino acids to adalimumab producing cell line 3, media 1 on viable cell density (n=2)

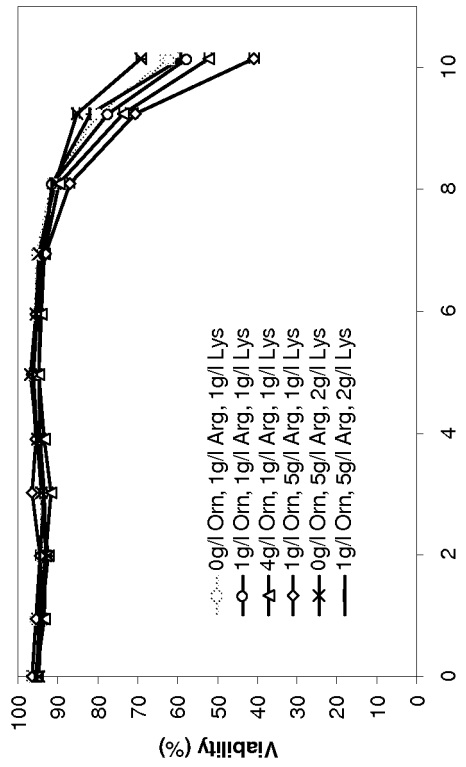


Figure 55) Effect of increase in multiple amino acids to adalimumab producing cell line 3, media 1 on viability

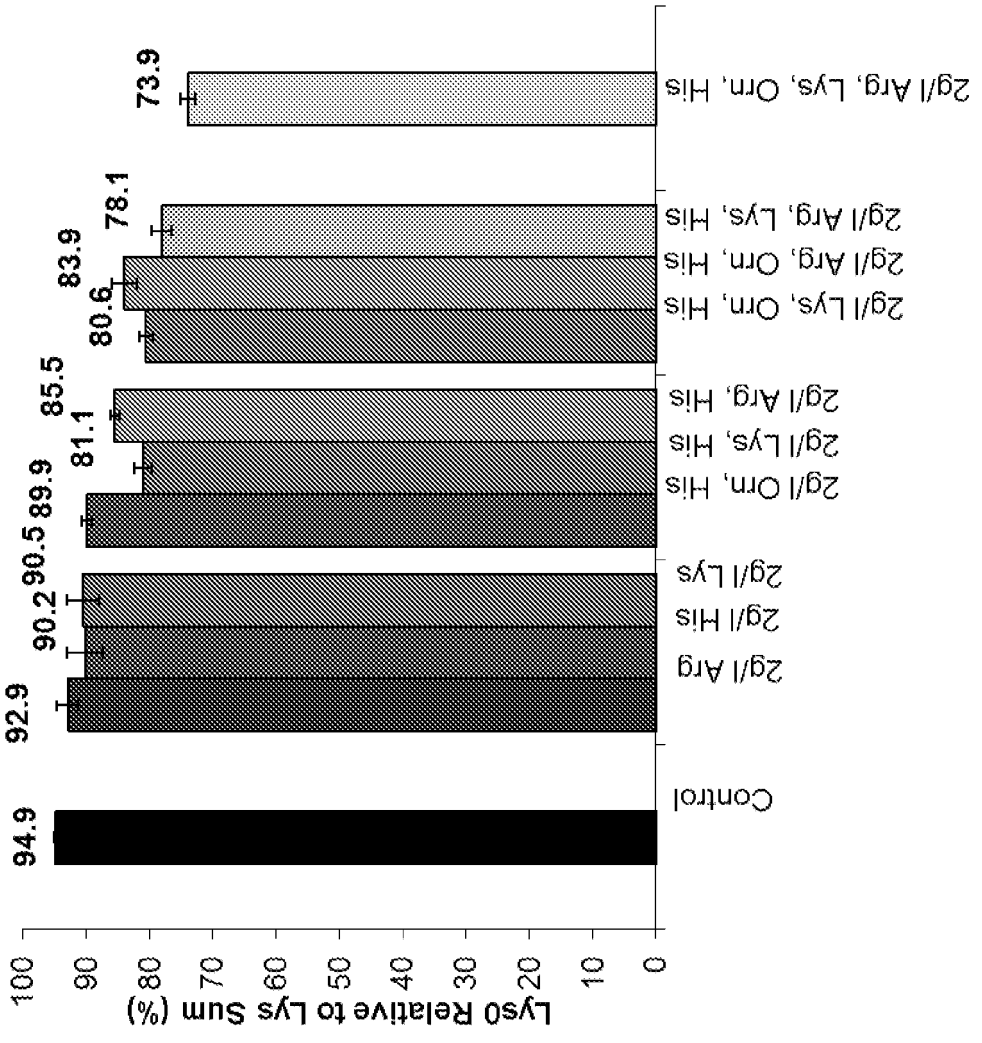


Figure 58) Effect of multiple amino acid additions to adalimumab producing cell line 2, media 1 containing 1g/l arginine and 1g/l lysine on WCX-10 profile relative lysine distribution (n=2)

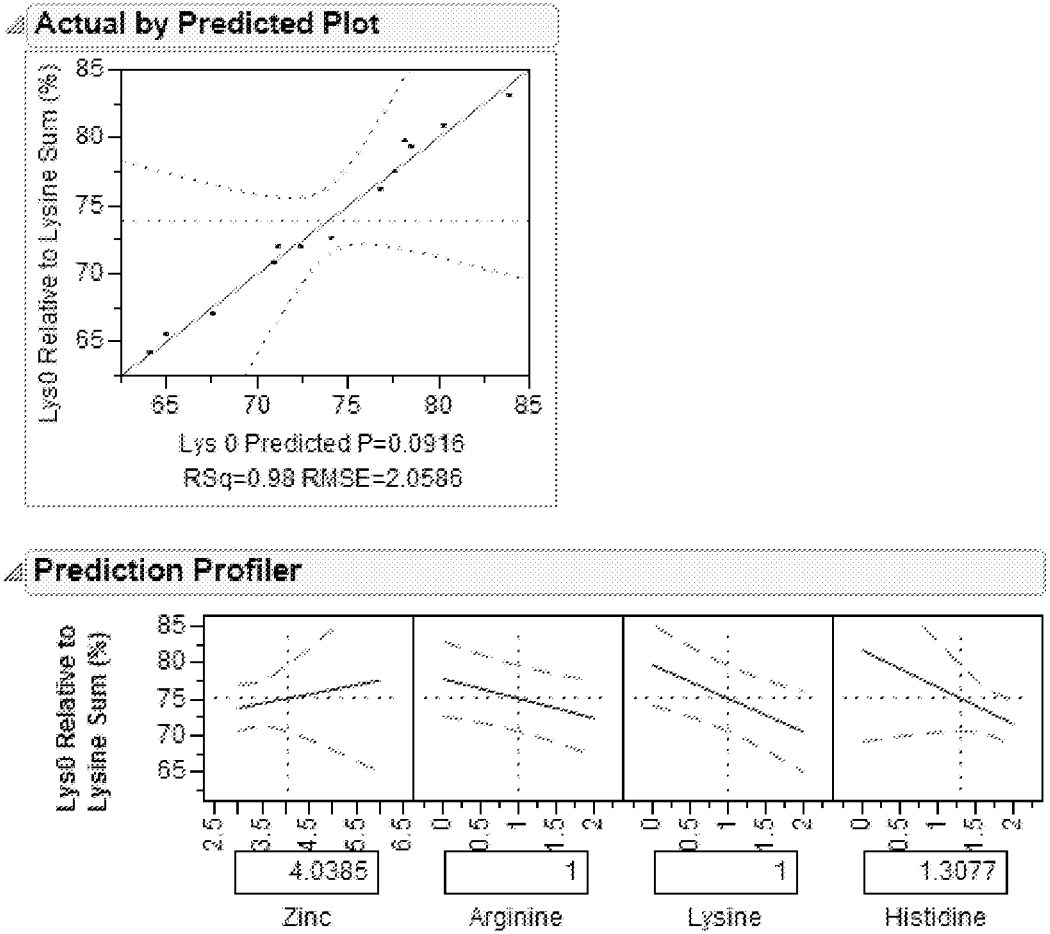


Figure 59) Effect of modulations of zinc and multiple amino acid concentrations in adalimumab producing cell line 1, media 1 on WCX-10 profile relative lysine distribution a) overall prediction plot, b) prediction plots for each additive

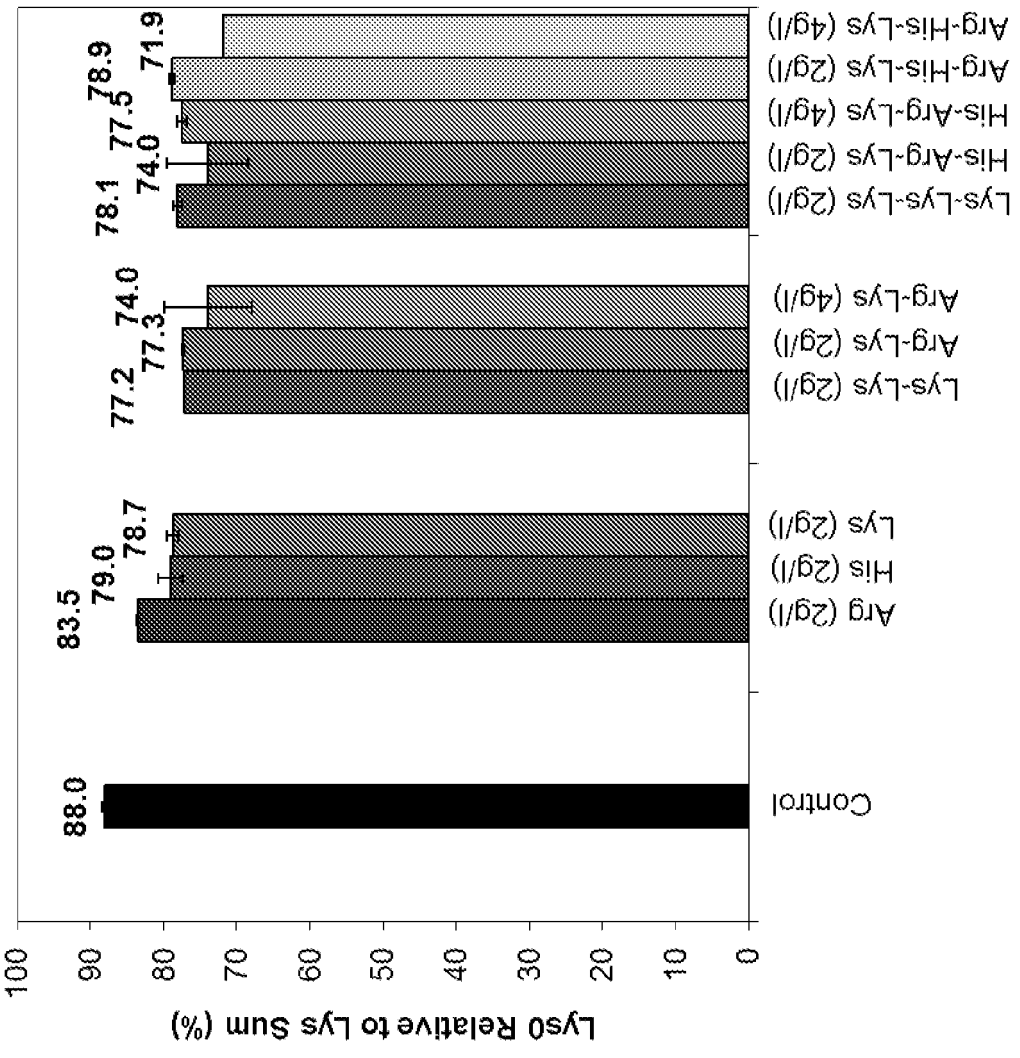


Figure 60) Effect of peptides of varying length addition to adalimumab producing cell line 2, media 1 containing 1g/l arginine and 1g/l lysine on WCX-10 profile relative lysine distribution (n=2)

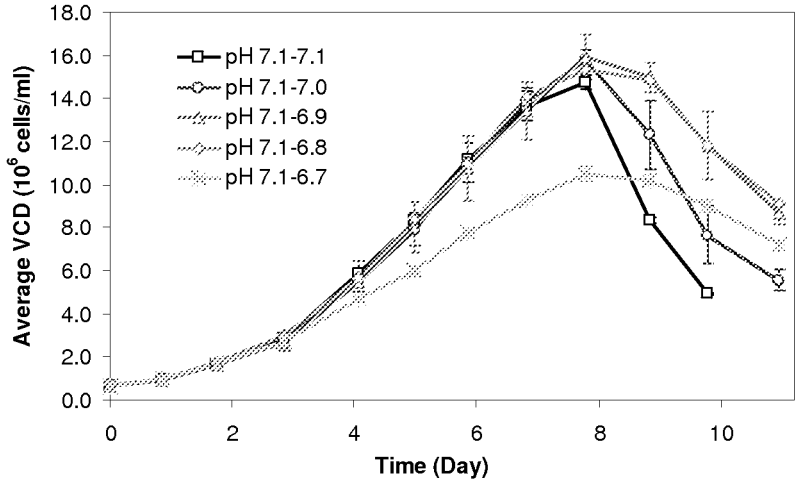


Figure 61) Effect of pH modulation to adalimumab producing cell line 1, media 1 on viable cell density

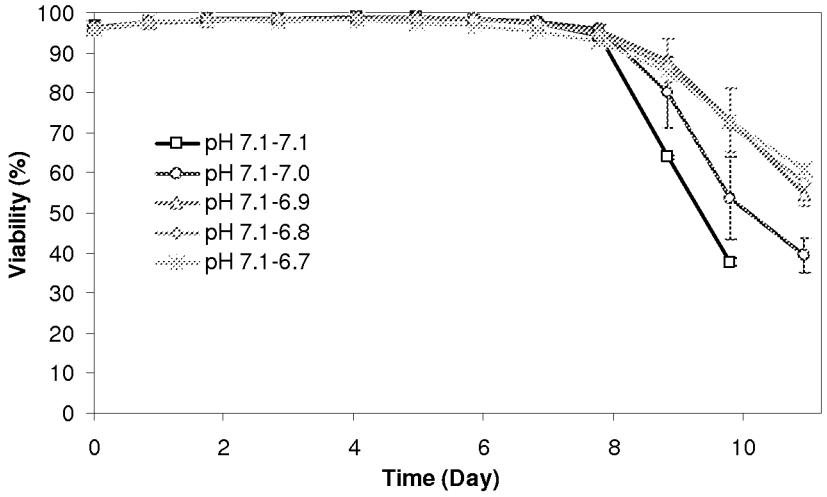


Figure 62) Effect of pH modulation to adalimumab producing cell line 1, media 1 on viability

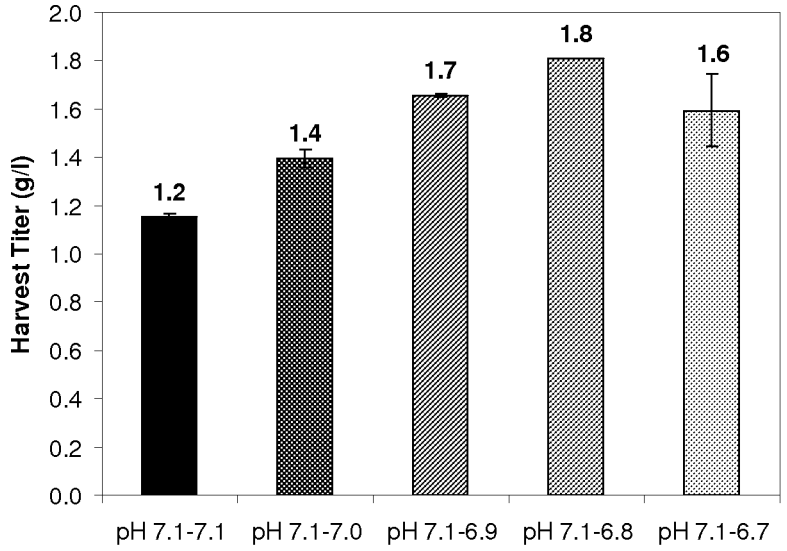


Figure 63) Effect of pH modulation to adalimumab producing cell line 1, media 1 on harvest titer

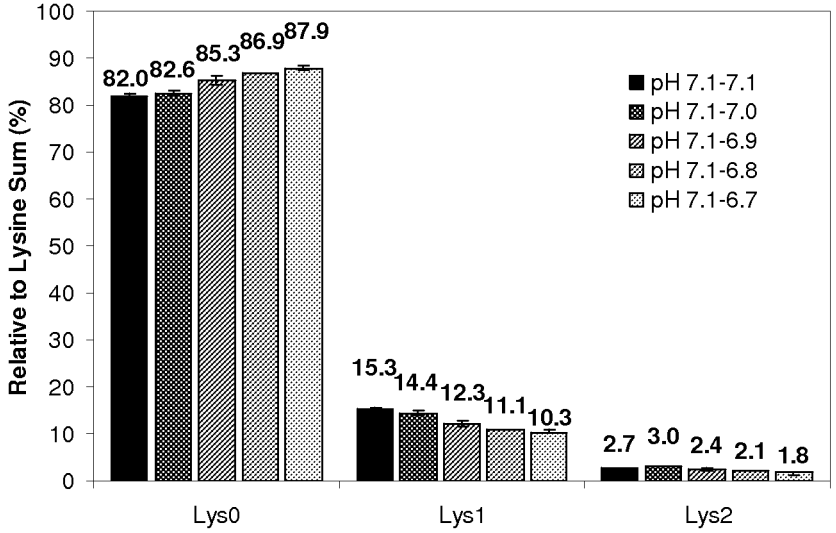


Figure 64) Effect of pH modulation to adalimumab producing cell line 1, media 1 on WCX-10 profile relative lysine distribution

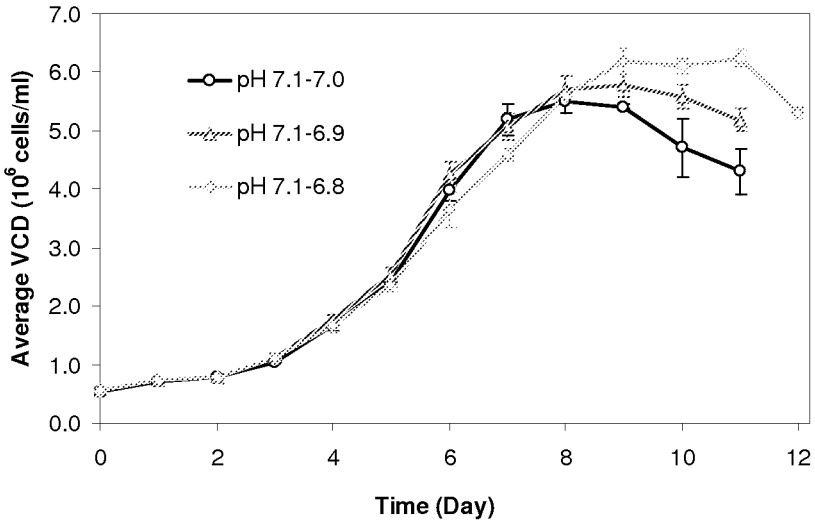


Figure 65) Effect of pH modulation to adalimumab producing cell line 1, media 2 on viable cell density

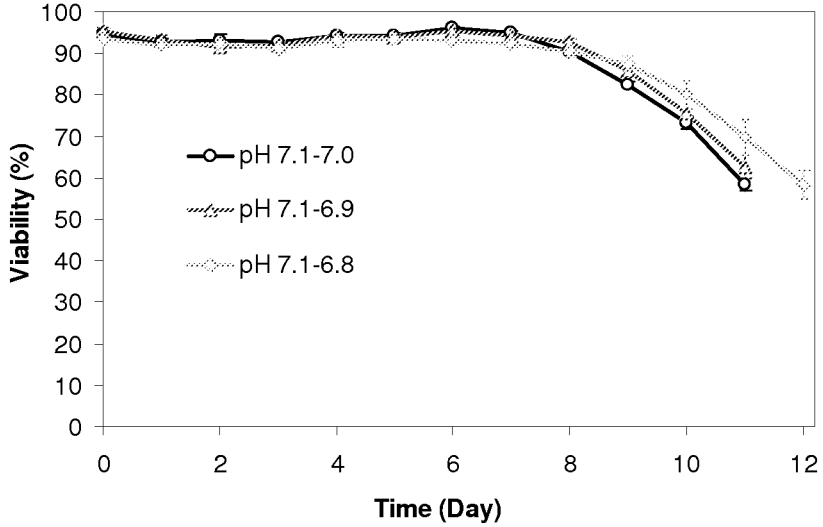


Figure 66) Effect of pH modulation to adalimumab producing cell line 1, media 2 on viability

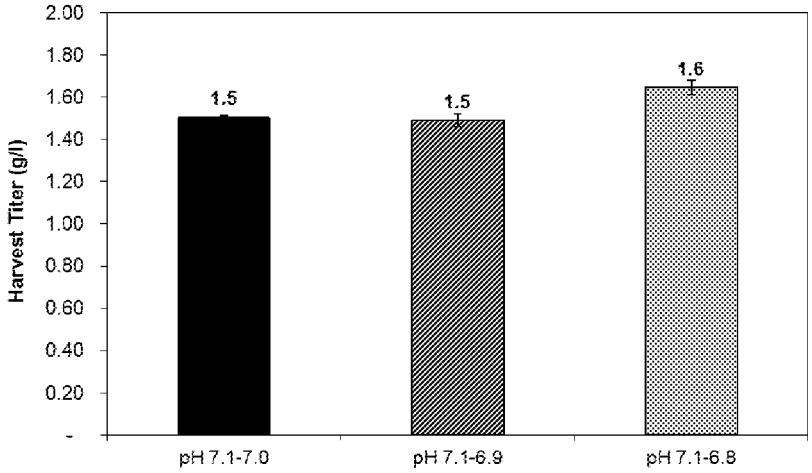


Figure 67) Effect of pH modulation to adalimumab producing cell line 1, media 2 on harvest titer

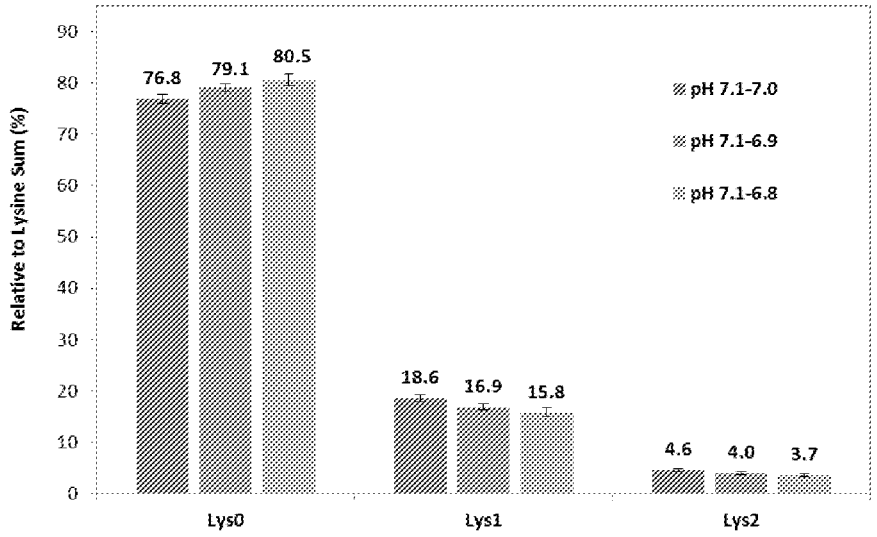


Figure 68) Effect of pH modulation to adalimumab producing cell line 1, media 2 on WCX-10 profile relative lysine distribution

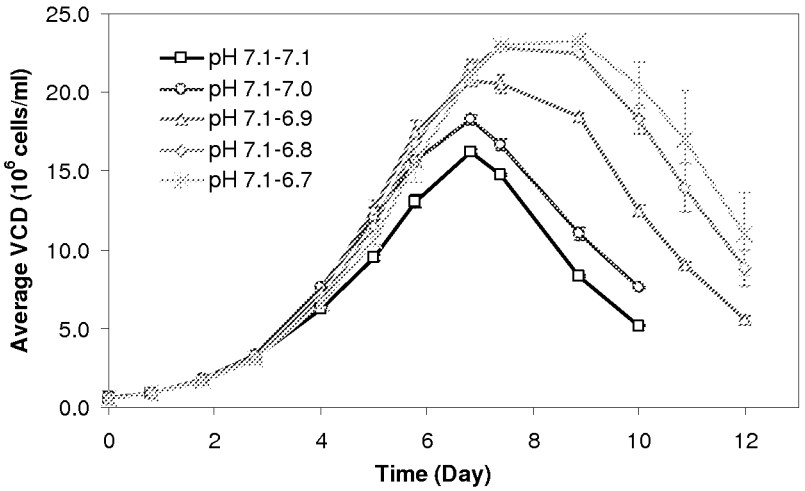


Figure 69) Effect of pH modulation to adalimumab producing cell line 3, media 1 on viable cell density

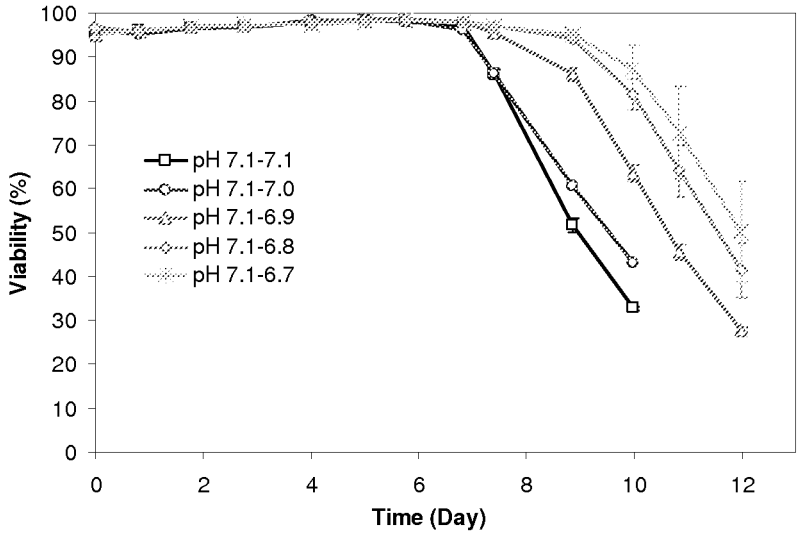


Figure 70) Effect of pH modulation to adalimumab producing cell line 3, media 1 on viability

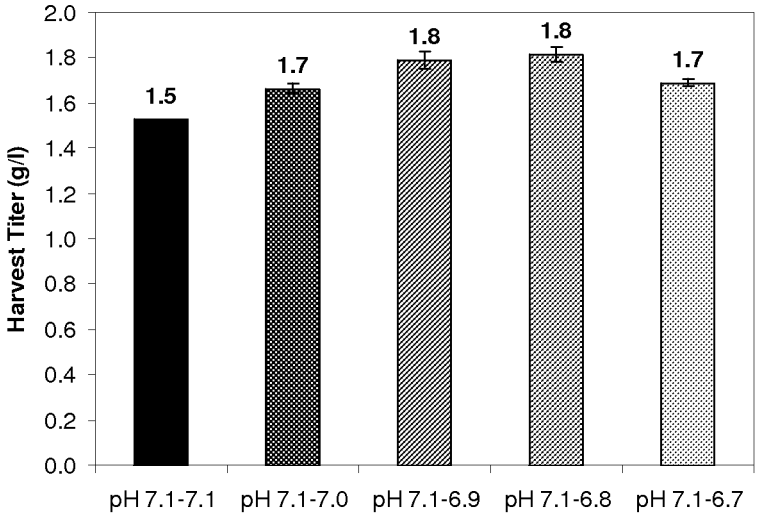


Figure 71) Effect of pH modulation to adalimumab producing cell line 3, media 1 on harvest titer

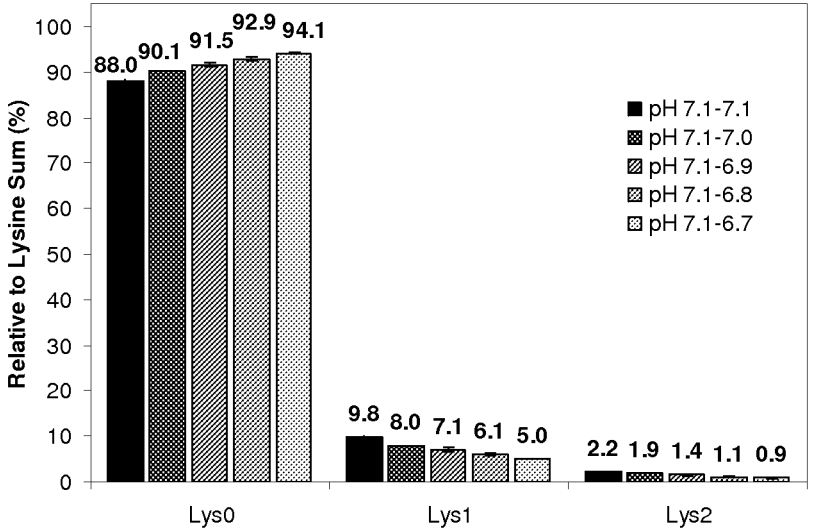


Figure 72) Effect of pH modulation to adalimumab producing cell line 3, media 1 on WCX-10 profile relative lysine distribution on day10

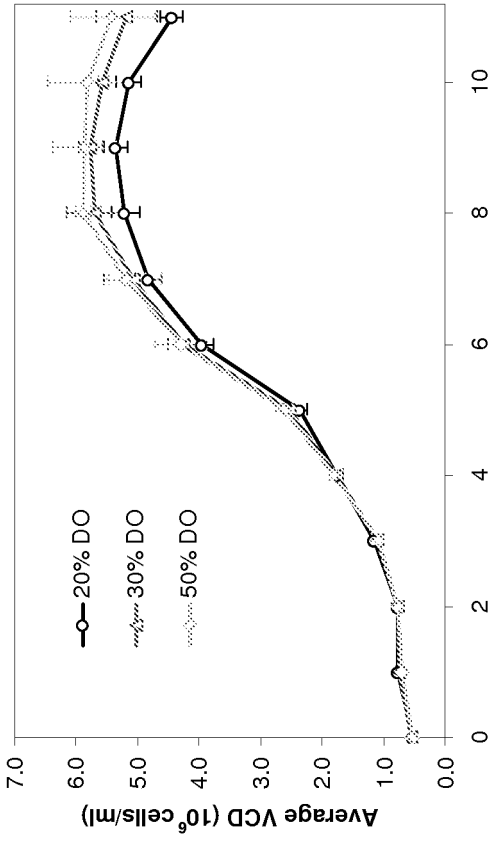


Figure 73) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 2 at 35°C on viable cell density

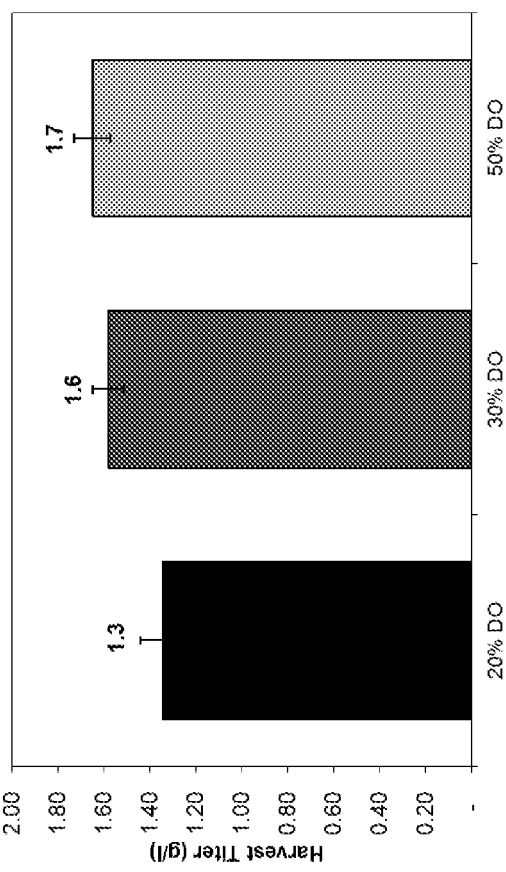


Figure 75) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 2 at 35°C on harvest titer

Figure 74) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 2 at 35°C on viability

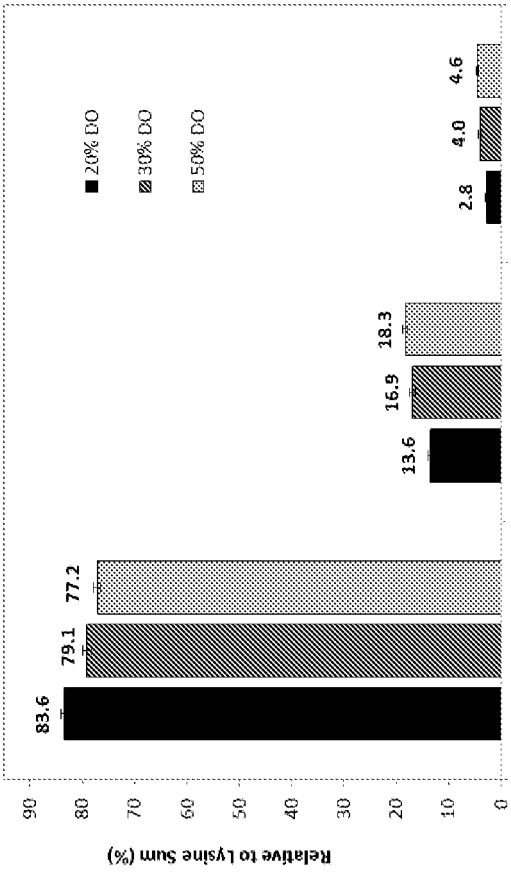


Figure 76) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 2 at 35°C on WCX-10 profile relative lysine distribution

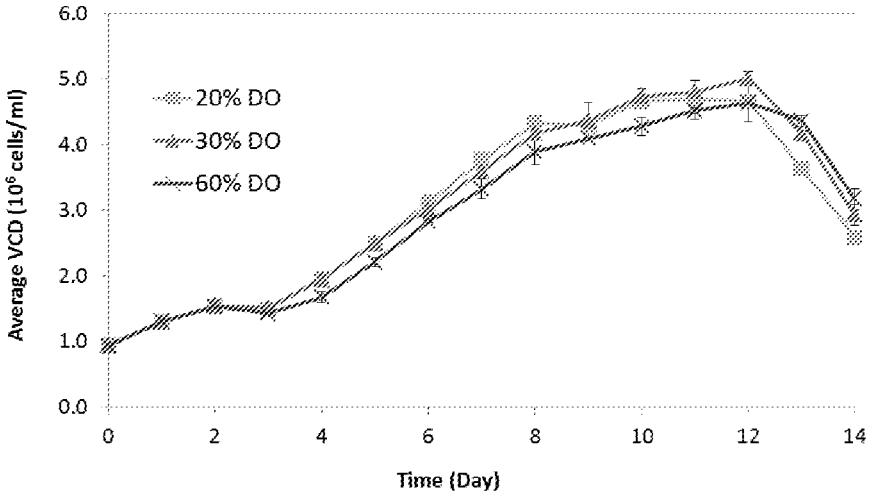


Figure 77) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 2 at 33°C on viable cell density

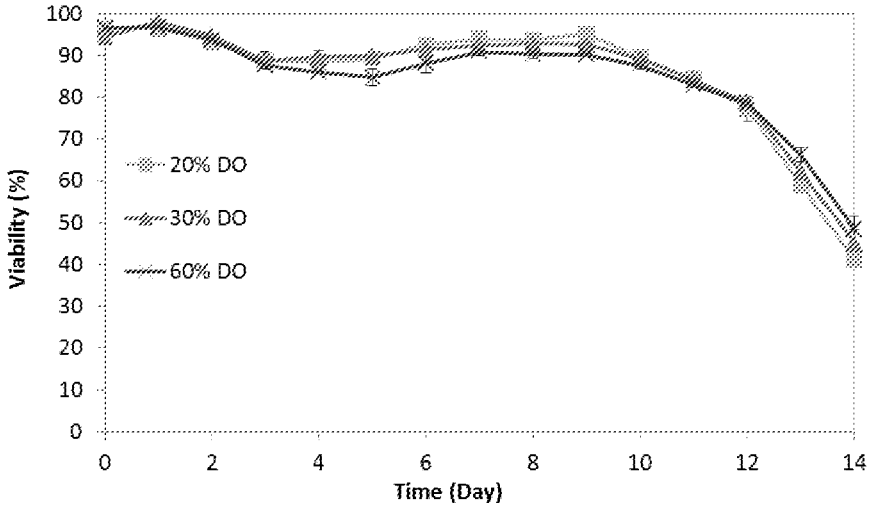


Figure 78) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 2 at 33°C on viability

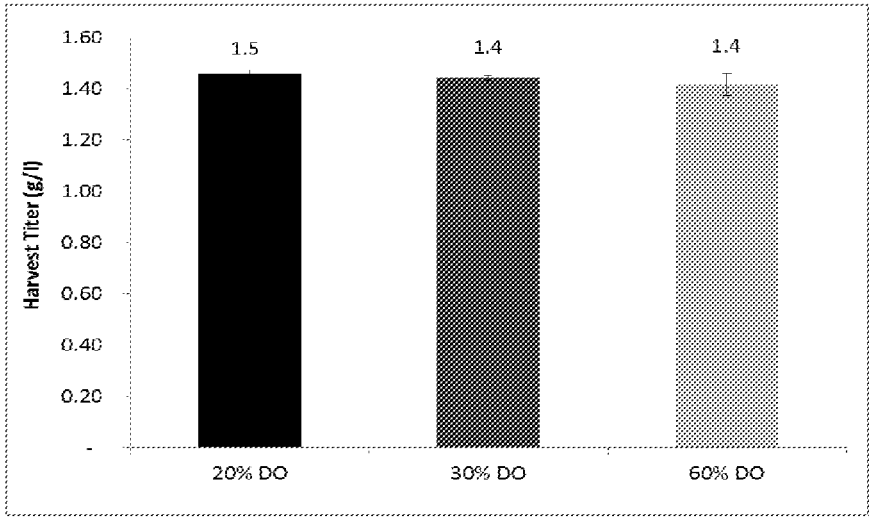


Figure 79) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 2 at 33°C on harvest titer

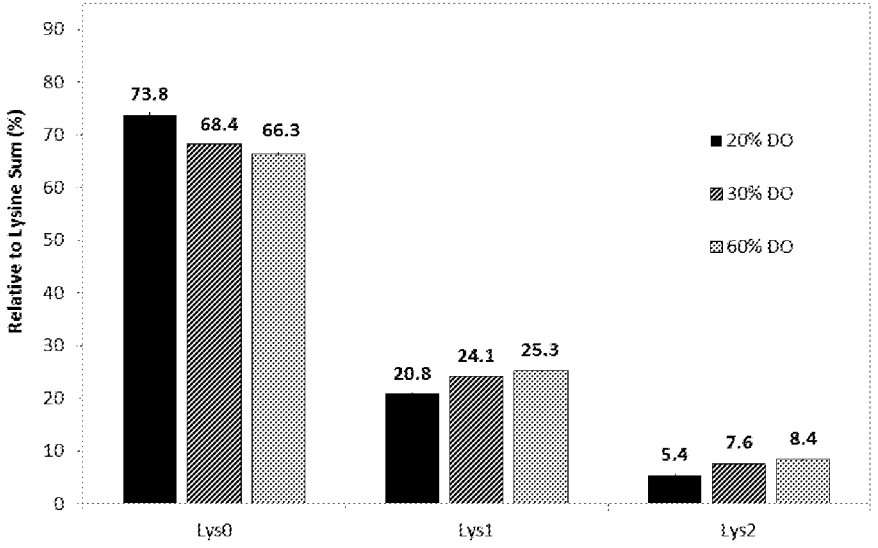


Figure 80) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 2 at 33°C on WCX-10 profile relative lysine distribution

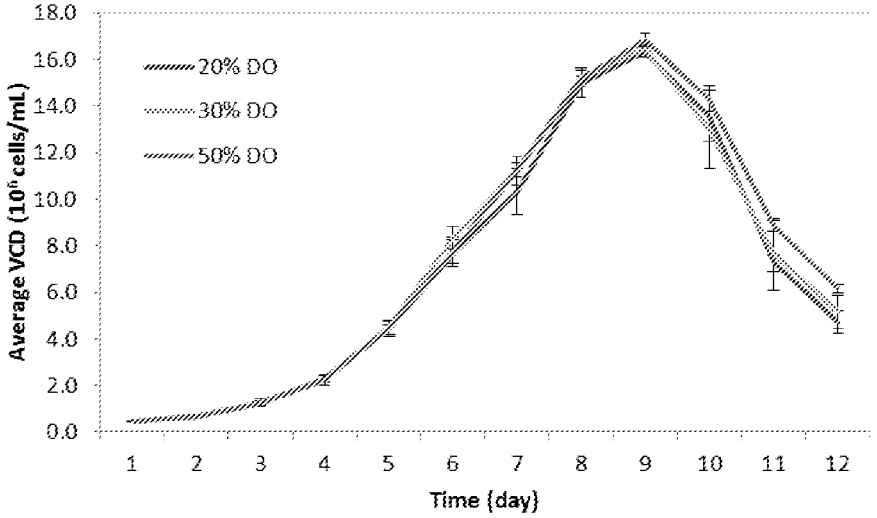


Figure 81) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 1 on viable cell density.

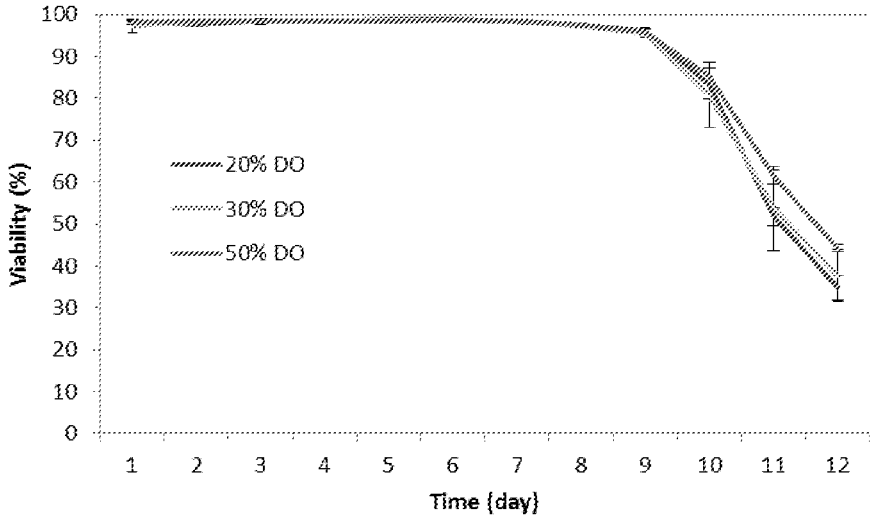


Figure 82) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 1 on viability.

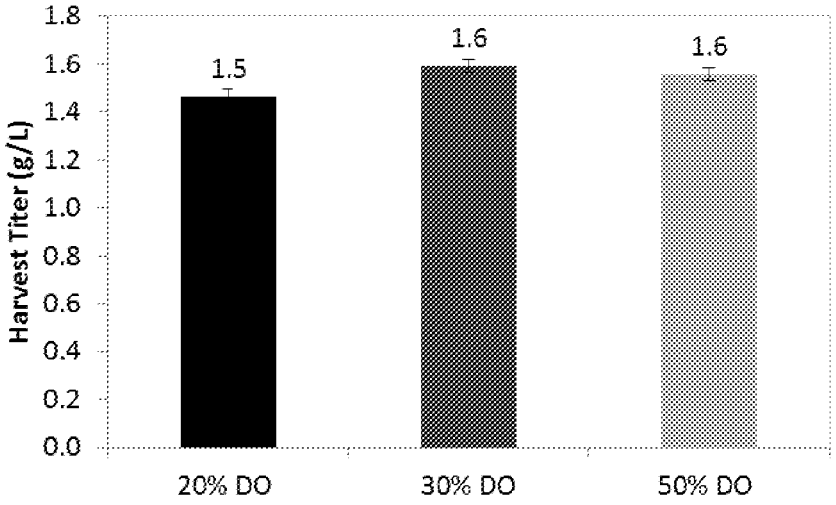


Figure 83) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 1 on harvest titer.

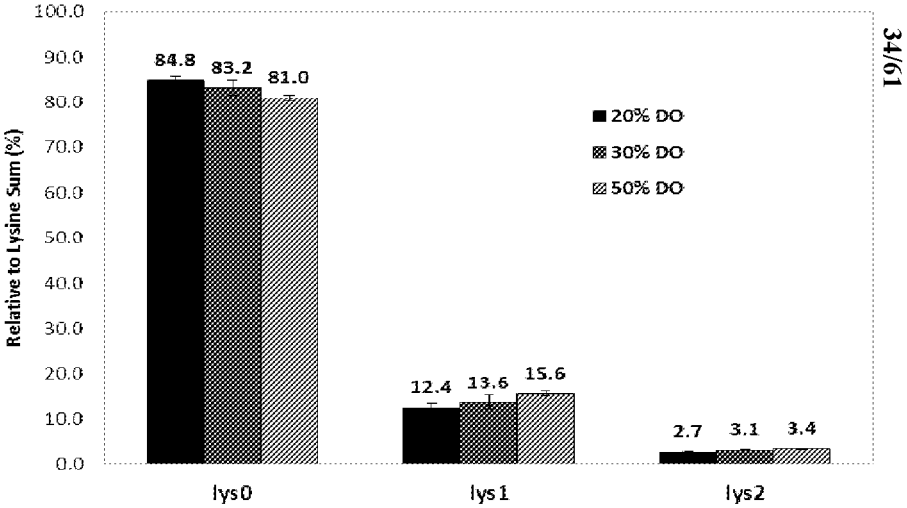


Figure 84) Effect of dissolved oxygen modulation to adalimumab producing cell line 1, media 1 on WCX-10 profile relative lysine distribution.

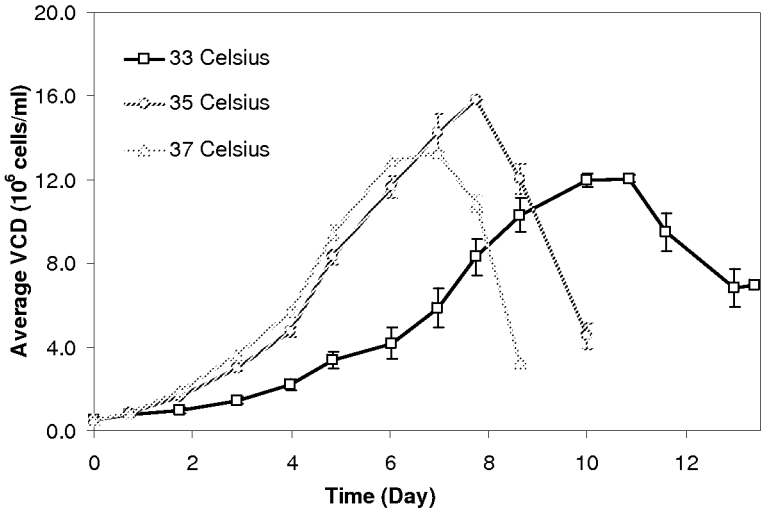


Figure 85) Effect of temperature modulation to adalimumab producing cell line 1, media 1 on viable cell density (n=2)

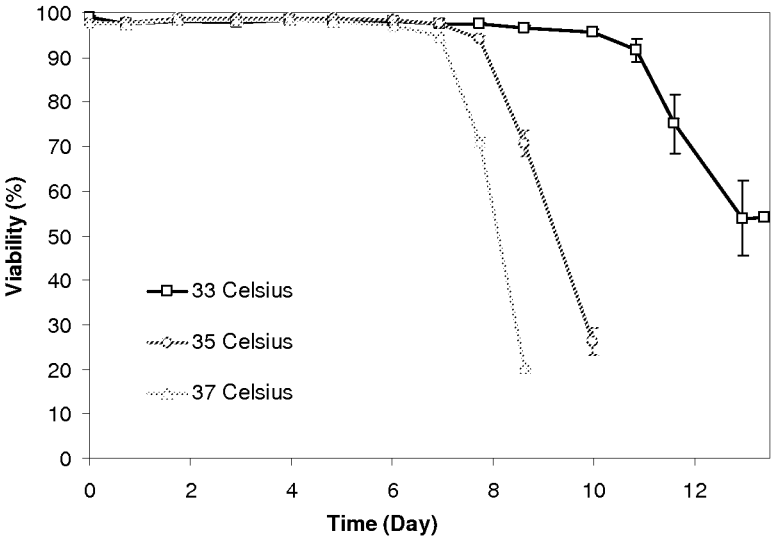


Figure 86) Effect of temperature modulation to adalimumab producing cell line 1, media 1 on viability (n=2)

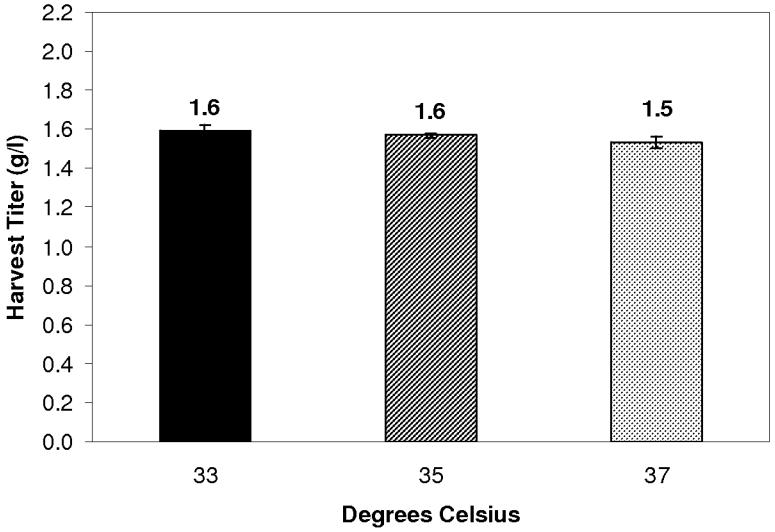


Figure 87) Effect of temperature modulation to adalimumab producing cell line 1, media 1 on harvest titer (n=2)

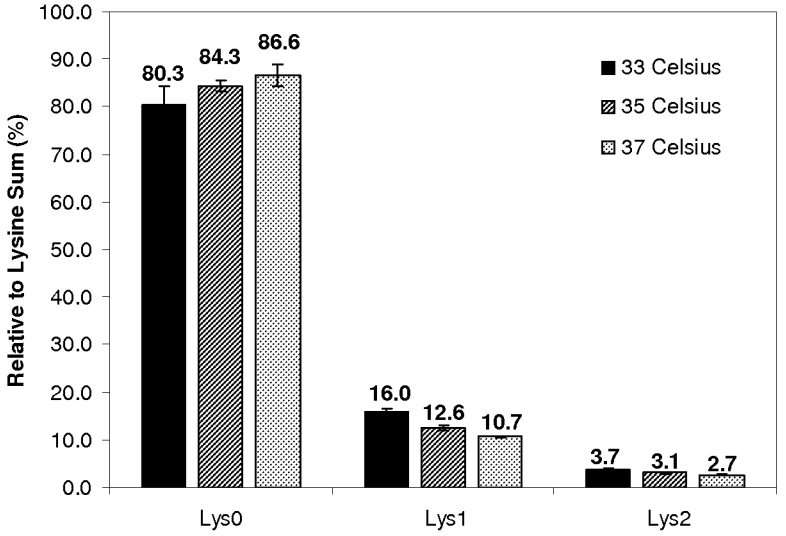


Figure 88) Effect of temperature modulation to adalimumab producing cell line 1, media 1 on WCX-10 profile relative lysine distribution (n=2)

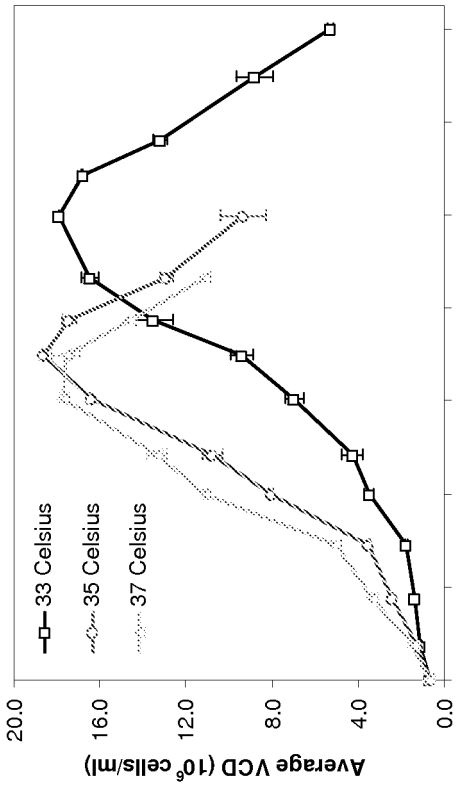


Figure 89) Effect of temperature modulation to adalimumab producing cell line 2, media 1 on viable cell density (n=2)

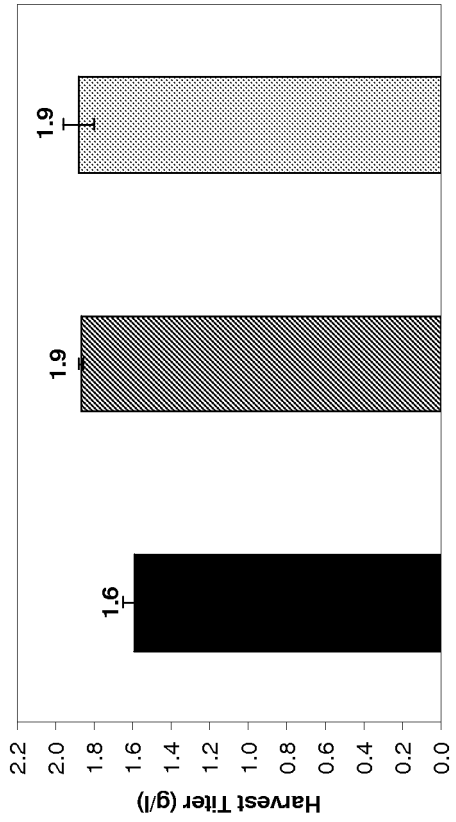


Figure 91) Effect of temperature modulation to adalimumab producing cell line 2, media 1 on harvest titer (n=2)

Figure 90) Effect of temperature modulation to adalimumab producing cell line 2, media 1 on viability (n=2)

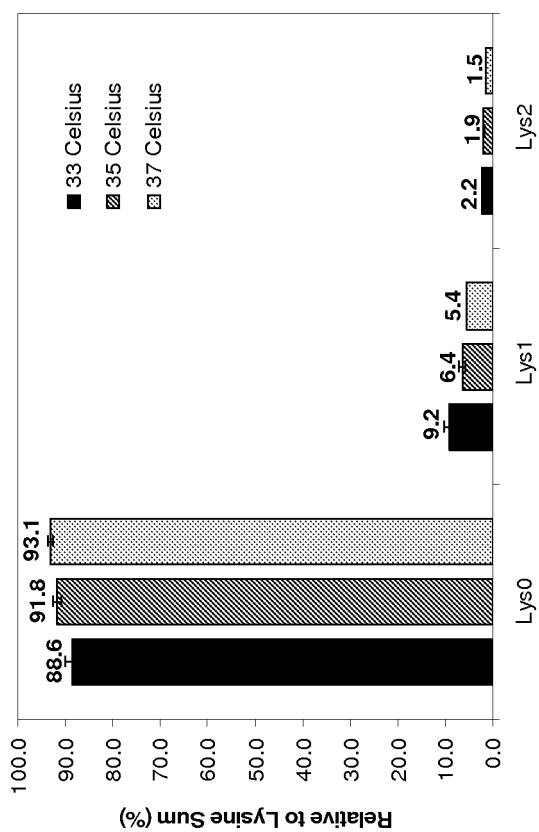


Figure 92) Effect of temperature modulation to adalimumab producing cell line 2, media 1 on WCX-10 profile relative lysine distribution (n=2)

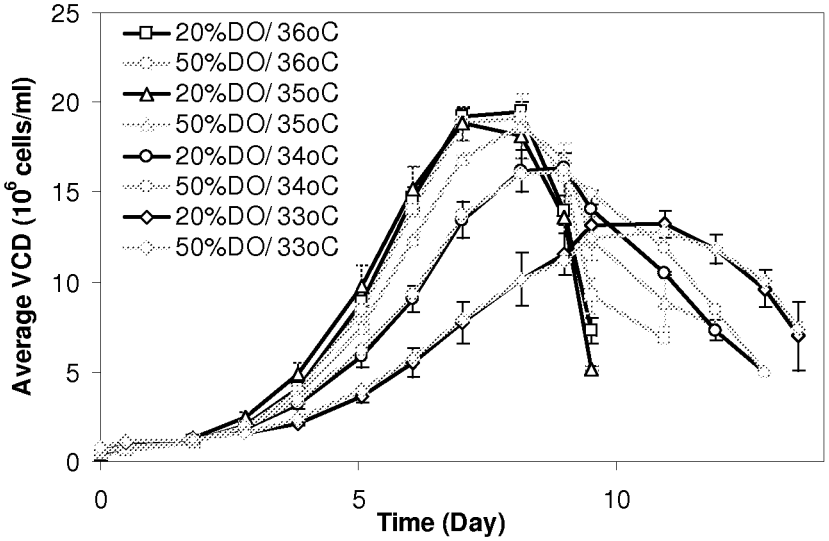


Figure 93) Effect of dissolved oxygen and temperature modulation to adalimumab producing cell line 3, media 1 on viable cell density

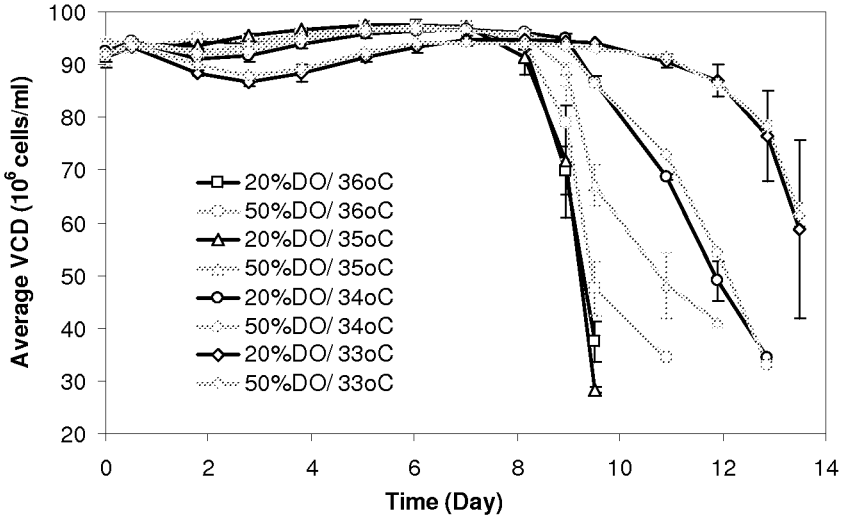


Figure 94) Effect of dissolved oxygen and temperature modulation to adalimumab producing cell line 3, media 1 on viability

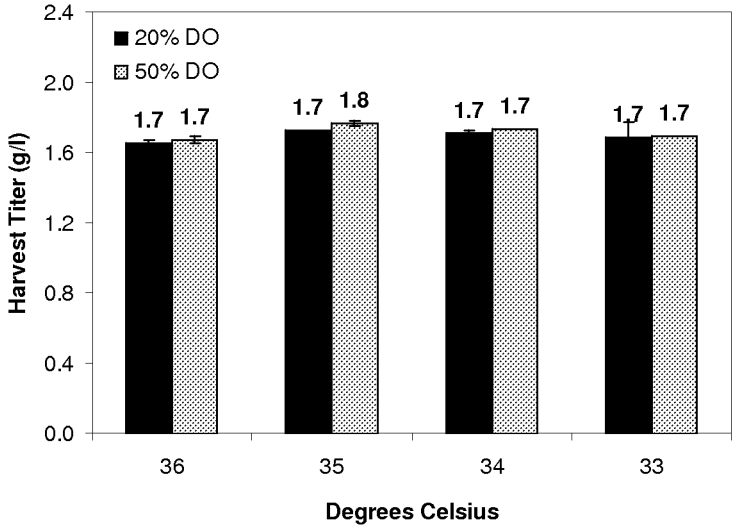


Figure 95) Effect of dissolve oxygen and temperature modulation to adalimumab producing cell line 3, media 1 on harvest titer

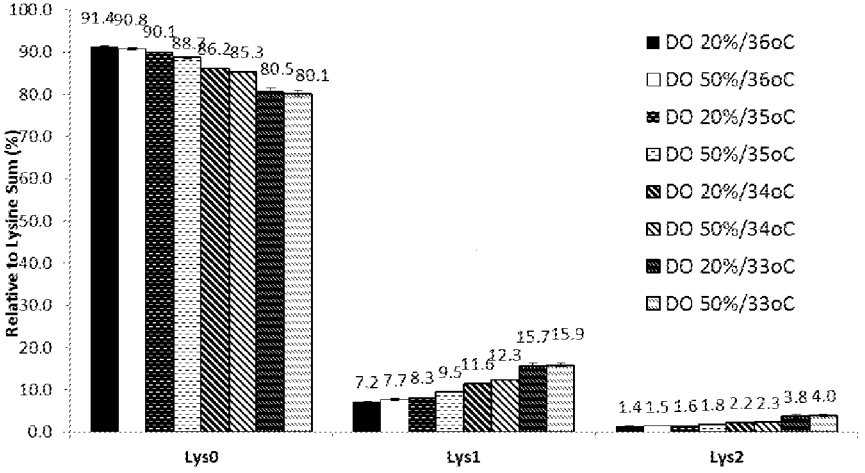


Figure 96) Effect of dissolved oxygen and temperature modulation to adalimumab producing cell line 3, media 1 on WCX-10 profile relative lysine distribution

Figure 97 Effect of varying phosphate concentration in chemically defined media with cell line 1 on a) viable cell density profile b) viability profile c) harvest titer d) lysine variant distribution

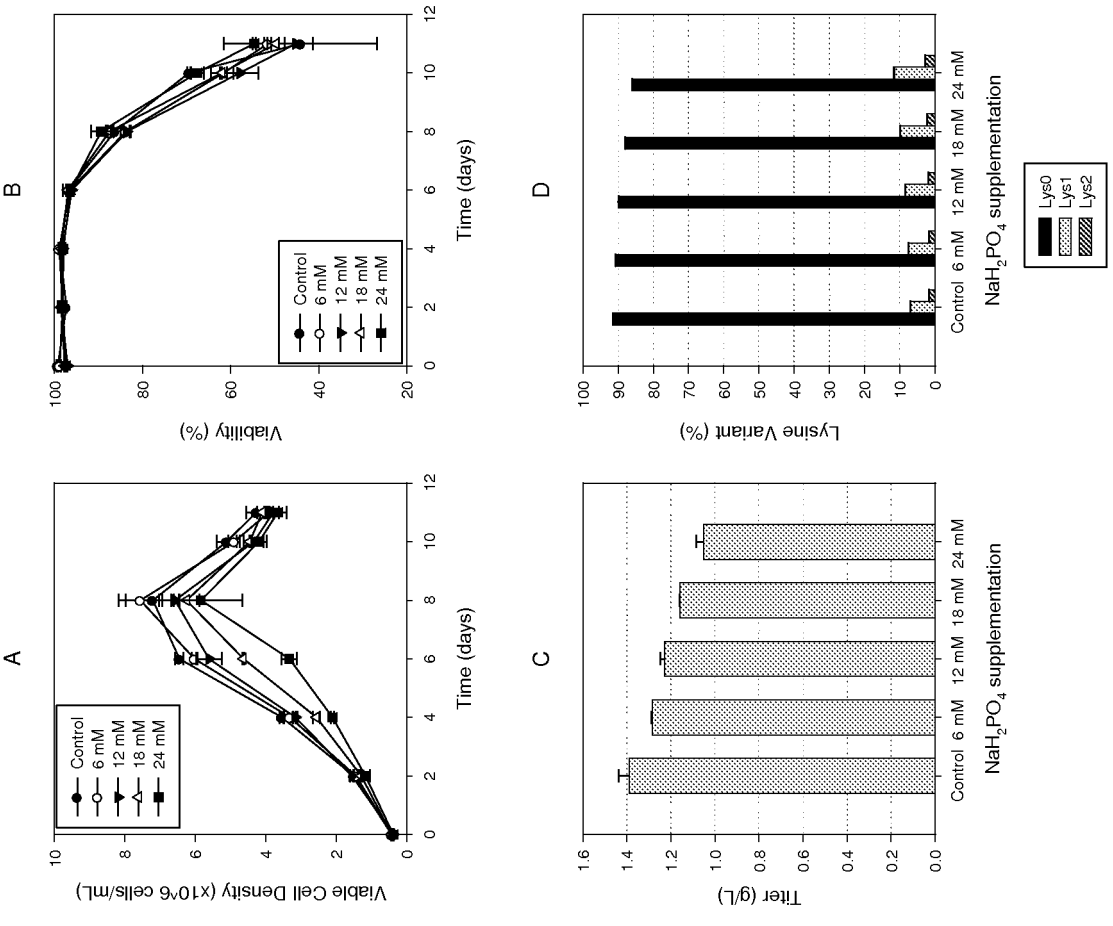
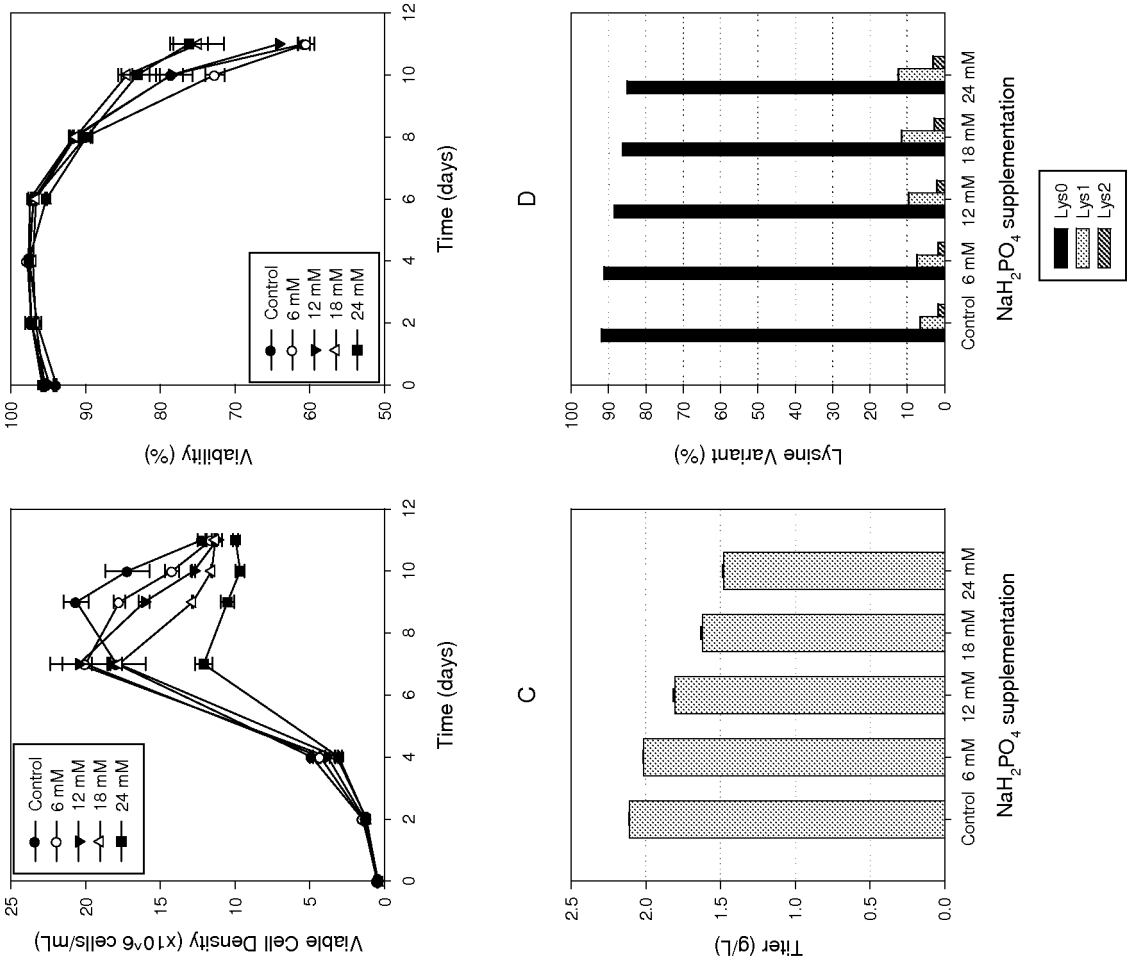


Figure 98 Effect of varying phosphate concentration in chemically defined media with cell line 2 on a) viable cell density profile b) viability profile c) harvest titer d) lysine variant distribution



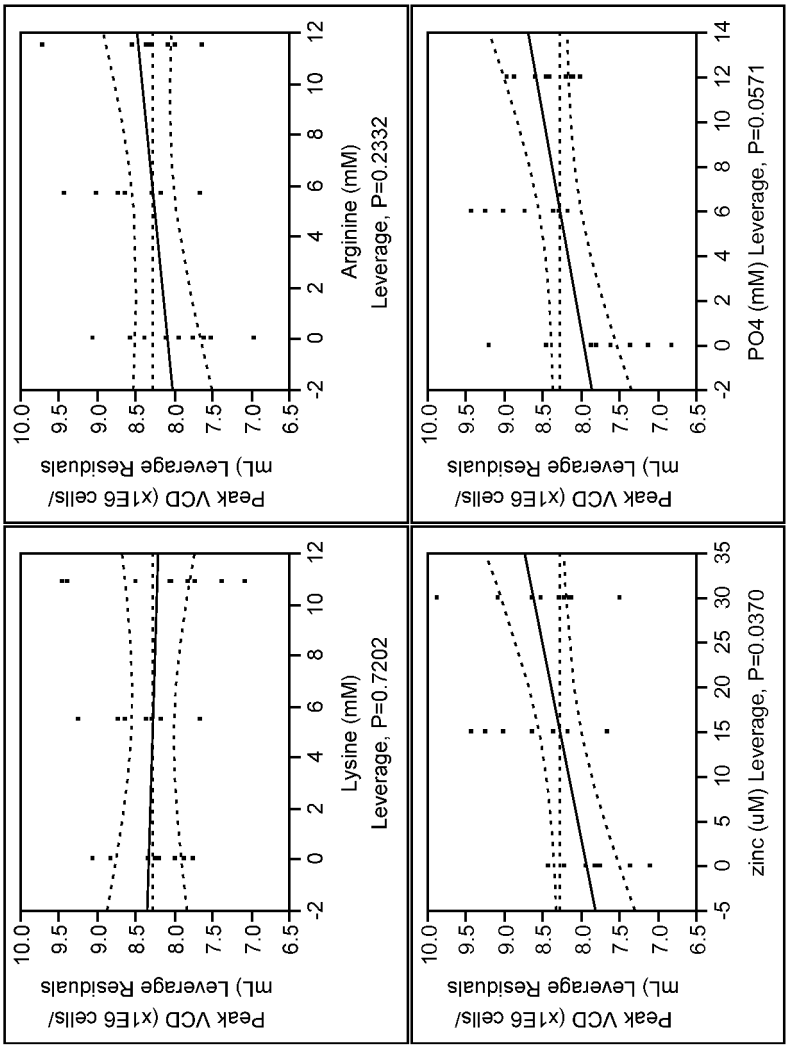


Figure 99A Effect of varying lysine, arginine, zinc and phosphate concentration in chemically defined media with cell line 1 on peak viable cell density

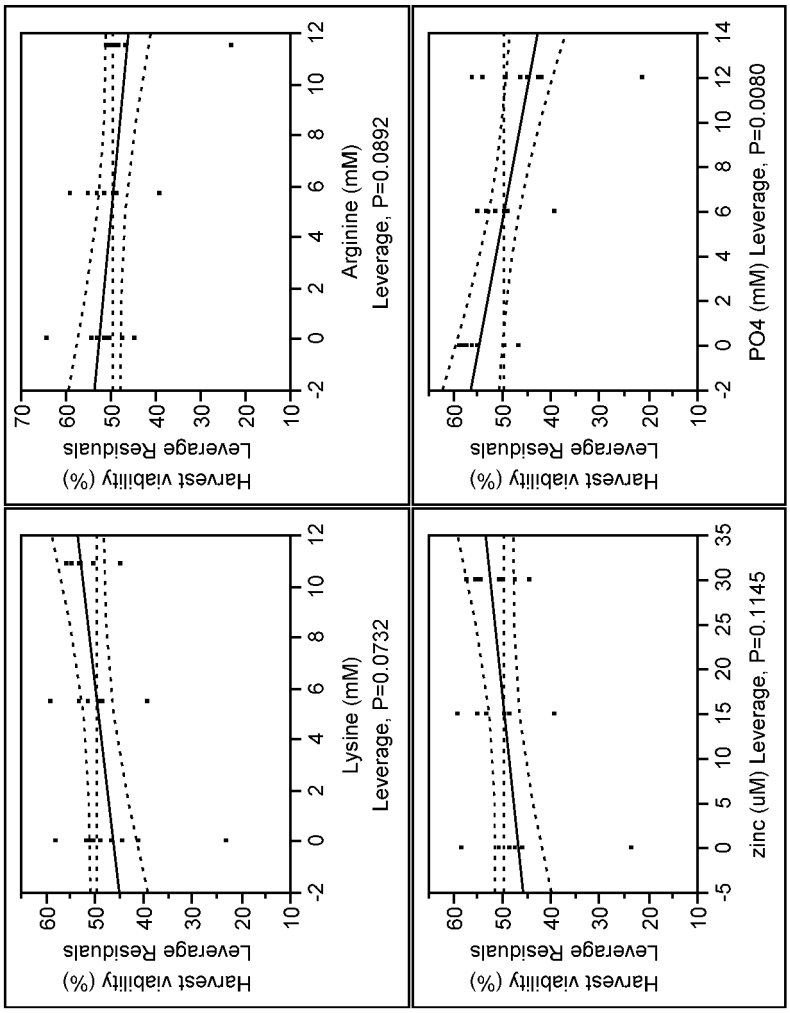
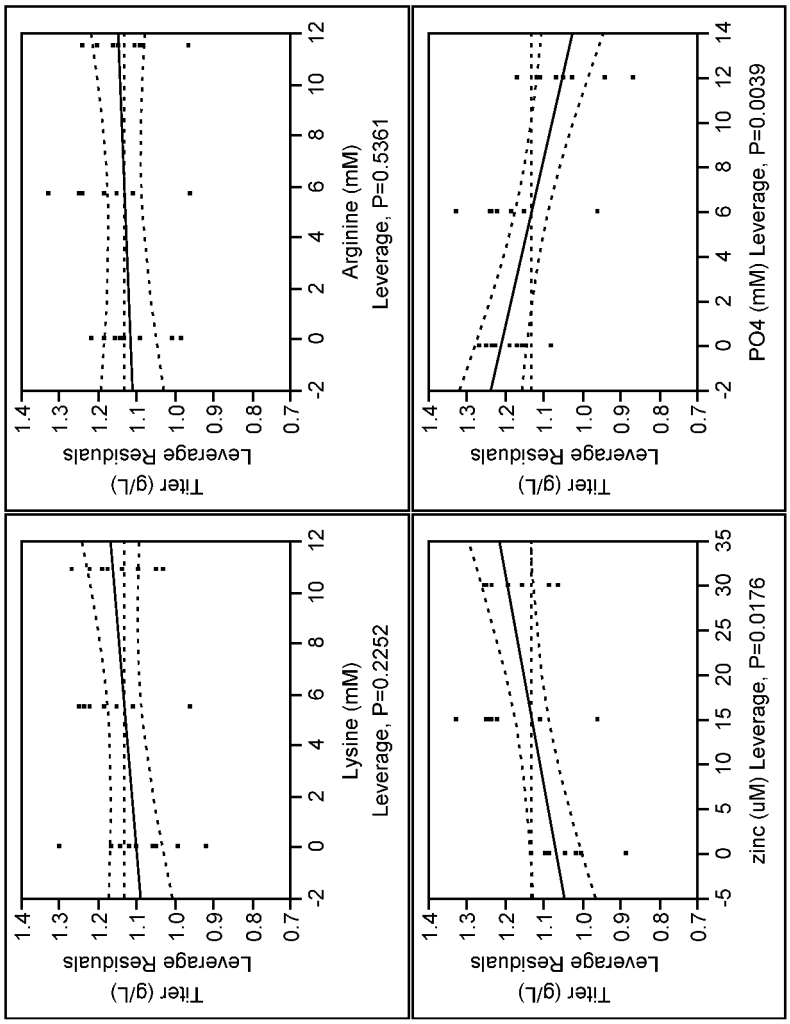


Figure 99B Effect of varying lysine, arginine, zinc and phosphate concentration in chemically defined media with cell line 1 on harvest viability

Figure 99C Effect of varying lysine, arginine, zinc and phosphate concentration in chemically defined media with cell line 1 on harvest titer



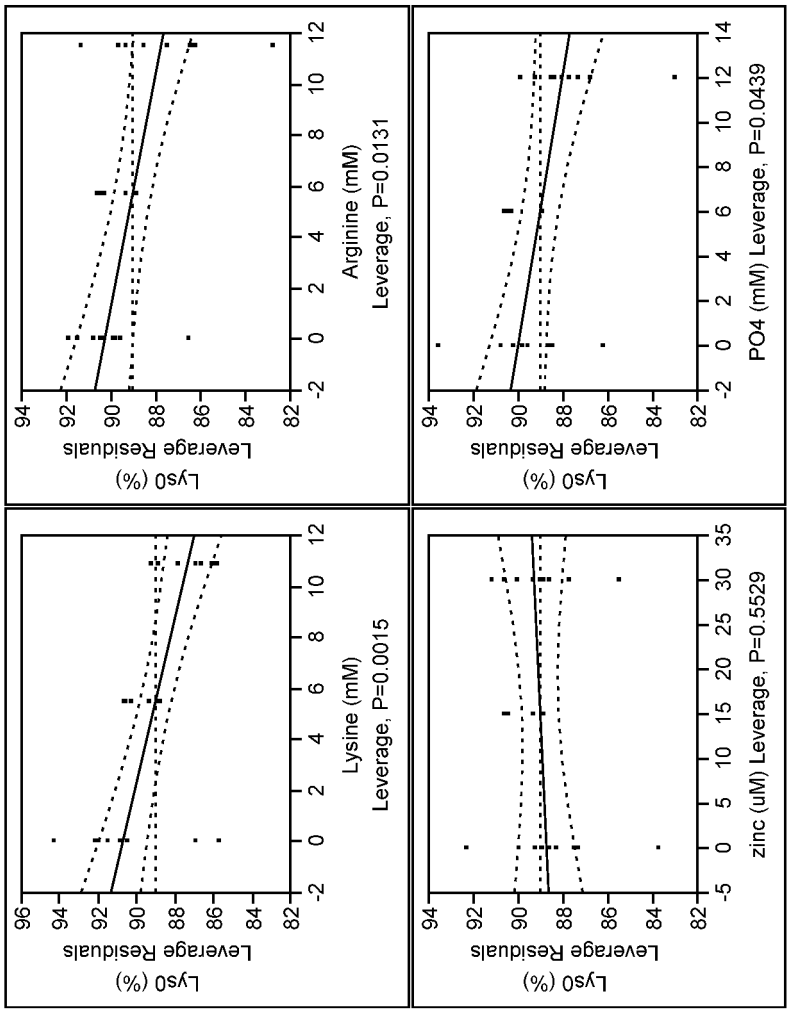


Figure 99D Effect of varying lysine, arginine, zinc and phosphate concentration in chemically defined media with cell line 1 on the relative fraction of Lys0

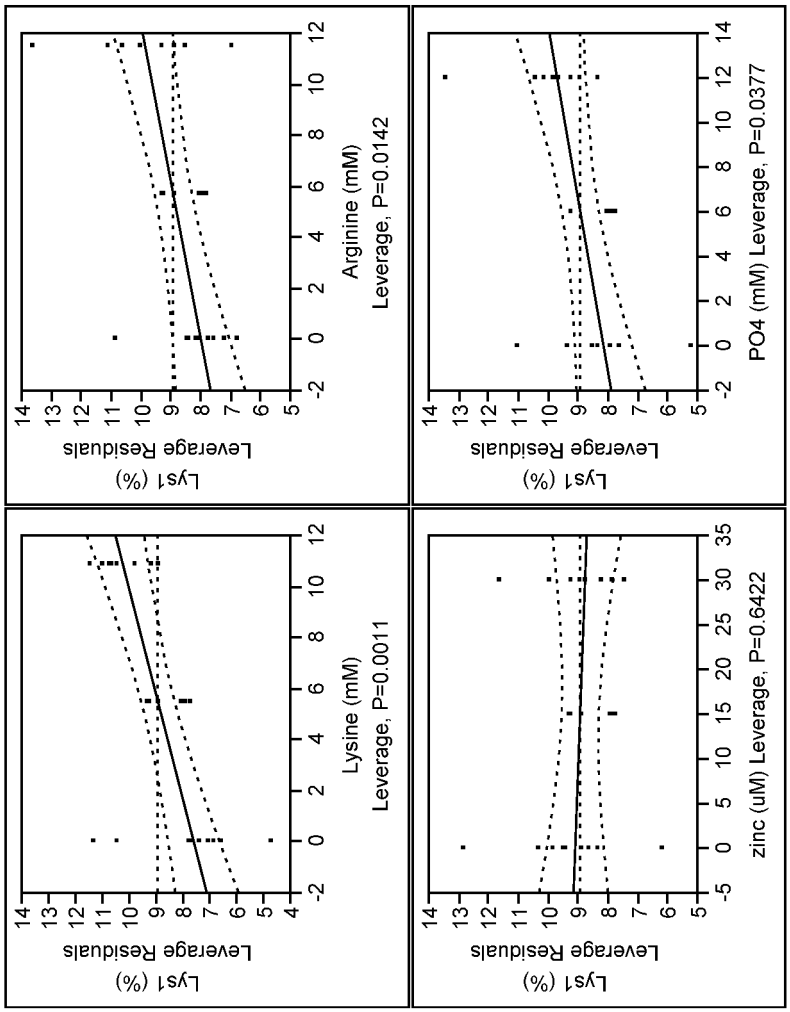


Figure 99E Effect of varying lysine, arginine, zinc and phosphate concentration in chemically defined media with cell line 1 on the relative fraction of Lys1

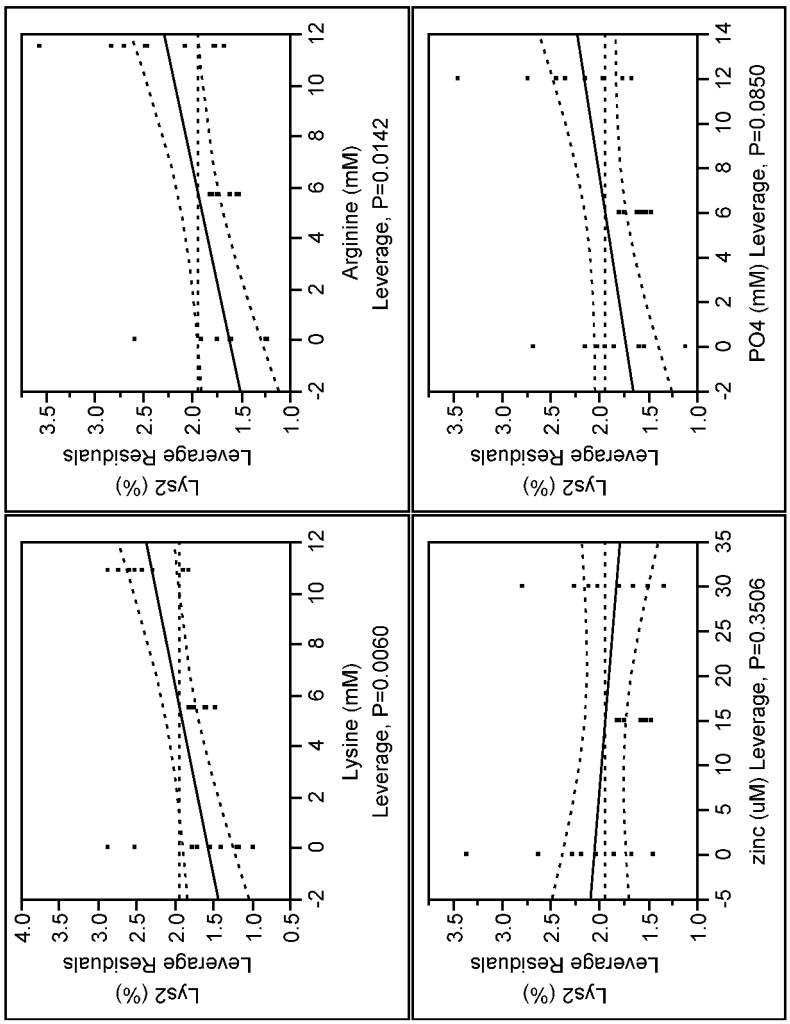


Figure 99F Effect of varying lysine, arginine, zinc and phosphate concentration in chemically defined media with cell line 1 on the relative fraction of Lys2

Figure 100

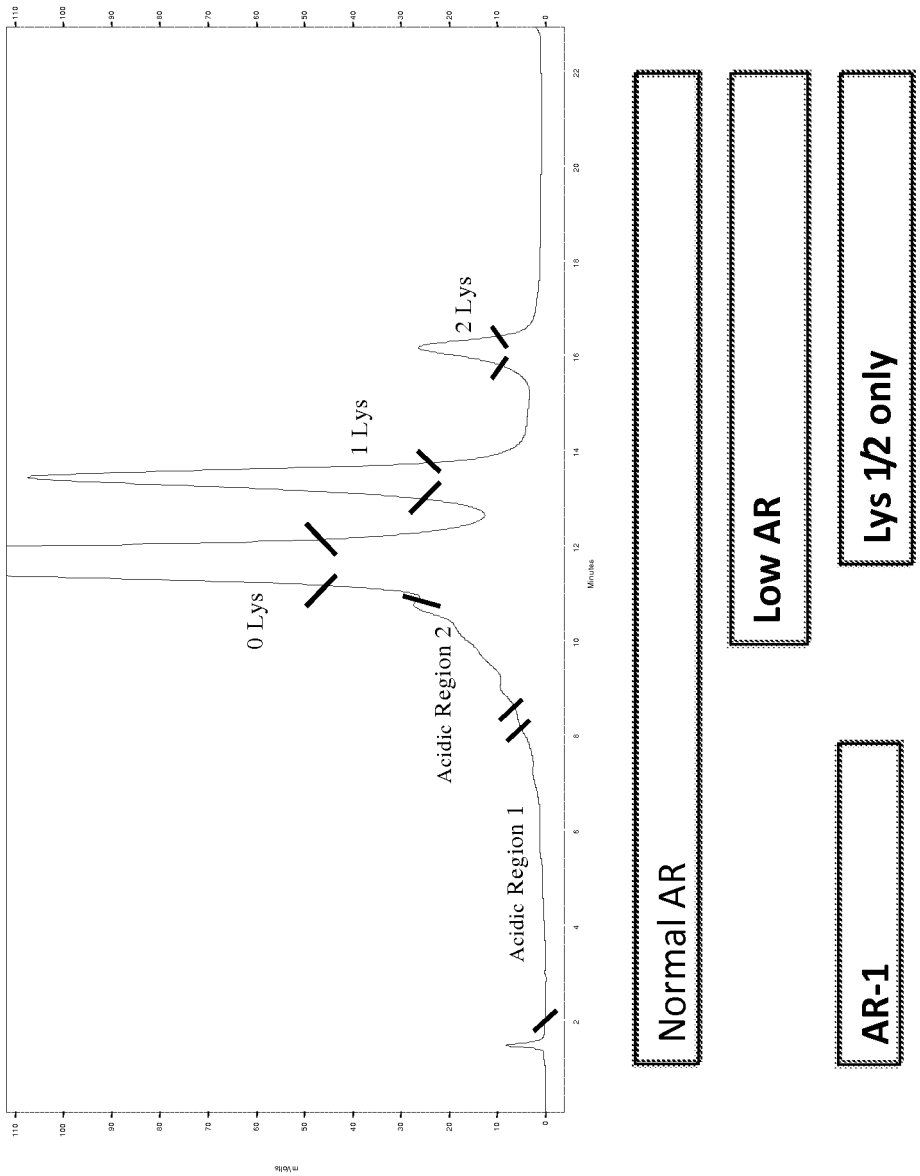

0 Lys
1 Lys
2 Lys
Acidic Region 1
Acidic Region 2
Minutes
Normal AR
Low AR
Lys 1/2 only
AR-1

Figure 101A

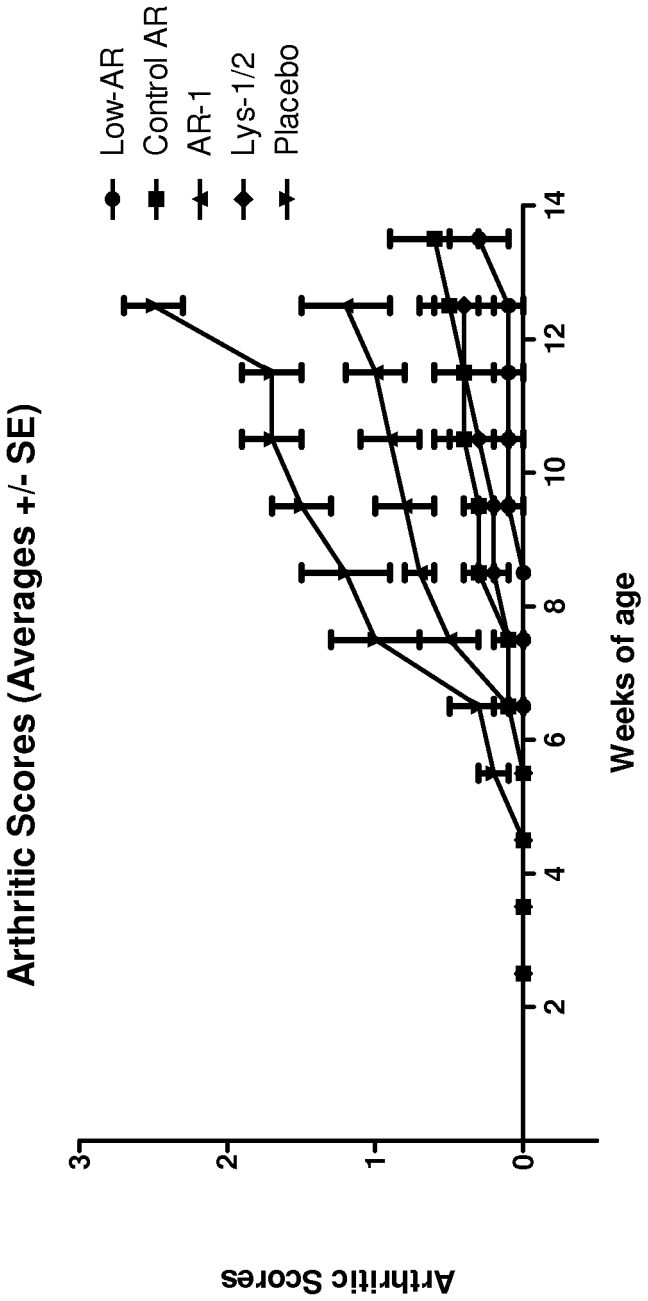
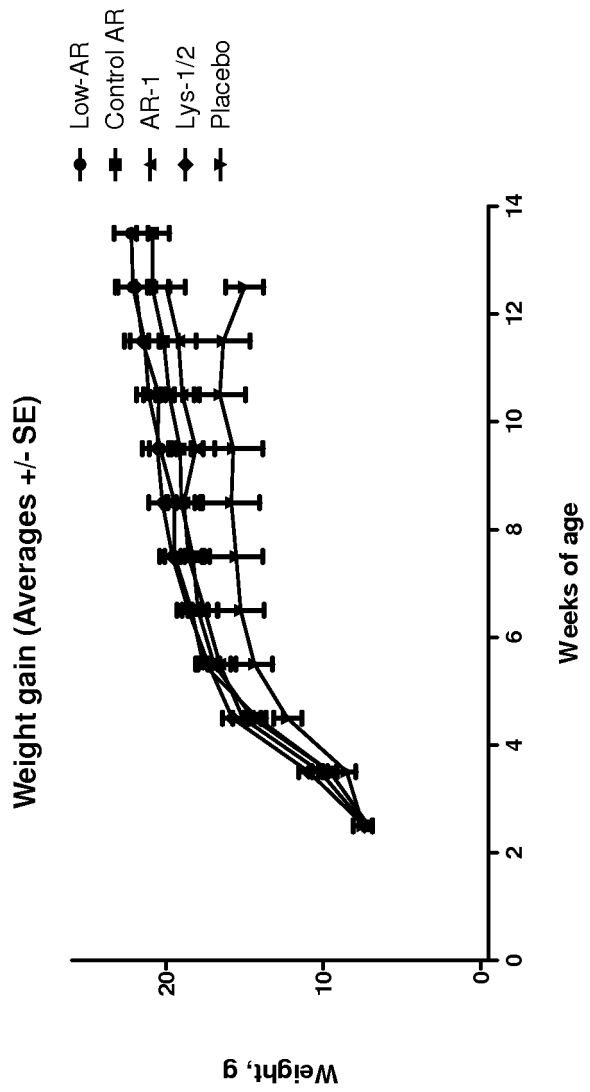

Arthritic Scores (Averages +/- SE)
Low-AR
Control AR
AR-1
Lys-1/2
Placebo
Arthritic Scores
0
1
2
3
Weeks of age
2
4
6
8
10
12
14

Figure 101B


Low-AR
Control AR
AR-1
Lys-1/2
Placebo
Weight gain (Averages +/- SE)
Weight, g
Weeks of age
0
10
20
0
2
4
6
8
10
12
14

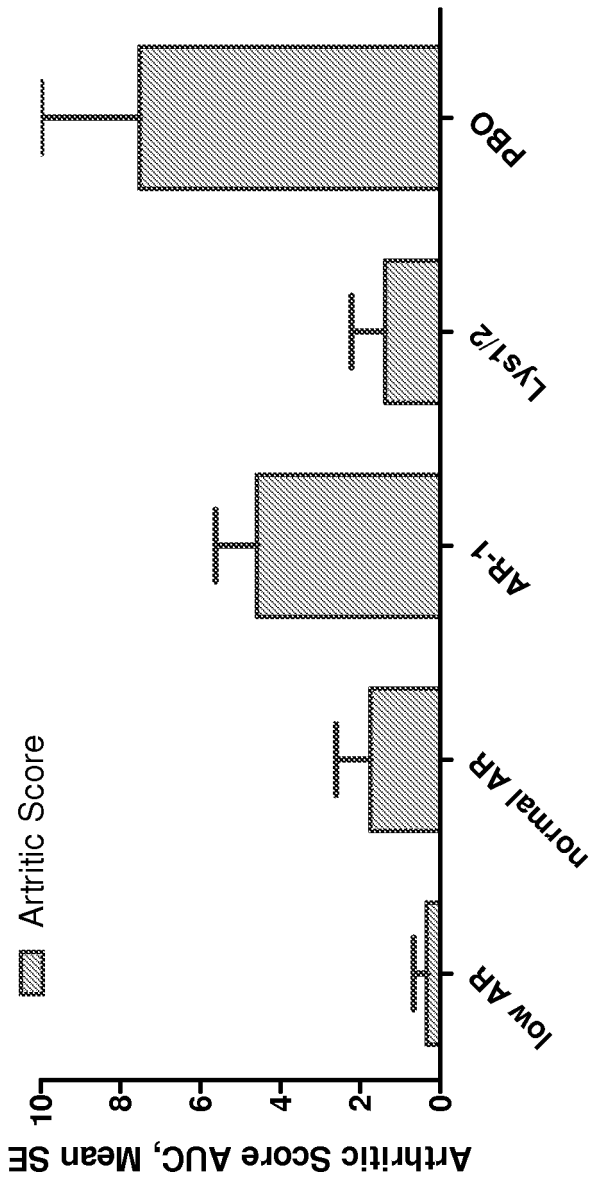

Artritic Score AUC, Mean SE
0
2
4
6
8
10
Artritic Score
low AR
normal AR
AR-1
Lys1/2
PBO

Figure102

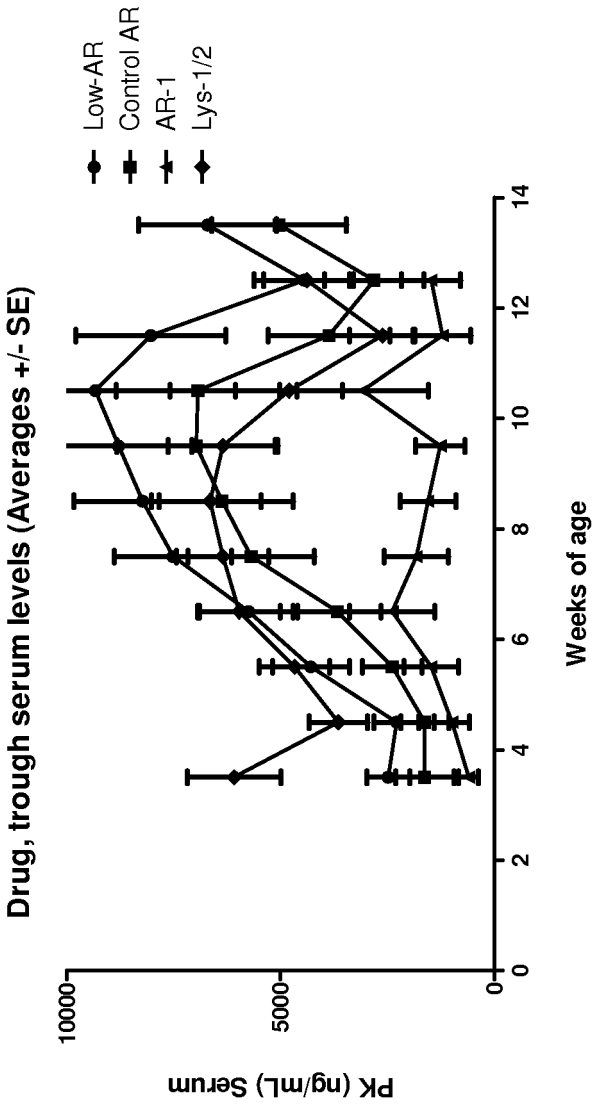

Drug, trough serum levels (Averages +/- SE)
Low-AR
Control AR
AR-1
Lys-1/2
PK (ng/mL) Serum
10000
5000
0
0
2
4
6
8
10
12
14
Weeks of age

Figure 103A

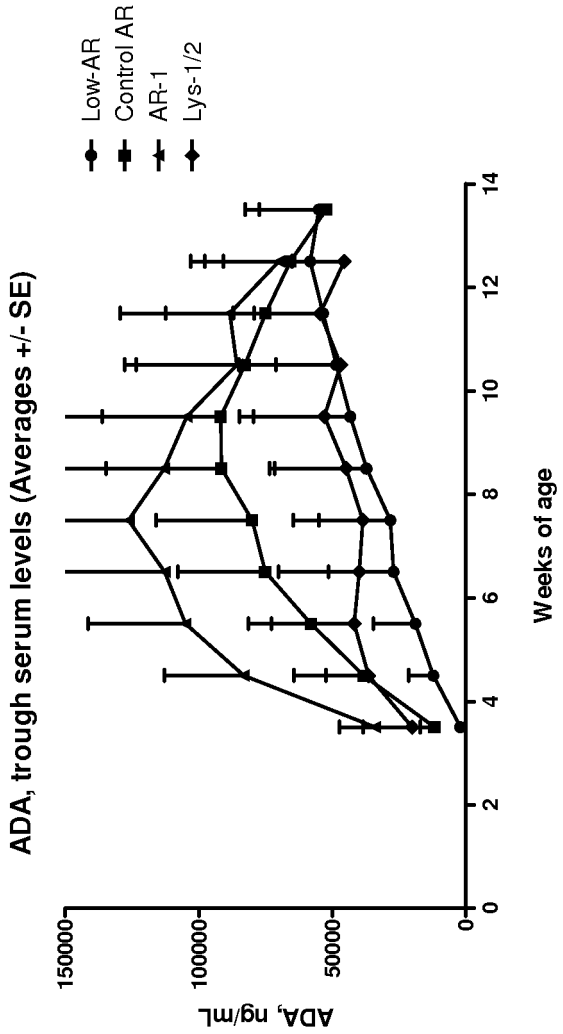

ADA, trough serum levels (Averages +/- SE)
Low-AR
Control AR
AR-1
Lys-1/2
ADA, ng/mL
150000
100000
50000
0
0
2
4
6
8
10
12
14
Weeks of age

Figure 103B

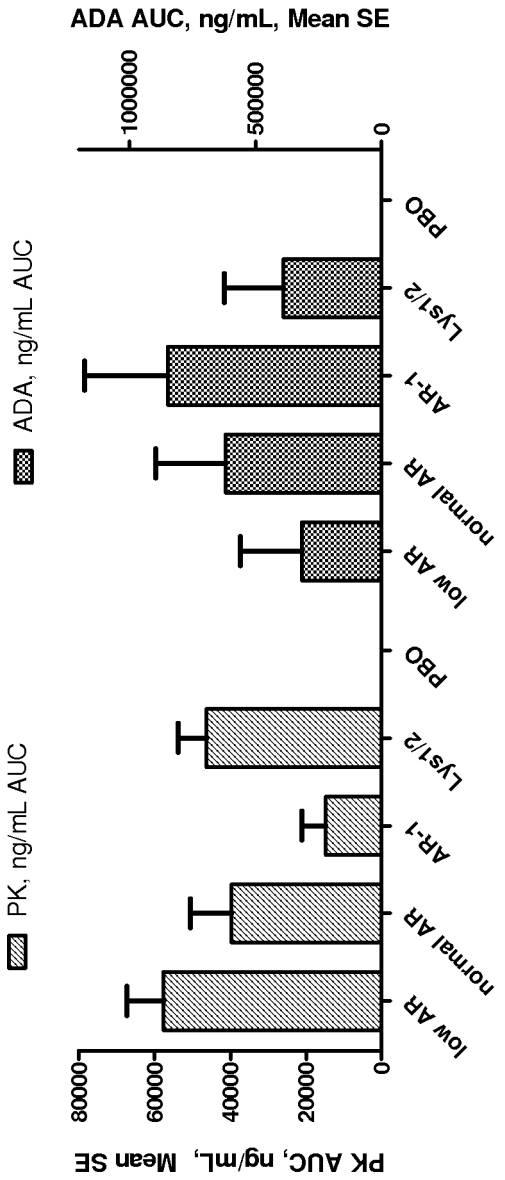

ADA AUC, ng/mL, Mean SE
1000000
500000
0
PBO
Lys1/2
AR-1
normal AR
low AR
PBO
Lys1/2
AR-1
normal AR
low AR
ADA, ng/mL AUC
PK, ng/mL AUC
80000
60000
40000
20000
0
PK AUC, ng/mL, Mean SE

Figure 104

Figure 105

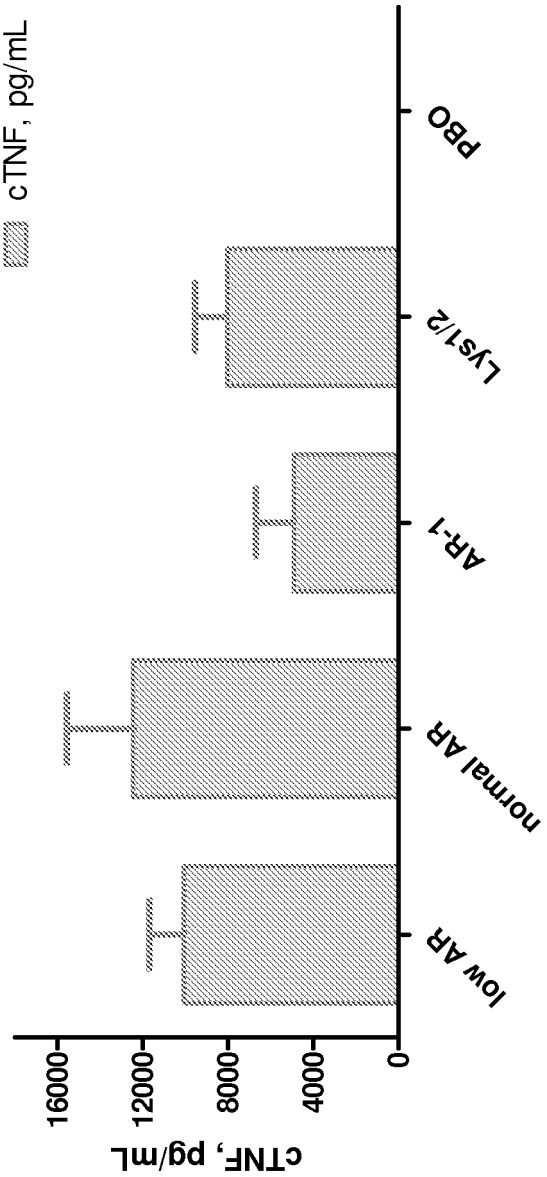

cTNF, pg/mL
16000
12000
8000
4000
0
low AR
normal AR
AR-1
Lys1/2
PBO
cTNF, pg/mL

Figure 106

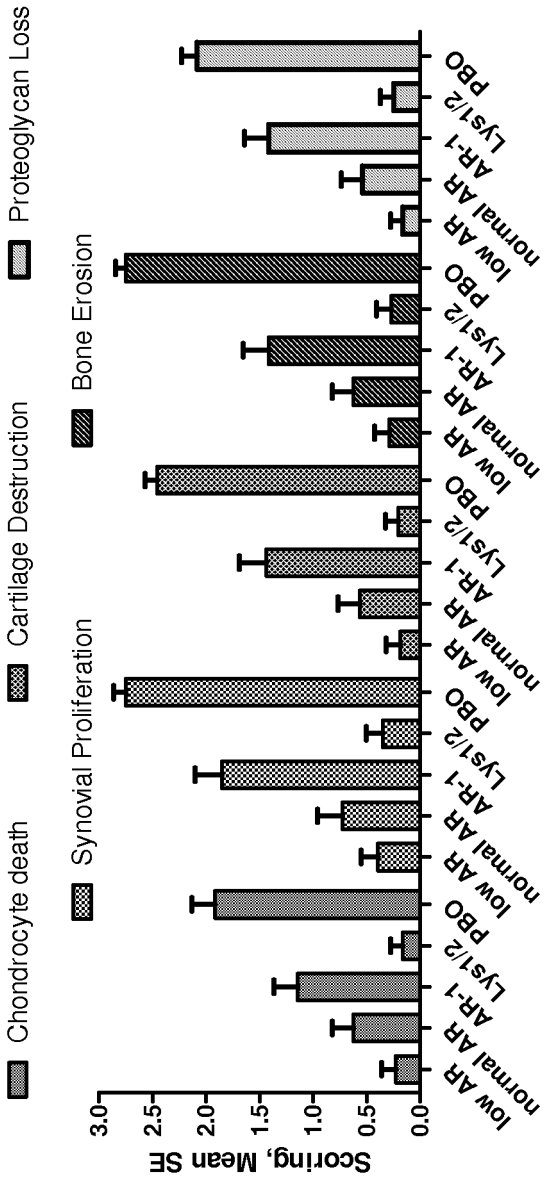

Chondrocyte death
Cartilage Destruction
Proteoglycan Loss
Synovial Proliferation
Bone Erosion
Scoring, Mean SE
3.0
2.5
2.0
1.5
1.0
0.5
0.0
low AR
normal AR
AR-1
Lys1/2
PBO

Figure 107A-D

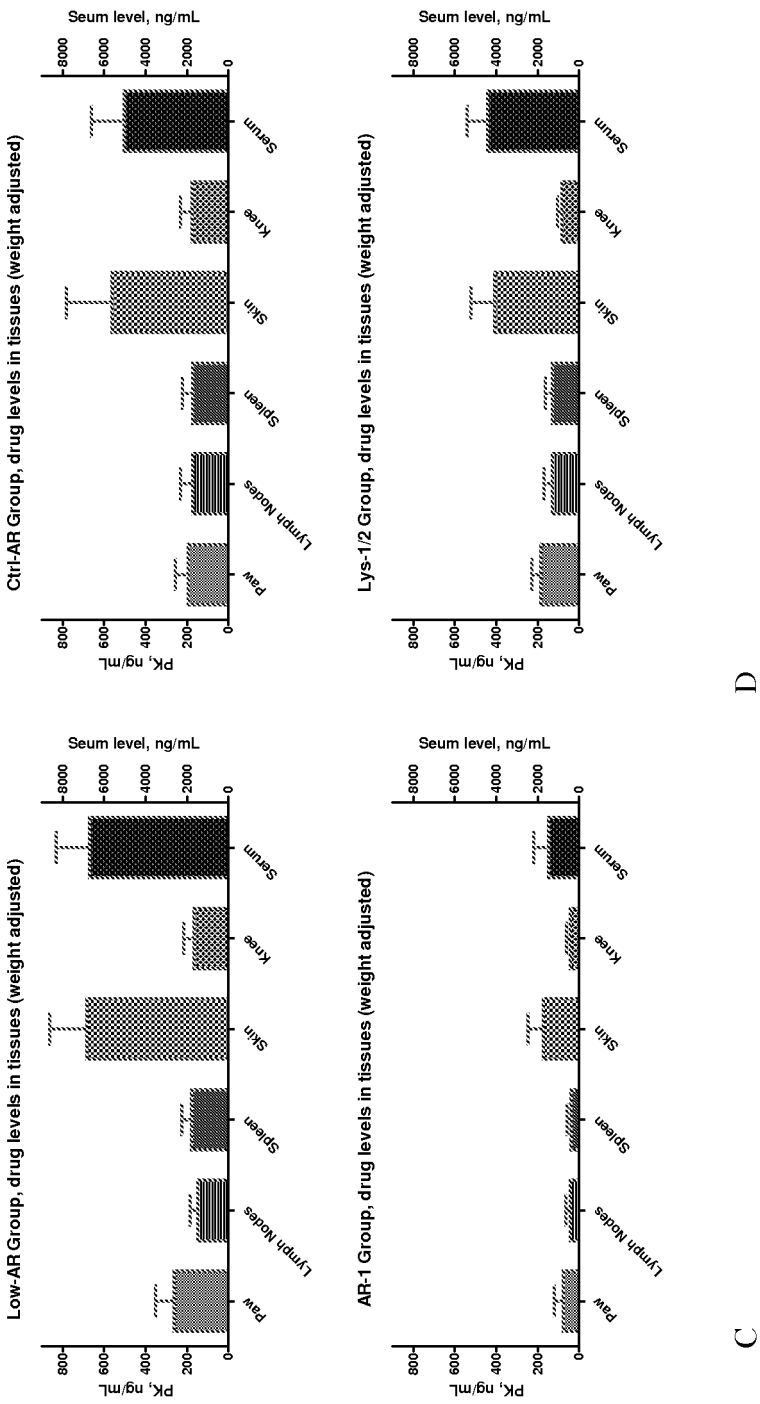


Figure 108A-D

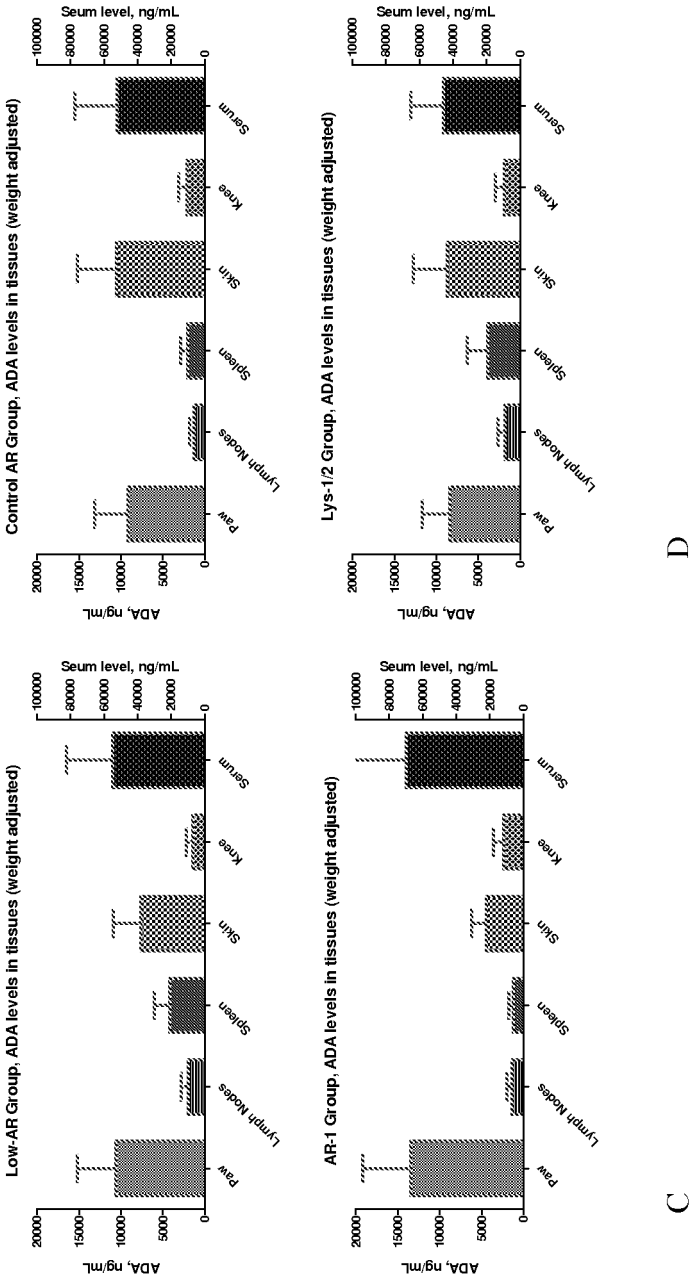


Figure 109A-D

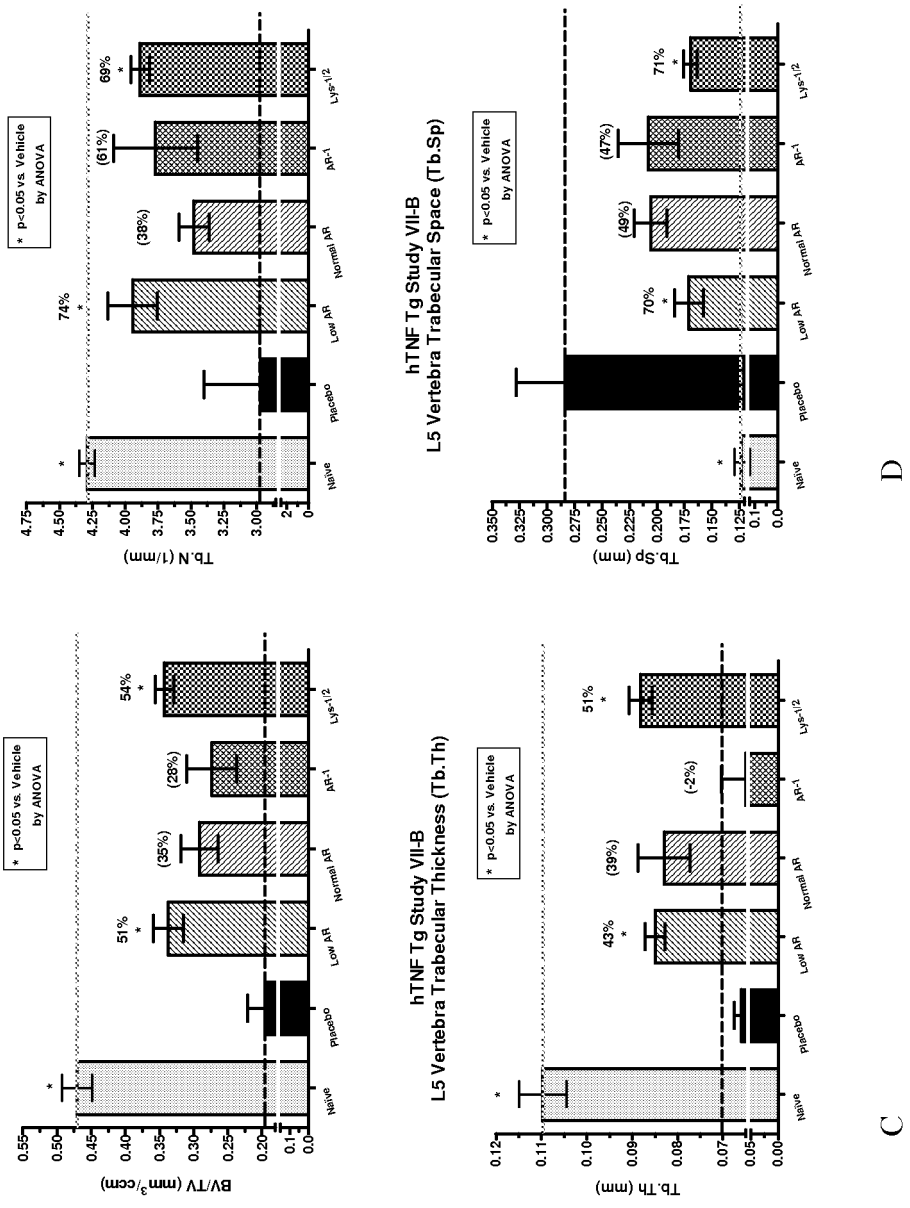


Figure 110A-D

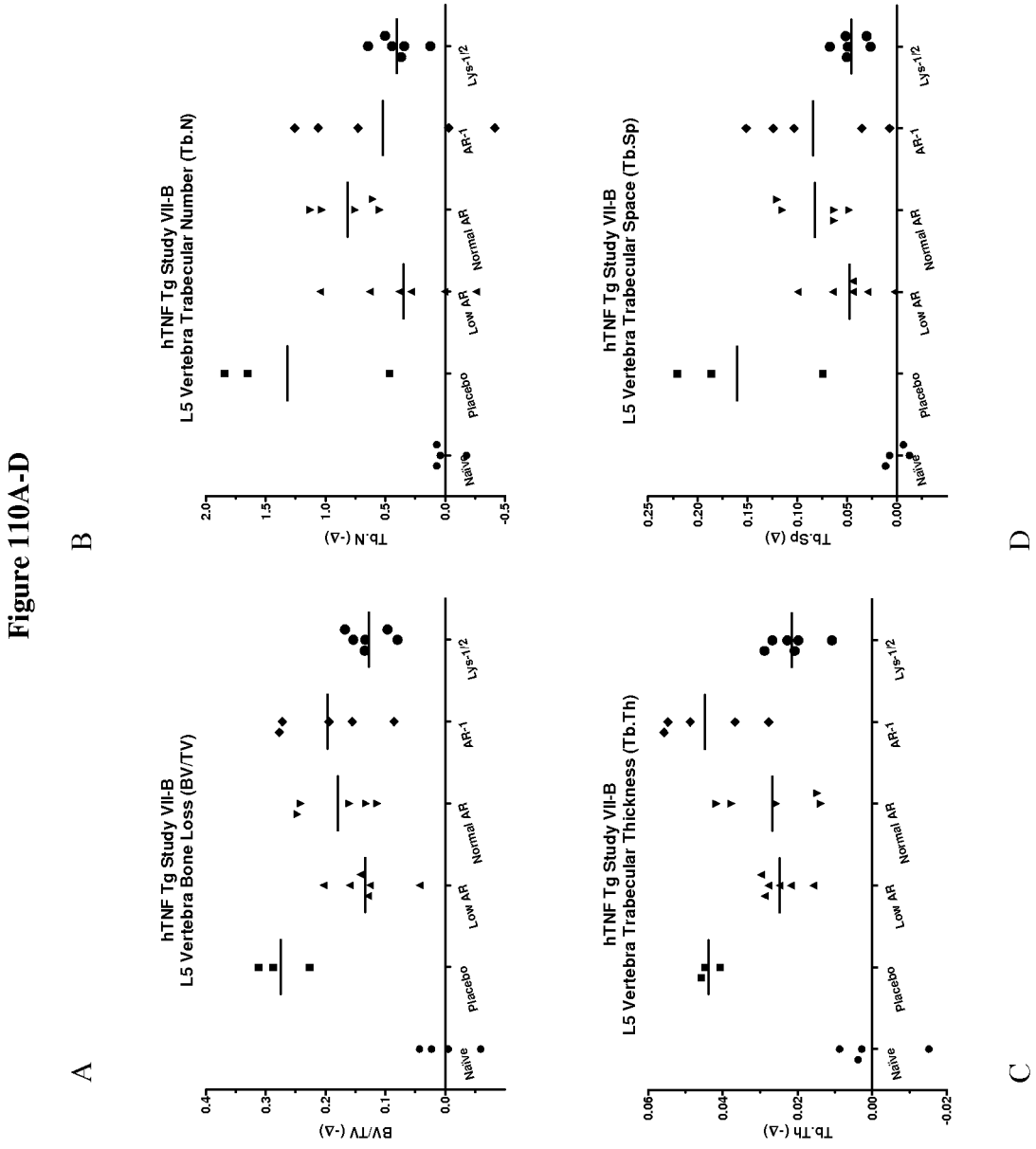
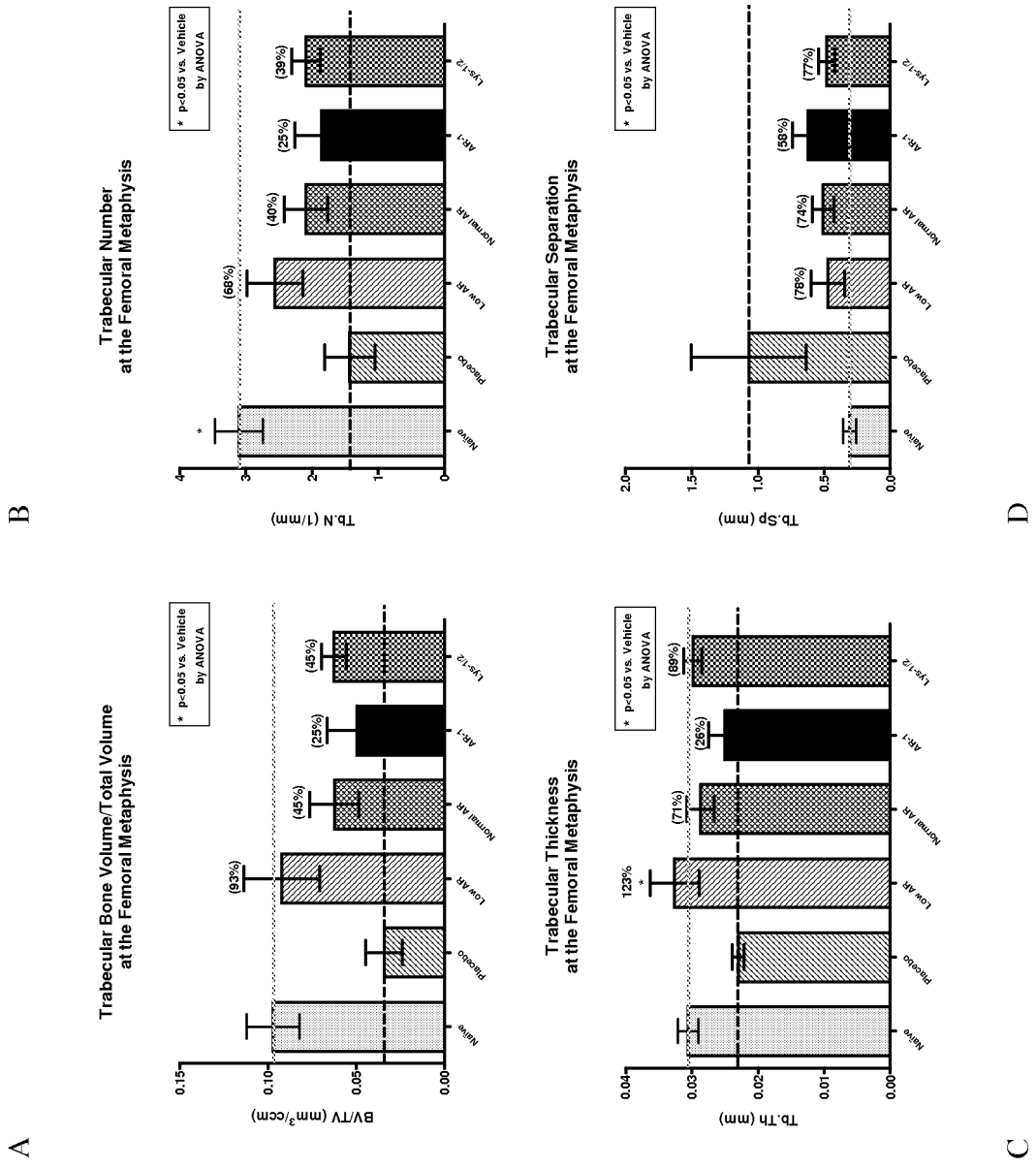


Figure 111A-D



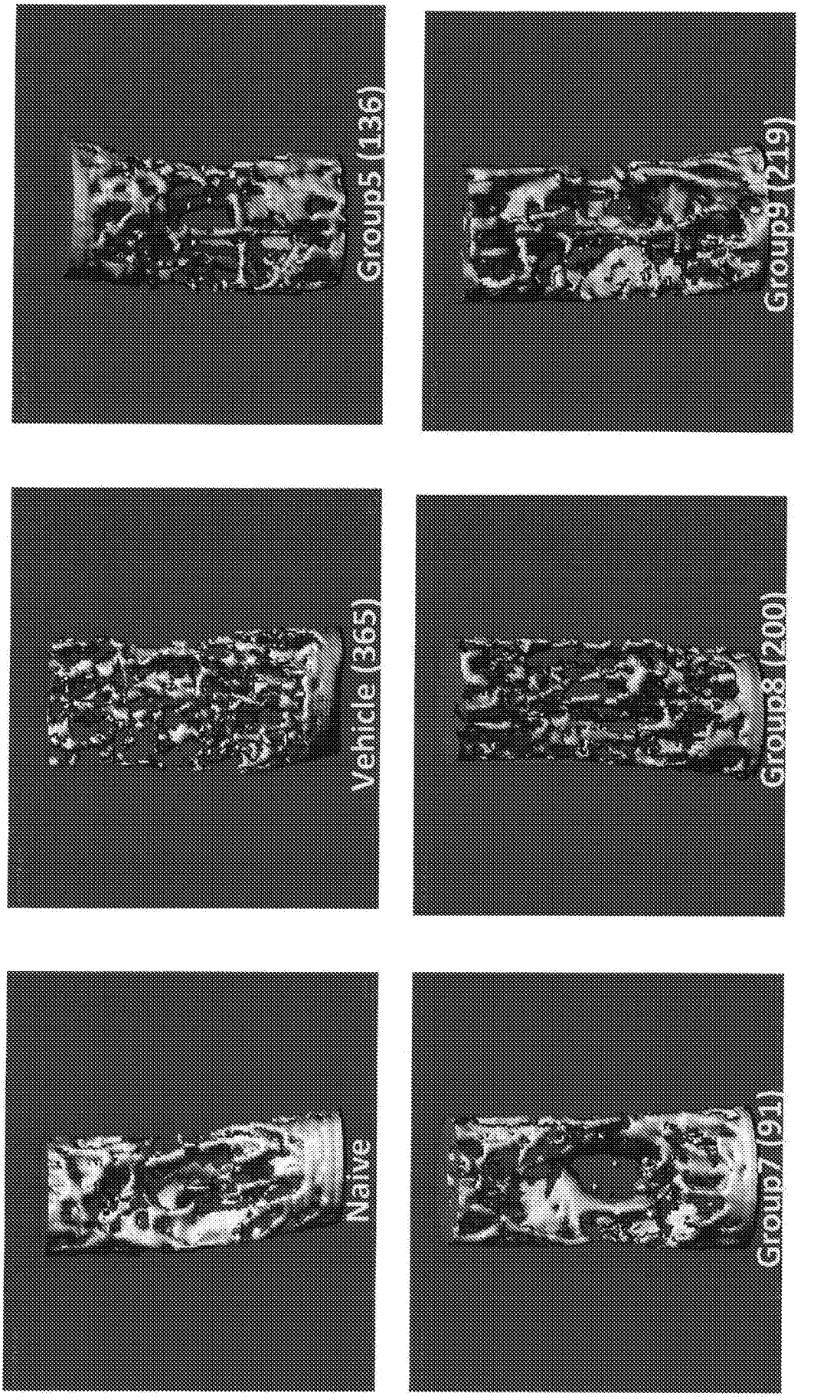

Group5 (136)
Group9 (219)
Vehicle (365)
Group8 (200)
Naive
Group7 (91)

Figure 112

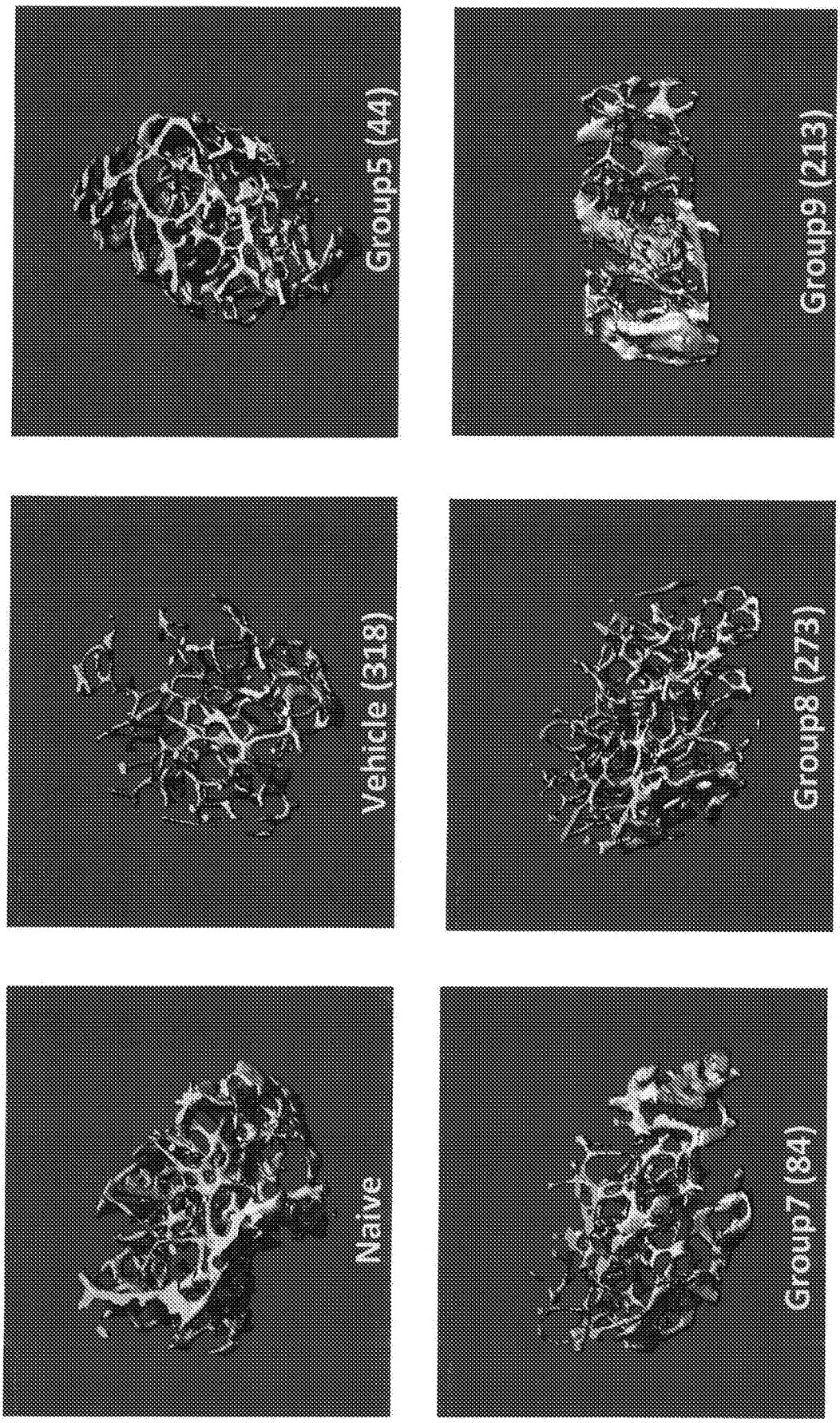


Figure 113