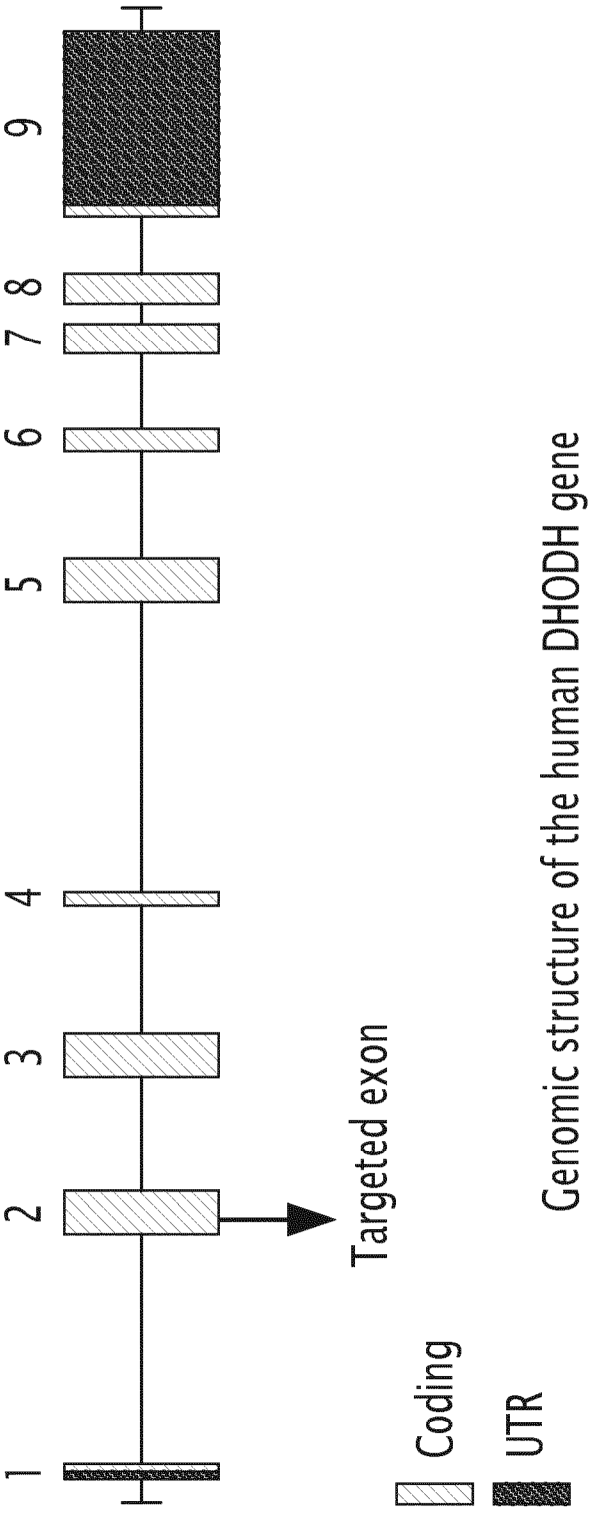

1
2
3
4
5
6
7
8
9
Targeted exon
Coding
UTR
Genomic structure of the human DHODH gene

FIG.1

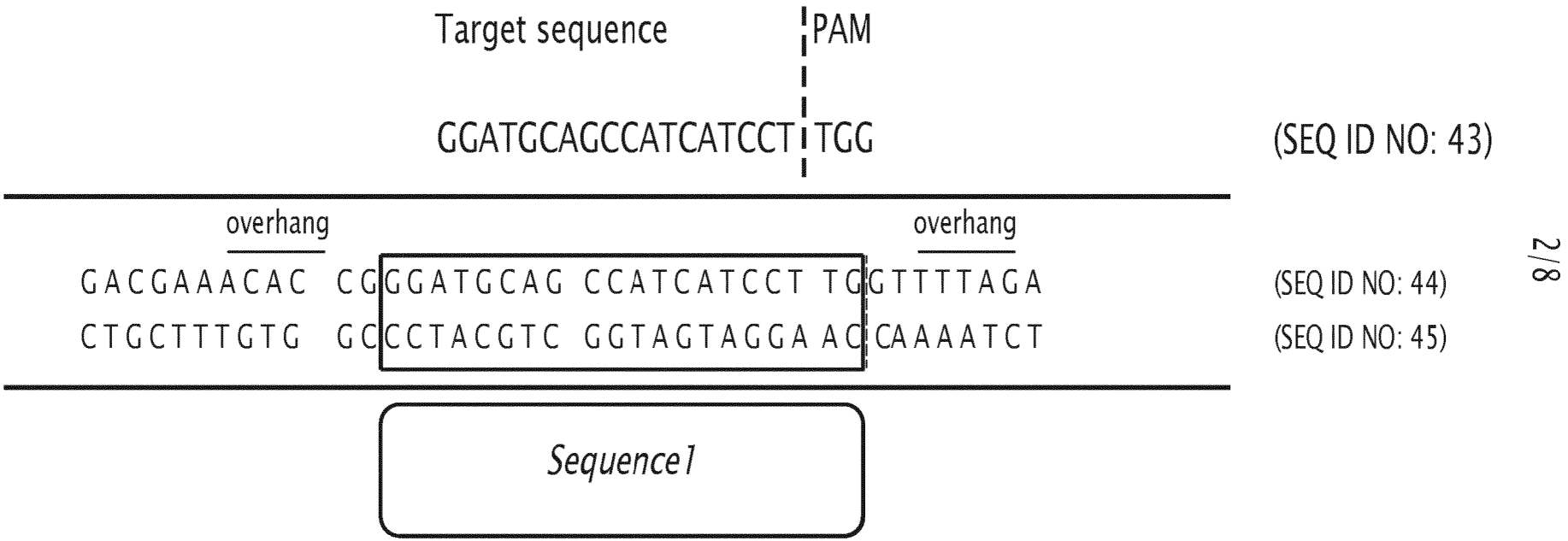

Target sequence
PAM
GGATGCAGCCATCATCCT TGG
(SEQ ID NO: 43)
overhang
overhang
GACGAAACAC CGGGATGCAG CCATCATCCT TGGTTTTAGA
(SEQ ID NO: 44)
CTGCTTTGTG GCCCTACGTC GGTAGTAGGA ACCAAAATCT
(SEQ ID NO: 45)
Sequence1

FIG.2

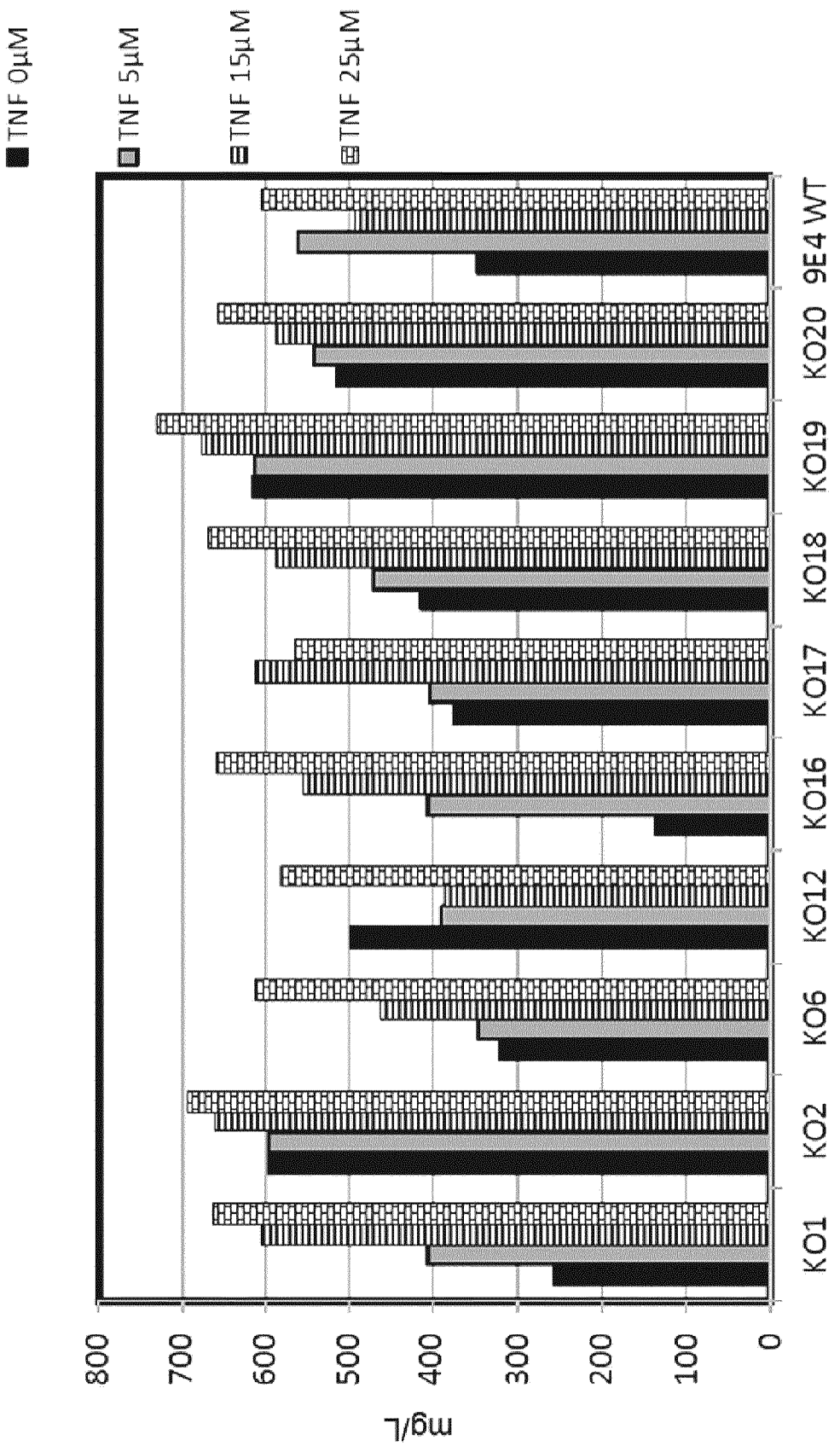

TNF 0µM
TNF 5µM
TNF 15µM
TNF 25µM
mg/L
800
700
600
500
400
300
200
100
0
KO1
KO2
KO6
KO12
KO16
KO17
KO18
KO19
KO20
9E4 WT

FIG.3

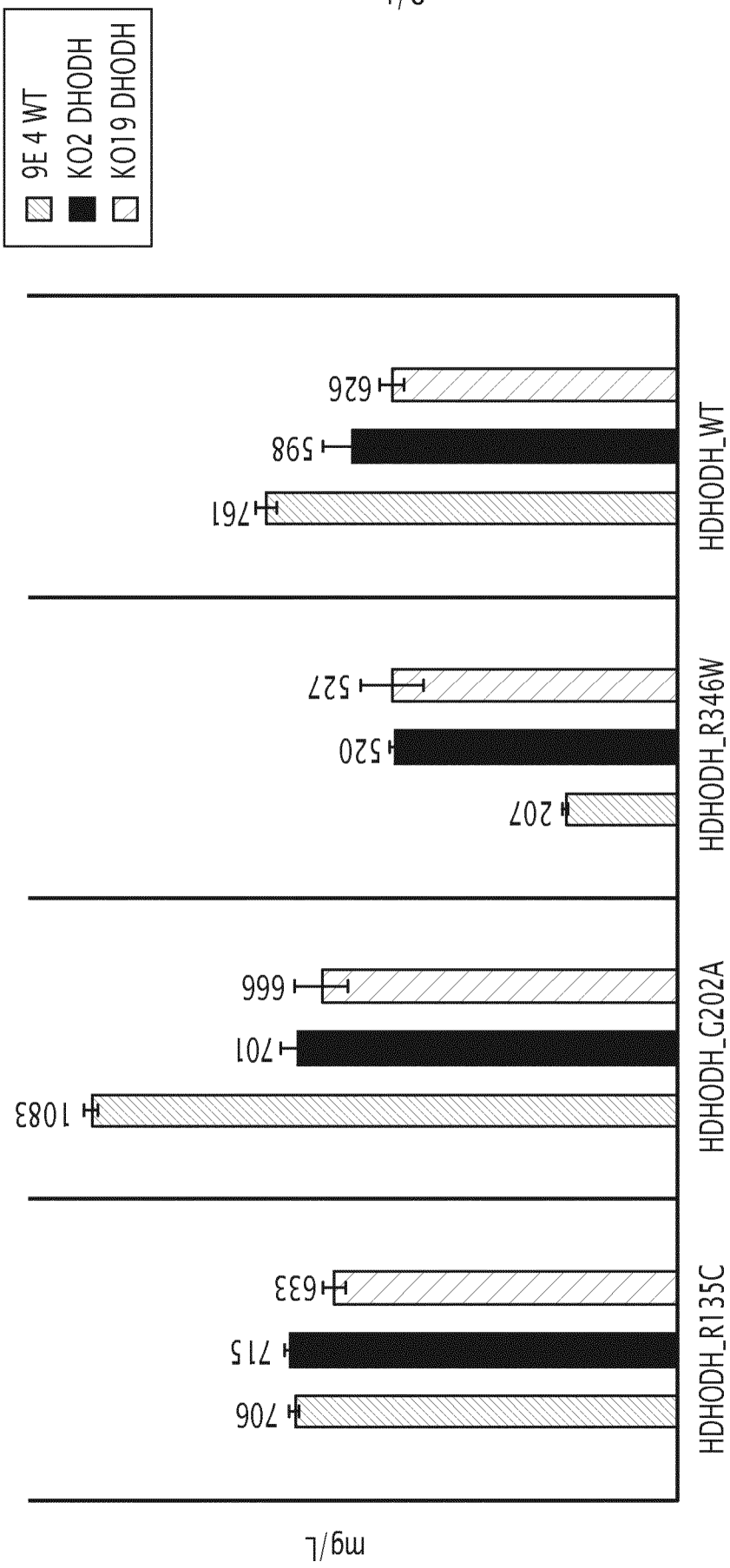

9E 4 WT
KO2 DHODH
KO19 DHODH
626
598
761
527
520
207
666
701
1083
633
715
706
HDHODH_WT
HDHODH_R346W
HDHODH_G202A
HDHODH_R135C
DHODH VARIANTS
mg/L

FIG.4

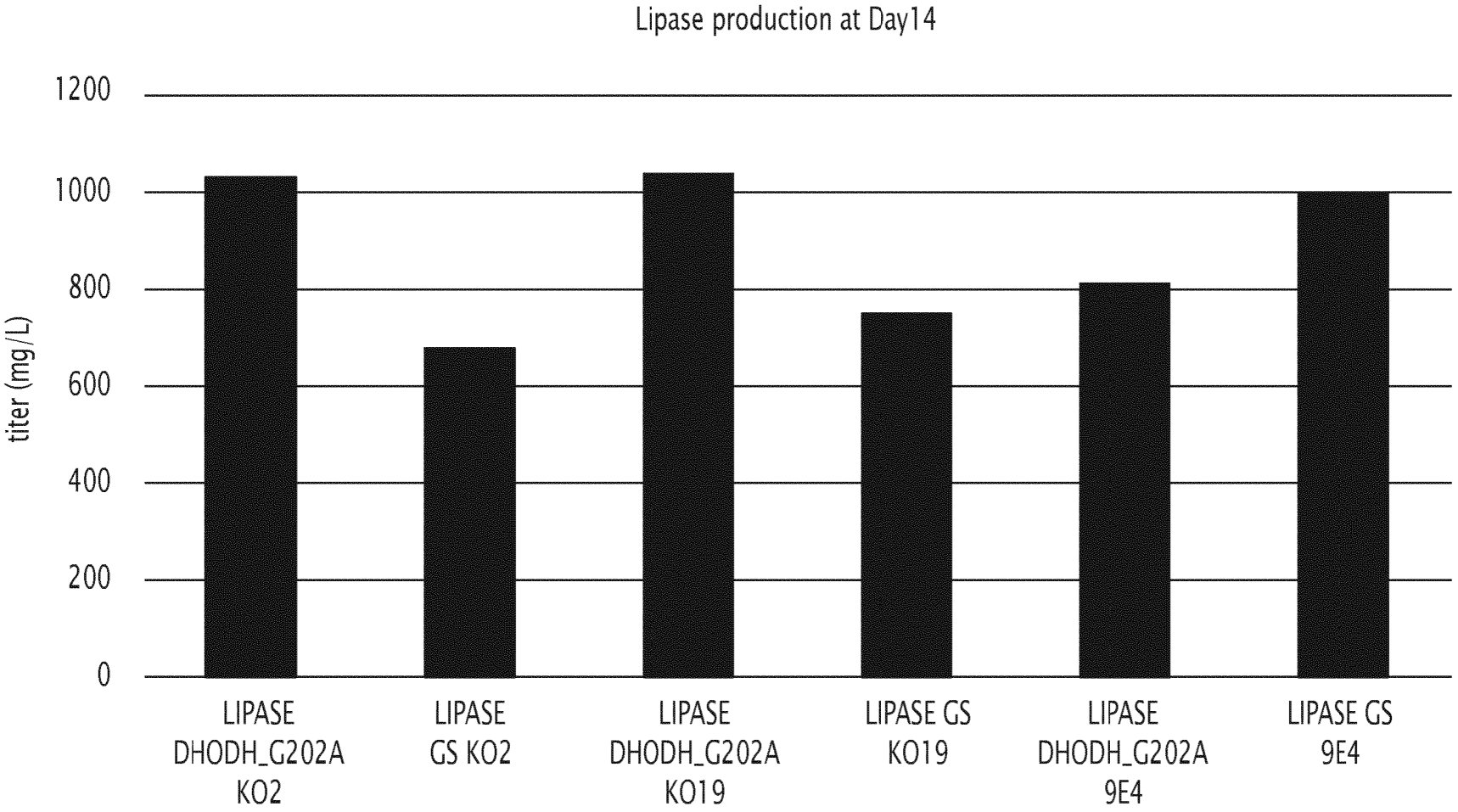

Lipase production at Day14
titer (mg/L)
1200
1000
800
600
400
200
0
LIPASE DHODH_G202A KO2
LIPASE GS KO2
LIPASE DHODH_G202A KO19
LIPASE GS KO19
LIPASE DHODH_G202A 9E4
LIPASE GS 9E4

FIG.5

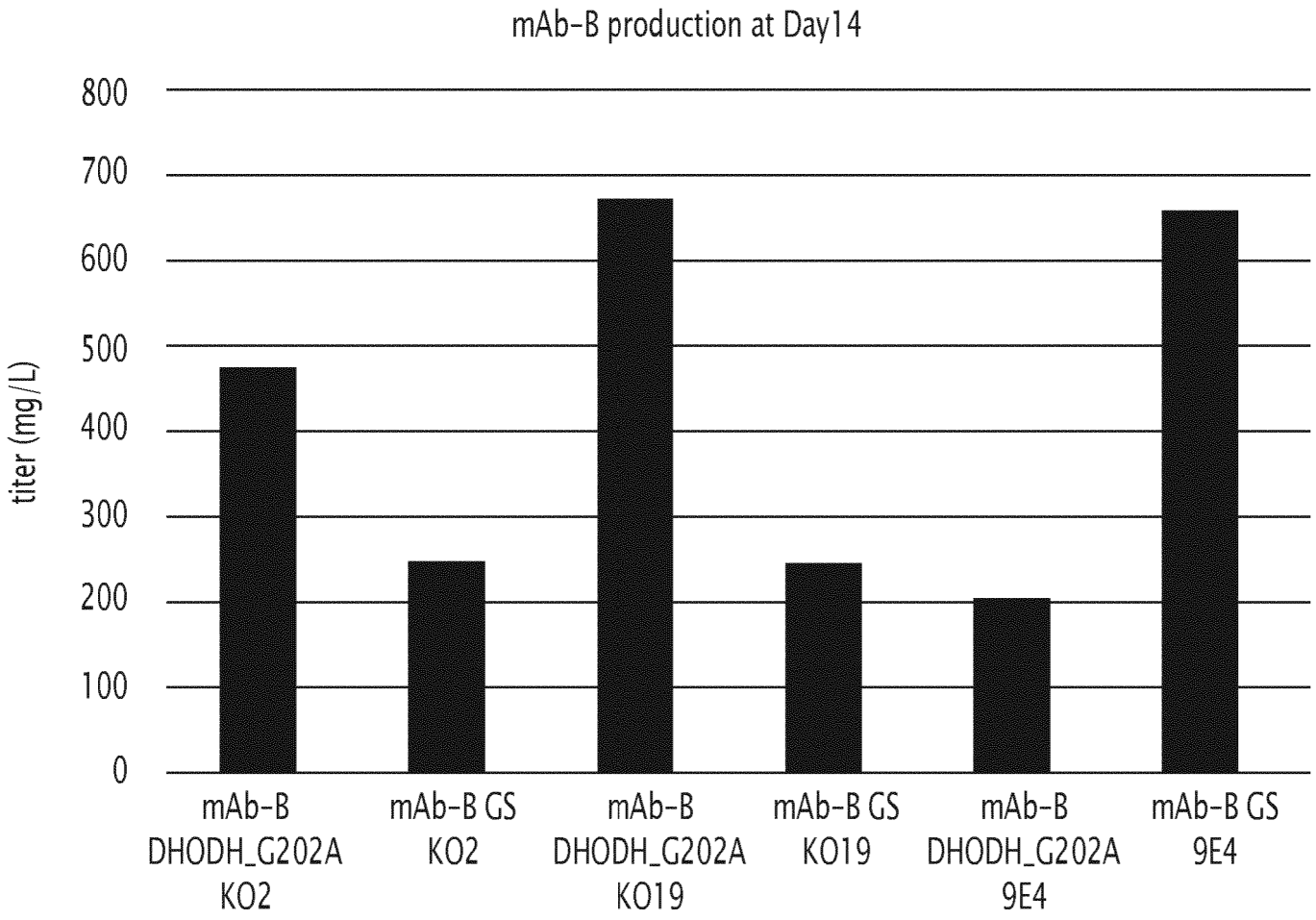

mAb-B production at Day14
titer (mg/L)
800
700
600
500
400
300
200
100
0
mAb-B DHODH_G202A KO2
mAb-B GS KO2
mAb-B DHODH_G202A KO19
mAb-B GS KO19
mAb-B DHODH_G202A 9E4
mAb-B GS 9E4

FIG.6

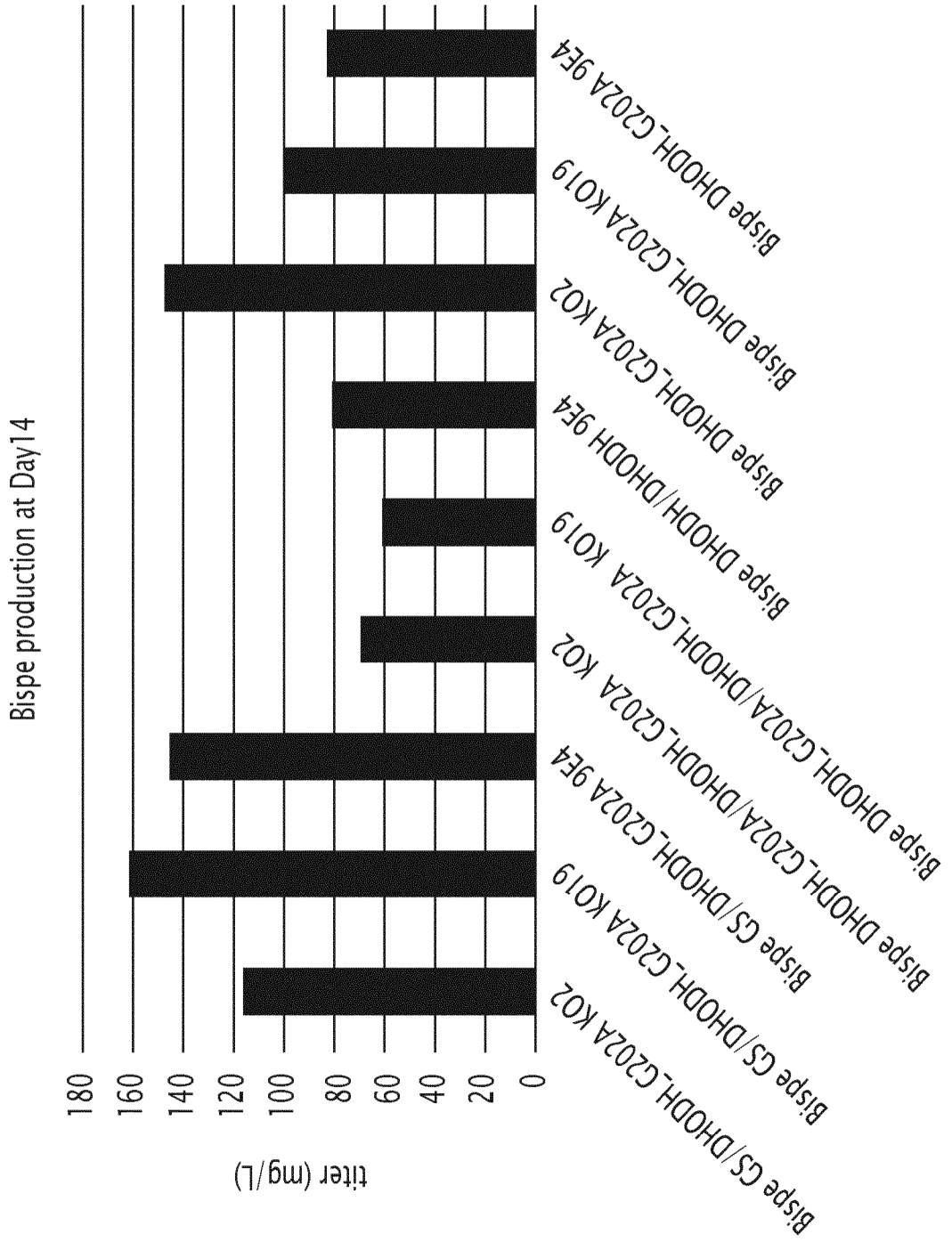

Bispe production at Day14
titer (mg/L)
0
20
40
60
80
100
120
140
160
180
Bispe CS/DHODH_G202A KO2
Bispe CS/DHODH_G202A KO19
Bispe CS/DHODH_G202A 9E4
Bispe DHODH_G202A/DHODH_G202A KO2
Bispe DHODH_G202A/DHODH_G202A KO19
Bispe DHODH/DHODH 9E4
Bispe DHODH_G202A KO2
Bispe DHODH_G202A KO19
Bispe DHODH_G202A 9E4

FIG.7

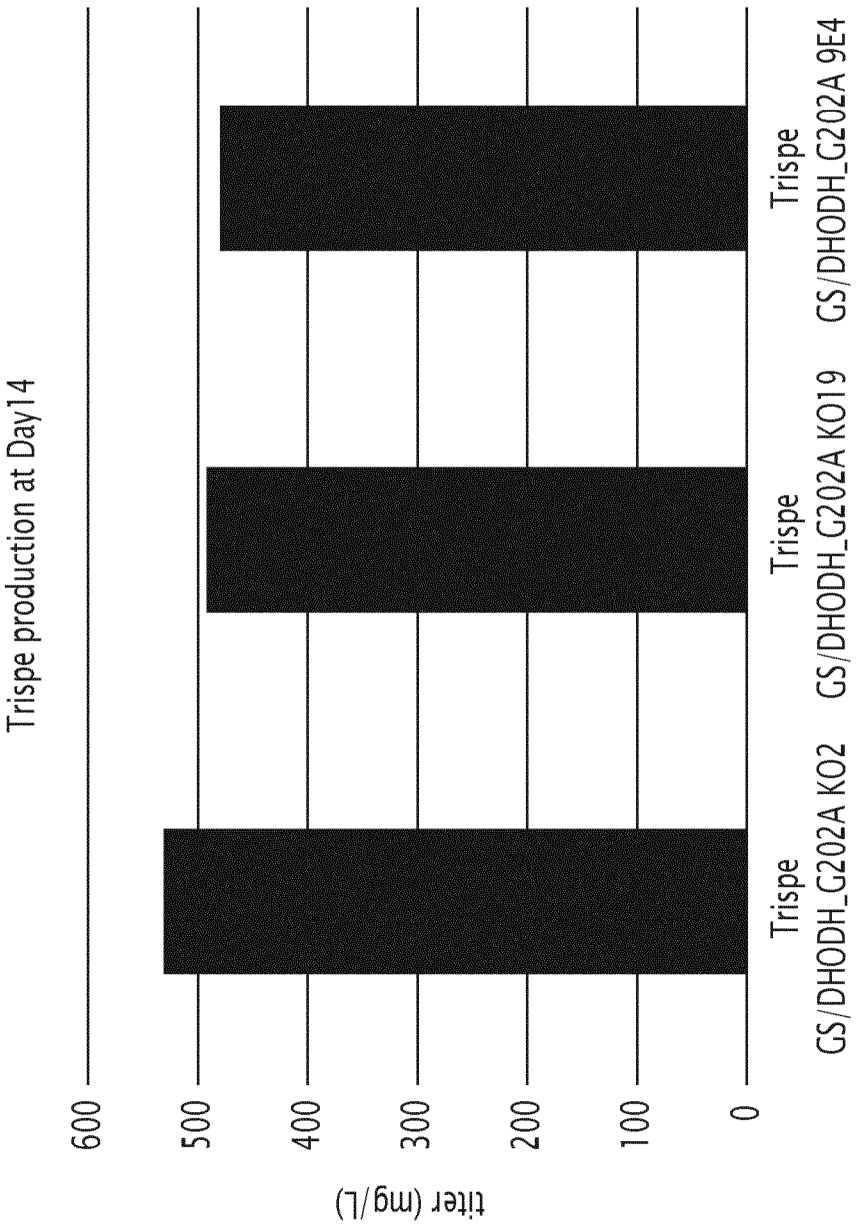

Trispe production at Day14
titer (mg/L)
600
500
400
300
200
100
0
Trispe GS/DHODH_G202A KO2
Trispe GS/DHODH_G202A KO19
Trispe GS/DHODH_G202A 9E4

FIG.8