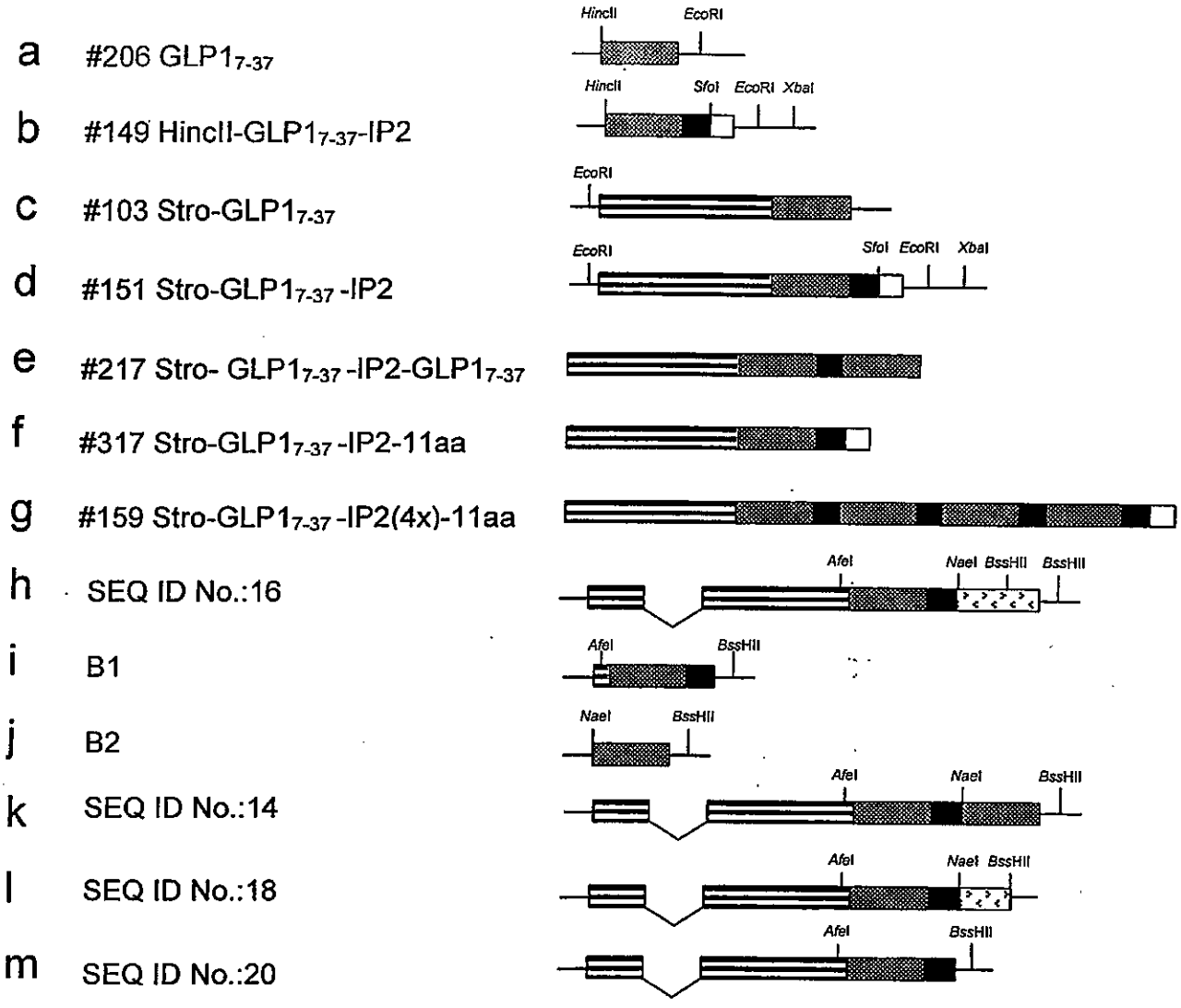
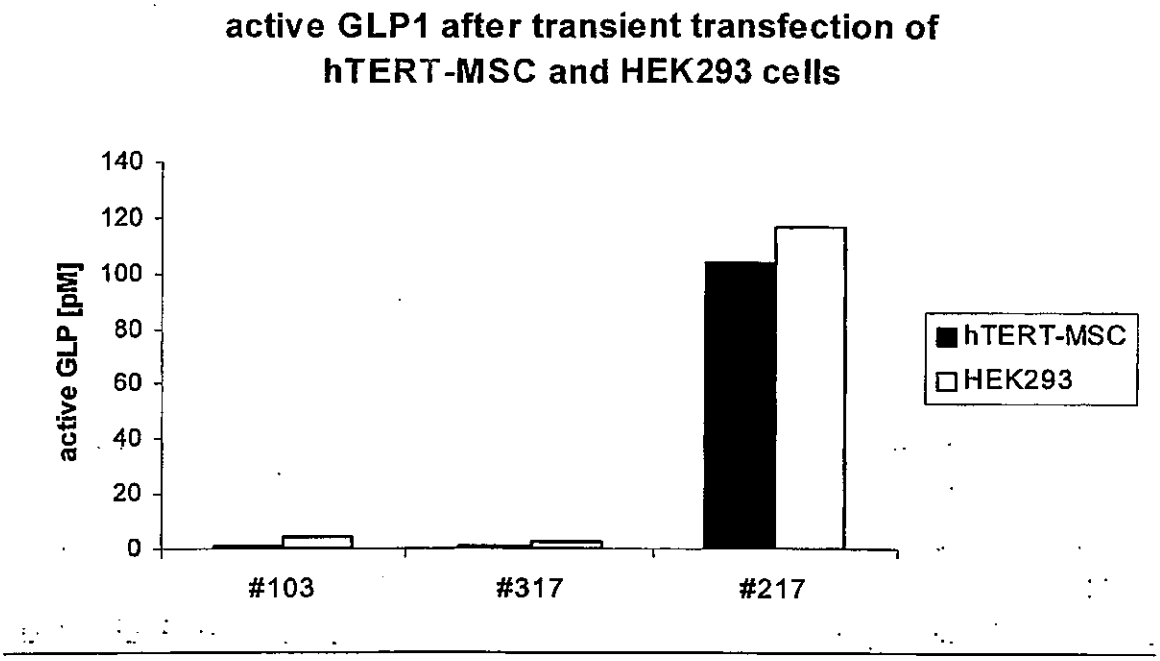
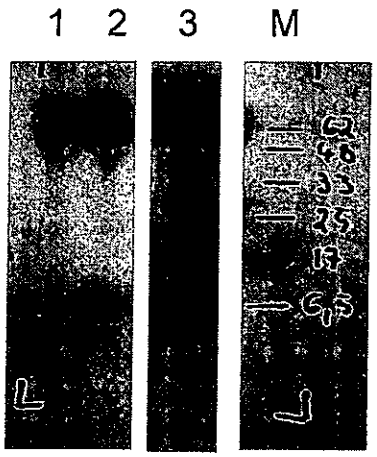

a #206 GLP1 7-37
HincII EcoRI
b #149 HincII-GLP1 7-37 -IP2
HincII SfoI EcoRI XbaI
c #103 Stro-GLP1 7-37
EcoRI
d #151 Stro-GLP1 7-37 -IP2
EcoRI SfoI EcoRI XbaI
e #217 Stro- GLP1 7-37 -IP2-GLP1 7-37
f #317 Stro-GLP1 7-37 -IP2-11aa
g #159 Stro-GLP1 7-37 -IP2(4x)-11aa
h SEQ ID No.:16
AfeI NaeI BssHII BssHII
i B1
AfeI BssHII
j B2
NaeI BssHII
k SEQ ID No.:14
AfeI NaeI BssHII
l SEQ ID No.:18
AfeI NaeI BssHII
m SEQ ID No.:20
AfeI BssHII
Stromelysin (Signalpeptide and Leader)
Stromelysin (Signalpeptide and leader, chimaeric intron)
GLP1 7-37
P2
GLP2 1-35 or shortened version GLP2 1-20

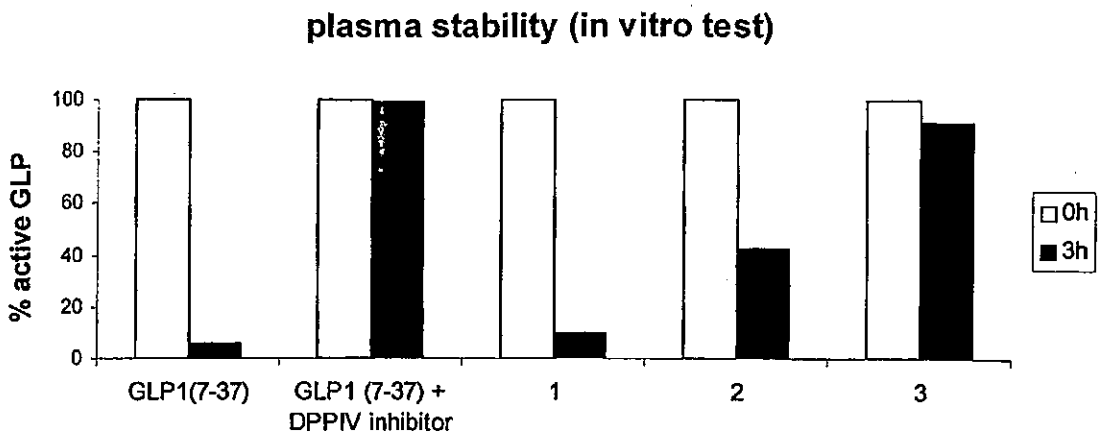
Figur 1


active GLP1 after transient transfection of
hTERT-MSC and HEK293 cells
active GLP [pM]
140
120
100
80
60
40
20
0
#103
#317
#217
hTERT-MSC
HEK293

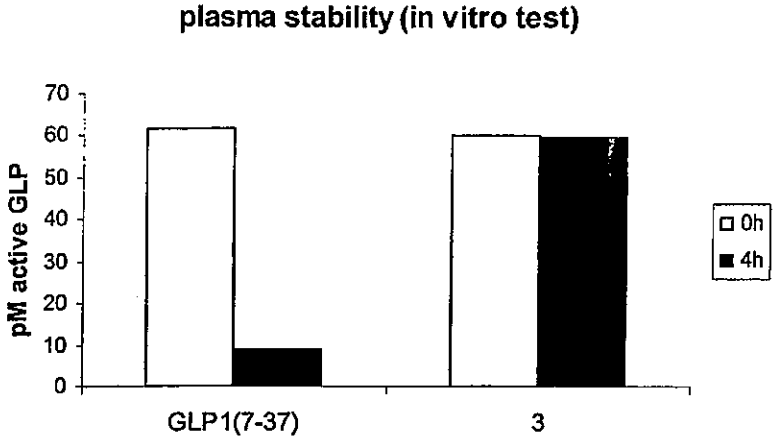
Figur 2



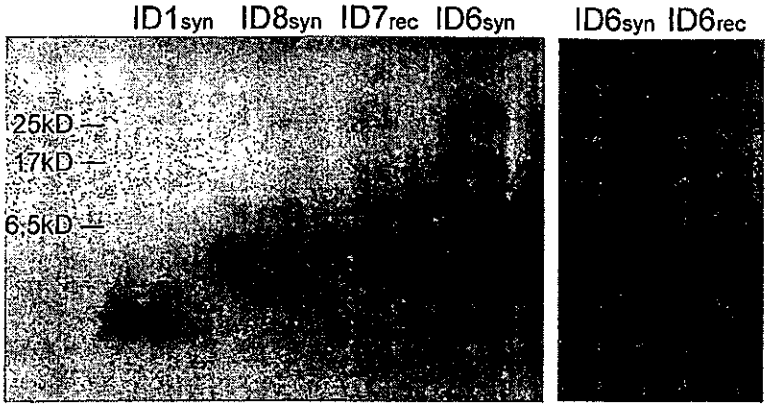
Figur 3


plasma stability (in vitro test)
% active GLP
100
80
60
40
20
0
GLP1(7-37)
GLP1 (7-37) + DPPIV inhibitor
1
2
3
0h
3h

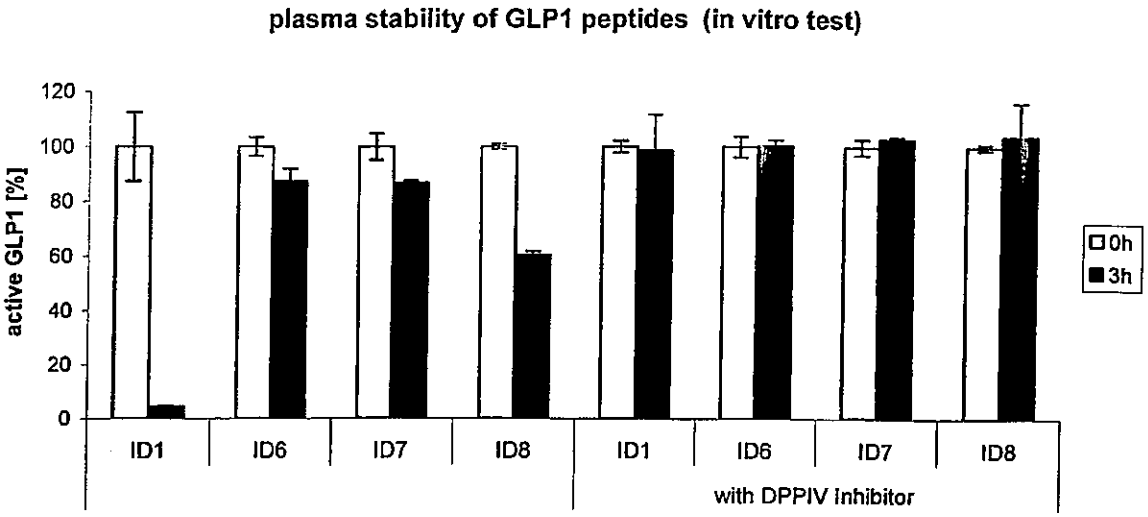
Figur 4


plasma stability (in vitro test)
pM active GLP
70
60
50
40
30
20
10
0
GLP1(7-37)
3
0h
4h

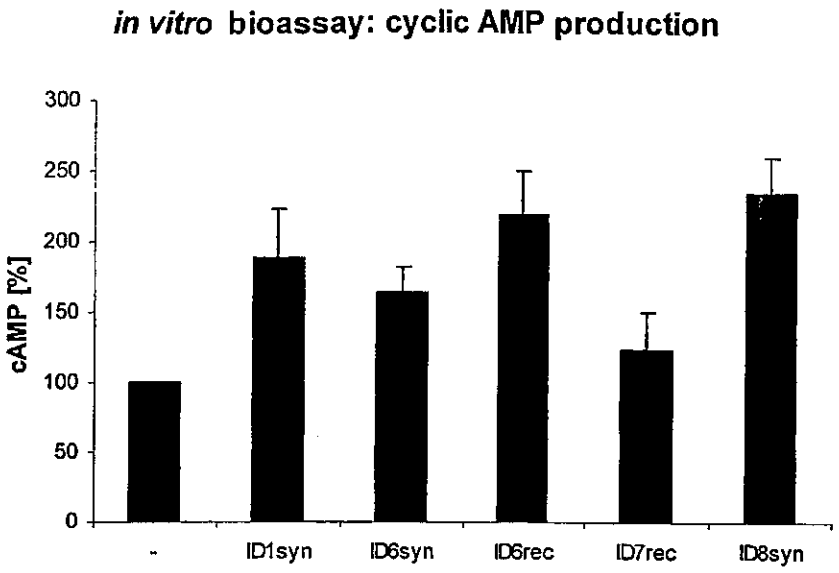
Figur 5



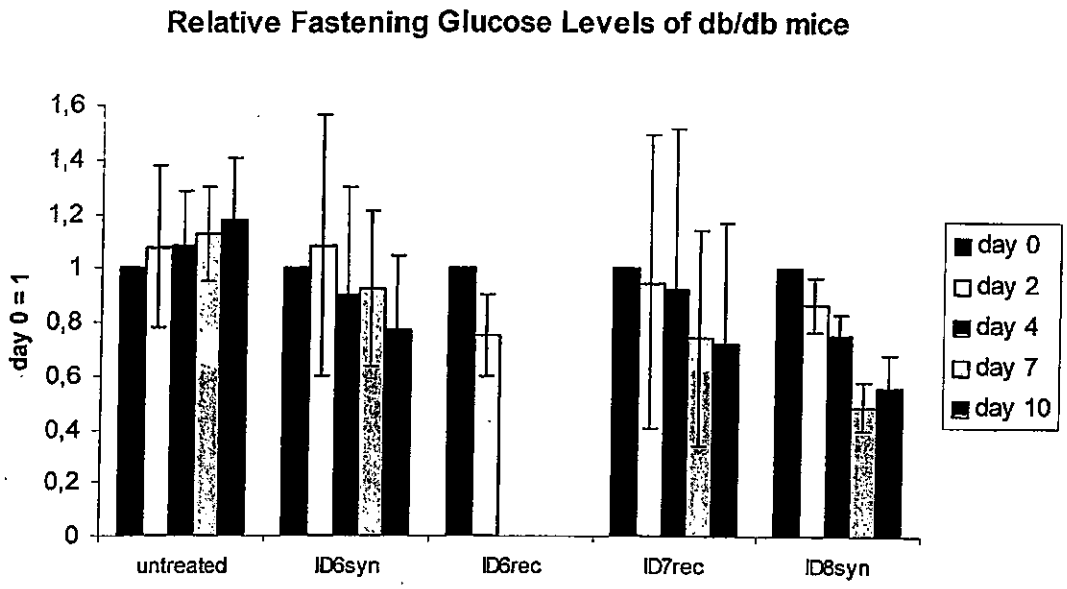
Figur 6


plasma stability of GLP1 peptides (in vitro test)
active GLP1 [%]
120
100
80
60
40
20
0
ID1
ID6
ID7
ID8
ID1
ID6
ID7
ID8
with DPPIV Inhibitor
0h
3h

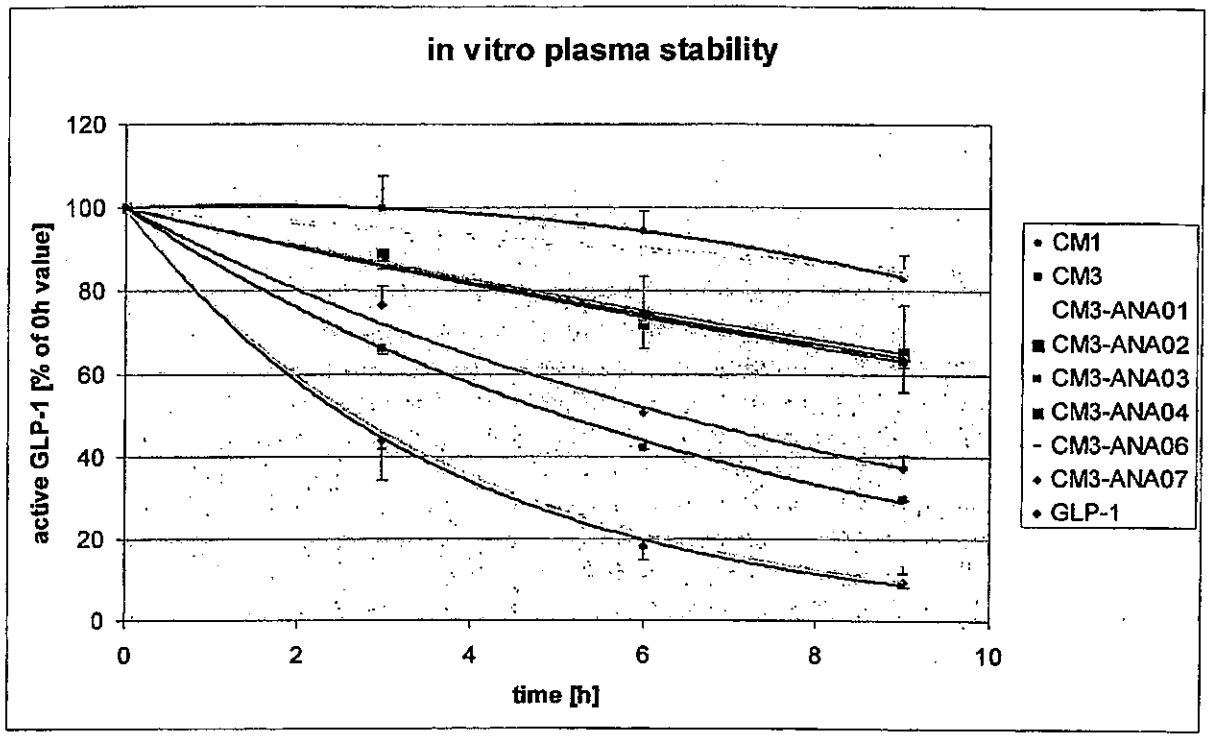
Figur 7


in vitro bioassay: cyclic AMP production
cAMP [%]
300
250
200
150
100
50
0
-
ID1syn
ID6syn
ID6rec
ID7rec
ID8syn

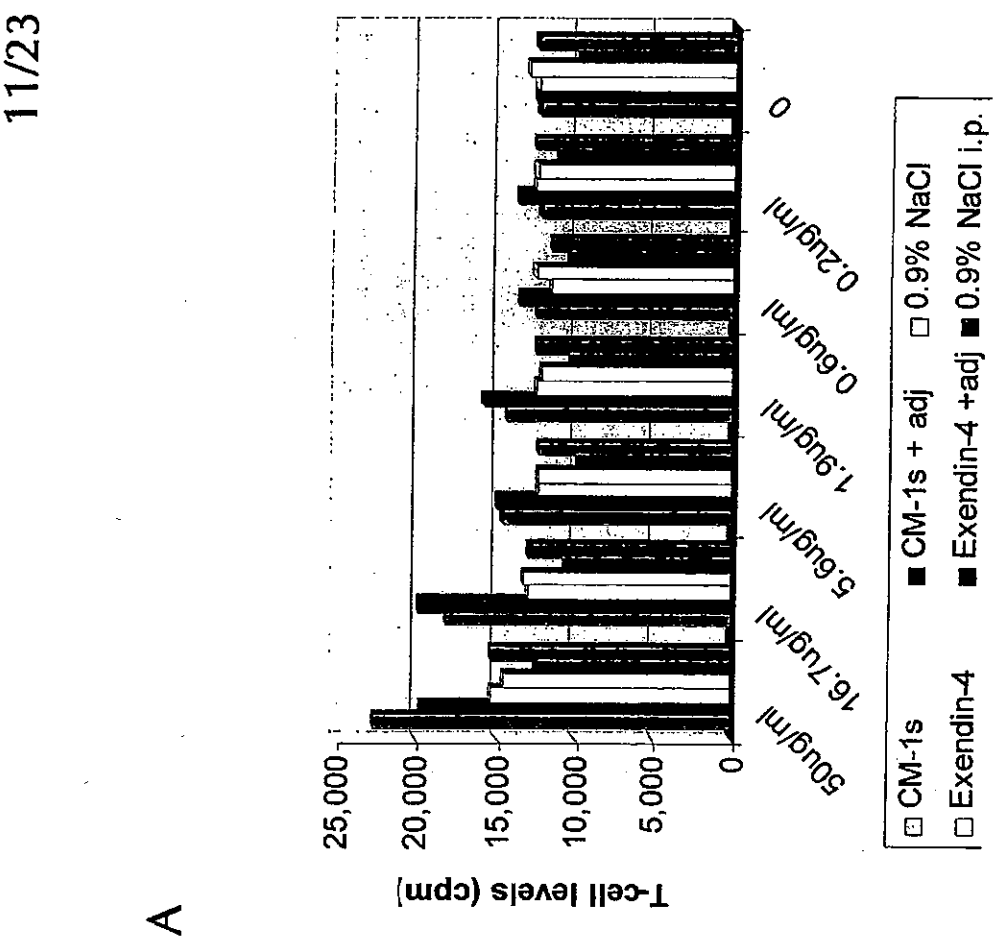
Figur 8


Relative Fastening Glucose Levels of db/db mice
day 0 = 1
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
untreated
ID6syn
ID6rec
ID7rec
ID8syn
day 0
day 2
day 4
day 7
day 10

Figur 9

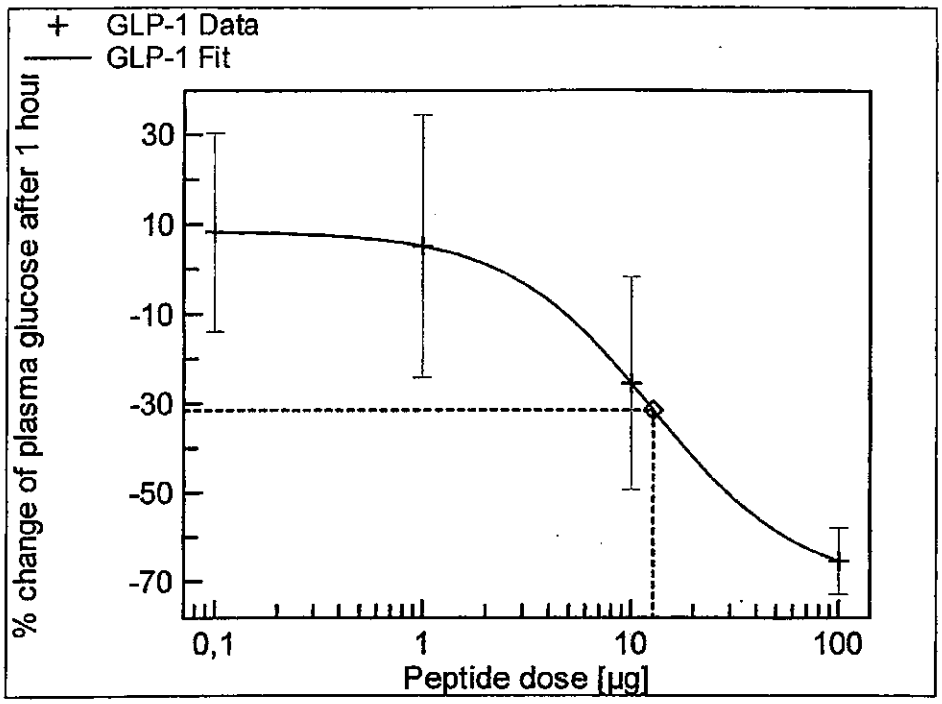

in vitro plasma stability
active GLP-1 [% of 0h value]
120
100
80
60
40
20
0
0
2
4
6
8
10
time [h]
CM1
CM3
CM3-ANA01
CM3-ANA02
CM3-ANA03
CM3-ANA04
CM3-ANA06
CM3-ANA07
GLP-1

Figur 10

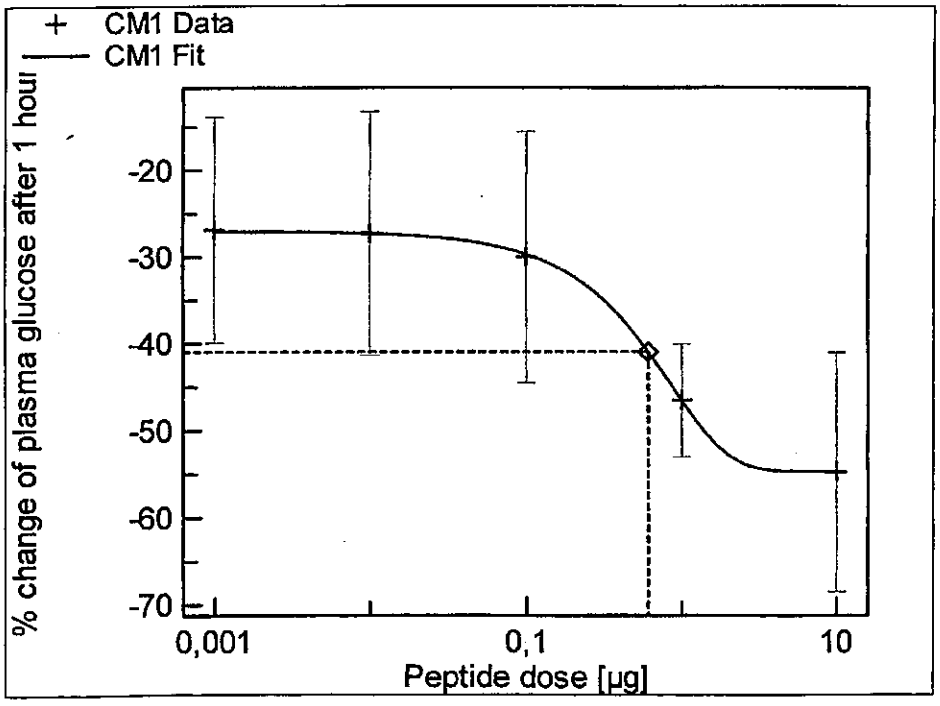

A
T-cell levels (cpm)
25,000
20,000
15,000
10,000
5,000
0
50ug/ml
16.7ug/ml
5.6ug/ml
1.9ug/ml
0.6ug/ml
0.2ug/ml
0
CM-1s
Exendin-4
CM-1s + adj
Exendin-4 +adj
0.9% NaCl
0.9% NaCl i.p.
B
Antigen- spezifischer IgG-Titer x 10^3
500
400
300
40
30
20
10
0
n = 5
n = 3
n = 3
n = 3
<LOQ
<LOQ
<LOQ
<LOQ
<LOQ
<LOQ
CM 1 i.v.
CM 1 + Adj. i.p.
0,9% NaCl i.p.
unbehandelt

Figur 11

A

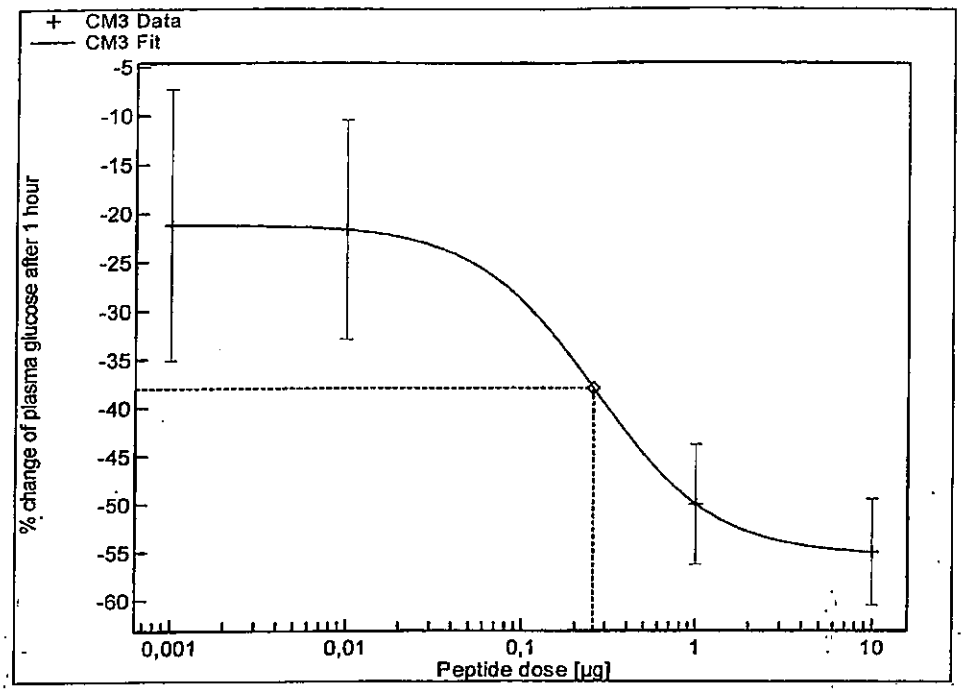

+ GLP-1 Data
GLP-1 Fit
% change of plasma glucose after 1 hour
30
10
-10
-30
-50
-70
0,1
1
10
100
Peptide dose [µg]

B

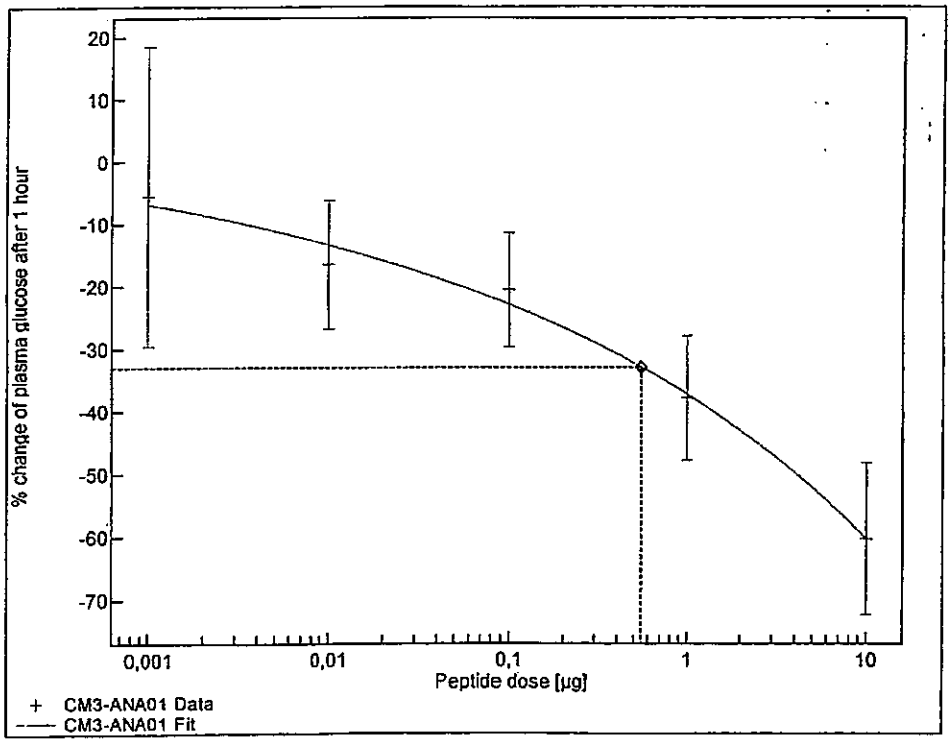

+ CM1 Data
CM1 Fit
% change of plasma glucose after 1 hour
-20
-30
-40
-50
-60
-70
0,001
0,1
10
Peptide dose [µg]

Figur 12

C

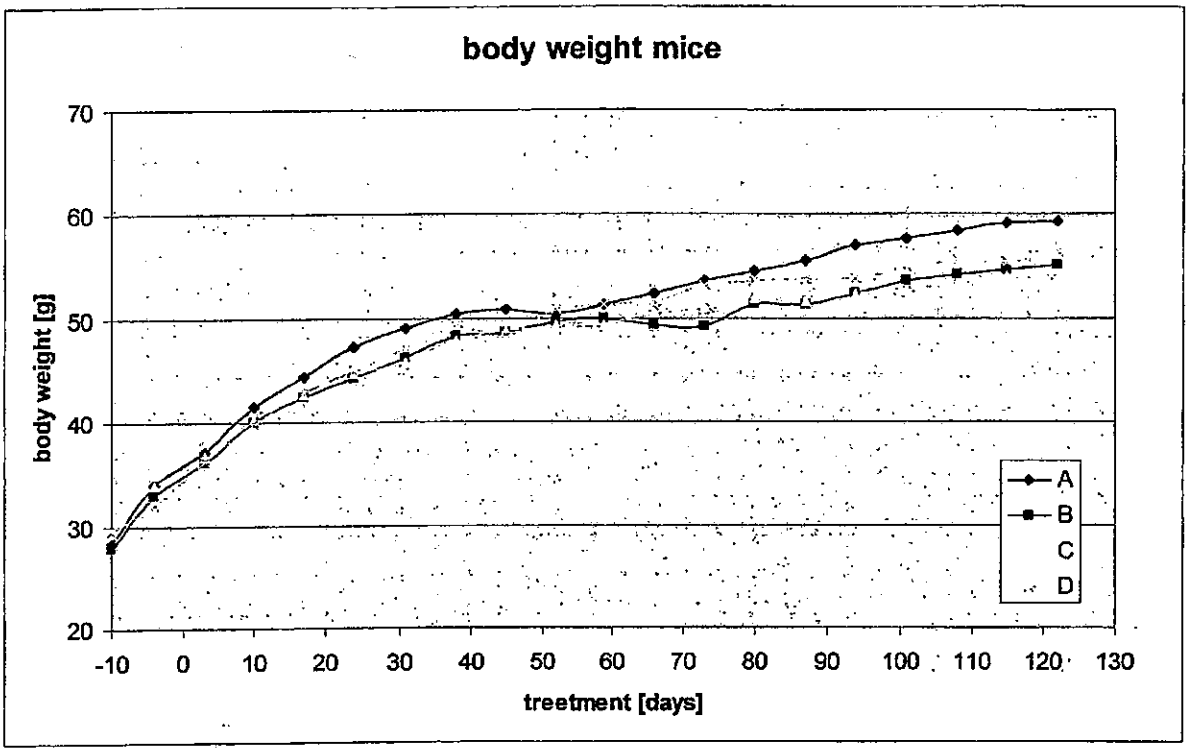


D

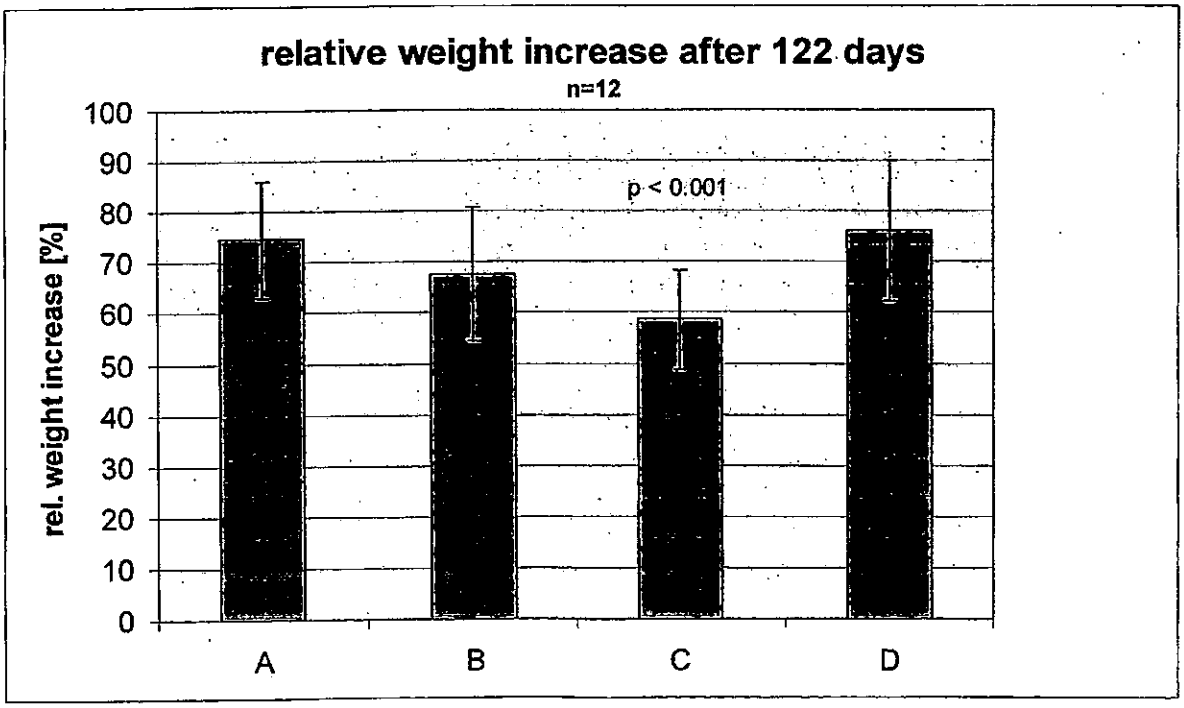


Figur 12 (continued)

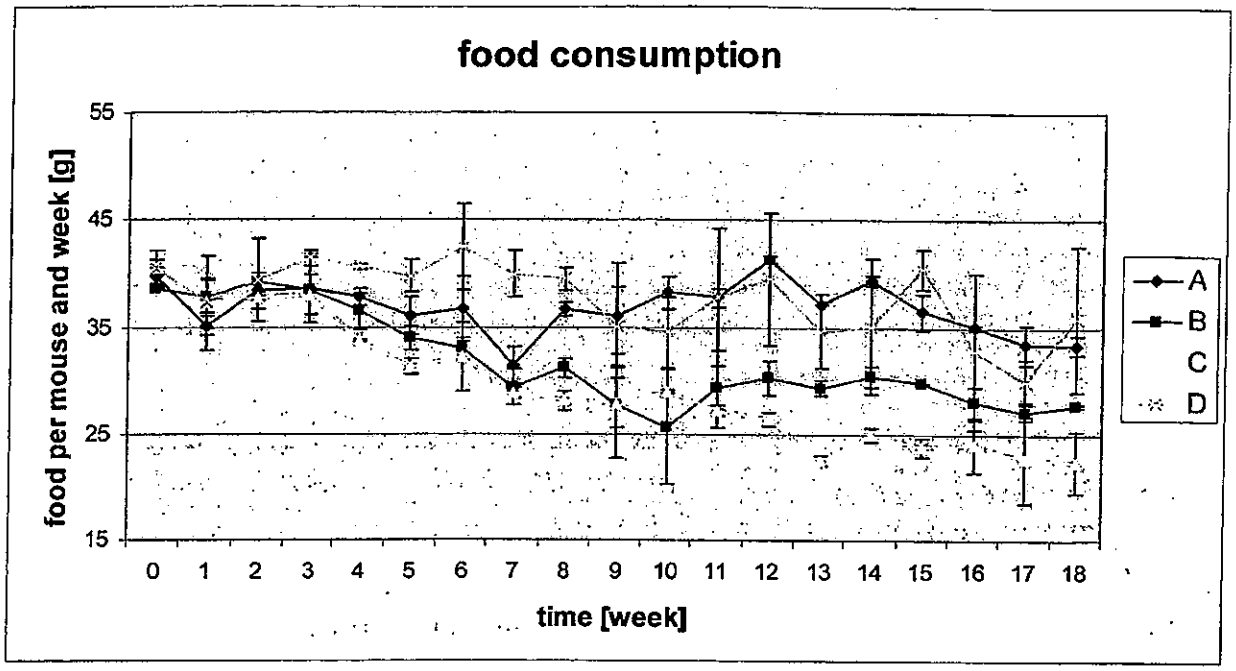
A


body weight mice
body weight [g]
70
60
50
40
30
20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
treetment [days]
A
B
C
D

B

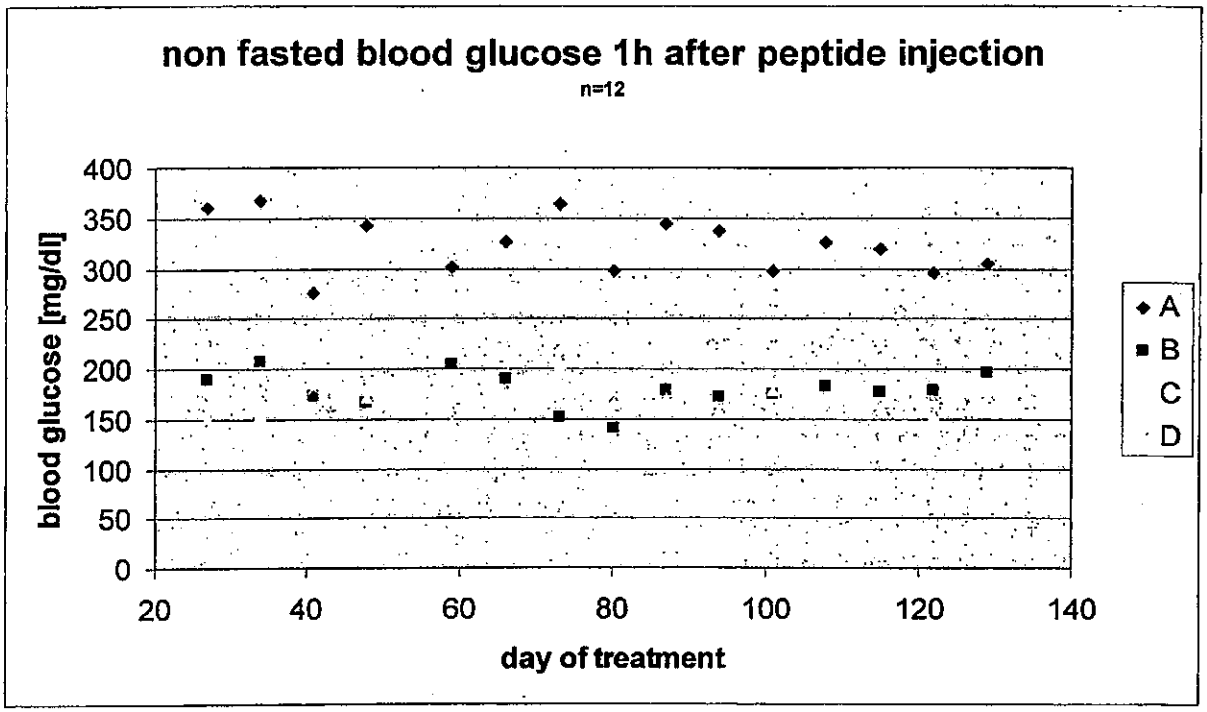

relative weight increase after 122 days
n=12
rel. weight increase [%]
100
90
80
70
60
50
40
30
20
10
0
p < 0.001
A
B
C
D

Figur 13

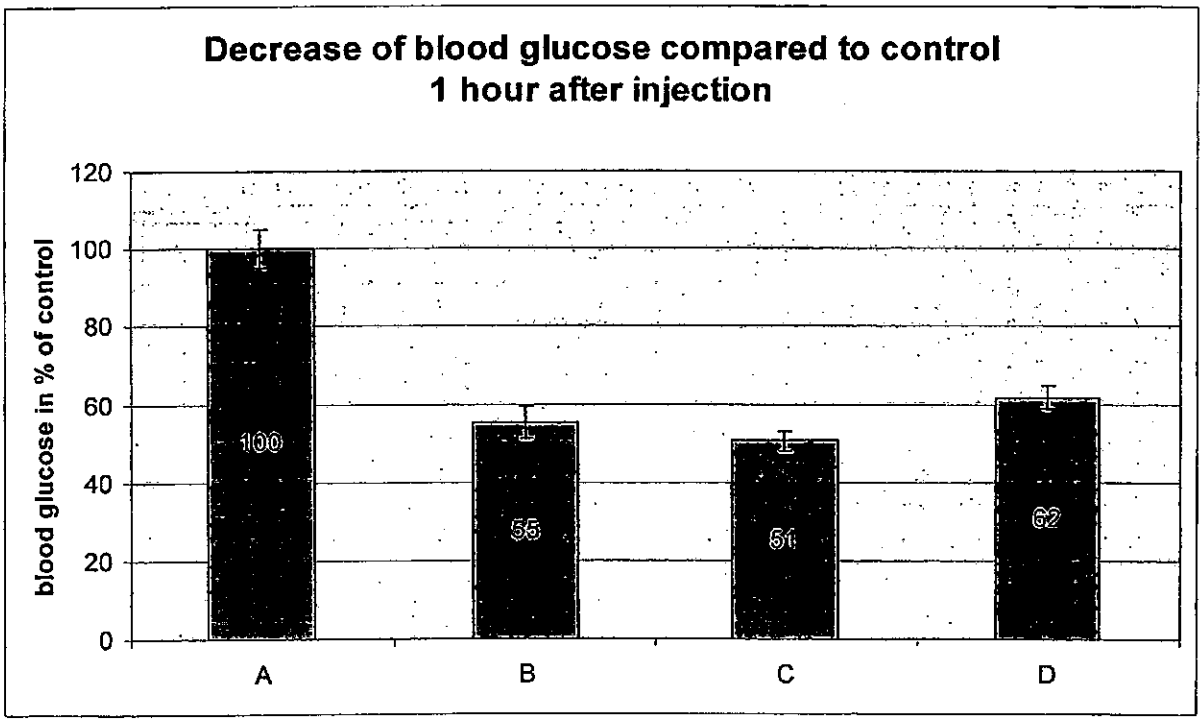

food consumption
food per mouse and week [g]
55
45
35
25
15
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
time [week]
A
B
C
D

Figur 14

A

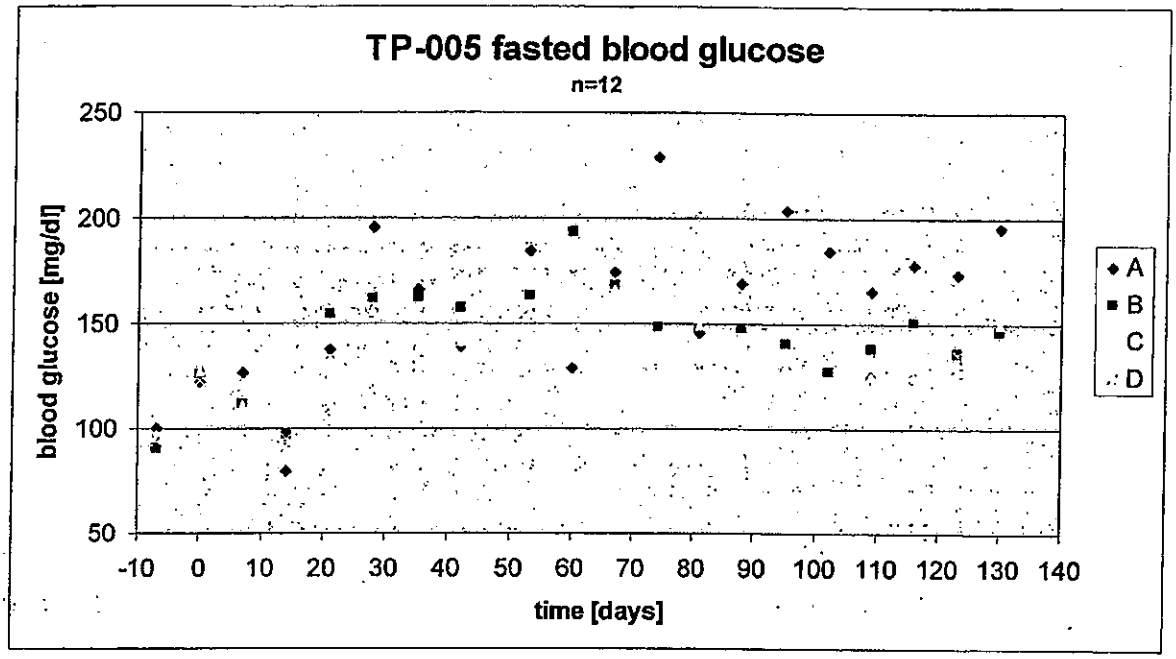

non fasted blood glucose 1h after peptide injection
n=12
blood glucose [mg/dl]
400
350
300
250
200
150
100
50
0
20
40
60
80
100
120
140
day of treatment
A
B
C
D

B


Decrease of blood glucose compared to control
1 hour after injection
blood glucose in % of control
120
100
80
60
40
20
0
100
55
51
62
A
B
C
D

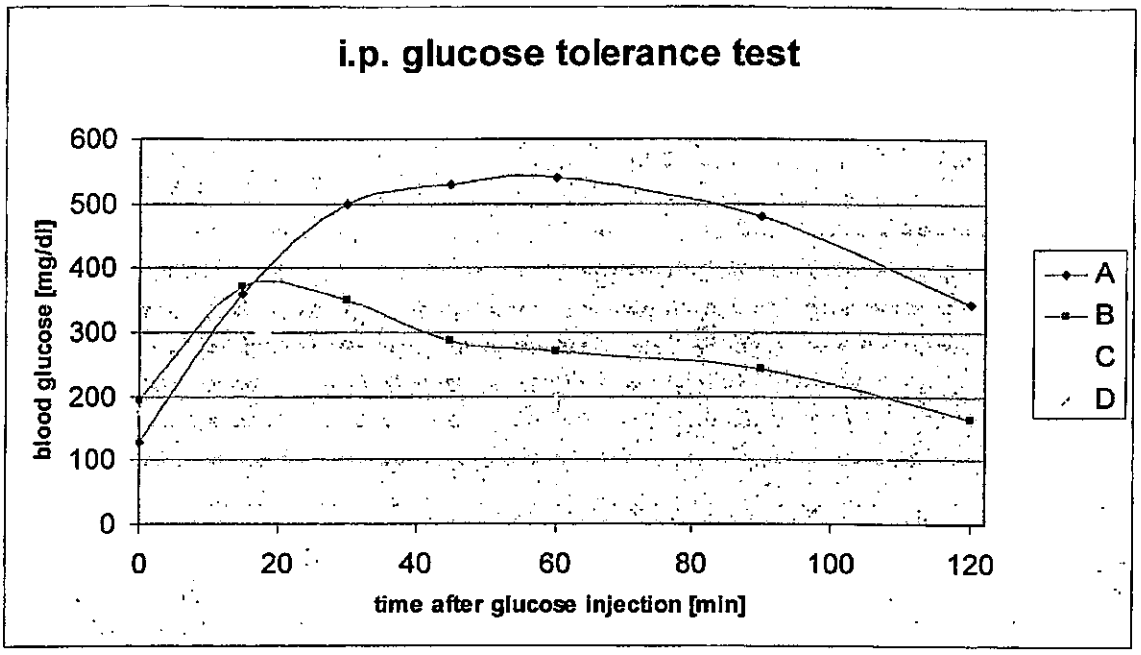
Figur 15

C

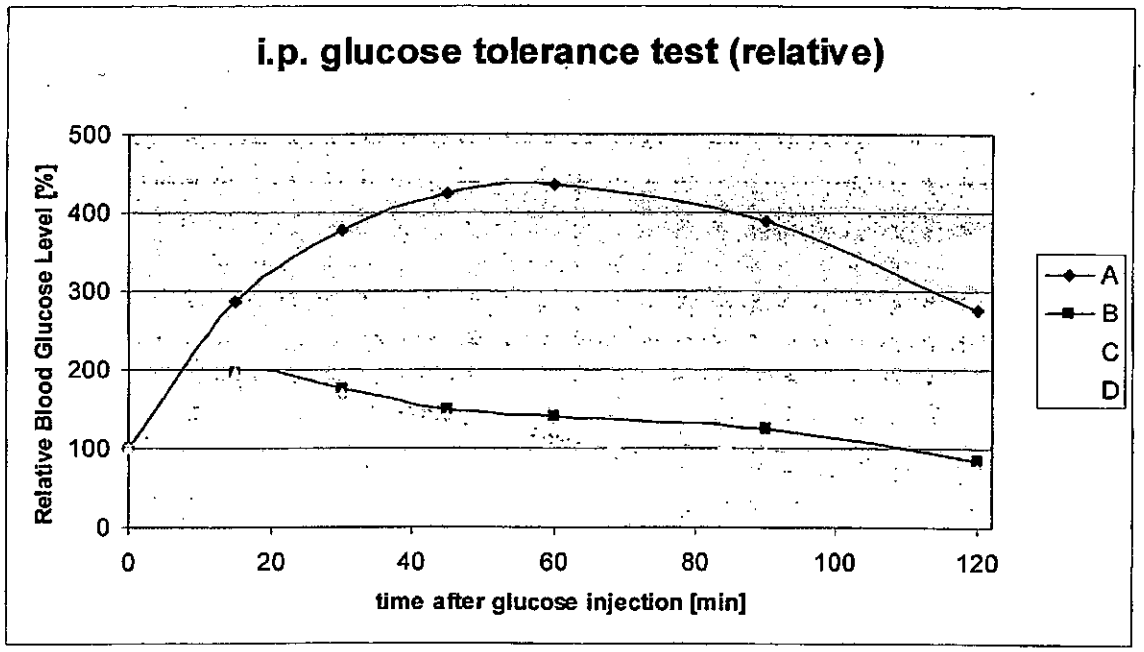


Figur 15 (continued)

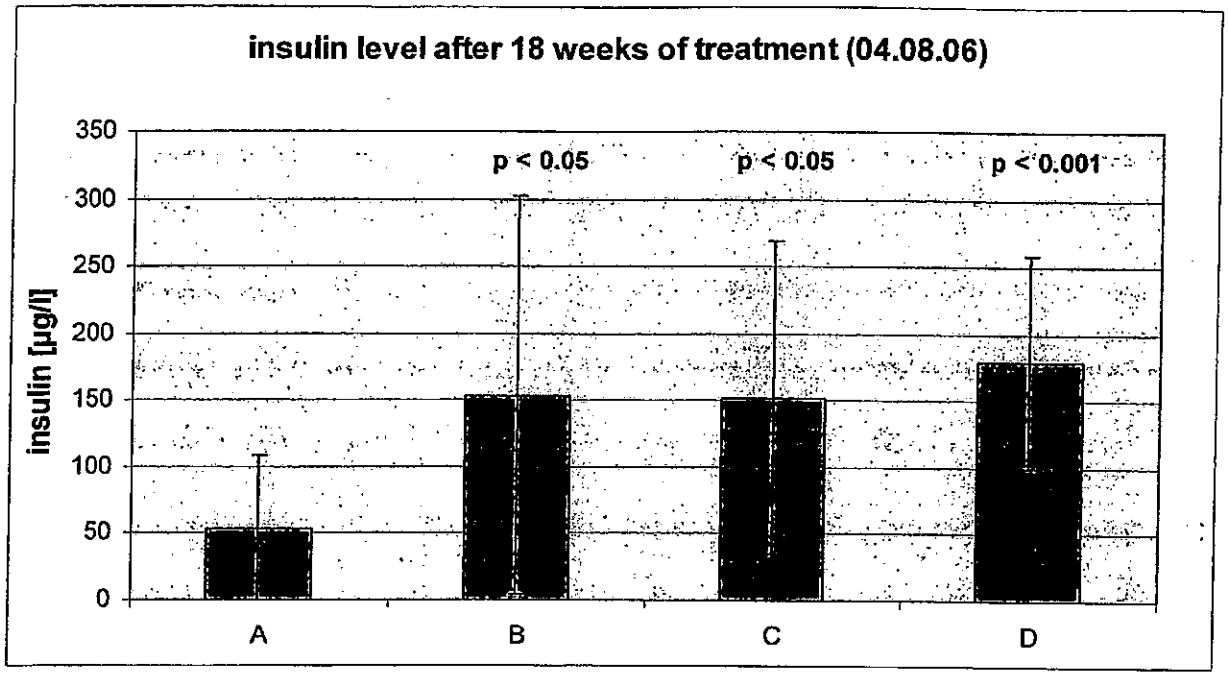
A


i.p. glucose tolerance test
blood glucose [mg/dl]
600
500
400
300
200
100
0
0
20
40
60
80
100
120
time after glucose injection [min]
A
B
C
D

B

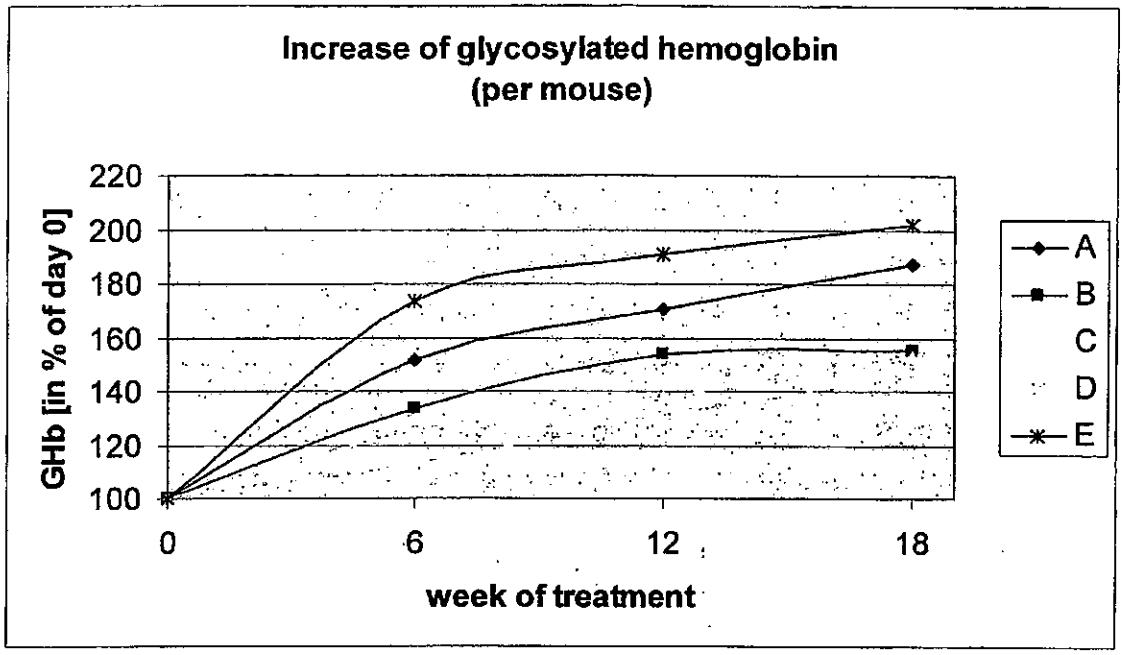

i.p. glucose tolerance test (relative)
Relative Blood Glucose Level [%]
500
400
300
200
100
0
0
20
40
60
80
100
120
time after glucose injection [min]
A
B
C
D

Figur 16

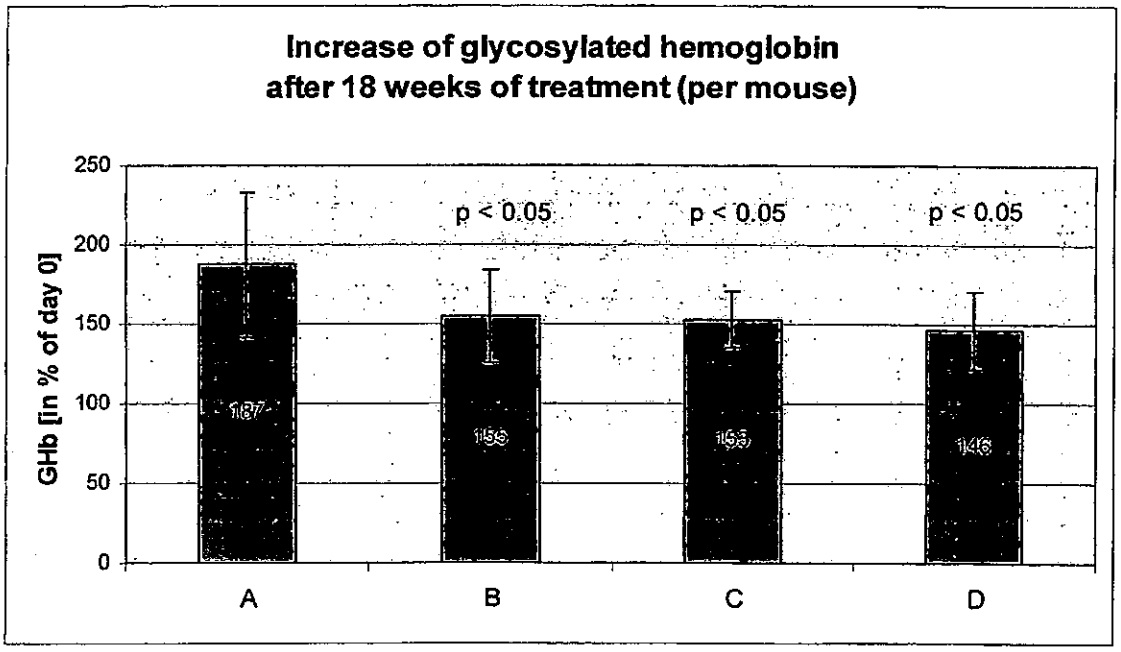

insulin level after 18 weeks of treatment (04.08.06)
insulin [µg/l]
350
300
250
200
150
100
50
0
p < 0.05
p < 0.05
p < 0.001
A
B
C
D

Figur 17

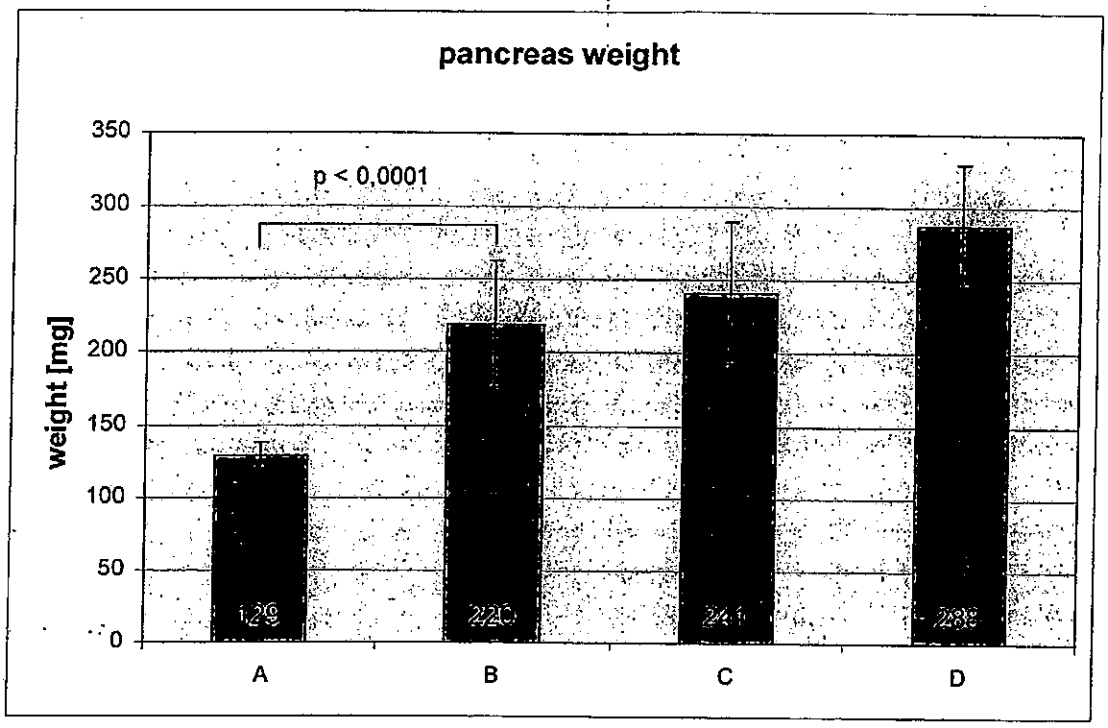
A


Increase of glycosylated hemoglobin
(per mouse)
GHb [in % of day 0]
220
200
180
160
140
120
100
0
6
12
18
week of treatment
A
B
C
D
E

B

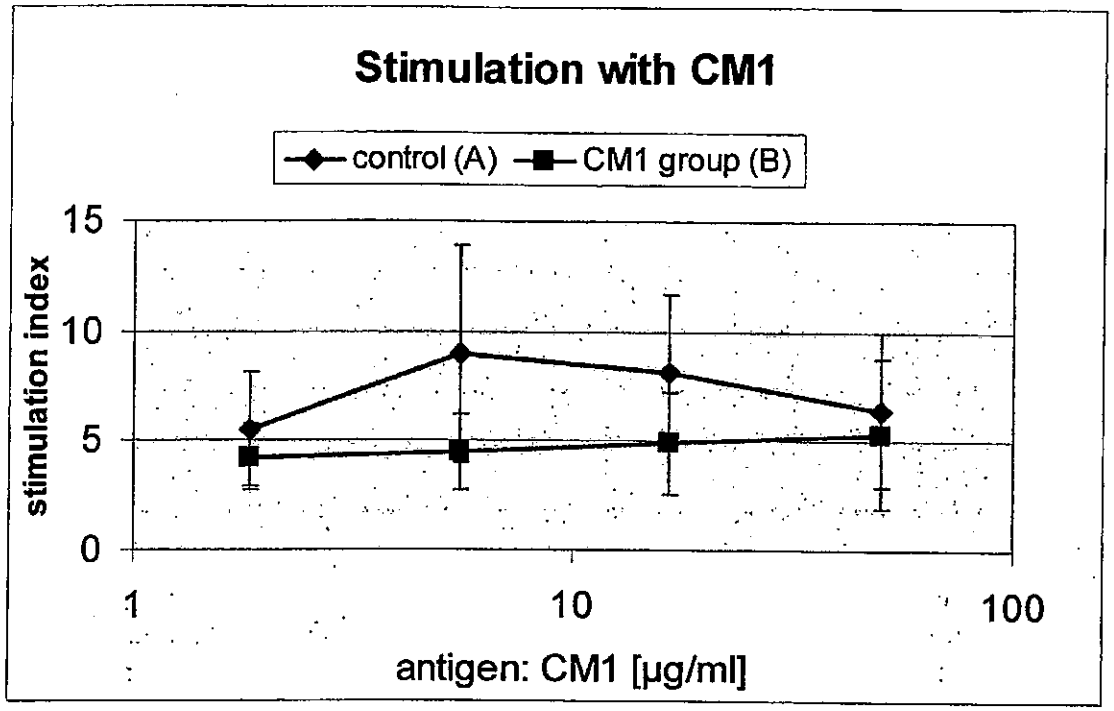

Increase of glycosylated hemoglobin
after 18 weeks of treatment (per mouse)
GHb [in % of day 0]
250
200
150
100
50
0
p < 0.05
p < 0.05
p < 0.05
187
155
153
146
A
B
C
D

Figur 18

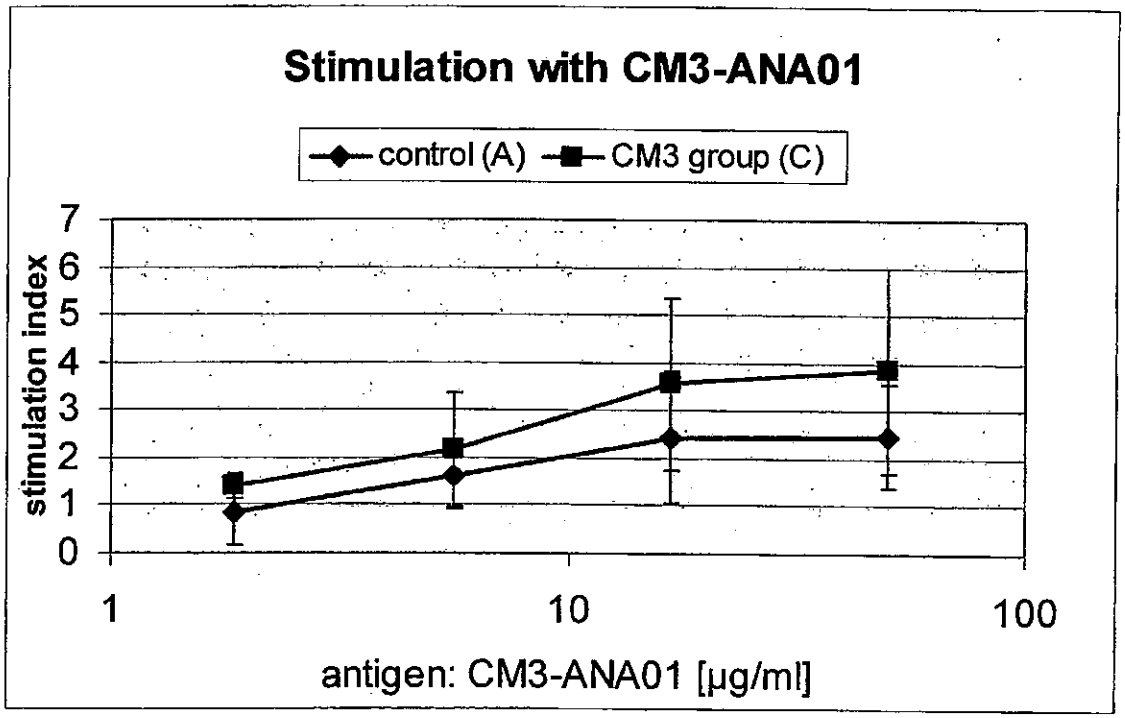

pancreas weight
p < 0,0001
weight [mg]
350
300
250
200
150
100
50
0
A
B
C
D

Figur 19

A

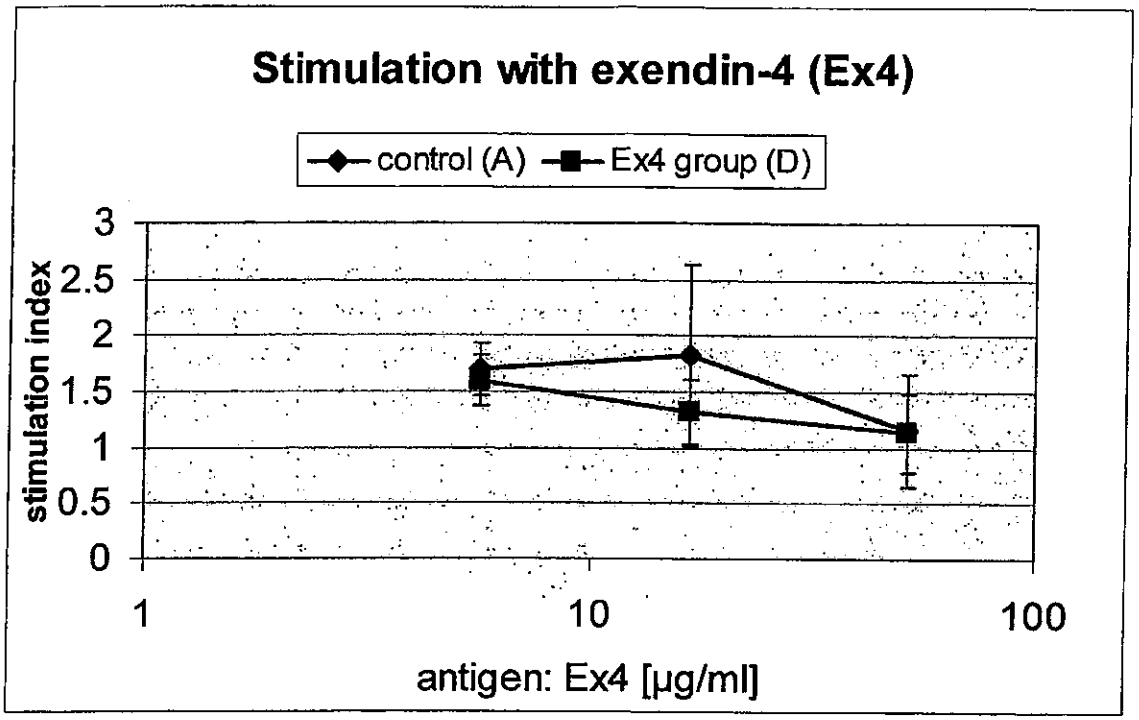

Stimulation with CM1
control (A)
CM1 group (B)
stimulation index
15
10
5
0
1
10
100
antigen: CM1 [µg/ml]

B


Stimulation with CM3-ANA01
control (A)
CM3 group (C)
stimulation index
7
6
5
4
3
2
1
0
1
10
100
antigen: CM3-ANA01 [µg/ml]

Figur 20

C



Figur 20 (continued)