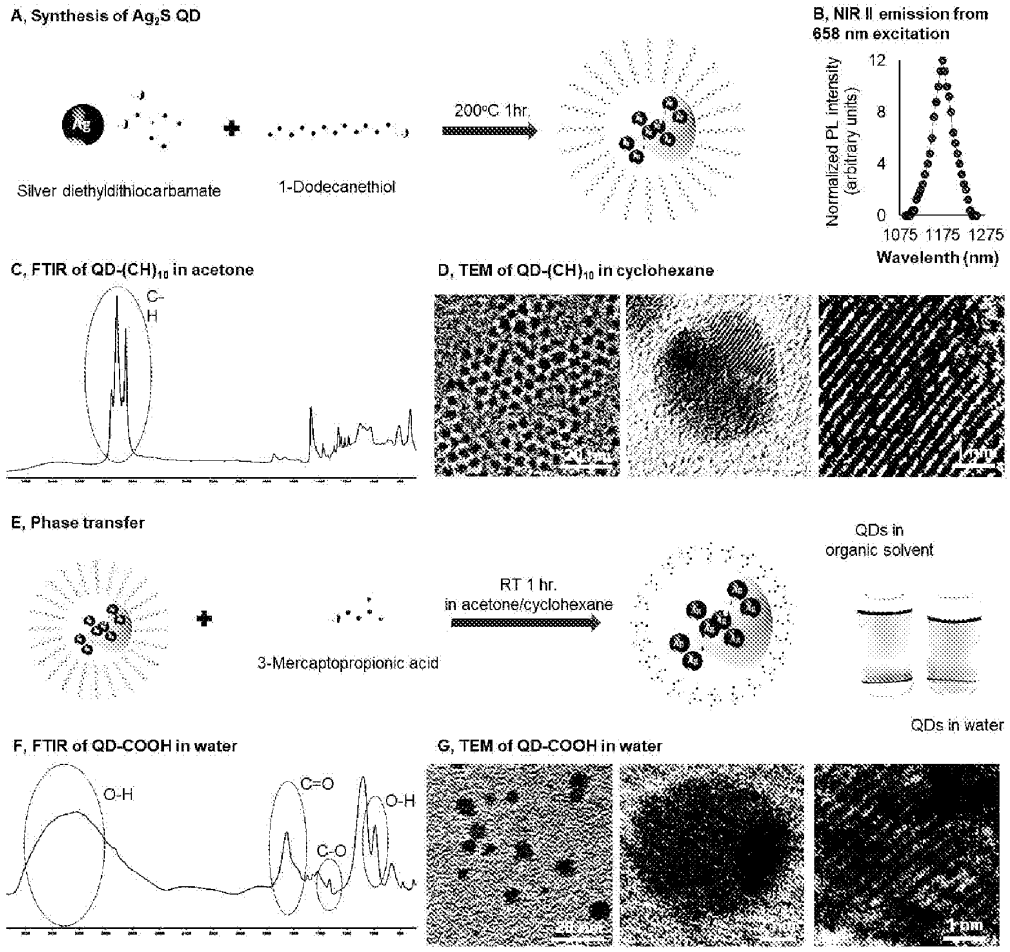

A, Synthesis of Ag_2S QD
Silver diethyldithiocarbamate
1-Dodecanethiol
200°C 1hr.
B, NIR II emission from 658 nm excitation
Normalized PL intensity (arbitrary units)
12
8
4
0
1075 1175 1275
Wavelenth (nm)
C, FTIR of QD-$(CH)_{10}$ in acetone
C-H
D, TEM of QD-$(CH)_{10}$ in cyclohexane
E, Phase transfer
3-Mercaptopropionic acid
RT 1 hr.
in acetone/cyclohexane
QDs in organic solvent
QDs in water
F, FTIR of QD-COOH in water
O-H
C=O
C-O
O-H
G, TEM of QD-COOH in water

Figure 1

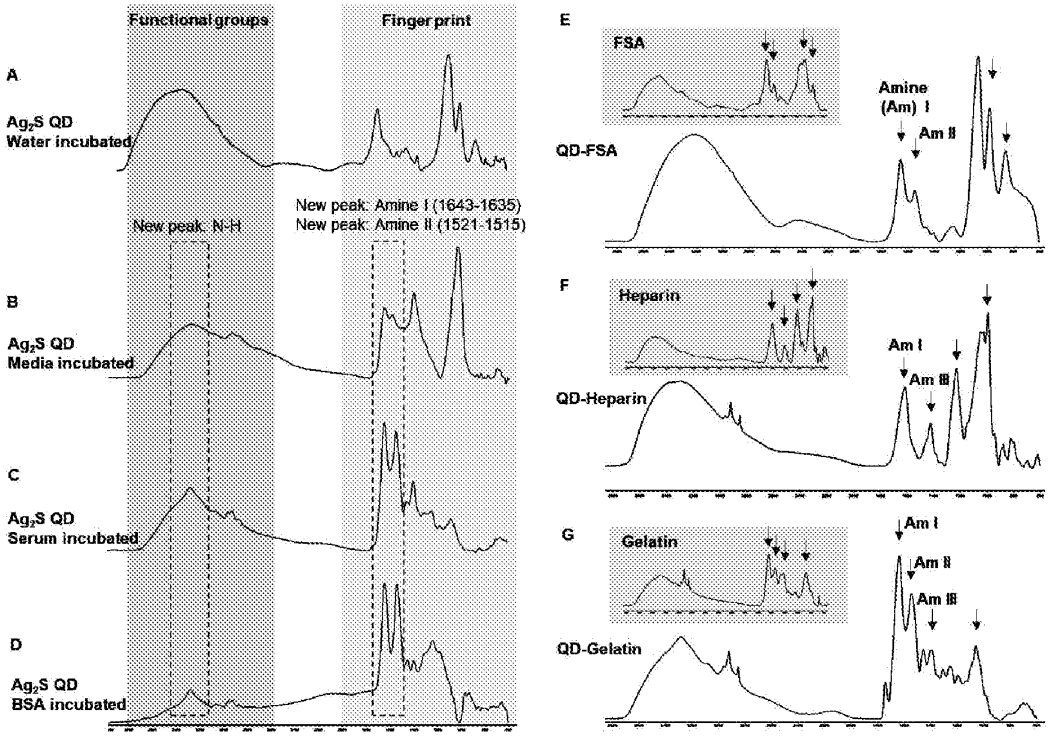

Functional groups
Fingerprint
A
Ag_2S QD
Water incubated
New peak: N-H
New peak: Amine I (1643-1635)
New peak: Amine II (1521-1515)
B
Ag_2S QD
Media incubated
C
Ag_2S QD
Serum incubated
D
Ag_2S QD
BSA incubated
E
FSA
Amine
(Am) I
Am II
QD-FSA
F
Heparin
Am I
Am III
QD-Heparin
G
Gelatin
Am I
Am II
Am III
QD-Gelatin

Figure 2

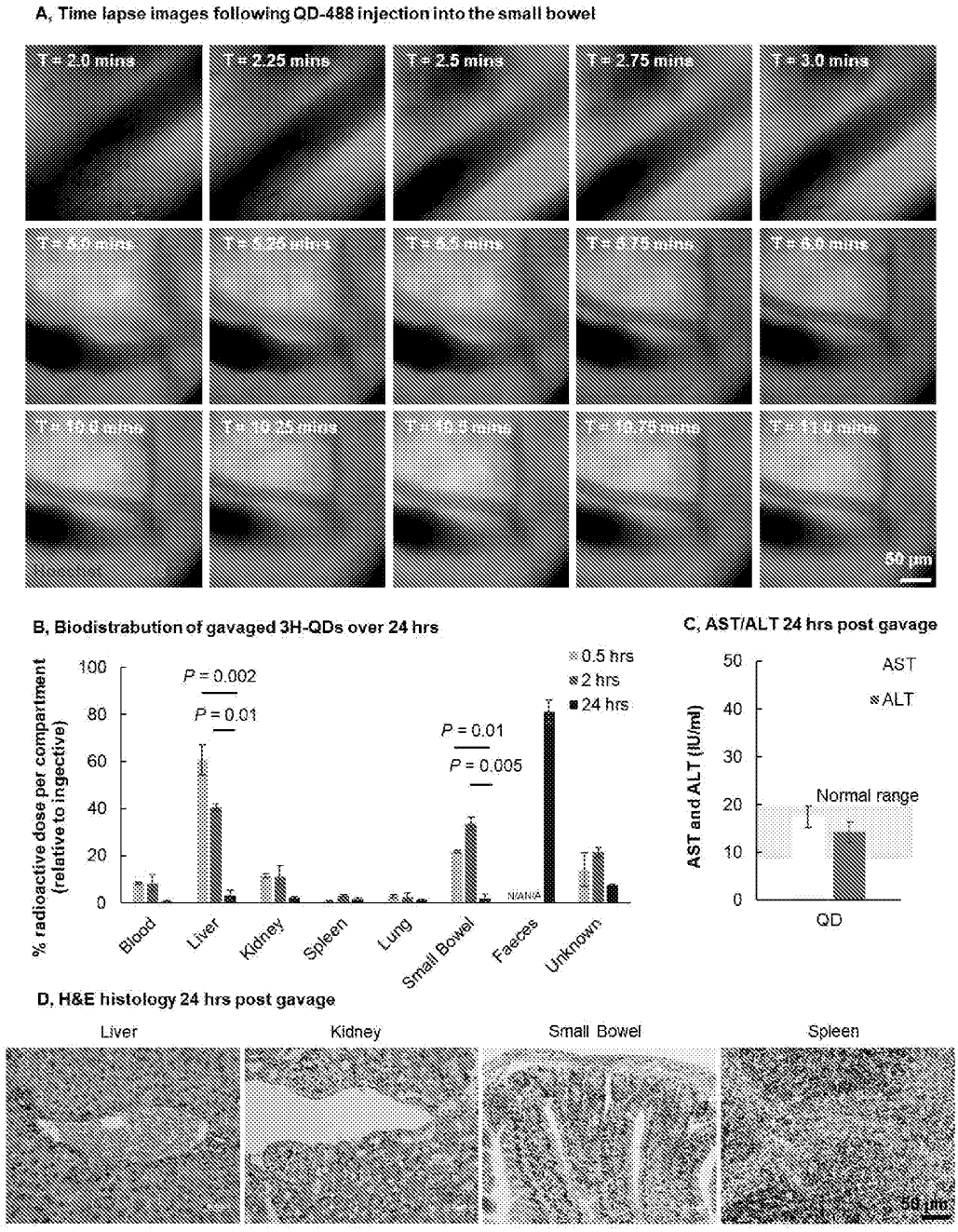
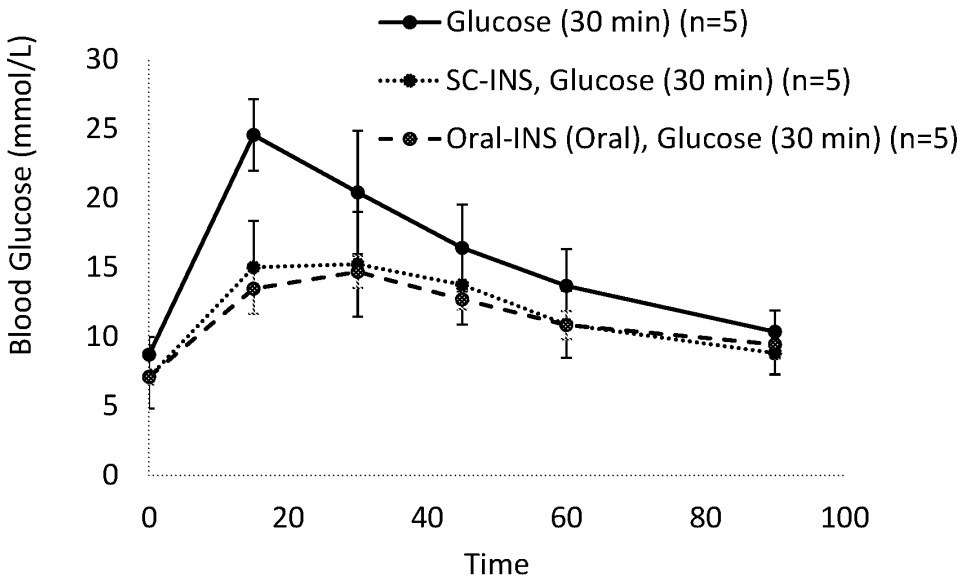

A, Time lapse images following QD-488 injection into the small bowel
T = 2.0 mins
T = 2.25 mins
T = 2.5 mins
T = 2.75 mins
T = 3.0 mins
T = 9.0 mins
T = 9.25 mins
T = 9.5 mins
T = 9.75 mins
T = 10.0 mins
T = 10.0 mins
T = 10.25 mins
T = 10.5 mins
T = 10.75 mins
T = 11.0 mins
50 µm
B, Biodistrabution of gavaged 3H-QDs over 24 hrs
% radioactive dose per compartment (relative to ingective)
0.5 hrs
2 hrs
24 hrs
P = 0.002
P = 0.01
P = 0.01
P = 0.005
N/A
N/A
Blood
Liver
Kidney
Spleen
Lung
Small Bowel
Faeces
Unknown
C, AST/ALT 24 hrs post gavage
AST and ALT (IU/ml)
AST
ALT
Normal range
QD
D, H&E histology 24 hrs post gavage
Liver
Kidney
Small Bowel
Spleen
50 µm

Figure 3


Glucose (30 min) (n=5)
SC-INS, Glucose (30 min) (n=5)
Oral-INS (Oral), Glucose (30 min) (n=5)
Blood Glucose (mmol/L)
30
25
20
15
10
5
0
0
20
40
60
80
100
Time

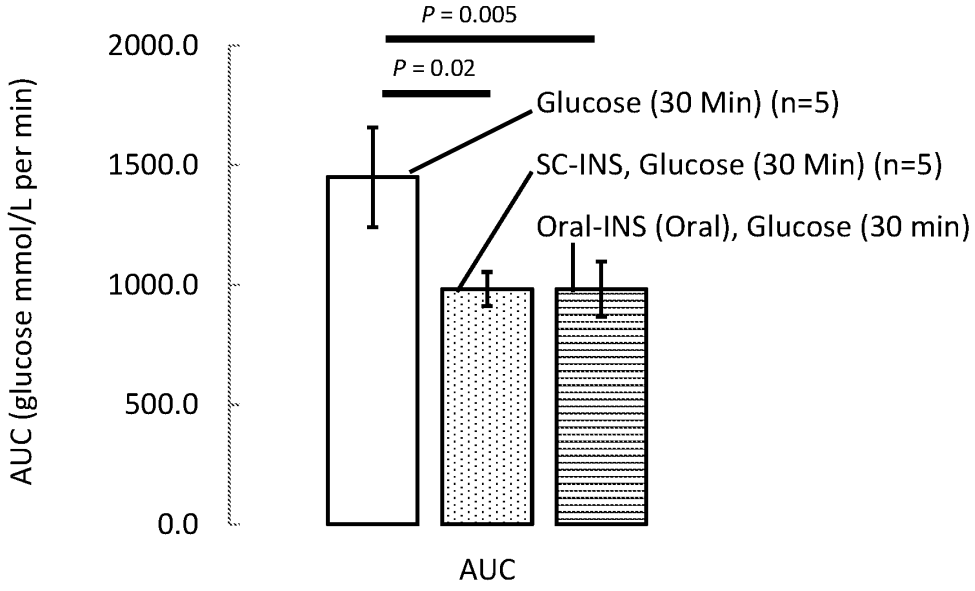
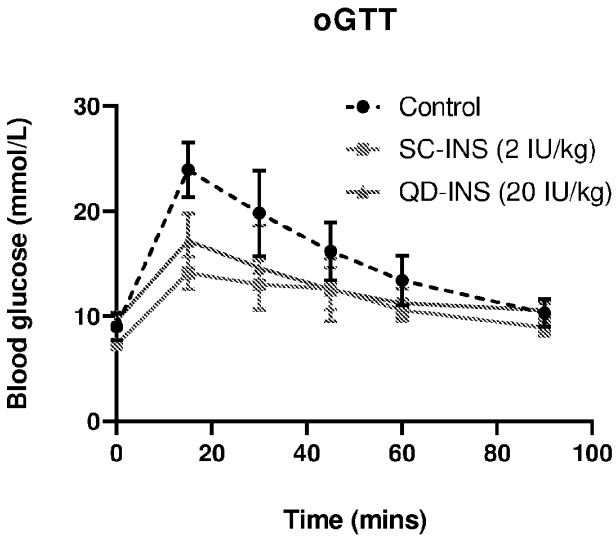

P = 0.005
P = 0.02
Glucose (30 Min) (n=5)
SC-INS, Glucose (30 Min) (n=5)
Oral-INS (Oral), Glucose (30 min)
AUC (glucose mmol/L per min)
2000.0
1500.0
1000.0
500.0
0.0
AUC

Figure 4


oGTT
Control
SC-INS (2 IU/kg)
QD-INS (20 IU/kg)
Blood glucose (mmol/L)
30
20
10
0
0
20
40
60
80
100
Time (mins)

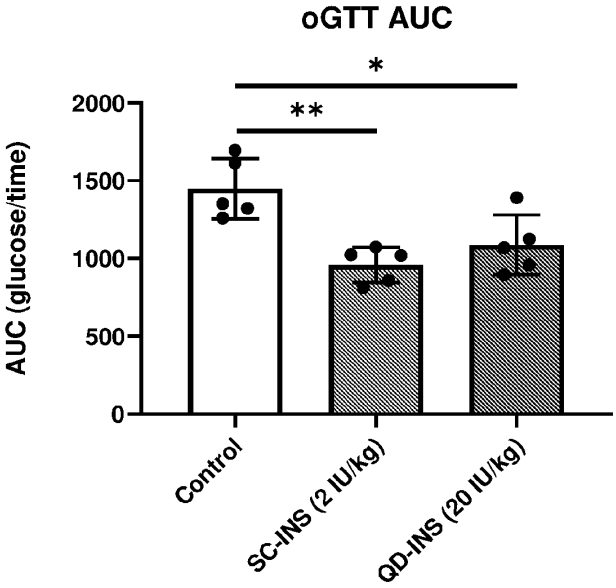

oGTT AUC
*
**
AUC (glucose/time)
2000
1500
1000
500
0
Control
SC-INS (2 IU/kg)
QD-INS (20 IU/kg)

Figure 5

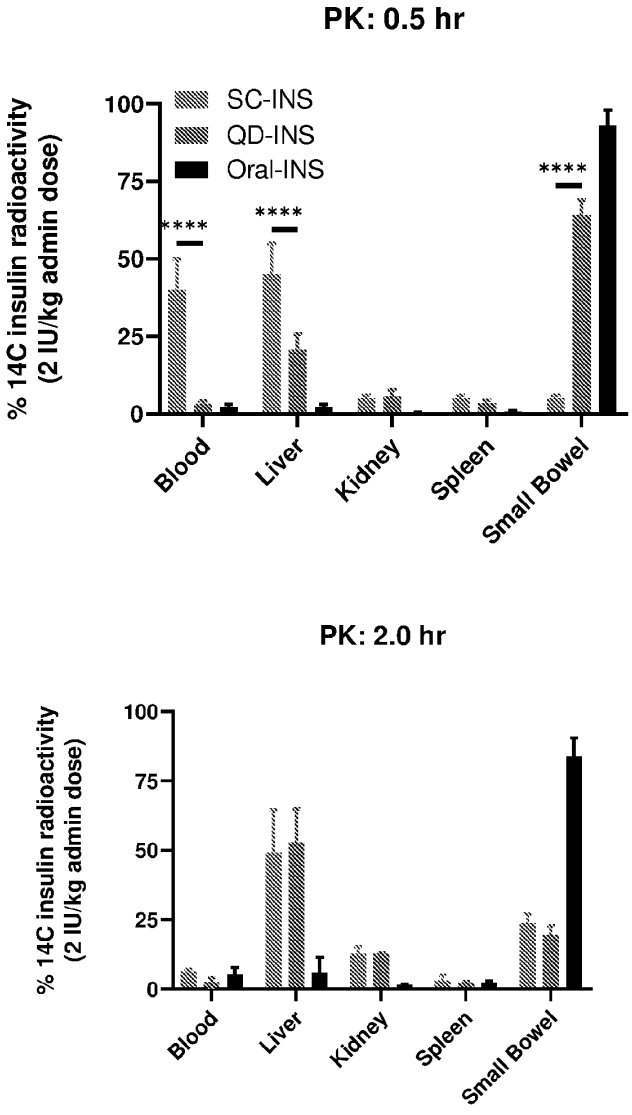
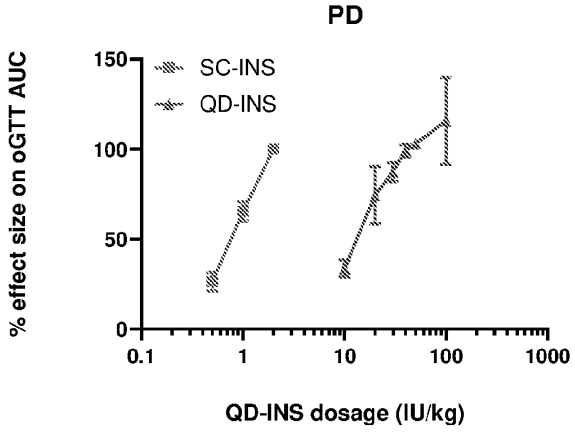

PK: 0.5 hr
% 14C insulin radioactivity (2 IU/kg admin dose)
SC-INS
QD-INS
Oral-INS
100
75
50
25
0
****
****
****
Blood
Liver
Kidney
Spleen
Small Bowel
PK: 2.0 hr
% 14C insulin radioactivity (2 IU/kg admin dose)
100
75
50
25
0
Blood
Liver
Kidney
Spleen
Small Bowel

Figure 6


PD
% effect size on oGTT AUC
150
100
50
0
SC-INS
QD-INS
0.1
1
10
100
1000
QD-INS dosage (IU/kg)

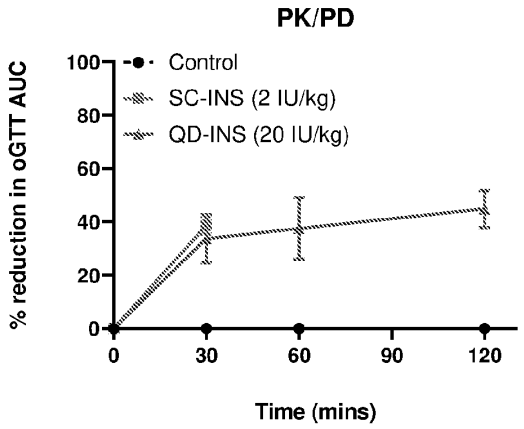

PK/PD
% reduction in oGTT AUC
100
80
60
40
20
0
Control
SC-INS (2 IU/kg)
QD-INS (20 IU/kg)
0
30
60
90
120
Time (mins)

Figure 7

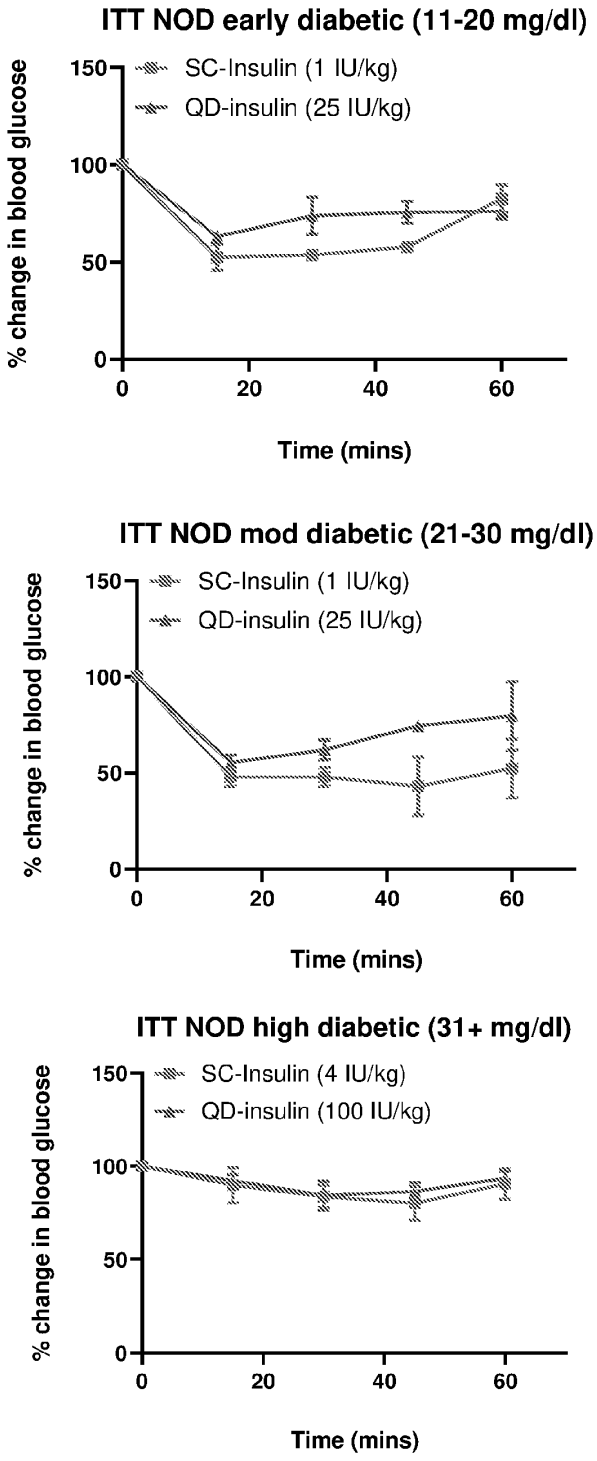

ITT NOD early diabetic (11-20 mg/dl)
% change in blood glucose
150
100
50
0
SC-Insulin (1 IU/kg)
QD-insulin (25 IU/kg)
0
20
40
60
Time (mins)
ITT NOD mod diabetic (21-30 mg/dl)
% change in blood glucose
150
100
50
0
SC-Insulin (1 IU/kg)
QD-insulin (25 IU/kg)
0
20
40
60
Time (mins)
ITT NOD high diabetic (31+ mg/dl)
% change in blood glucose
150
100
50
0
SC-Insulin (4 IU/kg)
QD-insulin (100 IU/kg)
0
20
40
60
Time (mins)

Figure 8

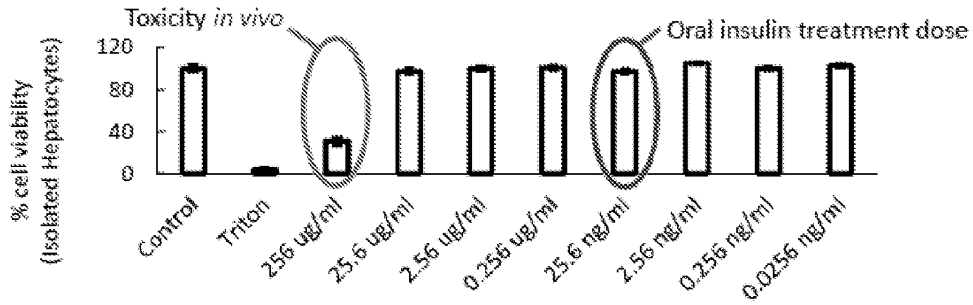

Toxicity *in vivo*
Oral insulin treatment dose
% cell viability (Isolated Hepatocytes)
120
80
40
0
Control
Triton
256 ug/ml
25.6 ug/ml
2.56 ug/ml
0.256 ug/ml
25.6 ng/ml
2.56 ng/ml
0.256 ng/ml
0.0256 ng/ml

Figure 9

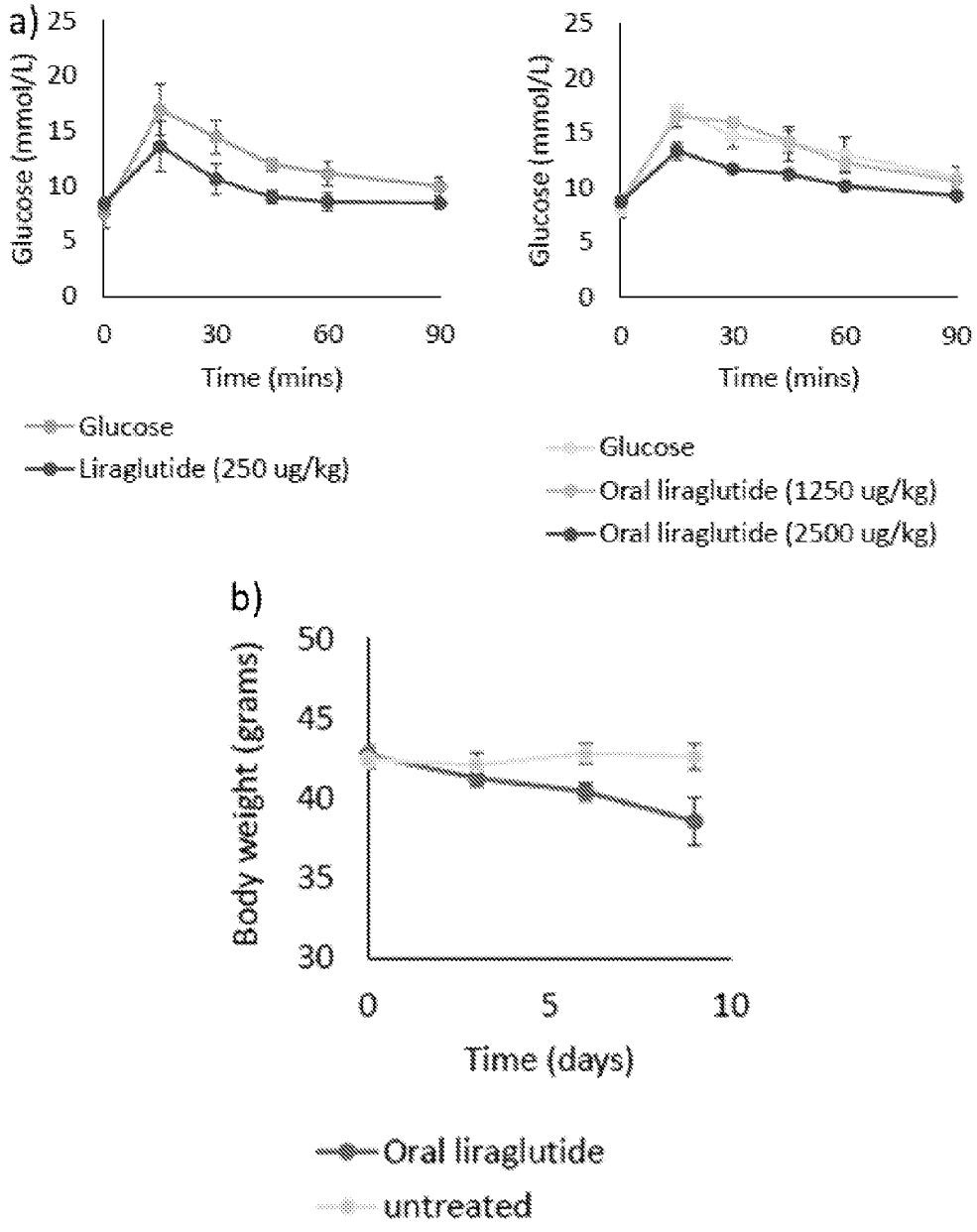

a)
Glucose (mmol/L)
25
20
15
10
5
0
0
30
60
90
Time (mins)
Glucose
Liraglutide (250 ug/kg)
Glucose (mmol/L)
Time (mins)
Glucose
Oral liraglutide (1250 ug/kg)
Oral liraglutide (2500 ug/kg)
b)
Body weight (grams)
50
45
40
35
30
0
5
10
Time (days)
Oral liraglutide
untreated

Figure 10

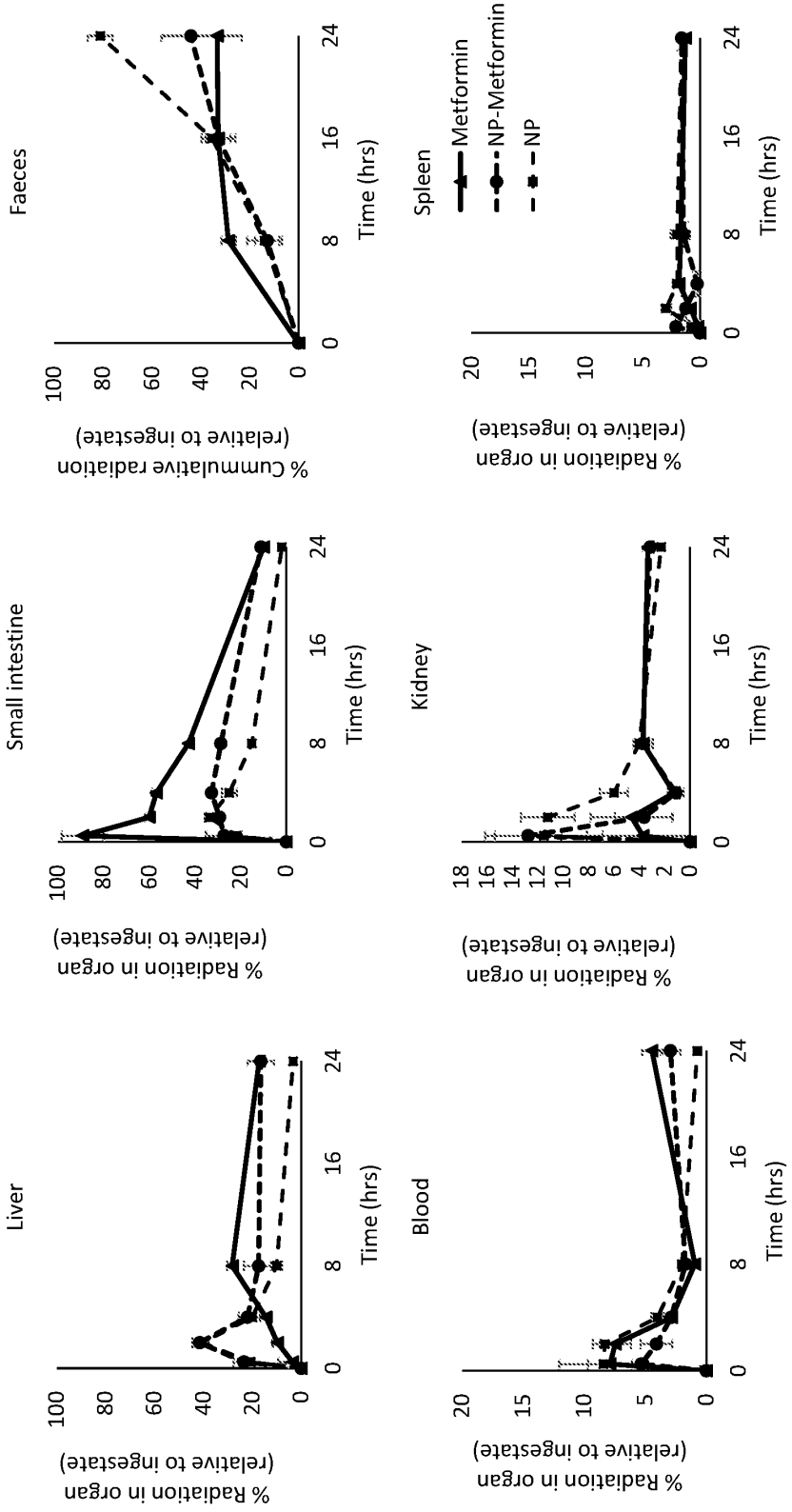

Faeces
% Cummulative radiation (relative to ingestate)
Time (hrs)
Spleen
Metformin
NP-Metformin
NP
% Radiation in organ (relative to ingestate)
Time (hrs)
Small intestine
% Radiation in organ (relative to ingestate)
Time (hrs)
Kidney
% Radiation in organ (relative to ingestate)
Time (hrs)
Liver
% Radiation in organ (relative to ingestate)
Time (hrs)
Blood
% Radiation in organ (relative to ingestate)
Time (hrs)

Figure 11