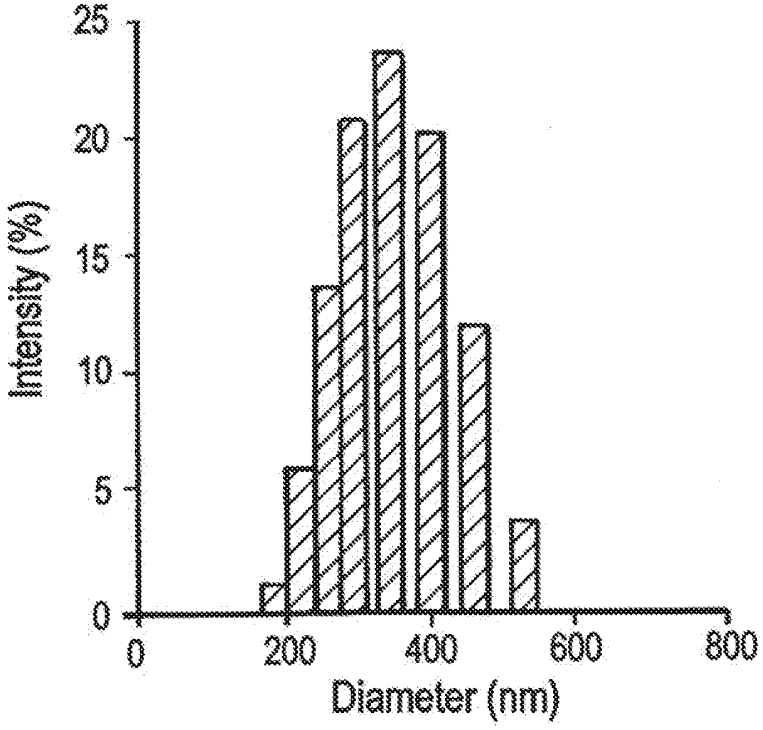
25
20
15
10
5
0
Intensity (%)
0
200
400
600
800
Diameter (nm)

FIG. 1

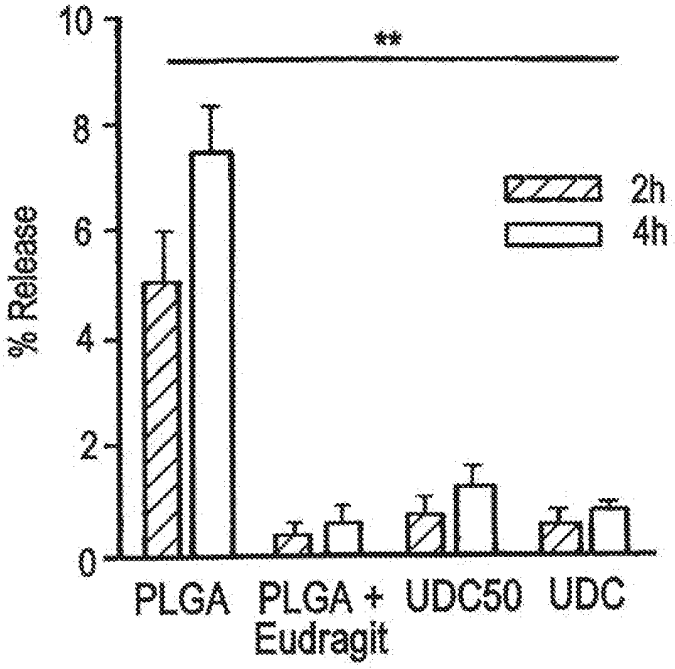
10
8
6
4
2
0
% Release
**
2h
4h
PLGA
PLGA + Eudragit
UDC50
UDC

FIG. 2A

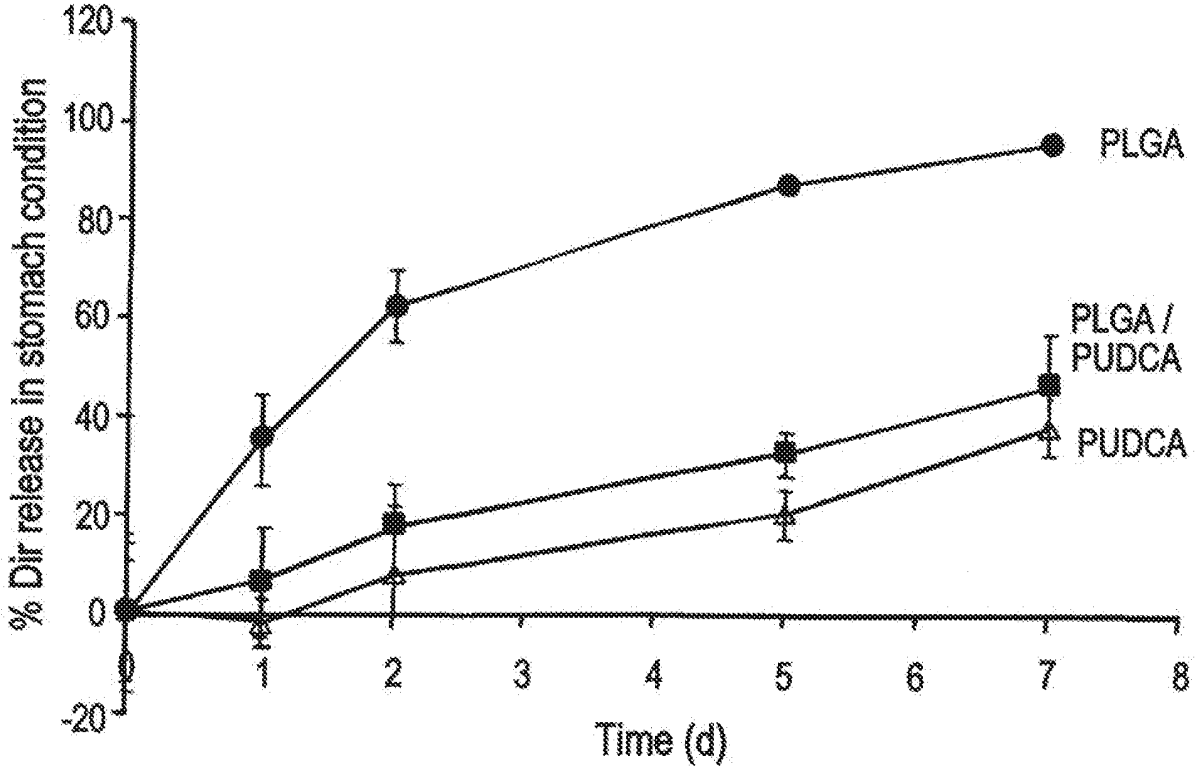
% Dir release in stomach condition
120
100
80
60
40
20
0
-20
0
1
2
3
4
5
6
7
8
Time (d)
PLGA
PLGA / PUDCA
PUDCA

FIG. 2B

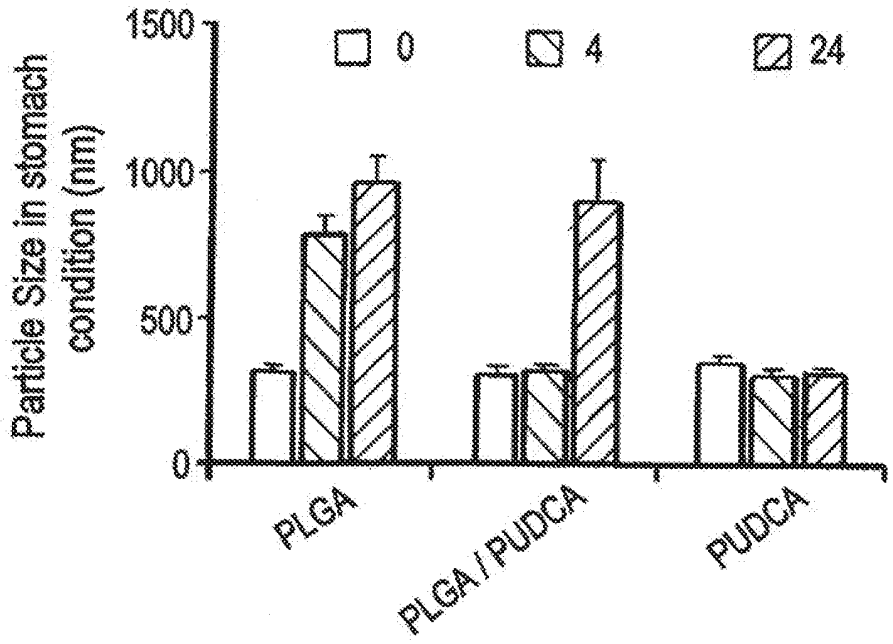
Particle Size in stomach condition (nm)
1500
1000
500
0
0
4
24
PLGA
PLGA / PUDCA
PUDCA

FIG. 2C

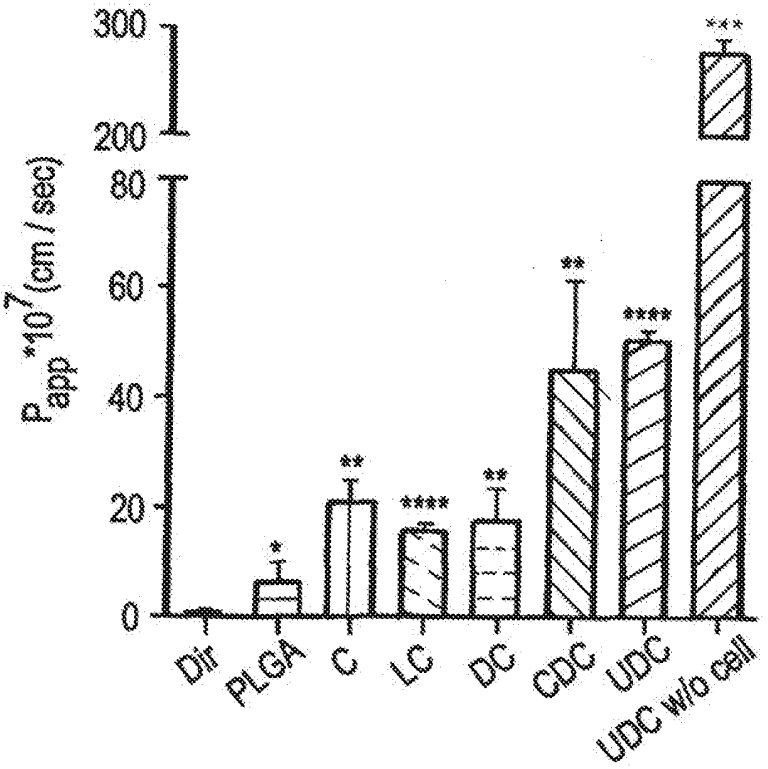
300
200
80
60
40
20
0
P_{app} *10^7 (cm / sec)
Dir
PLGA
C
LC
DC
CDC
UDC
UDC w/o cell

FIG. 2D

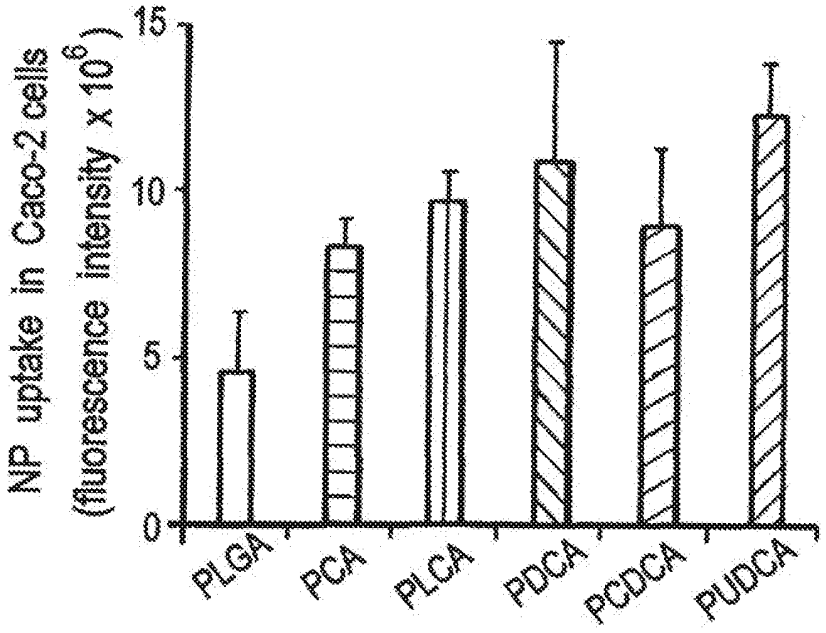
NP uptake in Caco-2 cells
(fluorescence intensity x 10^6)
15
10
5
0
PLGA
PCA
PLCA
PDCA
PCDCA
PUDCA

FIG. 2E

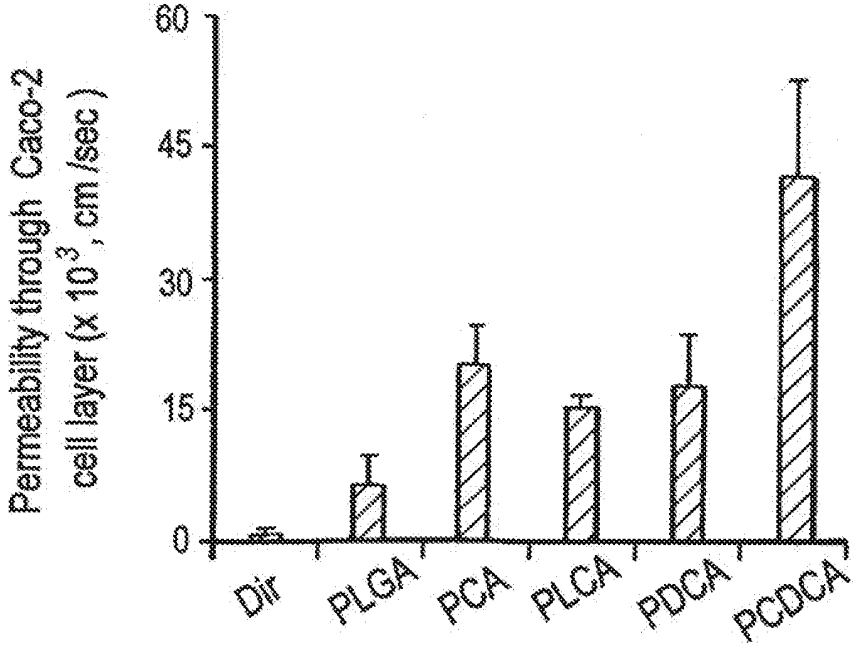
Permeability through Caco-2 cell layer (x 10^3, cm /sec)
60
45
30
15
0
Dir
PLGA
PCA
PLCA
PDCA
PCDCA

FIG. 2F

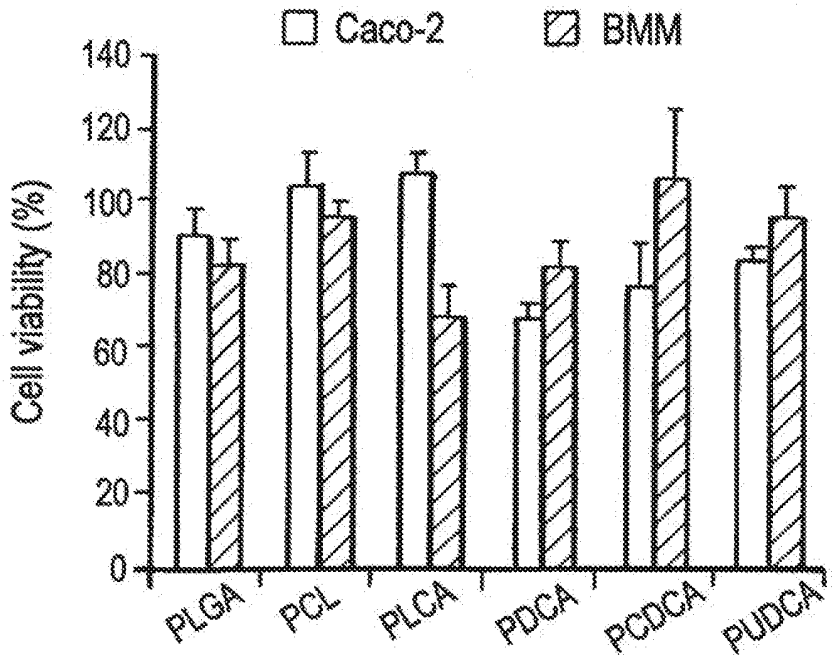
Caco-2
BMM
Cell viability (%)
140
120
100
80
60
40
20
0
PLGA
PCL
PLCA
PDCA
PCDCA
PUDCA

FIG. 2G

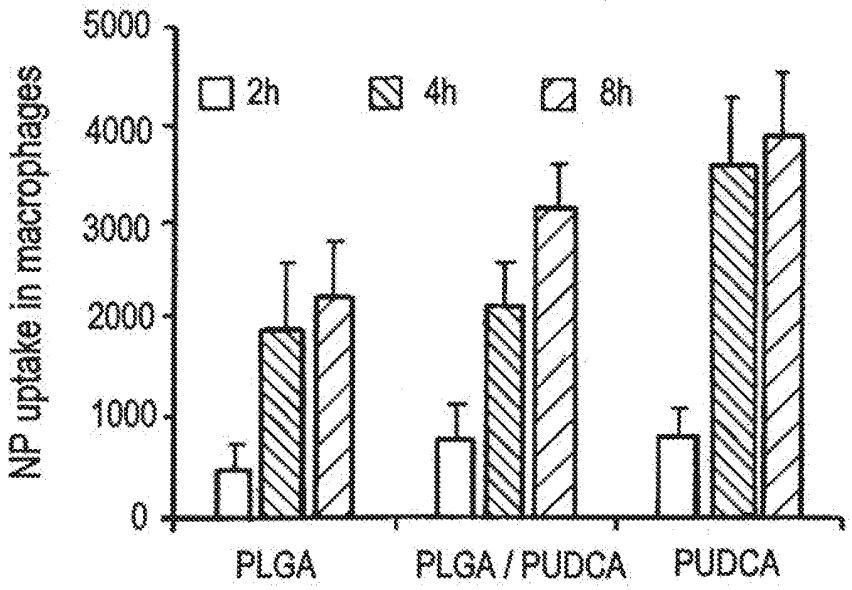
NP uptake in macrophages
5000
4000
3000
2000
1000
0
2h
4h
8h
PLGA
PLGA / PUDCA
PUDCA

FIG. 2H

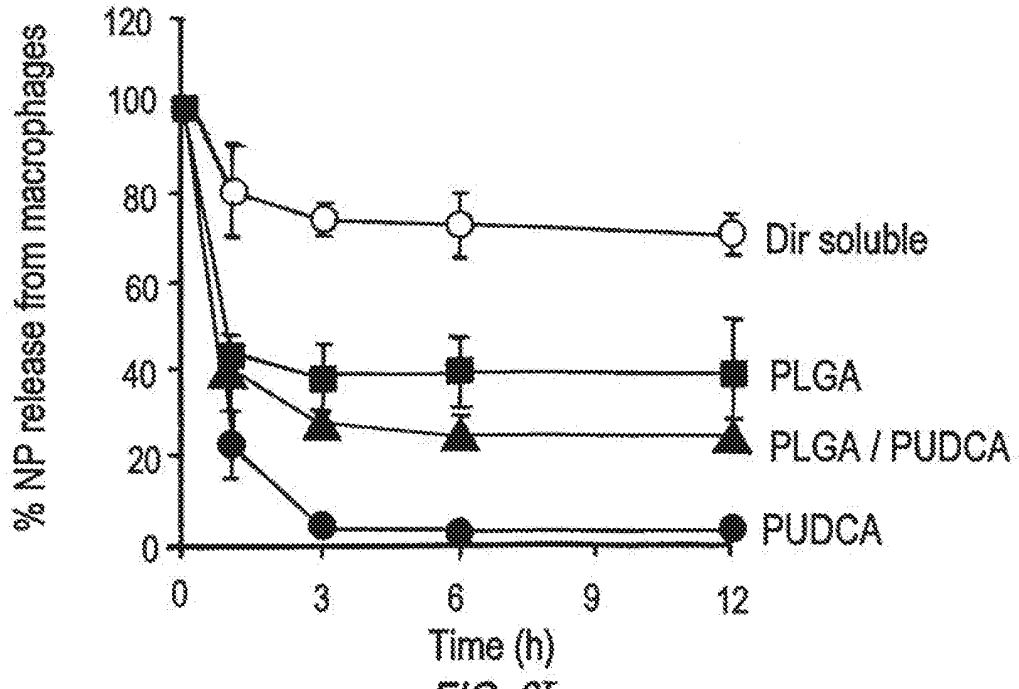
% NP release from macrophages
120
100
80
60
40
20
0
0
3
6
9
12
Time (h)
Dir soluble
PLGA
PLGA / PUDCA
PUDCA

FIG. 2I

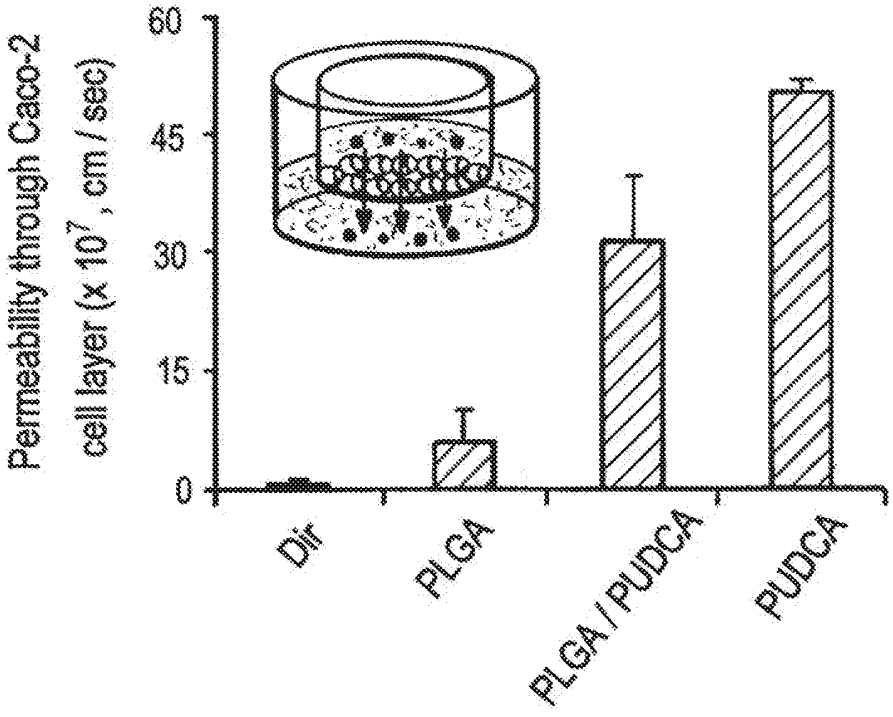
Permeability through Caco-2
cell layer (x 10^{7}, cm / sec)
60
45
30
15
0
Dir
PLGA
PLGA / PUDCA
PUDCA

FIG. 2J

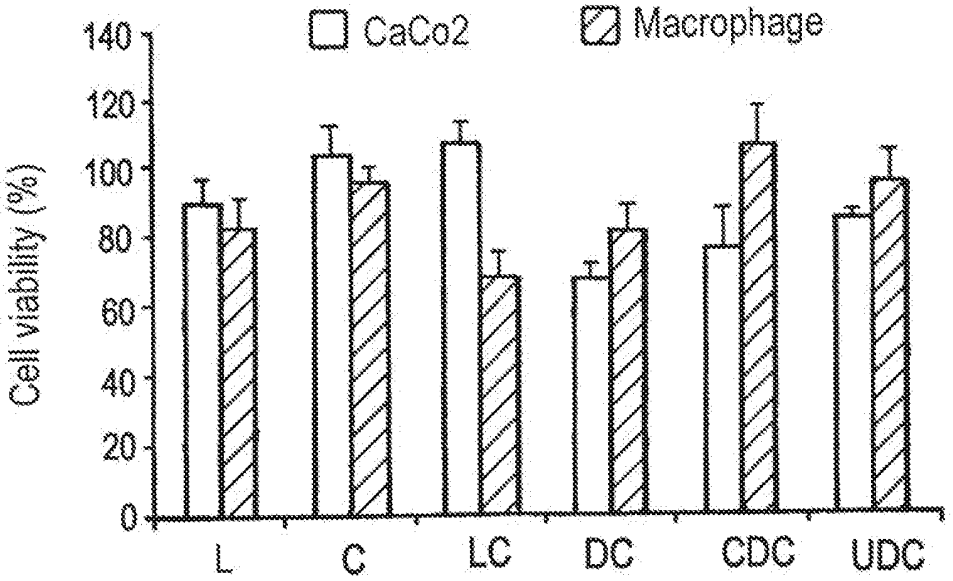
CaCo2
Macrophage
Cell viability (%)
140
120
100
80
60
40
20
0
L
C
LC
DC
CDC
UDC

FIG. 3A

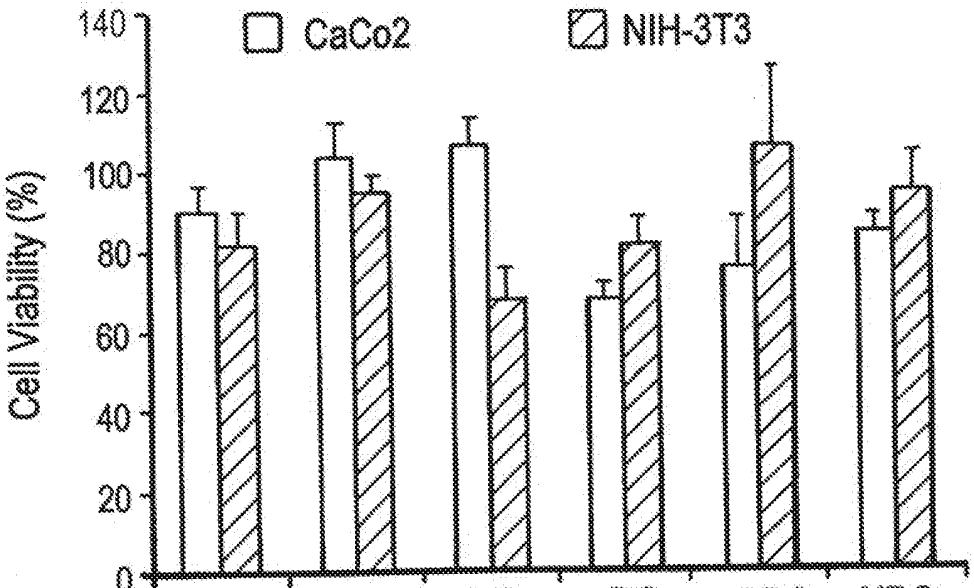
CaCo2
NIH-3T3
Cell Viability (%)
140
120
100
80
60
40
20
0
L
C
LC
DC
CDC
UDC

FIG. 3B

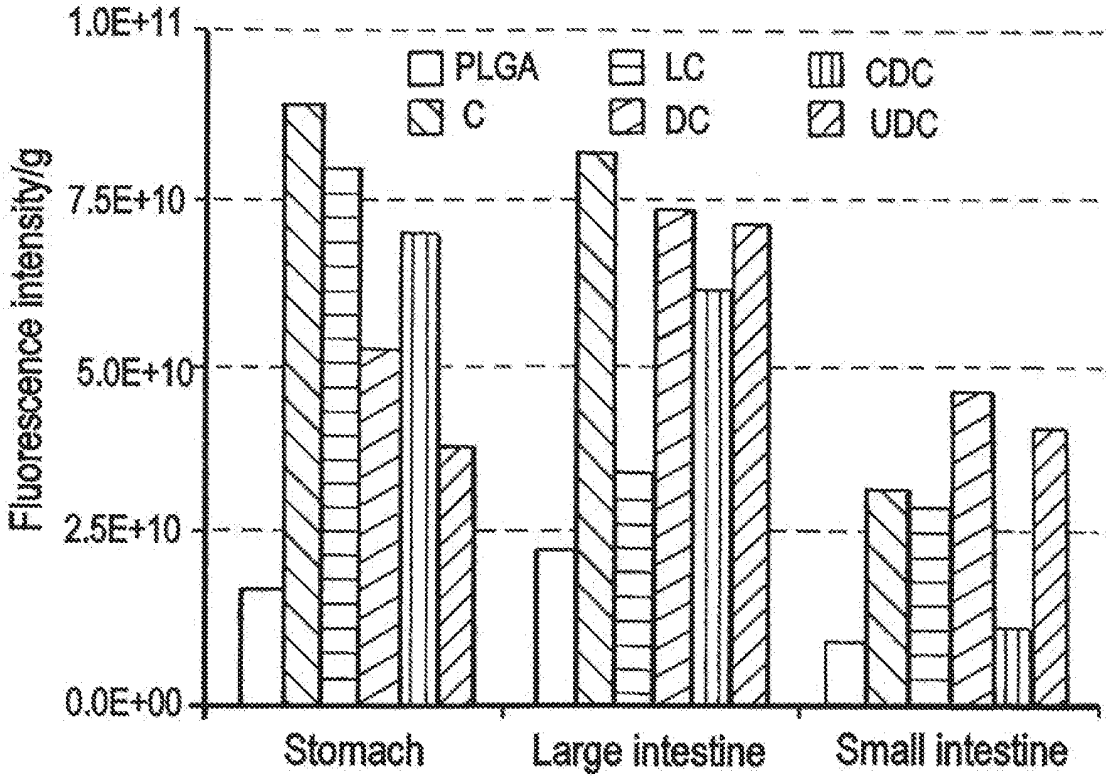
1.0E+11
7.5E+10
5.0E+10
2.5E+10
0.0E+00
Fluorescence intensity/g
PLGA
C
LC
DC
CDC
UDC
Stomach
Large intestine
Small intestine

FIG. 4A

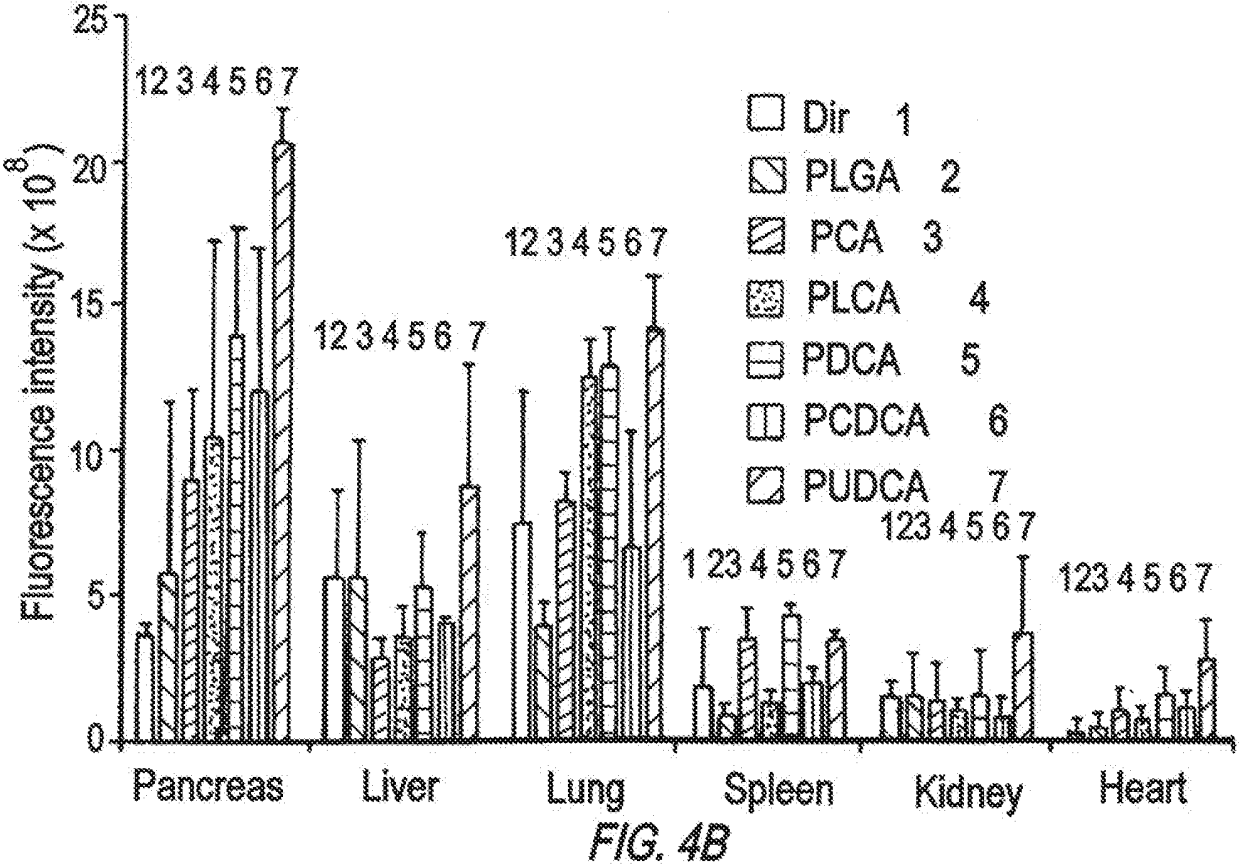
25
20
15
10
5
0
Fluorescence intensity (x 10^8)
1 2 3 4 5 6 7
Dir 1
PLGA 2
PCA 3
PLCA 4
PDCA 5
PCDCA 6
PUDCA 7
Pancreas
Liver
Lung
Spleen
Kidney
Heart

FIG. 4B

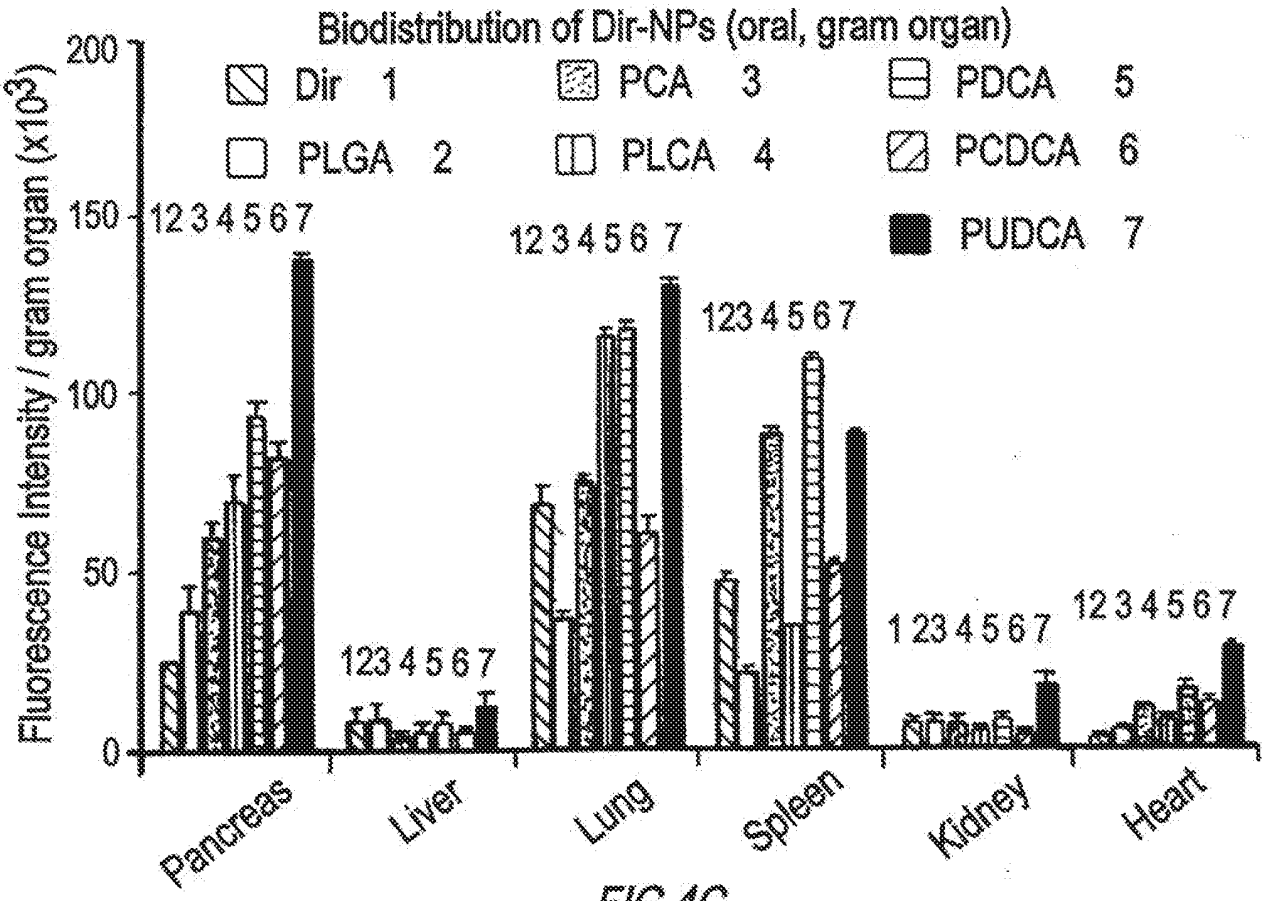
Biodistribution of Dir-NPs (oral, gram organ)
Dir 1
PLGA 2
PCA 3
PLCA 4
PDCA 5
PCDCA 6
PUDCA 7
Fluorescence Intensity / gram organ (x10^3)
200
150
100
50
0
Pancreas
Liver
Lung
Spleen
Kidney
Heart

FIG.4C

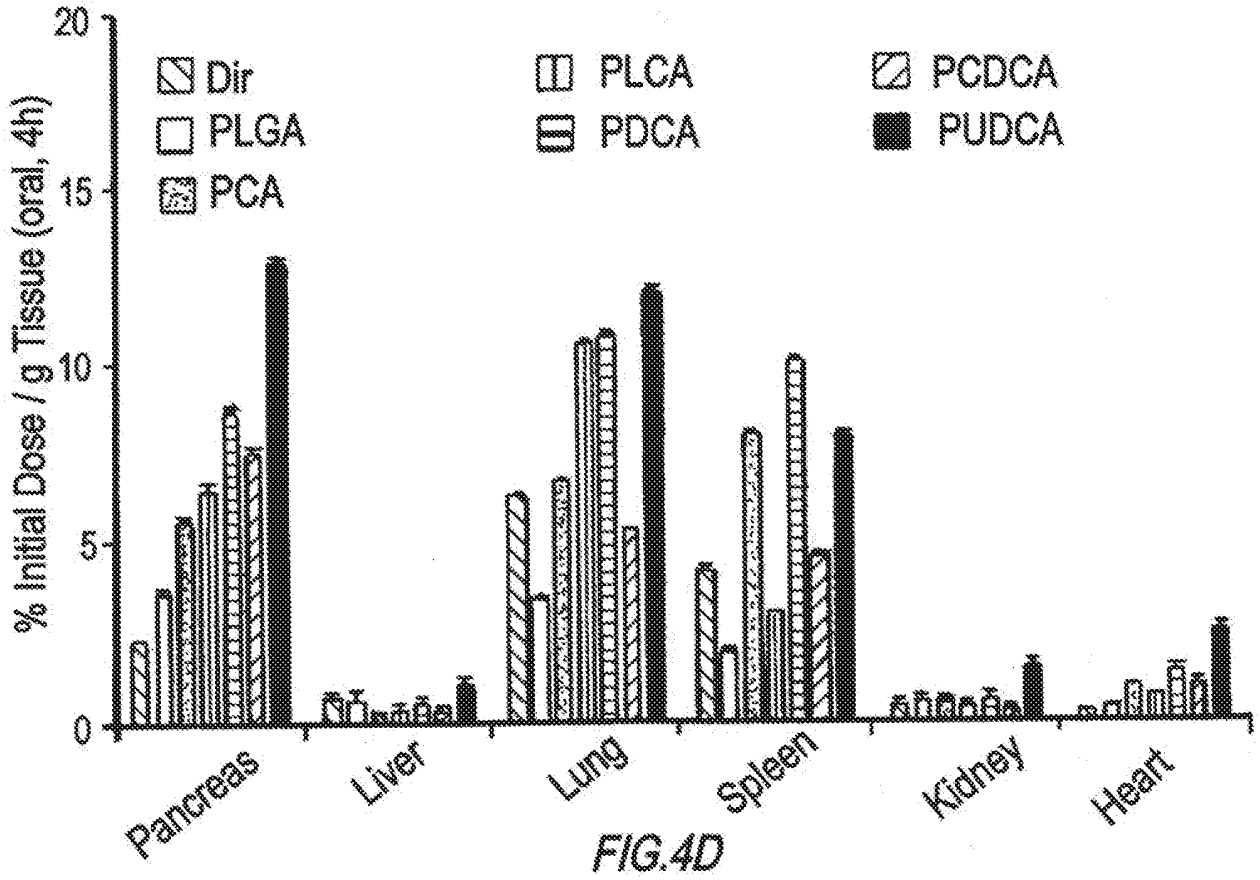
Dir
PLGA
PCA
PLCA
PDCA
PCDCA
PUDCA
% Initial Dose / g Tissue (oral, 4h)
20
15
10
5
0
Pancreas
Liver
Lung
Spleen
Kidney
Heart

FIG.4D

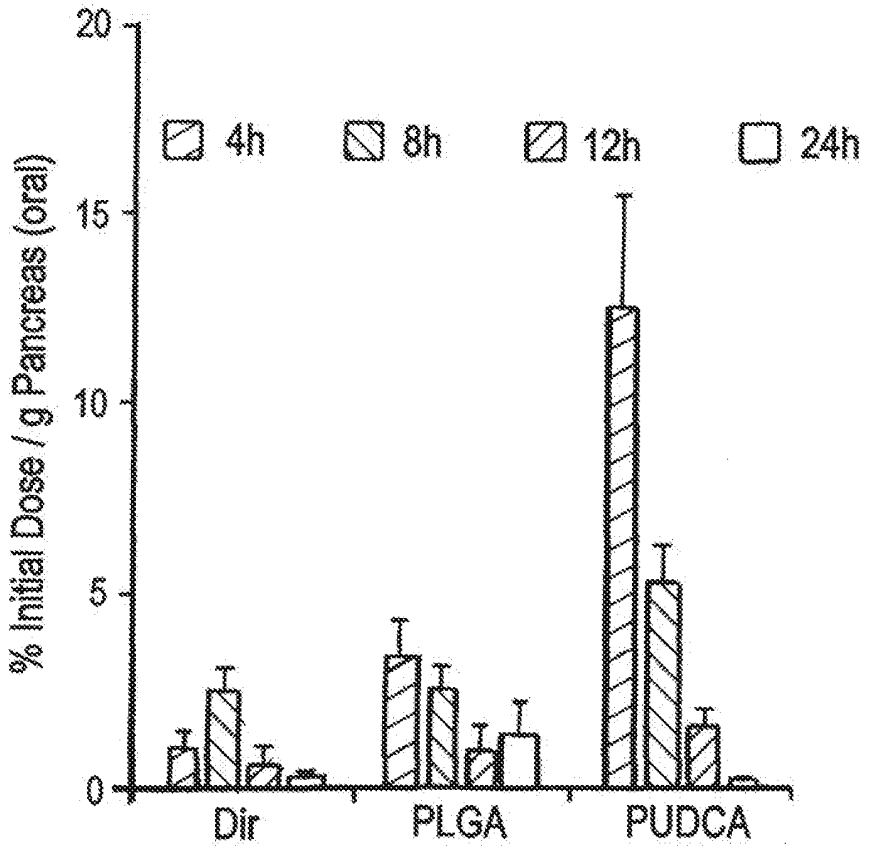
20
15
10
5
0
% Initial Dose / g Pancreas (oral)
4h
8h
12h
24h
Dir
PLGA
PUDCA

FIG. 4E

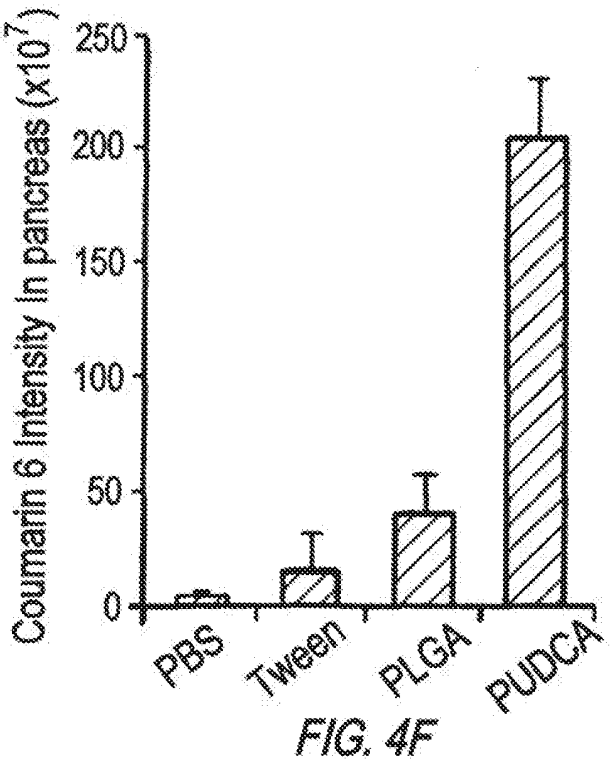
250
200
150
100
50
0
Coumarin 6 intensity in pancreas (x10^7)
PBS
Tween
PLGA
PUDCA

FIG. 4F

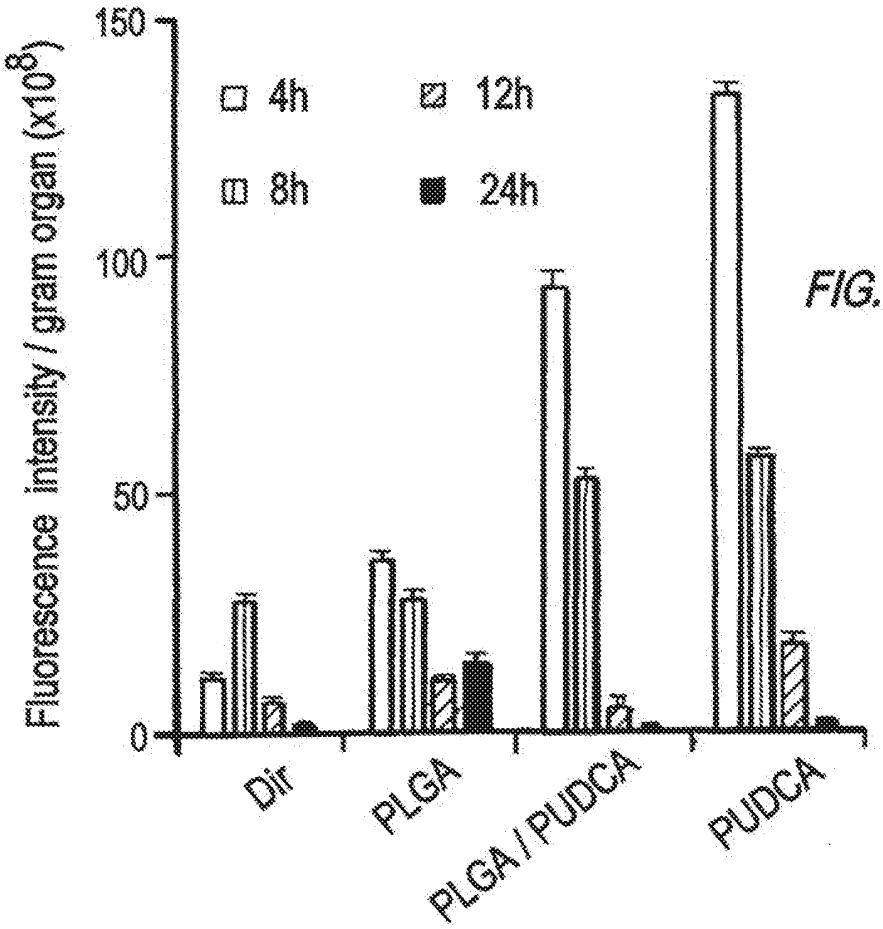
Fluorescence intensity / gram organ (x10^8)
150
100
50
0
4h
8h
12h
24h
Dir
PLGA
PLGA / PUDCA
PUDCA

FIG. 5A

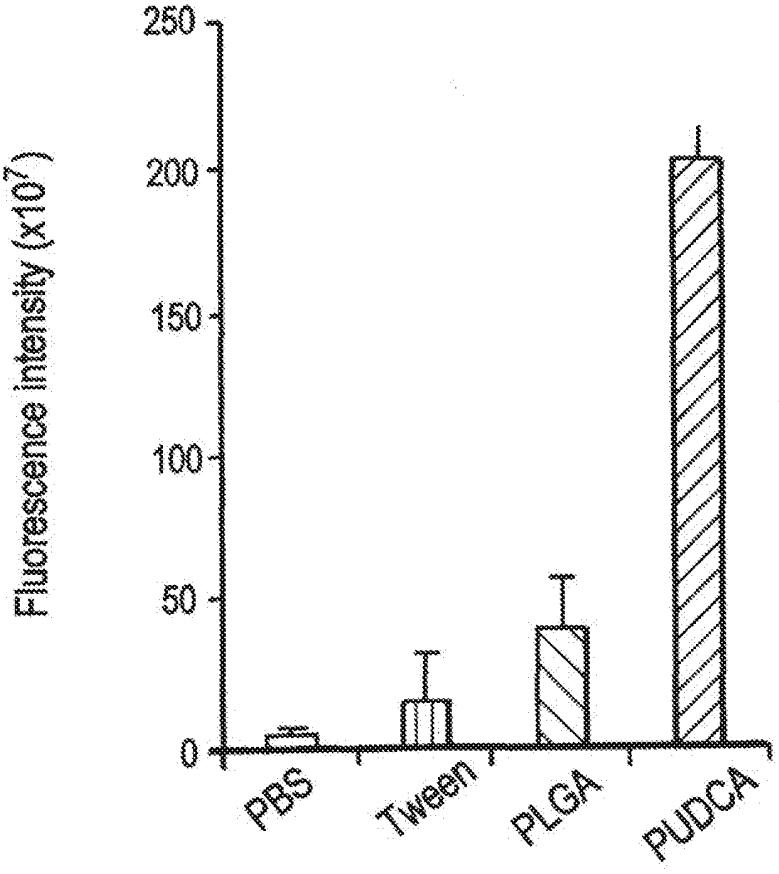
Fluorescence intensity (x10^7)
250
200
150
100
50
0
PBS
Tween
PLGA
PUDCA

FIG. 5B

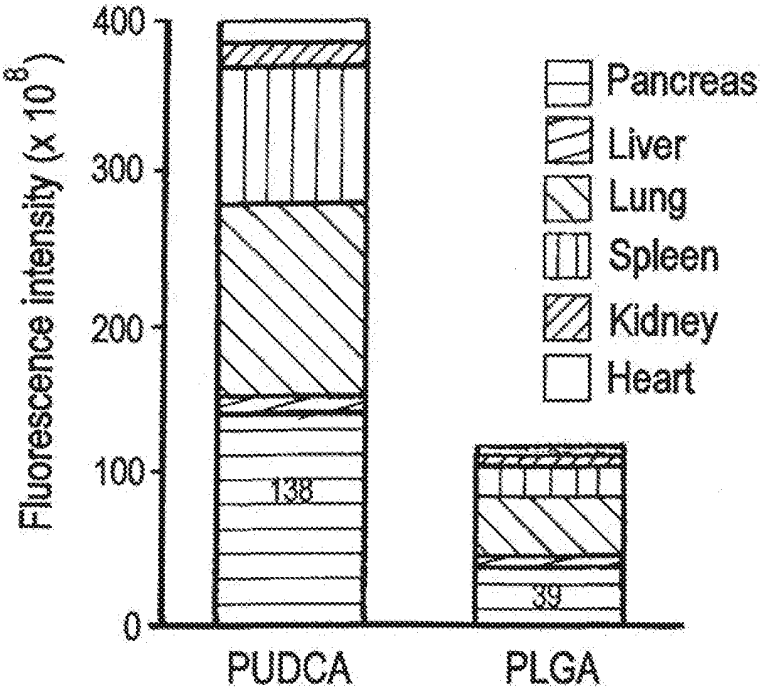
400
300
200
100
0
Fluorescence intensity (x 10^8)
138
39
PUDCA
PLGA
Pancreas
Liver
Lung
Spleen
Kidney
Heart

FIG. 5C

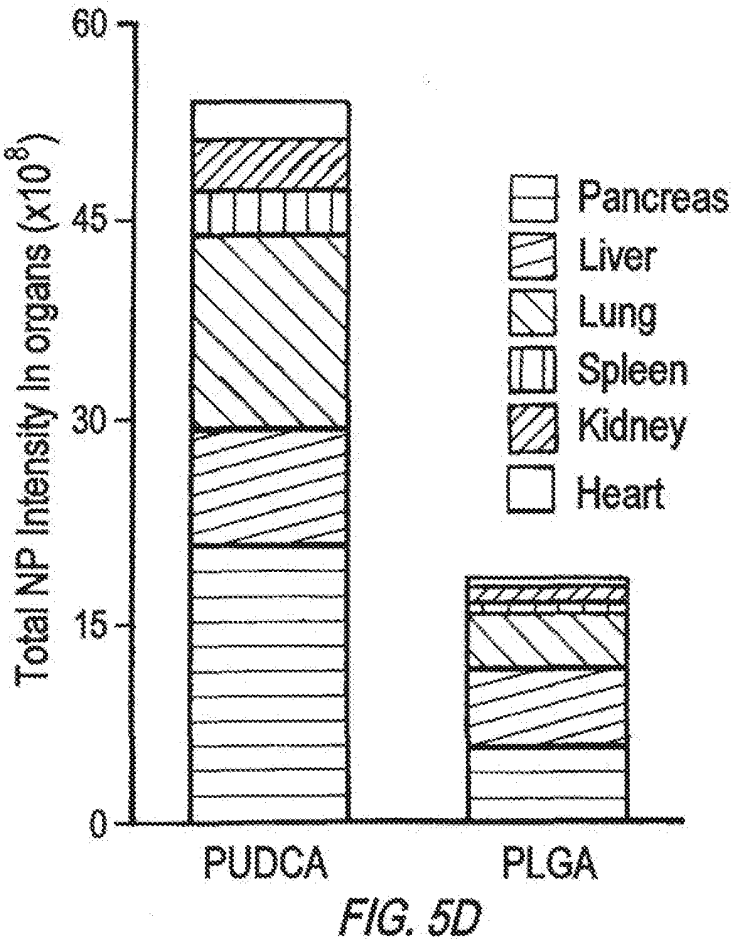
60
45
30
15
0
Total NP Intensity In organs (x10^8)
PUDCA
PLGA
Pancreas
Liver
Lung
Spleen
Kidney
Heart

FIG. 5D

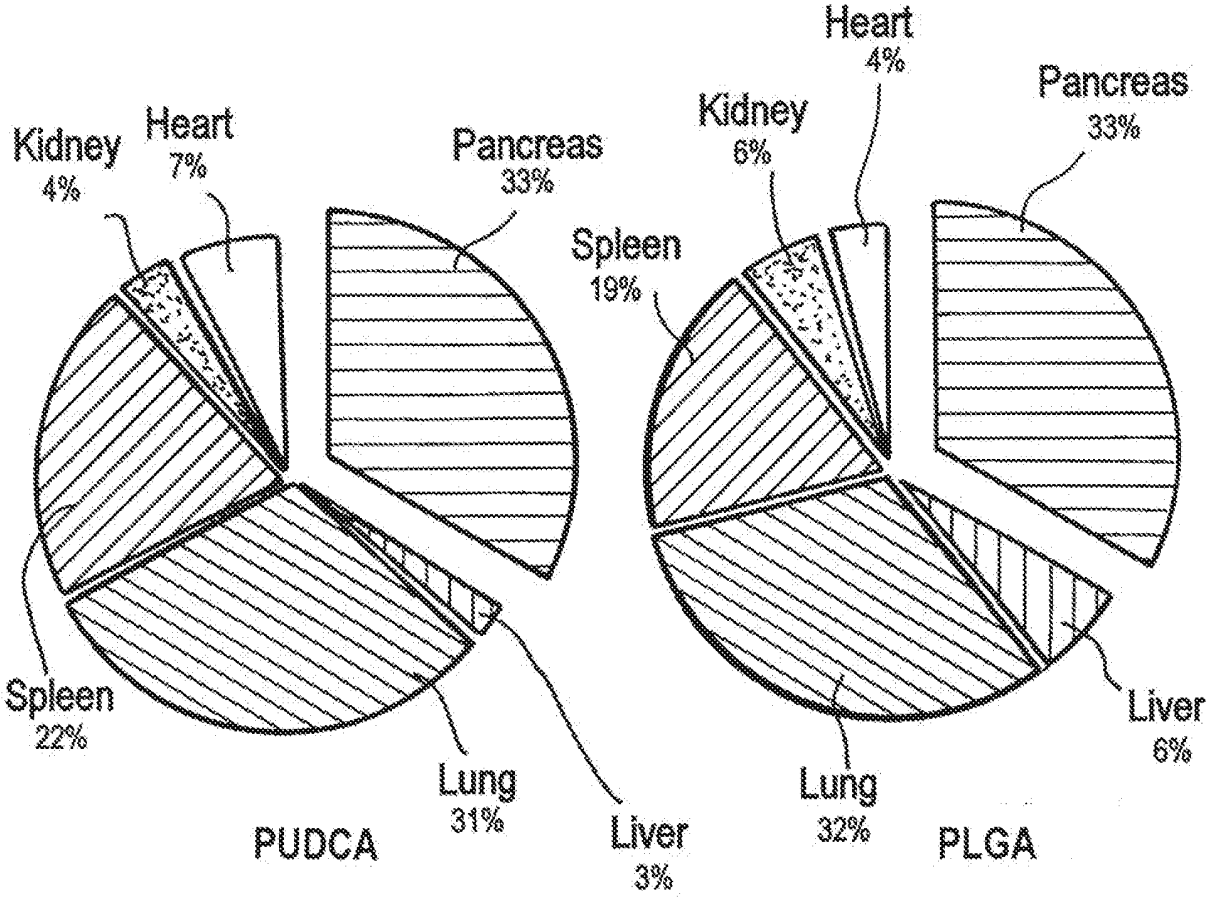
Kidney
4%
Heart
7%
Pancreas
33%
Spleen
22%
Lung
31%
Liver
3%
PUDCA
Heart
4%
Kidney
6%
Pancreas
33%
Spleen
19%
Liver
6%
Lung
32%
PLGA

FIG. 5E

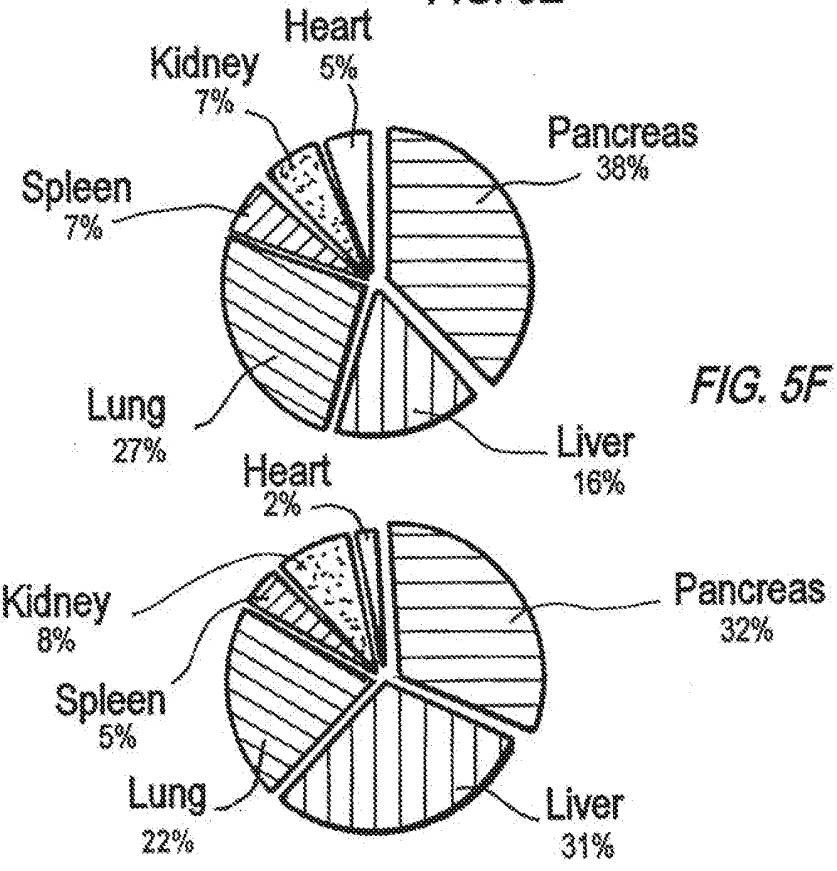
Heart
5%
Kidney
7%
Pancreas
38%
Spleen
7%
Lung
27%
Liver
16%
Heart
2%
Kidney
8%
Pancreas
32%
Spleen
5%
Lung
22%
Liver
31%

FIG. 5F

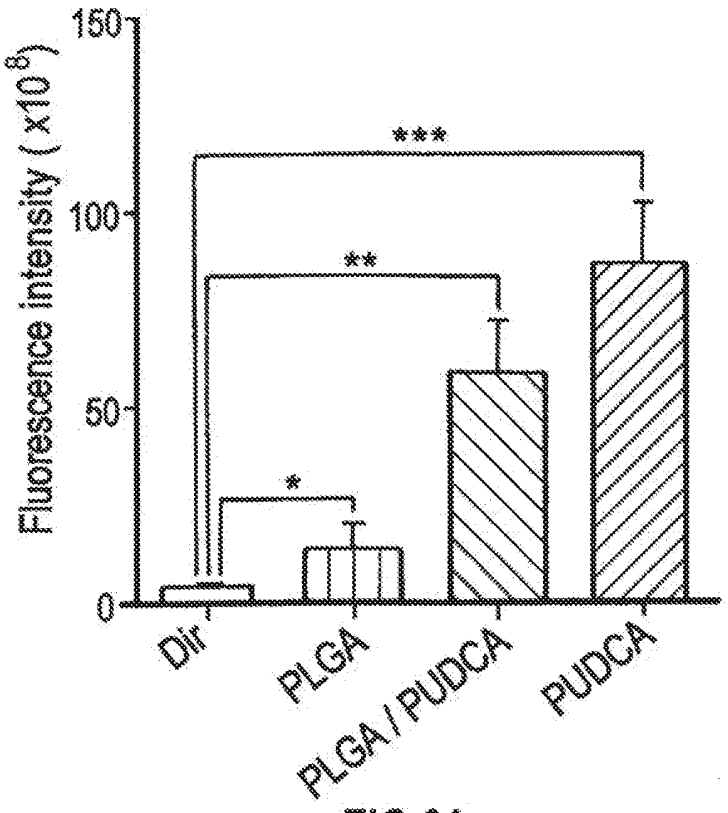
Fluorescence intensity (x10^8)
150
100
50
0
***
**
*
Dir
PLGA
PLGA / PUDCA
PUDCA

FIG.6A

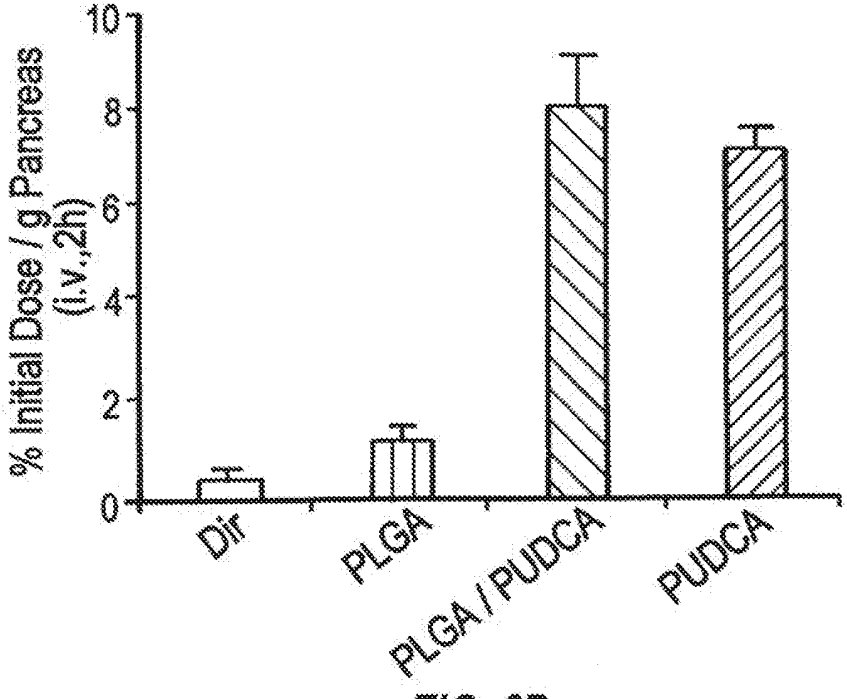
% Initial Dose / g Pancreas
(i.v.,2h)
10
8
6
4
2
0
Dir
PLGA
PLGA / PUDCA
PUDCA

FIG .6B

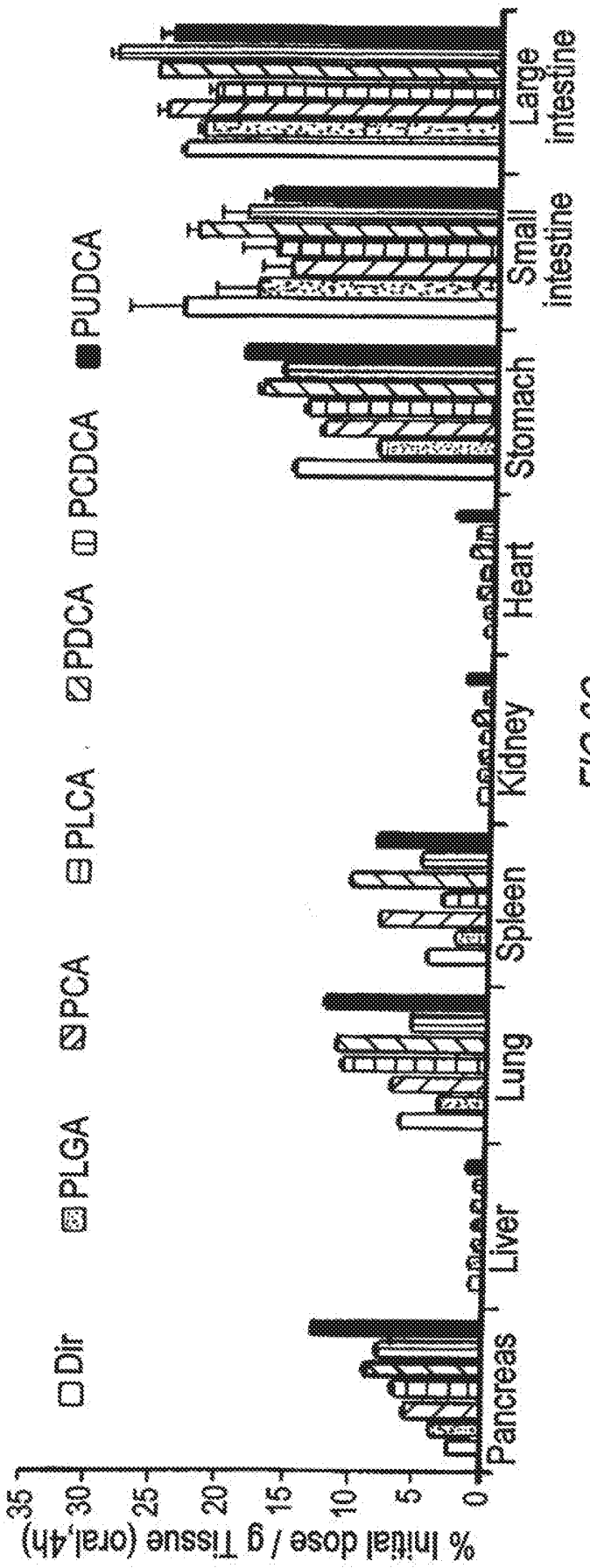
% Initial dose / g Tissue (oral,4h)
0
5
10
15
20
25
30
35
Dir
PLGA
PCA
PLCA
PDCA
PCDCA
PUDCA
Pancreas
Liver
Lung
Spleen
Kidney
Heart
Stomach
Small intestine
Large intestine

FIG.6C

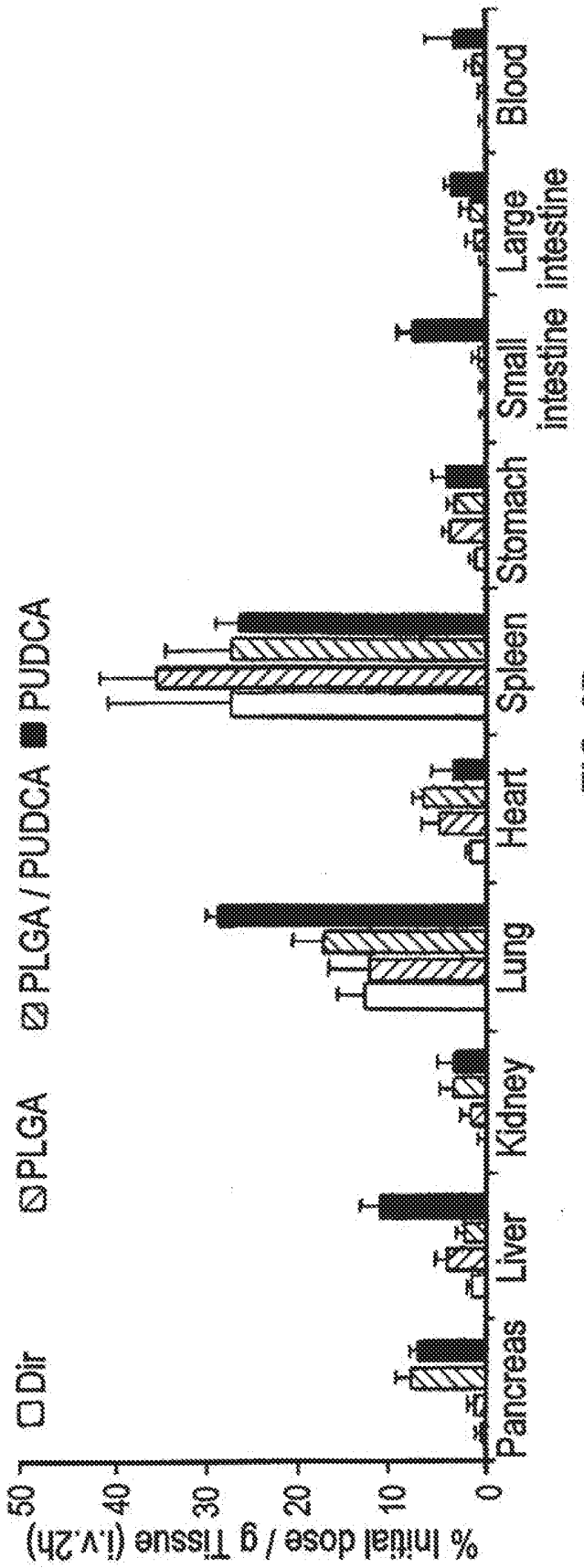
Dir
PLGA
PLGA / PUDCA
PUDCA
% Initial dose / g Tissue (i.v.2h)
0
10
20
30
40
50
Pancreas
Liver
Kidney
Lung
Heart
Spleen
Stomach
Small intestine
Large intestine
Blood

FIG. 6D

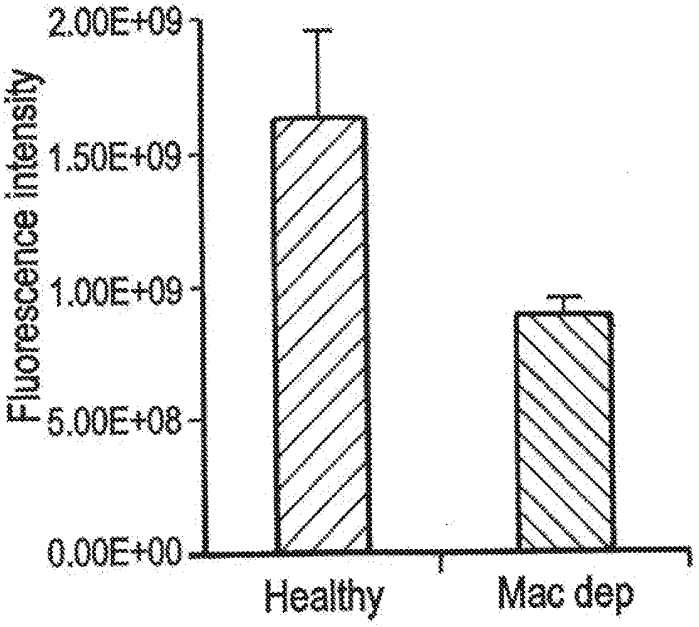
2.00E+09
1.50E+09
1.00E+09
5.00E+08
0.00E+00
Fluorescence intensity
Healthy
Mac dep

FIG. 6E

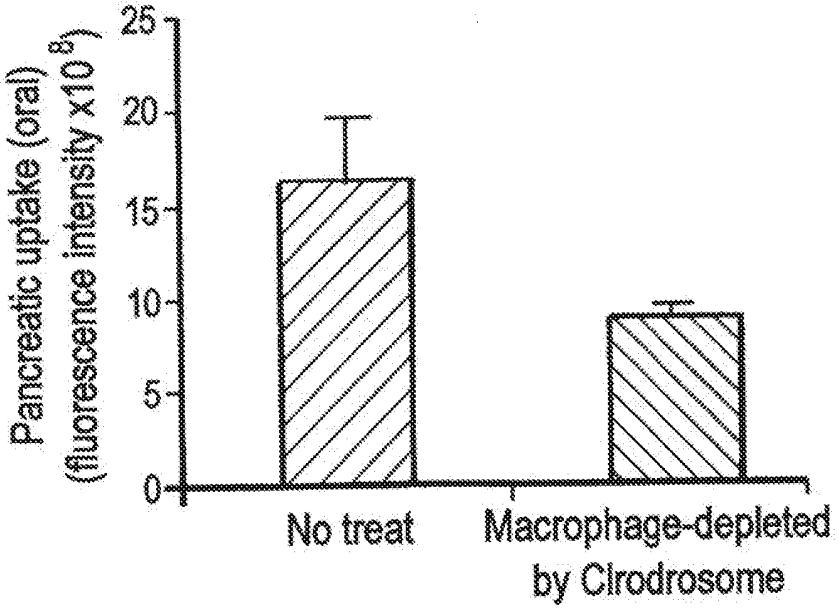
25
20
15
10
5
0
Pancreatic uptake (oral)
(fluorescence intensity x10^6)
No treat
Macrophage-depleted
by Clrodrosome

FIG. 6F

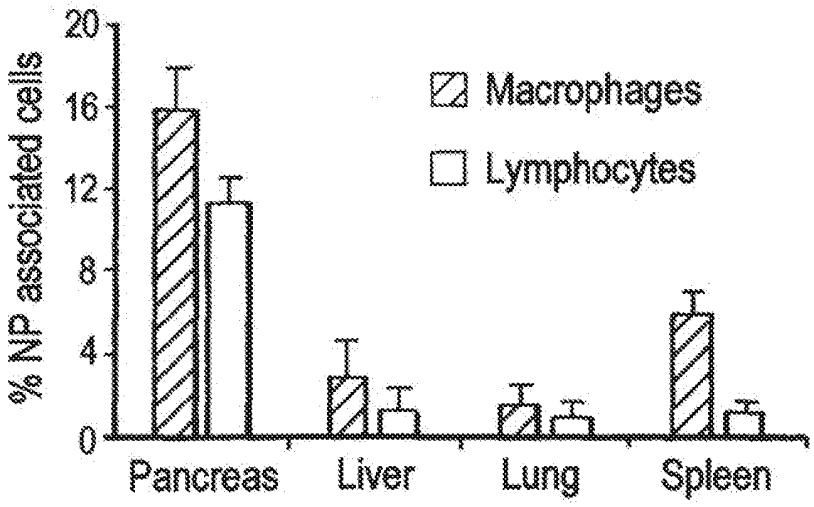
% NP associated cells
20
16
12
8
4
0
Macrophages
Lymphocytes
Pancreas
Liver
Lung
Spleen

FIG. 6G

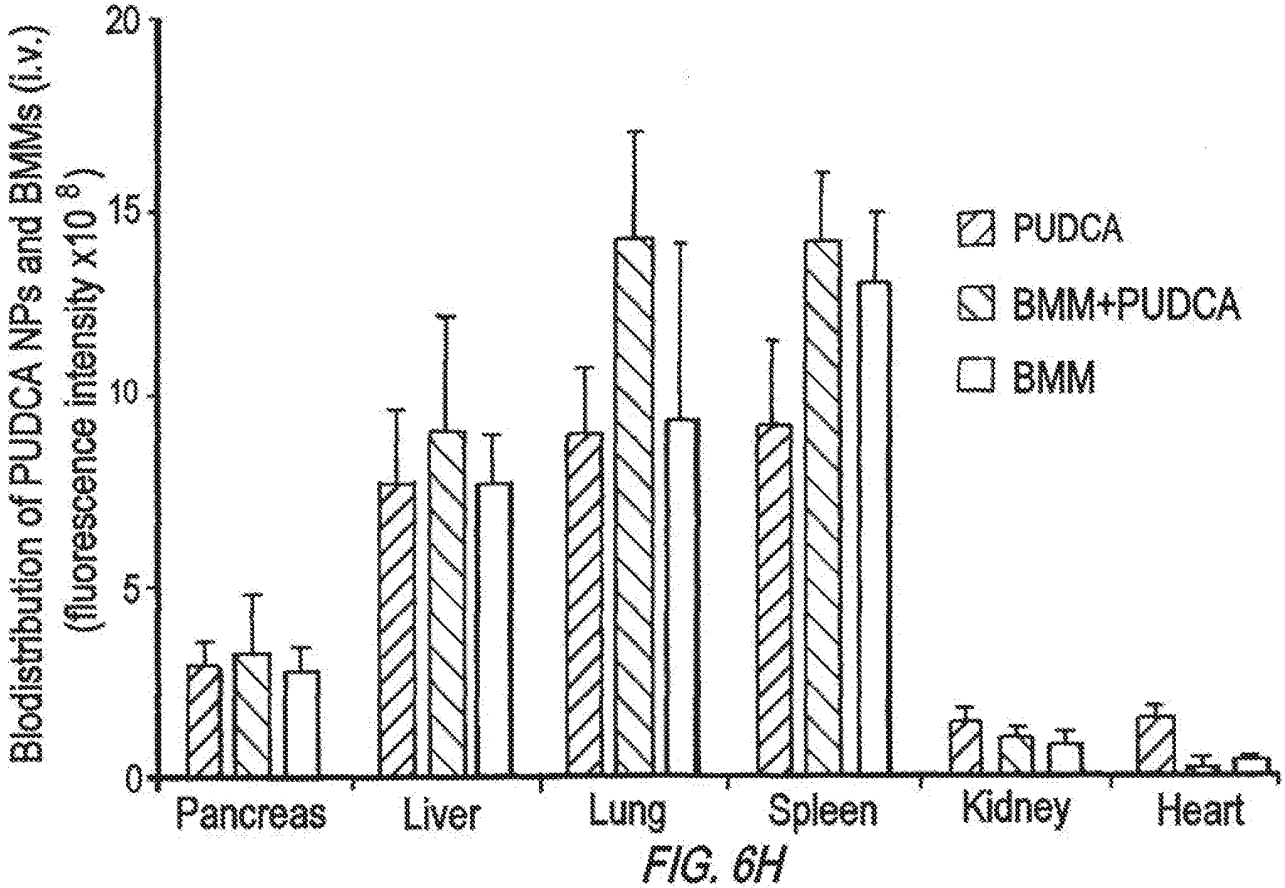
Blodistribution of PUDCA NPs and BMMs (i.v.)
(fluorescence intensity x10 8)
20
15
10
5
0
PUDCA
BMM+PUDCA
BMM
Pancreas
Liver
Lung
Spleen
Kidney
Heart

FIG. 6H

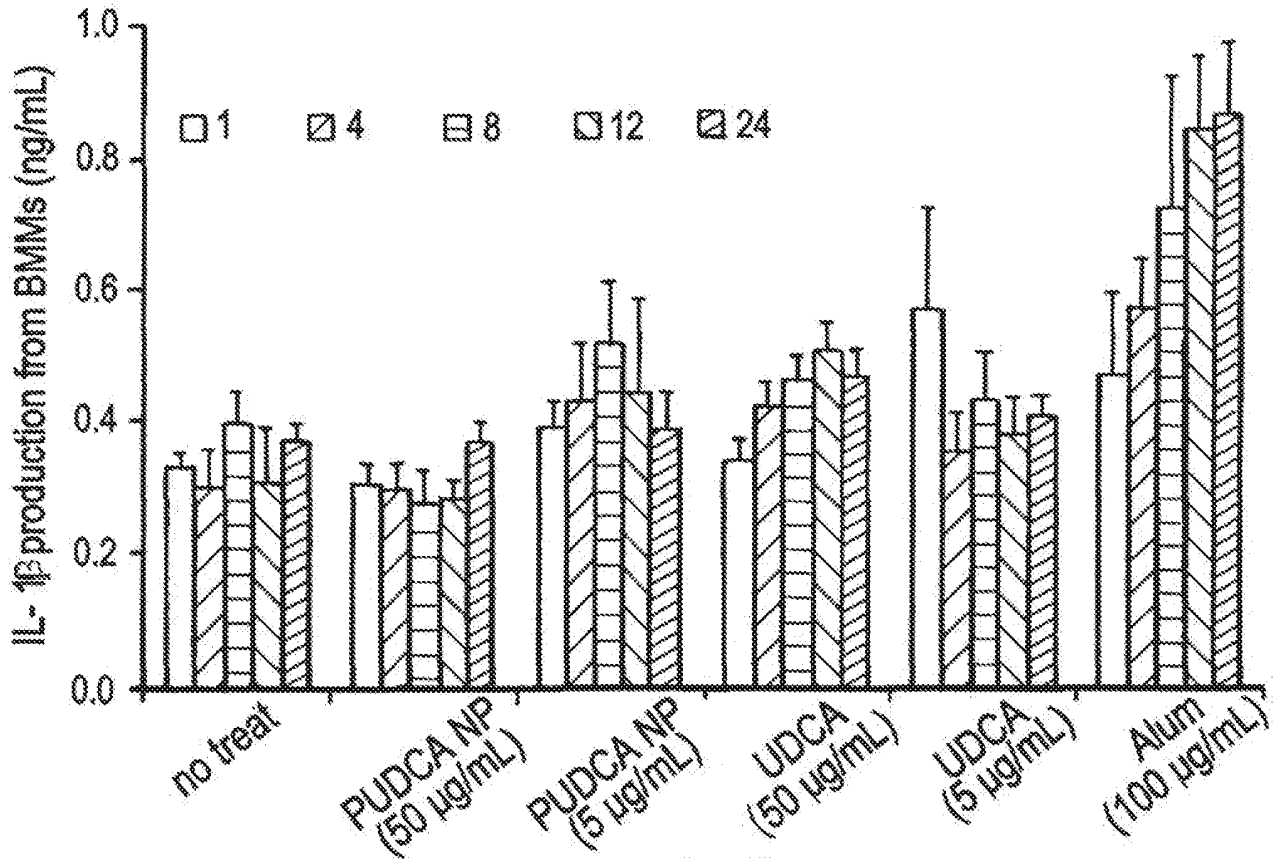
IL-1β production from BMMs (ng/mL)
1.0
0.8
0.6
0.4
0.2
0.0
1
4
8
12
24
no treat
PUDCA NP (50 μg/mL)
PUDCA NP (5 μg/mL)
UDCA (50 μg/mL)
UDCA (5 μg/mL)
Alum (100 μg/mL)

FIG. 6I

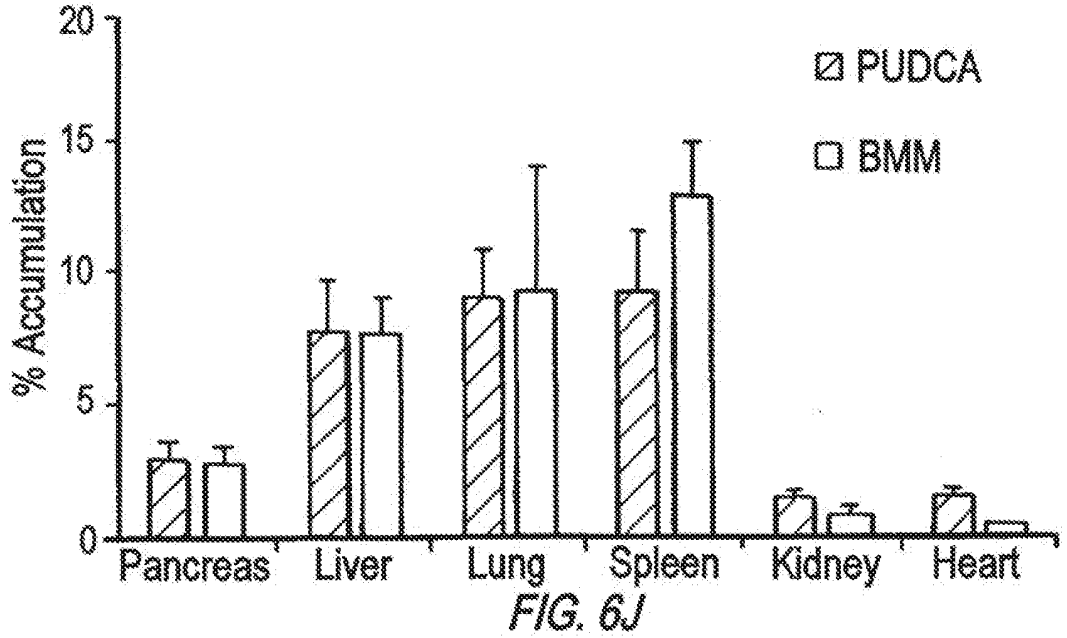
% Accumulation
20
15
10
5
0
PUDCA
BMM
Pancreas
Liver
Lung
Spleen
Kidney
Heart

FIG. 6J

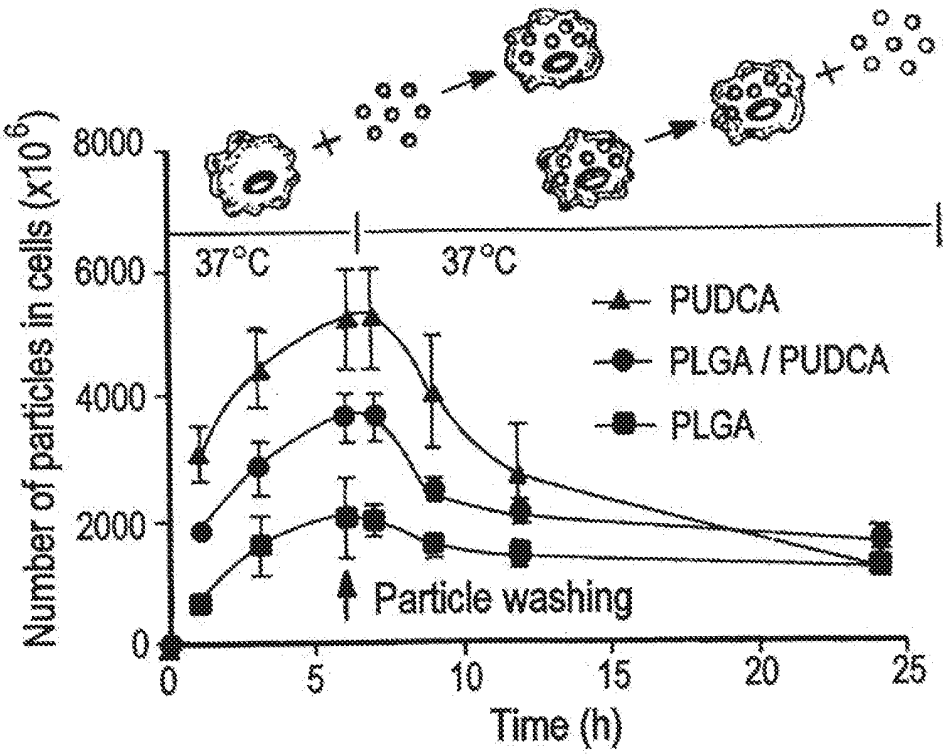
Number of particles in cells (x10^6)
8000
6000
4000
2000
0
37°C
37°C
PUDCA
PLGA / PUDCA
PLGA
Particle washing
0
5
10
15
20
25
Time (h)

FIG. 6K

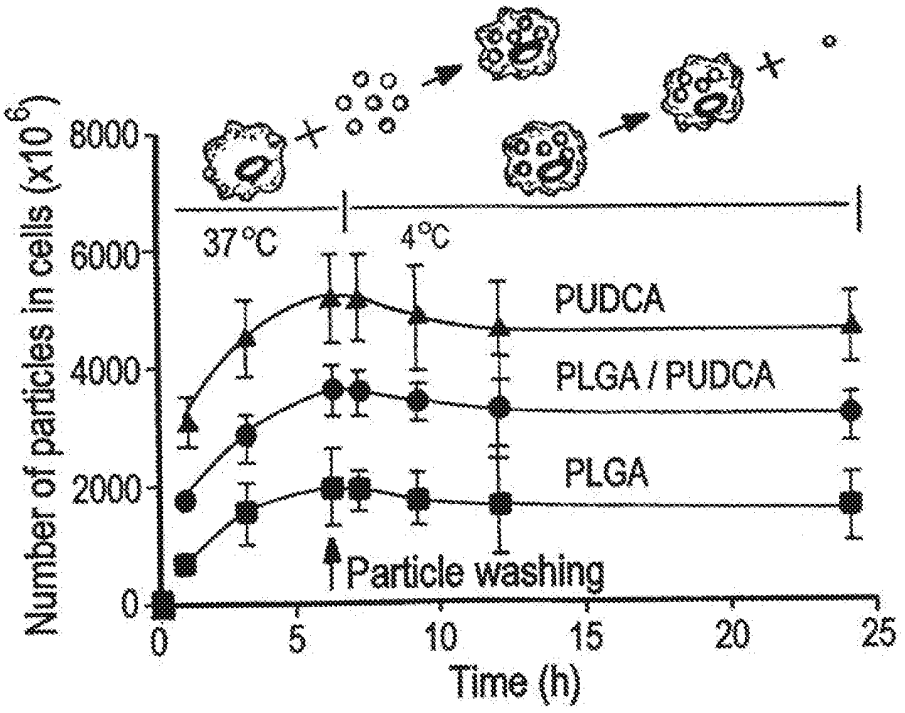
Number of particles in cells (x10^6)
8000
6000
4000
2000
0
37°C
4°C
PUDCA
PLGA / PUDCA
PLGA
Particle washing
0
5
10
15
20
25
Time (h)

FIG. 6L

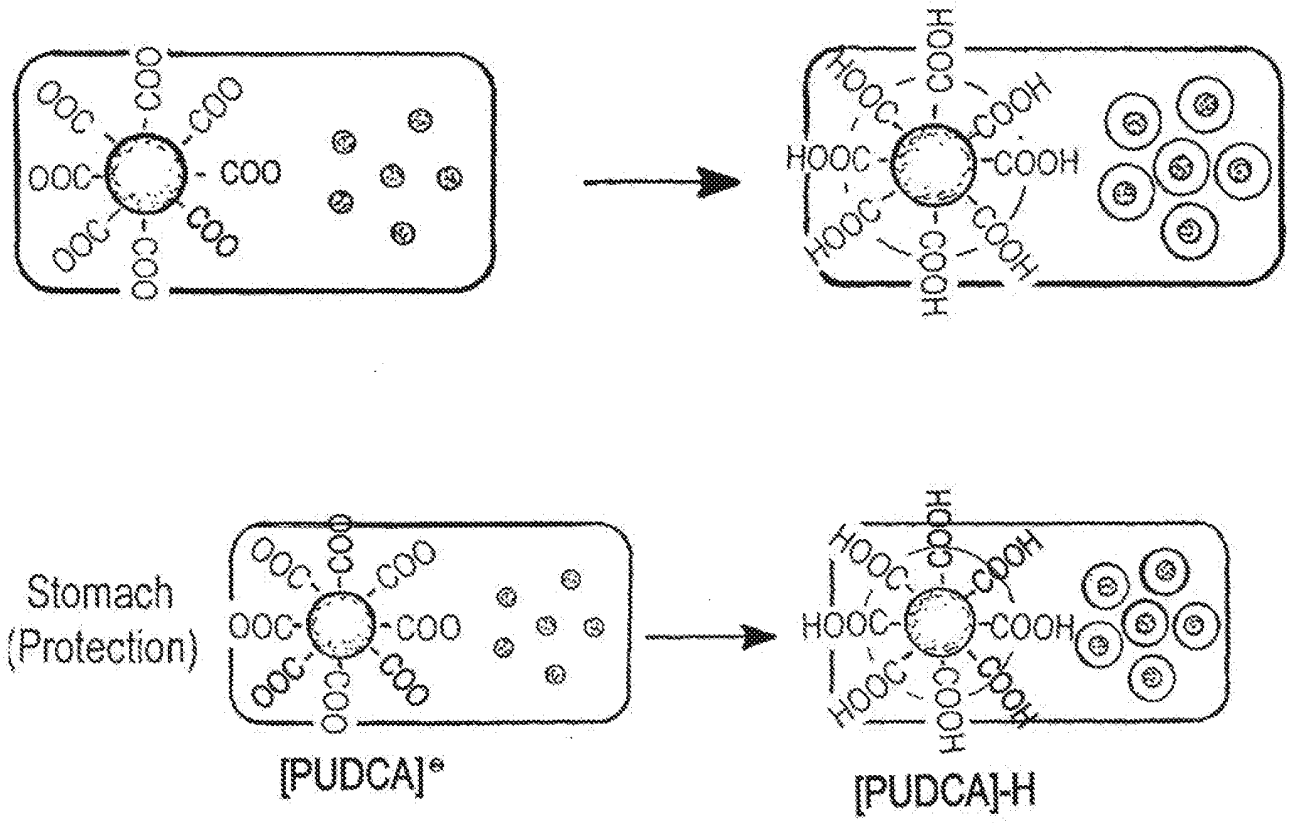
Stomach
(Protection)
[PUDCA]⁻
[PUDCA]-H
Gut
(Rapid absorption)
(Endocytosis)
M cell
Epithelial cells
PUDCA NP
Macrophage
Pancreatic
Microenvironment
(Exocytosis)
Pancreas

FIG. 6M

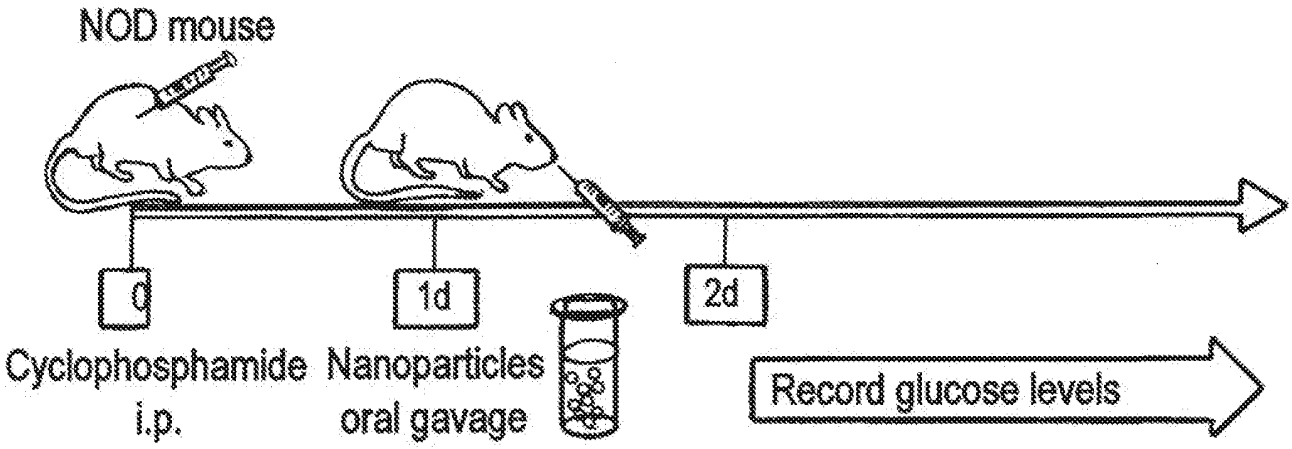
NOD mouse
0
1d
2d
Cyclophosphamide
i.p.
Nanoparticles
oral gavage
Record glucose levels

FIG. 7A

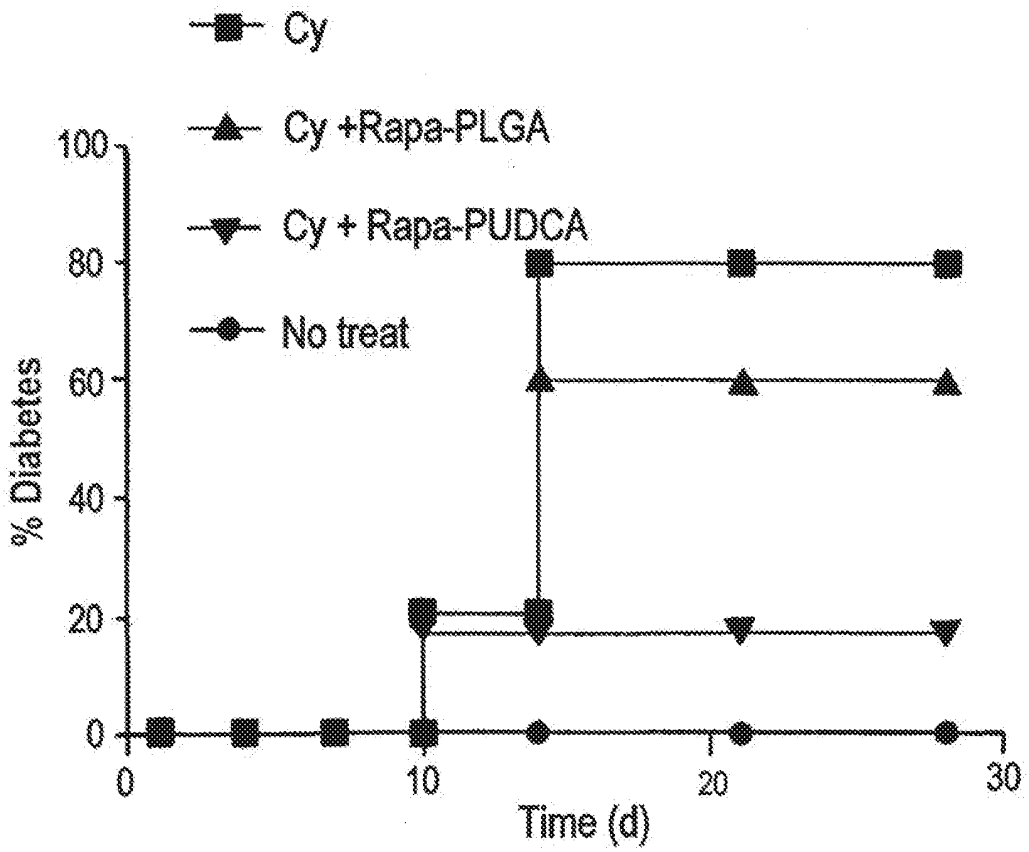
Cy
Cy +Rapa-PLGA
Cy + Rapa-PUDCA
No treat
% Diabetes
100
80
60
40
20
0
0
10
20
30
Time (d)

FIG. 7B

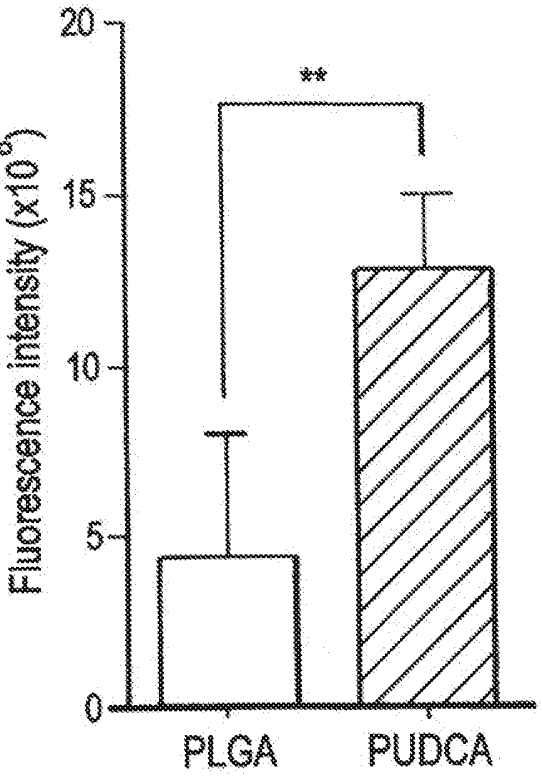
20
15
10
5
0
**
Fluorescence intensity (x10^8)
PLGA
PUDCA

FIG. 7C

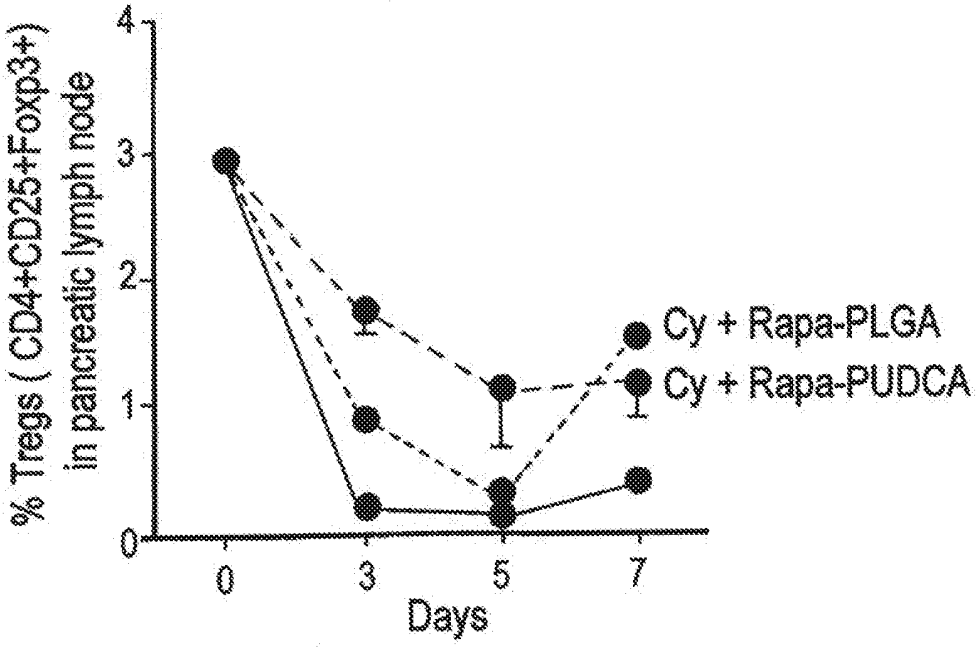
4
3
2
1
0
% Tregs (CD4+CD25+Foxp3+) in pancreatic lymph node
0
3
5
7
Days
Cy + Rapa-PLGA
Cy + Rapa-PUDCA

FIG. 7D

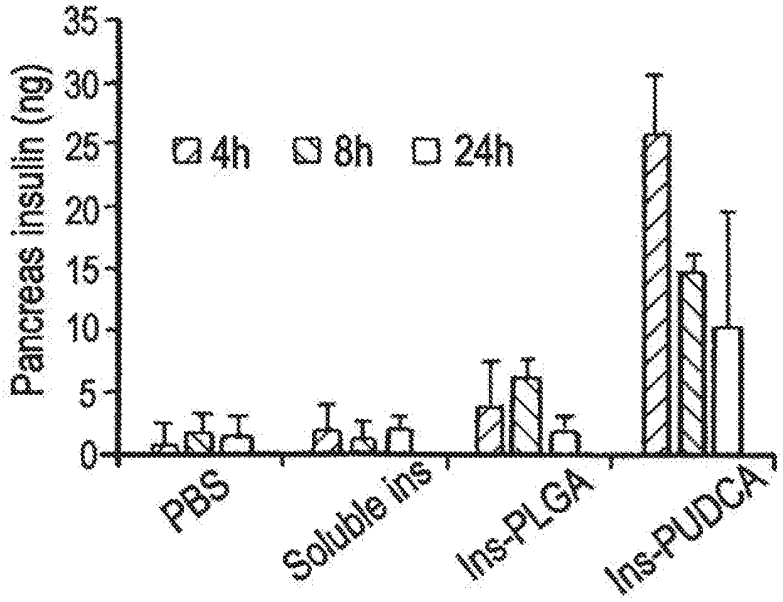
Pancreas insulin (ng)
35
30
25
20
15
10
5
0
4h
8h
24h
PBS
Soluble ins
Ins-PLGA
Ins-PUDCA

FIG. 8A

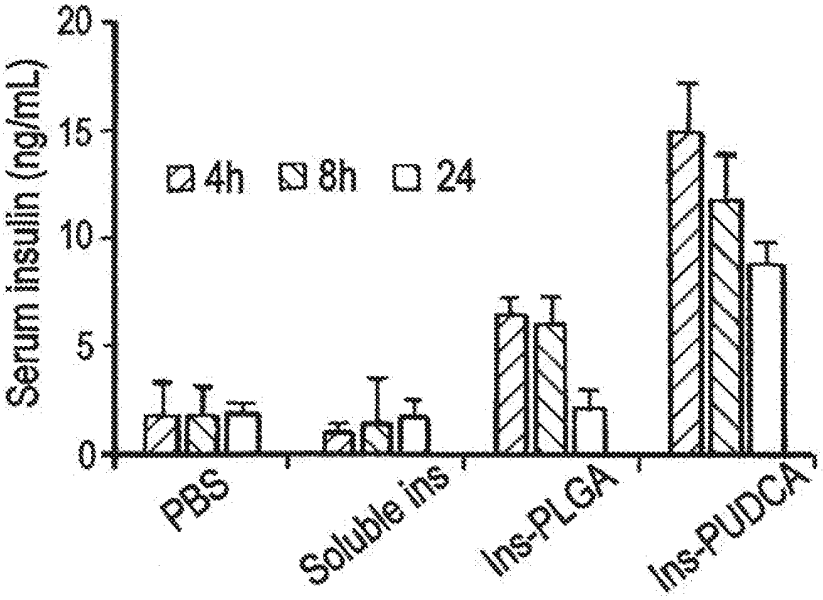
Serum insulin (ng/mL)
20
15
10
5
0
4h
8h
24
PBS
Soluble ins
Ins-PLGA
Ins-PUDCA

FIG. 8B

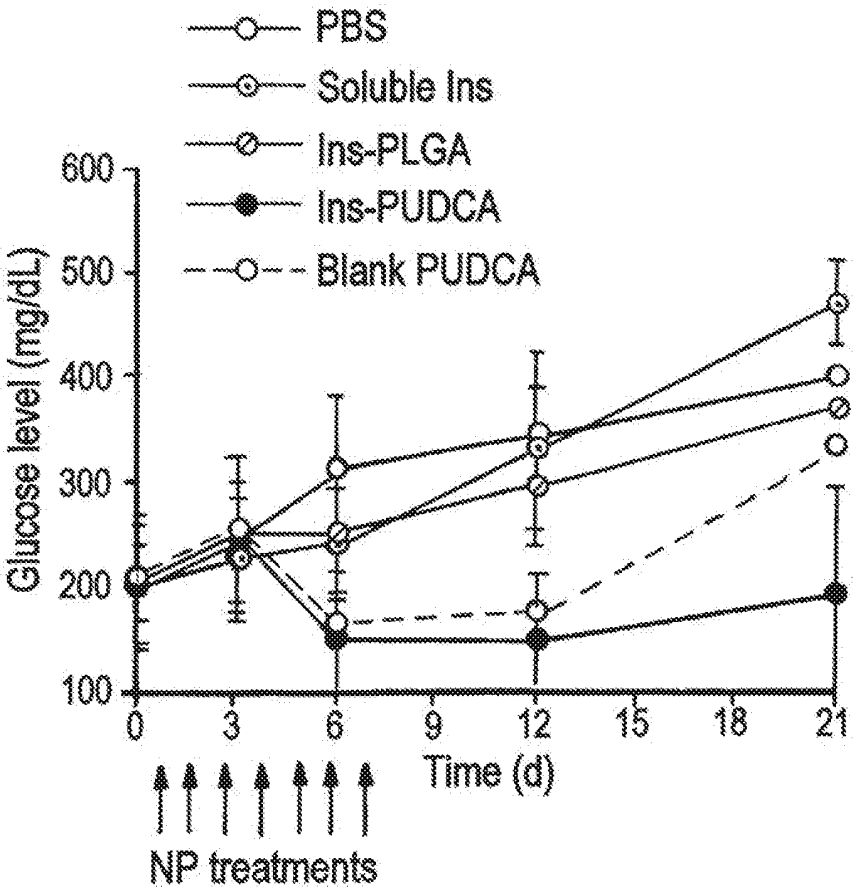
PBS
Soluble Ins
Ins-PLGA
Ins-PUDCA
Blank PUDCA
Glucose level (mg/dL)
600
500
400
300
200
100
0
3
6
9
12
15
18
21
Time (d)
NP treatments

FIG. 8C

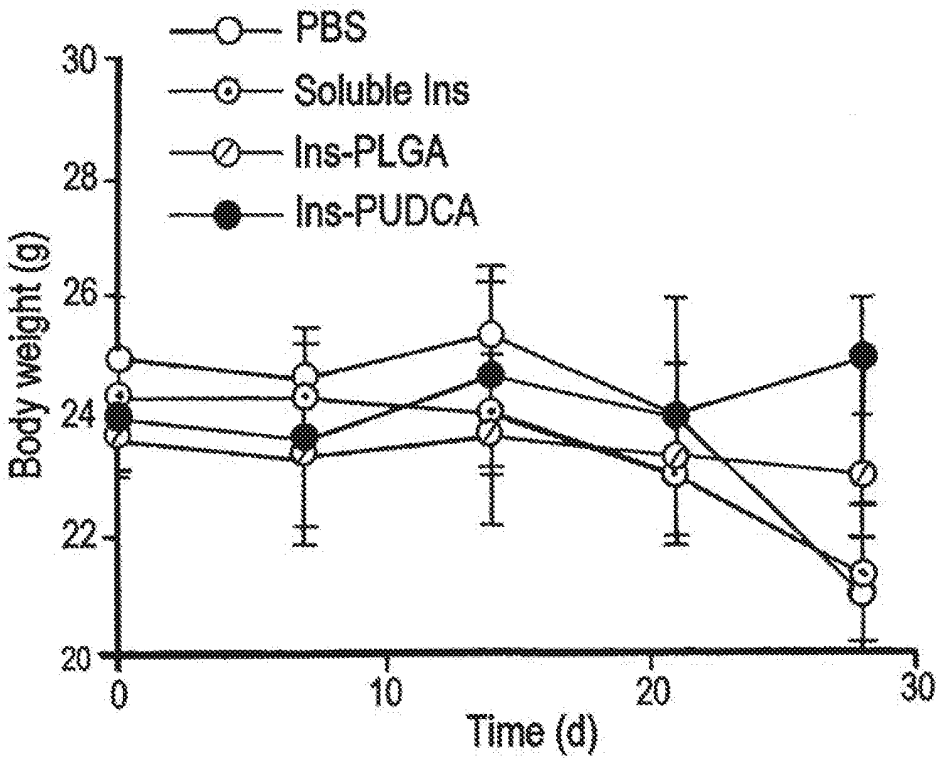
PBS
Soluble Ins
Ins-PLGA
Ins-PUDCA
Body weight (g)
30
28
26
24
22
20
0
10
20
30
Time (d)

FIG. 8D

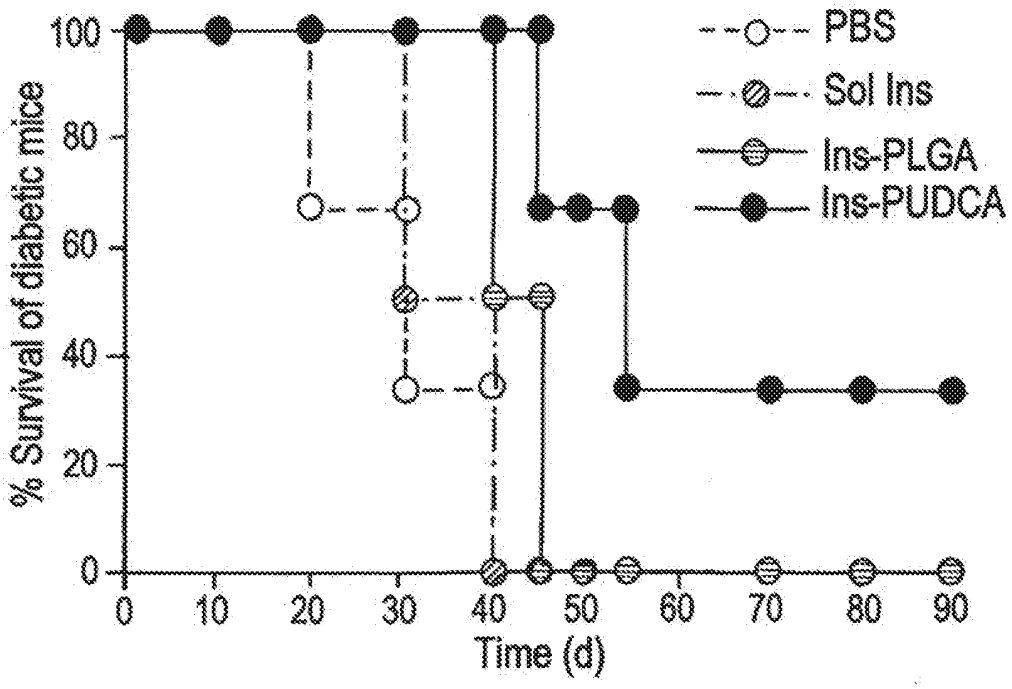
% Survival of diabetic mice
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
Time (d)
PBS
Sol Ins
Ins-PLGA
Ins-PUDCA

FIG. 8E

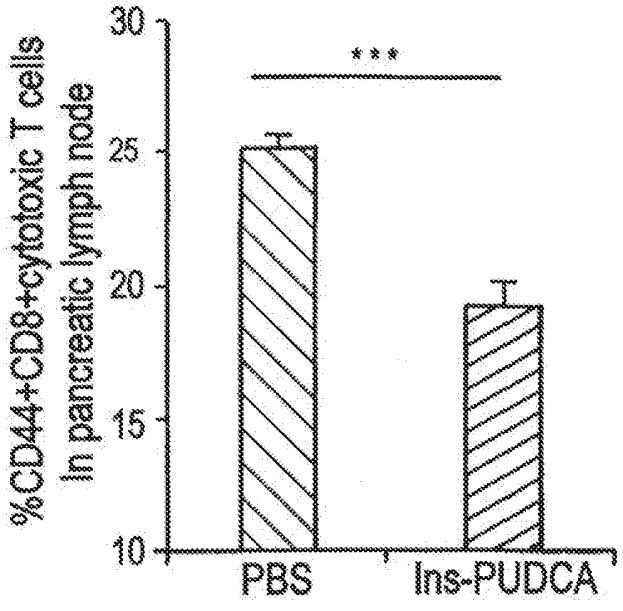
%CD44+CD8+cytotoxic T cells
In pancreatic lymph node
30
25
20
15
10
***
PBS
Ins-PUDCA

FIG. 9A

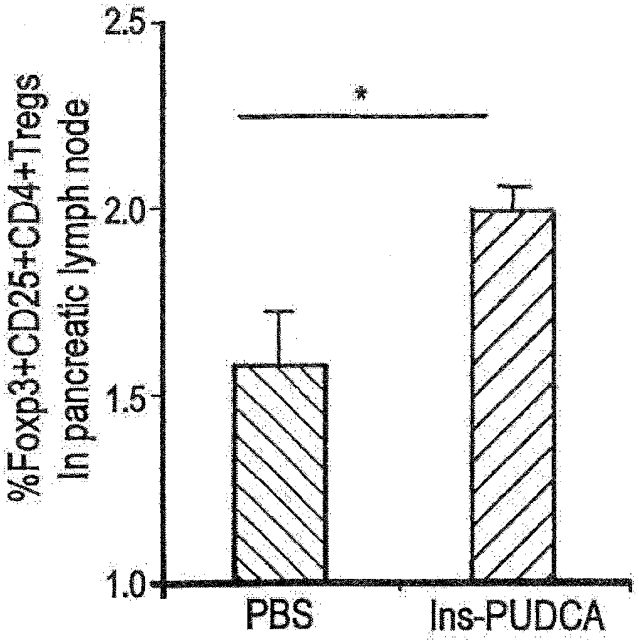
%Foxp3+CD25+CD4+Tregs
In pancreatic lymph node
2.5
2.0
1.5
1.0
*
PBS
Ins-PUDCA

FIG. 9B

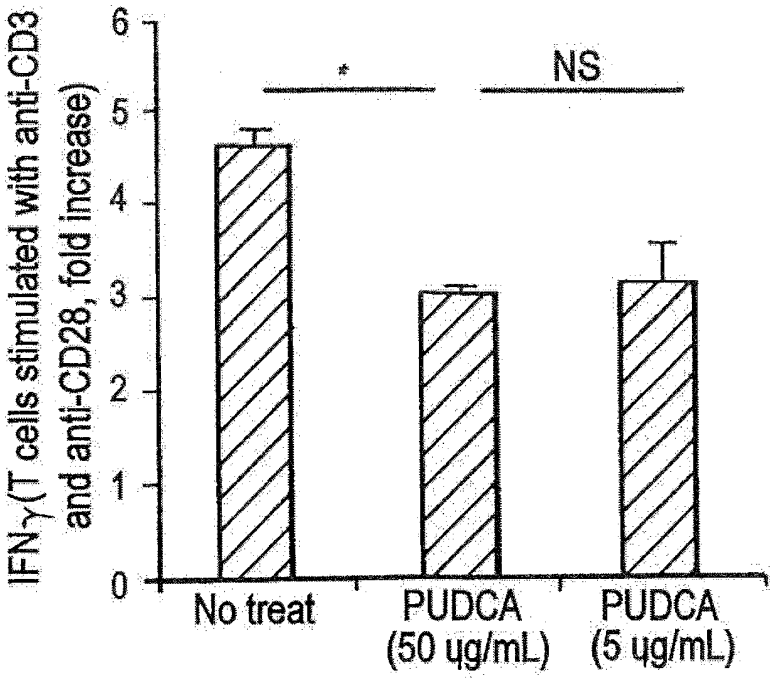
IFNγ(T cells stimulated with anti-CD3
and anti-CD28, fold increase)
6
5
4
3
2
1
0
*
NS
No treat
PUDCA
(50 ug/mL)
PUDCA
(5 ug/mL)

FIG. 9C

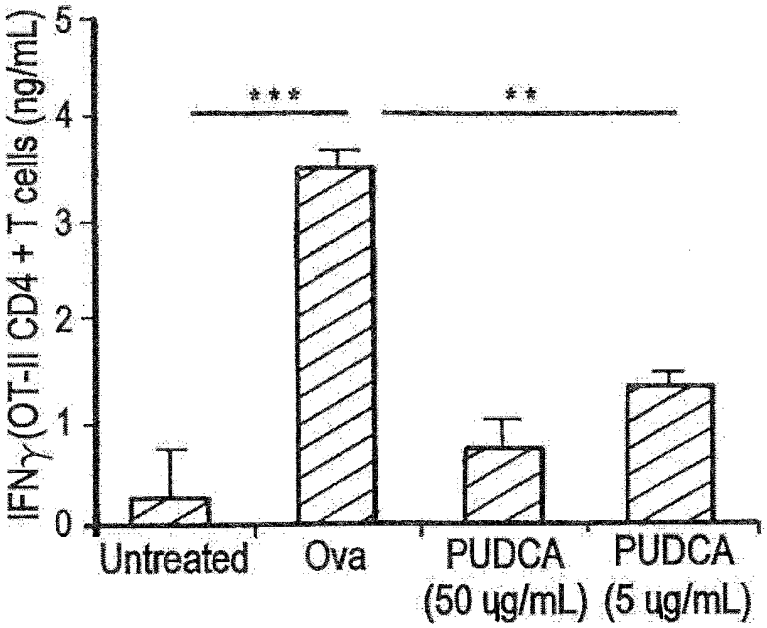
IFNγ(OT-II CD4 + T cells (ng/mL)
5
4
3
2
1
0
***
**
Untreated
Ova
PUDCA (50 ug/mL)
PUDCA (5 ug/mL)

FIG. 9D

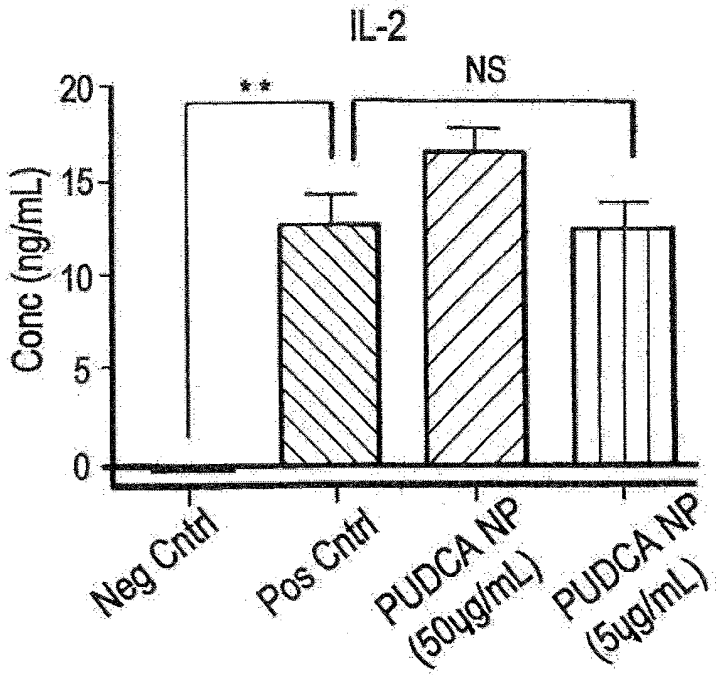
IL-2
Conc (ng/mL)
20
15
10
5
0
**
NS
Neg Cntrl
Pos Cntrl
PUDCA NP (50ug/mL)
PUDCA NP (5ug/mL)

FIG. 9E

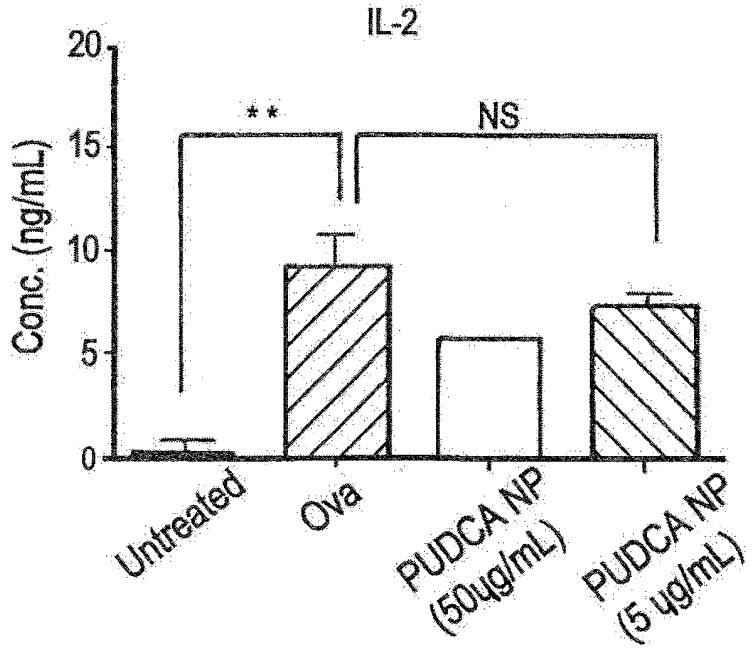
IL-2
Conc. (ng/mL)
20
15
10
5
0
**
NS
Untreated
Ova
PUDCA NP (50ug/mL)
PUDCA NP (5 ug/mL)

FIG. 9F

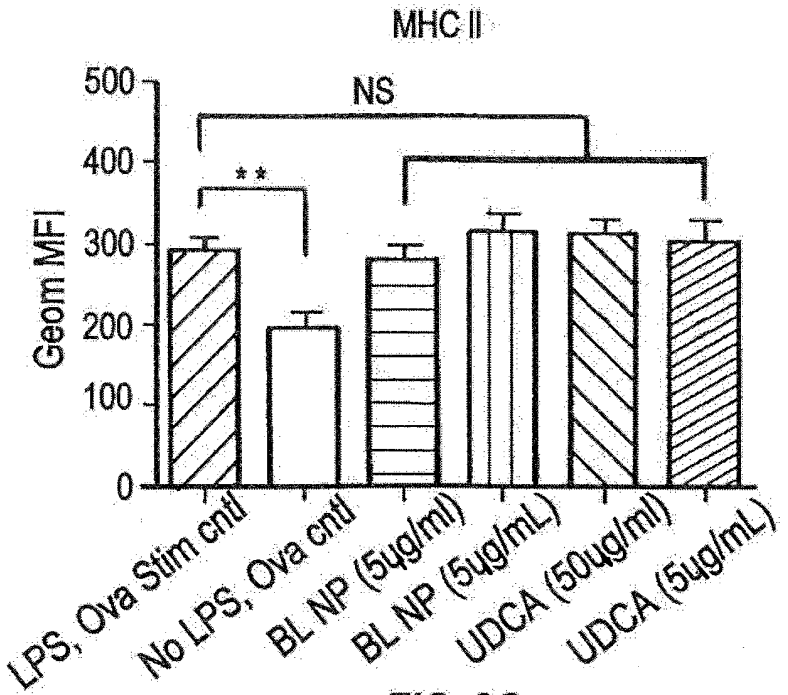
MHC II
Geom MFI
500
400
300
200
100
0
NS
**
LPS, Ova Stim cntl
No LPS, Ova cntl
BL NP (5ug/ml)
BL NP (5ug/mL)
UDCA (50ug/ml)
UDCA (5ug/mL)

FIG. 9G

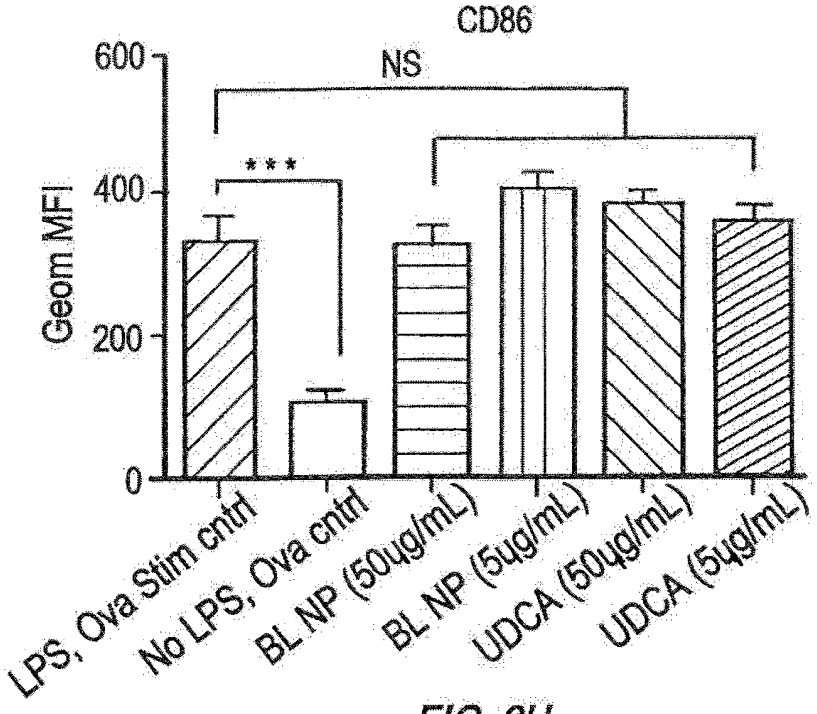
CD86
600
400
200
0
Geom MFI
NS
***
LPS, Ova Stim cntrl
No LPS, Ova cntrl
BL NP (50ug/mL)
BL NP (5ug/mL)
UDCA (50ug/mL)
UDCA (5ug/mL)

FIG. 9H

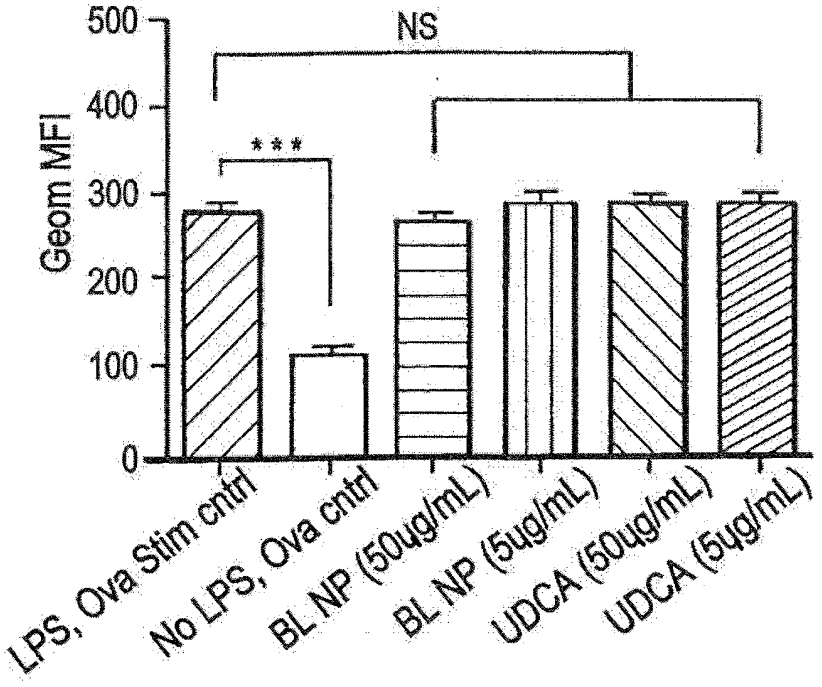
500
400
300
200
100
0
Geom MFI
NS
***
LPS, Ova Stim cntrl
No LPS, Ova cntrl
BL NP (50ug/mL)
BL NP (5ug/mL)
UDCA (50ug/mL)
UDCA (5ug/mL)

FIG. 9I

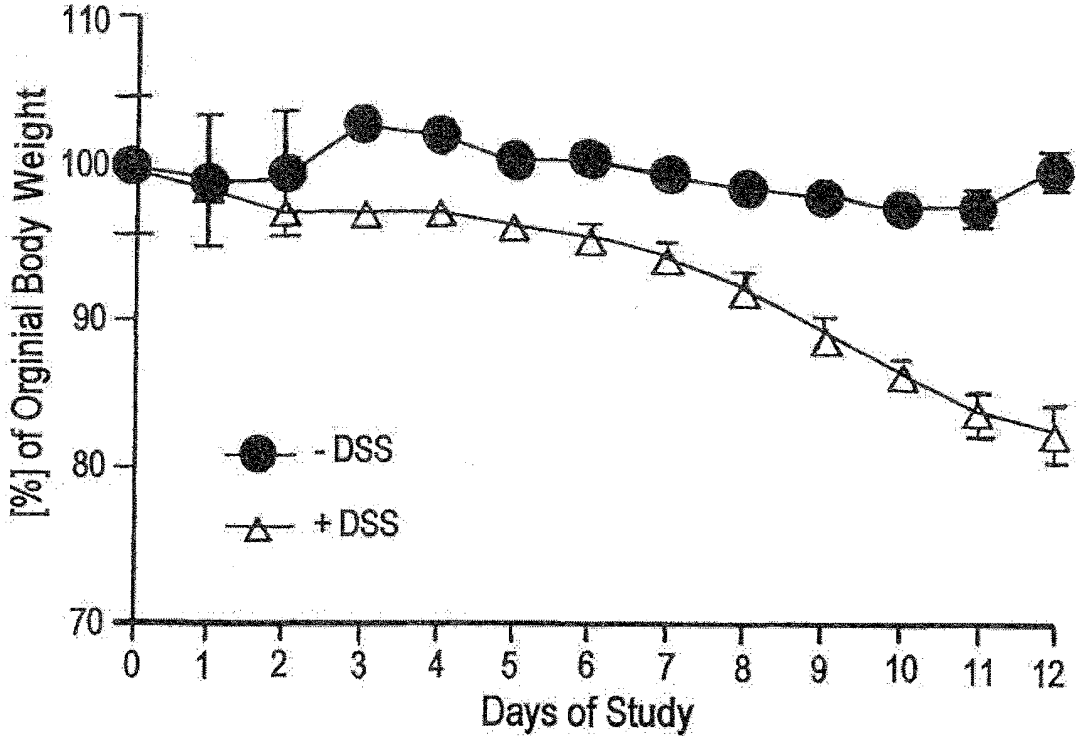

FIG. 10A

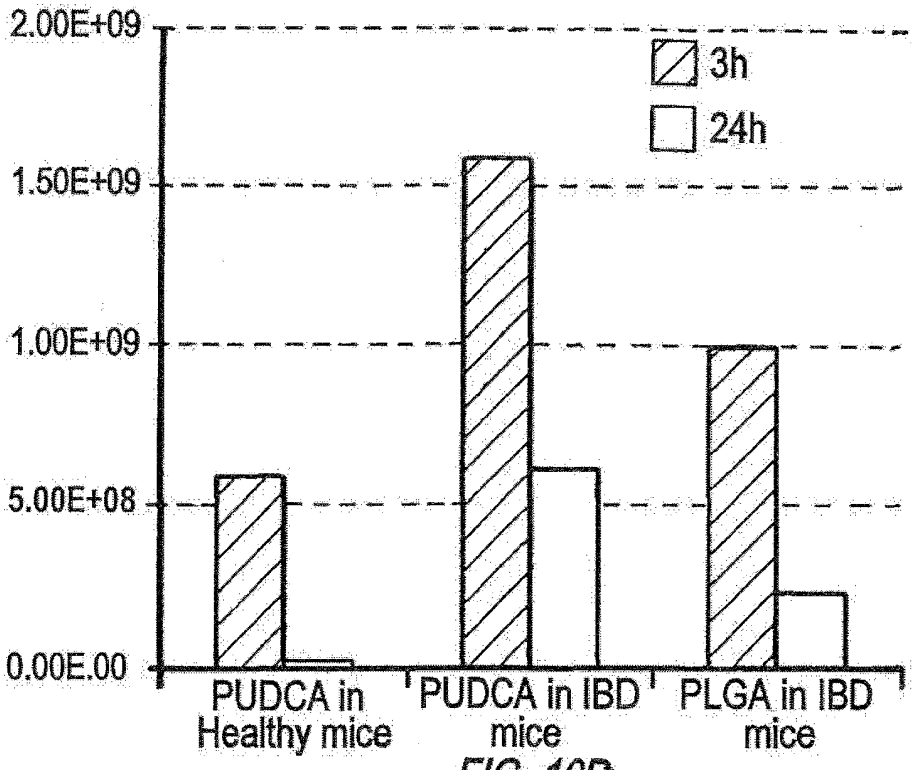

FIG. 10B