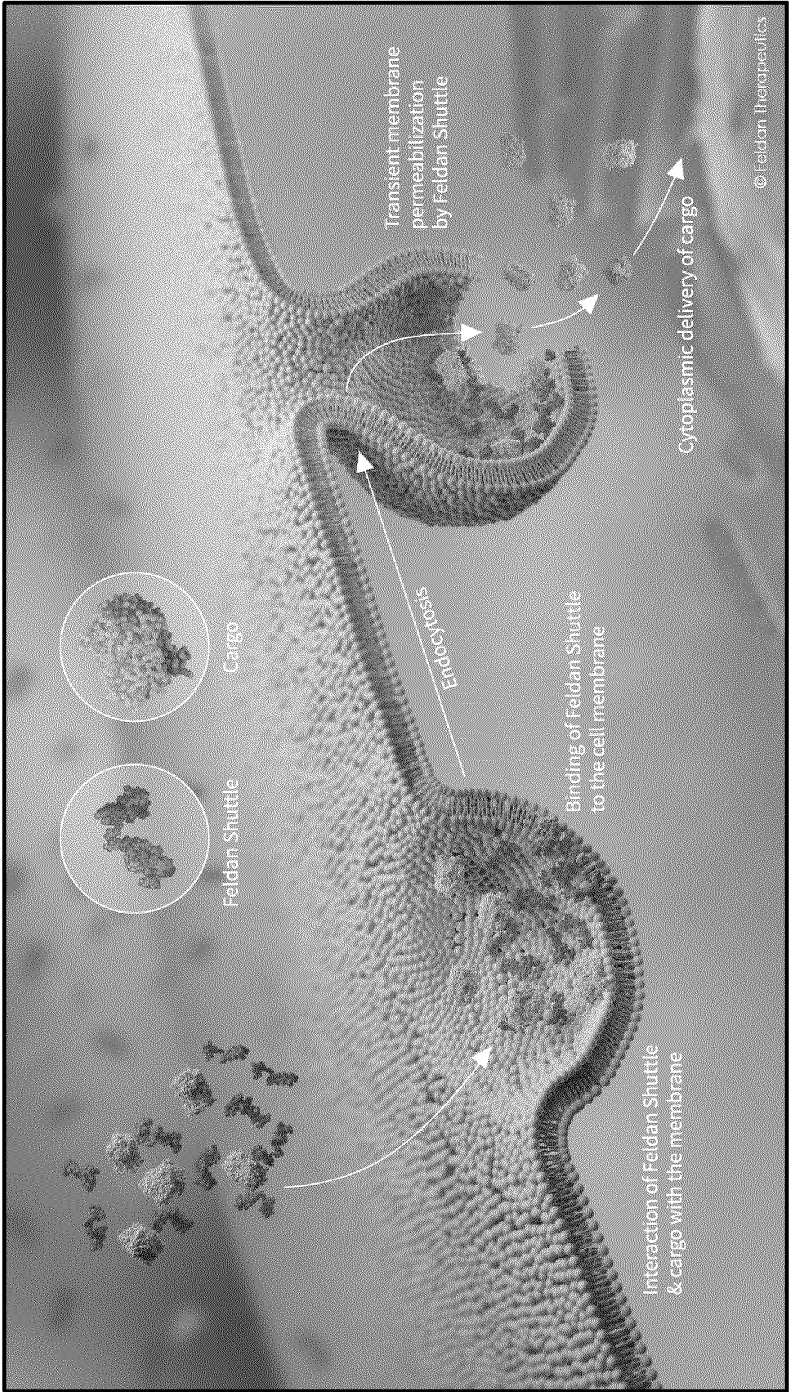


Fig. 1



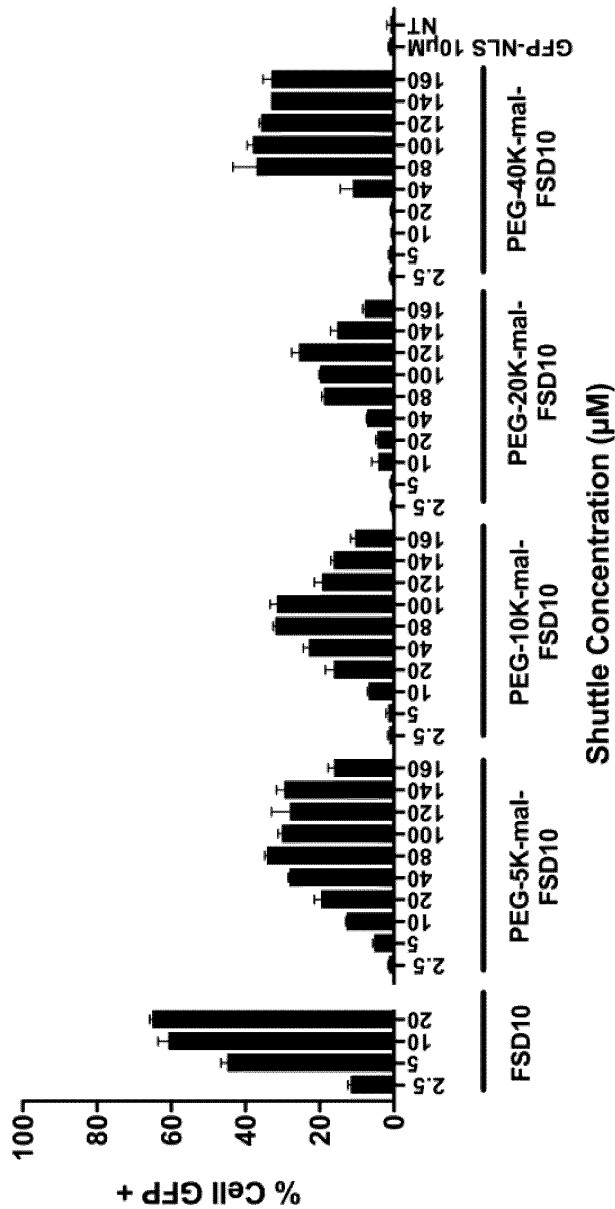


Fig. 2A

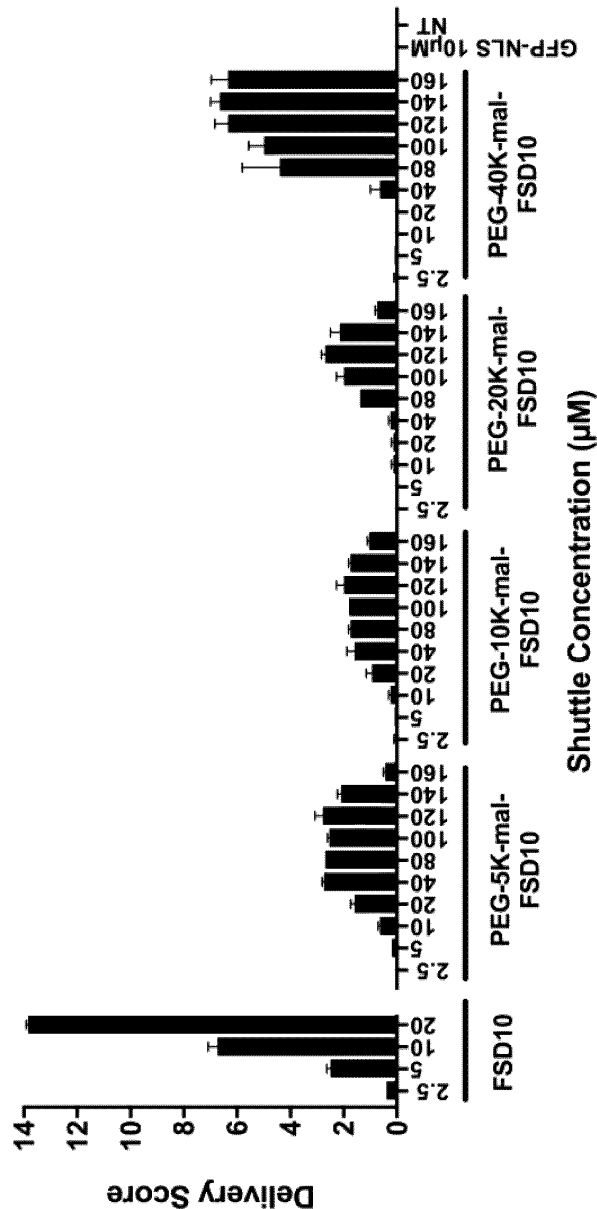


Fig. 2B

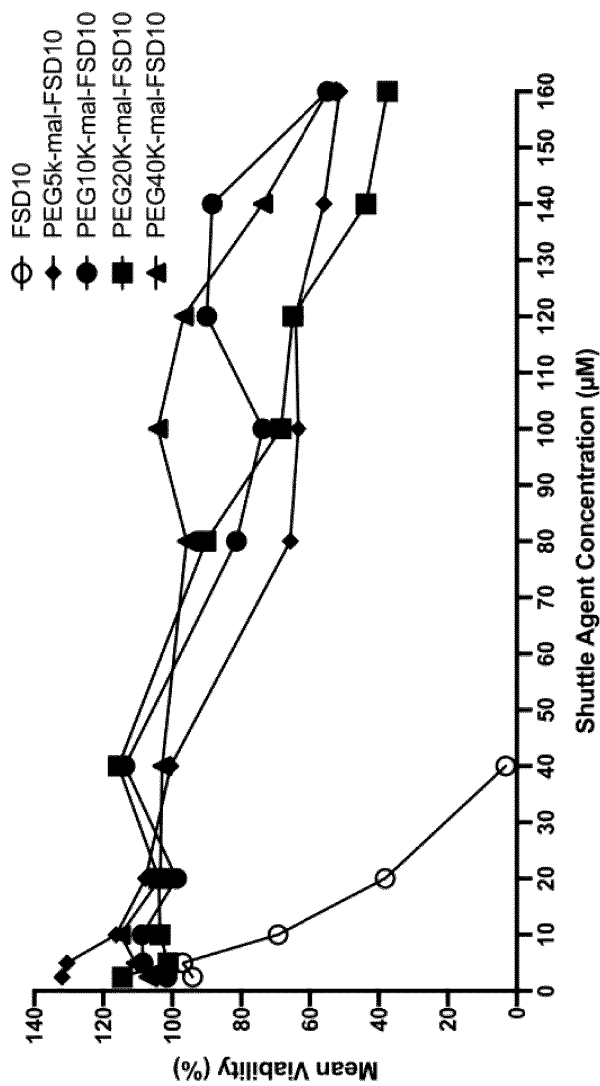


Fig. 3A

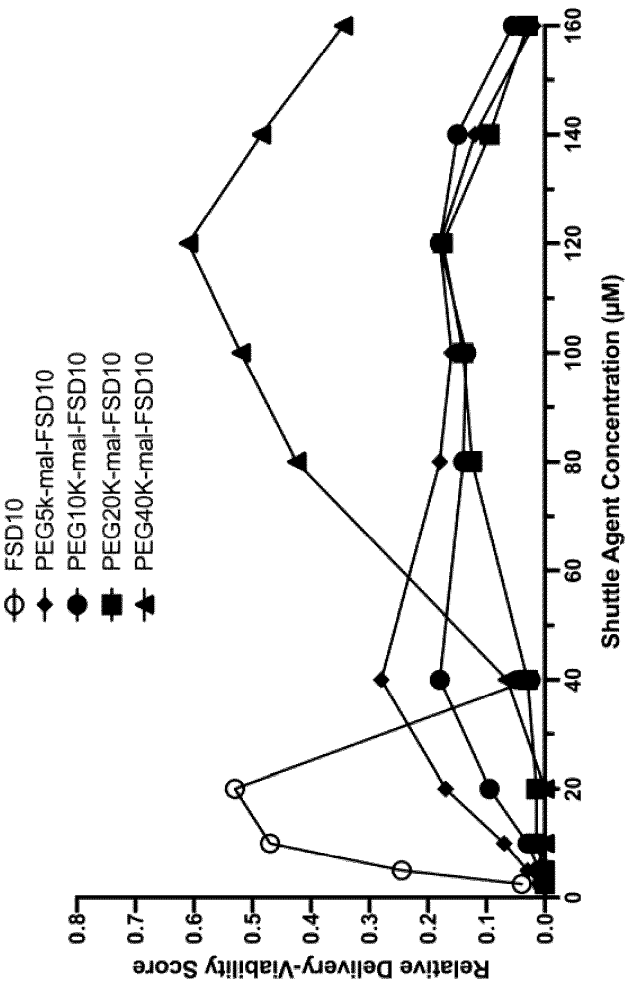


Fig. 3B

Fig. 4

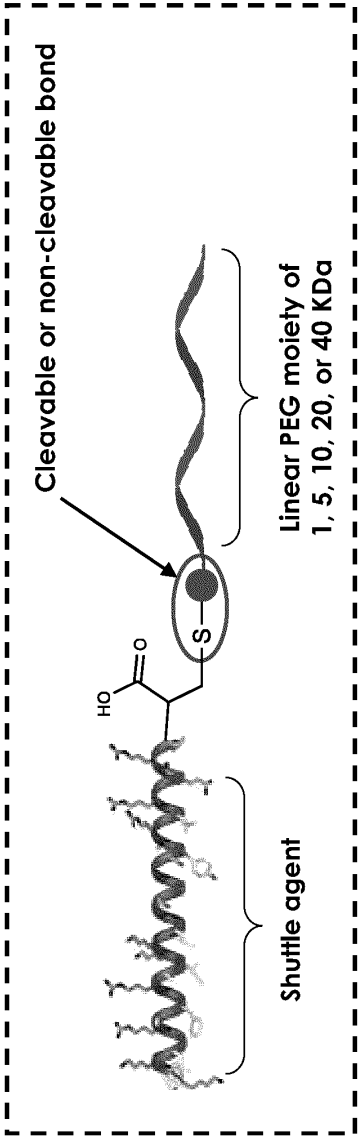


Fig. 5

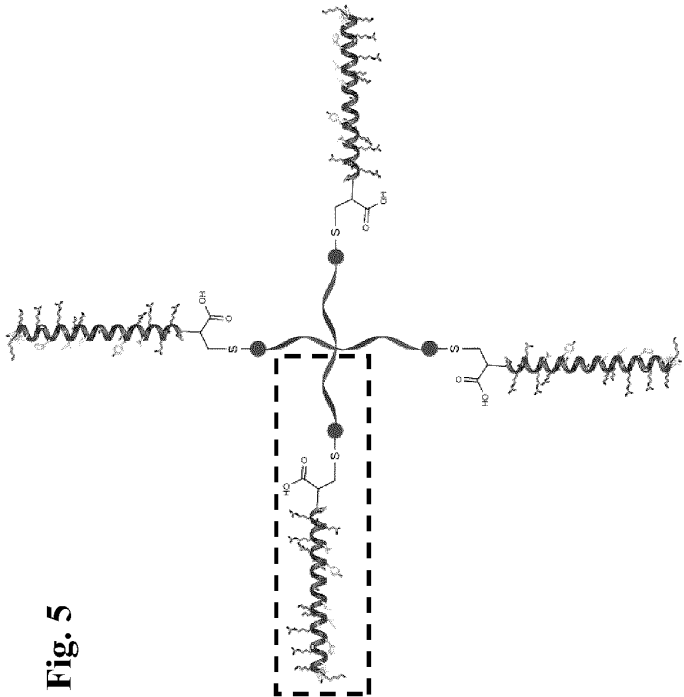
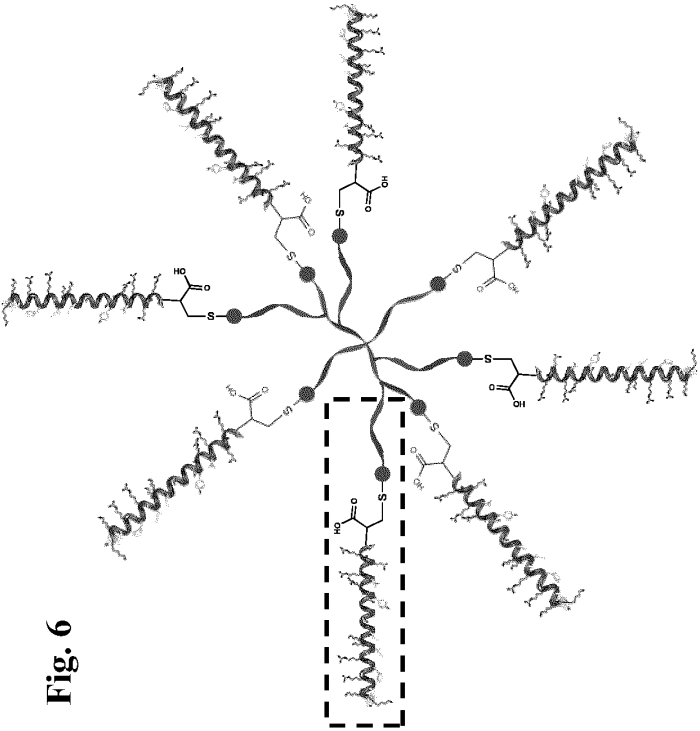


Fig. 6



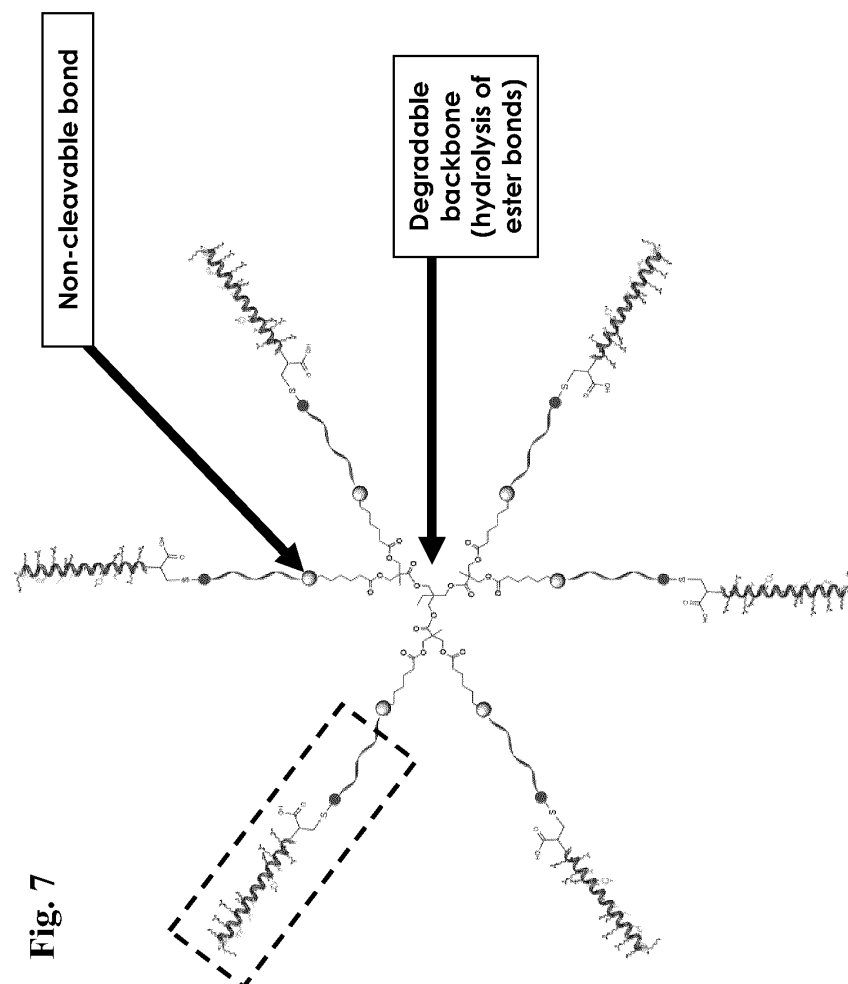


Fig. 7

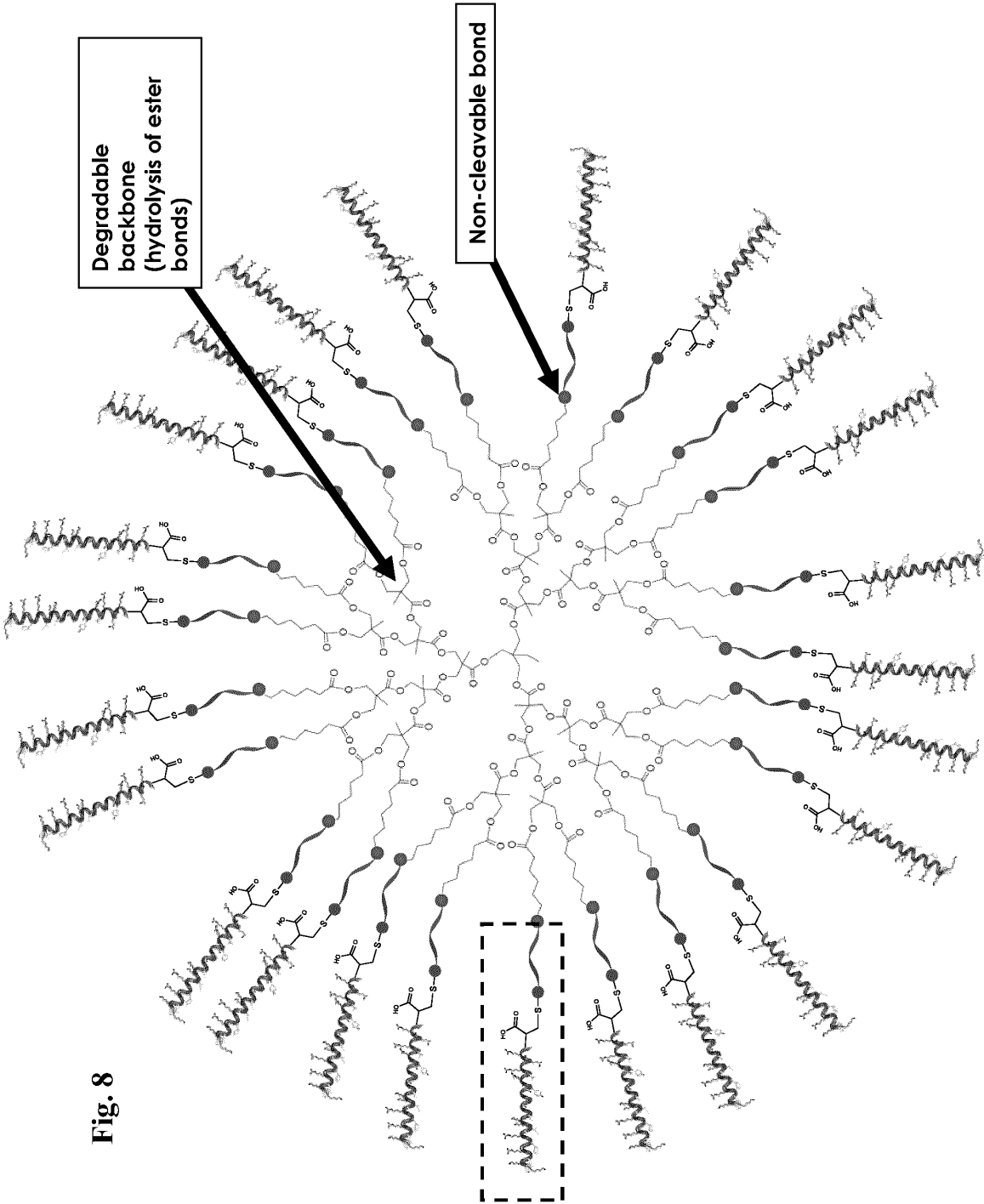


Fig. 8

Fig. 9

FSD10-mal-PEG5K

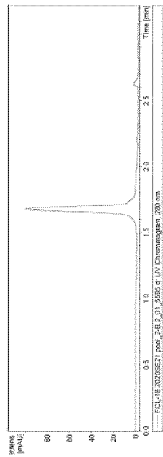


Fig. 13

FSD10-SS-PEG40K

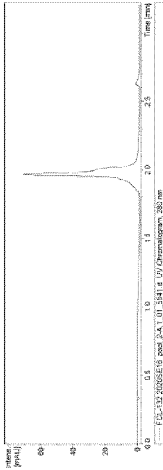


Fig. 10

FSD10-SS-PEG10K

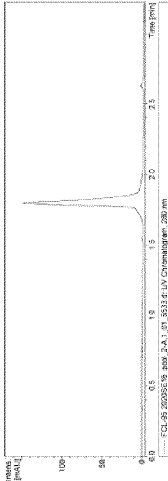


Fig. 14

[FSD10-mal-PEG1K-]₁₂₄(Polyester)

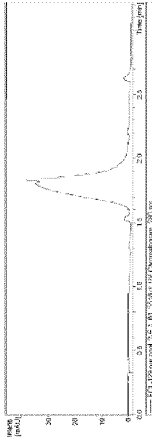


Fig. 11

FSD10-SS-PEG20K

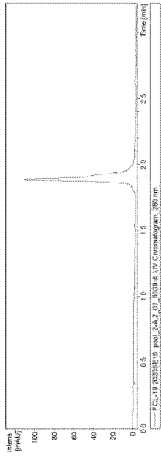


Fig. 15

[FSD10-mal-PEG1K-]₆(Polyester)

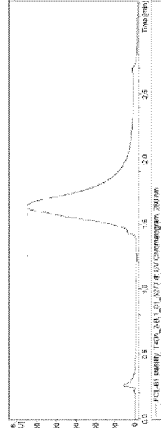
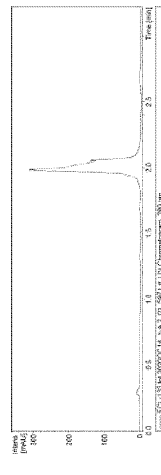
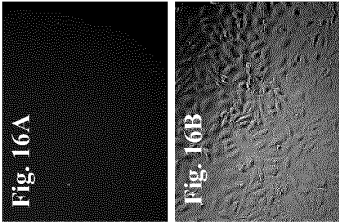


Fig. 12

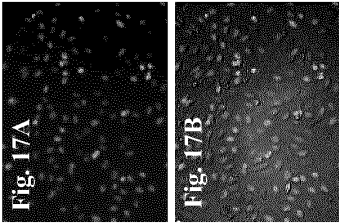
FSD10-mal-PEG40K



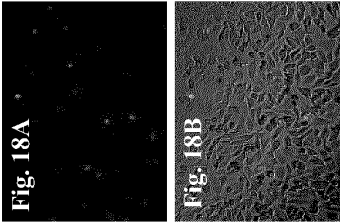
GFP-NLS alone



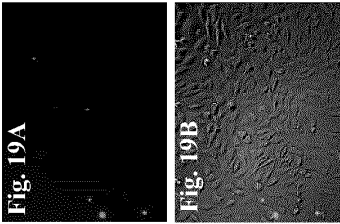
FSD10



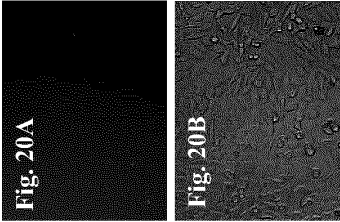
FSD10scr



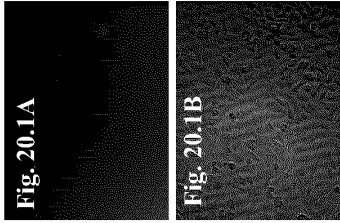
FSD10scr-SS-PEG10K



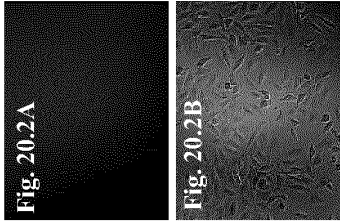
FSD10scr-SS-PEG20K



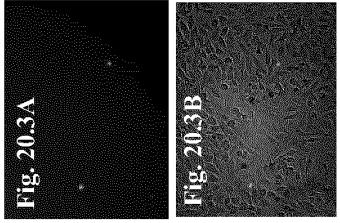
TAT



TAT-SS-PEG10K



PEG10K-SS-TAT



FSD10-Mal-PEG10K



Fig. 24A



Fig. 24B

FSD10-SS-PEG10K



Fig. 23A

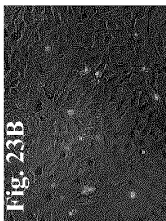


Fig. 23B

FSD10-mal-PEG40K

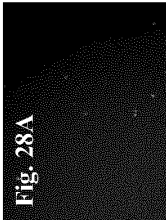


Fig. 28A

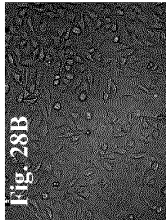


Fig. 28B

FSD10-SS-PEG40K

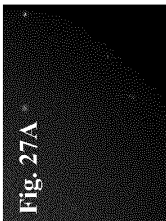


Fig. 27A



Fig. 27B

FSD10-Mal-PEG5K



Fig. 22A

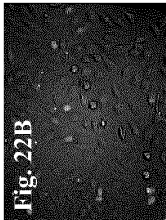


Fig. 22B

FSD10-mal-PEG20K

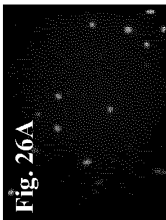


Fig. 26A

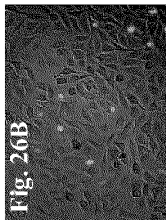


Fig. 26B

FSD10-SS-PEG5K

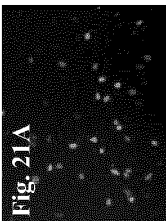


Fig. 21A

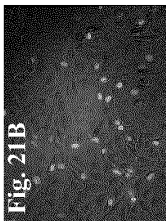


Fig. 21B

FSD10-SS-PEG20K



Fig. 25A

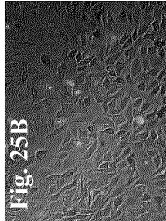
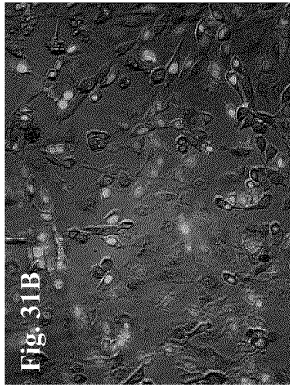
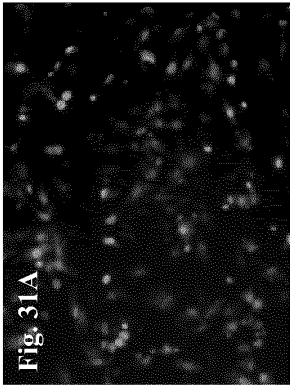
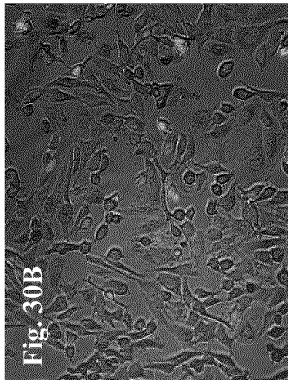
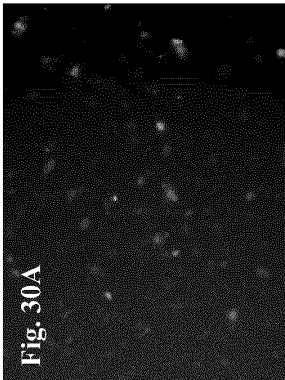


Fig. 25B

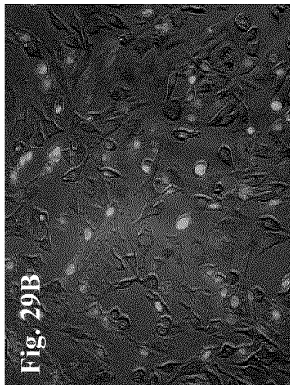
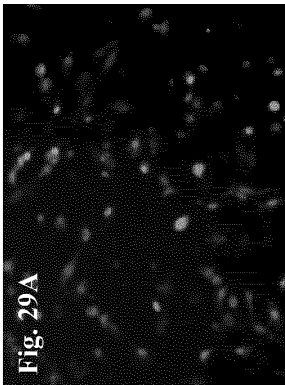
[FSD10-SS-1₈(PEG20K)
(20 μM)



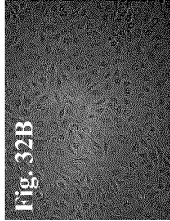
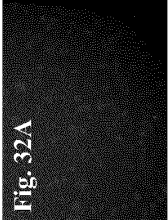
[FSD10-SS-1₈(PEG20K)
(10 μM)



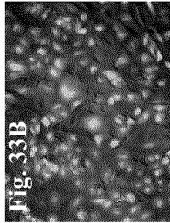
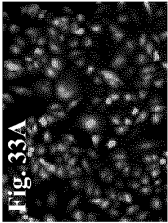
[FSD10-SS-1₄(PEG20K)
(10 μM)



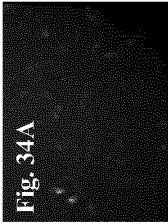
DRI-NLS⁶⁴⁷ alone



FSD10



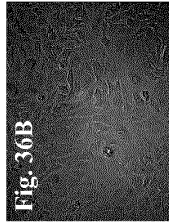
FSD10scr

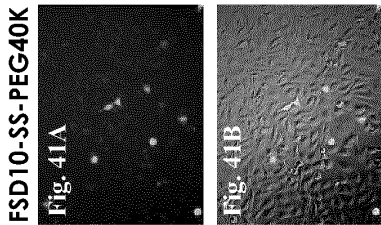
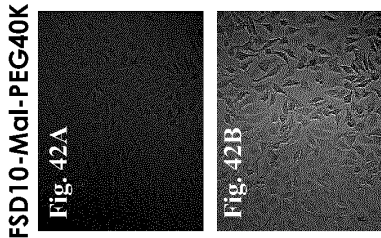
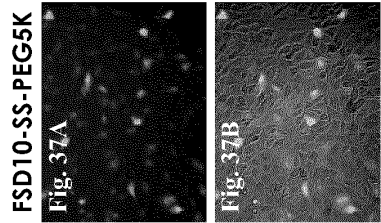
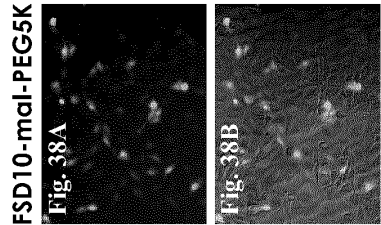
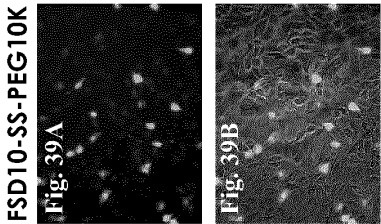
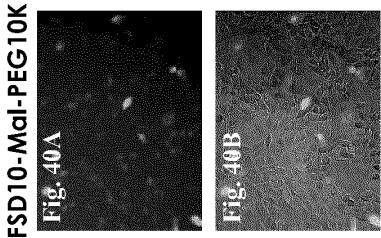


FSD10scr-SS-PEG10K

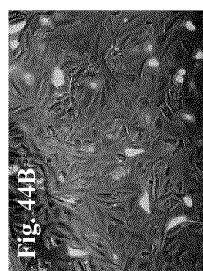
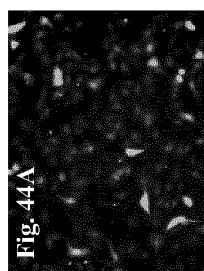


FSD10scr-SS-PEG20K

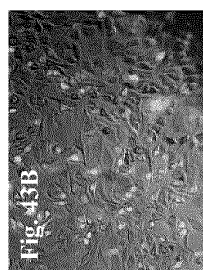
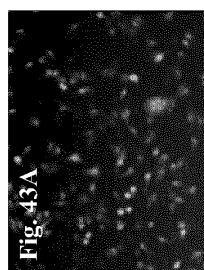




[FSD10-mal-PEG1K]₁₂₄(Polyester)
(140 μM)



[FSD10-mal-PEG1K]₈(Polyester)
(40 μM)



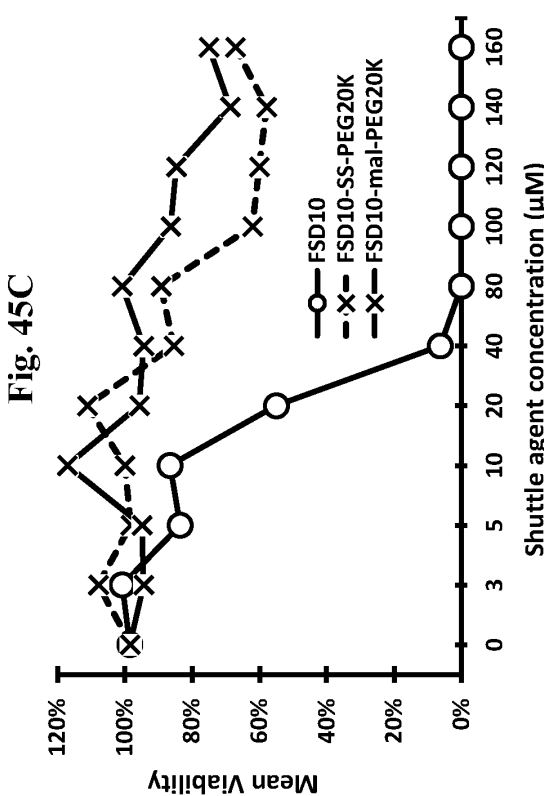
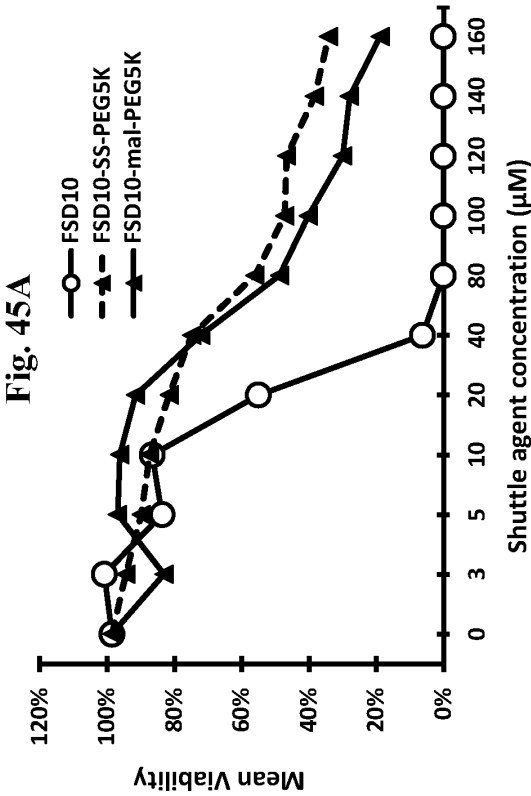
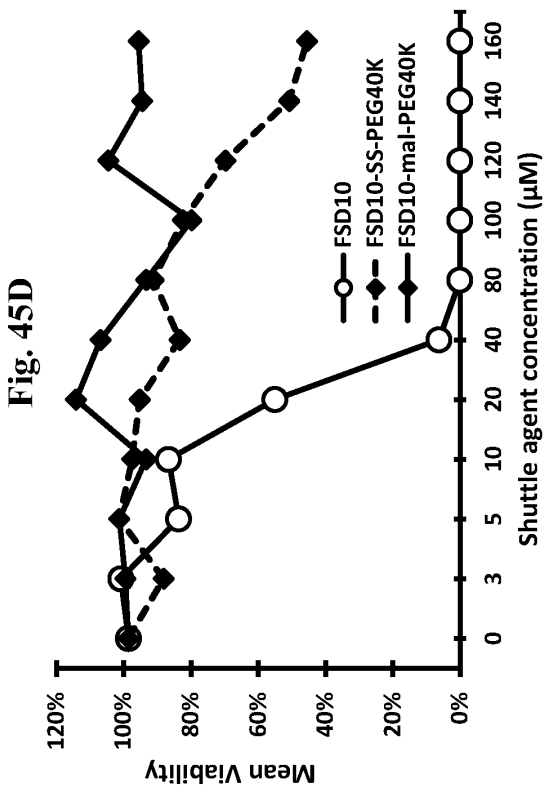
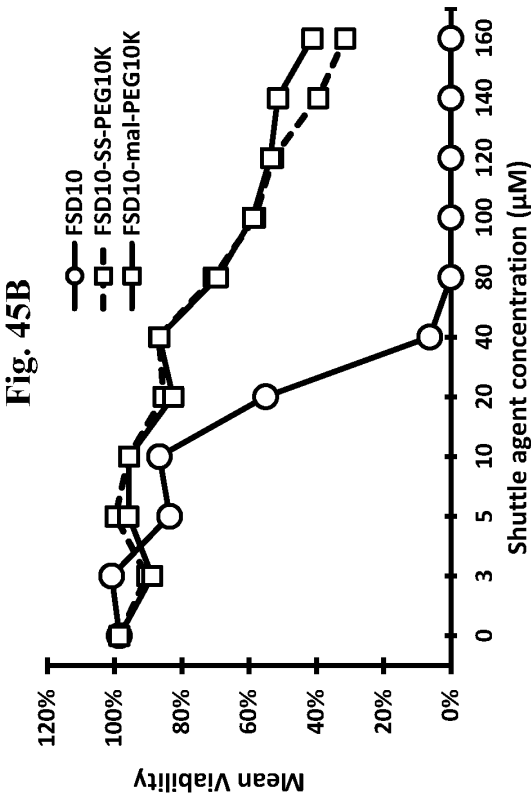


Fig. 45E

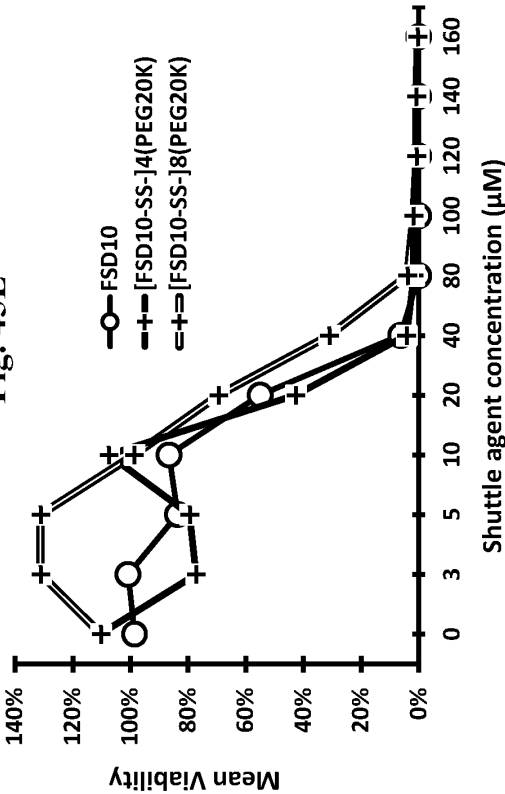
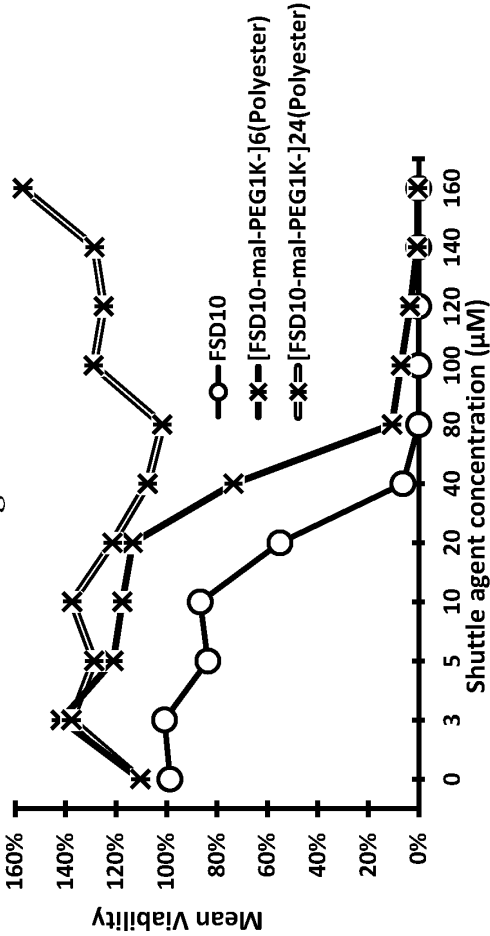
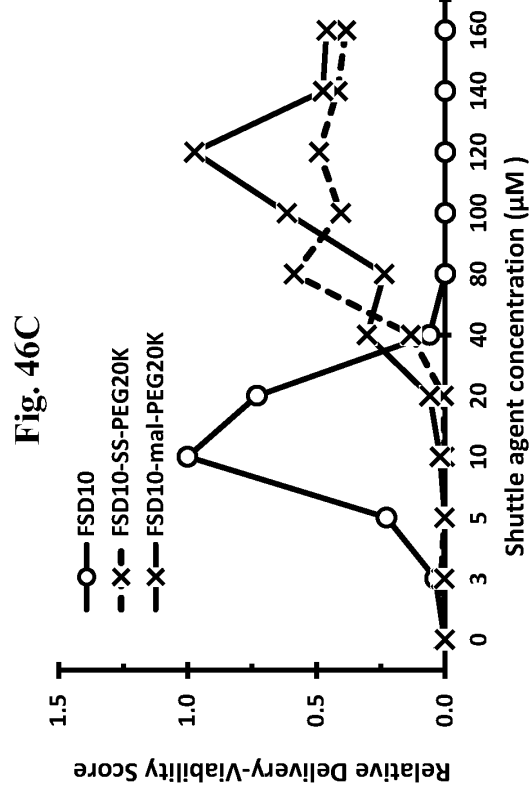
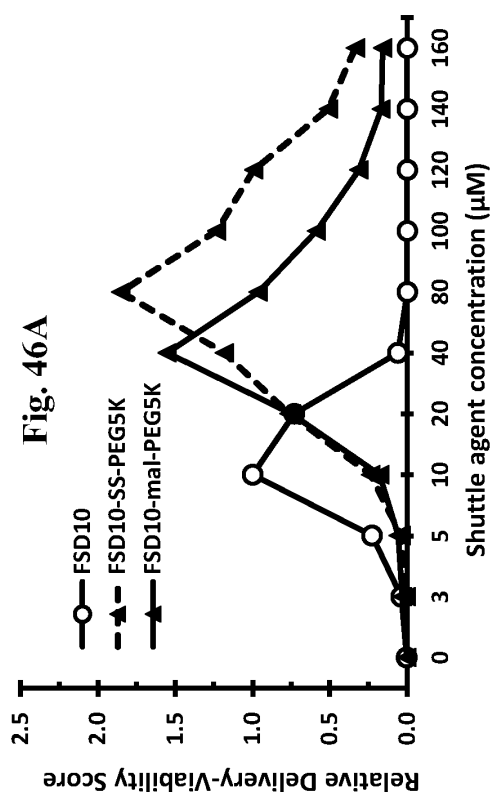
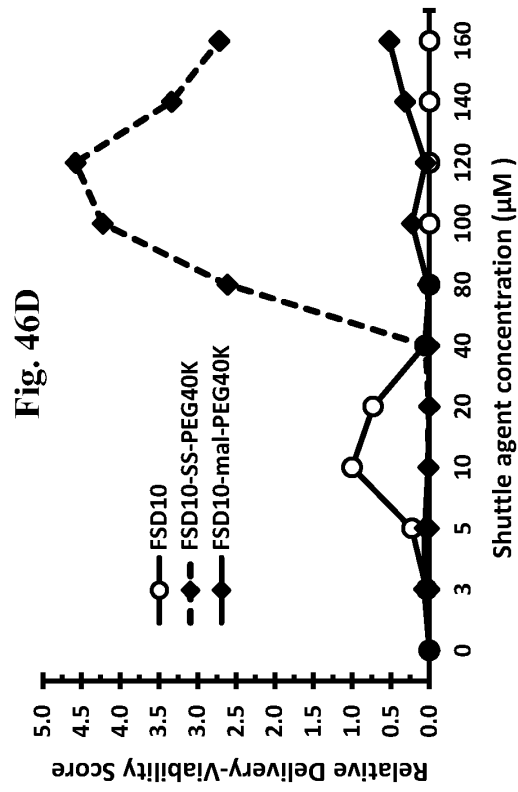
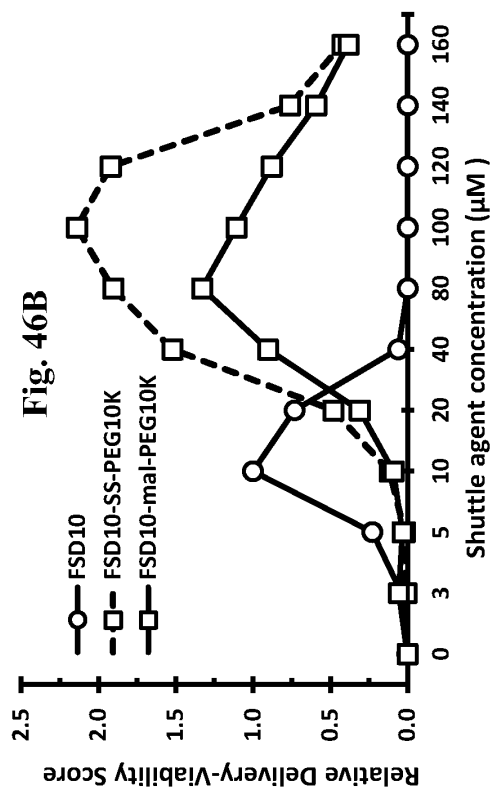


Fig. 45F





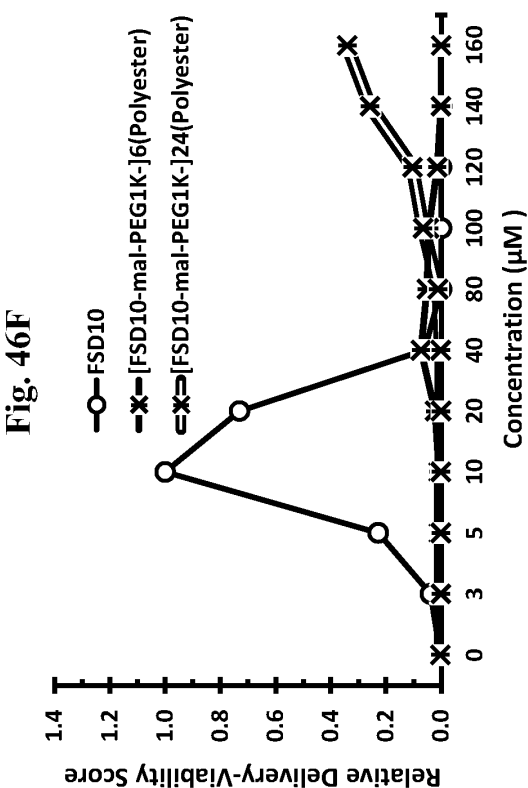
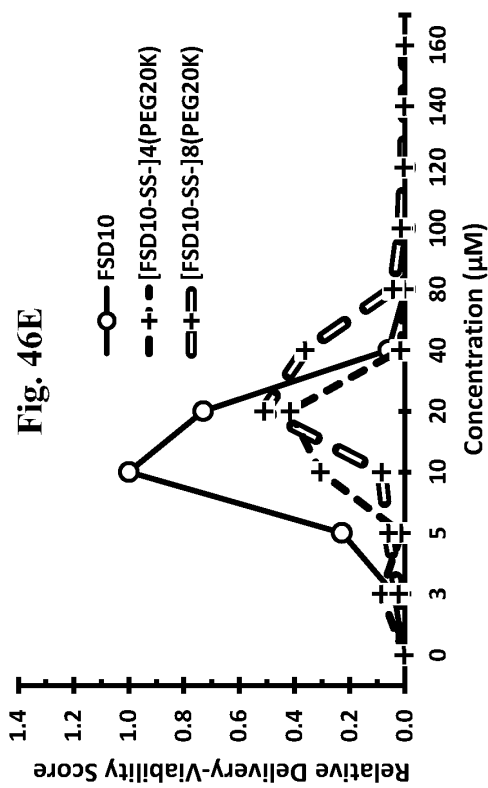


Fig. 47

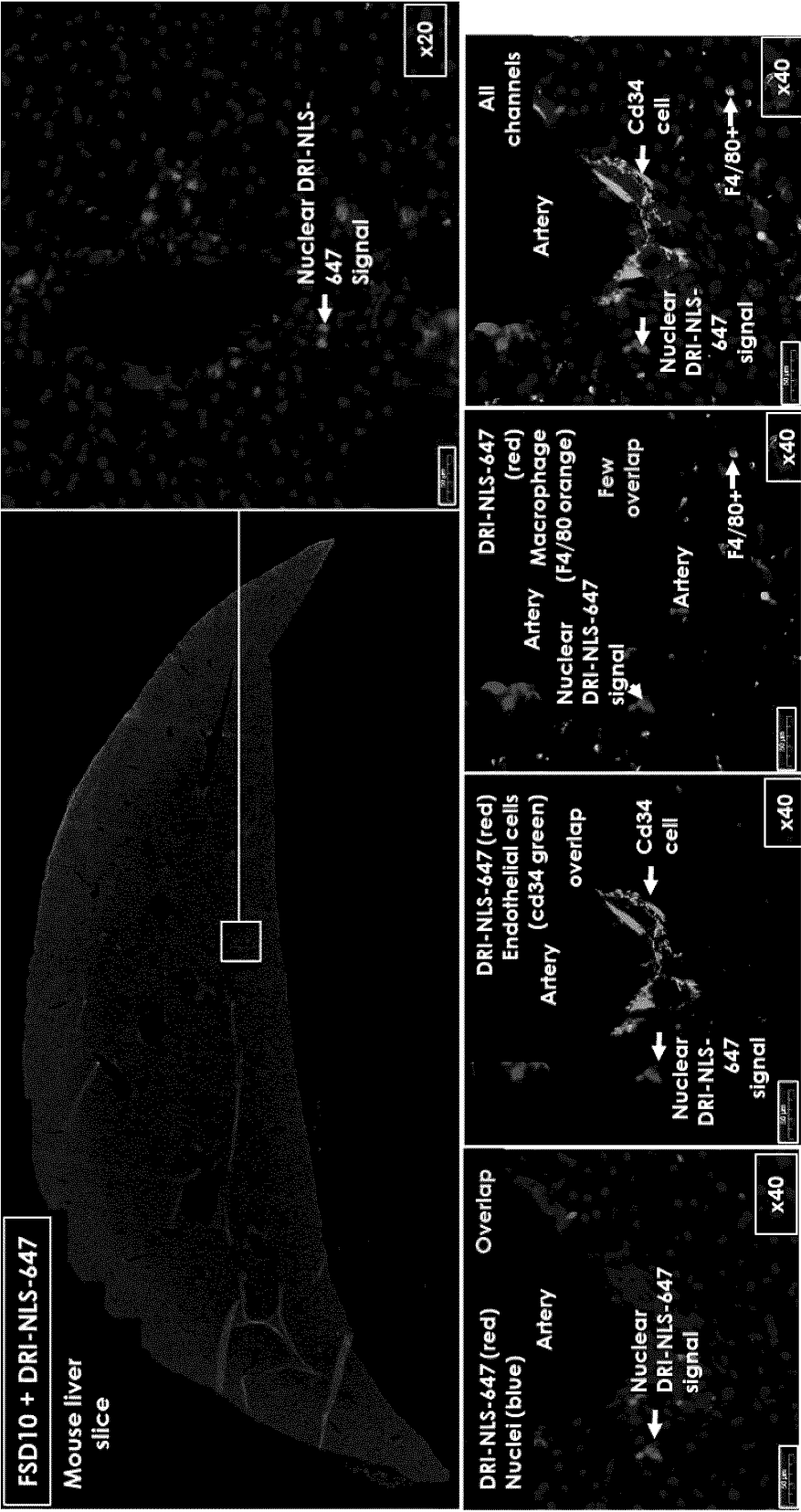


Fig. 48

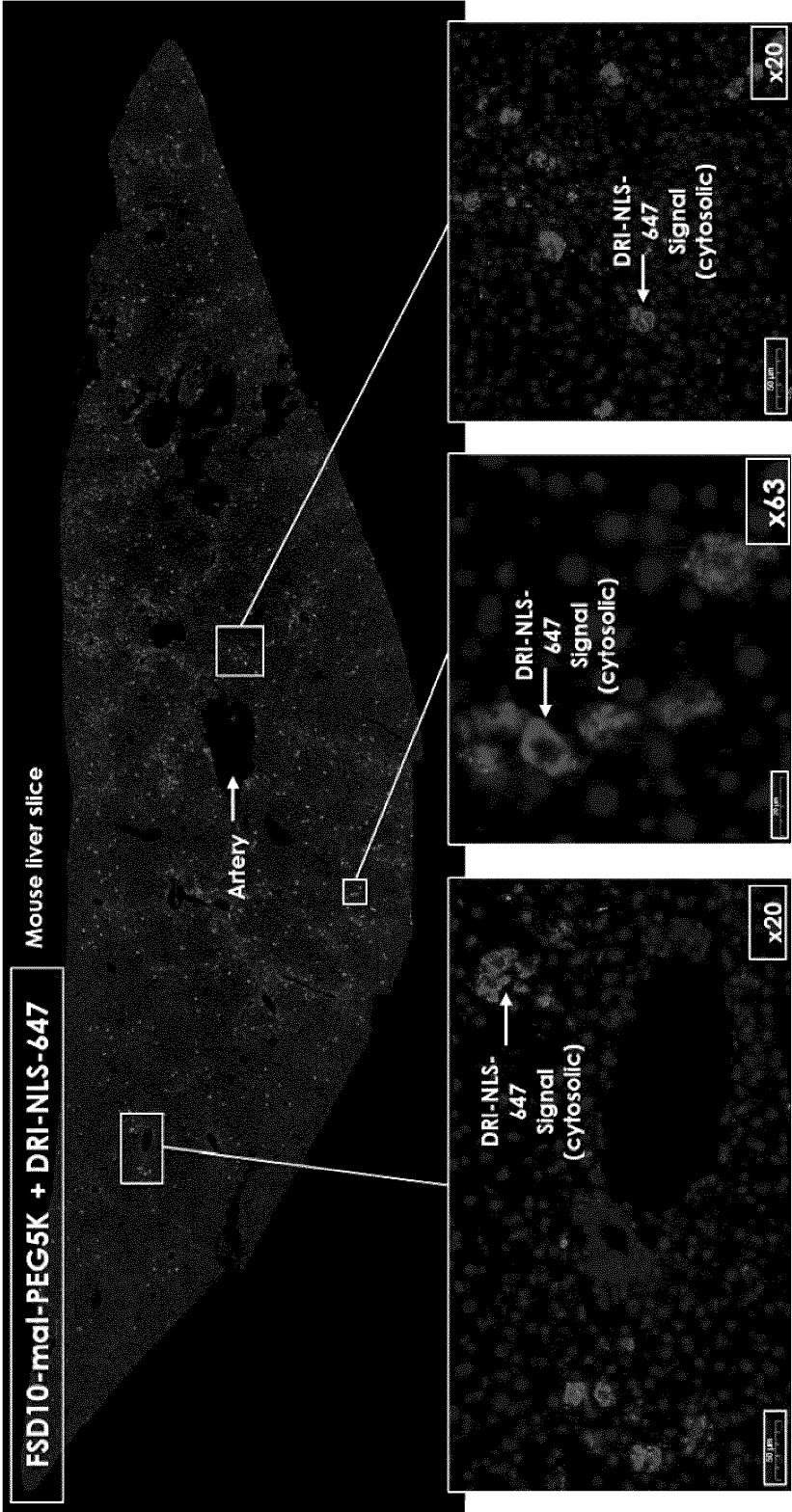


Fig. 49

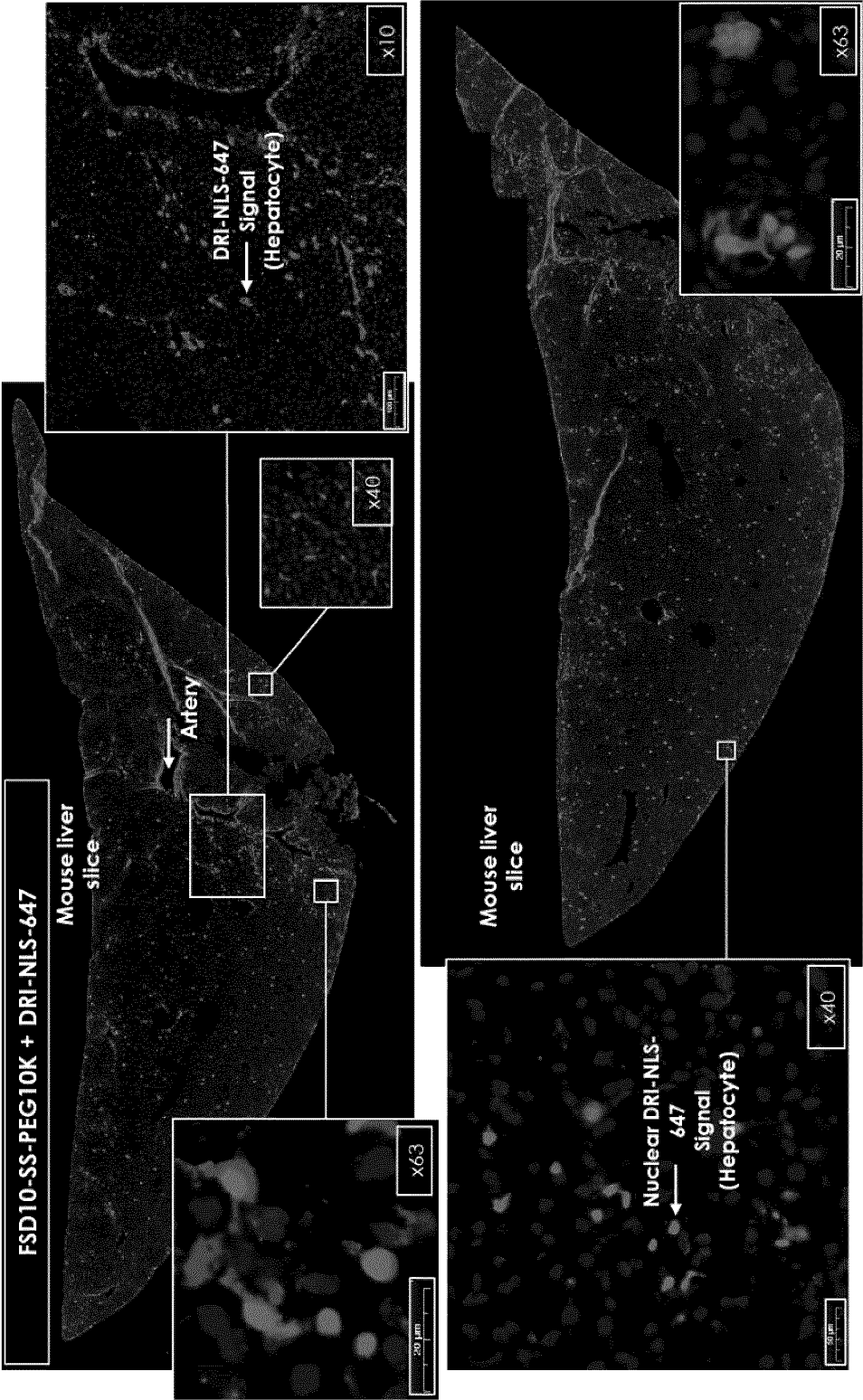


Fig. 50

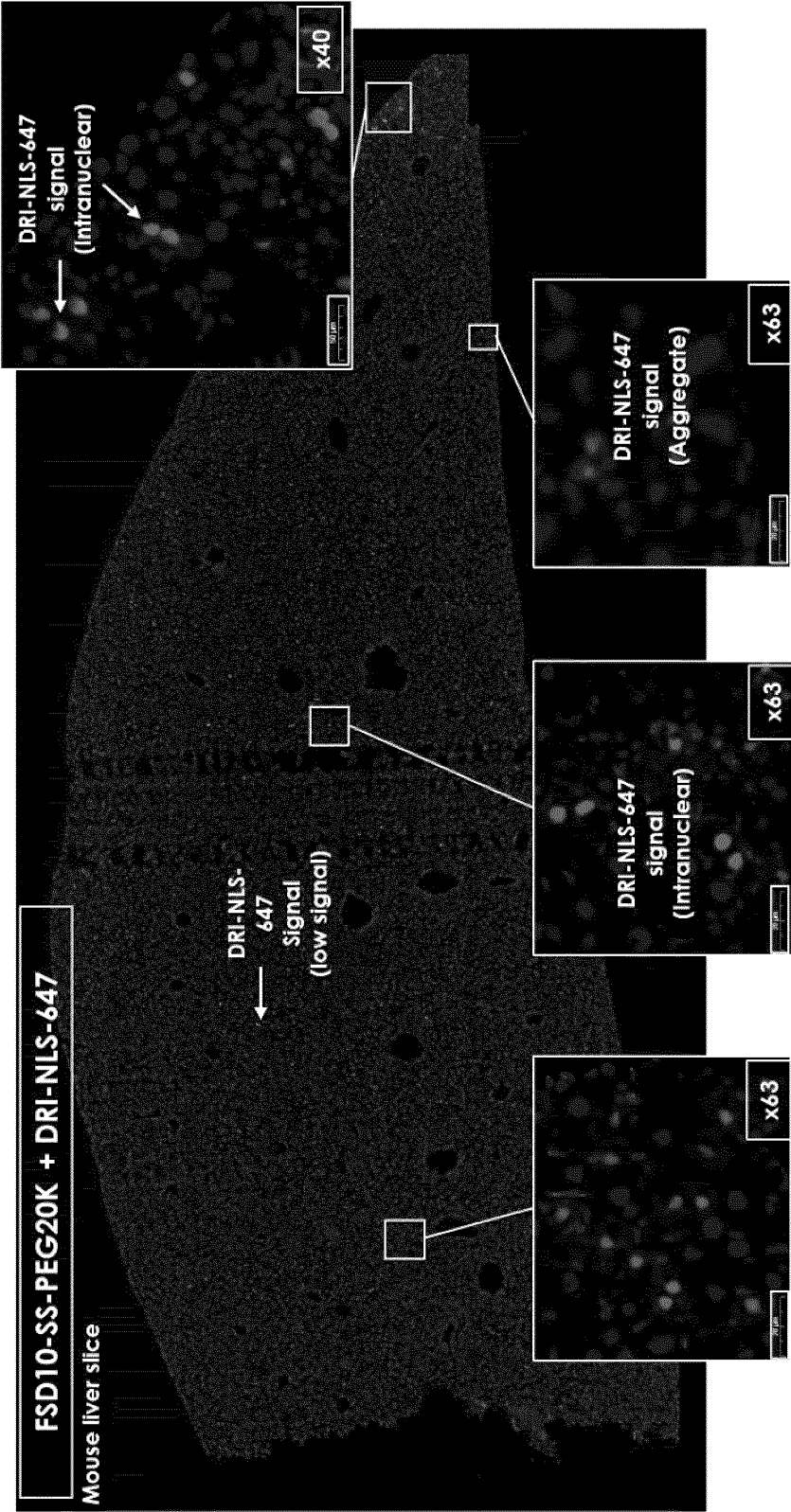


Fig. 51

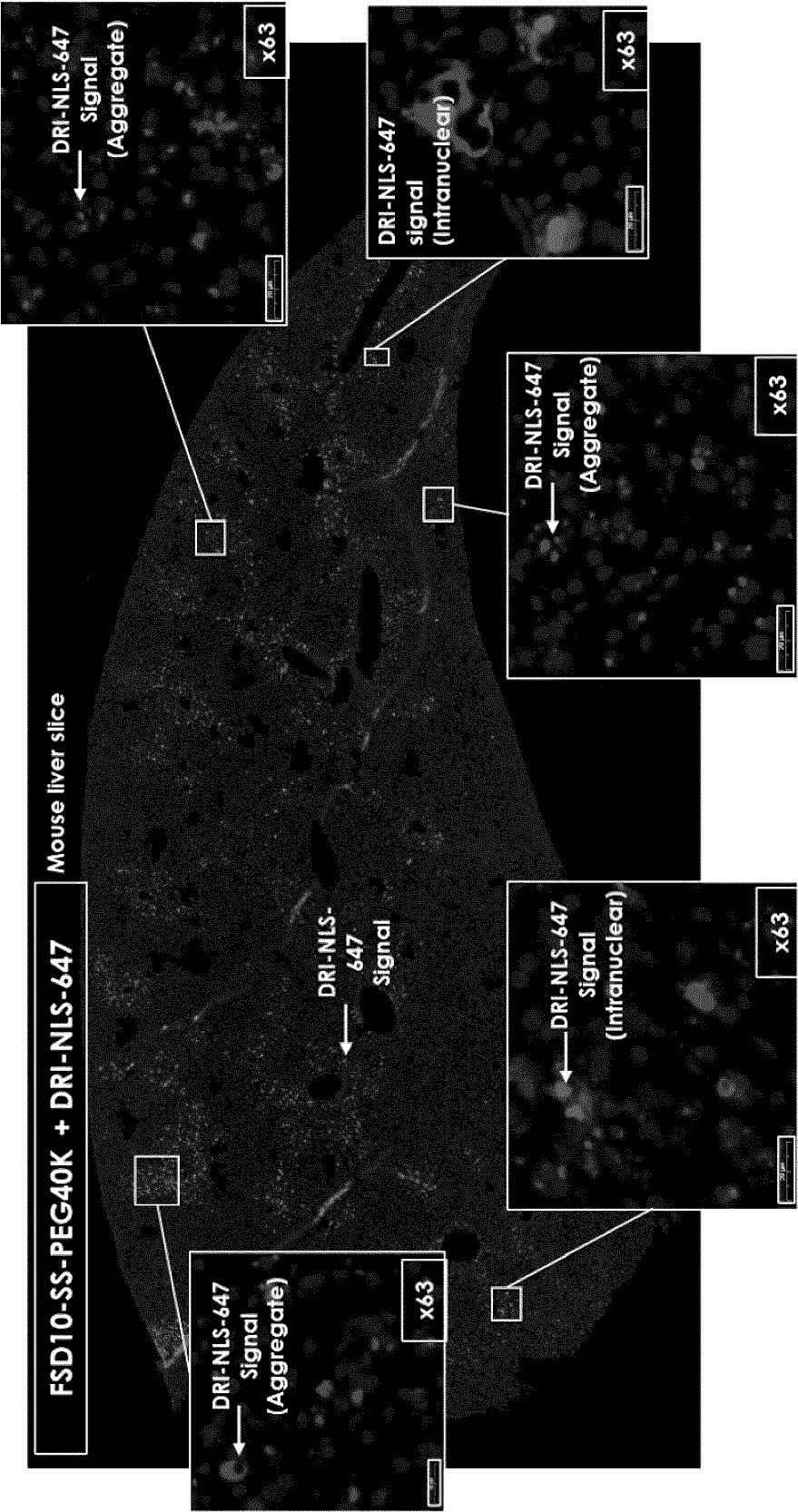


Fig. 52

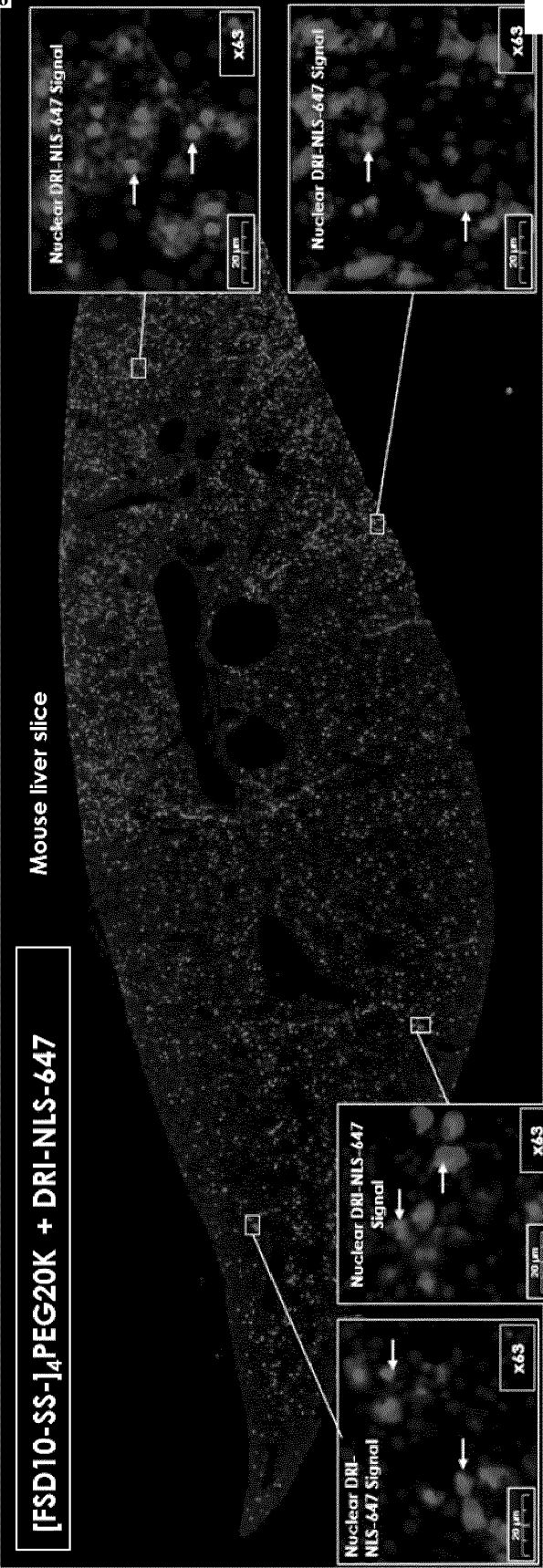


Fig. 53

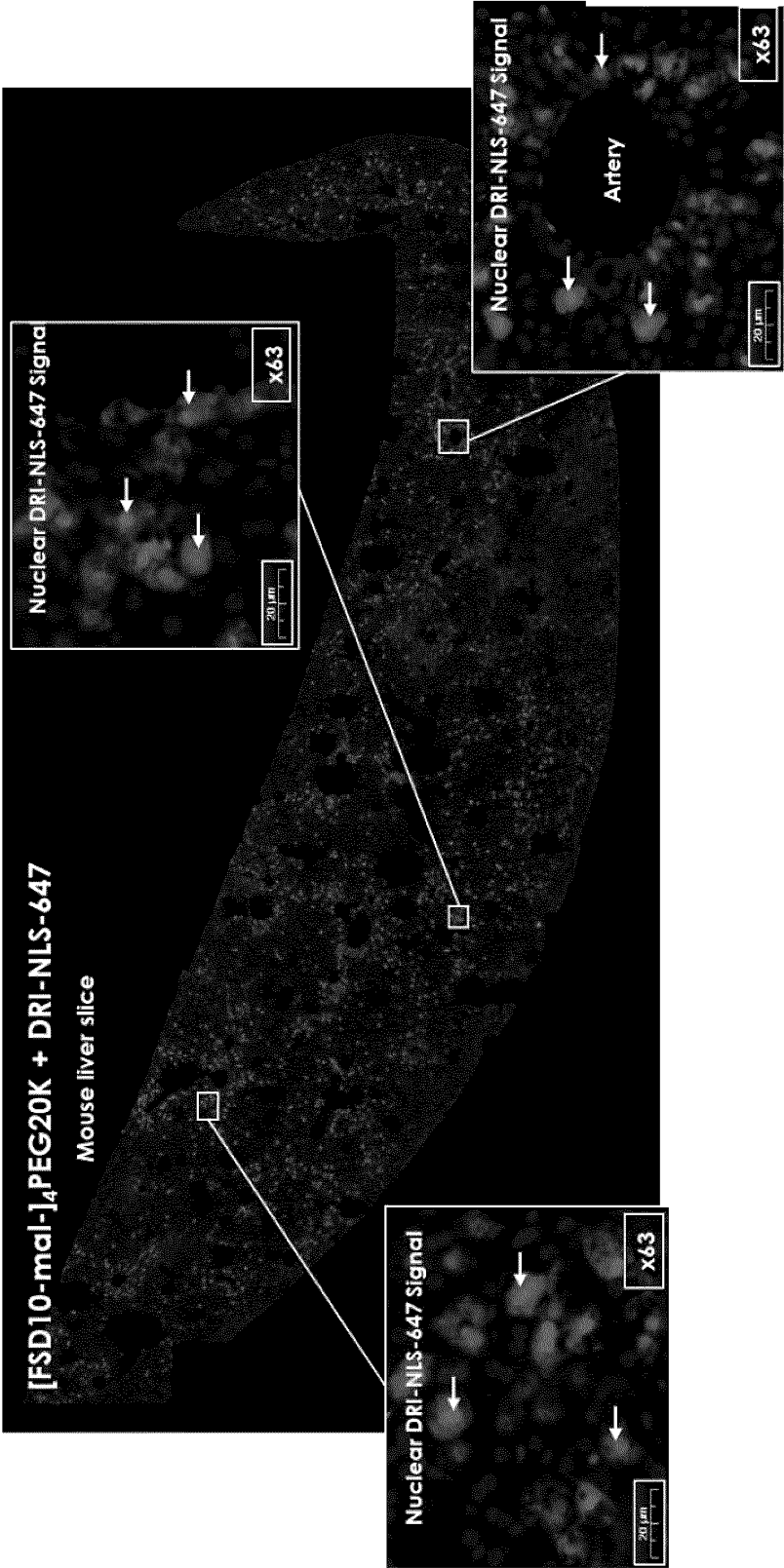


Fig. 54

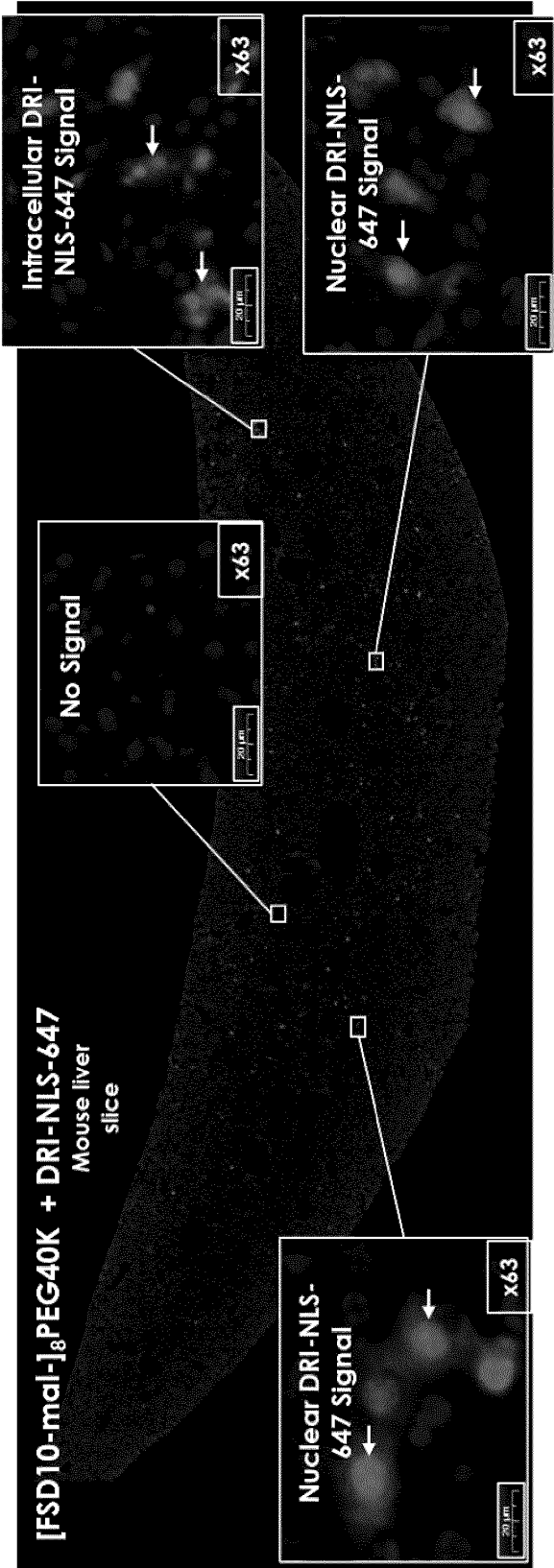


Fig. 55

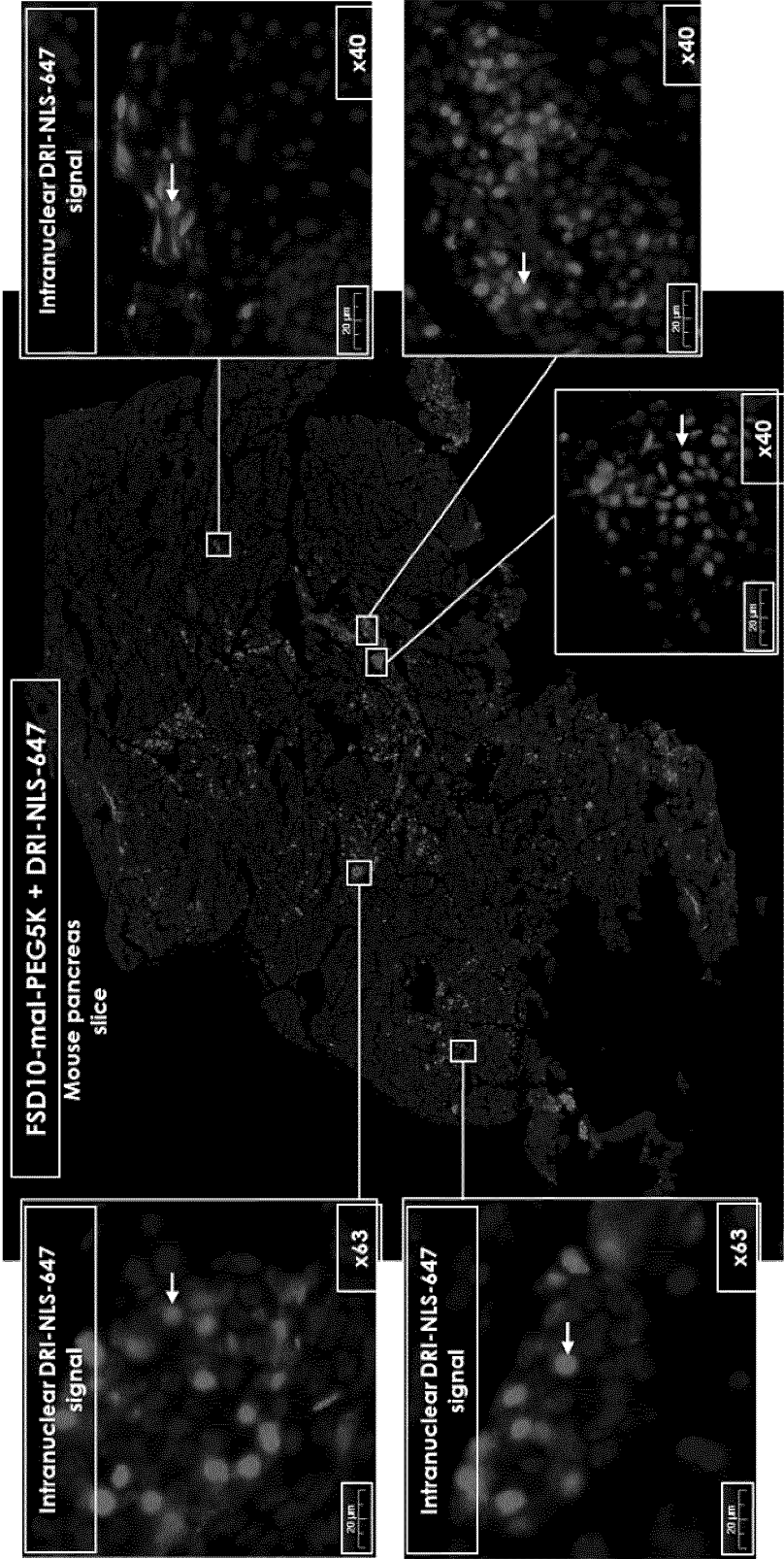


Fig. 56

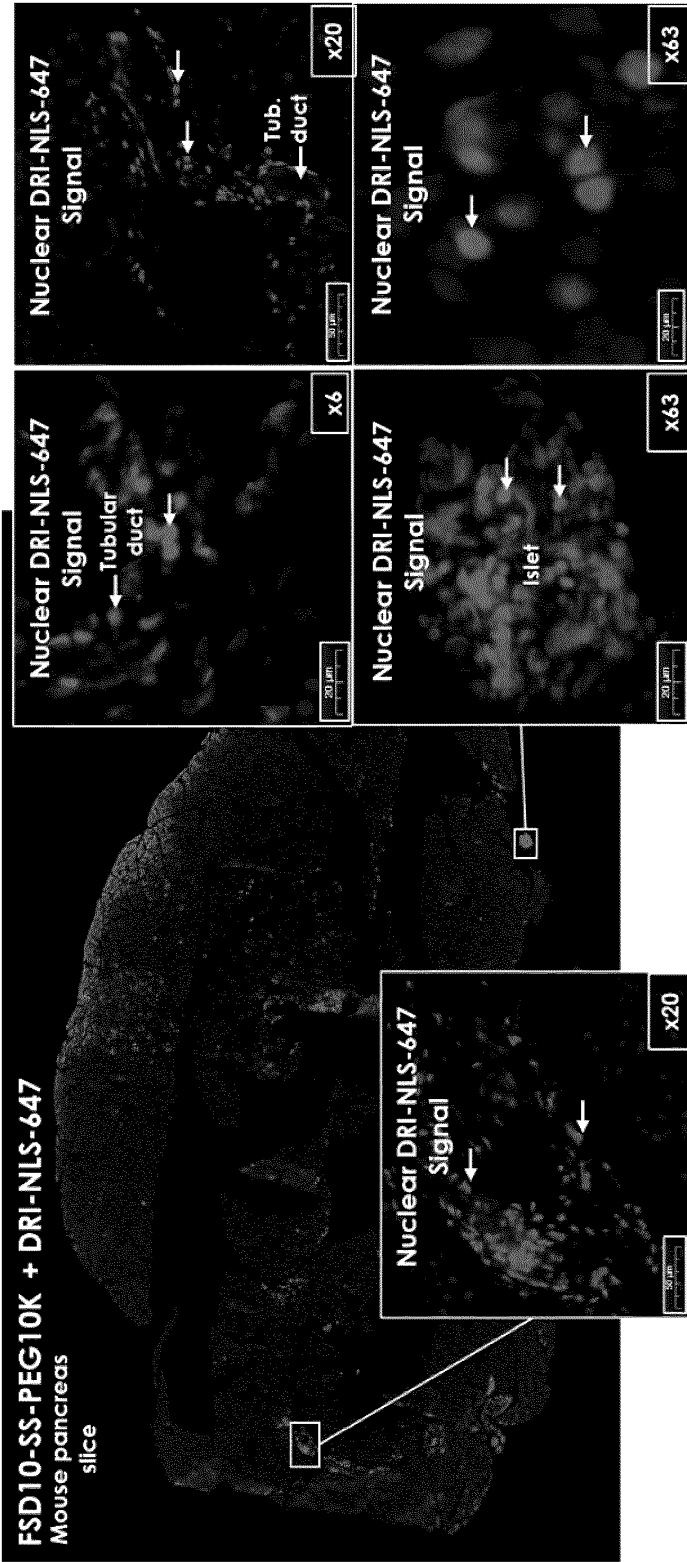


Fig. 57

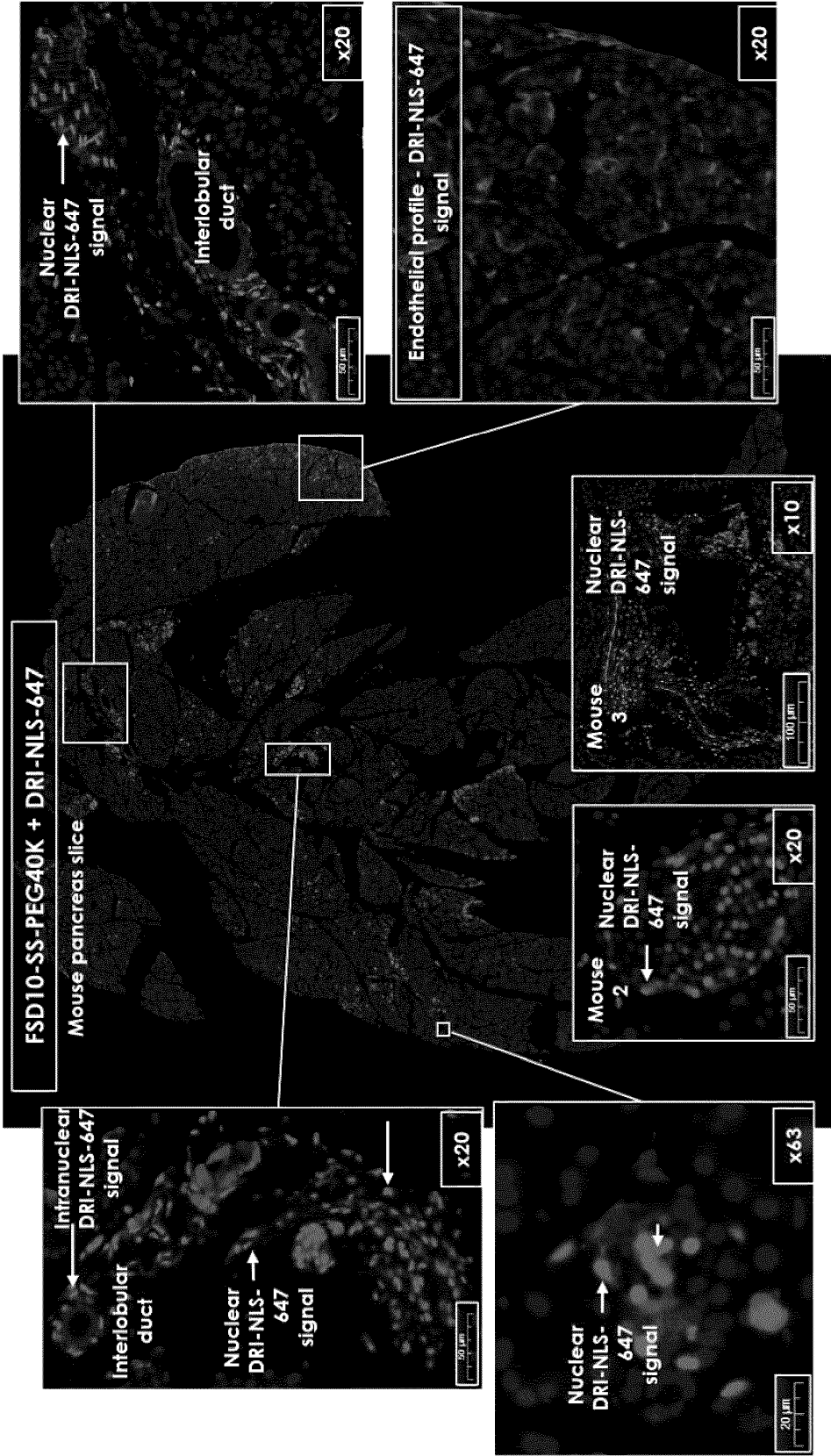
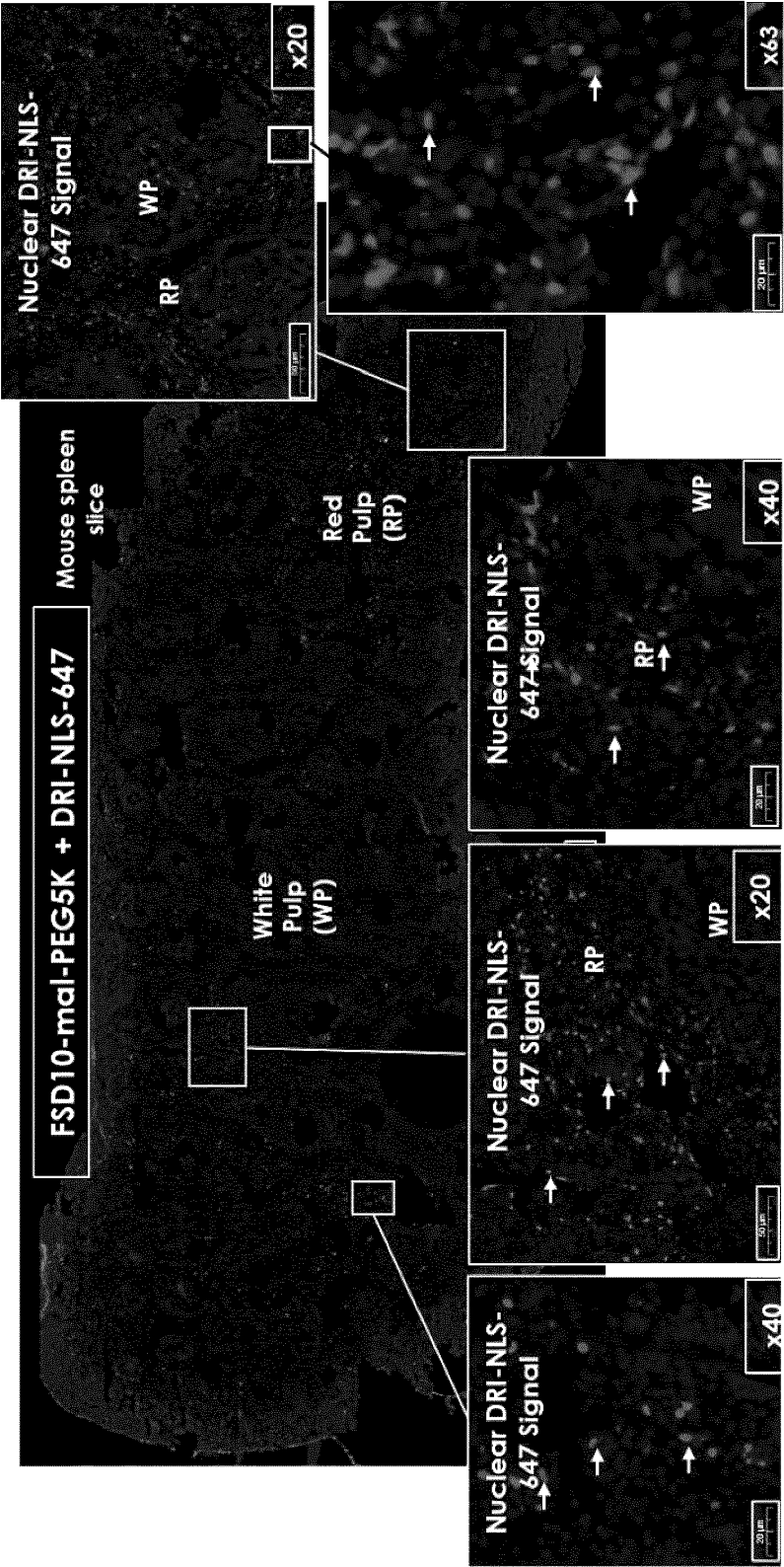


Fig. 58



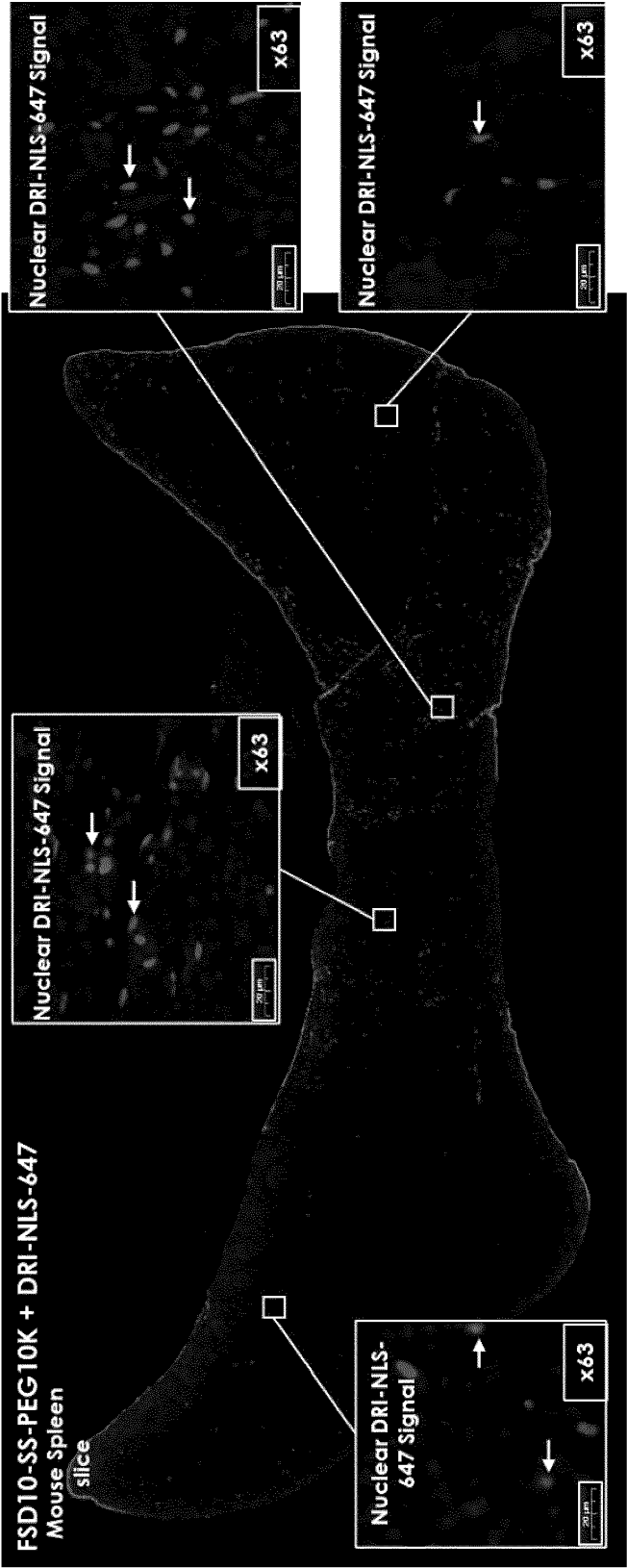


Fig. 59

Fig. 60

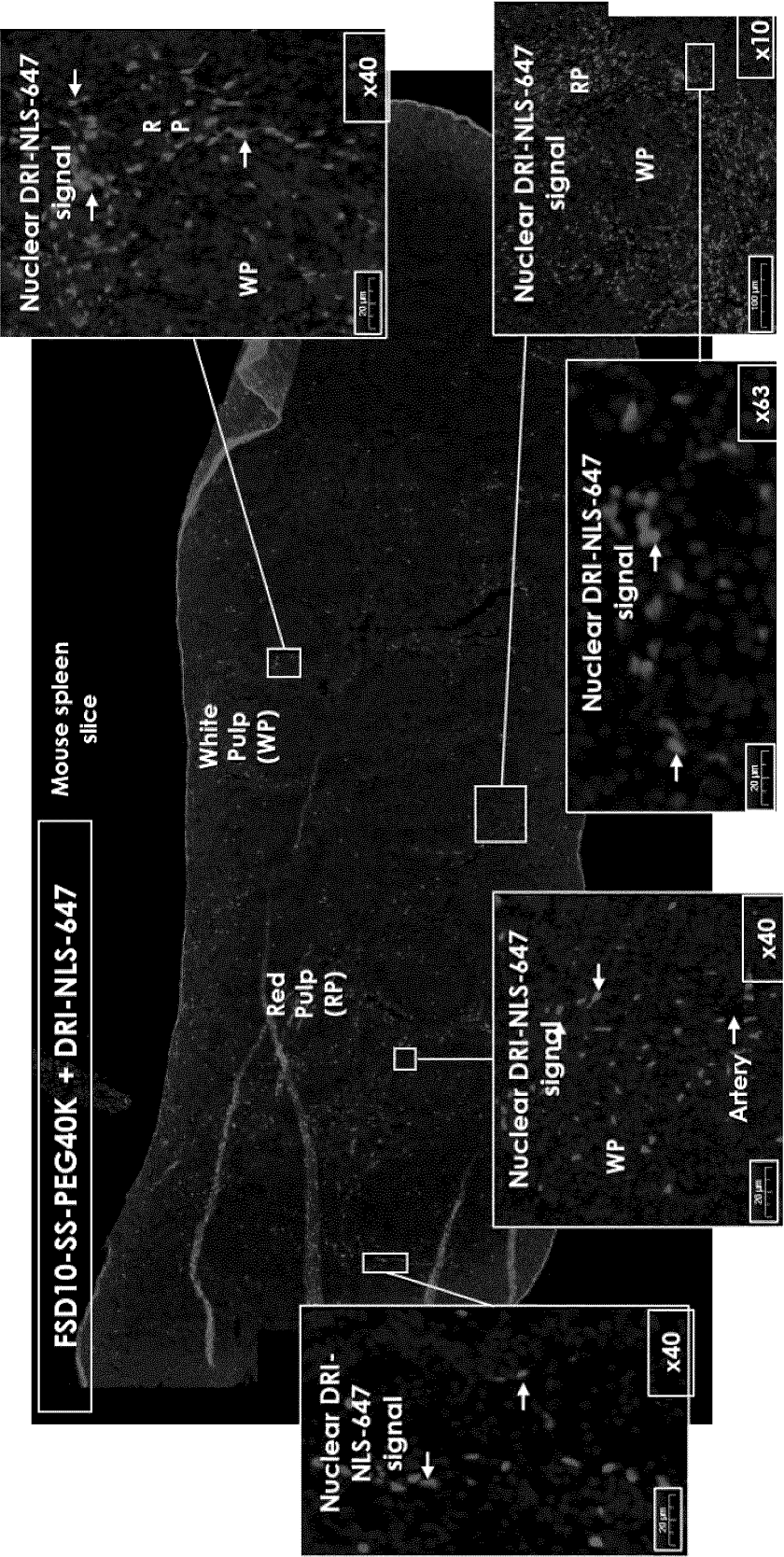


Fig. 61

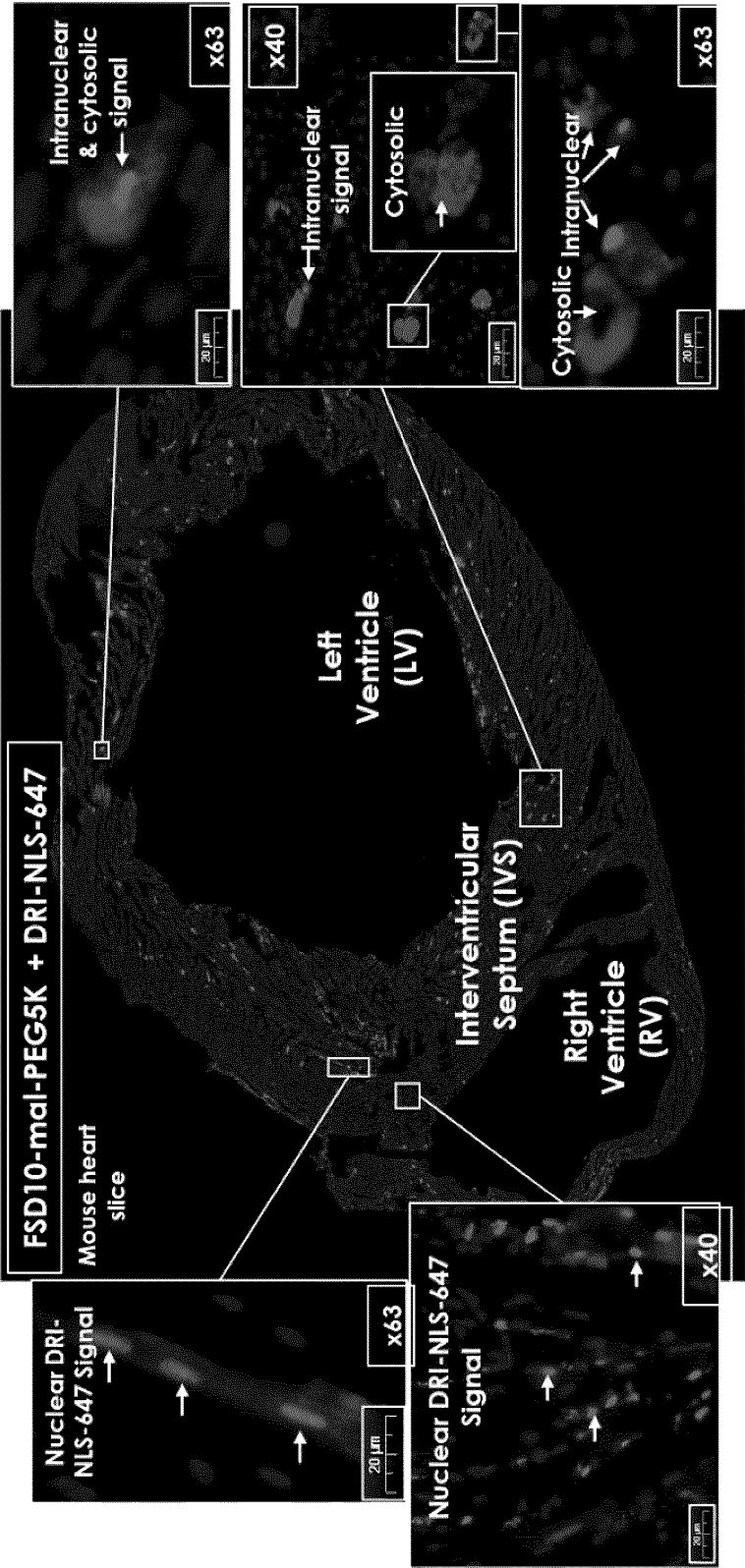


Fig. 62

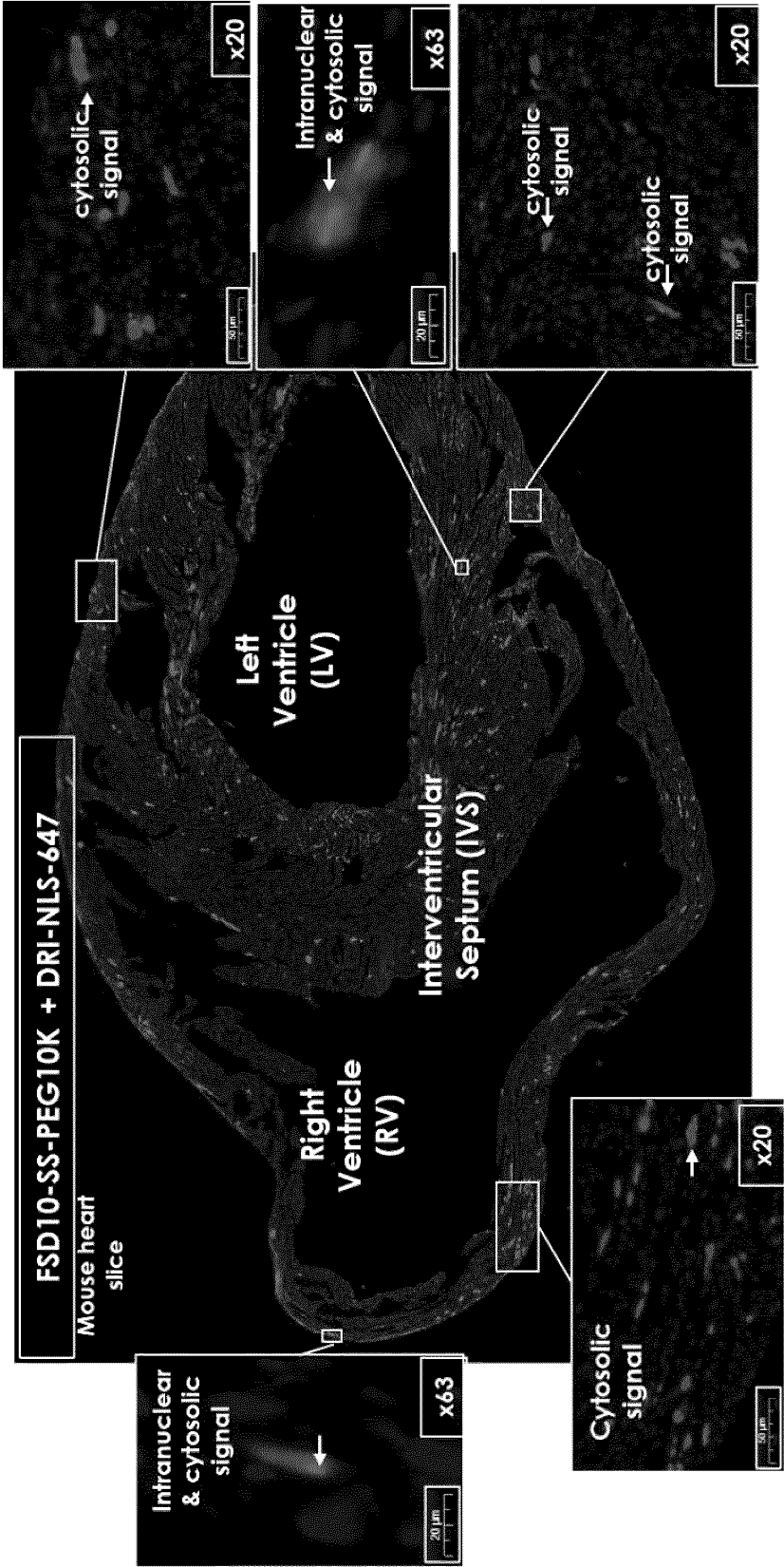


Fig. 63

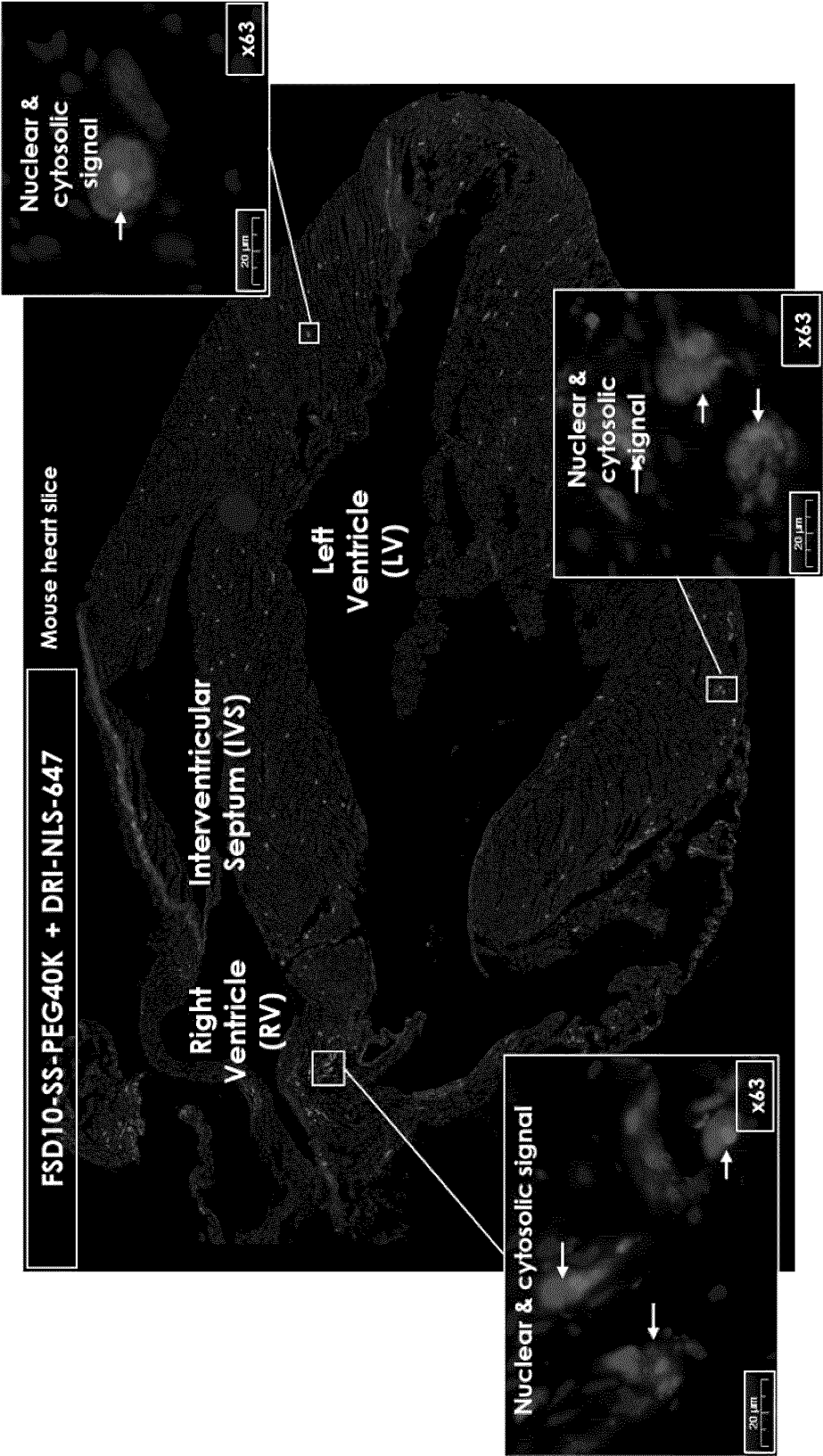


Fig. 63.1

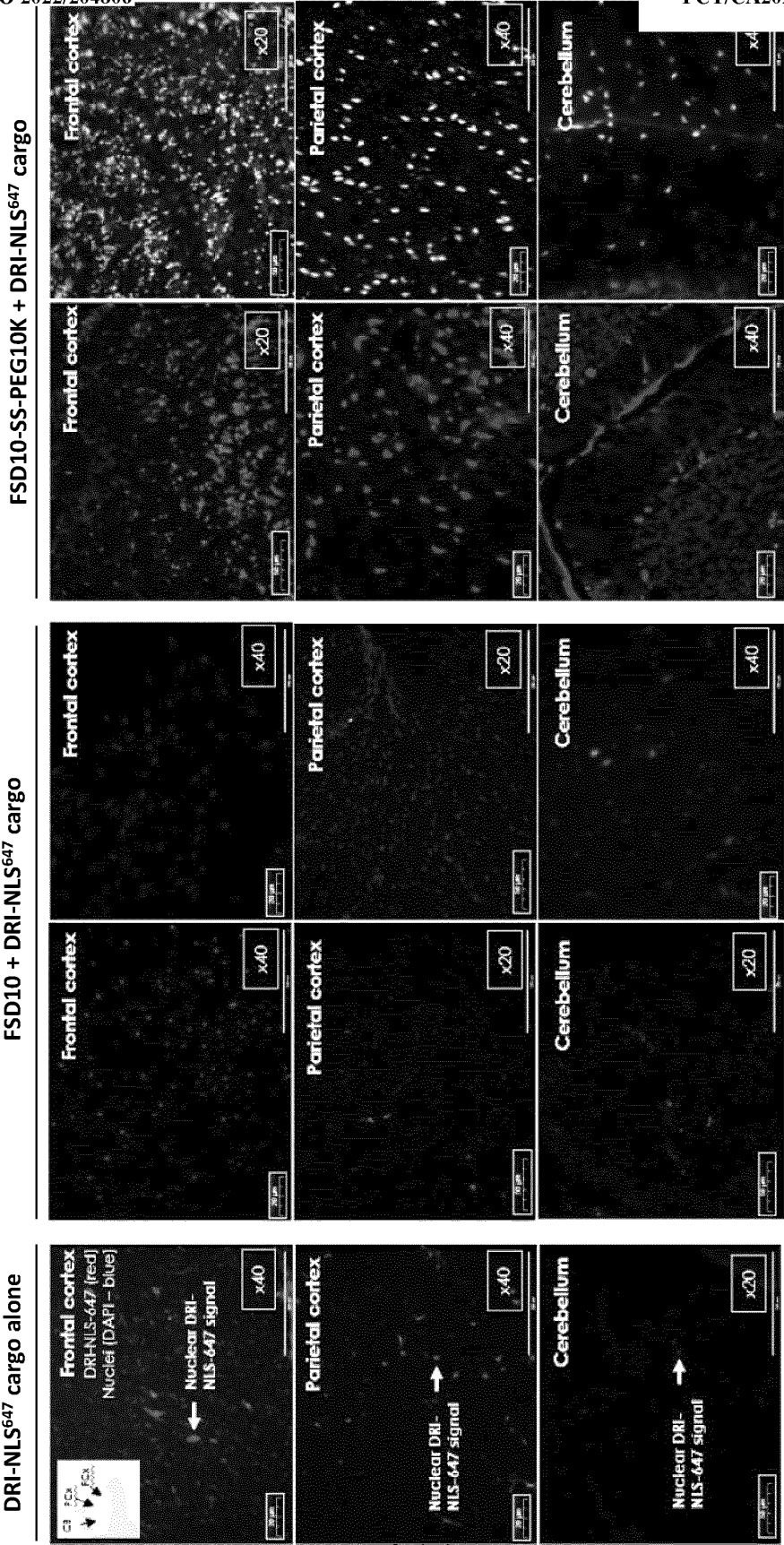
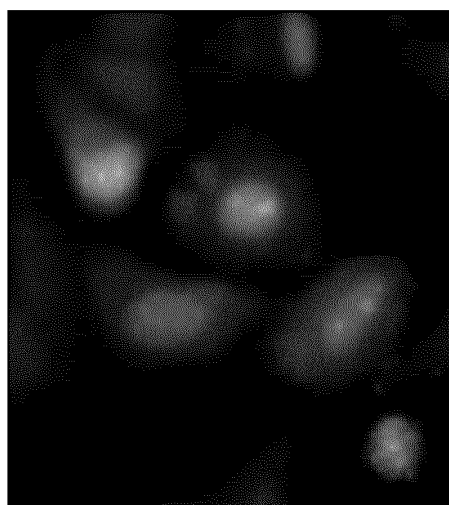


Fig. 64

	Shuttle agent / multimer (conc.)	Liver	Pancreas	Spleen	Heart	Brain	Lung	Kidney
non- PEGylated	FSD10 (250 µM)	+	++	++		No delivery (Fig. 63.1)	+	No delivery
	FSD250 (250 µM)	No delivery	+	+		No delivery	+	No delivery
	FSD250D (250 µM)	No delivery	No delivery	No delivery		No delivery	No delivery	No delivery
PEG5K	FSD10-mal-PEG5K (1 mM)	++ (Fig. 45)	++++ (Fig. 52)	++++ (Fig. 55)	+++ (Fig. 58)	+	+	No delivery
	FSD10-SS-PEG5K (500 µM)	+	++	+++	No delivery	++	No delivery	No delivery
	FSD10-SS-PEG10K (500 µM)	+++ (Fig. 46)	++++ (Fig. 53)	++++ (Fig. 56)	+++ (Fig. 59)	++	+	+
PEG10K	FSD10-mal-PEG10K (500 µM)	+	+	+++	No delivery	+++	No delivery	No delivery
	FSD10D-SS-PEG10K (500 µM)	+				No delivery		
	FSD10D-mal-PEG10K (500 µM)	No delivery	No delivery	No delivery	No delivery	No delivery	No delivery	No delivery
PEG20K	FSD10-SS-PEG20K (1 mM)	+++ (Fig. 47)			+++	+++ (Fig. 63.1)		No delivery
	FSD10-mal-PEG20K (500 µM)	+	No delivery	+		+++	No delivery	No delivery
PEG40K	FSD10-SS-PEG40K (1 mM)	+++ (Fig. 48)	++++ (Fig. 54)	++++ (Fig. 57)	+++ (Fig. 60)		No delivery	No delivery
	FSD10-mal-PEG40K (250 µM)	No delivery	No delivery	+++	No delivery		No delivery	No delivery
	FSD10D-SS-PEG40K (250 µM)	++	++	++			No delivery	No delivery
Branched PEG core	[FSD10-SS-]₄(PEG20K) (500 µM)	+++++	No delivery	+			+	No delivery
	[FSD10-mal-]₄(PEG20K) (500 µM)	+++++	++++	+++++				+
	[FSD10-mal-]₈(PEG40K) (500 µM)	+++ (Fig. 51)	No delivery	+++				No delivery
	[FSD10-mal-]₈(PEG20K) (500 µM)	No delivery	No delivery	No delivery				No delivery
Polyester core	[FSD10-SS-]₈(PEG20K) (500 µM)	No delivery	No delivery	++				No delivery
	[FSD10-mal-PEG1K-]₆(Polyester)							
	[FSD10-mal-PEG1K-]₂(Polyester)							

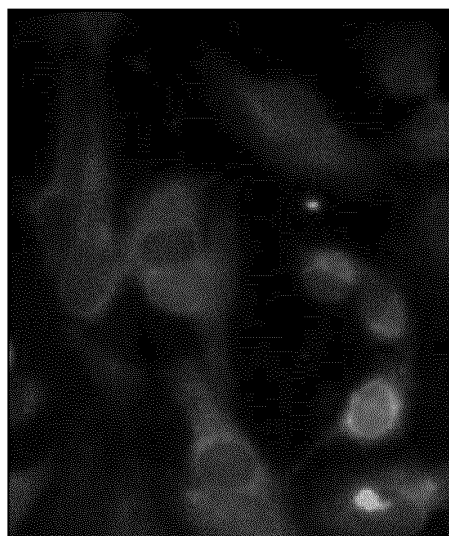
“No delivery”: no delivery events; “+”: rare delivery events; “++”: homogenous and low nuclear delivery events; “+++”: homogenous and moderate nuclear delivery events; “++++”: homogenous and high nuclear delivery events; “+++++”: homogenous and massive nuclear delivery events; “*”: delivery events observed but events were non-nuclear (e.g., cytosolic); Blank: results not available. (Delivery levels based on microscopy observations).

Fig. 65



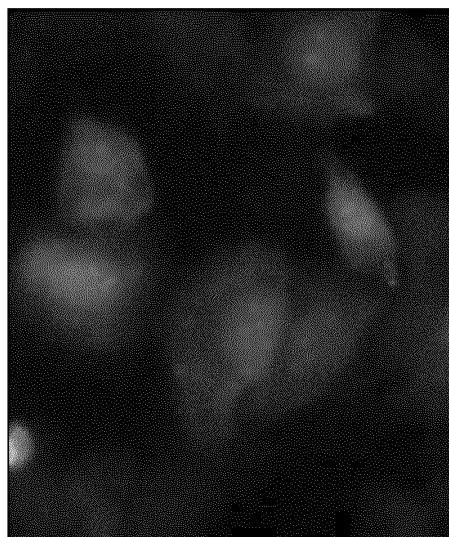
FSD10-C + DRI-NLS⁶⁴⁷ cargo

Fig. 66



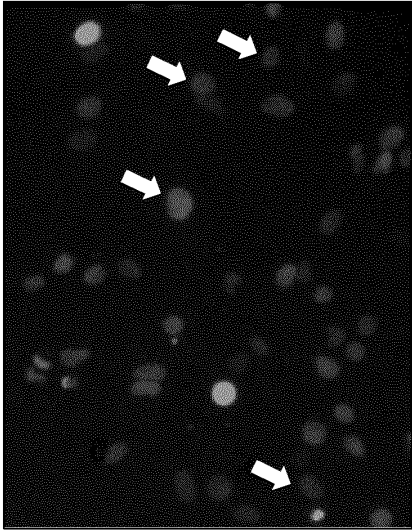
FSD10-C-mal-DRI-NLS⁶⁴⁷

Fig. 67



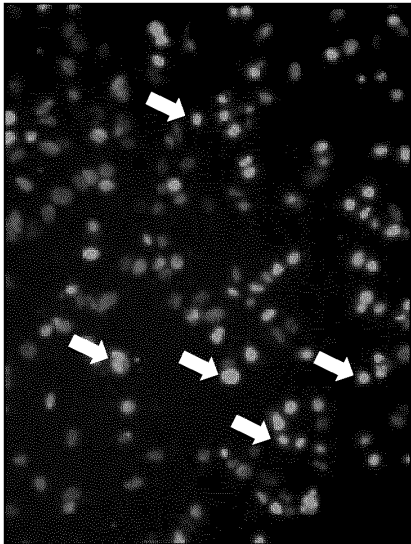
FSD10-C-SS-DRI-NLS⁶⁴⁷

Fig. 68B



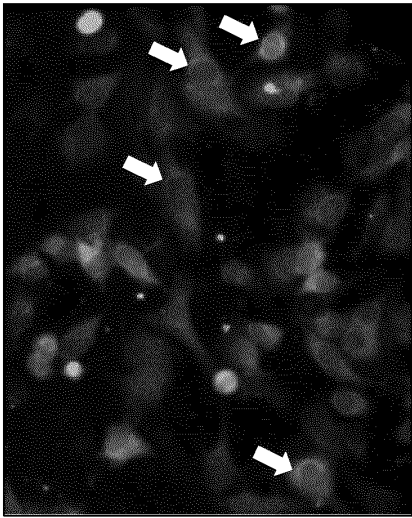
GFP-NLS

Fig. 69B



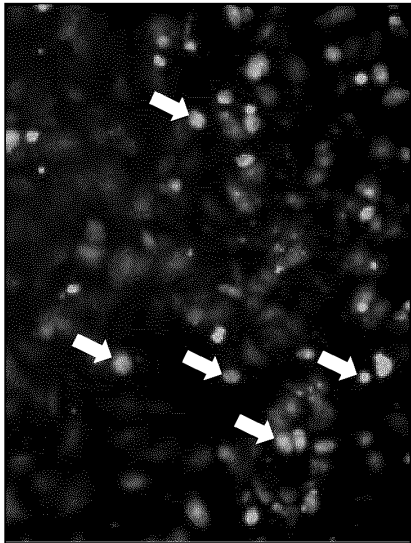
GFP-NLS

Fig. 68A



FSD10-C-mal-PEG1K-DRI-NLS⁶⁴⁷

Fig. 69A



FSD10-C-SS-PEG1K-DRI-NLS⁶⁴⁷

Fig. 70A

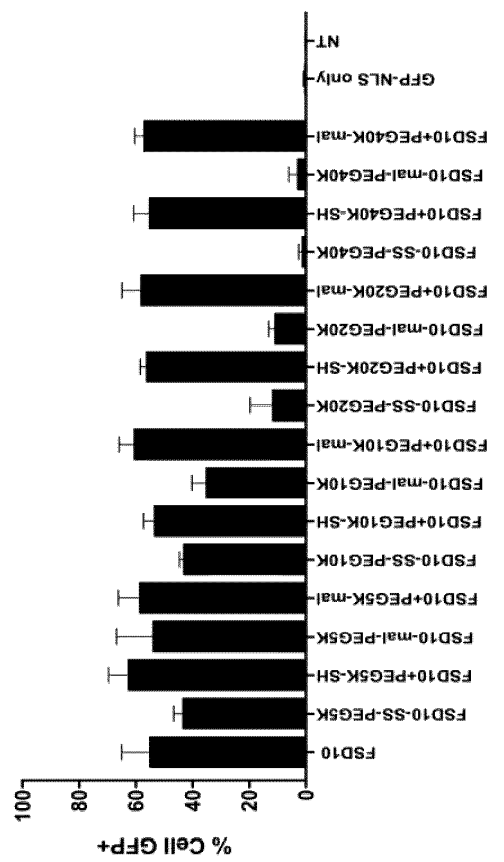


Fig. 70B

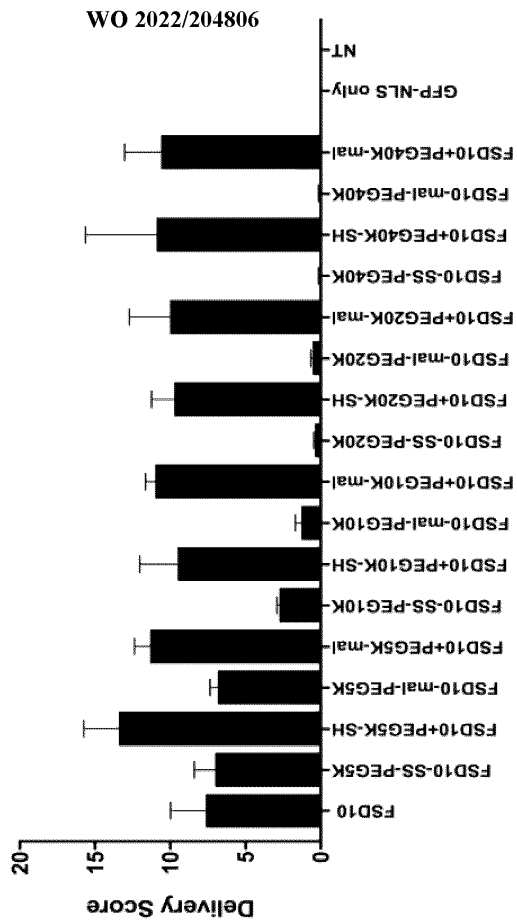


Fig. 70C

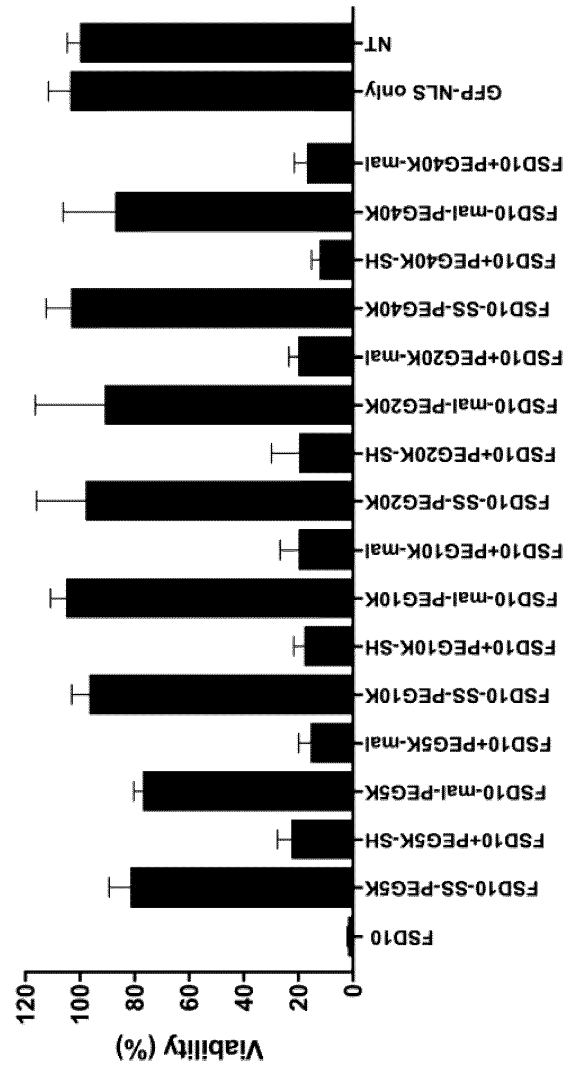


Fig. 71A

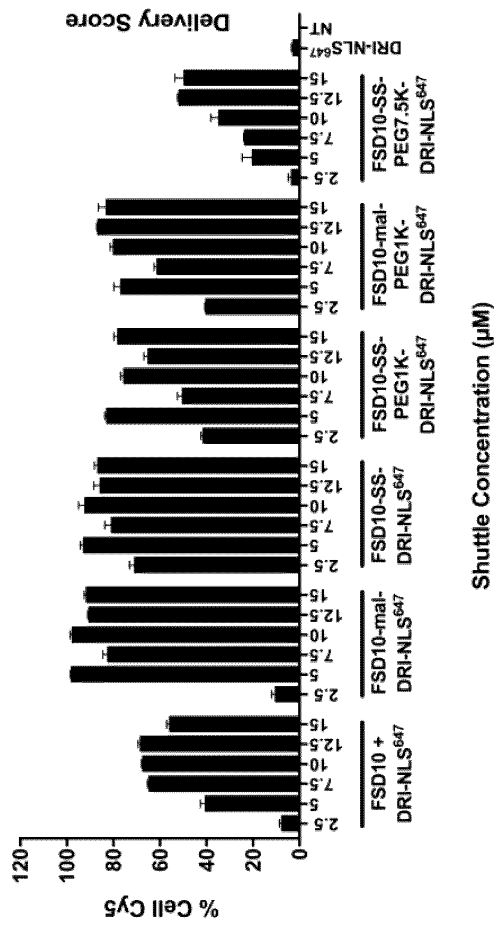


Fig. 71B

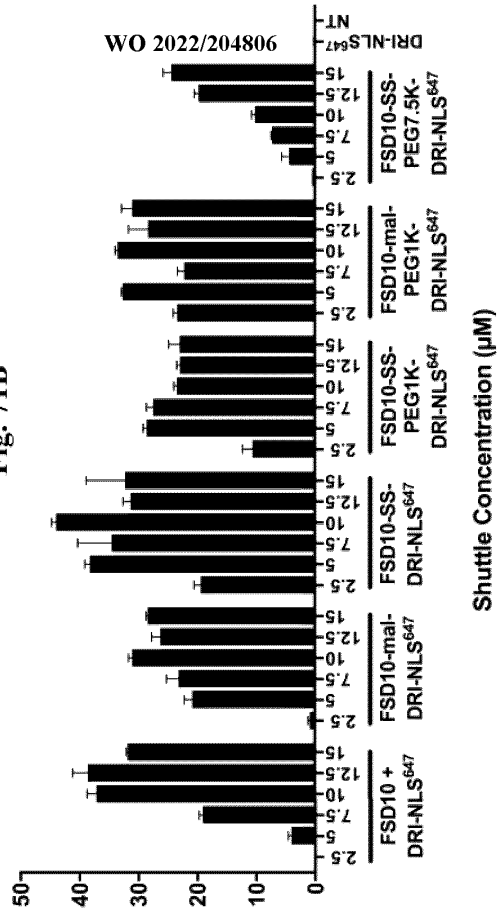


Fig. 71C

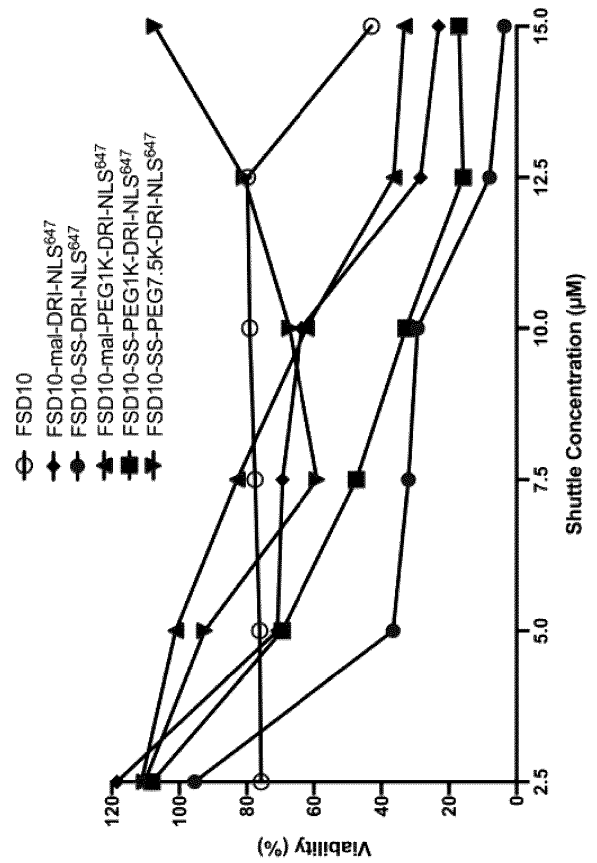


Fig. 71D

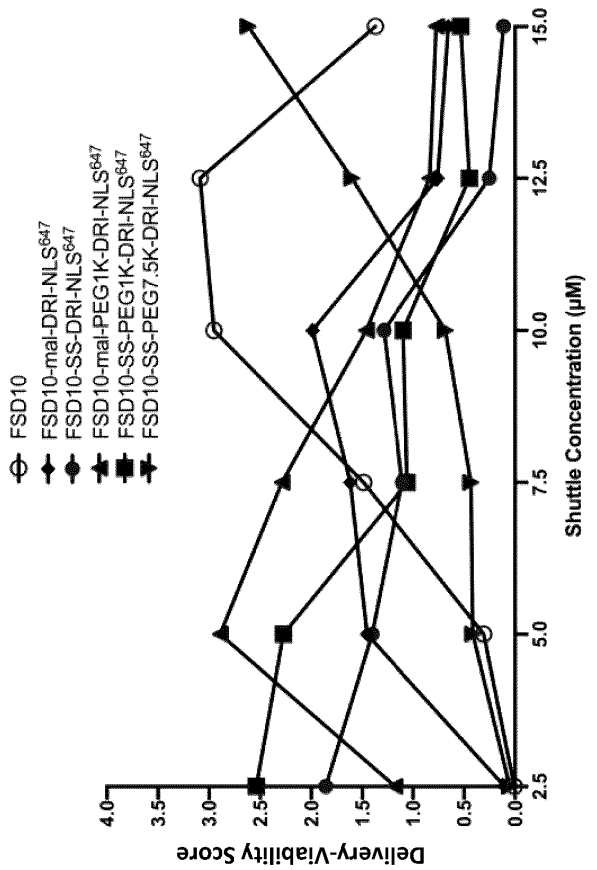


Fig. 72

	Peptide conc.	Cargo conc.	DRI-NLS ⁶⁴⁷ Delivery	GFP-NLS Delivery
Shuttle + cargo				
(PBS control)	-	-	-	-
DRI-NLS ⁶⁴⁷ (alone)	-	2.5 μ M	-	-
	-	3.5 μ M	-	-
	-	4.5 μ M	-	-
	-	5 μ M	-	-
	-	10 μ M	-	-
	-	20 μ M	-	-
	-	40 μ M	-	-
GFP-NLS (alone)	-	2.5 μ M	-	-
	-	3.5 μ M	-	-
	-	4.5 μ M	-	-
	-	5 μ M	-	-
	-	10 μ M	-	-
	-	20 μ M	-	-
FSD10 + DRI-NLS ⁶⁴⁷	2.5 μ M	2.5 μ M	+	+
	3.5 μ M	3.5 μ M	+++	+
	4.5 μ M	4.5 μ M	+++	+
	5 μ M	5 μ M	++++	++++
Shuttle-cargo chimeras				
FSD10-mal-DRI-NLS ⁶⁴⁷	2.5 μ M	2.5 μ M	++	++
	3.5 μ M	3.5 μ M	++	+++
	4.5 μ M	4.5 μ M	++	++++
	5 μ M	5 μ M	++	++++
FSD10-SS-DRI-NLS ⁶⁴⁷	2.5 μ M	2.5 μ M	+++	++
	3.5 μ M	3.5 μ M	+++	+++
	4.5 μ M	4.5 μ M	+++	++++
	5 μ M	5 μ M	+++	++++
FSD10-mal-PEG1K-DRI-NLS ⁶⁴⁷	2.5 μ M	2.5 μ M	++	+++
	3.5 μ M	3.5 μ M	++	+++
	4.5 μ M	4.5 μ M	+++	+++
	5 μ M	5 μ M	+++	+++
FSD10-SS-PEG1K-DRI-NLS ⁶⁴⁷	2.5 μ M	2.5 μ M	+++	+++
	3.5 μ M	3.5 μ M	+++	+++
	4.5 μ M	4.5 μ M	+++	+++
	5 μ M	5 μ M	++++	+++
FSD10-SS-PEG7.5K-DRI-NLS ⁶⁴⁷	2.5 μ M	2.5 μ M	-	-
	3.5 μ M	3.5 μ M	+	++
	4.5 μ M	4.5 μ M	+	++
	5 μ M	5 μ M	+	++
	10 μ M	10 μ M	++	+
	20 μ M	20 μ M	+++	++
	40 μ M	40 μ M	++++	+++

Legend (Delivery levels based on microscopy observations)

“Blank” : results not available

“-“ : No delivery

“+” : rare delivery events

“++” : homogenous and low nuclear delivery events

“+++” : homogenous and moderate nuclear delivery events

“++++” : homogenous and high nuclear delivery events

“+++++” : homogenous and massive nuclear delivery events

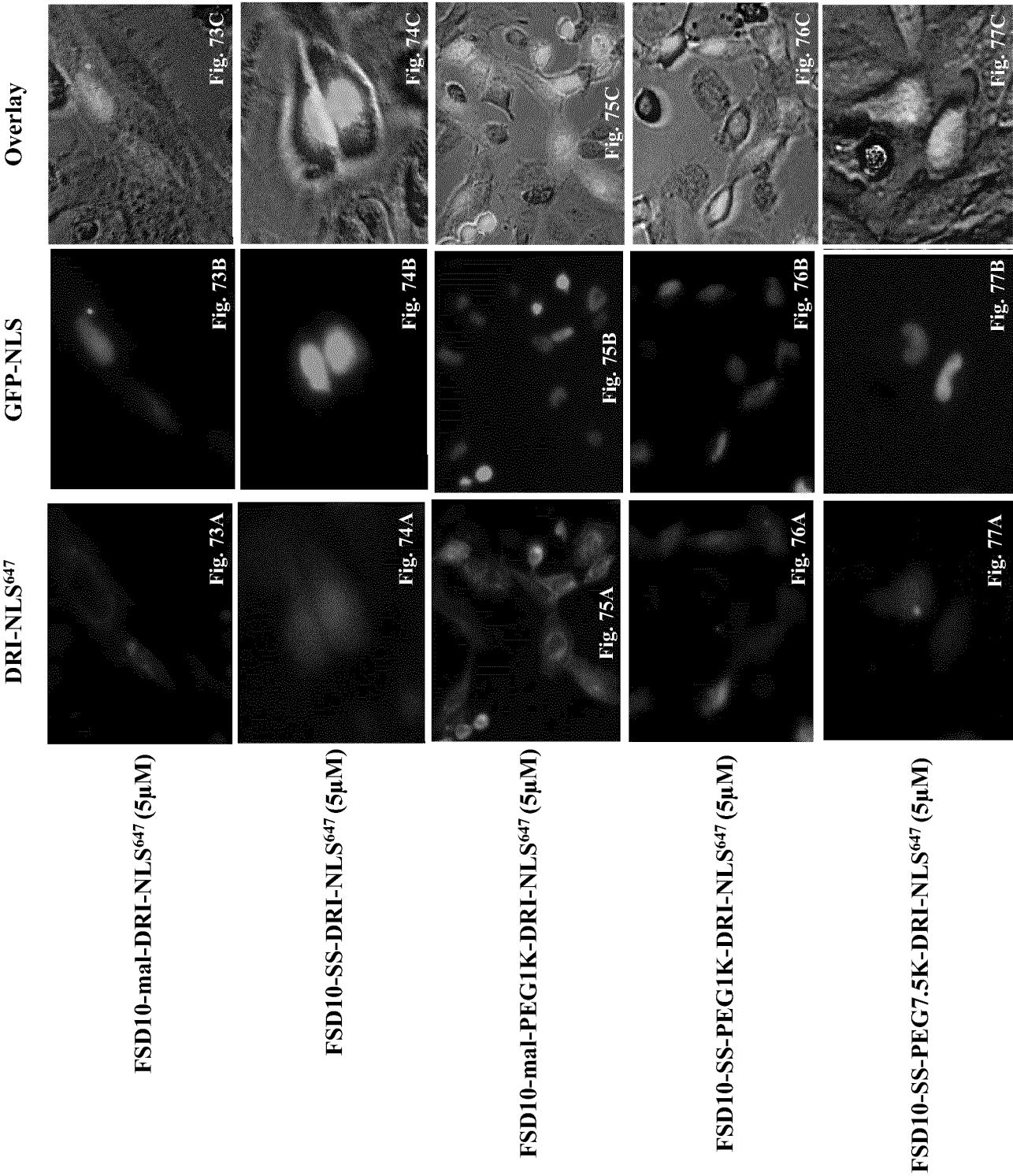


Fig. 78B

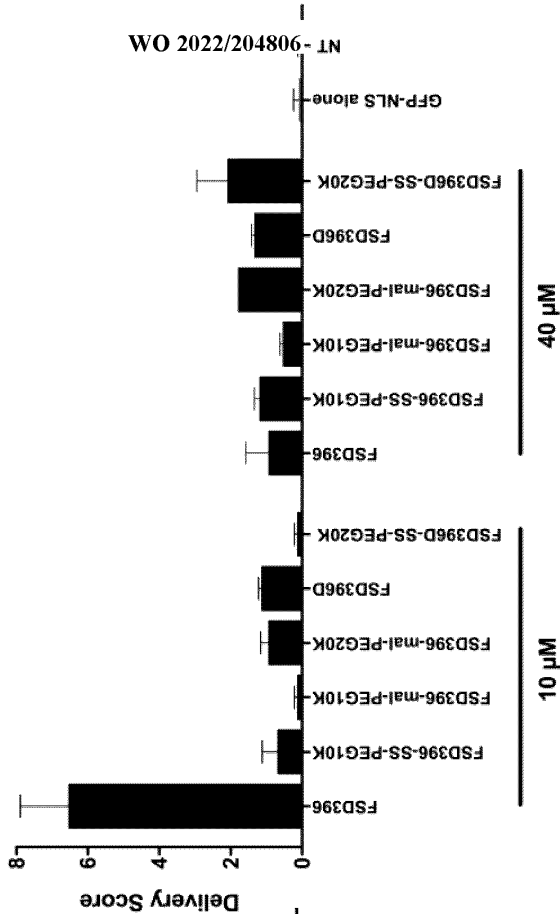


Fig. 78A

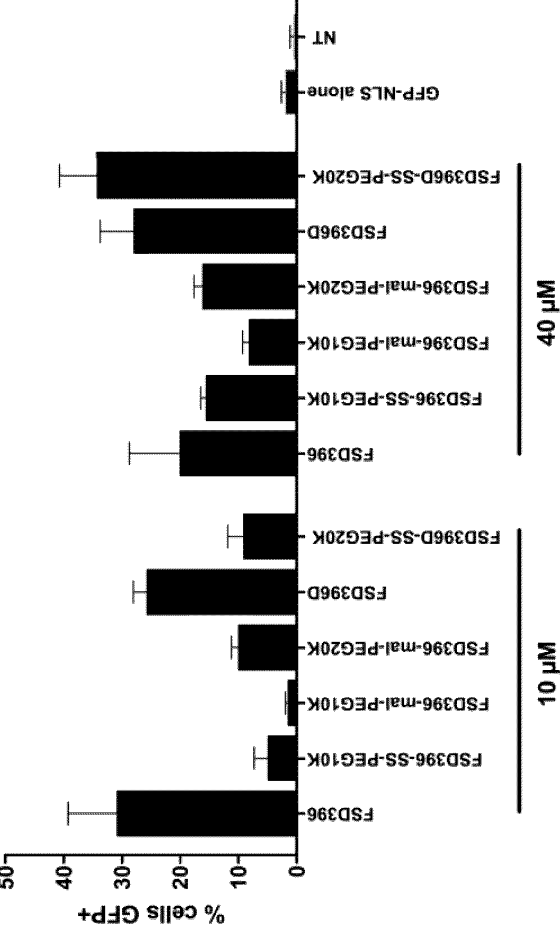


Fig. 78C

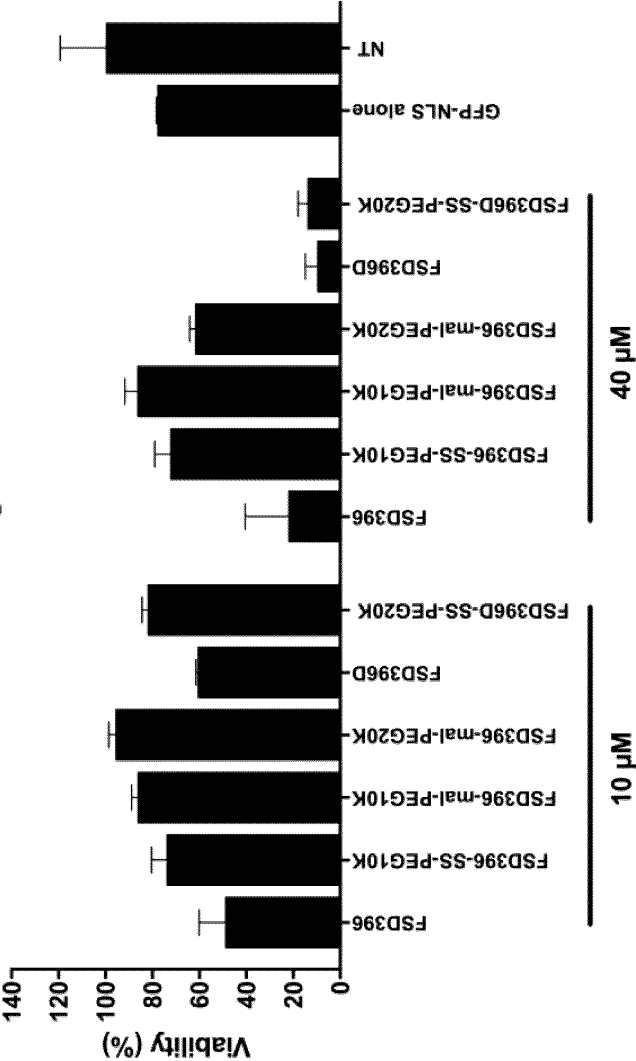


Fig. 79A

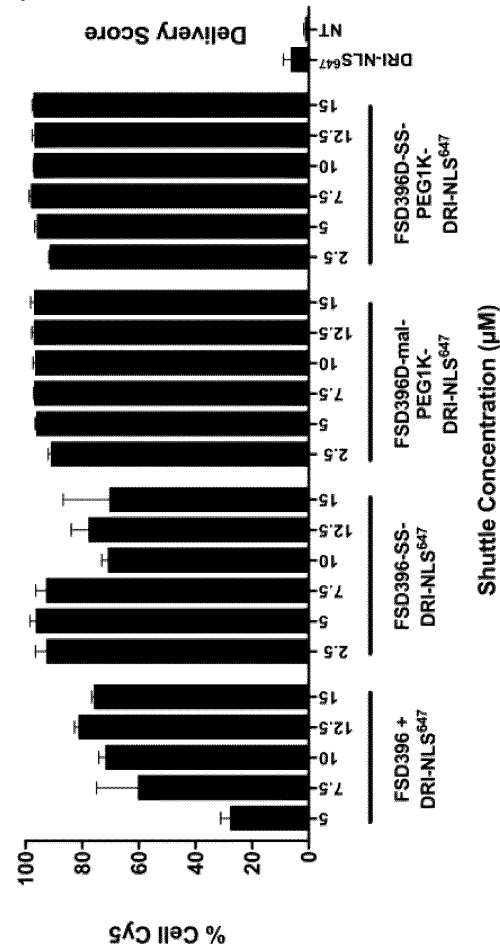


Fig. 79B

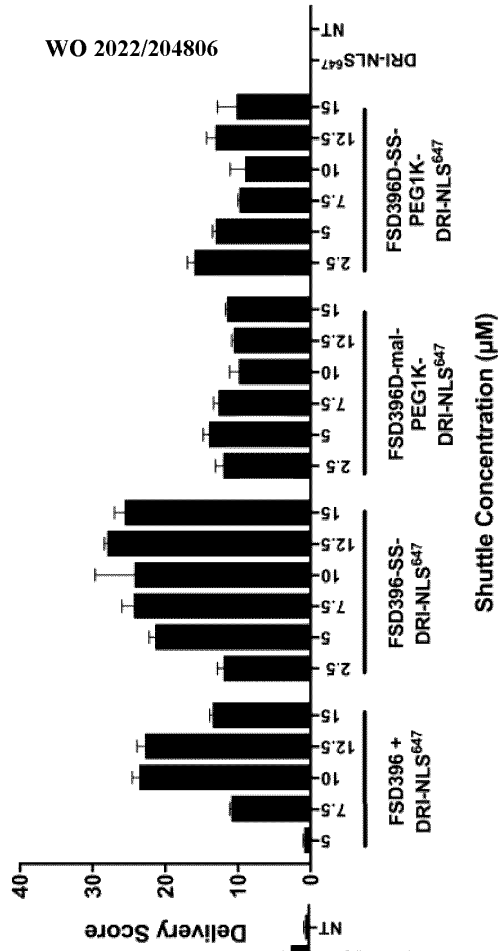


Fig. 79C

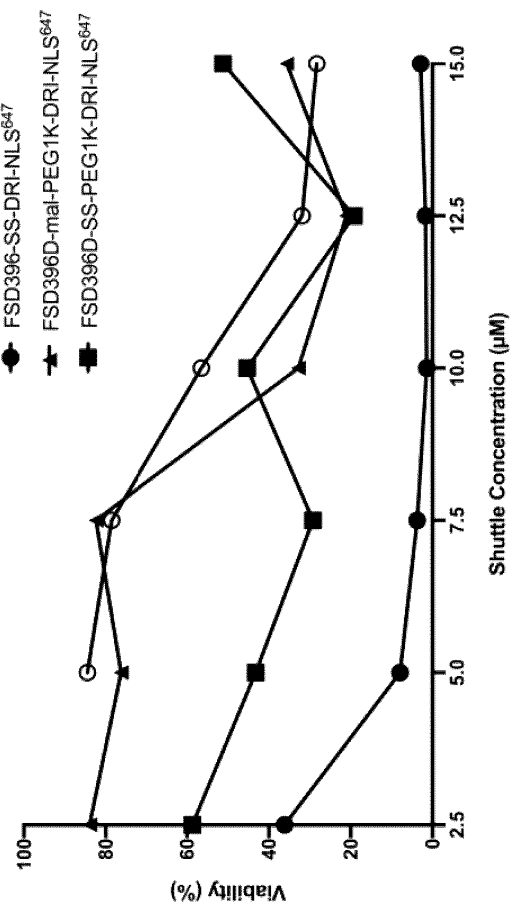


Fig. 79D

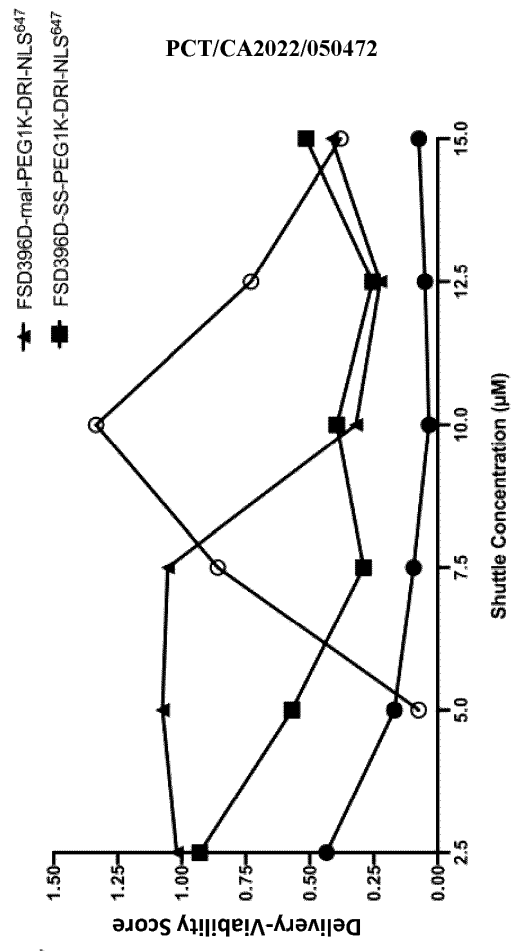


Fig. 80

	Shuttle agent / multimer (conc.) / Cargo (conc.)	Liver	Pancreas	Lung	Kidney	Spleen	Brain
	FSD10 (250 µM) + DRI-NLS ⁶⁴⁷ (150 µg)	No delivery		No delivery	No delivery	++	No delivery
No PEG	FSD10-mal-DRI-NLS ⁶⁴⁷ (250 µM)	+++ Near arteries	++	+++ vascular	++ glomeruli	++	+++
	FSD10-SS-DRI-NLS ⁶⁴⁷ (250 µM)	++	++	+++ vascular	+ glomeruli	+++	+++
	FSD10-SS-DRI-NLS ⁶⁴⁷ (125 µM)	++++	+++	+++ vascular	+ glomeruli	++	+++
	FSD10-SS-DRI-NLS ⁶⁴⁷ (62.5 µM)	No delivery	+	+ vascular	No delivery		+
PEG1K	FSD10-SS-PEG1K-DRI-NLS ⁶⁴⁷ (250 µM)	No delivery	++++ islets	++ vascular	No delivery	+++	+
	FSD10-mal-PEG1K-DRI-NLS ⁶⁴⁷ (250 µM)	+++	+++ islets	+++ vascular	+ glomeruli	+++	+
	FSD10-mal-PEG1K-DRI-NLS ⁶⁴⁷ (125 µM)	No delivery	+++ islets	+ vascular	No delivery	++ vascular	+
PEG7.5K	FSD10-SS-PEG7.5K-DRI-NLS ⁶⁴⁷ (400 µM)	No delivery	+ vascular	+ vascular	No delivery	+++ vascular	+
	FSD10-SS-PEG7.5K-DRI-NLS ⁶⁴⁷ (250 µM)	No delivery	+ vascular	+ vascular	No delivery	+++ vascular	+

“No delivery”: no delivery events; “+”: rare delivery events; “++”: homogenous and low delivery events; “+++”: homogenous and moderate delivery events; “++++”: homogenous and high delivery events; “+++++”: homogenous and massive delivery events; Blank: results not available. (Delivery levels based on microscopy observations).

Fig. 81

Experiment		Peptide conc.	Independent cargo	Cargo conc.	% Whole lung cells (1h)	% Proximal lung cells (1h)	% Middle lung cells (1h)	% Distal lungs (1h)	% DRI Epithelial cells (CD45-CD326+CD31-)	% DRI Club cells (CD45-CC10+)	% DRI Alveolar type 1 (CD45-CD326+MHCII+Podoplanin+)	% DRI Alveolar type 2 (CD45-CD326+MHCII+)	% DRI Endothelial (CD45-CD31+CD326-)	% DRI Leukocytes (CD45+)
Shuttle + cargo														
a	(PBS control)	-	-	40 μ M	0	0	0	0	0.38	4.85	0	0.7	0.01	0.13
		40 μ M		40 μ M	4.5	1.0	6.0	24	0.23	0	0	0	0	0.09
a	(Cargo alone)	-	DRI-NLS ⁶⁴⁷	40 μ M	4.5	1.0	6.0	6.0	24	26.1	8.53	40.8	2.33	4.11
		40 μ M	DRI-NLS ⁶⁴⁷	40 μ M	46.5	0	0	0	0	0	0	0	0	0
a	FSD10 scramble	40 μ M	DRI-NLS ⁶⁴⁷	40 μ M	46.5	0	48.7	46	25.4	20.44	18.35	48.7	0.49	3.76
b	FSD10	40 μ M	DRI-NLS ⁶⁴⁷	40 μ M	37.1	26.9	48.7	42.8	9.81	4.31	4.83	8.49	0.06	9.84
b		80 μ M	DRI-NLS ⁶⁴⁷	40 μ M	34.3	35.1	28.6	31.3	6.09	0	0	3.09	0.05	4.80
b		160 μ M	DRI-NLS ⁶⁴⁷	40 μ M	43.8	37.0	47.2	47.2	9.46	0	0.53	0.35	0.03	4.99
c		40 μ M	GFP-NLS	20 μ M	55	55								
a	FSD10-SS-PEG5K	40 μ M	DRI-NLS ⁶⁴⁷	40 μ M	11.2	13.2	9.8	9.8	12.27	33.75	1.09	24.4	0.14	6.83
b	FSD10-SS-PEG10K	40 μ M	DRI-NLS ⁶⁴⁷	40 μ M	31.5	32.9	29.3	29.3	3.18	1.66	1.05	5.77	0.11	8.07
b		80 μ M	DRI-NLS ⁶⁴⁷	40 μ M	29.5	27.6	31.3	31.3	3.26	1.06	1.63	2.99	0.23	4.57
b		160 μ M	DRI-NLS ⁶⁴⁷	40 μ M	70	70			3.37	0	1.09	0.93	0.02	3.82
a	[FSD10-SS-] ₄ (PEG20K)	40 μ M	DRI-NLS ⁶⁴⁷	40 μ M					9.13	36.6	1.08	19.6	0.21	4.03
a	[FSD10-SS-] ₈ (PEG20K)	40 μ M	DRI-NLS ⁶⁴⁷	40 μ M	19.1	11.1	20.8	6.9	17.74	38.9	2.24	25.3	0.32	5.72
b		40 μ M	DRI-NLS ⁶⁴⁷	40 μ M	15.29	11.1	23.5	23.5	1.61	3.53	0.17	1.63	0.04	1.87
b		80 μ M	DRI-NLS ⁶⁴⁷	40 μ M	27.96	17.6	44.7	44.7	5.43	4.08	1.75	2.92	0.26	5.57
b		160 μ M	DRI-NLS ⁶⁴⁷	40 μ M	19.63	2.4	29.9	29.9	3.01	2.98	0.77	0.7	0.09	2.12
Shuttle-cargo chimeras														
c	FSD10-mal-DRI-NLS ⁶⁴⁷	20 μ M	-	-	<1	2.70	0.63	0.27	13.29	14.3	5.26	18	0.37	1.32
a		40 μ M	-	-	22.8	20.2	20	20						
c	FSD10-SS-DRI-NLS ⁶⁴⁷	40 μ M	-	-	57.6	56.3	63.4	42.1	25.36	35.26	19.48	21.43	1.98	2.78
a		40 μ M	-	-	63.6	64.2	65.7	65.7	12.96	9.11	8.77	10.55	0.27	3.68
b		40 μ M	-	-	61.4	56.5	40.3	40.3	11.42	8.02	14.75	13.75	1.46	2.81
b		80 μ M	-	-	36.5	35.2	29.0	29.0	1.10	6.82	0.34	0.86	0.01	0.32
a		160 μ M	-	-	26.7	25.4			1.10	6.82	0.34	0.86	0.01	0.32
b	FSD10-SS-PEG1K-DRI-NLS ⁶⁴⁷	40 μ M	-	-	79.2	79.5	77.4	77.4	11.33	5.17	3.62	6.77	0.29	3.82
c		50 μ M	-	-	47.7	47.7	35.1	17.6						
b		80 μ M	-	-	30.7	30.0	32.6	32.6	5.47	2.77	0	2.72	0.12	1.20
b	FSD10-mal-PEG1K-DRI-NLS ⁶⁴⁷	160 μ M	-	-	32.5	30.8	32.7	32.7	1.39	0	0.52	0.79	0.02	0.31
a		32 μ M	-	-	58.2	27.9	17.1	10.6	6.71	18.75	5.16	5.02	0.28	1.46
a		40 μ M	-	-	11.3	17.8	10.6							

Results are presented as simple mean data.

Fig. 82A

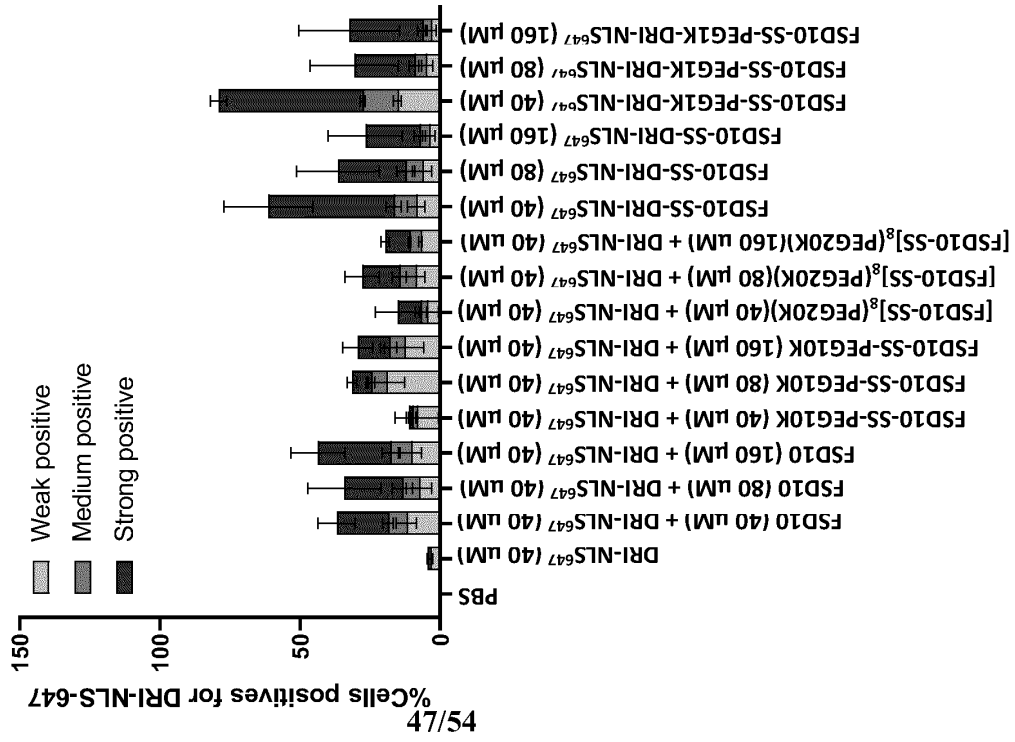
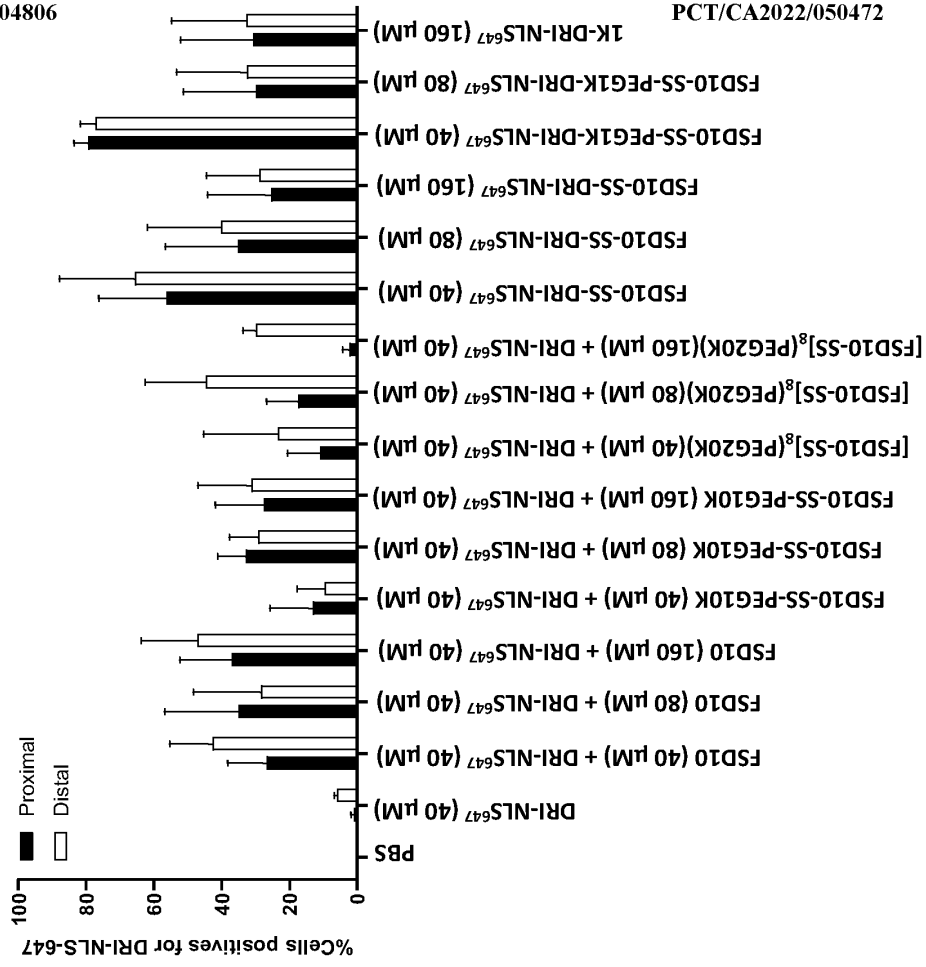


Fig. 82B



PCT/CA2022/050472

WO 2022/204806

Fig. 82C

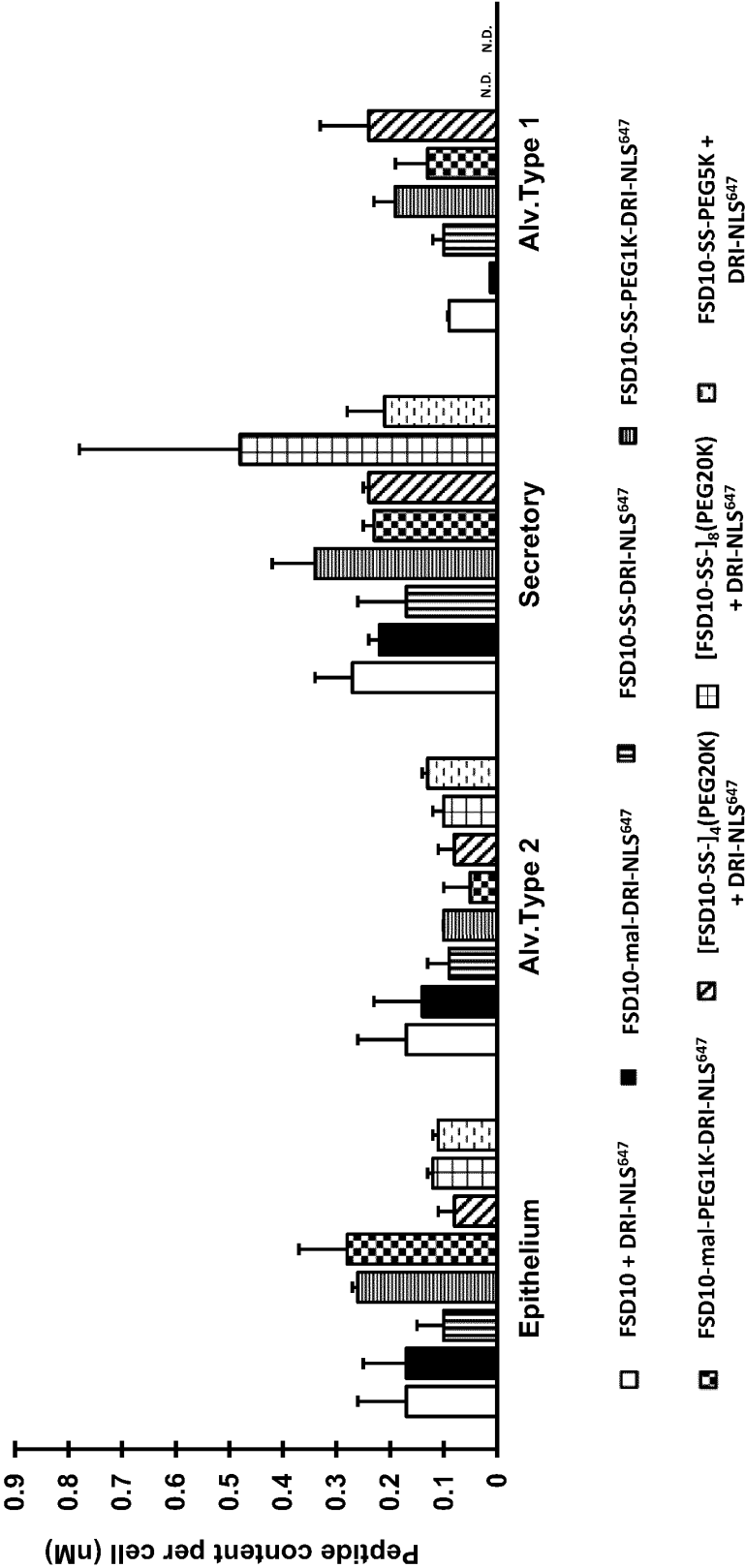


Fig. 83A

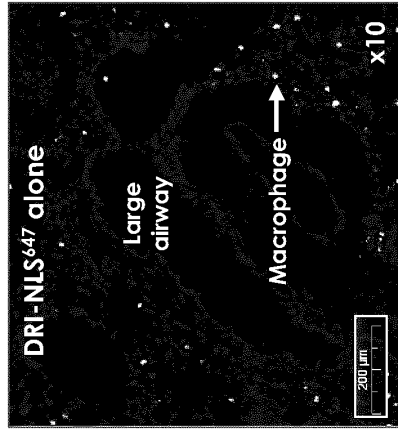


Fig. 83B

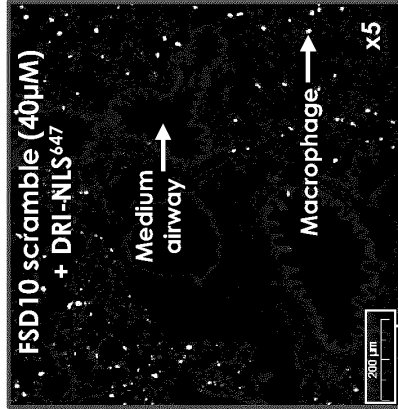


Fig. 83C

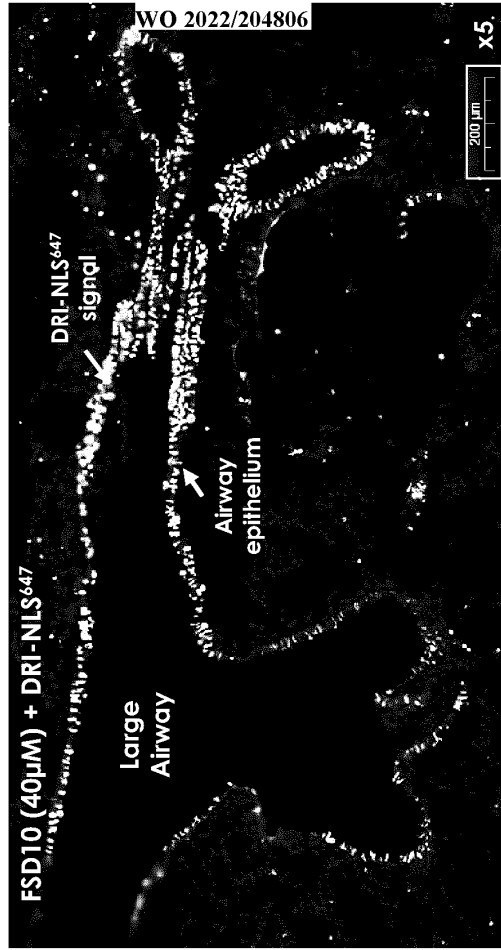


Fig. 83D

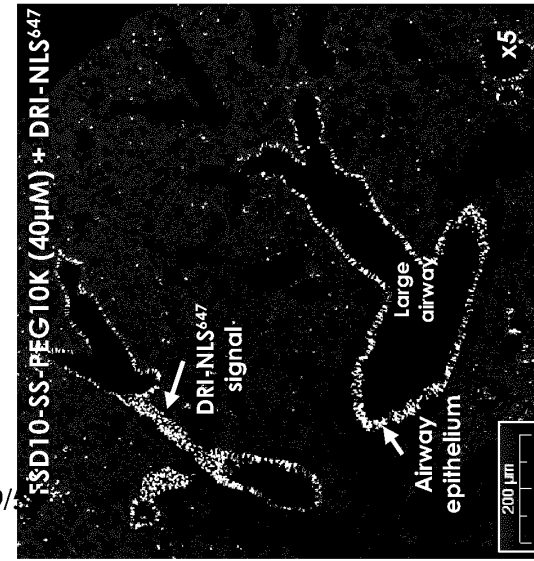


Fig. 83E

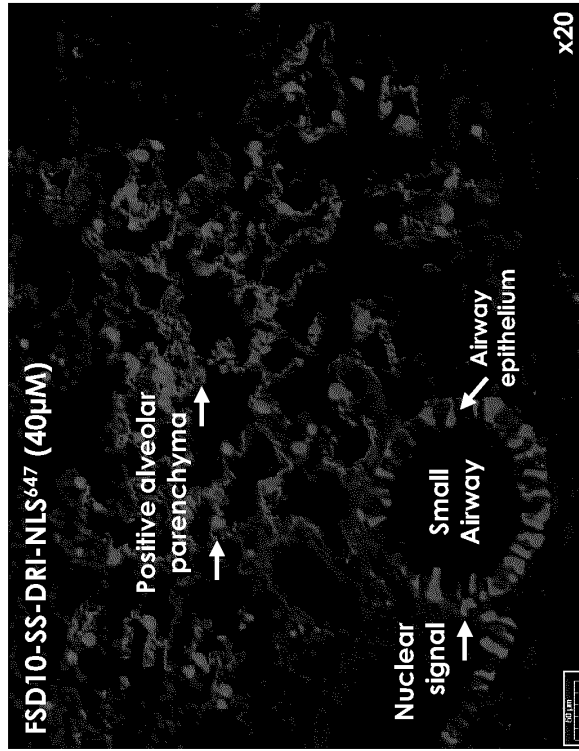
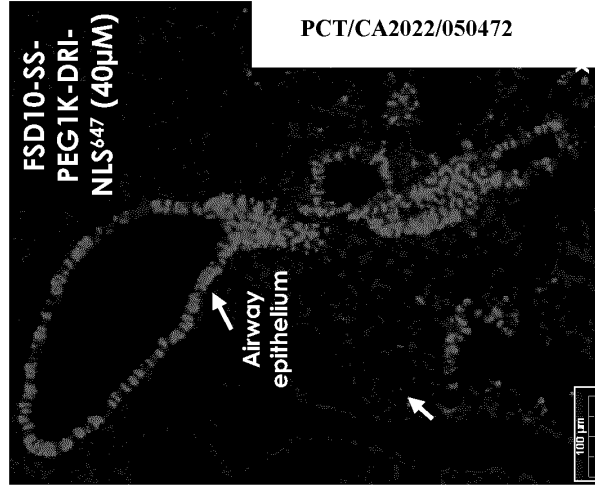
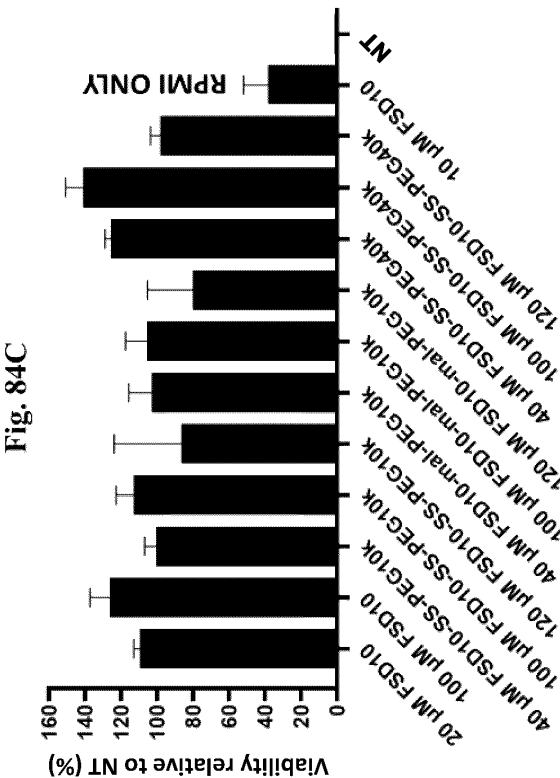
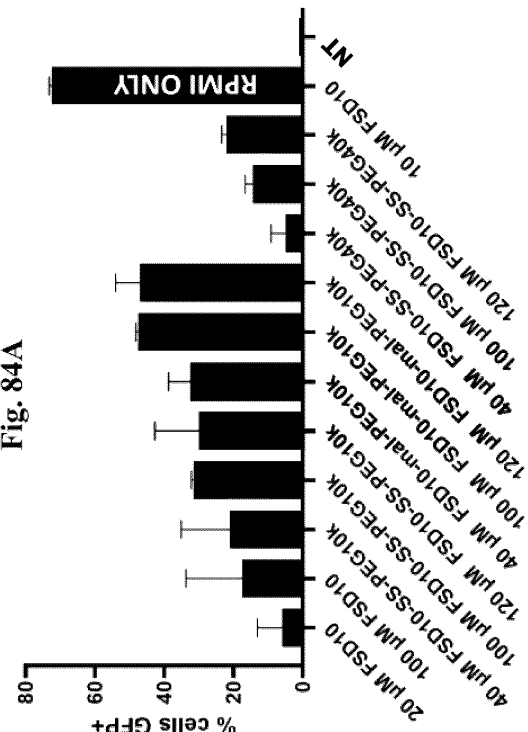
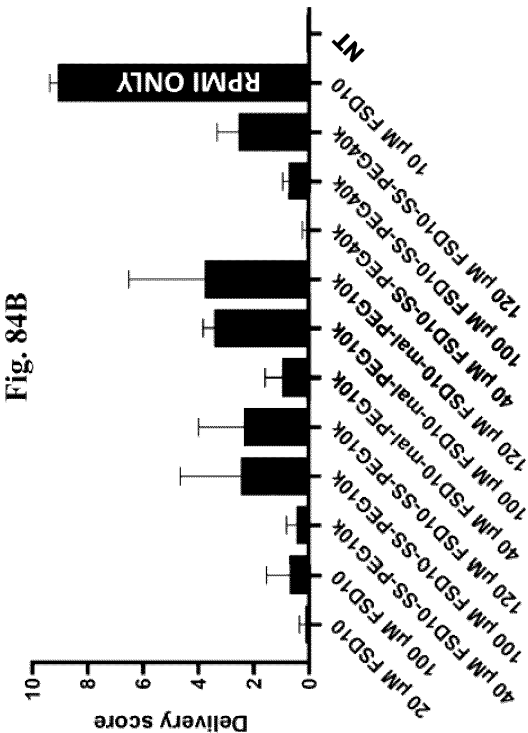


Fig. 83F





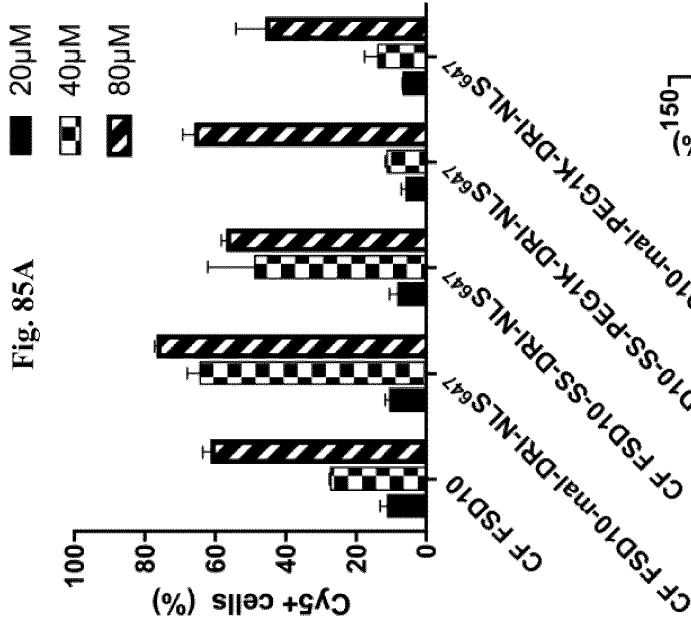
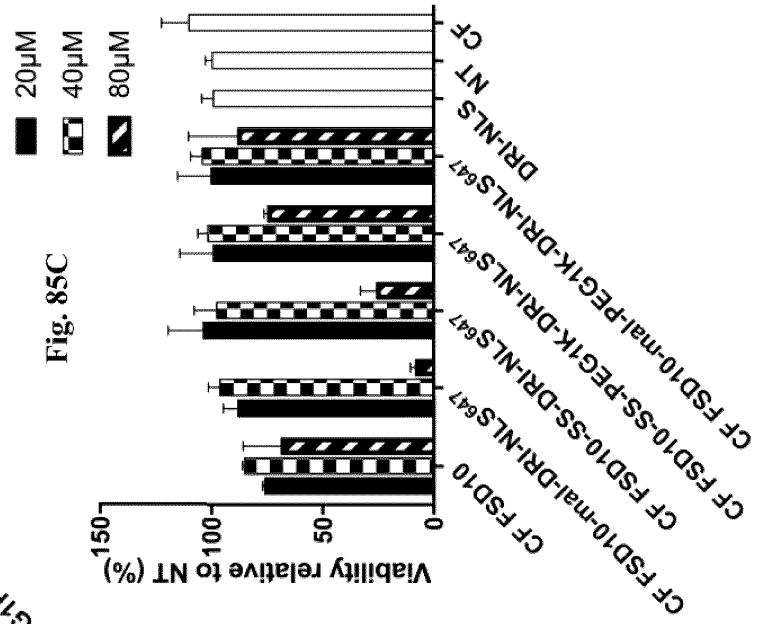
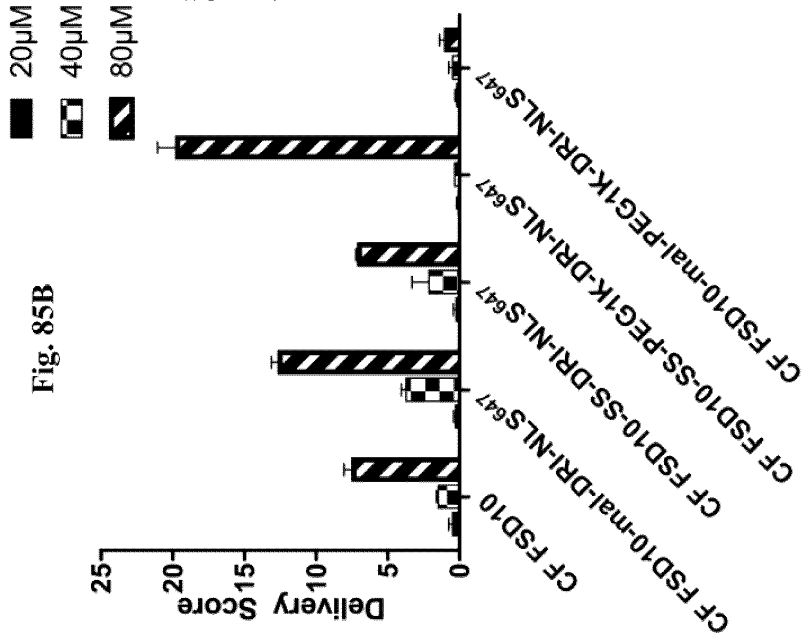


Fig. 86A

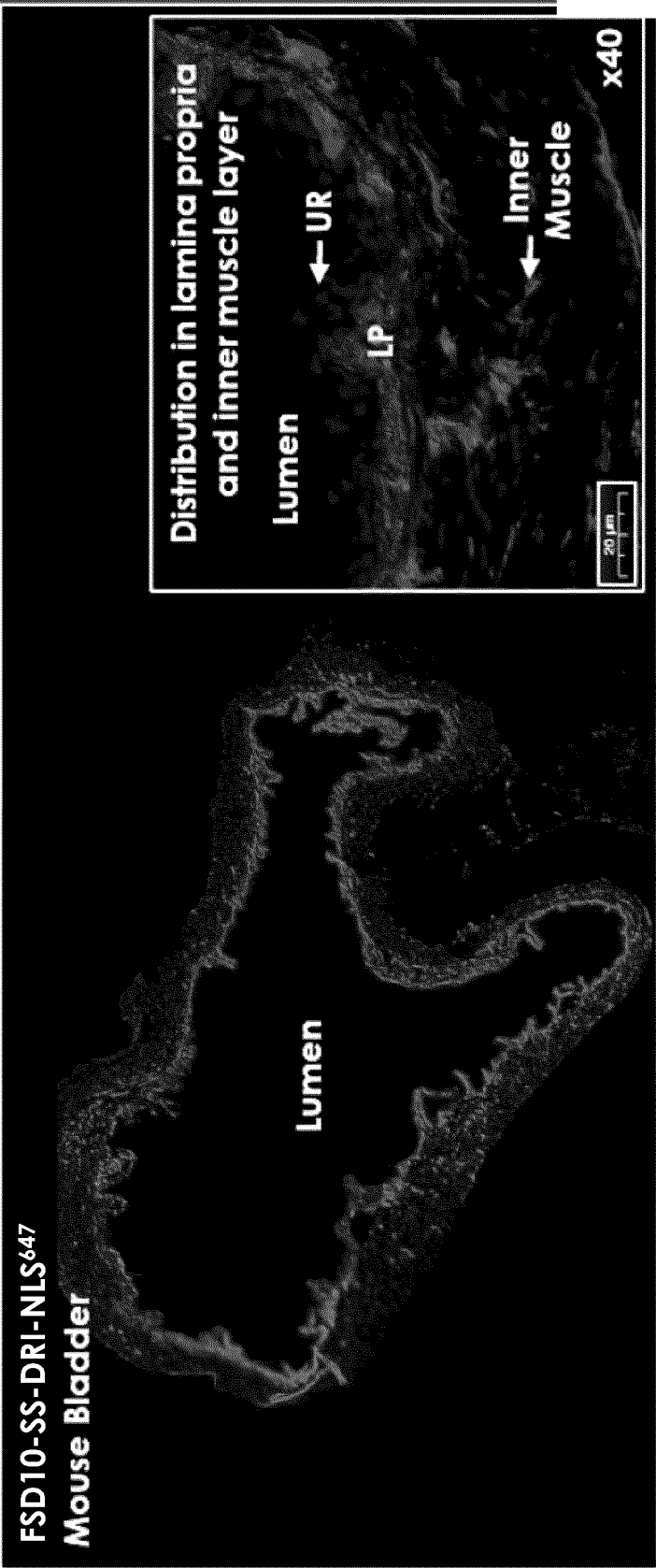


Fig. 86B

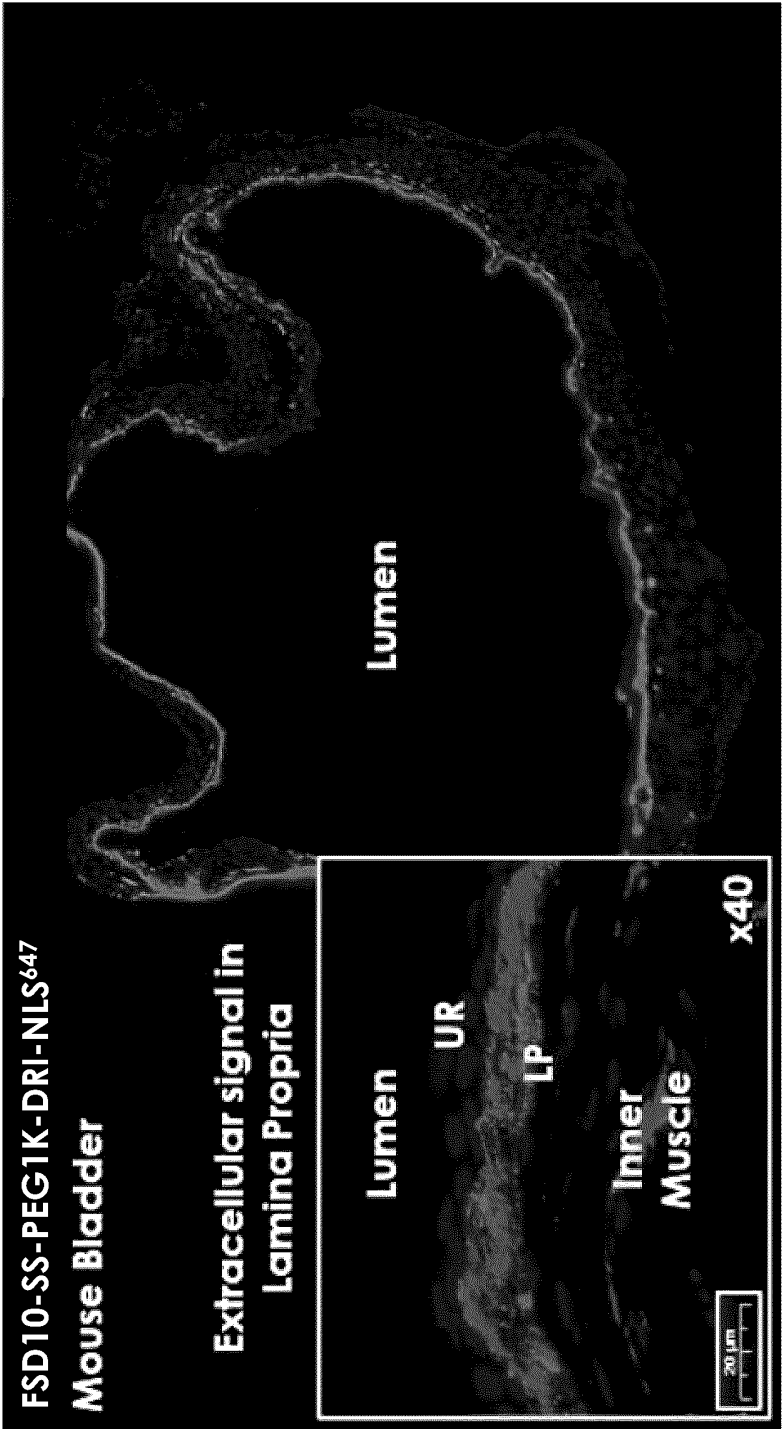


Fig. 86C

