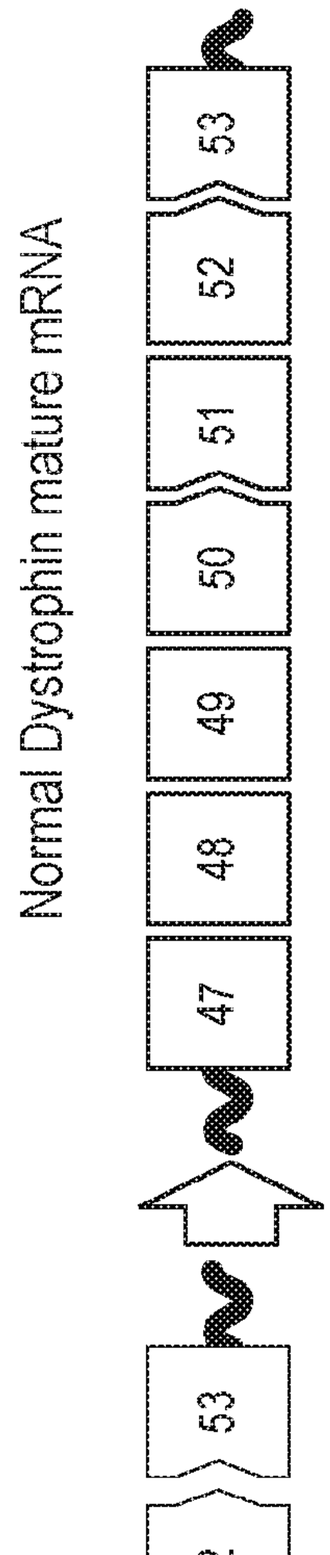

a) Normal Dystrophin pre-mRNA
49
50
51
52
53
Normal Dystrophin mature mRNA
47
48
49
50
51
52
53

Figure 1

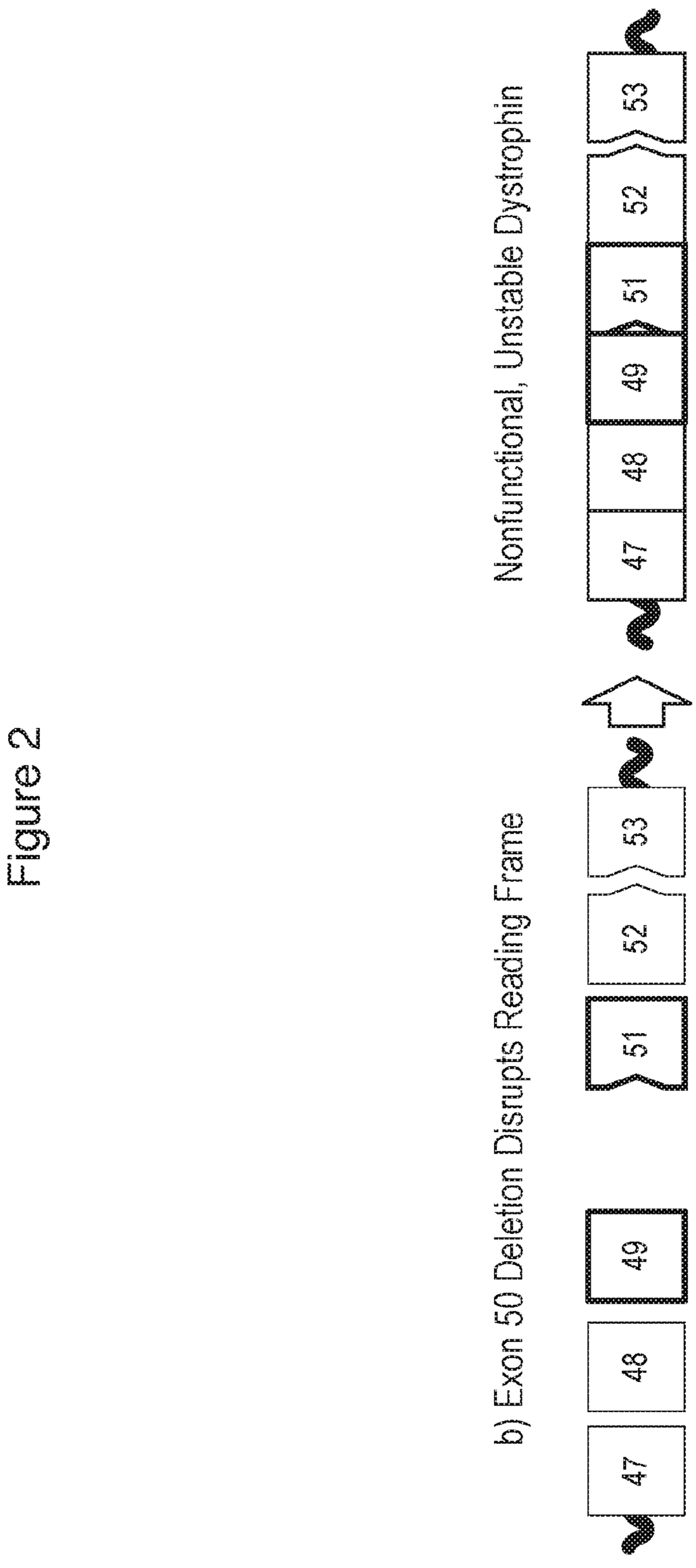

a) Exon 50 Deletion Disrupts Reading Frame
49
51
52
53
Nonfunctional, Unstable Dystrophin
47
48
49
51
52
53
b) Exon 51 Deletion Disrupts Reading Frame
47
48
49
51
52
53

Figure 2

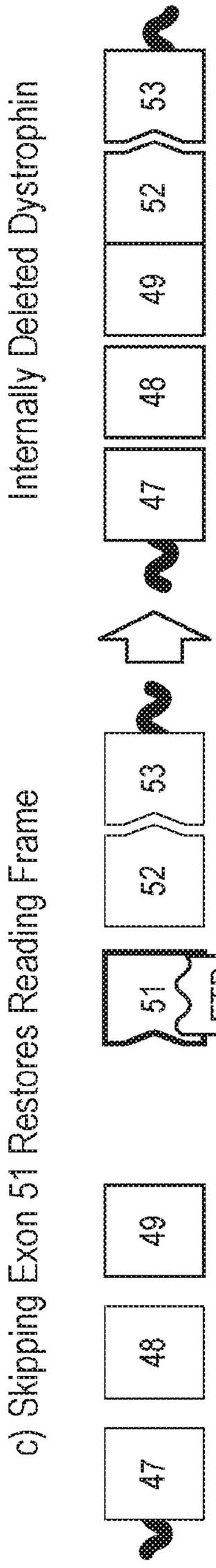

Internally Deleted Dystrophin
47
48
49
52
53
c) Skipping Exon 51 Restores Reading Frame
49
51
ETP
52
53
47
48
Source: Adapted from Kole 2012.

Figure 3

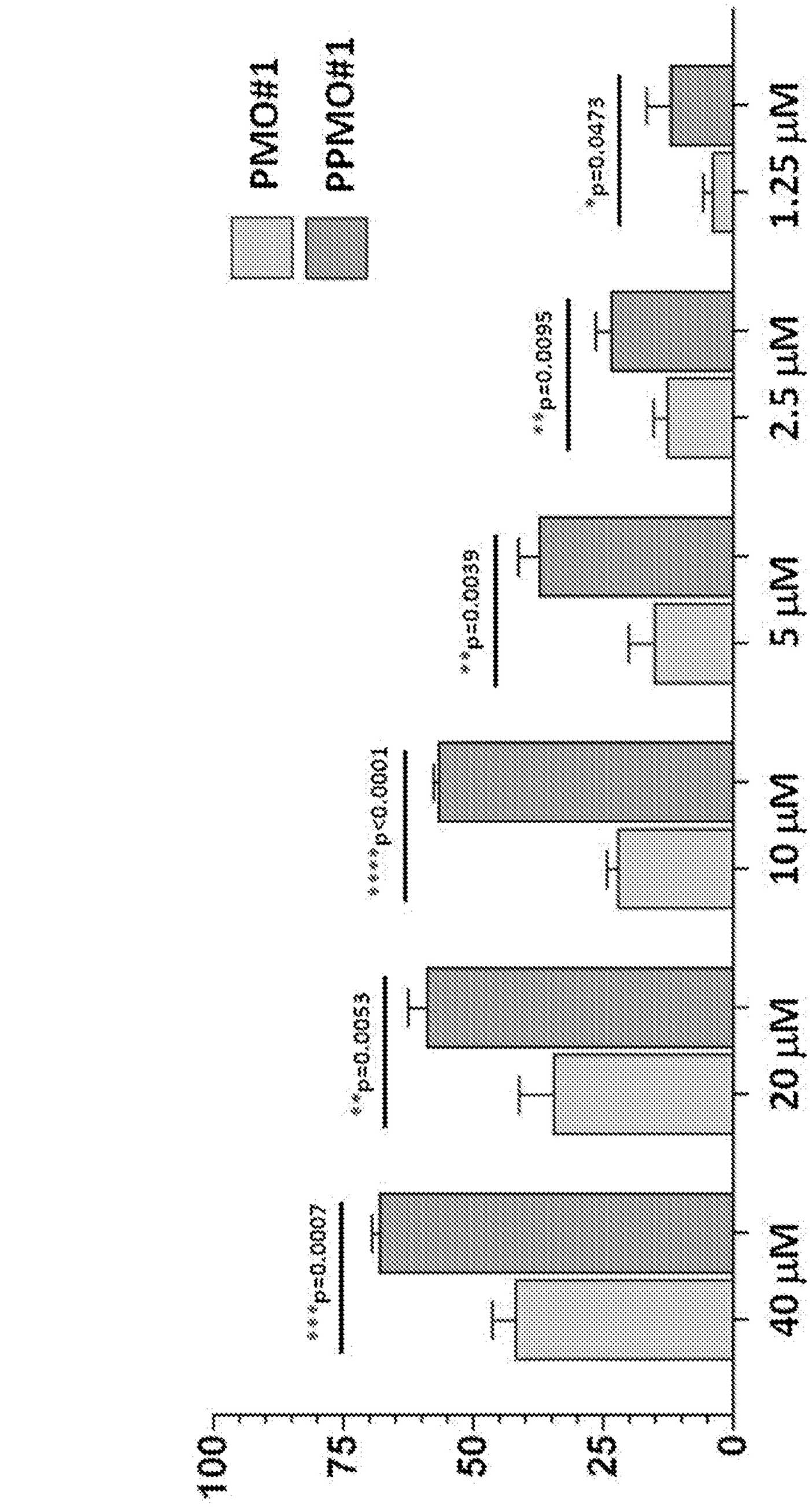

PMO#1
PPMO#1
1.25 µM
2.5 µM
5 µM
10 µM
20 µM
40 µM
*p=0.0473
**p=0.0095
**p=0.0039
***p<0.0001
**p=0.0053
***p=0.0007
Exon 51 Skipping (%)
100
75
50
25
0
Mean +/- SE

Figure 4

Figure 5A

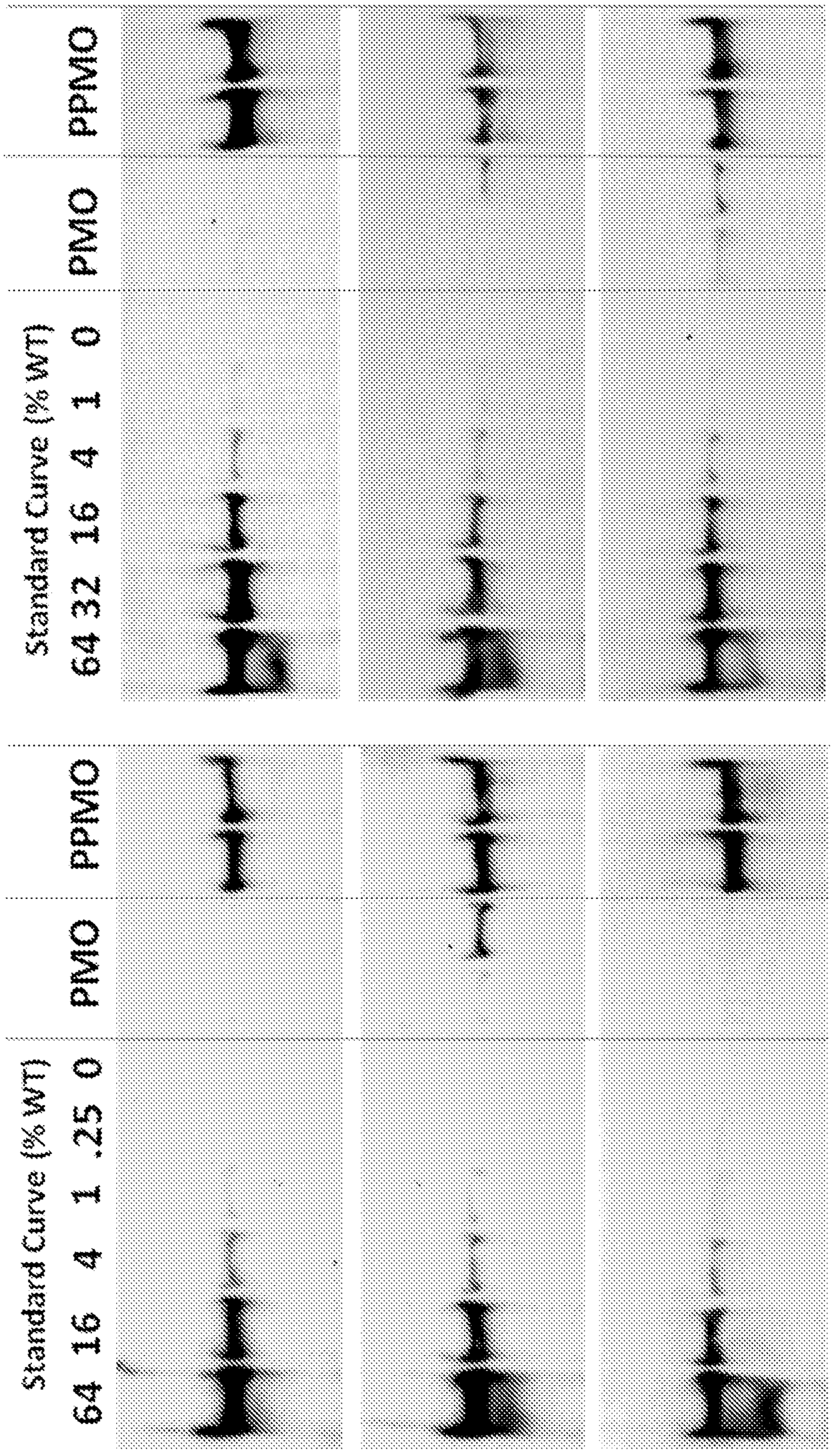


Figure 5B

Figure 5C

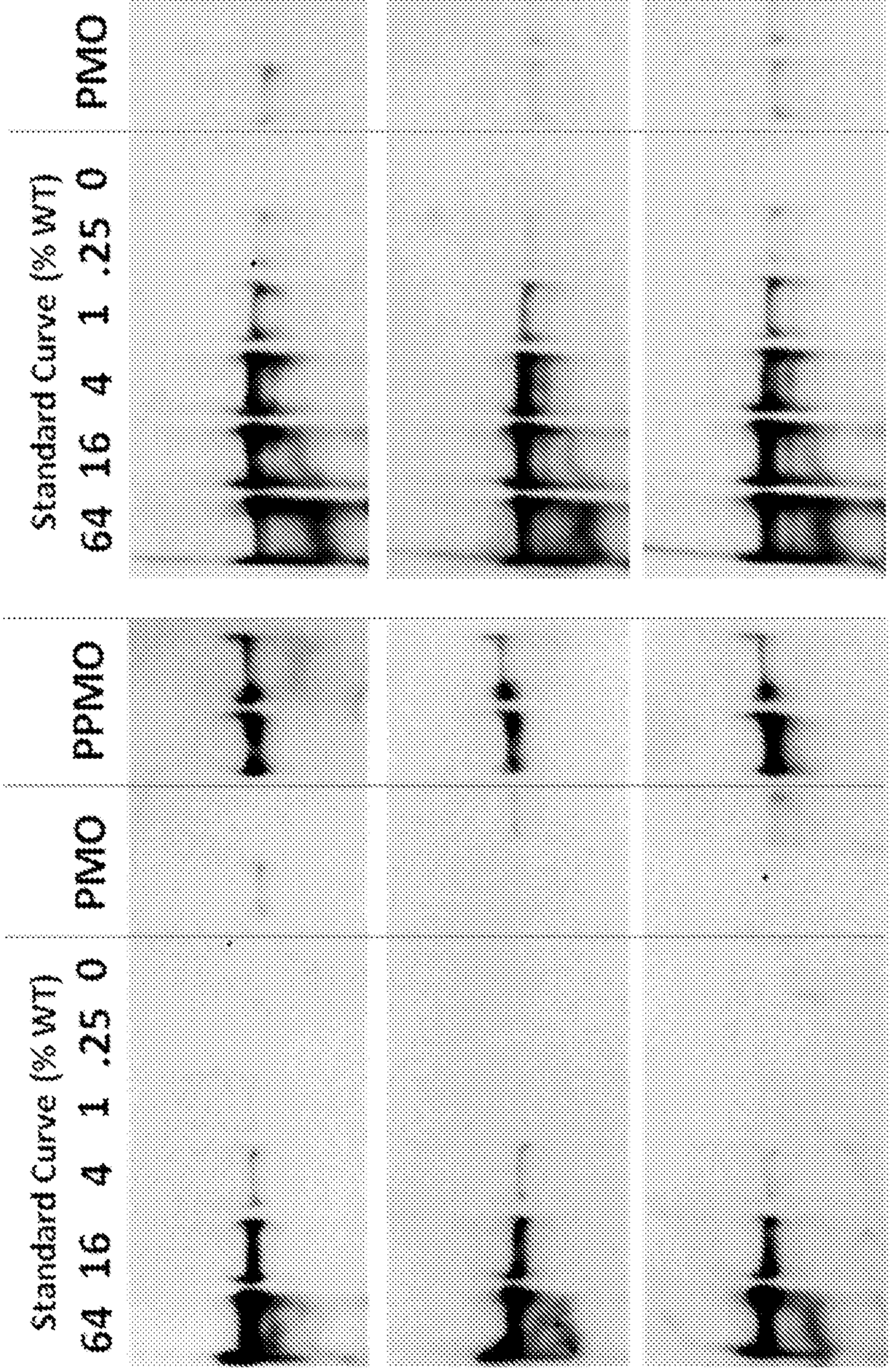


Figure 5D

Figure 6A

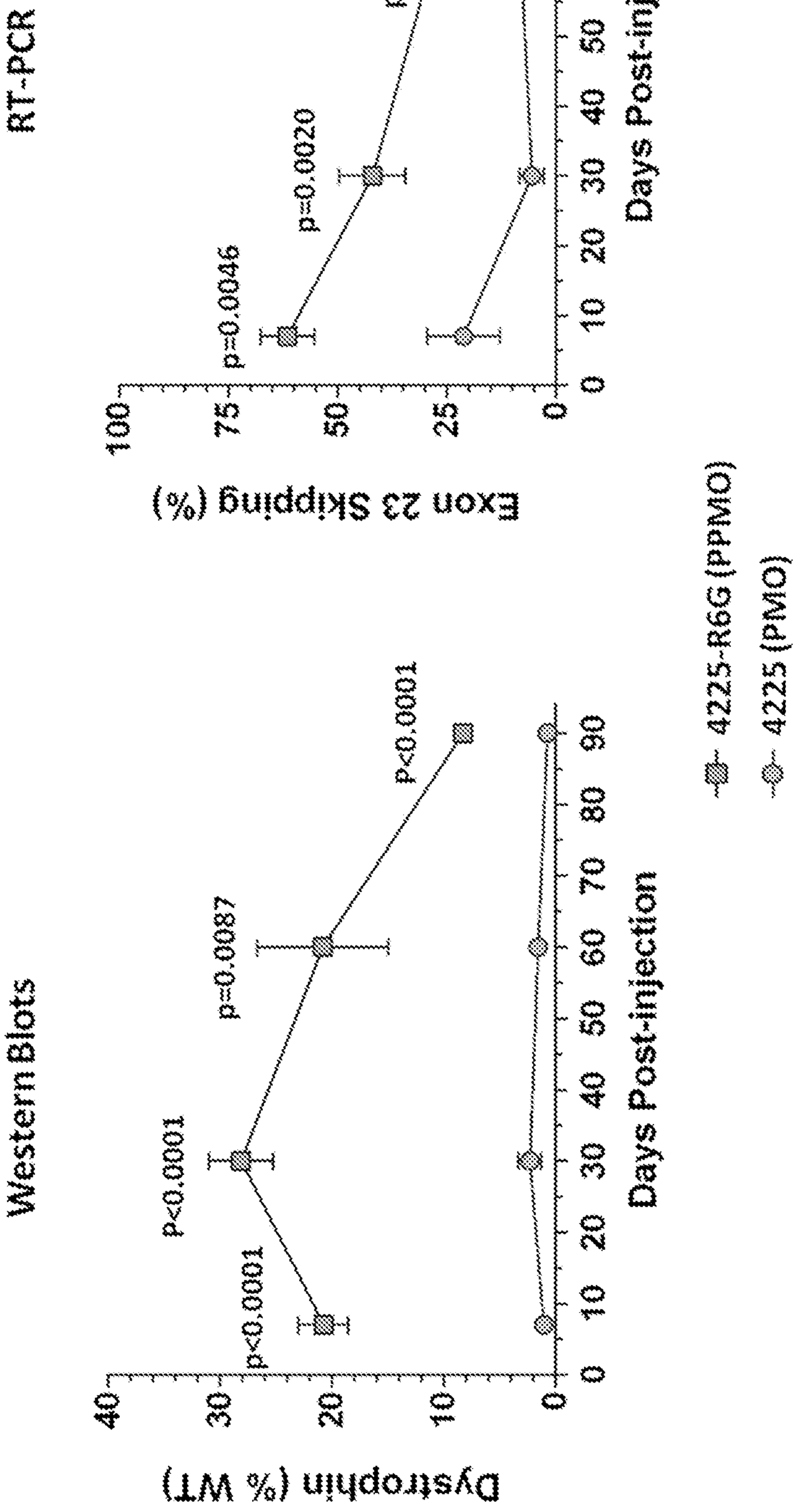


Figure 6B

Figure 7B
30 Days

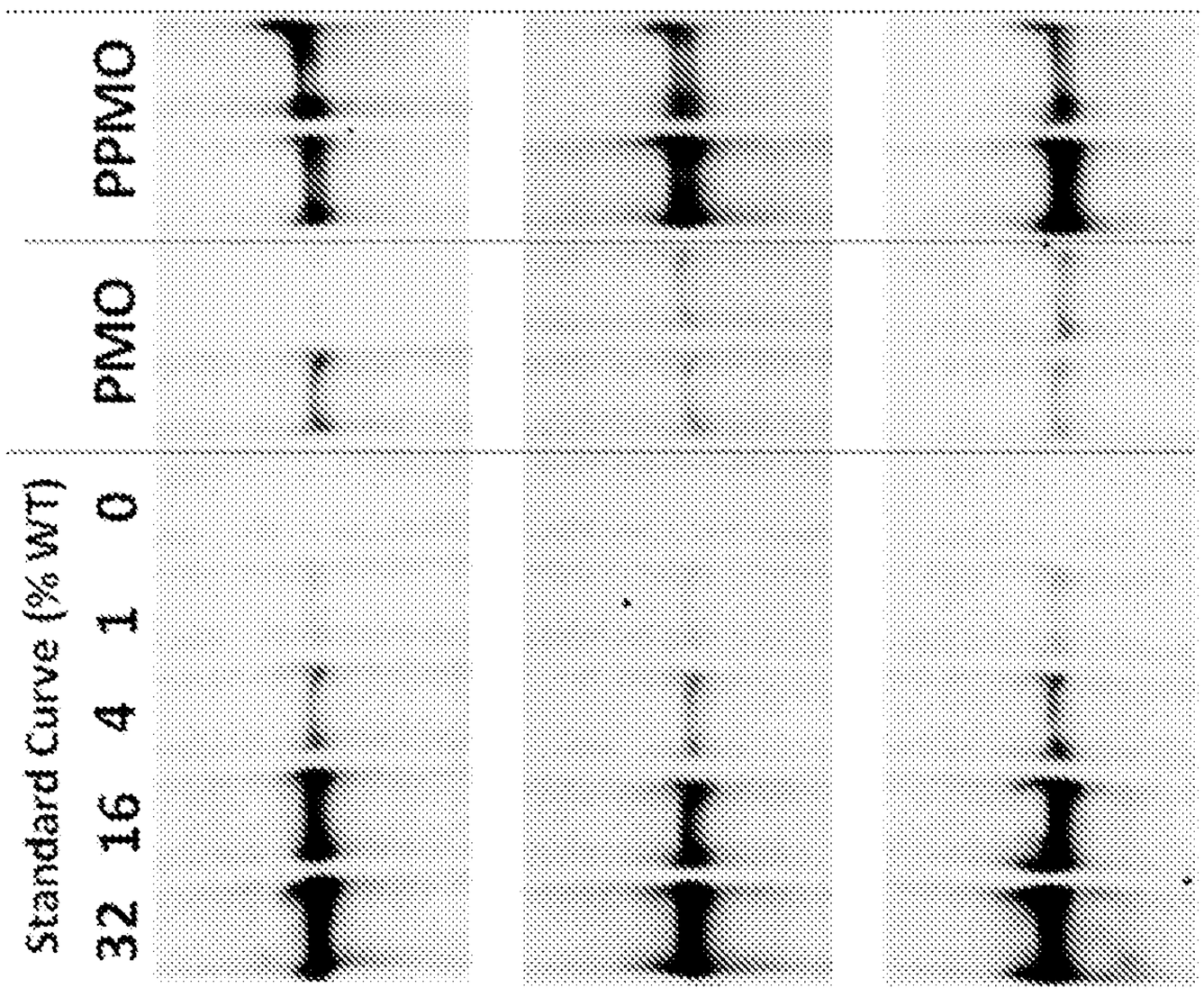


Figure 7A
7 Days

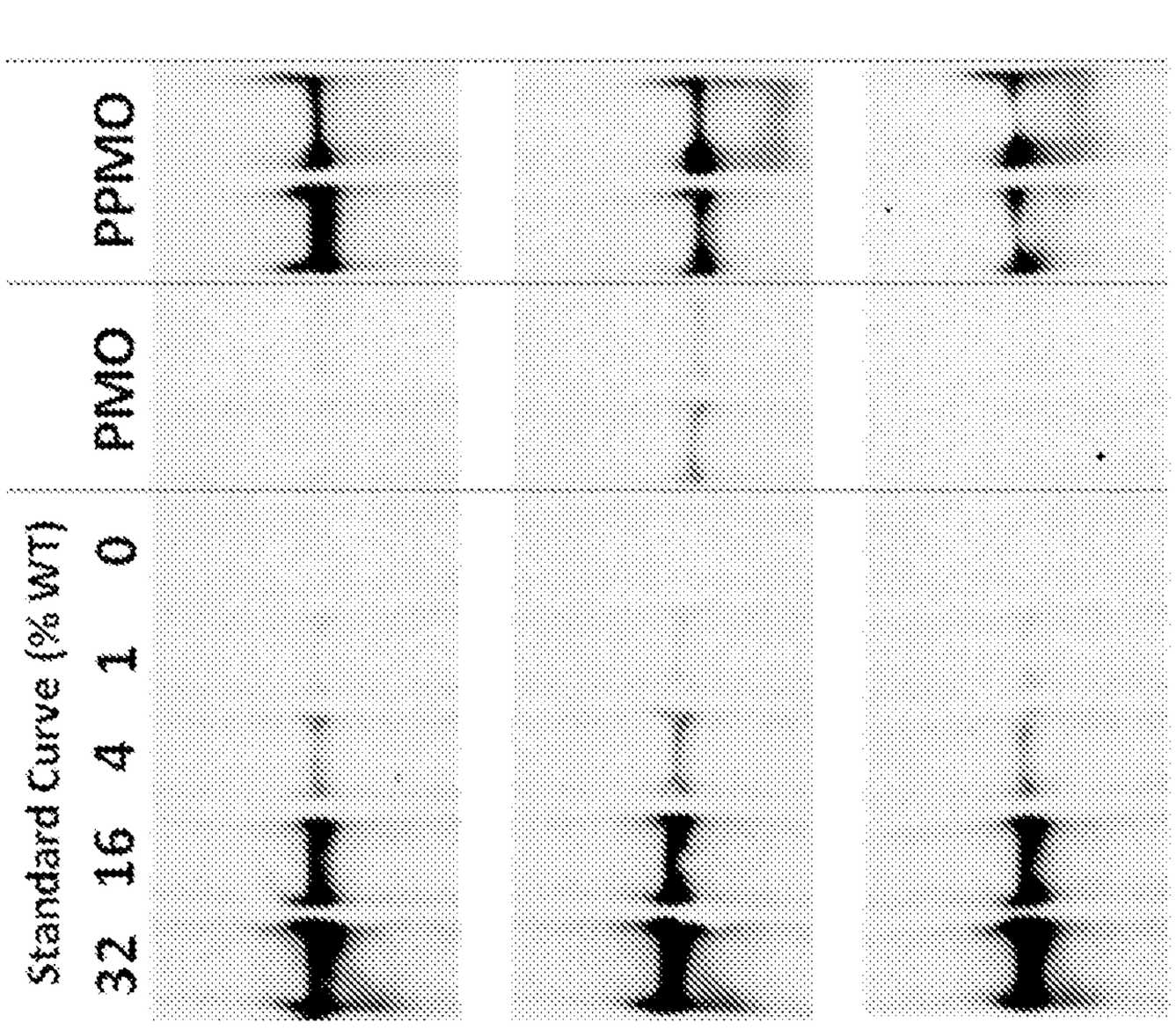


Figure 7D

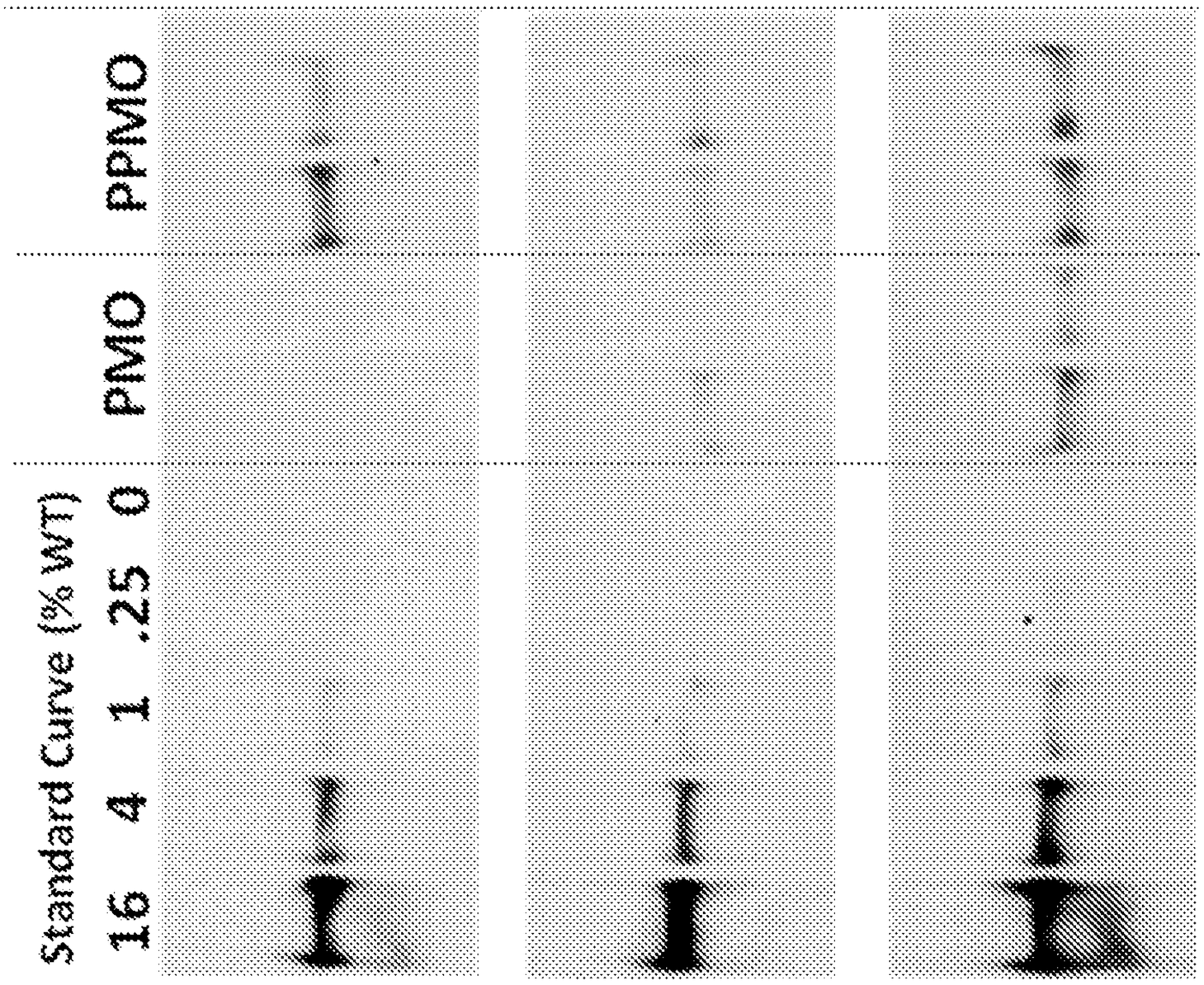


Figure 7C

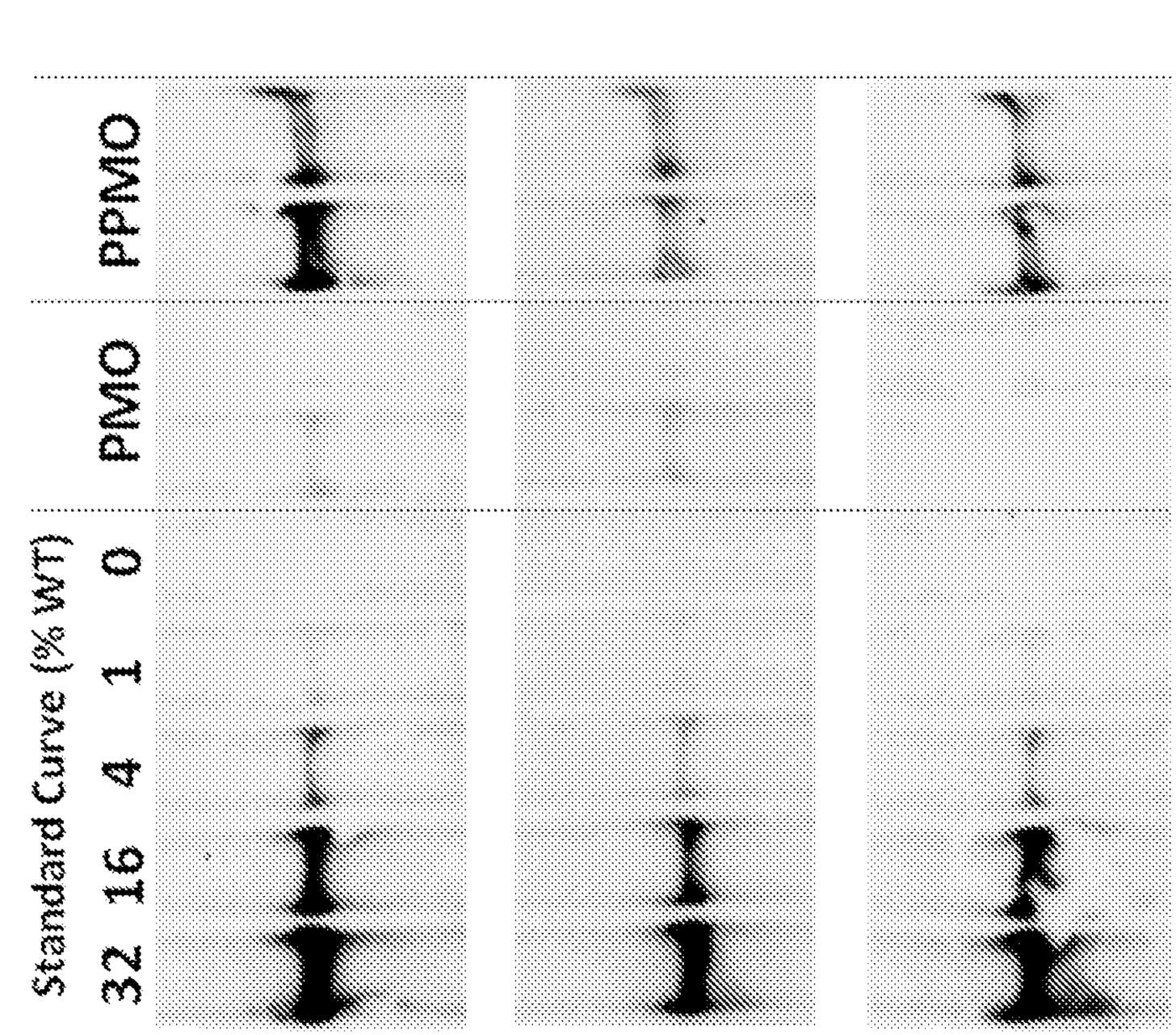


Figure 8A

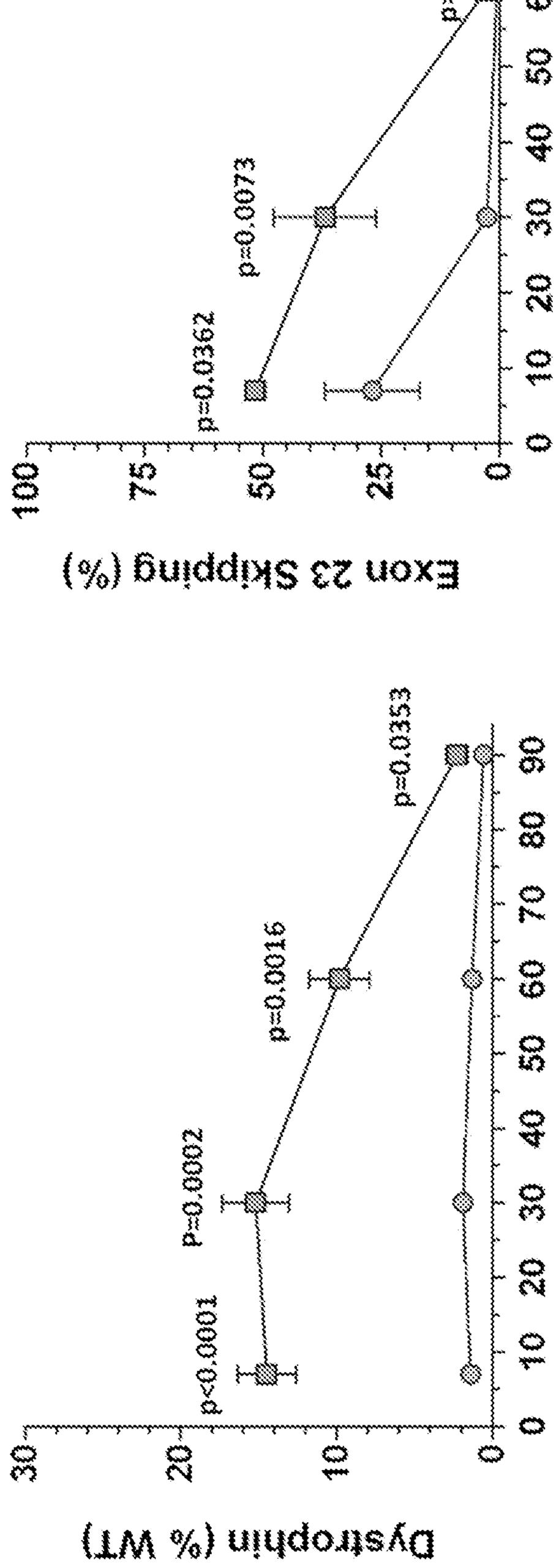


Figure 8B

Figure 9A

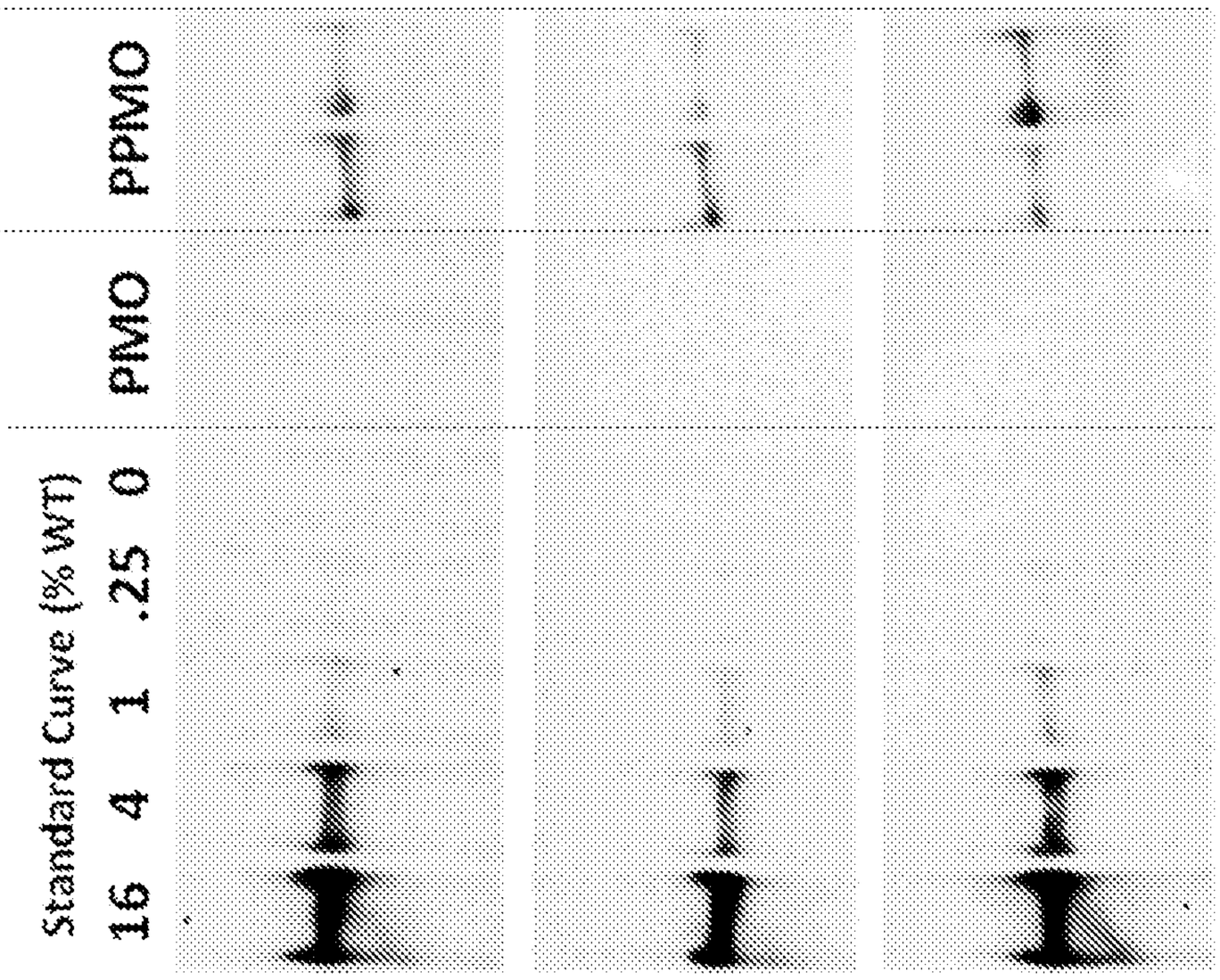
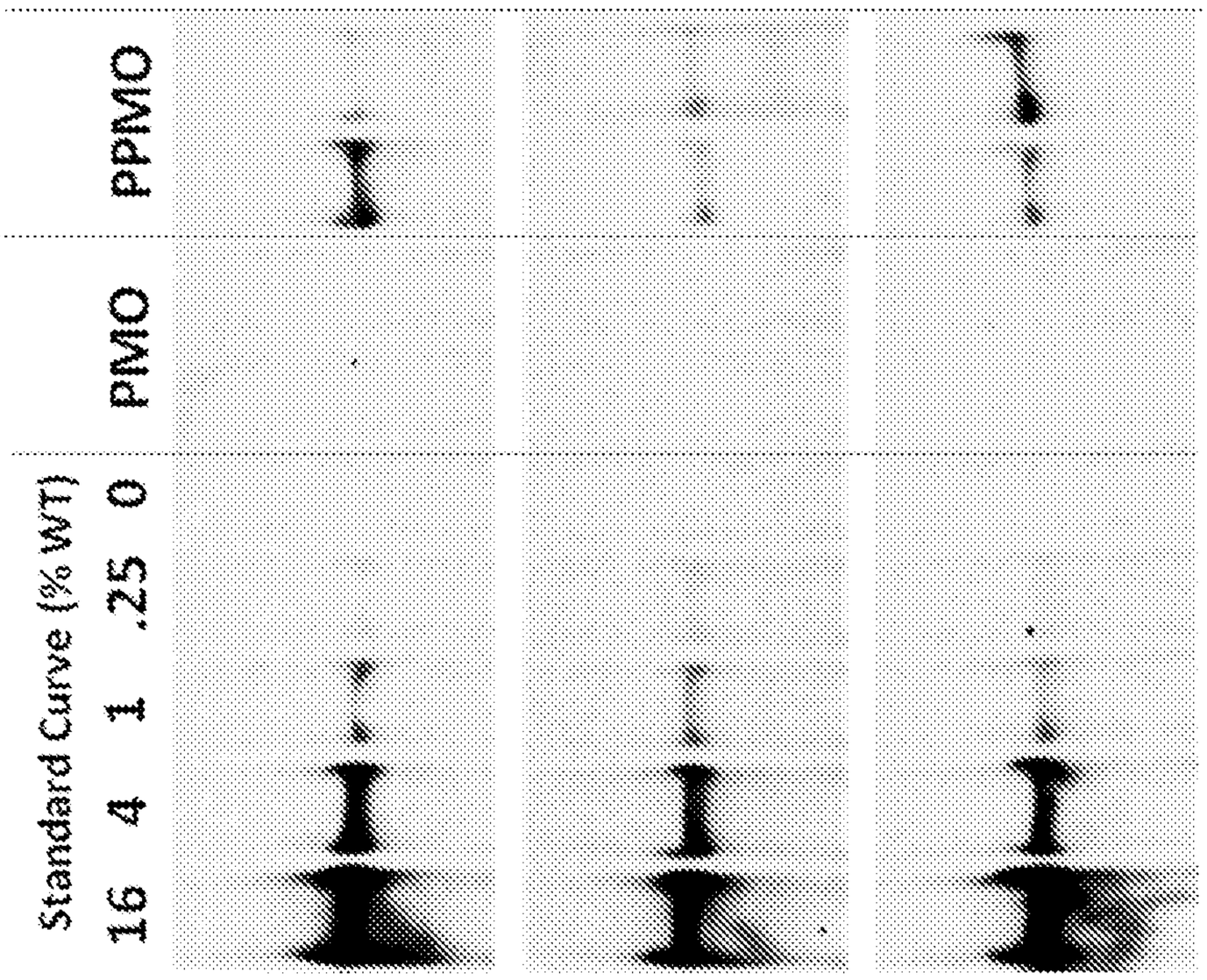


Figure 9B



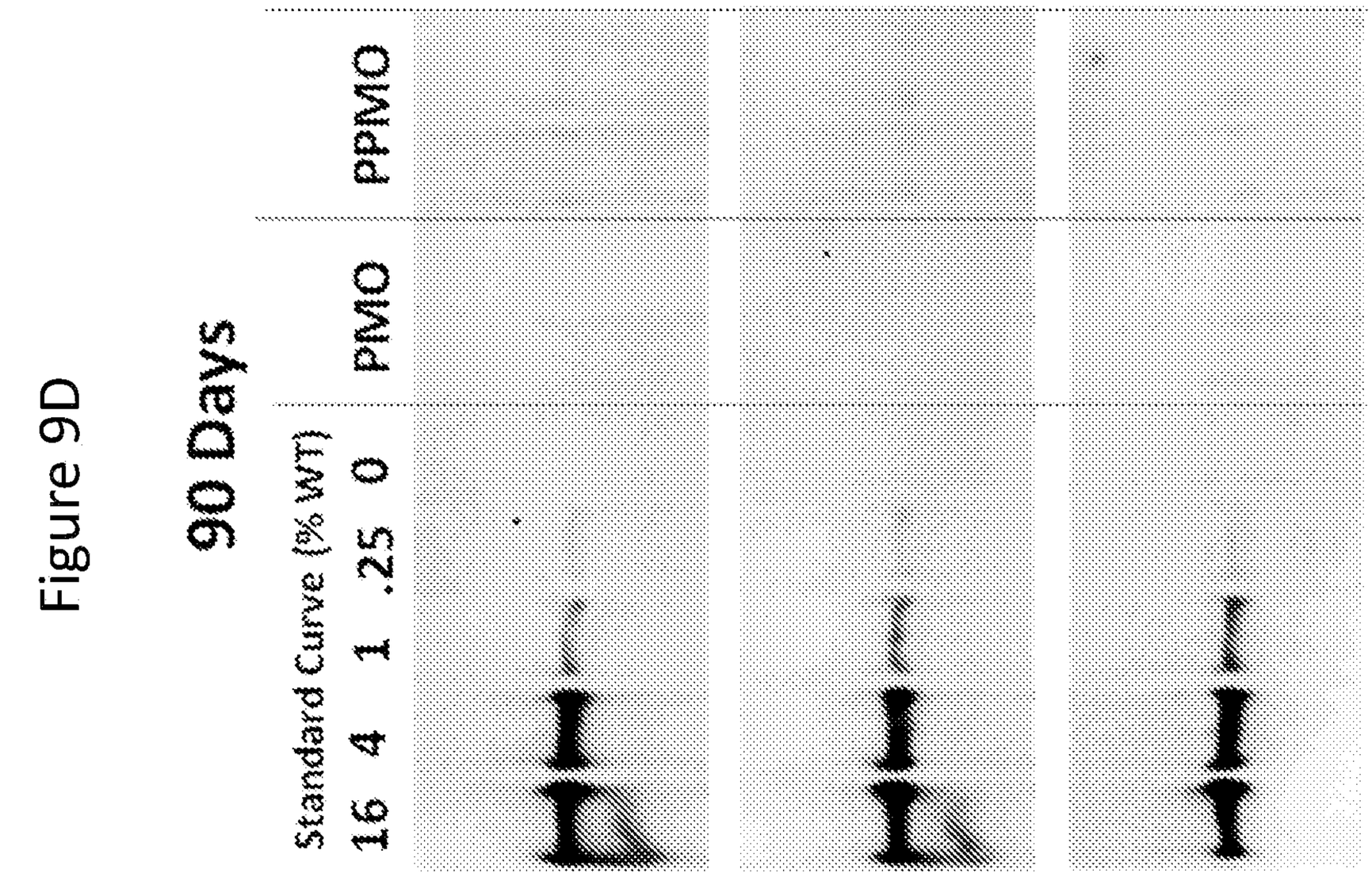


Figure 9D

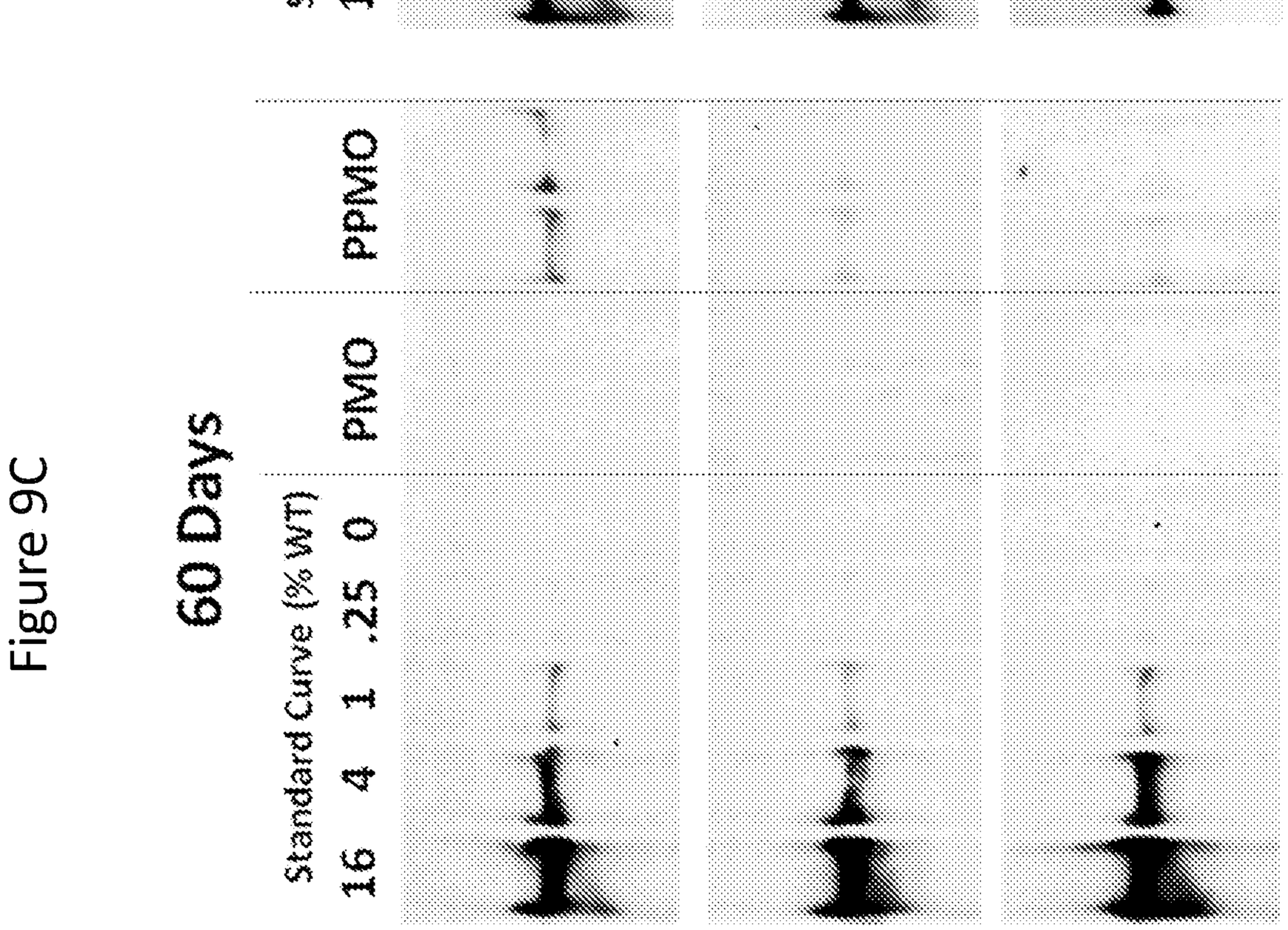


Figure 9C

Figure 10A

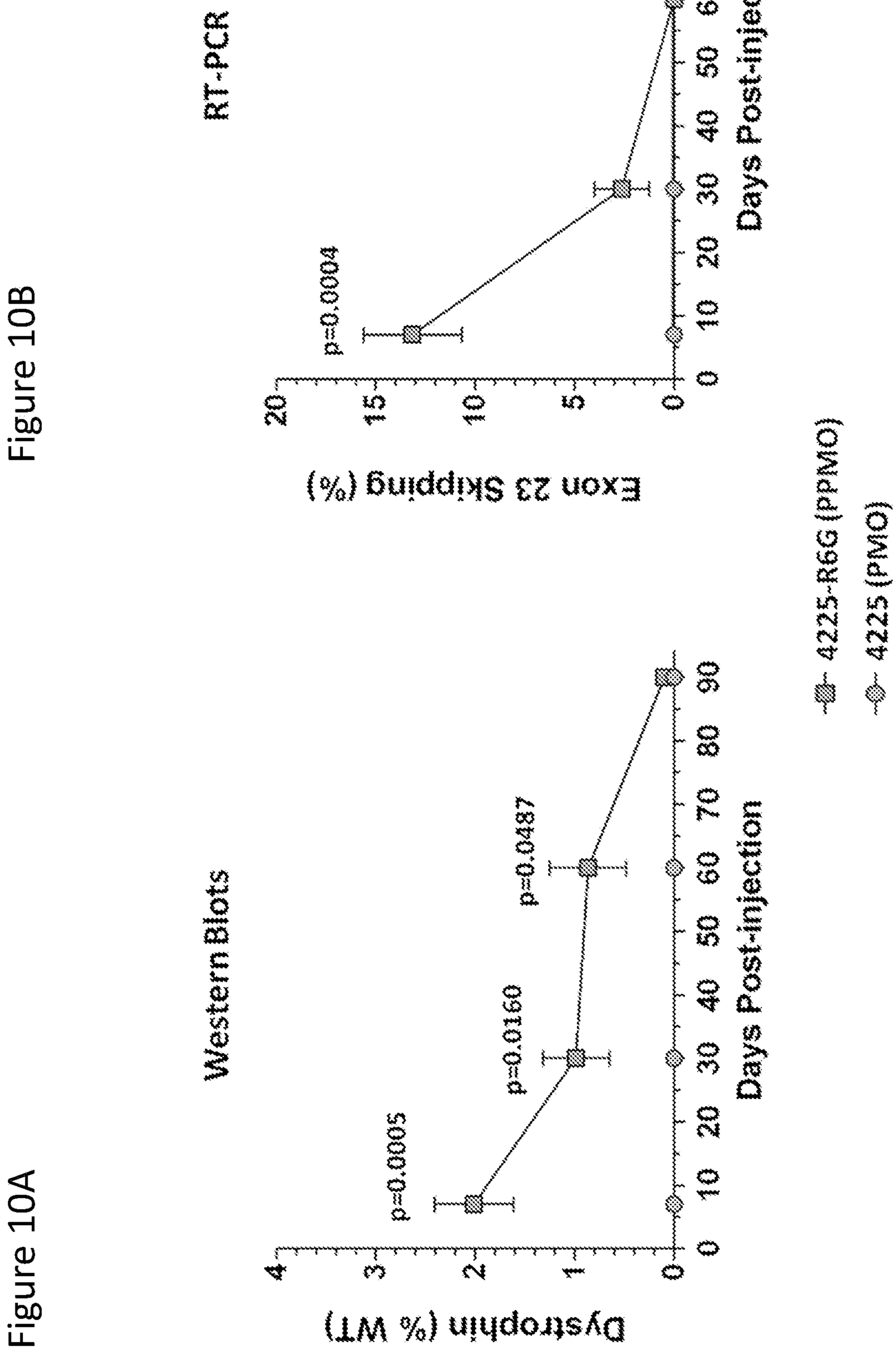


Figure 10B

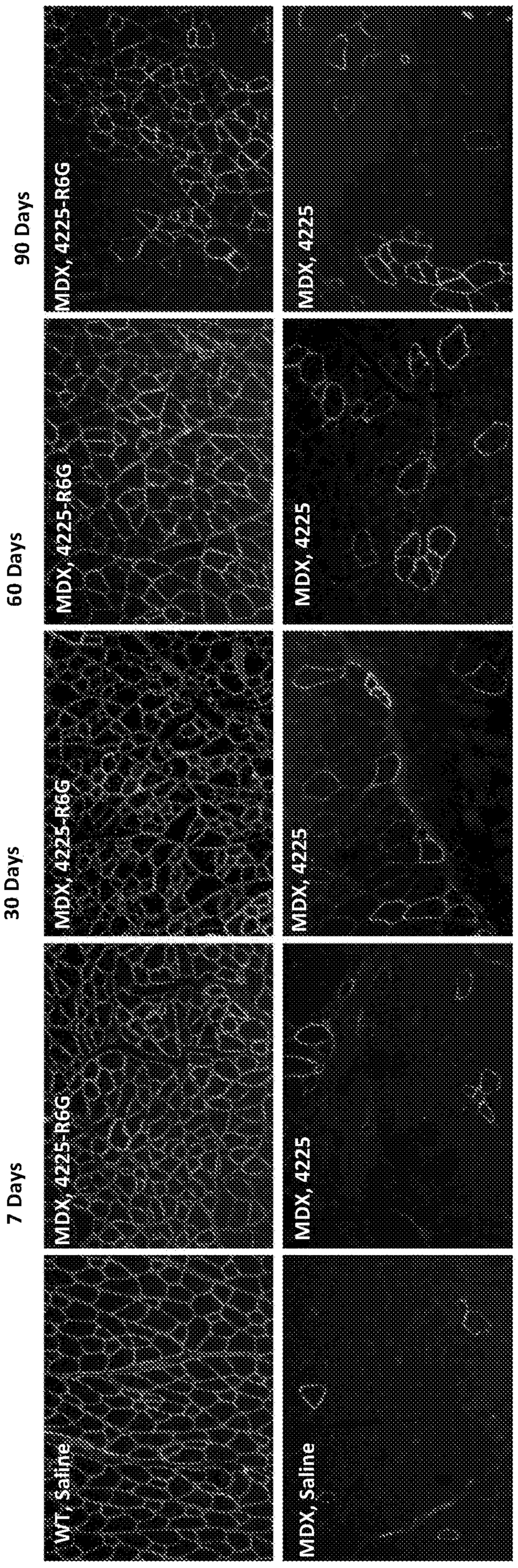

90 Days
MDX, 4225-R6G
MDX, 4225
60 Days
MDX, 4225-R6G
MDX, 4225
30 Days
MDX, 4225-R6G
MDX, 4225
7 Days
MDX, 4225-R6G
MDX, 4225
WT, Saline
MDX, Saline

Figure 11

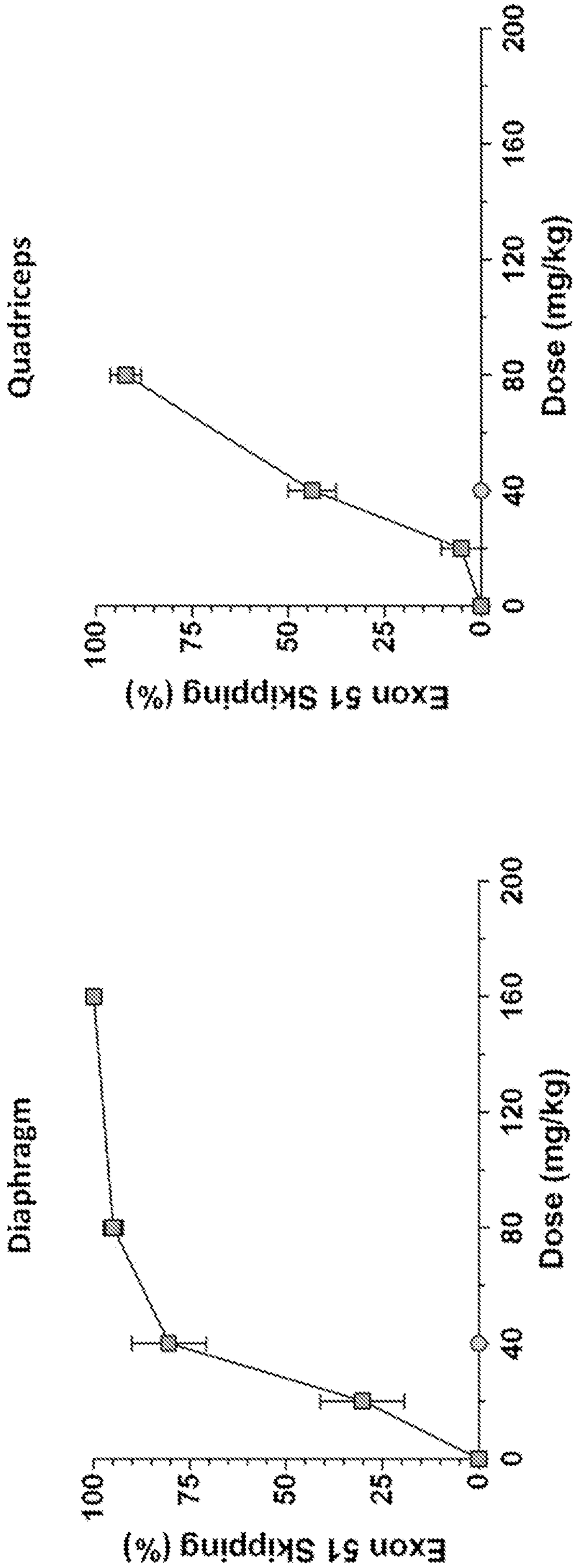

Quadriceps
Exon 51 Skipping (%)
100
75
50
25
0
0
40
80
120
160
200
Dose (mg/kg)
Diaphragm
Exon 51 Skipping (%)
100
75
50
25
0
0
40
80
120
160
200
Dose (mg/kg)
PMO#1
PMO#1

Figure 12

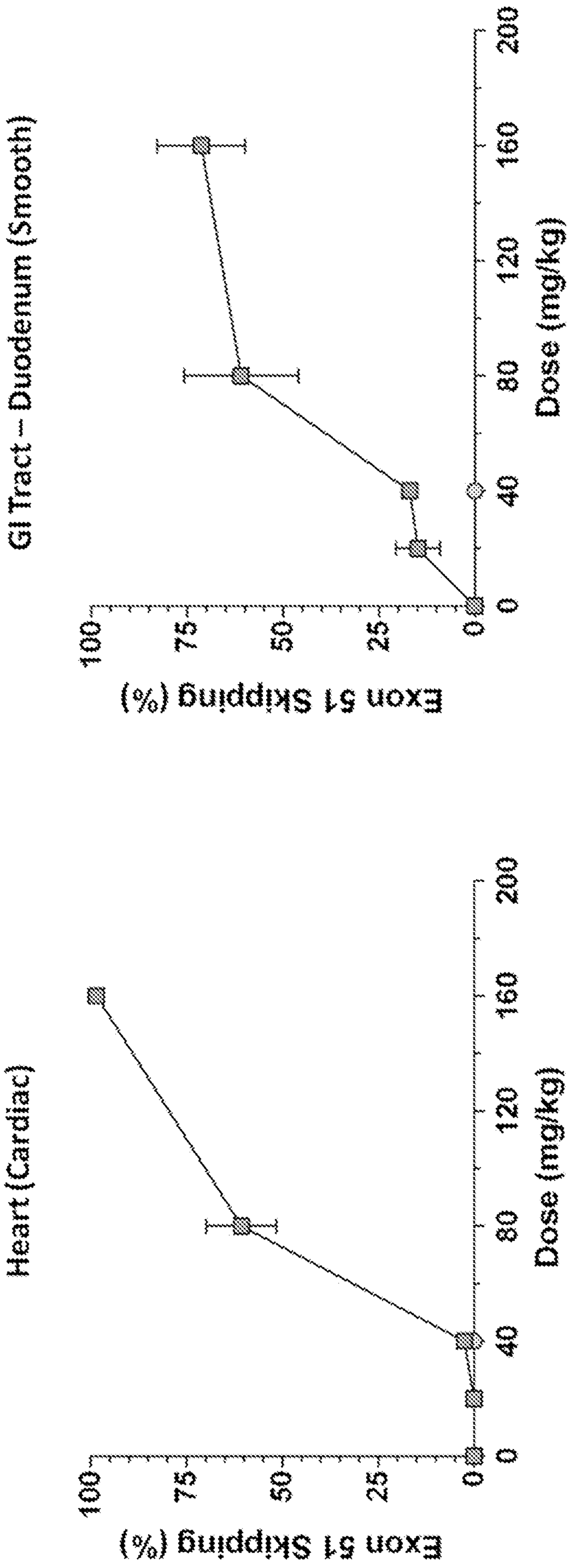
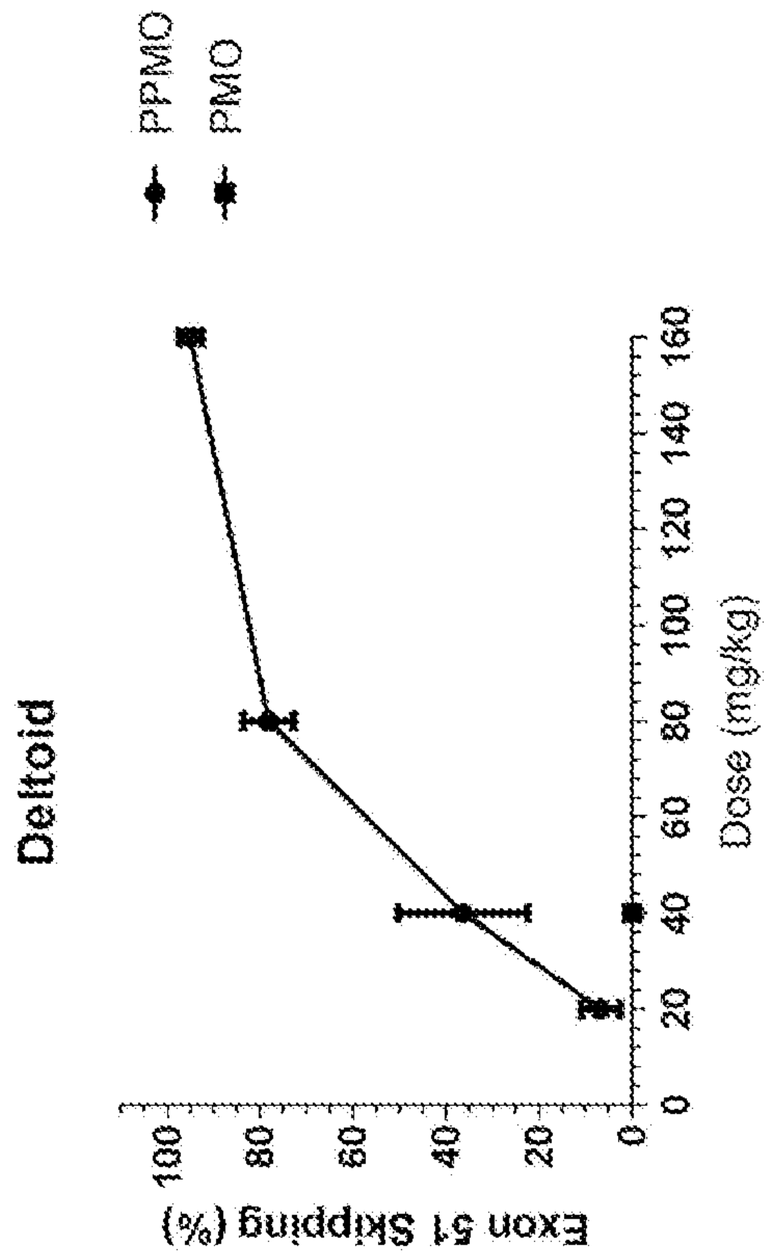

GI Tract – Duodenum (Smooth)
Exon 51 Skipping (%)
100
75
50
25
0
0
40
80
120
160
200
Dose (mg/kg)
Heart (Cardiac)
Exon 51 Skipping (%)
100
75
50
25
0
0
40
80
120
160
200
Dose (mg/kg)
PMO#1
PMO#1

Figure 13


Deltoid
PPMO
PMO
Exon 51 Skipping (%)
0
20
40
60
80
100
0
20
40
60
80
100
120
140
160
Dose (mg/kg)

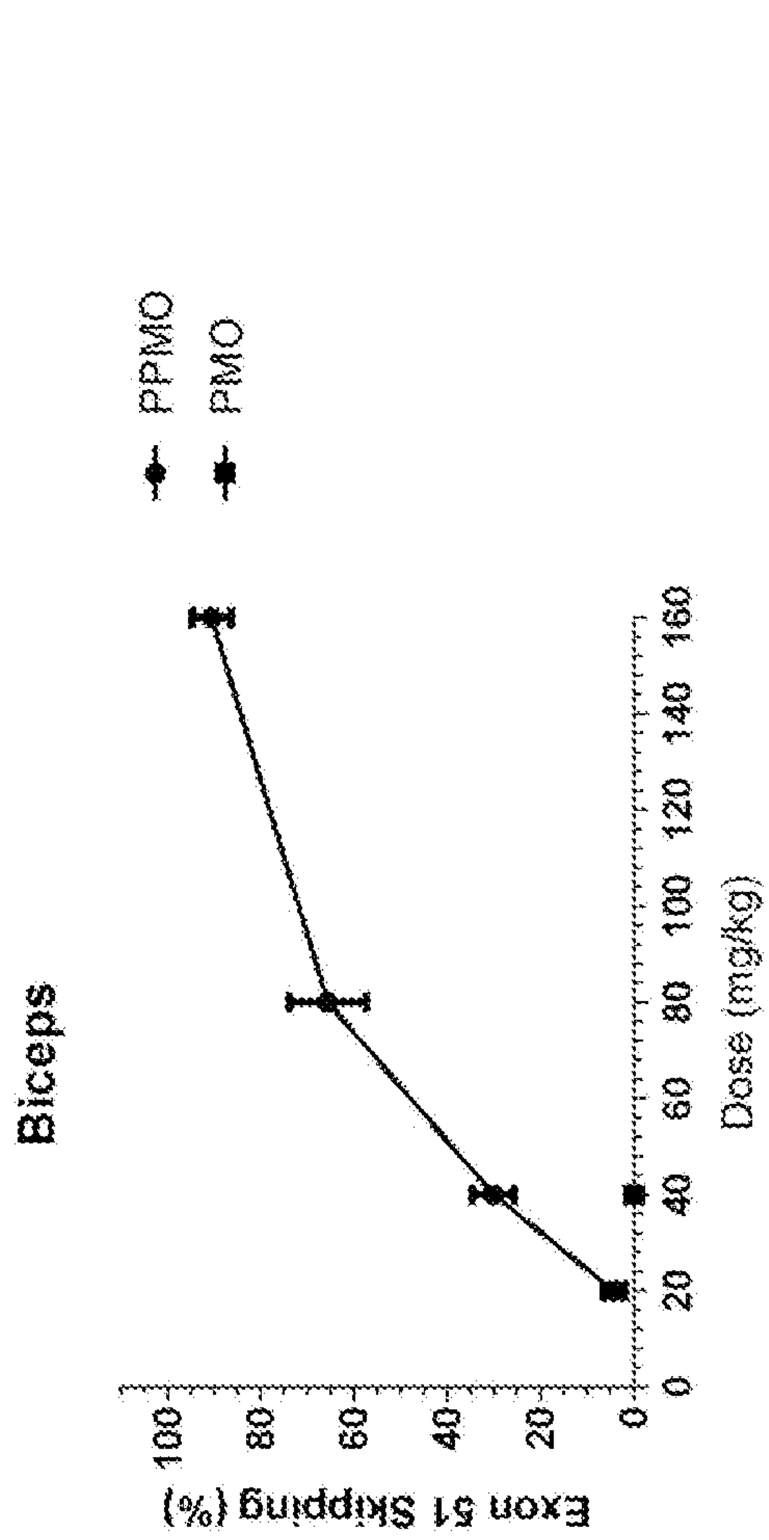

Biceps
PPMO
PMO
Exon 51 Skipping (%)
0
20
40
60
80
100
0
20
40
60
80
100
120
140
160
Dose (mg/kg)

Figure 14

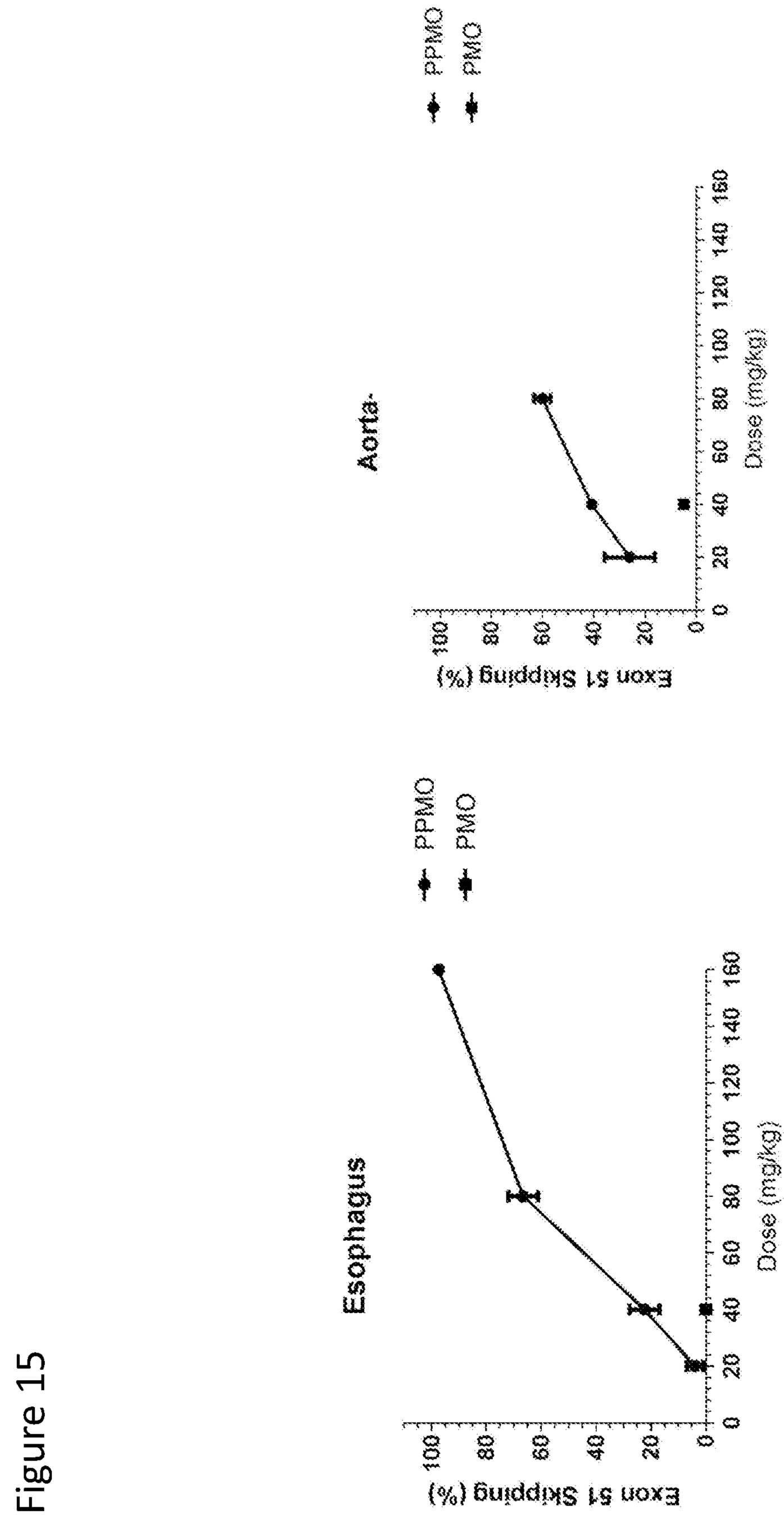

Aorta
Exon 51 Skipping (%)
0
20
40
60
80
100
0
20
40
60
80
100
120
140
160
Dose (mg/kg)
PPMO
PMO
Esophagus
Exon 51 Skipping (%)
0
20
40
60
80
100
0
20
40
60
80
100
120
140
160
Dose (mg/kg)
PPMO
PMO

Figure 15

Figure 16A

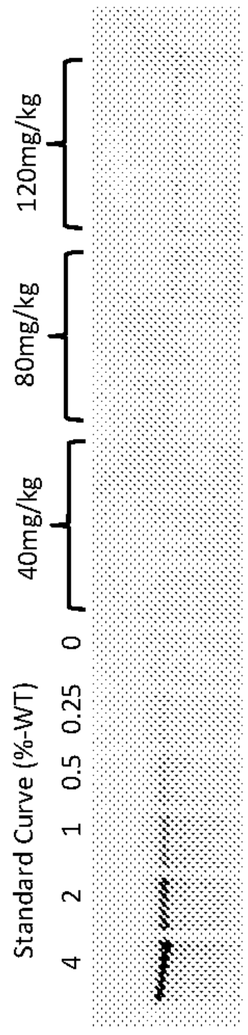


Figure 16B

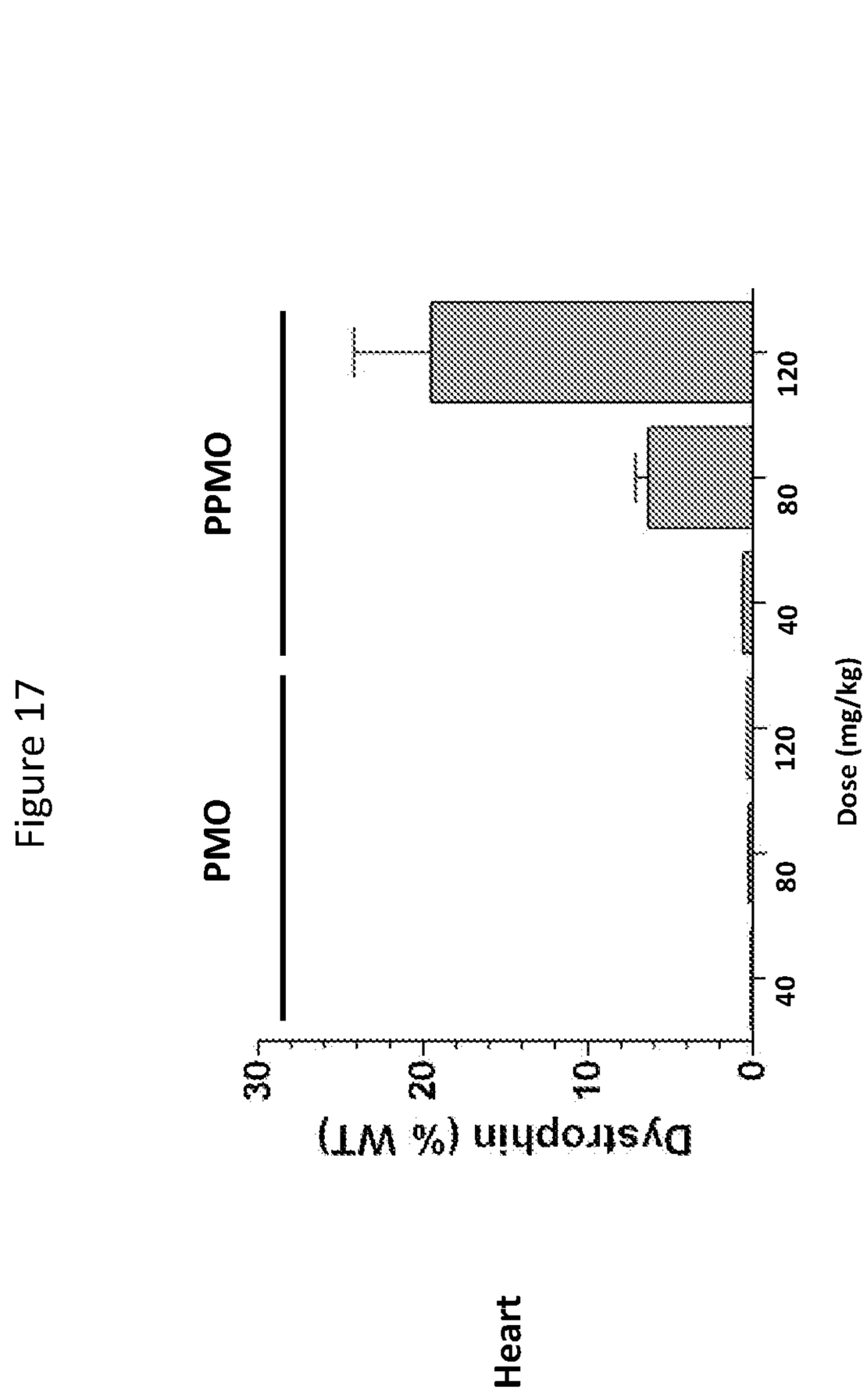


Figure 17

Figure 18B

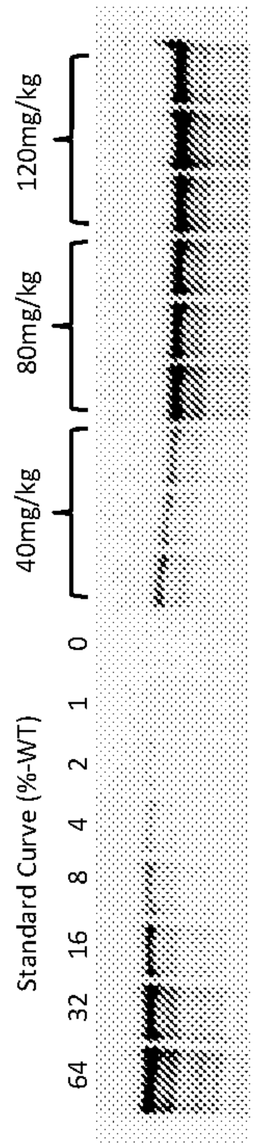
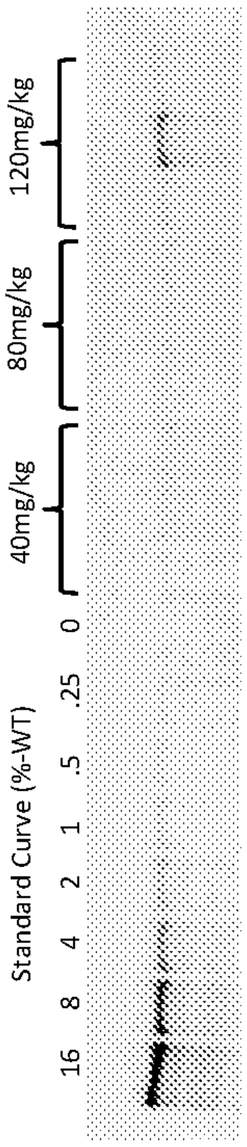


Figure 18A



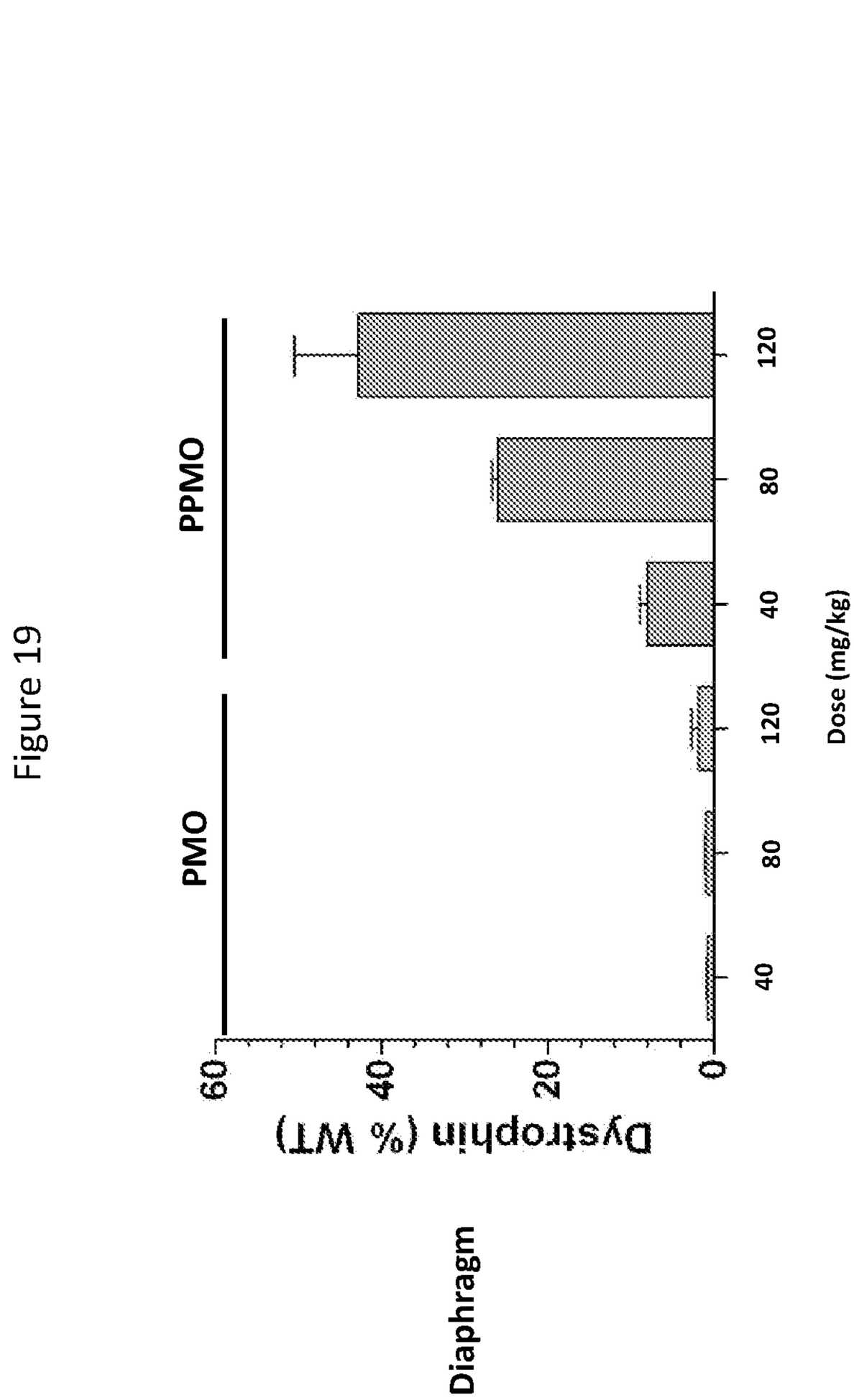

PPMO
PMO
Dystrophin (% WT)
0
20
40
60
40
80
120
Dose (mg/kg)
Diaphragm

Figure 19

Figure 20A

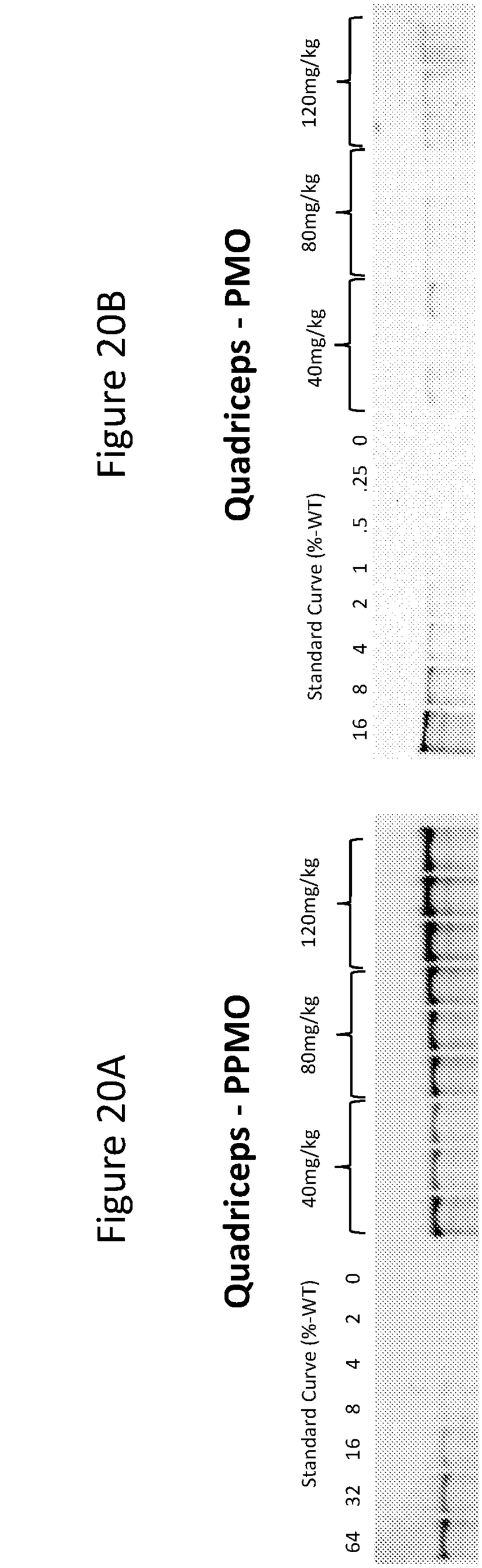
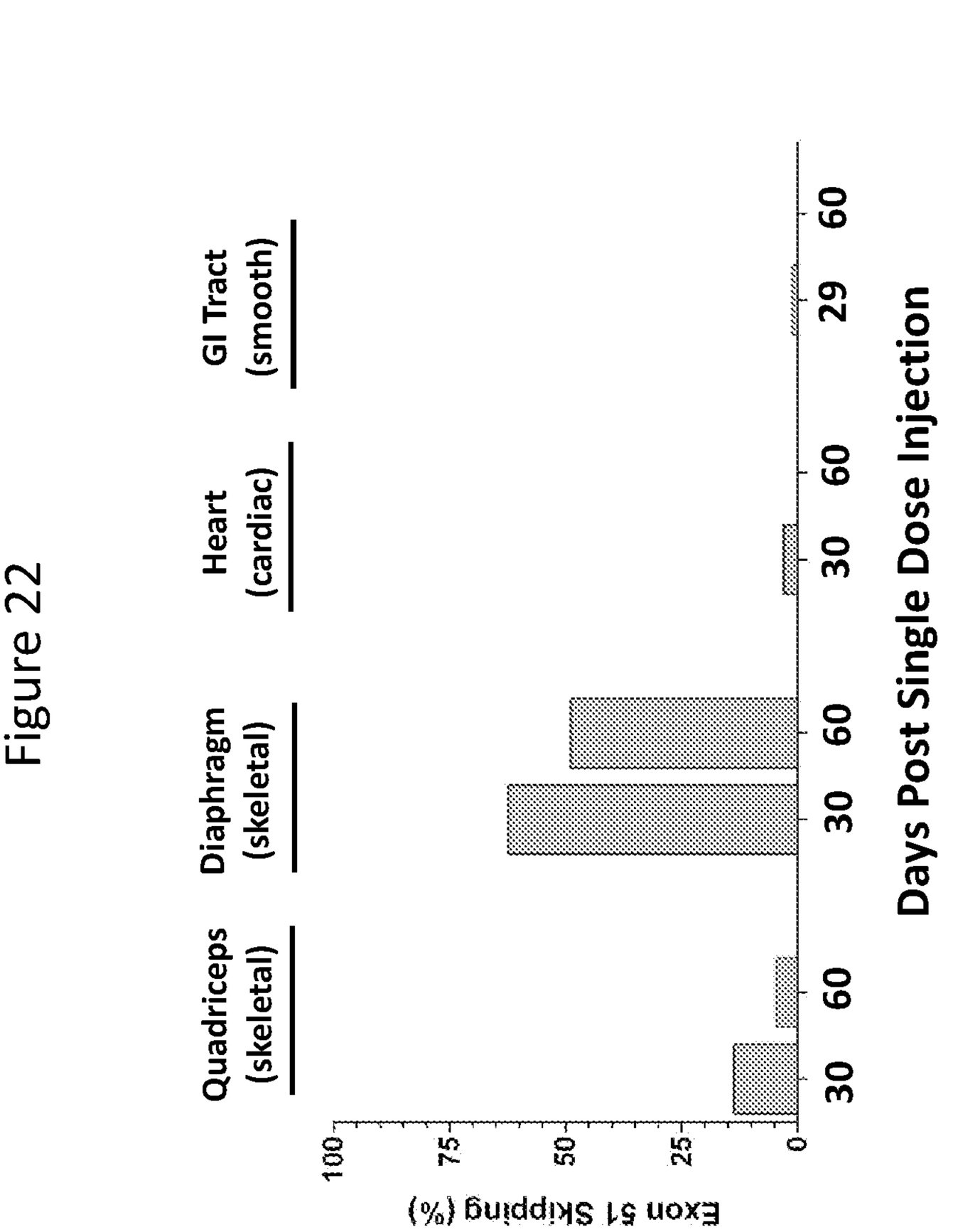


Figure 20B

Figure 21

PPMO
PMO
Dystrophin (%WT)
200
150
100
50
0
40
80
120
Dose (mg/kg)
Quadriceps

Figure 22


Heart (cardiac)
GI Tract (smooth)
Quadriceps (skeletal)
Diaphragm (skeletal)
Exon 51 Skipping (%)
100
75
50
25
0
30
60
30
60
30
60
29
60
Days Post Single Dose Injection

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
1:C	5.5L	a) 5,5L b) 5.5L, 122ml	3x5.5L	5.5L	536.7g; 195 ml NEM; 3.2L DMI	5	5.5L	2x5.5L
2:T	7.0L	a) 7L b) 7L, 158ml	3x7L	2x7L	468.2g and 195ml NEM 3.2L DMI	4.25	7L	2x7L[2]
3:C	8L	a) 8L b) 8L, 182ml	3x8L	2x8L	536.7g; 195ml NEM; 3.4L DMI	4.25	8L	2x8L
4:C	9L	a) 9L b) 9L, 206ml	3x9L	2x9L	536.7g; 195ml NEM; 3.6L DMI	4.25	9L	2x9L[3]
5:A	9.5L	a) 9.5L b) 9.5L, 220ml	3x9.5L	2x9.5L	555.2g; 195ml NEM; 3.4L DMI	4.25	9.5L	2x9.5L
6:A	10L	a) 10L b) 10L, 232ml	3x10L	2x10 L	555.2g; 195ml NEM; 3.45L DMI	4.25	10L	2x10L[4]
7:C	11L	a) 11L b) 11L, 256ml	3x11L	2x11L	536.7g; 195ml NEM;	4.25	11L	2x11L

Figure 23

[1] ml indicates the amount of 1:1 NEM/DCM

[2] Resin held at this step for ½ day

[3] Resin held at this step for ½ day

[4] Resin held at this stage for 0.4 days

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
					3.57L DMI			
8:A	11L	a) 11L b) 11L, 256ml	3x11L	2x11L	555.2g; 195ml NEM; 3.64L DMI	4.25	11L	2x11L[5]
9:T	11.5L	a) 11.5L b) 11.5L 268ml	3x11.5L	2x 11.5L	468.2g; 195ml NEM; 3.72L DMI	4.25	11.5L	2x11.5L
10:C	12L	a) 12L b) 12L, 280ml	3x12L	2x12L	536.7g; 195ml NEM; 3.96L DMI	4.25	12L	2x12L[6]
11:A	13.5L	a) 13.5L b) 13.5L, 204ml	3x13.5L	2x 13.5L	721.7g; 253ml NEM; 4.02L DMI	4.25	13.5L	2x13.5L
12:A	13.5L	a) 13.5L b) 13.5L, 204ml	3x13.5L	2x 13.5L	721.7g; 253ml NEM; 4.02L DMI	4.25	13.5L	2x13.5L[7]
13:DPG	14L	a) 14L b) 14L, 216ml	3x14L	2x14L	941.9g; 253ml NEM; 4.02L DMI	4.25	14L	2x14L
14:DPG	14.5L	a) 14.5L b) 14.5L, 228ml	3x14.5L	2x 14.5L	941.9g; 253ml NEM;	4.25	14.5L	2x14.5L[8]

Figure 23 (continued)

[5] Resin held at this stage for 2.5 days

[6] Resin held at this stage for ½ day

[7] Resin held at this stage for 0.4 days

[8] Resin held at this stage for 0.4 days

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
					4.1L DMI			
15:A	15.5L	a) 15.5L b) 15.5L, 254ml	3x15.5L	2x 15.5L	721.7g; 253ml NEM; 4.26L DMI	4.25	15.5L	2x15.5L
16:A	15.5L	a) 15.5L b) 15.5L, 254ml	3x15.5L	2x 15.5L	721.7g; 253ml NEM; 4.26L DMI	4.25	15.5L	2x15.5L[9]
17:DPG	16L	a) 16L b) 16L, 366ml	3x16L	2x16L	941.9g; 253ml NEM; 4.4L DMI	4.75	16L	2x16L
18:A	16.5L	a) 16.5L b) 16.5L, 378ml	3x16.5L	2x 16.5L	721.7g; 253ml NEM; 4.4L DMI	4.25	16.5L	2x16.5L[10]
19:T	16.5L	a) 16.5L b) 16.5L, 378ml	3x16.5L	2x 16.5L	608.7g; 253ml NEM; 4.57L DMI	4.25	16.5L	2x16.5L
20:DPG	17L	a) 17L b) 17L, 390ml	3x17L	2x17L	941.9g; 253ml NEM; 4.57L DMI	4.75	17L	2x17L[11]
21:DPG	17L	a) 17L b) 17L, 390ml	3x17L	2x17L	1159.2g; 311ml NEM;	4.25	17L	2x17L

Figure 23 (continued)

[9] Resin held at this stage for 0.4 days

[10] Resin held at this stage for 1.5 days

[11] Resin held at this stage for 0.3 days

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
					4.72L DMI			
22:C	17.5L	a) 17.5L b) 17.5L, 402ml	3x17.5L	2x 17.5L	858.7g; 311ml NEM; 4.72L DMI	4.75	17.5L	2x17.5L[12]
23:A	17.5L	a) 17.5L b) 17.5L, 402ml	3x17.5L	2x 17.5L	888.3g; 311ml NEM; 4.88L DMI	4.25	17.5L	2x17.5L
24:T	18L	a) 18L b) 18L, 414ml	3x18L	2x18L	749.1g; 311ml NEM; 4.95L DMI	4.25	18L	2x18L[13]
25:T	18L	a) 18L b) 18L, 414ml	3x18L	2x18L	749.1g; 311ml NEM; 5.1L DMI	4.25	18L	2x18L
26:T	18.5L	a) 18.5L b) 18.5L, 426ml	3x18.5L	2x 18.5L	749.1g; 311ml NEM; 5.1L DMI	4.25	18.5L	2x18.5L[14]
27:C	18.5L	a) 18.5L b) 18.5L, 426ml	3x18.5L	2x 18.5L	858.7g; 311ml NEM; 5.25L DMI	4.25	18.5L	2x18.5L
28:T	19L	a) 19L b) 19L, 438ml	3x19L	2x19L	749.1g; 311ml NEM;	4.25	19L	2x19L[15]

Figure 23 (continued)

[12] Resin held at this stage for 0.4 days

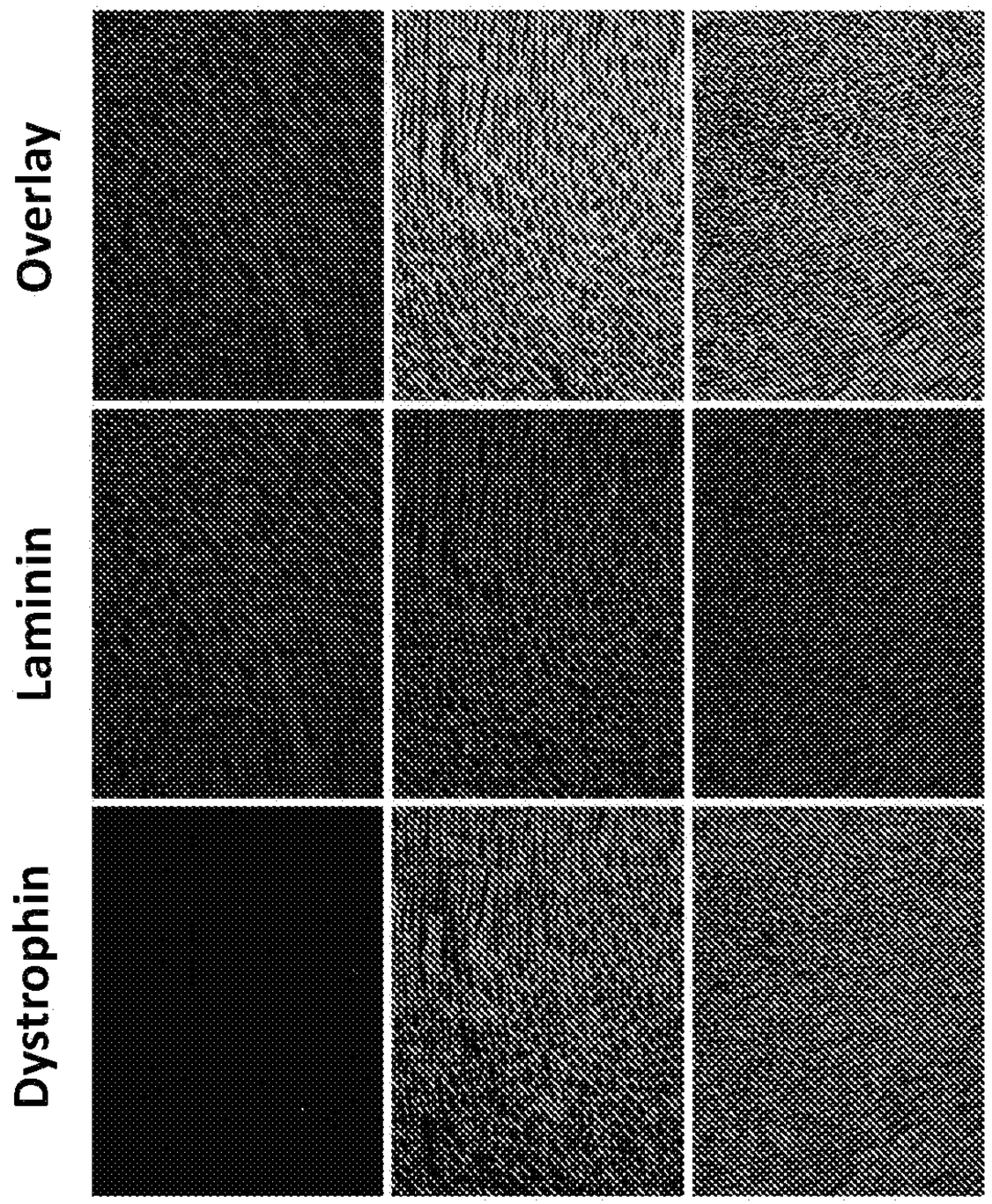
[13] Resin held at this stage for 0.4 days

[14] Resin held at this stage for 0.4 days

[15] Resin held at this stage for 0.3 days

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
					5.25L DMI			
29:A	19L	a) 19L b) 19L, 438ml	3x19L	2x19L	888.3g; 311ml NEM; 5.41L DMI	4.25	19L	2x19L
30:DPG	19.5L	a) 19.5L b) 19.5L, 450ml	3x19.5L	2x 19.5L	1159.2g; 311ml NEM; 5.44L DMI	4.75	19.5L	2x19.5L

Figure 23 (continued)


Heart
Dystrophin
Laminin
Overlay
MDX Saline
MDX PPMO
WT Saline

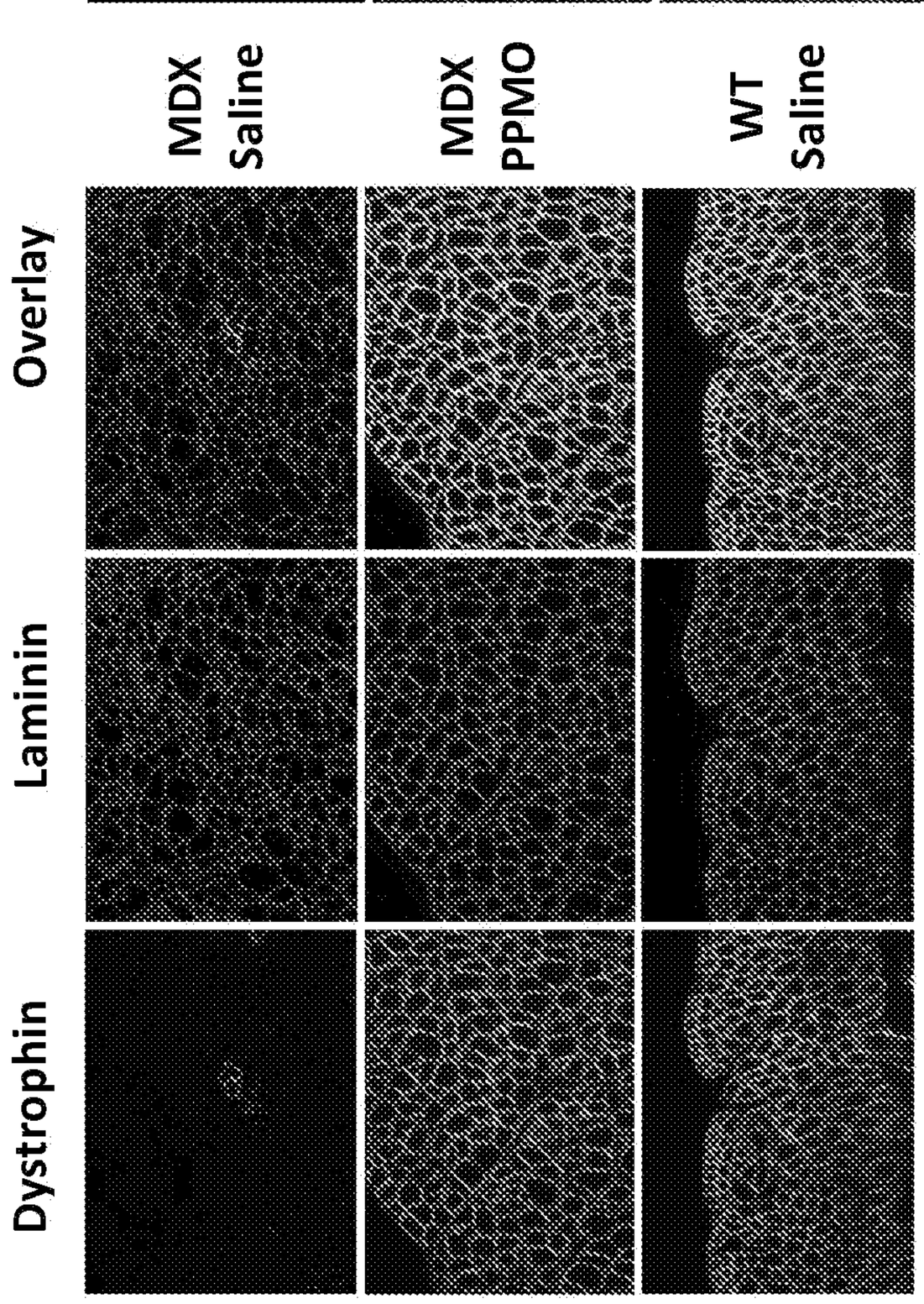

Diaphragm
Laminin
Overlay
Dystrophin

Figure 24

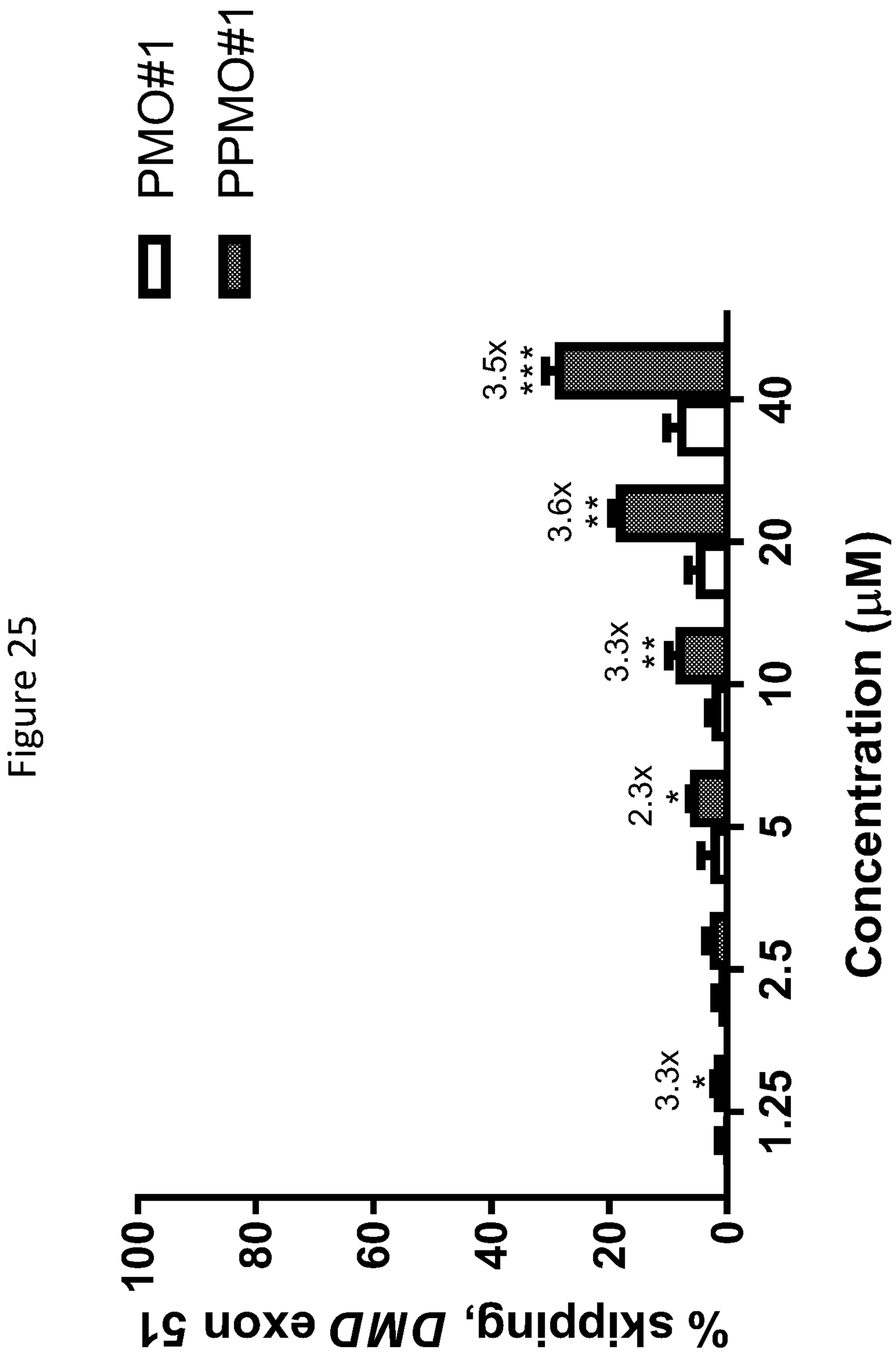

PMO#1
PMO#1
3.5x
***
3.6x
**
3.3x
**
2.3x
*
3.3x
*
40
20
10
5
2.5
1.25
Concentration (μM)
100
80
60
40
20
0
% skipping, DMD exon 51

Figure 25

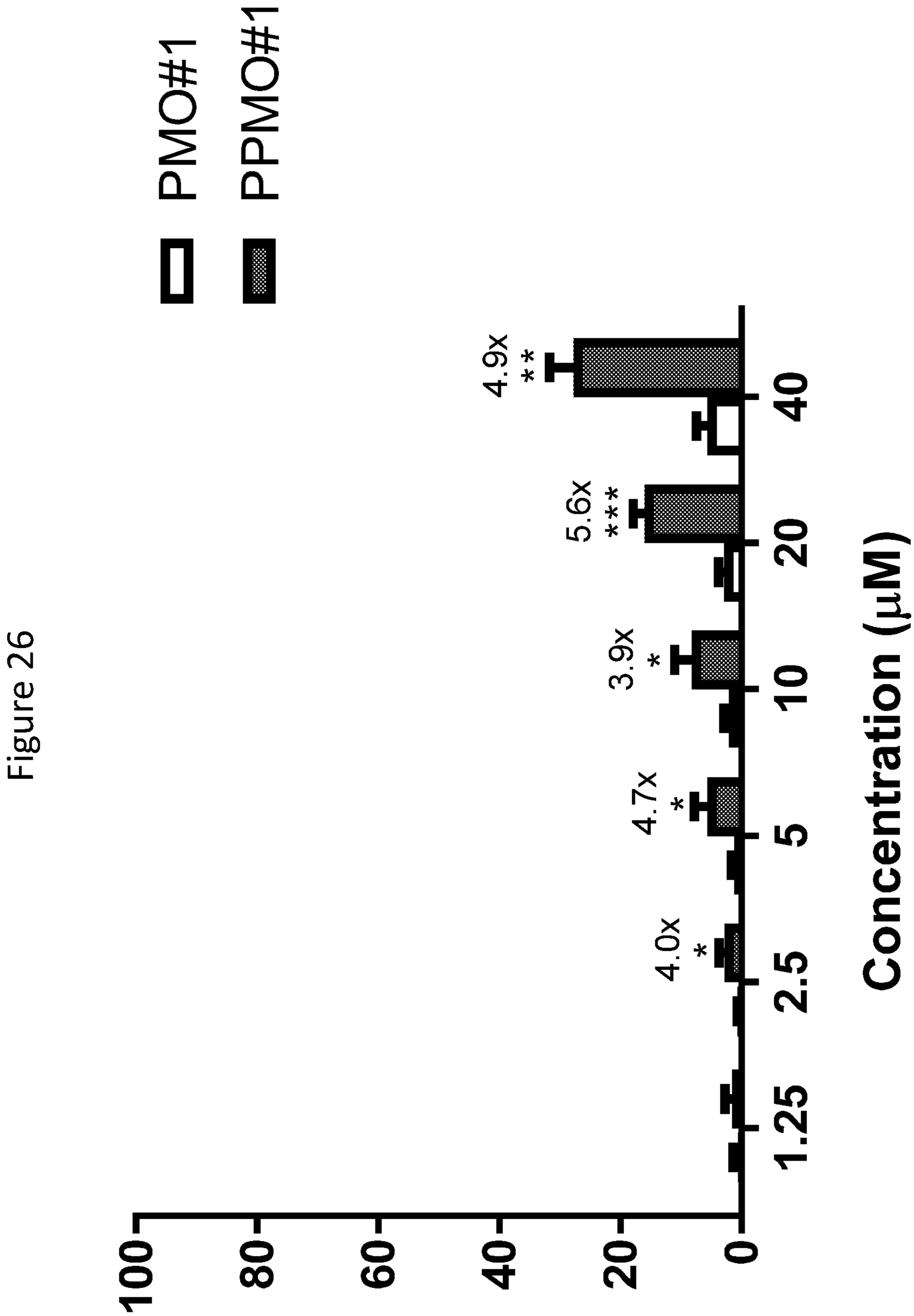

PMO#1
PPMO#1
4.9x
**
5.6x
***
3.9x
*
4.7x
*
4.0x
*
40
20
10
5
2.5
1.25
Concentration (μM)
100
80
60
40
20
0
% skipping, DMD exon 51

Figure 26