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(71) Demandeurs/Applicants:
GAMAMABS PHARMA, FR;
INSTITUT CURIE, FR

(72) Inventeurs/Inventors:
BARRET, JEAN-MARC, FR;
PROST, JEAN-FRANCOIS, FR;
LAHMAR, MEHDI, FR;
DEGOVE, STEPHANE, FR;
DUBREUIL, OLIVIER, FR;
NICOLAS, ANDRE, FR;
MESEURE, DIDIER, FR

(74) Agent: ROBIC

(54) Titre : COMPOSES DE LIAISON A L'AMHR2 POUR LA PREVENTION OU LE TRAITEMENT DE CANCERS
(54) Title: AMHR2-BINDING COMPOUNDS FOR PREVENTING OR TREATING CANCERS

(57) Abrégé/Abstract:

The present invention relates to a human AMHR2-binding agent for its use for preventing or treating a cancer selected in a group of cancers comprising colon cancer, liver cancer, hepatocellular carcinoma, testis cancer, thyroid cancer, gastric cancer, gastrointestinal cancer, bladder cancer, pancreatic cancer, head and neck cancer, kidney cancer, liposarcoma, pleuramesothelioma, melanoma, sarcoma, brain cancer, osteocarcinoma and leukemia.

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(71) Applicants: **GAMAMABS PHARMA** [FR/FR]; Centre Pierre Potier 1, place Pierre Potier ONCOPOLE entrée B, 31106 TOULOUSE (FR). **INSTITUT CURIE** [FR/FR]; 26 rue d'Ulm, 75248 PARIS CEDEX 05 (FR).

(72) Inventors: **BARRET, Jean-Marc**; 5, rue du Trésor, 81100 CASTRES (FR). **PROST, Jean-François**; 21, avenue Villeneuve l'Etang, 78000 VERSAILLES (FR). **LAHMAR, Mehdi**; 154, rue des Prés aux Bois, 78220 VIROFLAY (FR). **DEGOVE, Stéphane**; 21, rue Jules Auffret, 93500 PANTIN (FR). **DUBREUIL, Olivier**; 1, rue des Maronniers, 31190 MAURESSAC (FR). **NICOLAS, André**; 34, rue Sorbier, 75020 PARIS (FR). **MESURE, Didier**; 13, rue Lasson, 75012 PARIS (FR).

(74) Agent: **CABINET NONY**; 11 rue Saint-Georges, 75009 PARIS (FR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: AMHRII-BINDING COMPOUNDS FOR PREVENTING OR TREATING CANCERS

(57) Abstract: The present invention relates to a human AMHRII-binding agent for its use for preventing or treating a cancer selected in a group of cancers comprising colon cancer, liver cancer, hepatocellular carcinoma, testis cancer, thyroid cancer, gastric cancer, gastrointestinal cancer, bladder cancer, pancreatic cancer, head and neck cancer, kidney cancer, liposarcoma, pleuramesothelioma, melanoma, sarcoma, brain cancer, osteocarcinoma and leukemia.

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CLAIMS

1. A human AMHRII-binding agent for use in a method for preventing or treating a non-gynecologic cancer.

5

2. The AMHRII-binding agent for its use according to claim 1, wherein the non-gynecologic cancer is selected in a group comprising colon cancer, liver cancer, hepatocellular carcinoma, testis cancer, thyroid cancer, gastric cancer, gastrointestinal cancer, bladder cancer, pancreatic cancer, head and neck cancer, kidney cancer, liposarcoma, fibrosarcoma, pleuramesothelioma, melanoma, sarcoma, brain cancer, osteocarcinoma, breast cancer, prostate cancer and leukemia.

10

3. The human AMHRII-binding agent for its use according to any one of claims 1 and 2, which is selected in the group consisting of a monoclonal anti-AMHRII antibody and AMHRII-binding fragments thereof.

15

4. The human AMHRII-binding agent for its use according to any one of claims 1 to 3, which is a monoclonal antibody selected in the group consisting of the following antibodies:

20

a) a light chain comprising SEQ ID NO: 2 and a heavy chain comprising SEQ ID NO: 4 (3C23 VL and VH sequences without leaders);

b) a light chain comprising SEQ ID NO: 6 and a heavy chain comprising SEQ ID NO: 8 (3C23K VL and VH sequences without leaders);

c) a light chain comprising SEQ ID NO: 10 and a heavy chain comprising SEQ ID NO: 12 (3C23 light and heavy chains without leaders);

25

d) a light chain comprising SEQ ID NO: 14 and a heavy chain comprising SEQ ID NO: 16 (3C23K light and heavy chains without leaders).

5. The human AMHRII-binding agent for its use according to claim 1, which is a monoclonal antibody comprising CDRs comprising the following sequences:

- CDRL-1: RASX1X2VX3X4X5A (SEQ ID NO. 65), where X1 and X2 are, independently, S or P, X3 is R or W or G, X4 is T or D, and X5 is I or T;
 - CDRL-2 is PTSSLX6S (SEQ ID NO. 66) where X6 is K or E; and
 - CDRL-3 is LQWSSYPWT (SEQ ID NO. 67);
 - 5 - CDRH-1 is KASGYX7FTX8X9HIH (SEQ ID NO. 68) where X7 is S or T, X8 is S or G and X9 is Y or N;
 - CDRH-2 is WIYPX10DDSTKYSQKFQG (SEQ ID NO. 69) where X10 is G or E; and
 - CDRH-3 is GDRFAY (SEQ ID NO. 70)
- 10 6. The human AMHRII-binding agent for its use according to any one of claims 1 to 5, wherein the said binding agent consists of an Antibody Drug Conjugate (ADC).
7. The human AMHRII-binding agent for its use according to claim 1, which is an AMHRII-binding engineered receptor.
- 15 8. The human AMHRII-binding agent for its use according to claim 1, which is a cell expressing an AMHRII-binding engineered receptor.
9. The human AMHRII-binding agent for its use according to claim 8, which is a CAR T-cell
- 20 or a NK T-cell expressing an AMHRII-binding engineered receptor.
10. The human AMHRII-binding agent for its use according to any one of claims 1 to 9, in combination with another anti-cancer treatment.
- 25 11. A method for determining whether an individual is responsive to a cancer treatment with an AMHRII-binding agent as defined in any one of claims 1 to 10, wherein the said method comprises the step of determining whether a tumor tissue sample previously obtained from the said individual express the AMHRII protein at the cell surface.

VH domain		FR1		CDR1	FR2		CDR2	FR3		CDR3	FR4				
		10		30	40		50	60	70		80	90		103	110
SEQ ID															
19	3C23K	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
20	3C23KR	QVQLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
21	5B42	QVQLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRD A SASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
22	K4D24	RVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
23	K4D20	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTS N HHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
24	K4A12	QVRLVQSGAEVKKPG T SVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
25	K5D05	QVRLVQSGAEVKKPGASVKVSC		KASGYTFT G YHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
26	K5D14	QVRLVQSGAEVKKPGASVKVSC		KASGY S FTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
27	K4D123	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQ S LIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
28	K4D127	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVT T ITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
29	5C14	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVT F ITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
30	5C26	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	R M ITITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
31	5C27	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQ RPE WMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
32	5C60	QVRLVQSGA KVR KPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
33	6C13	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYP E DDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				
34	6C18	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLRSEDTAVYY CAR	GDRF--AY		WGQGTLLVTVSS				
35	6C54	QVRLVQSGAEVKKPGASVKVSC		KASGYTFTSYHHI	WVRQAPGQRLIEWMG		WIYPGDDSTKYSQKFQG	RVTITRDTSASTAYMELSSLR P EDTAVYYCTR	GDRF--AY		WGQGTLLVTVSS				

Figure 1A

VL domain	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
SEQ ID	10	30	40	50	70	90	100
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38	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
39	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
40	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
41	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
42	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
43	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
44	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
45	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
46	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
47	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
48	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
49	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
50	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
51	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
52	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
53	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
54	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
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57	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
58	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
59	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
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63	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC
64	DIQMTQSPSTLSASVGD	RASSS-VRYIA	WYQQKPGKAPKLLTY	PTSSLES	GVPSRFSGSGSGTEFTLT	ISSLQPD	DFATYYC

Figure 1B

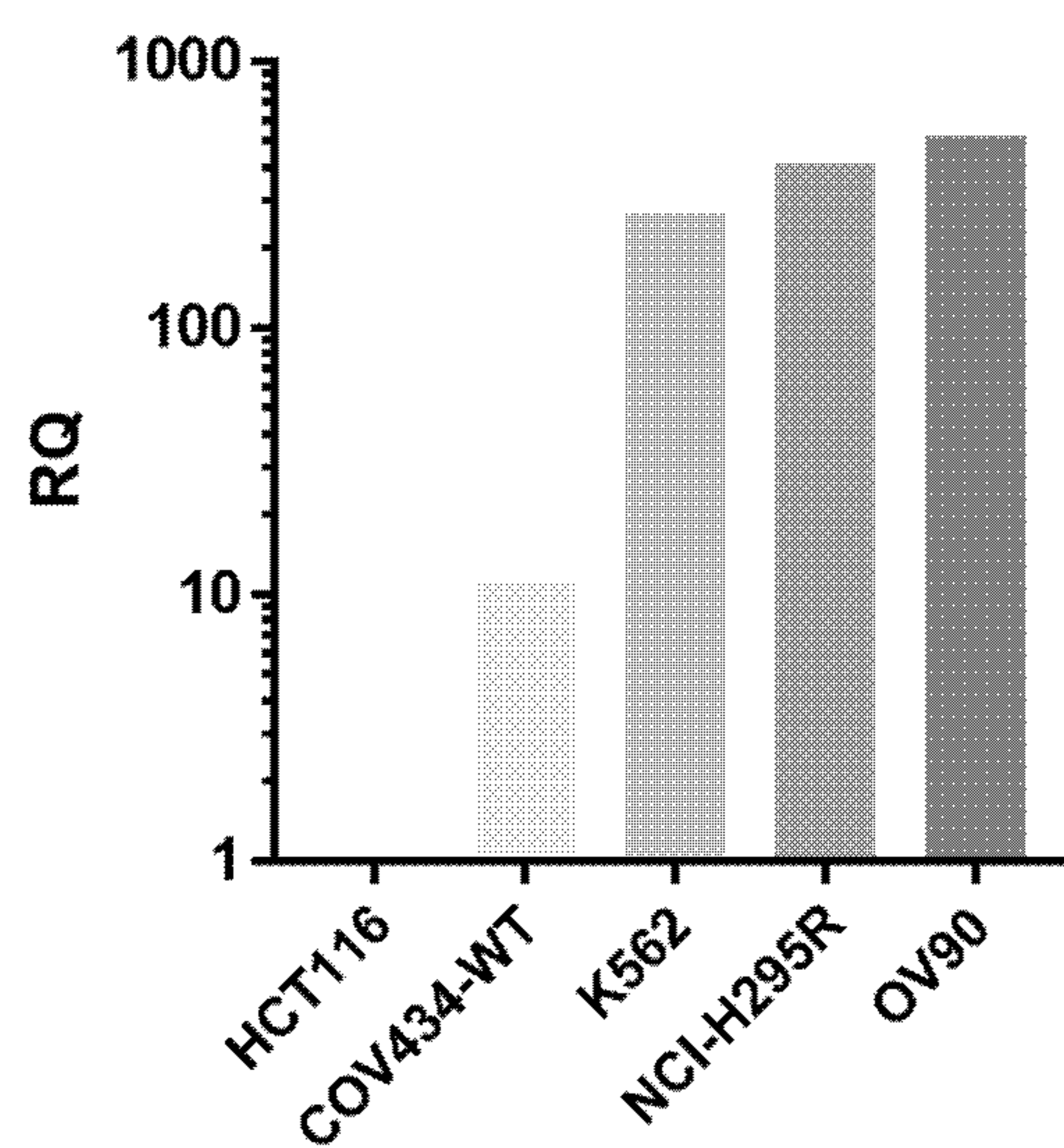


Figure 2A

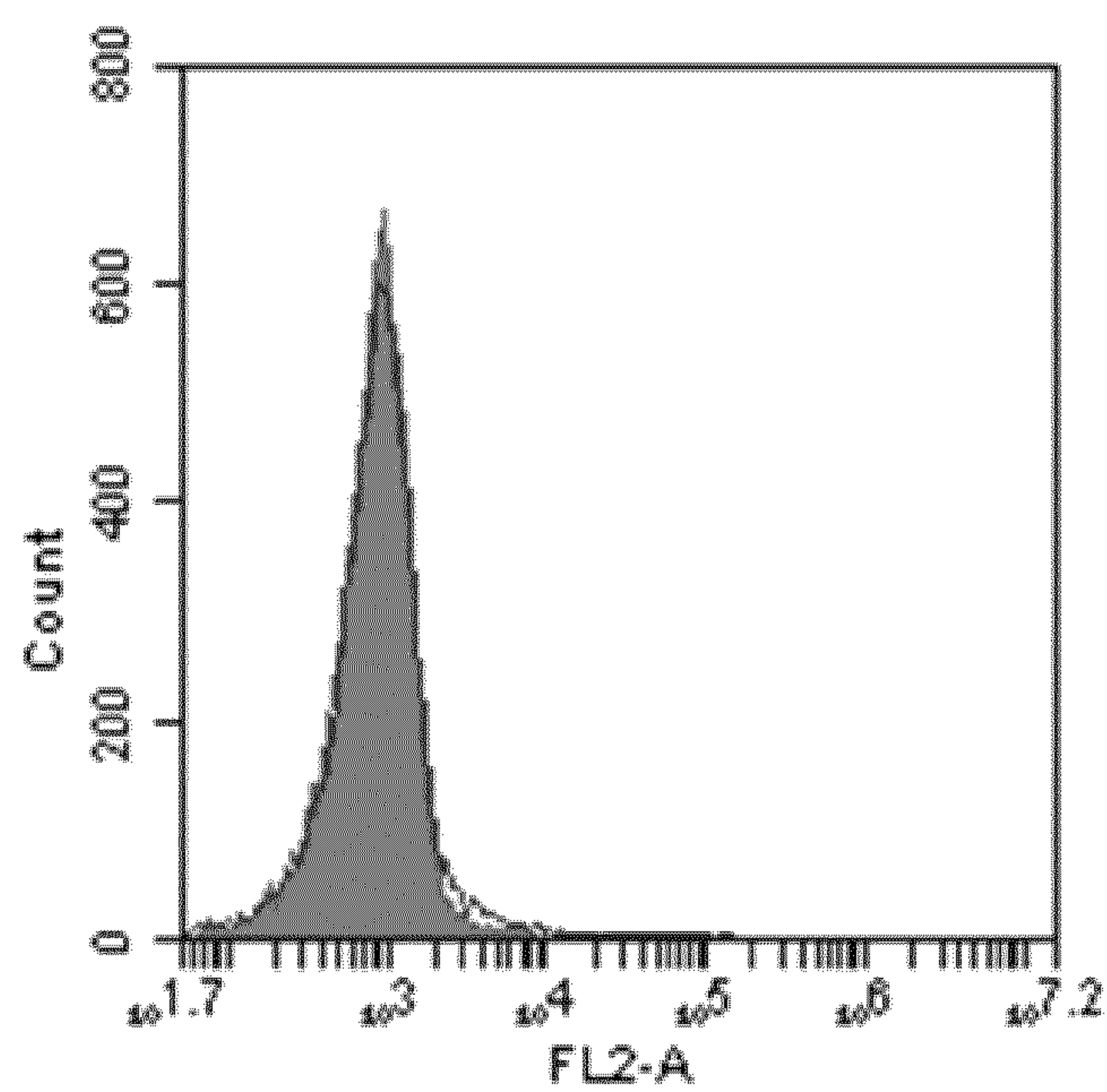


Figure 2B

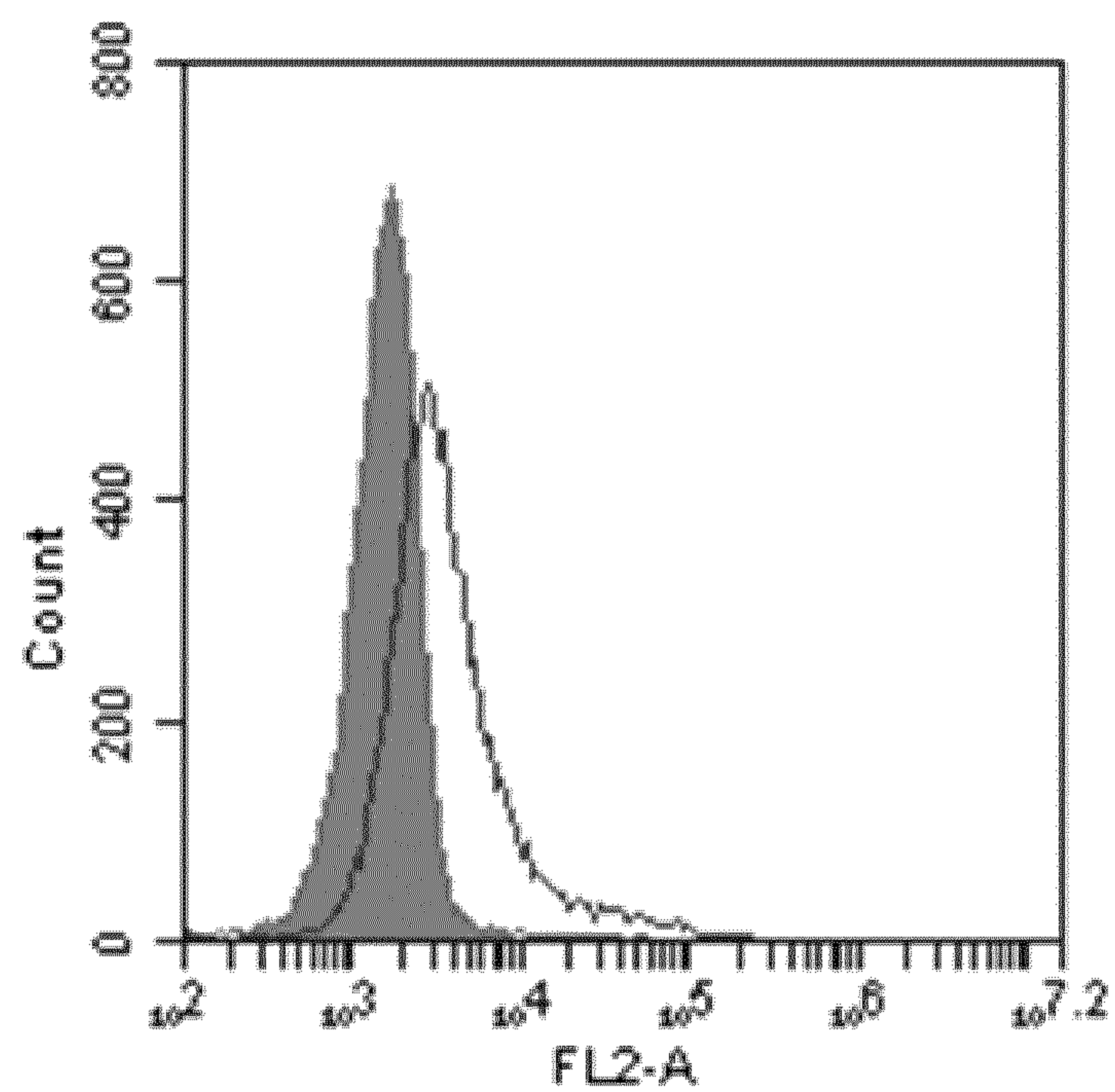


Figure 2C

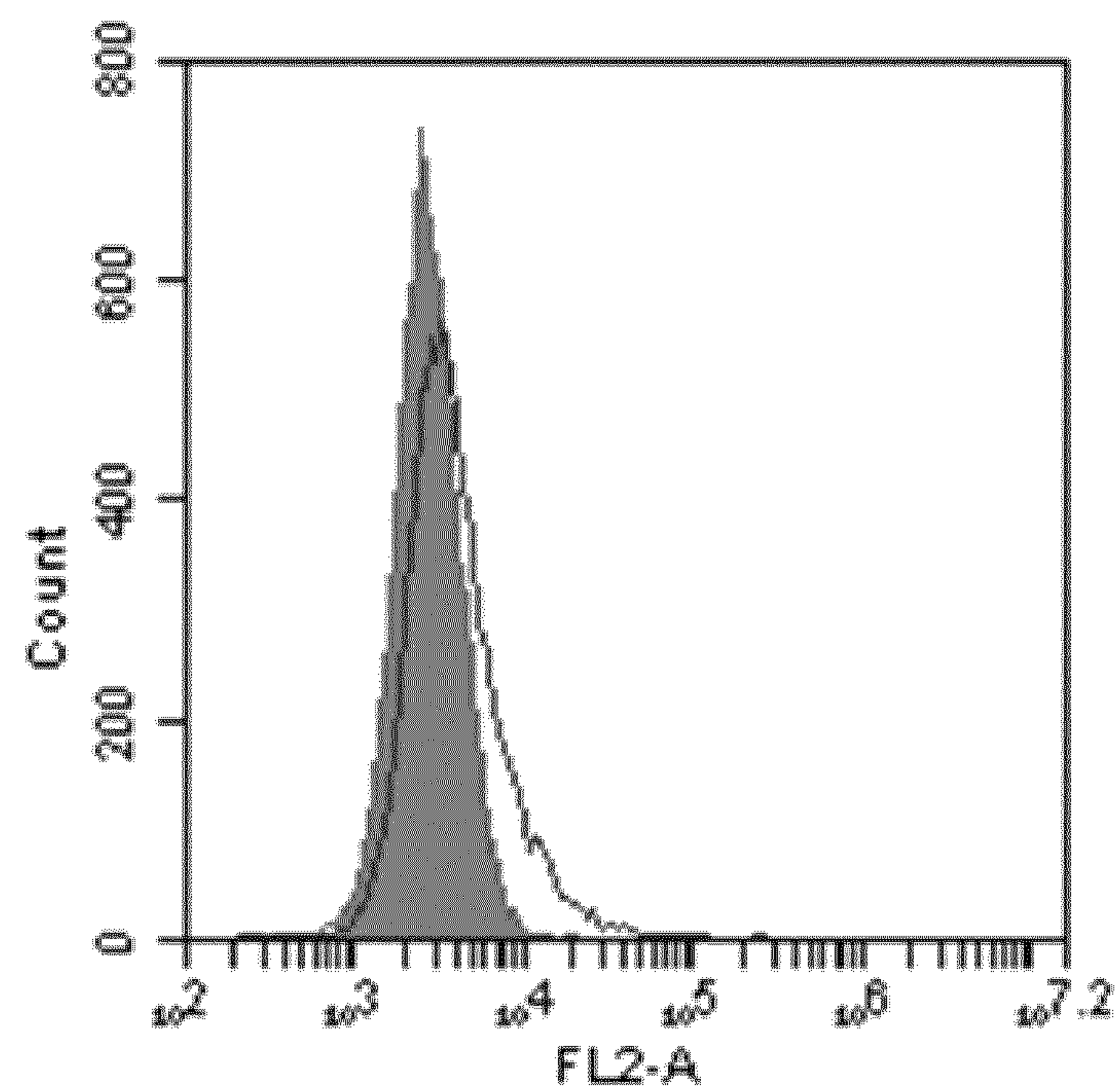


Figure 2D

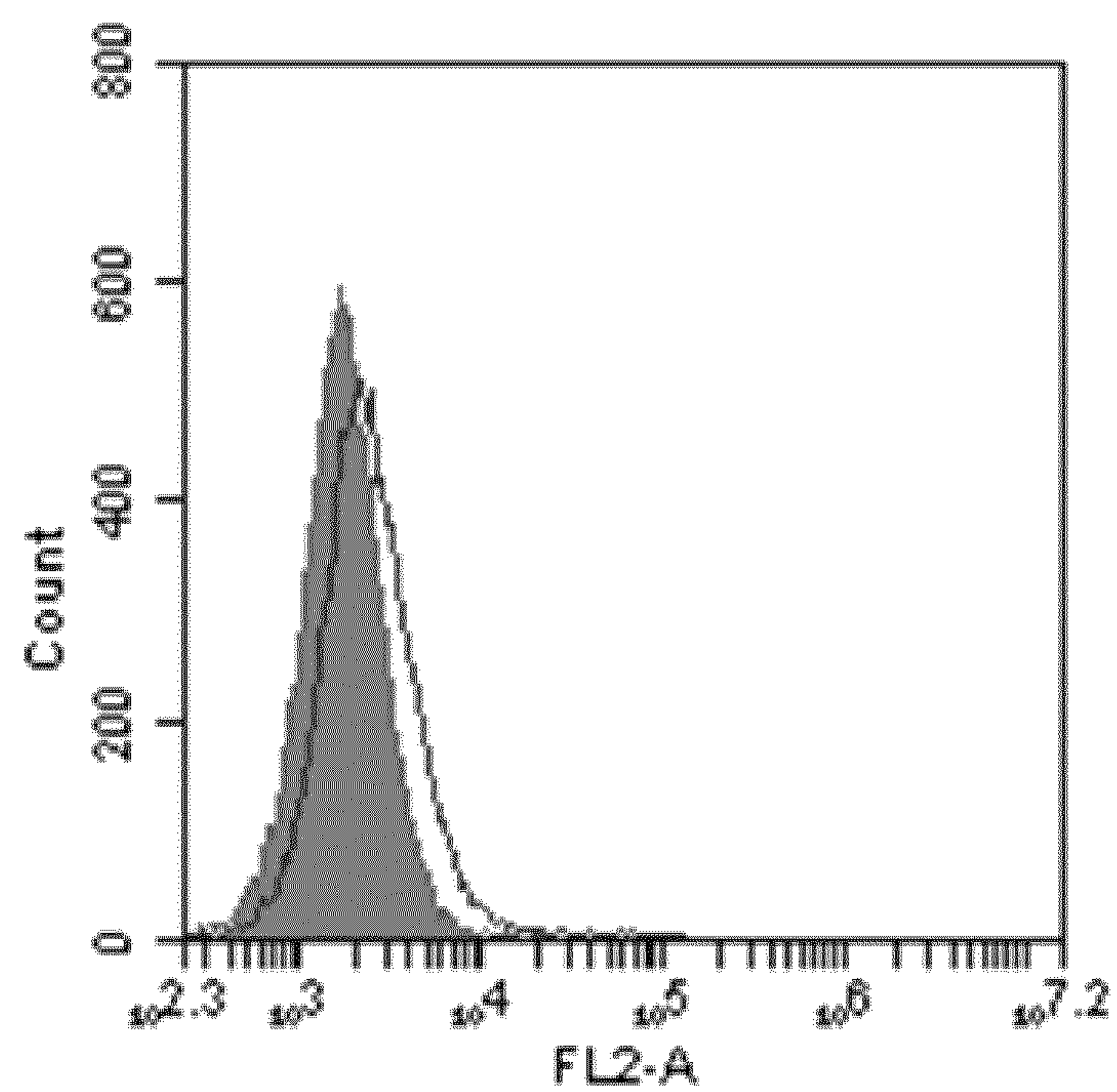


Figure 2E

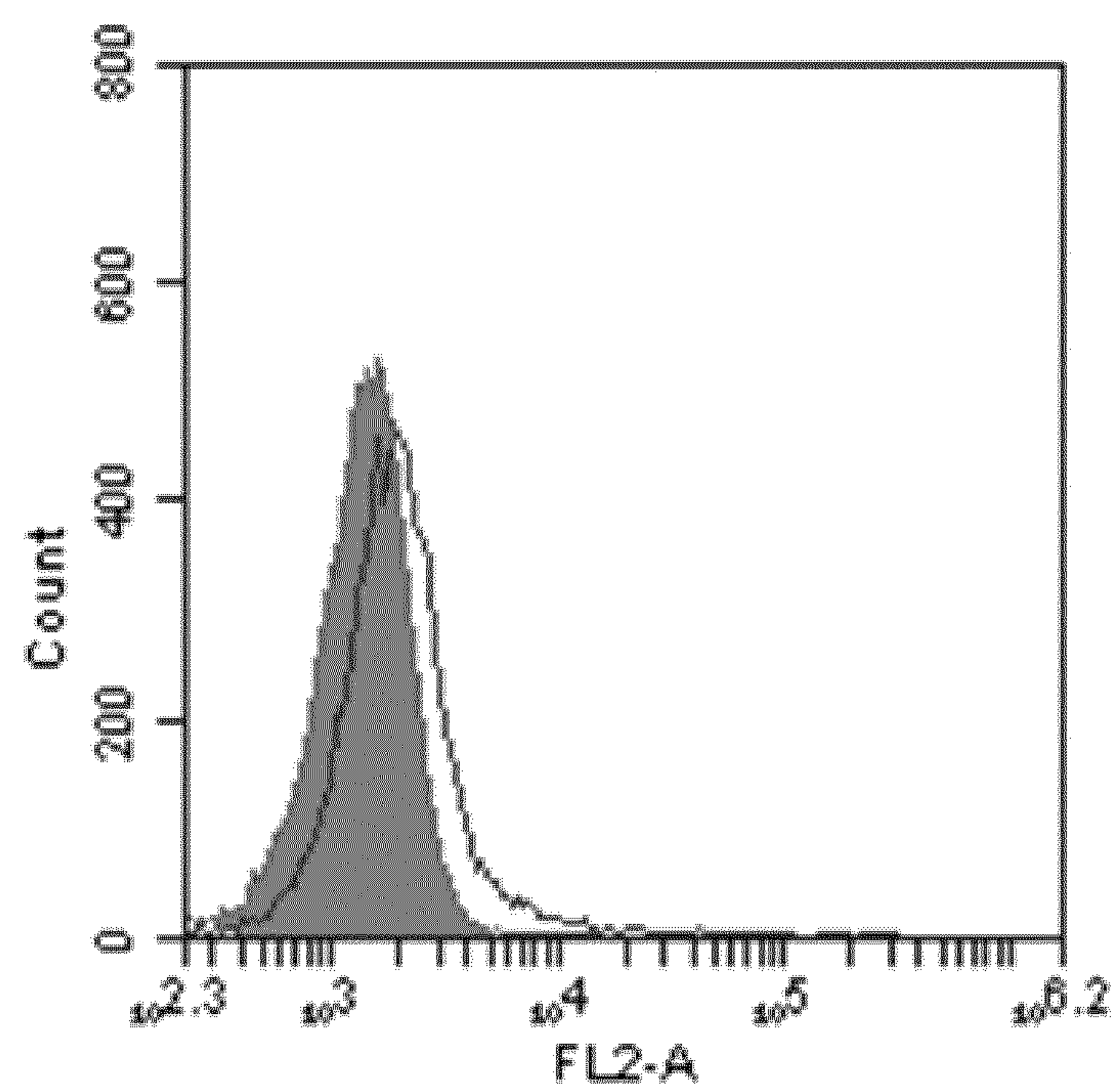


Figure 2F

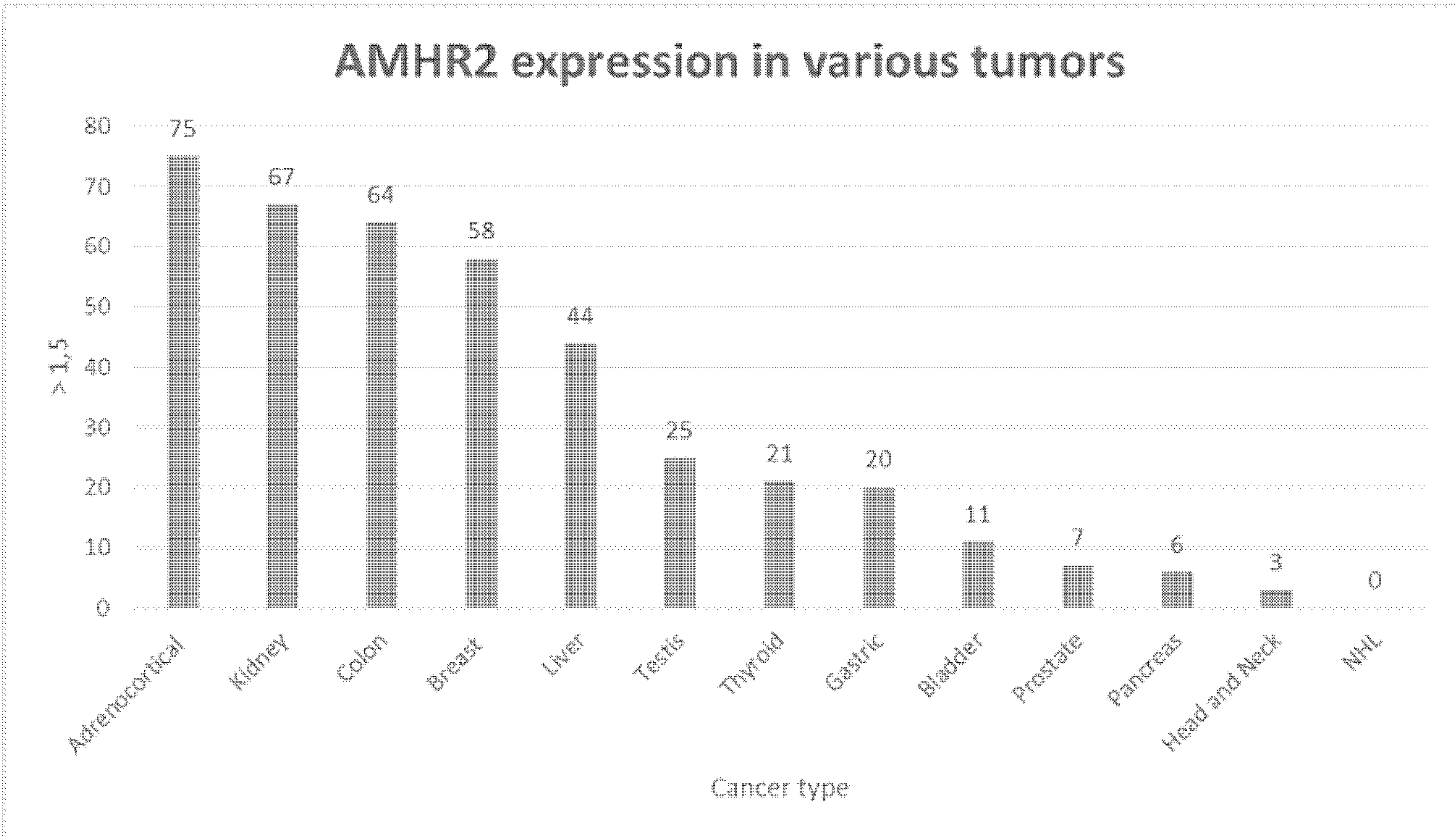


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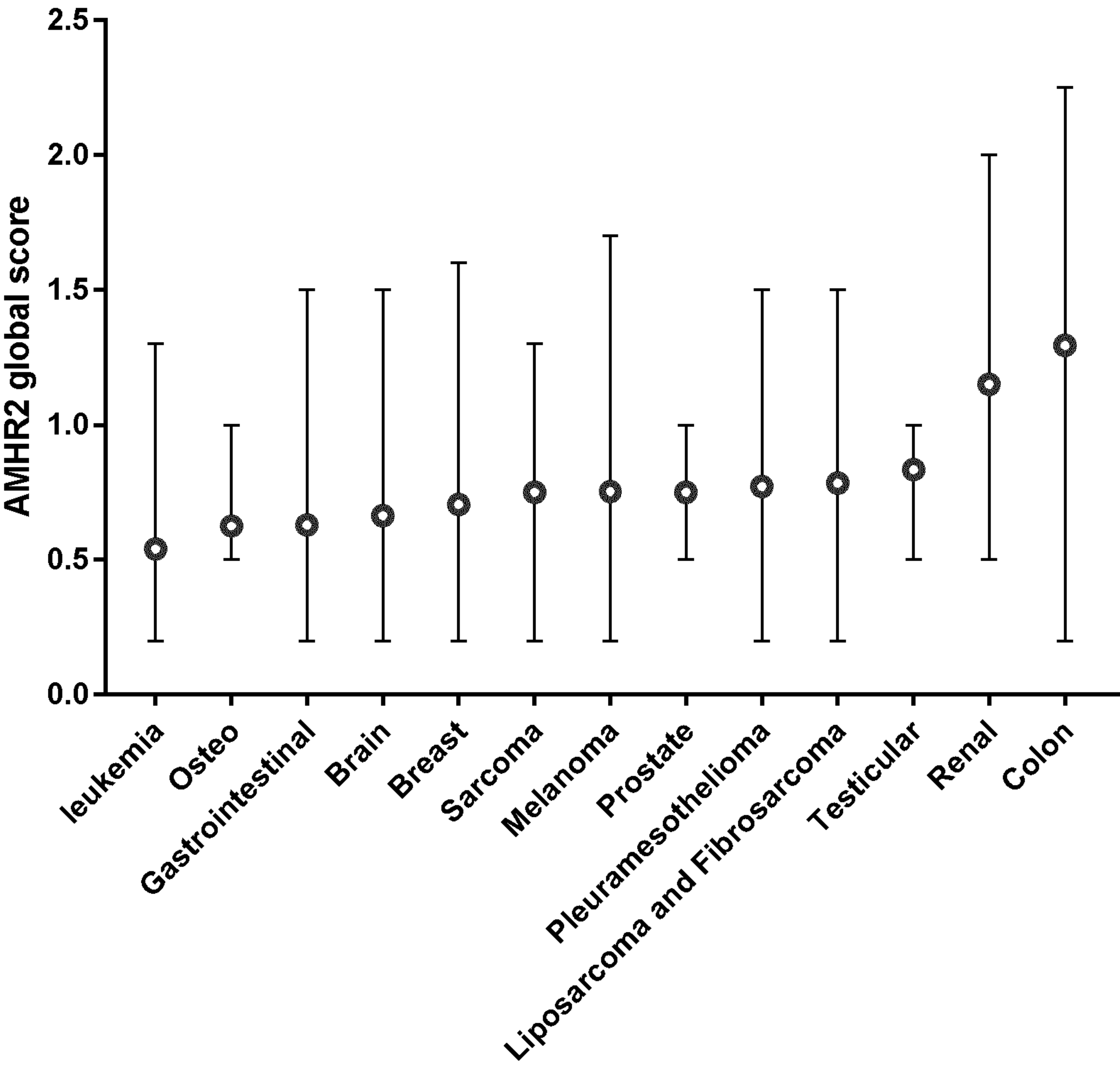


Figure 4

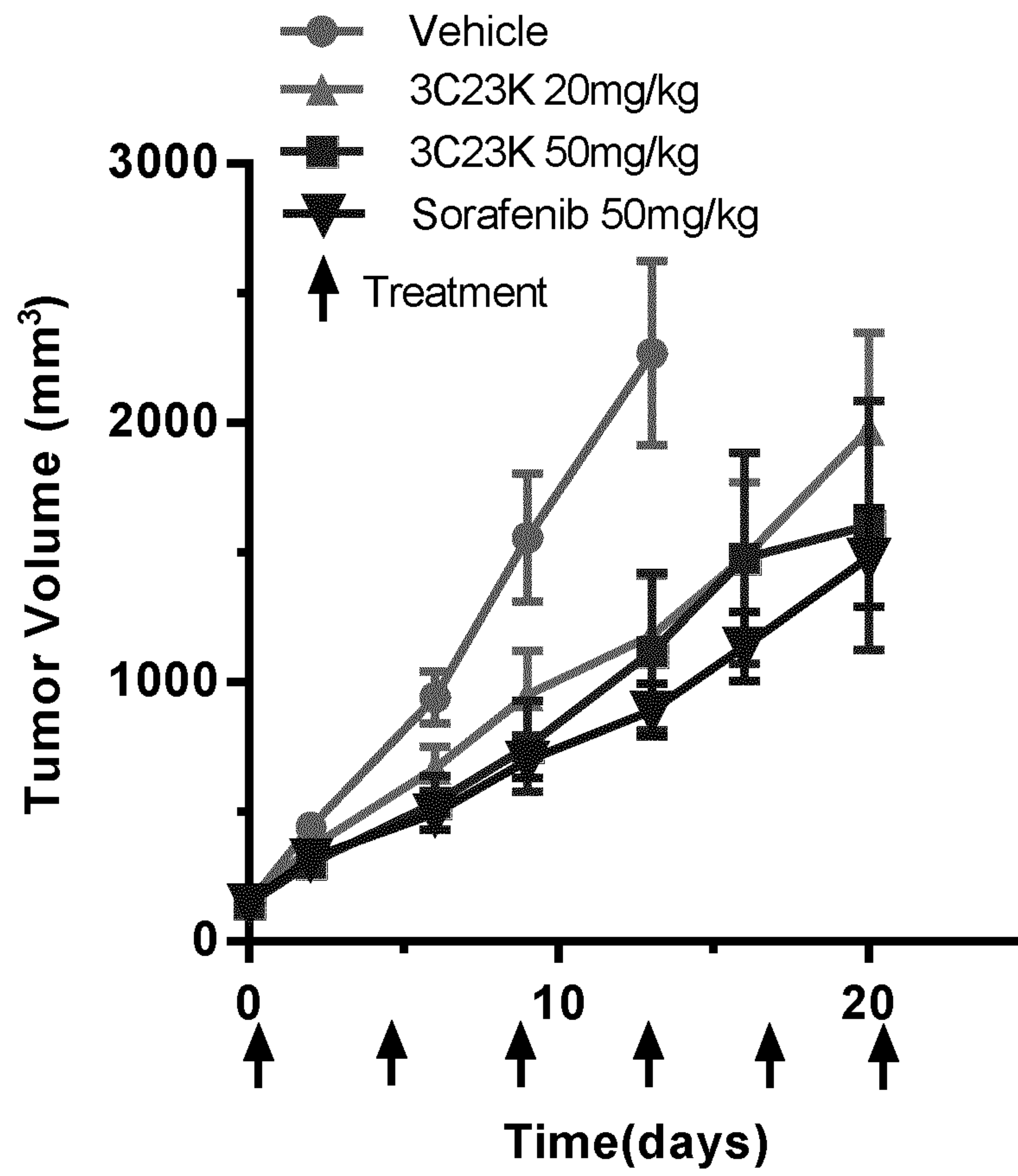


Figure 5

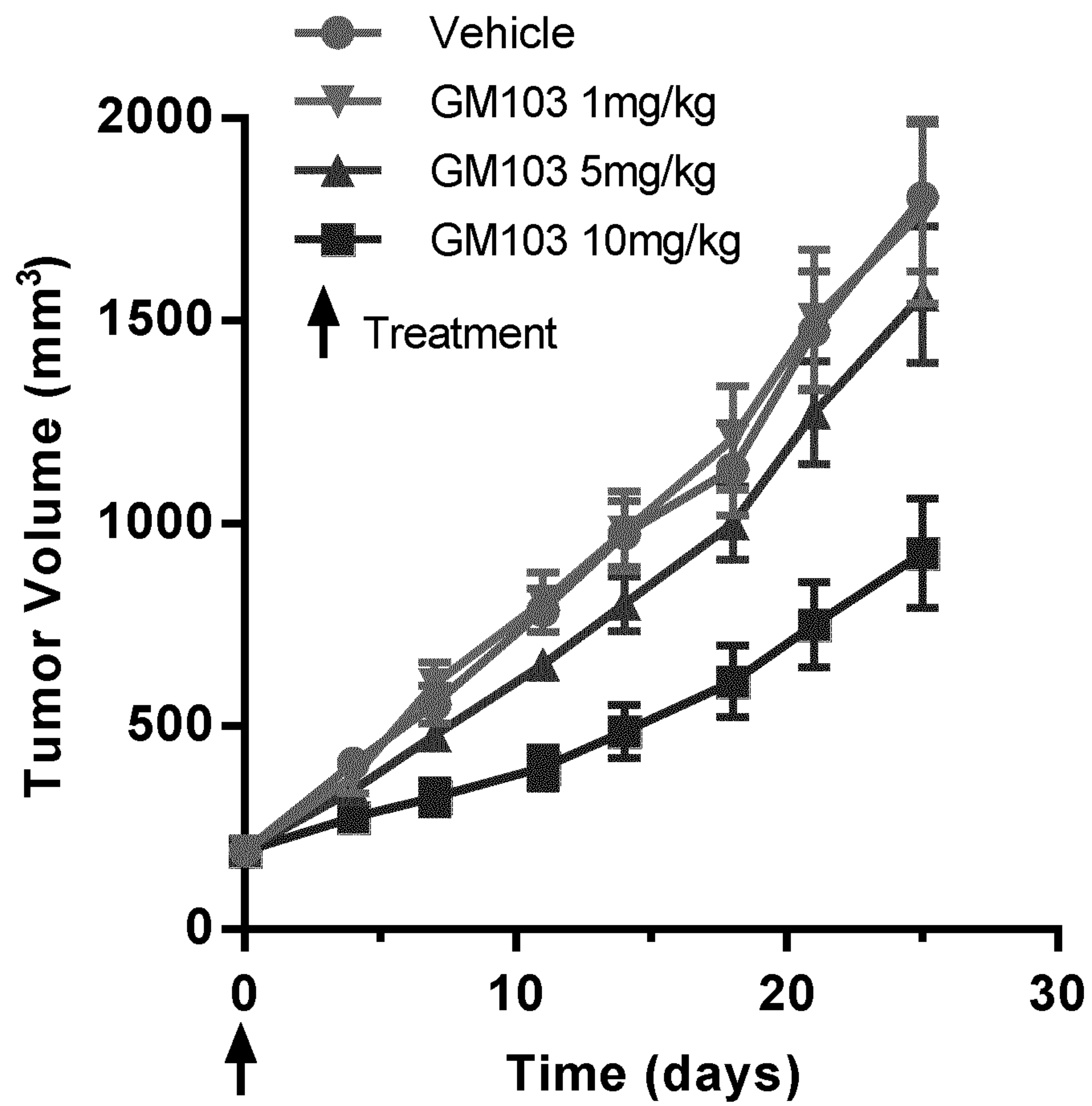
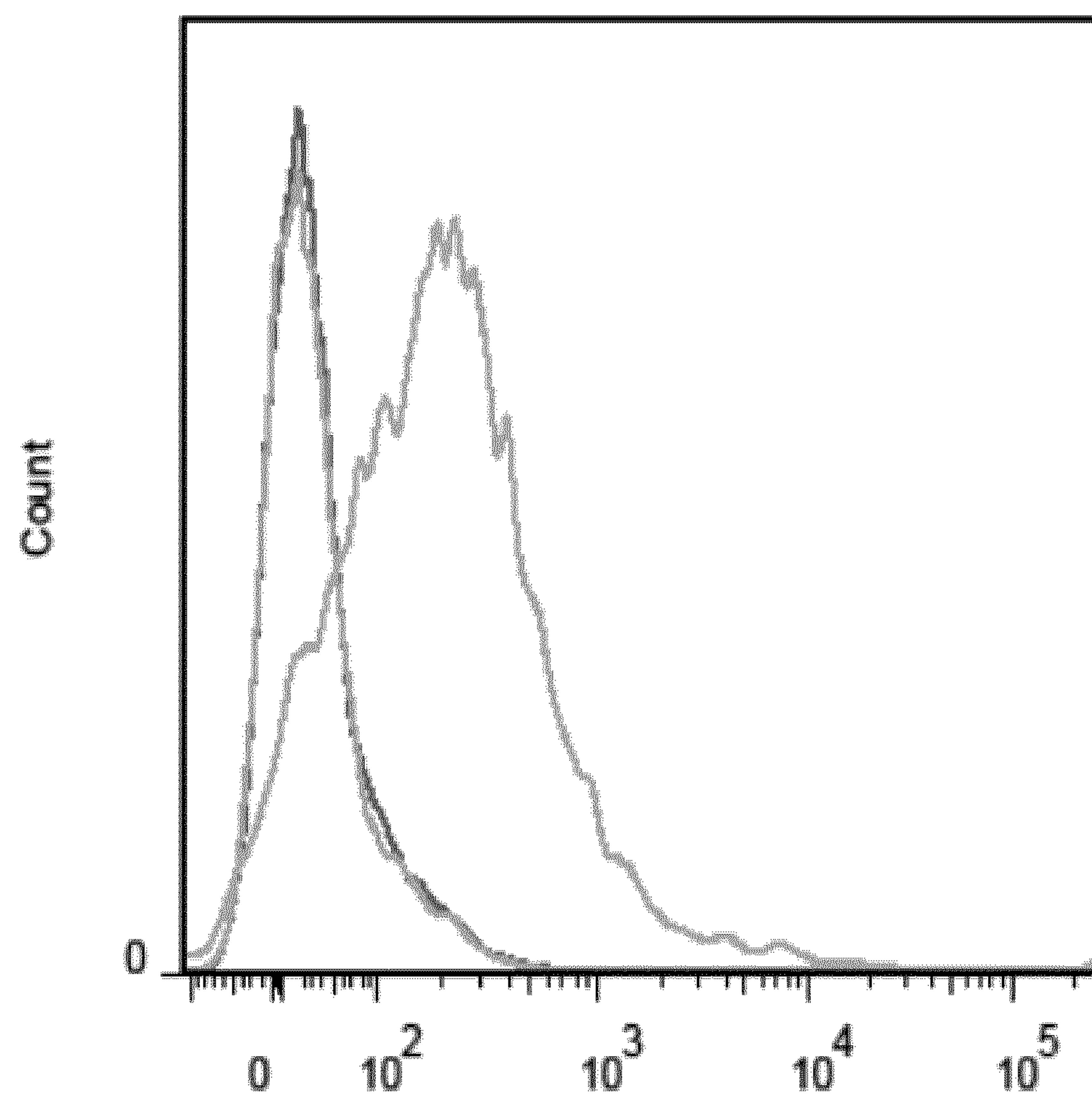
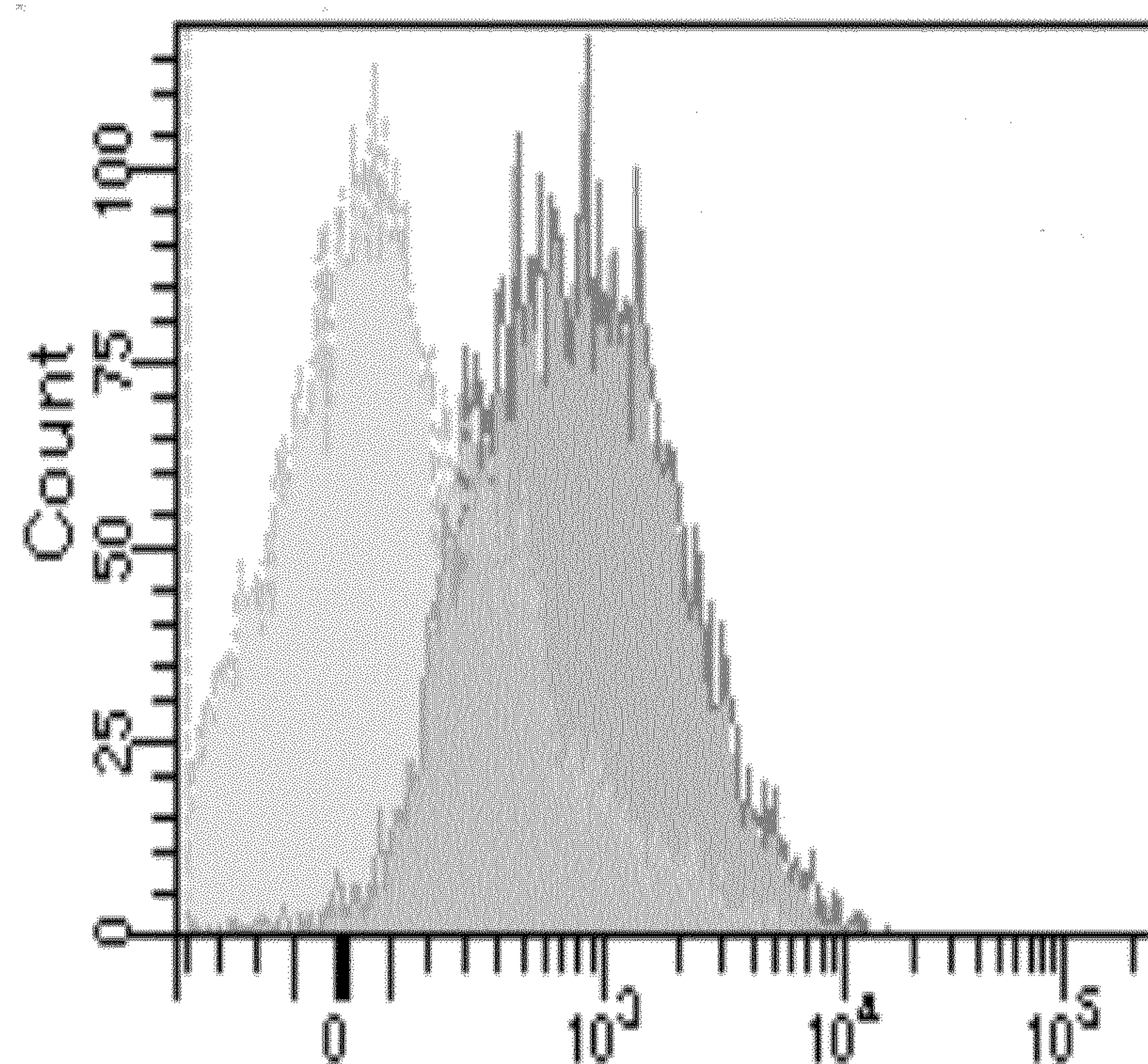


Figure 6

**Figure 7A****Figure 7B**

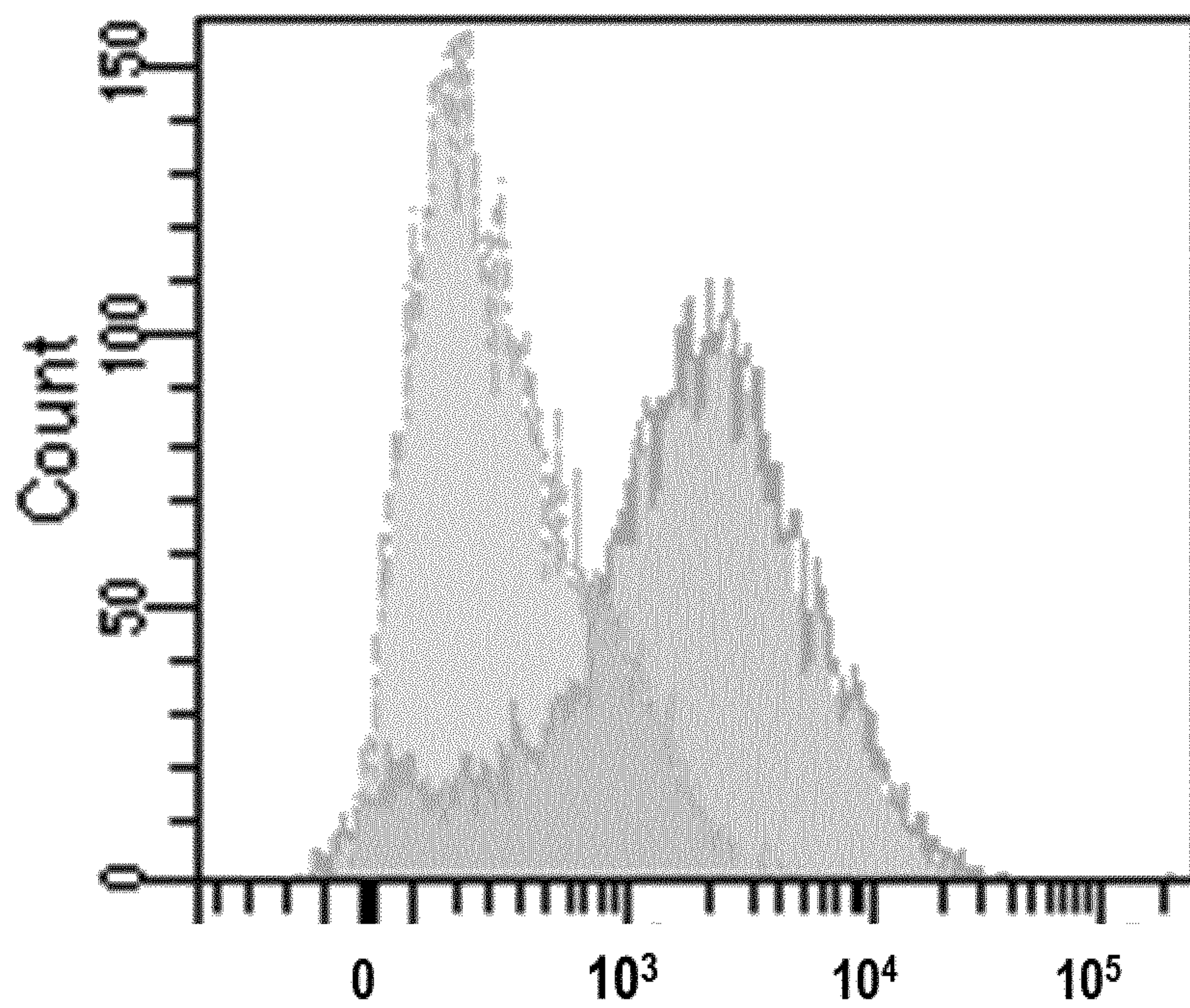


Figure 7C

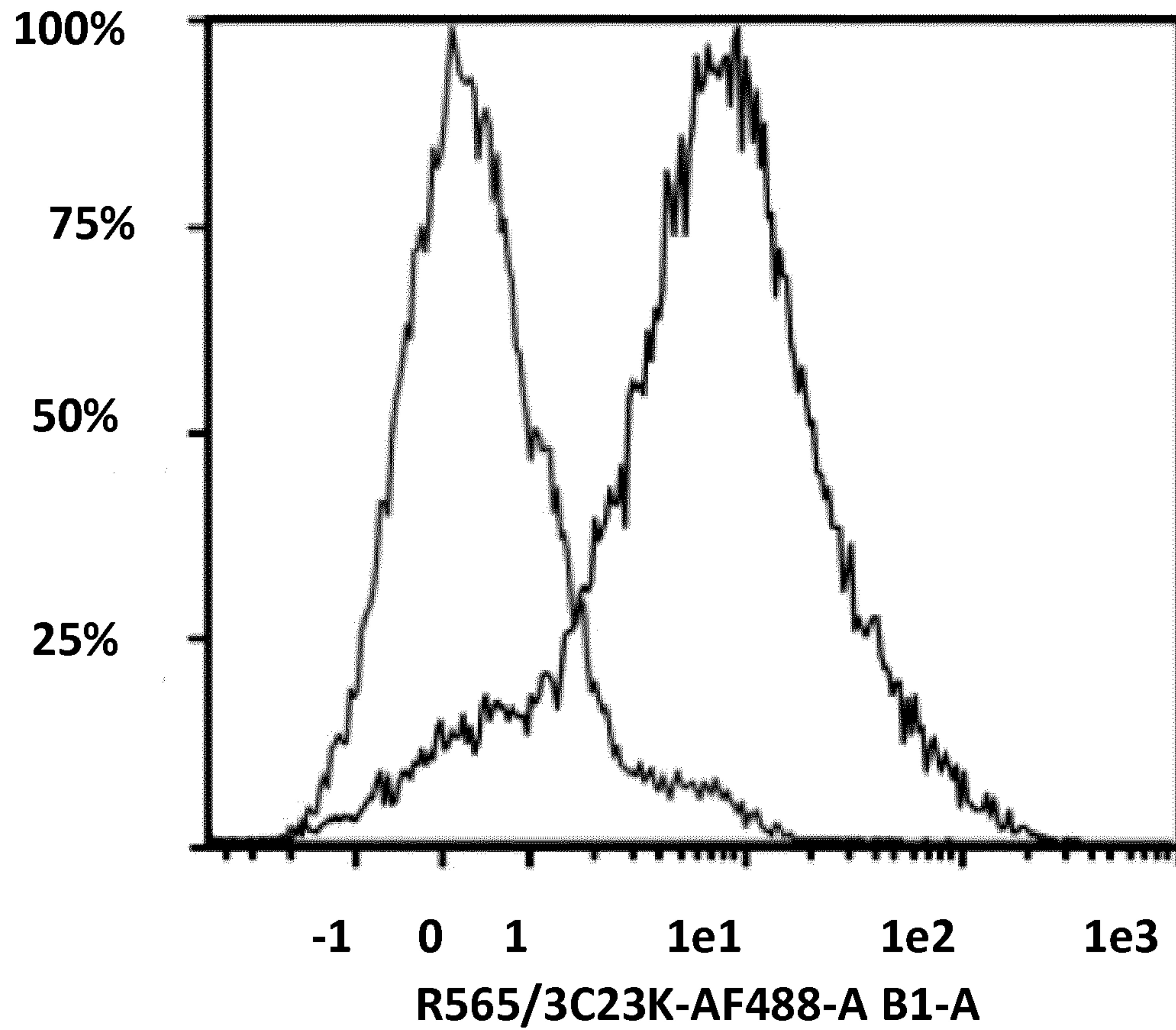
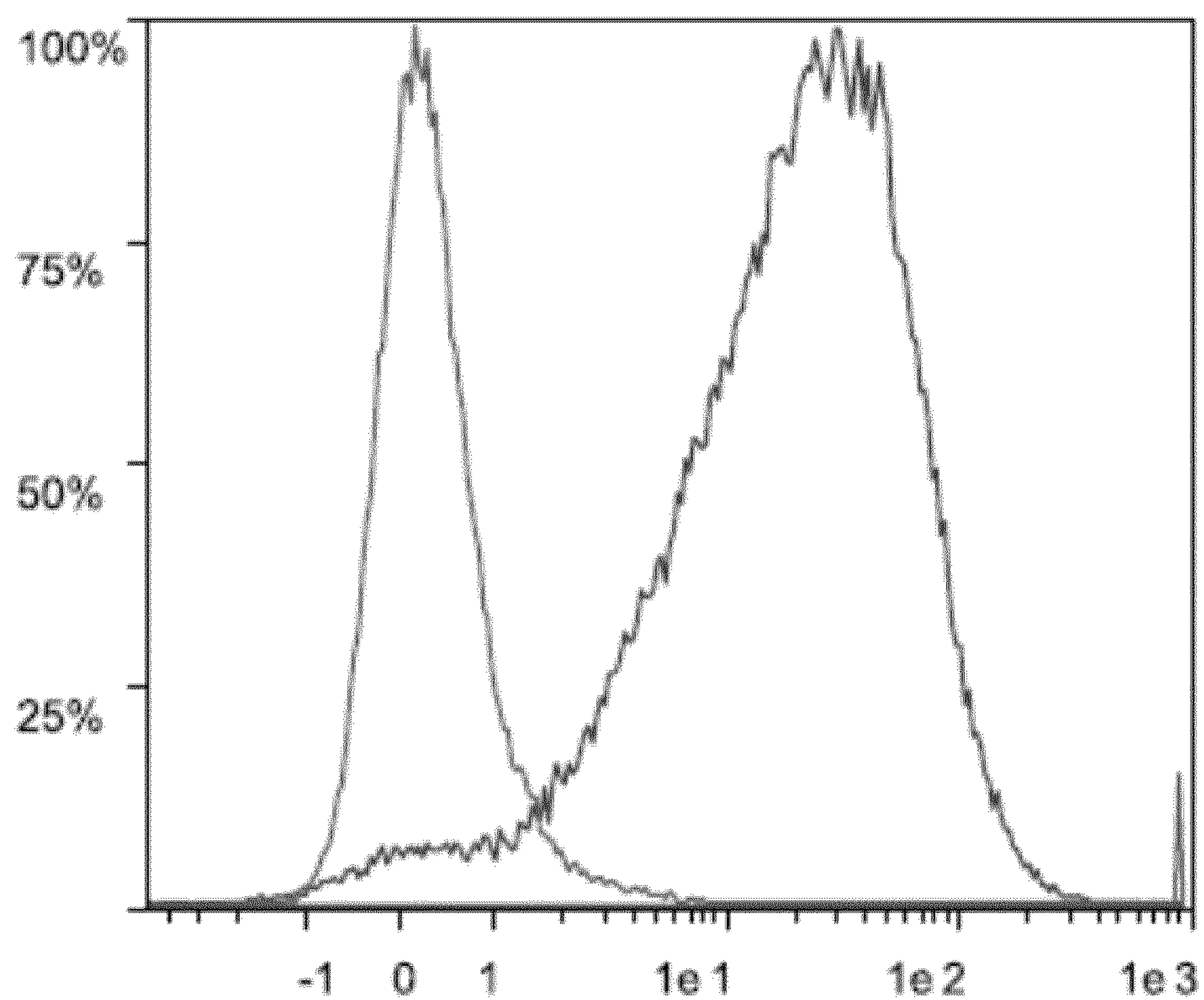
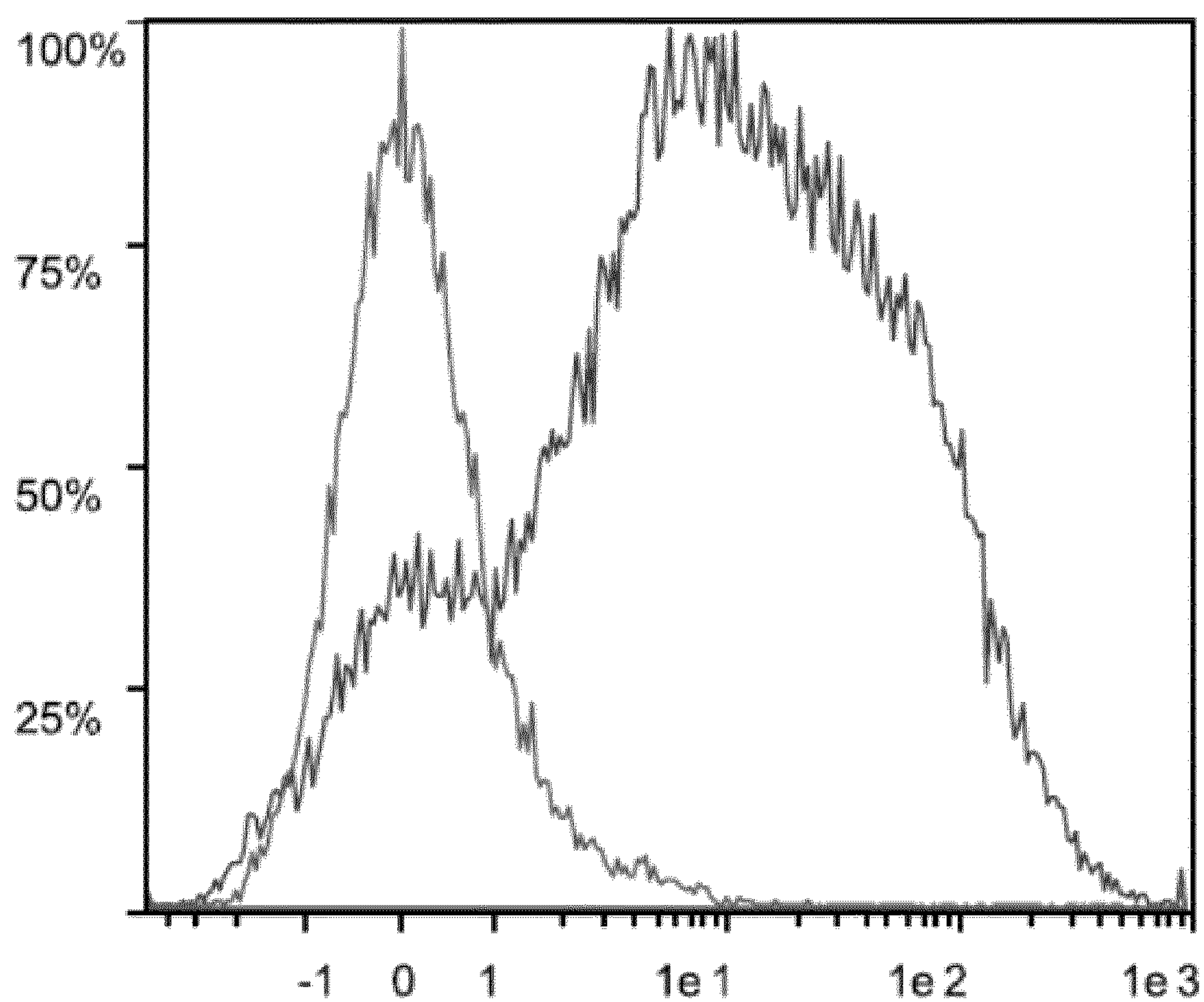
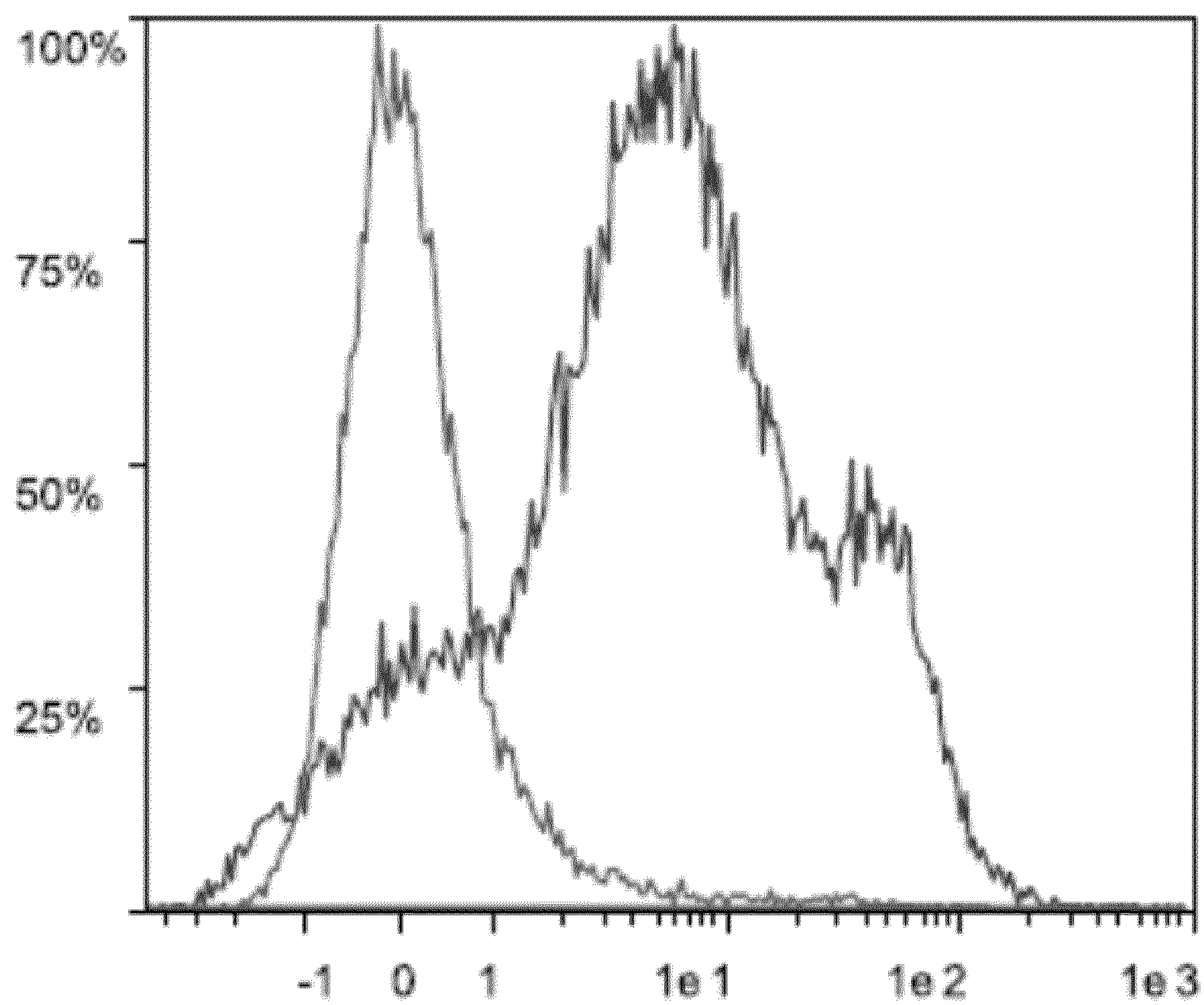
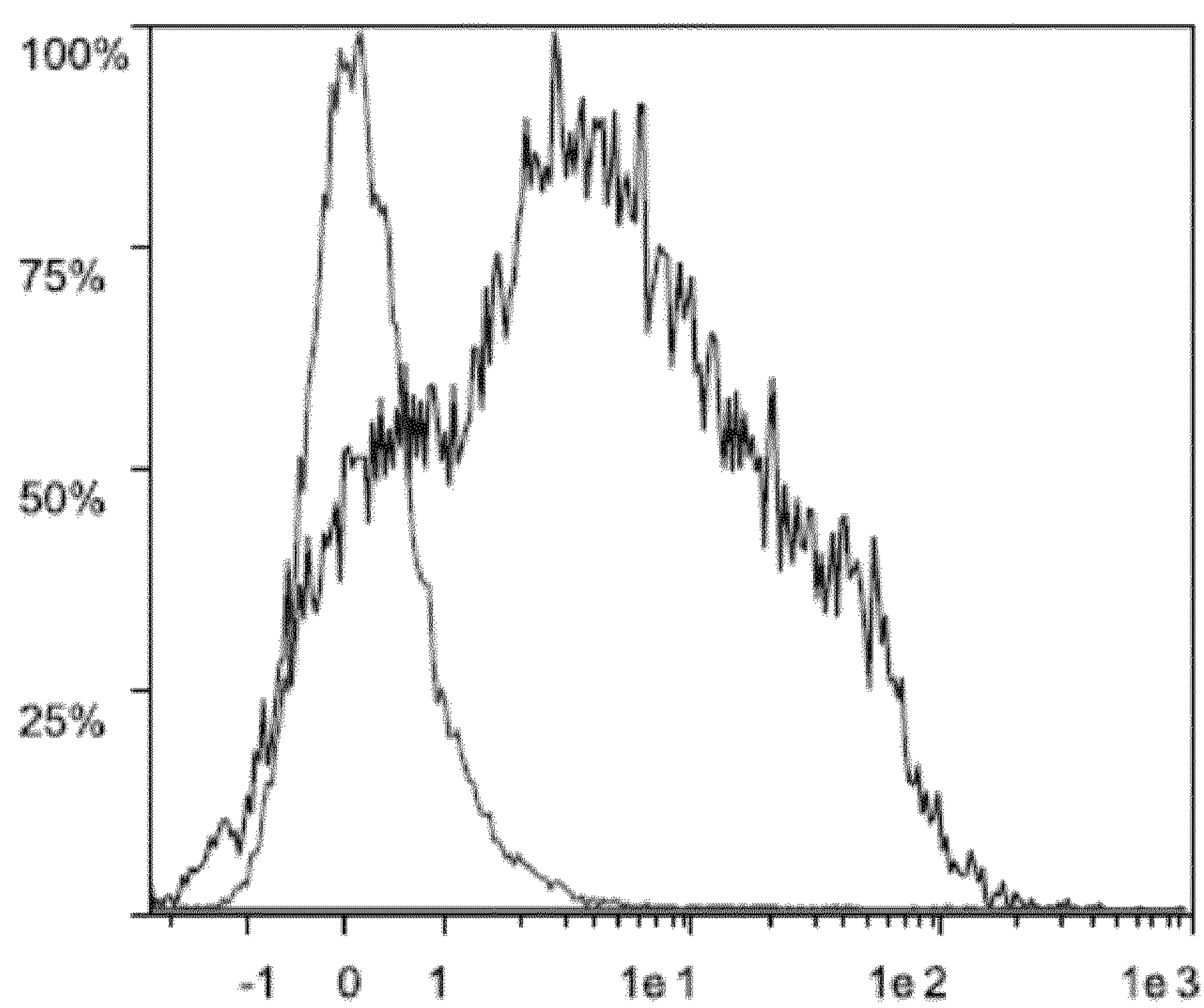


Figure 7D

**Figure 8A****Figure 8B**

**Figure 8C****Figure 8D**

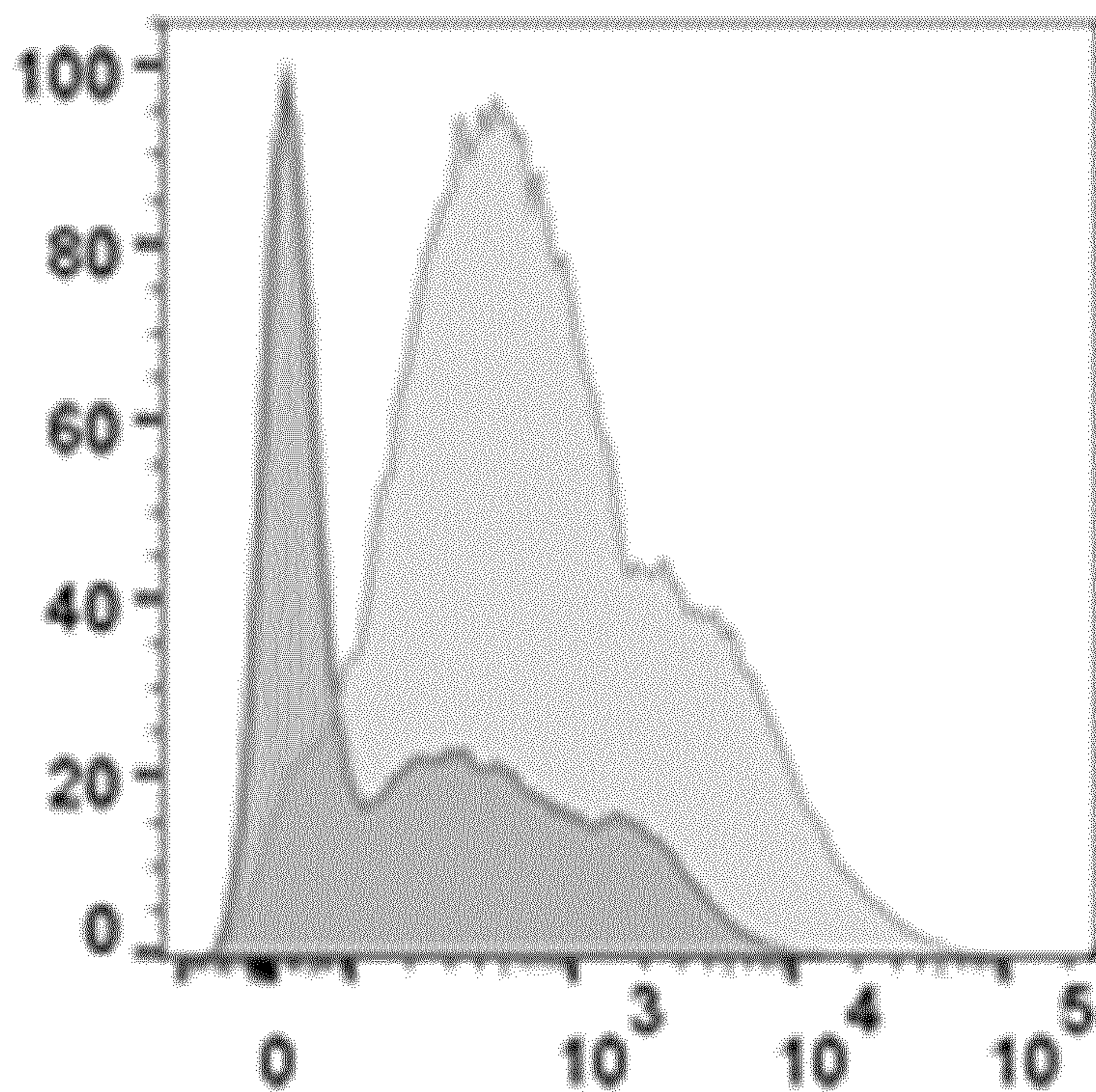


Figure 9A

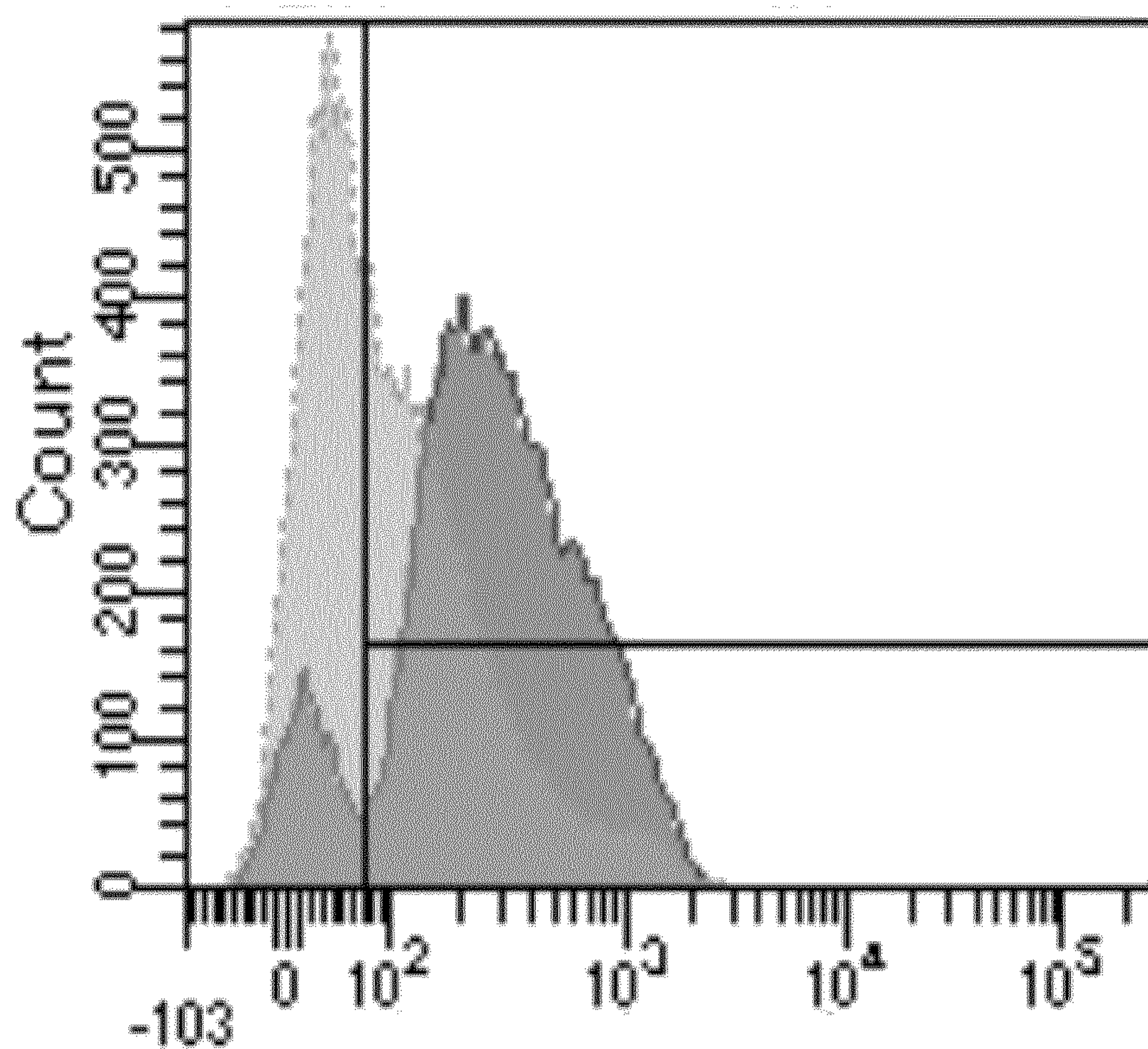


Figure 9B

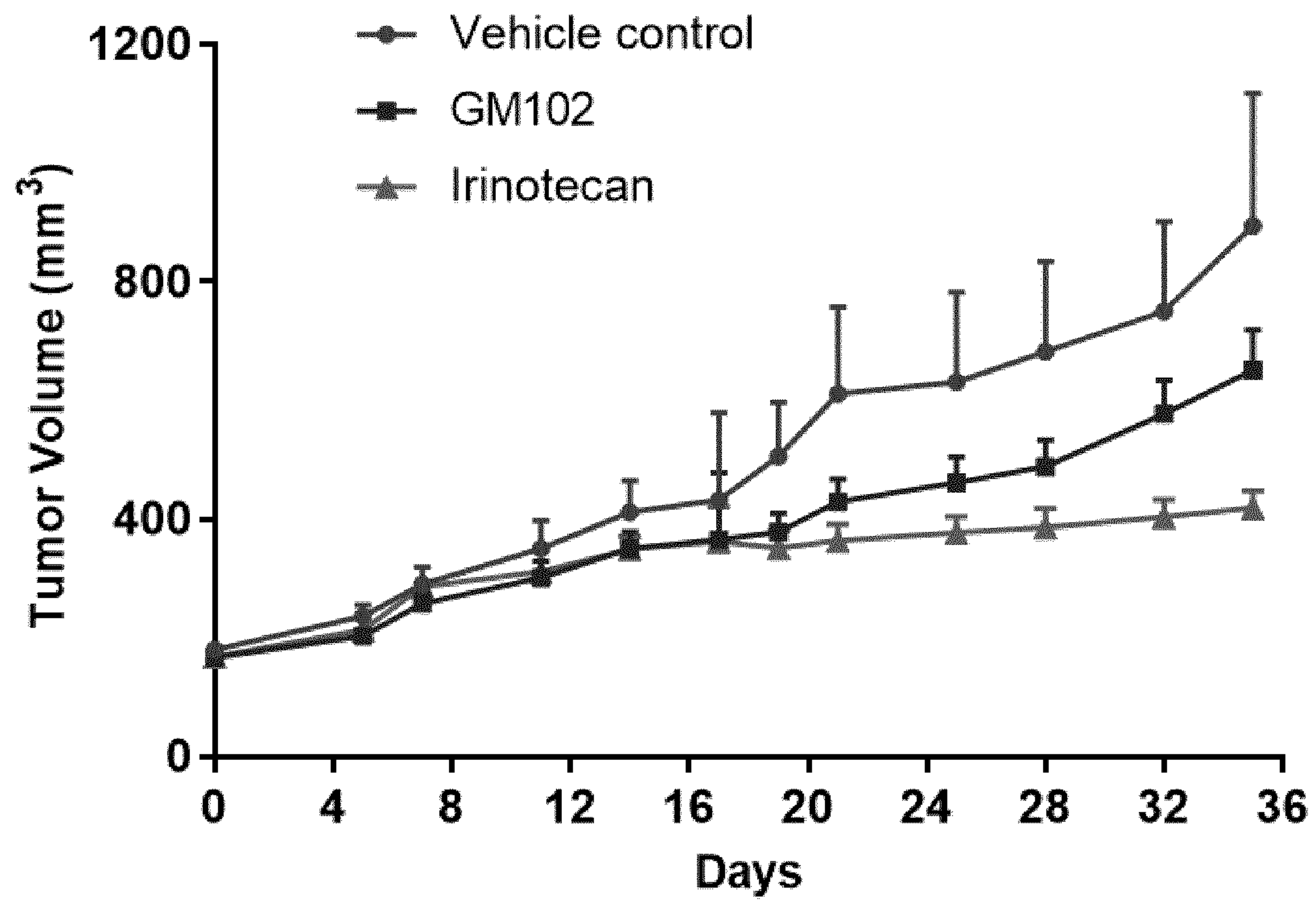


Figure 10