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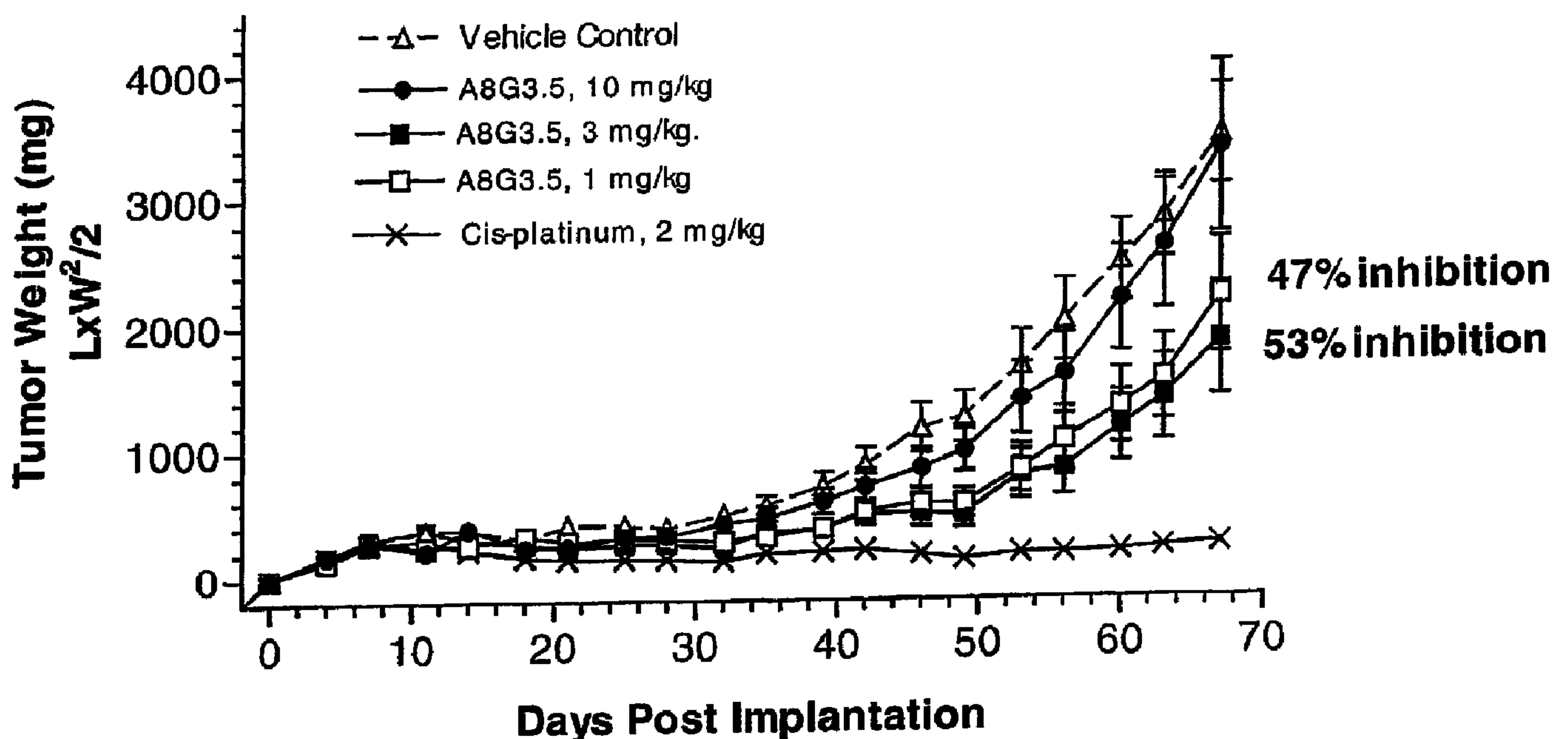
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(54) Titre : ANTICORPS DE BLOCAGE CRIPTO ET UTILISATIONS CORRESPONDANTES

(54) Title: CRIPTO BLOCKING ANTIBODIES AND USES THEREOF

Response of the NCCIT, Human Testicular Carcinoma Cell Line, to anti-CFC blocking Cripto mAb A8G3.5



(57) Abrégé/Abstract:

The invention provides Cripto blocking antibodies, or biologically functional fragments thereof, and uses thereof. Antibodies which bind Cripto and modulate Cripto signalling are provided. Antibodies which bind Cripto and block the interaction between Cripto and ALK4 are provided. Antibodies which bind Cripto and modulate tumor growth are also provided. Antibodies which bind Cripto,



(57) Abrégé(suite)/Abstract(continued):

modulate signalling, and modulate tumor growth are also provided. Antibodies which bind Cripto, block the interaction between Cripto and ALK4 and modulate tumor growth are provided. The invention also provides methods of using these antibodies in therapeutic, diagnostic, and research applications.

ABSTRACT

The invention provides Cripto blocking antibodies, or biologically functional fragments thereof, and uses thereof. Antibodies which bind Cripto and modulate Cripto signalling are provided. Antibodies which bind Cripto and block the interaction between Cripto and ALK4 are provided. Antibodies which bind Cripto and modulate tumor growth are also provided. Antibodies which bind Cripto, modulate signalling, and modulate tumor growth are also provided. Antibodies which bind Cripto, block the interaction between Cripto and ALK4 and modulate tumor growth are provided. The invention also provides methods of using these antibodies in therapeutic, diagnostic, and research applications.

We claim:

1. An antibody that specifically binds to an epitope in the ligand/receptor binding domain of Cripto.
2. The antibody of claim 1 wherein the Cripto is selected from the group consisting of SEQ ID NO: 1 or 2.
3. The antibody of claim 2 wherein the epitope is in an EGF-like domain.
4. The antibody of claim 2 wherein the epitope is in a cys-rich domain.
5. The antibody of claim 2 which is selected from the group consisting of A6C12.11, A6F8.6, A7H1.19, A8F1.30, A8G3.5, A8H3.1, A8H3.2, A19A10.30, A10B2.18, A27F6.1, A40G12.8, A2D3.23, A7A10.29, A9G9.9, A15C12.10, A15E4.14, A17A2.16, A17C12.28, A17G12.1, A17H6.1, A18B3.11, A19E2.7, B3F6.17, and B6G7.10.
6. The antibody of claim 3 which is selected from the group consisting of A40G12.8, A8H3.1, A27F6.1, B6G7.10, A17G12.1 and A18B3.11.
7. The antibody of claim 4 which is selected from the group consisting of A19A10.30, A8G3.5, A6F8.6 and A6C12.11.
8. An antibody that specifically binds to an epitope comprised in the domain spanning amino acid residues 46-62 of Cripto.
9. The antibody of claim 8 which is A10B2.18 and B3F6.17.
10. An antibody which binds specifically to an epitope selected from the group of epitopes to which antibodies A6C12.11, A6F8.6, A7H1.19, A8F1.30, A8G3.5, A8H3.1, A8H3.2, A19A10.30, A10B2.18, A27F6.1, A40G12.8, A2D3.23, A7A10.29, A9G9.9, A15C12.10, A15E4.14, A17A2.16, A17C12.28, A17G12.1, A17H6.1, A18B3.11, A19E2.7, B3F6.17, and B6G7.10 bind.

11. An antibody which binds specifically to Cripto and is capable of modulating Cripto signaling.

12. The antibody of claim 11 which specifically binds to an epitope in an EGF-like domain of Cripto.

5 13. The antibody of claim 12 which is selected from A40G12.8, A8H3.1 and A27F6.1.

14. The antibody of claim 11 which specifically binds to an epitope in a cys-rich domain of Cripto.

15. The antibody of claim 14 which is A6C12.11.

10 16. The antibody of claim 11 which is selected from the group consisting of A40G12.8, A8H3.1, A27F6.1, and A6C12.11.

17. An antibody which binds specifically to Cripto and is capable of modulating tumor growth.

15 18. The antibody of claim 17 which specifically binds to an epitope in an EGF-like domain of Cripto.

19. The antibody of claim 17 which specifically binds to an epitope in a cys-rich domain of Cripto.

20 20. The antibody of claim 17 which is selected from the group consisting of A27F6.1, A8G3.5 and B6G7.10.

21. An antibody which binds specifically to Cripto, which is capable of modulating Cripto signaling, and which is capable of modulating tumor growth.

22. The antibody of claim 21 which specifically binds to an epitope in an EGF-like domain of Cripto.

25 23. The antibody of claim 21 which specifically binds to an epitope in a cys-rich domain of Cripto.

24. The antibody of claim 21 which is A27F6.1.

25. An antibody produced by a hybridoma selected from the group consisting of A6F8.6 (ATCC Accession No. PTA-3318), A8G3.5 (ATCC Accession No. PTA-3317), A8H3.1 (ATCC Accession No. PTA-3315), A10B2.18 (ATCC Accession No. PTA-3311), A27F6.1 (ATCC Accession No. PTA-3310), A40G12.8 (ATCC Accession No. PTA-3316), A17G12.1 (ATCC Accession No. PTA-3314), A18B3.11 (ATCC Accession No. PTA-3312), B3F6.17 (ATCC Accession No. PTA-3319), and B6G7.10 (ATCC Accession No. PTA-3313).

26. An antibody which binds specifically to Cripto and is capable of blocking the interaction between Cripto and ALK4.

27. The antibody of claim 26 which specifically binds to an epitope in an EGF-like domain of Cripto.

28. The antibody of claim 26 which specifically binds to an epitope in a cysteine-rich domain of Cripto.

29. The antibody of claim 26 which is selected from the group consisting of A8G3.5, A6F8.6 and A6C12.11.

30. An antibody which binds specifically to Cripto, which is capable of blocking the interaction between Cripto and ALK4, and which is capable of modulating tumor growth.

31. The antibody of claim 30 which specifically binds to an epitope in an EGF-like domain of Cripto.

32. The antibody of claim 30 which specifically binds to an epitope in a cysteine-rich domain of Cripto.

33. The antibody of claim 30 which is A8G3.5.

34. A Cripto antibody capable of internalizing Cripto.

35. The antibody of claim 34 wherein the antibody is conjugated to a
chemotherapeutic.

36. The antibody of claim 34 which is selected from A27F6.1 and B3F6.17.

37. A composition for administration to a subject having a tumor that expresses
5 Cripto comprising at least one of the antibodies of any of claims 1-35.

38. The composition according to claim 37, wherein the subject is human.

39. The composition according to claim 37, further comprising a
pharmaceutically acceptable excipient.

40. The composition according to claim 37, wherein the antibody is conjugated
10 to a chemotherapeutic.

41. The composition according to claim 37, further comprising a
nonconjugated chemotherapeutic.

42. A method of modulating growth of tumor cells *in vitro* in a sample
comprising the step of adding to the sample the composition of claim 37.

43. A method of modulating growth of tumor cells *in vivo* in a subject
15 comprising the step of administering to the subject an effective amount of the
composition of claim 37.

44. The method according to claim 43, wherein the subject is human.

45. A method of treating a subject having a tumor that over-expresses Cripto
20 comprising administering to said subject the composition of claim 37 in an effective
amount.

46. A method of treating a patient having a tumor that over-expresses Cripto
comprising administering to said patient the composition of claim 39 in an effective
amount.

47. A method of treating a patient having a tumor that over-expresses Cripto comprising administering to said patient the composition of claim 40 in an effective amount.

48. A method of treating a patient having a tumor that over-expresses Cripto
5 comprising administering to said patient the composition of claim 41 in an effective amount.

49. The method according to claim 42, wherein the tumor cell is selected from the group consisting of breast, testicular, colon, lung, ovary, bladder, uterine, cervical, pancreatic, and stomach tumor cells.

10 50. The method according to claim 43, wherein the tumor cell is selected from the group consisting of breast, testicular, colon, lung, ovary, bladder, uterine, cervical, pancreatic, and stomach tumor cells.

51. The method according to claim 44, wherein the tumor cell is selected from the group consisting of breast, testicular, colon, lung, ovary, bladder, uterine, cervical,
15 pancreatic, and stomach tumor cells.

52. The method according to claim 45, wherein the tumor is selected from the group consisting of breast, testicular, colon, lung, ovary, bladder, uterine, cervical, pancreatic, and stomach tumors.

53. The method according to claim 46, wherein the tumor is selected from the
20 group consisting of breast, testicular, colon, lung, ovary, bladder, uterine, cervical, pancreatic, and stomach tumors.

54. The method according to claim 47, wherein the tumor is selected from the group consisting of breast, testicular, colon, lung, ovary, bladder, uterine, cervical, pancreatic, and stomach tumors.

55. The method according to claim 48, wherein the tumor is selected from the group consisting of breast, testicular, colon, lung, ovary, bladder, uterine, cervical, pancreatic, and stomach tumors.

56. A method of determining whether a tissue expresses Cripto, comprising the
5 step of analyzing tissue from the subject in an immunoassay using an antibody of any of claims 1-37.

57. A method of determining whether a cell line overexpresses Cripto, comprising the step of analyzing the cell line in an immunoassay using an antibody of any of claims 1-37.

10 58. The antibody of claim 1 wherein the antibody is monoclonal antibodies.

59. The antibody of claim 1 wherein the antibody is humanized antibodies.

60. The antibody of claim 1 wherein the antibody is human antibodies.

61. A method of treating a subject for a condition associated with undesired
cell proliferation, said method comprising administering to said subject the composition
15 of claim 37.

FIGURE 1
Response of the NCCIT, Human Testicular
Carcinoma Cell Line, to anti-CFC blocking
Cripto mAb A8G3.5

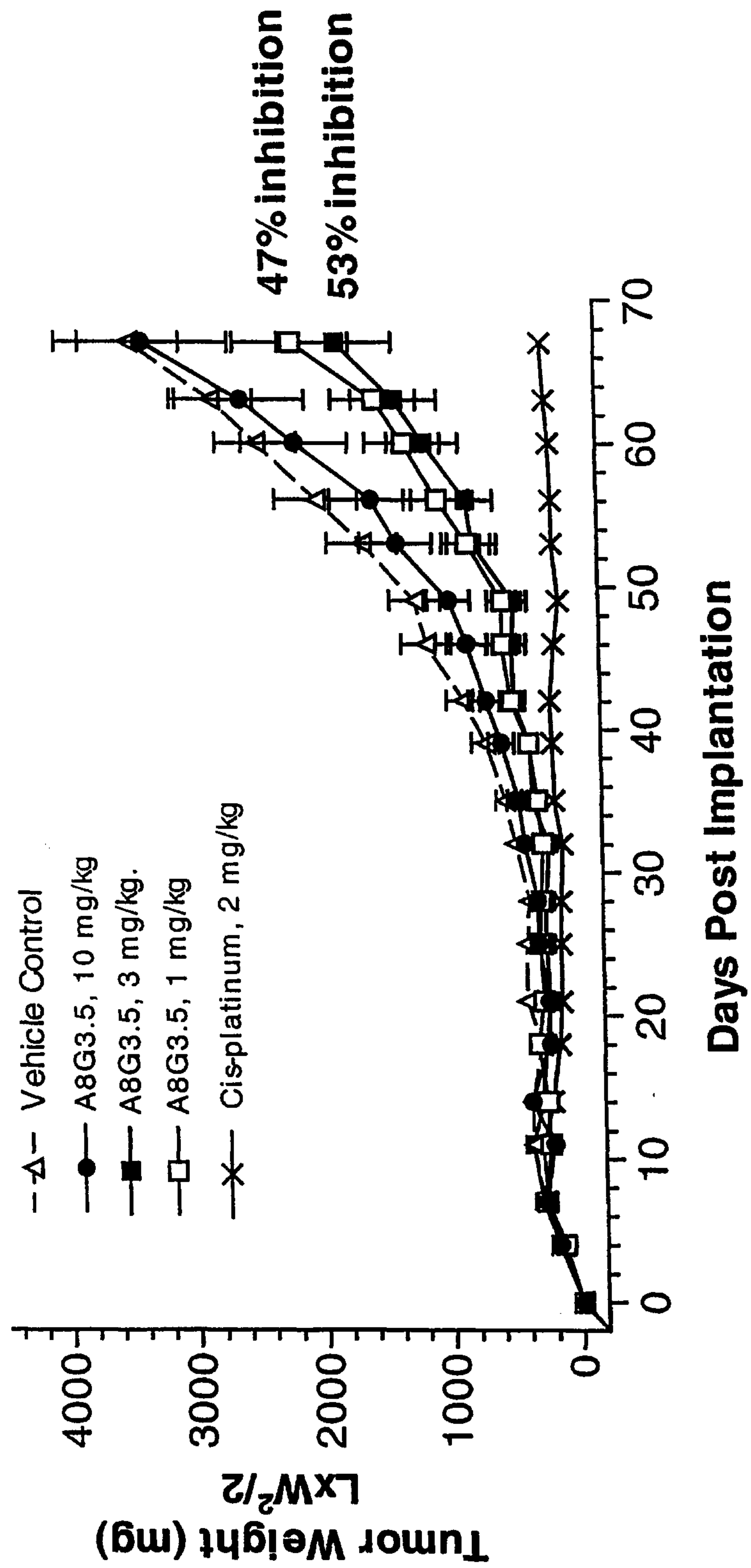


FIGURE 2

**Response of the NCCIT, Human Testicular
Carcinoma Cell Line, to anti-EGF blocking
Cripto mAb A27F6.1**

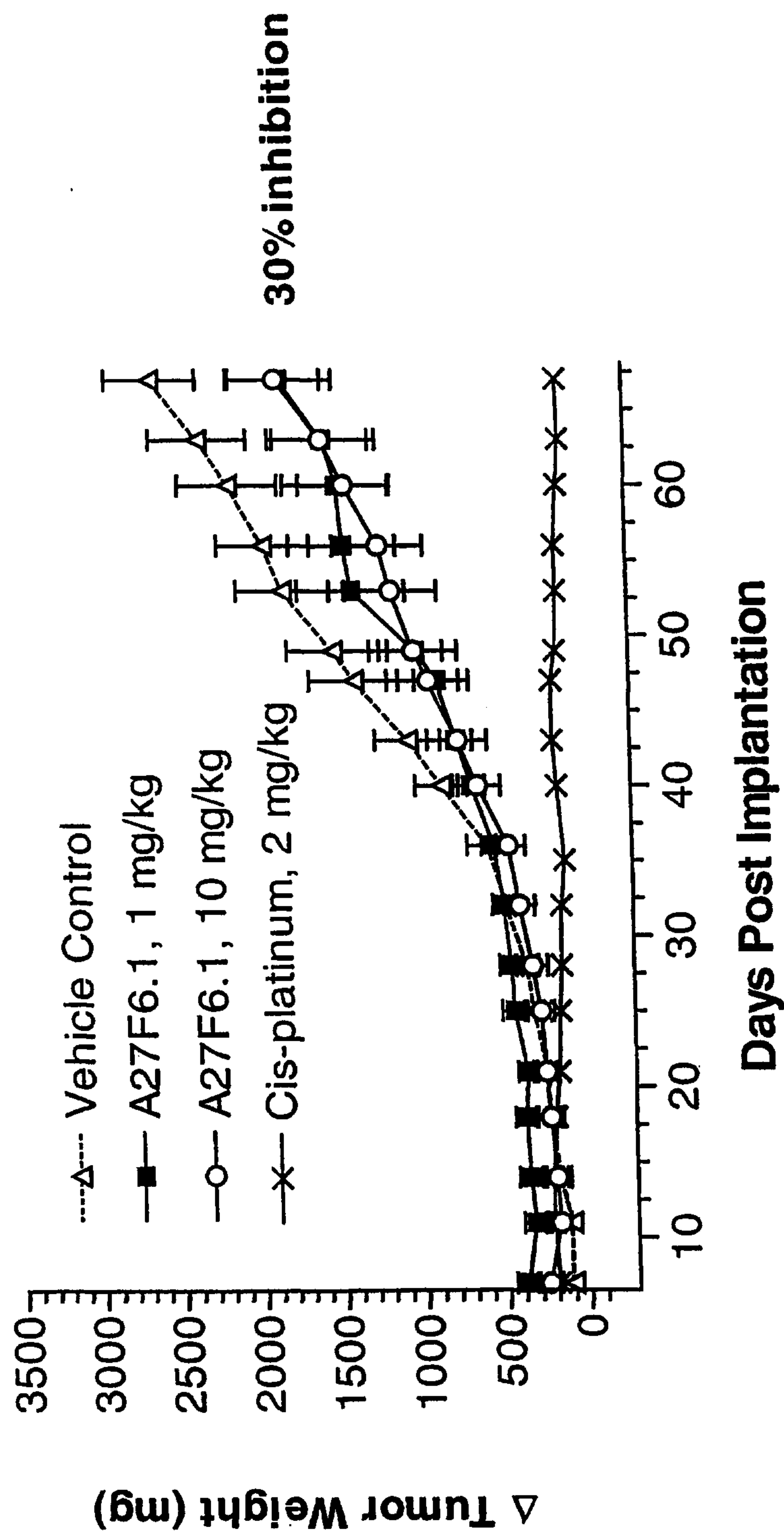
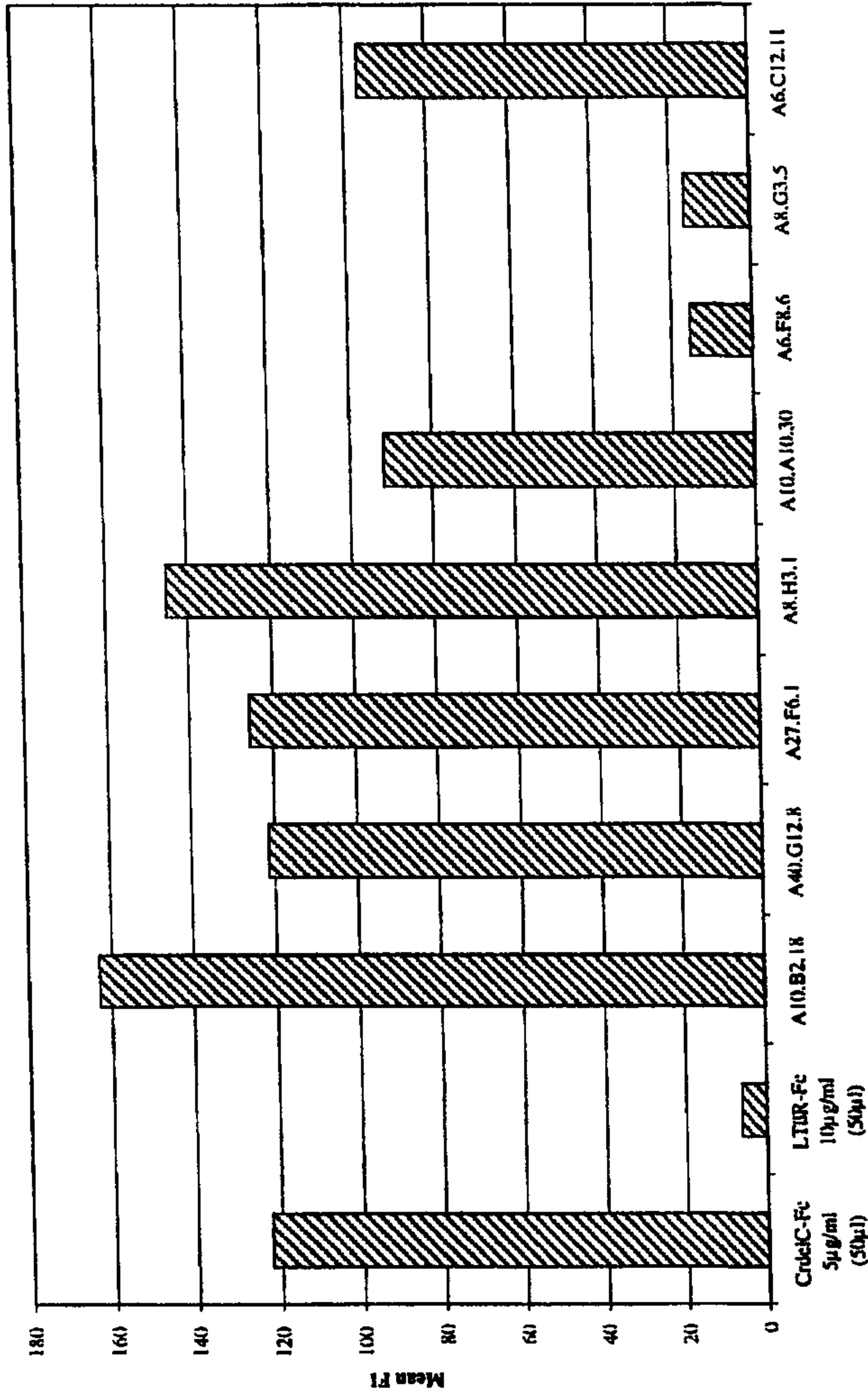


FIGURE 3

FACS: 293/ALK4 cells binding CR-Fc



Response of the NCCIT, Human Testicular Carcinoma Cell Line, to anti-CFC blocking Cripto mAb A8G3.5

