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(54) **PEGYLATION OF LINKERS IMPROVES ANTITUMOR ACTIVITY AND REDUCES TOXICITY OF IMMUNOCONJUGATES**

PEGYLATION VON LINKER VERBESSERT DIE ANTITUMOR-AKTIVITÄT UND VERRINGERT DIE TOXIZITÄT VON IMMUNKONJUGATEN

PEGYLATION DE LIEURS AMELIORANT L'ACTIVITE ANTITUMORALE ET REDUISANT LA TOXICITE D'IMMUNOCONJUGUES

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22.06.2000 US 213804 P</p> <p>(43) Date of publication of application:
15.10.2003 Bulletin 2003/42</p> <p>(73) Proprietor: The Government of The United States of America, as represented by The Department of Health and Human Services Bethesda, MD 20892 (US)</p> <p>(72) Inventors:
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 <ul style="list-style-type: none"> • Y. TSUTSUMI ET AL: "Site-specific chemical modification with polyethylene glycol of recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) improves antitumor activity and reduces animal toxicity and immunogenicity" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 97, no. 15, 18 July 2000 (2000-07-18), pages 8548-8553, XP002227760 • R. J. KREITMAN ET AL: "Complete regression of human B-cell lymphoma xenografts in mice treated with recombinant anti-CD22 immunotoxin RFB4(dsFv)-PE38 at doses tolerated by cynomolgus monkeys" INTERNATIONAL JOURNAL OF ACNCER, vol. 81, 1999, pages 148-155, XP002227761 cited in the application </p> |
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Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

- R. J. KREITMAN ET AL: "Responses in Refractory Hairy Cell Leukemia to a Recombinant Immunotoxin" BLOOD, vol. 94, no. 10, 15 November 1999 (1999-11-15), pages 3340-3348, XP002227762 cited in the application
- MILTON HARRIS J ET AL: "PEGYLATION A NOVEL PROCESS FOR MODIFYING PHARMACOKINETICS" CLINICAL PHARMACOKINETICS, LEA & FEBIGER, PHILADELPHIA, PA, US, vol. 40, no. 7, 2001, pages 539-551, XP001106431
- REITER Y ET AL: "IMPROVED BINDING AND ANTITUMOR ACTIVITY OF A RECOMBINANT ANTI-ERBB2IMMUNOTOXIN BY DISULFIDE STABILIZATION OF THE FV FRAGMENT" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 269, no. 28, 15 July 1994 (1994-07-15), pages 18327-18331, XP000941643 ISSN: 0021-9258 cited in the application
- CHIEN-TSUN KUAN ET AL: "PSEUDOMONAS EXTOXIN A MUTANTS REPLACEMENT OF SURFACE EXPOSED RESIDUES IN DOMAIN IN WITH CYSTEINERESIDUES THAT CAN BE MODIFIED WITH POLYETHYLENE GLYCOL IN A SITE-SPECIFIC MANNER" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 269, no. 10, 11 March 1994 (1994-03-11), pages 7610-7616, XP000563744 ISSN: 0021-9258 cited in the application
- DATABASE MEDLINE [Online] October 1996 (1996-10) TSUTSUMI Y ET AL: "Molecular design of hybrid tumour necrosis factor-alpha. II: The molecular size of polyethylene glycol-modified tumour necrosis factor-alpha affects its anti-tumour potency." Database accession no. NLM8855980 XP002227763 cited in the application & BRITISH JOURNAL OF CANCER. SCOTLAND OCT 1996, vol. 74, no. 7, October 1996 (1996-10), pages 1090-1095, ISSN: 0007-0920