

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 November 2004 (18.11.2004)

PCT

(10) International Publication Number
WO 2004/099244 A3

(51) International Patent Classification⁷: **C07K 14/525**,
C12N 15/28, A61K 38/19, 48/00, 39/00

(21) International Application Number:
PCT/DK2004/000329

(22) International Filing Date: 6 May 2004 (06.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2003 00701 9 May 2003 (09.05.2003) DK
60/469,491 9 May 2003 (09.05.2003) US

(71) Applicant (for all designated States except US):
PHARMEXA A/S [DK/DK]; Kogle Allé 6, DK-2970
Hørsholm (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BRATT, Tomas**
[SE/DK]; c/o Pharmexa A/S, Kogle Allé 6, DK-2970 Hørsholm (DK). **KLYSNER, Steen** [DK/DK]; c/o Pharmexa A/S, Kogle Allé 6, DK-2970 Hørsholm (DK). **NIELSEN, Finn** [DK/DK]; c/o Pharmexa A/S, Kogle Allé 6, DK-2970 Hørsholm (DK). **MOURITSEN, Søren** [DK/DK]; Høveltevej 78, DK-3460 Birkerød (DK). **VOLDBORG, Bjørn** [DK/DK]; c/o Pharmexa A/S, Kogle Allé 6, DK-2970 Hørsholm (DK).

(74) Agent: **INSPICOS A/S**; Bøge Allé 5, P.O. Box 45,
DK-2970 Hørsholm (DK).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
29 December 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMMUNOGENIC HUMAN TNF ALPHA ANALOGUES WITH REDUCED CYTOTOXICITY AND METHODS OF THEIR PREPARATION

(57) Abstract: The present invention provides for an immunogenic analogue of a human TNF α protein, wherein said analogue comprises an immunogenized monomeric TNF α polypeptide or TNF α di- or trimer, and wherein the analogue further comprises a toxicity reducing or abolishing mutation selected from the group consisting of Y87S, D143N or A145R, the amino acid numbering setting out from the N-terminal valine in human TNF α . The invention also provides for a nucleic acid fragment encoding the analogue as well as to vectors and transformed cells useful in the preparation of the analogue. Also disclosed are methods of down-regulating TNF α in a subject in need thereof.



WO 2004/099244 A3