(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 March 2022 (31.03.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/064428 A1

(51) International Patent Classification:
C12N 5/0783 (2010.01) *C12N 15/10* (2006.01)
A61K 35/17 (2015.01) *C12N 15/85* (2006.01)

(21) International Application Number:
PCT/IB2021/058704

(22) International Filing Date:
23 September 2021 (23.09.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/082,357 23 September 2020 (23.09.2020) US
63/124,429 11 December 2020 (11.12.2020) US
63/225,673 26 July 2021 (26.07.2021) US

(71) Applicant: **CRISPR THERAPEUTICS AG** [CH/CH]; Baarerstrasse 14, 6300 Zug (CH).

(72) Inventors: **DEQUEANT, Mary-Lee**; 610 Main Street, Cambridge, Massachusetts 02139 (US). **KALAITZIDIS, Demetrios**; 610 Main Street, Cambridge, Massachusetts 02139 (US). **GHONIME, Mohammed**; 610 Main Street, Cambridge, Massachusetts 02139 (US).

(74) Agent: **VOSSIUS & PARTNER**; Patentanwälte Rechtsanwälte mbB, Siebertstrasse 3, 81675 München (DE).

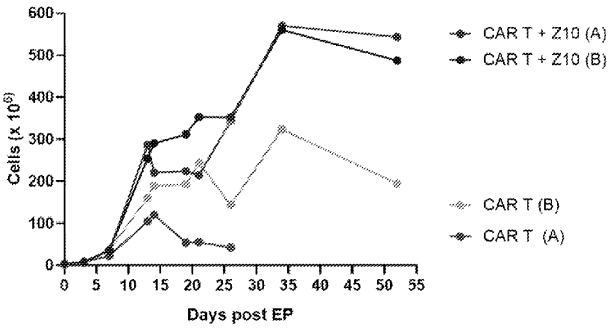
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, 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, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: GENETICALLY ENGINEERED T CELLS WITH REGNASE-1 AND/OR TGFBRII DISRUPTION HAVE IMPROVED FUNCTIONALITY AND PERSISTENCE

FIG. 1B



(57) Abstract: A population of genetically engineered T cells, comprising a disrupted Reg1 gene and/or a disrupted TGFBRII gene. Such genetically engineered T cells may comprise further genetic modifications, for example, a disrupted CD70 gene. The population of genetically engineered T cells exhibit one or more of (a) improved cell growth activity; (b) enhanced persistence; and (c) reduced T cell exhaustion, (d) enhanced cytotoxicity activity, (e) resistant to inhibitory effects induced by TGF-b, and (f) resistant to inhibitory effects by fibroblasts and/or inhibitory factors secreted thereby, as compared to non-engineered T cell counterparts.

WO 2022/064428 A1