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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 August 2011 (04.08.2011)

PCT

(10) International Publication Number
WO 2011/094467 A2

(51) International Patent Classification:
C07K 16/22 (2006.01)

(21) International Application Number:
PCT/US2011/022817

(22) International Filing Date:
28 January 2011 (28.01.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/299,801	29 January 2010 (29.01.2010)	US
61/361,687	6 July 2010 (06.07.2010)	US
61/388,697	1 October 2010 (01.10.2010)	US

(71) Applicant *(for all designated States except US)*: **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **SKOKOS, Dimitris** [GR/US]; 400 East 84th Street, Apt. 15C, New York, NY 10028 (US).

(74) Agent: **YOKOYAMA, Izumi**; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2011/094467 A2

(54) **Title**: METHODS OF TREATING DIABETES WITH DLL4 ANTAGONISTS

(57) **Abstract**: The present invention provides methods of preventing, treating or ameliorating diabetes by administering to a subject in need thereof a therapeutically effective amount of Dll4 antagonists that block Dll4-Notch signal pathways. As observed in a mouse model of diabetes, Dll4 antagonists exhibit protective effects on pancreatic islets, lower blood glucose levels, and block the production of auto-antibodies, including those against insulin and glutamic acid decarboxylase 65 (GAD65), via the expansion of regulatory T cells (Tregs). Thus, the present invention further provides methods of lowering the levels of blood glucose, and/or reducing or blocking the production of auto-antibodies, by administering to a subject in need thereof a therapeutically effective amount of Dll4 antagonists. Suitable Dll4 antagonists for the invention include antibodies or antibody fragments that specifically bind Dll4 and block Dll4-Notch interactions, the extracellular domain of Dll4, and the like.