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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2014 (24.12.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/204726 A1

(51) International Patent Classification:
C12N 15/63 (2006.01) *C40B 40/08* (2006.01)
C12N 15/10 (2006.01) *C12N 9/22* (2006.01)

(21) International Application Number:
PCT/US2014/041804

(22) International Filing Date:
10 June 2014 (10.06.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/836,123	17 June 2013 (17.06.2013)	US
61/847,537	17 July 2013 (17.07.2013)	US
61/862,355	5 August 2013 (05.08.2013)	US
61/871,301	28 August 2013 (28.08.2013)	US
PCT/US2013/0074667	12 December 2013 (12.12.2013)	US
61/915,325	12 December 2013 (12.12.2013)	US
61/979,733	15 April 2014 (15.04.2014)	US

(71) Applicants: **THE BROAD INSTITUTE INC.** [US/US]; 7 Cambridge Center, Cambridge, MA 02142 (US). **MASSACHUSETTS INSTITUTE OF TECHNOLOGY** [US/US]; 77 Massachusetts Ave., Cambridge, MA 02142 (US).

(72) Inventors; and
(71) Applicants : **ZHANG, Feng** [US/US]; 100 Pacific Street, Apt. 11, Cambridge, MA 02139 (US). **CONG, Le** [CN/US]; 375 Harvard Street, Apt. 14, Cambridge, MA 02138 (US). **RAN, Fei** [US/US]; 129 St. Botolph Street, Apt. 2, Boston, MA 02115 (US).

(74) Agents: **LU, Deborah, L.** et al.; Vedder Price P.C., 1633 Broadway, New York, NY 10019 (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, BN, 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, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, RW, SD, SL, 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))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title**: DELIVERY AND USE OF THE CRISPR-CAS SYSTEMS, VECTORS AND COMPOSITIONS FOR HEPATIC TARGETING AND THERAPY

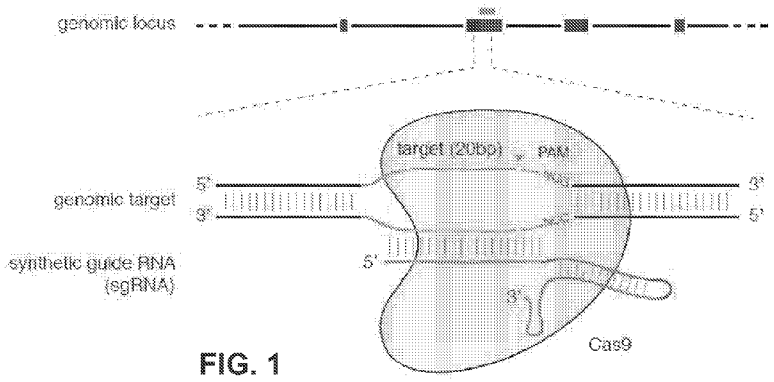


FIG. 1

(57) **Abstract**: The invention provides for delivery, engineering and optimization of systems, methods, and compositions for manipulation of sequences and/or activities of target sequences. Provided are deliver)' systems and tissues or organ which are targeted as sites for delivery. Also provided are vectors and vector systems some of which encode one or more components of a CRISPR complex, as well as methods for the design and use of such vectors. Also provided are methods of directing CRISPR complex formation in eukaryotic cells to ensure enhanced specificity for target recognition and avoidance of toxicity and to edit or modify a target site in a genomic locus of interest to alter or improve the status of a disease or a condition.

WO 2014/204726 A1