

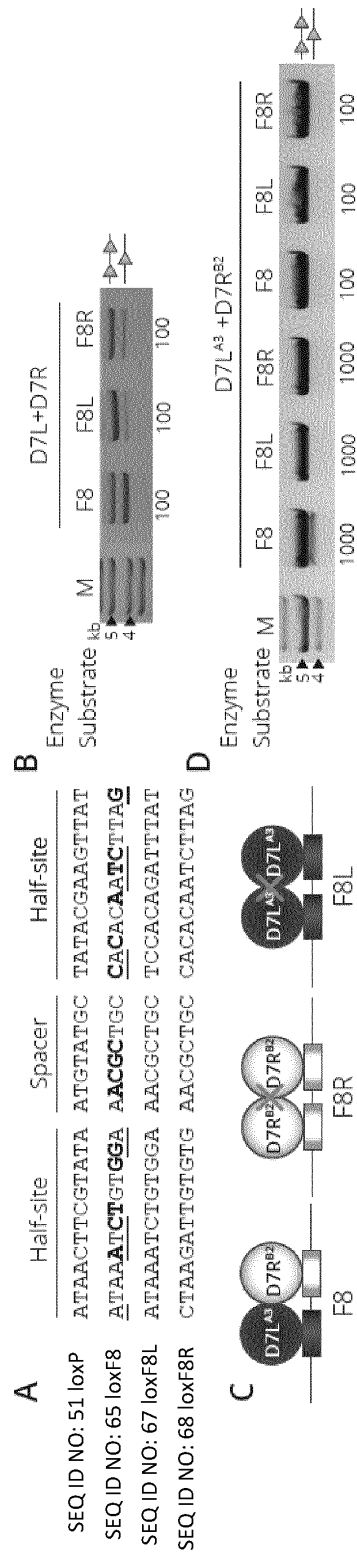
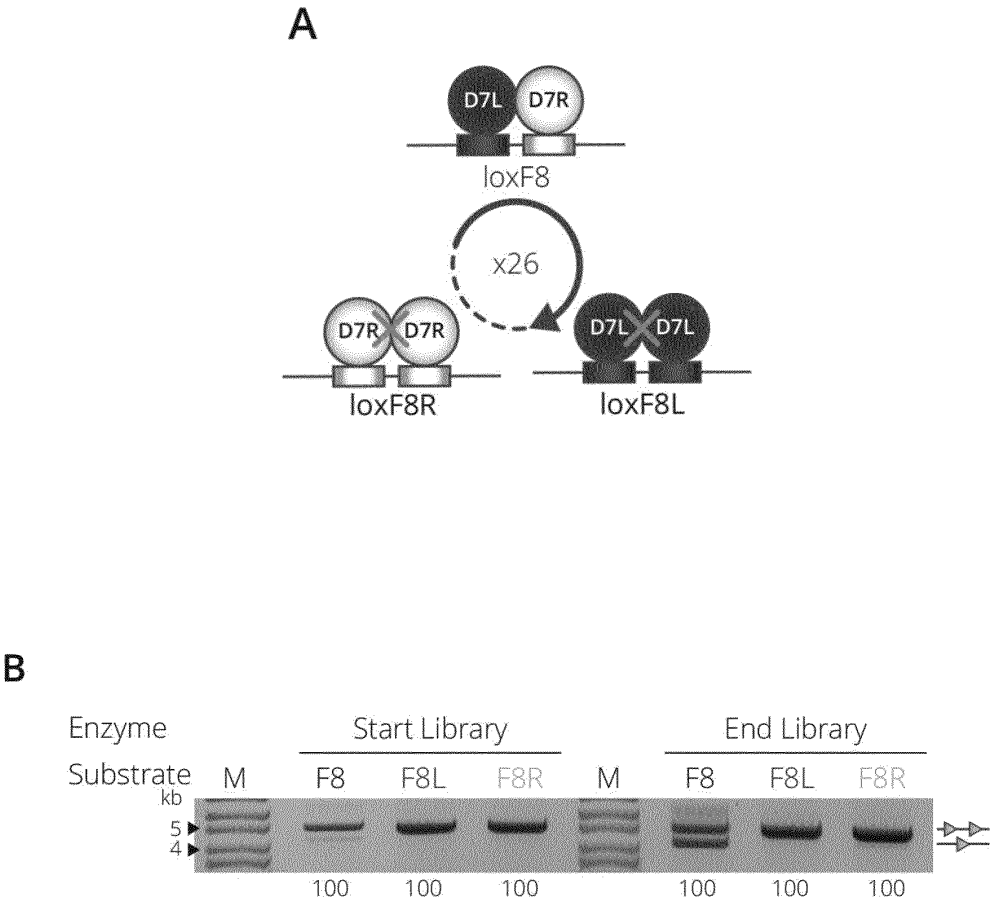


Fig. 1



C

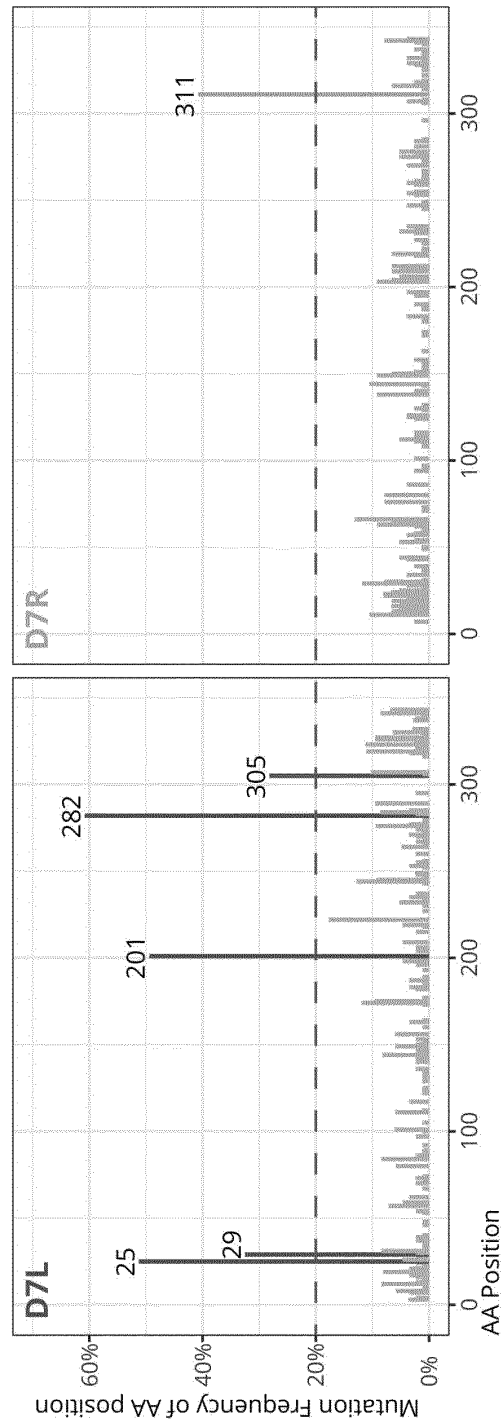
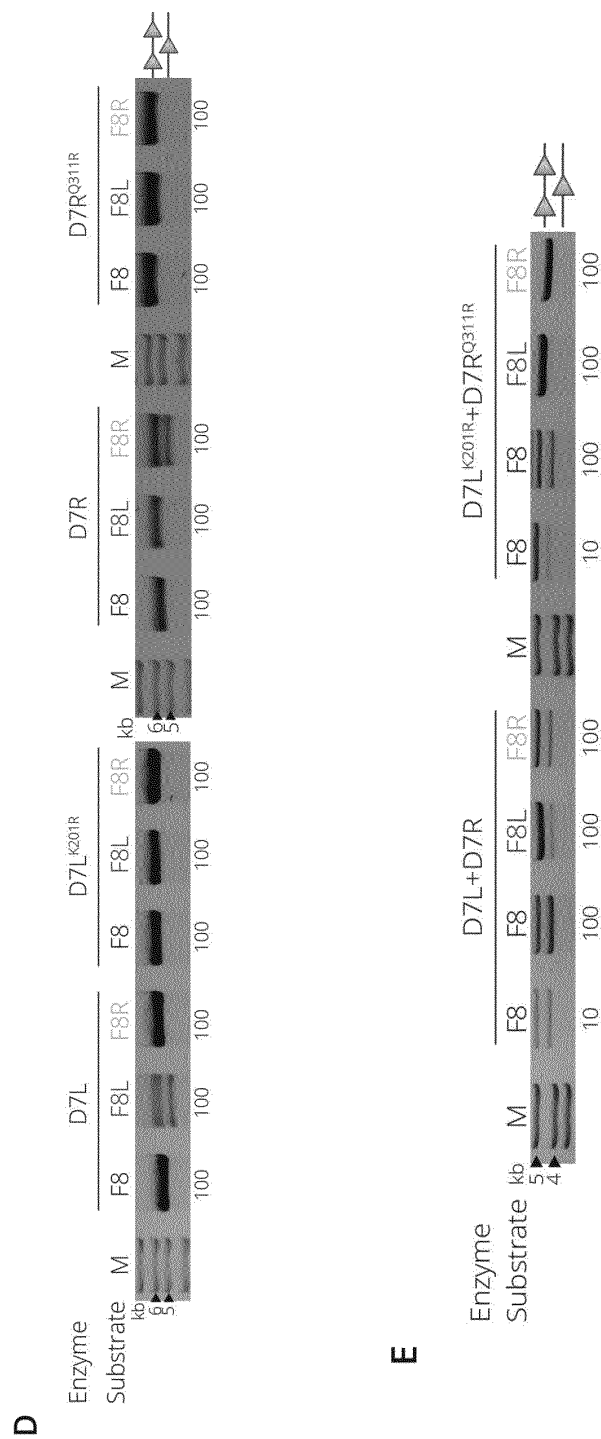


Fig. 2 continued



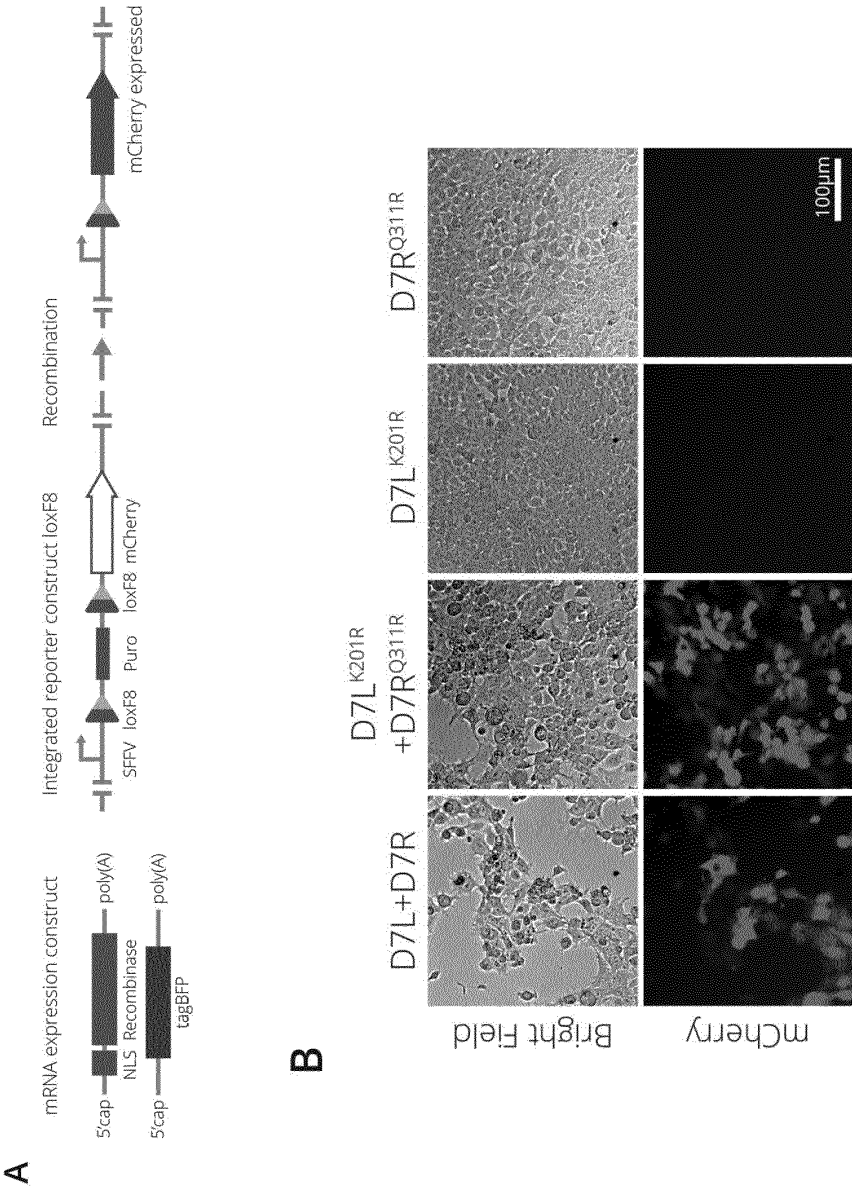


Fig. 3

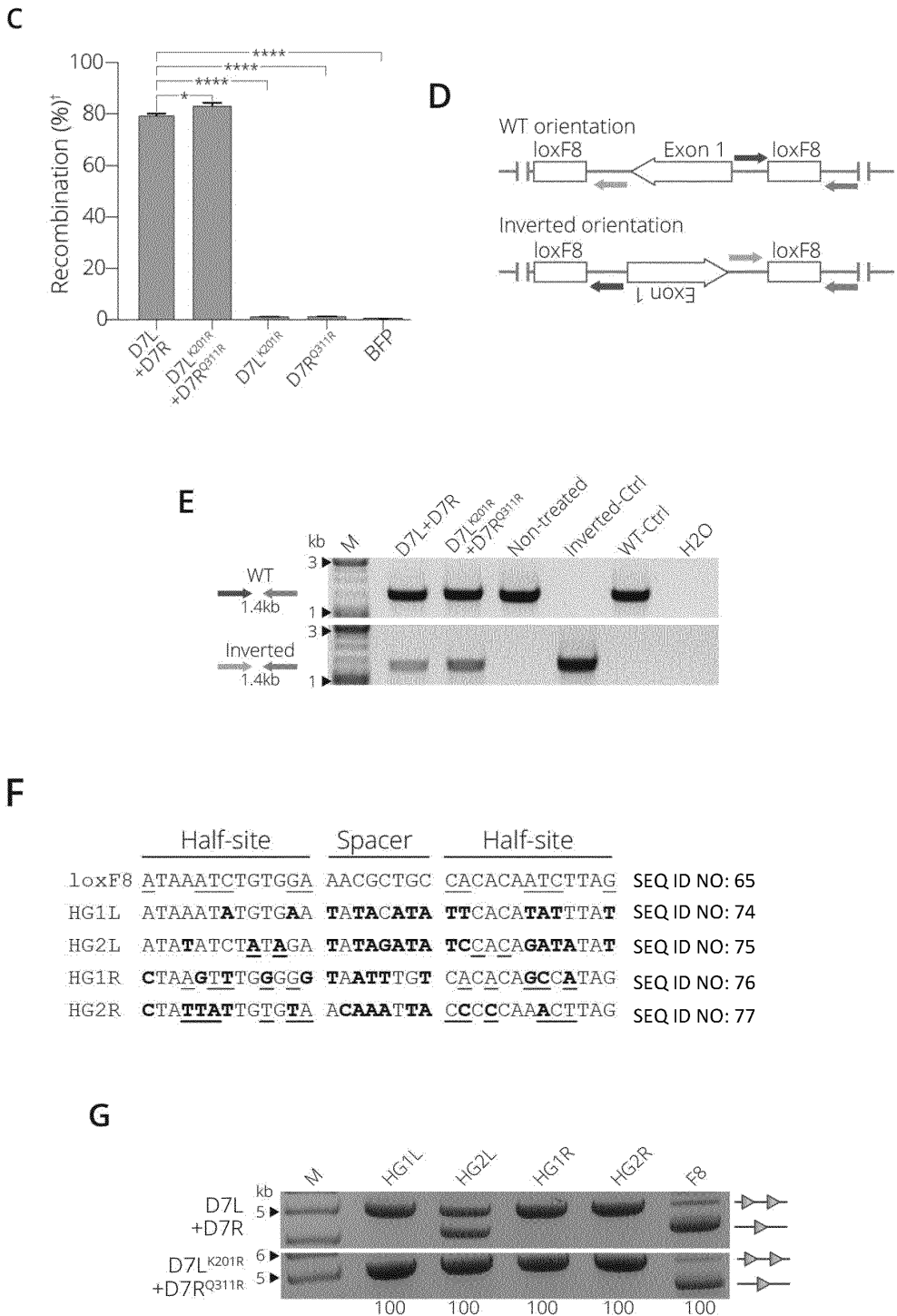


Fig. 3 continued

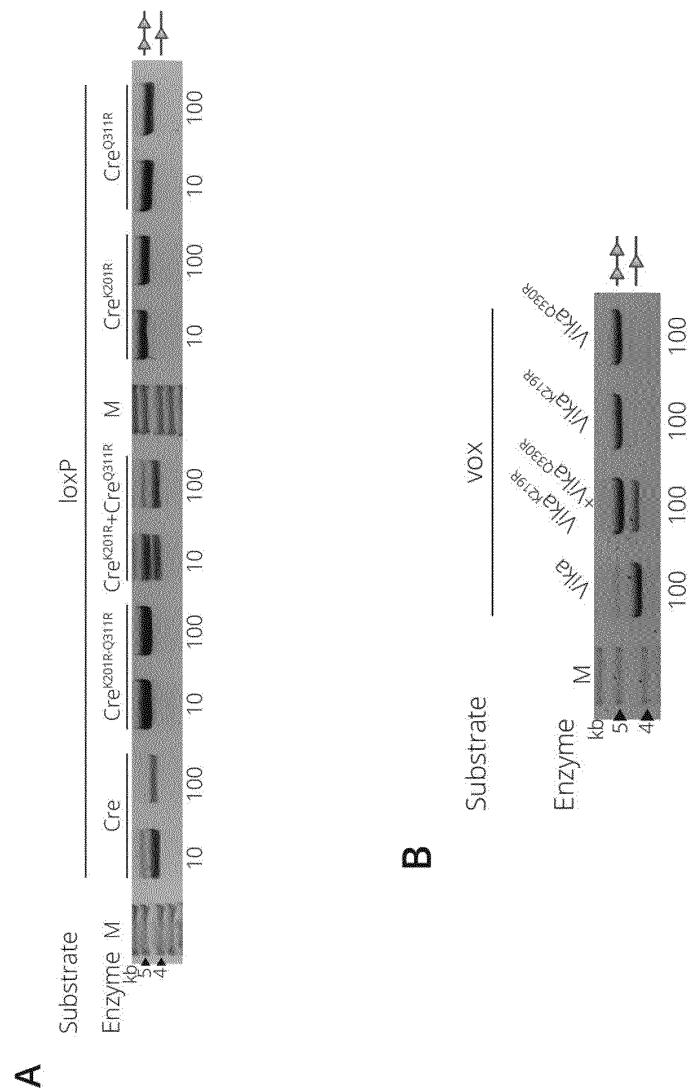


Fig. 4



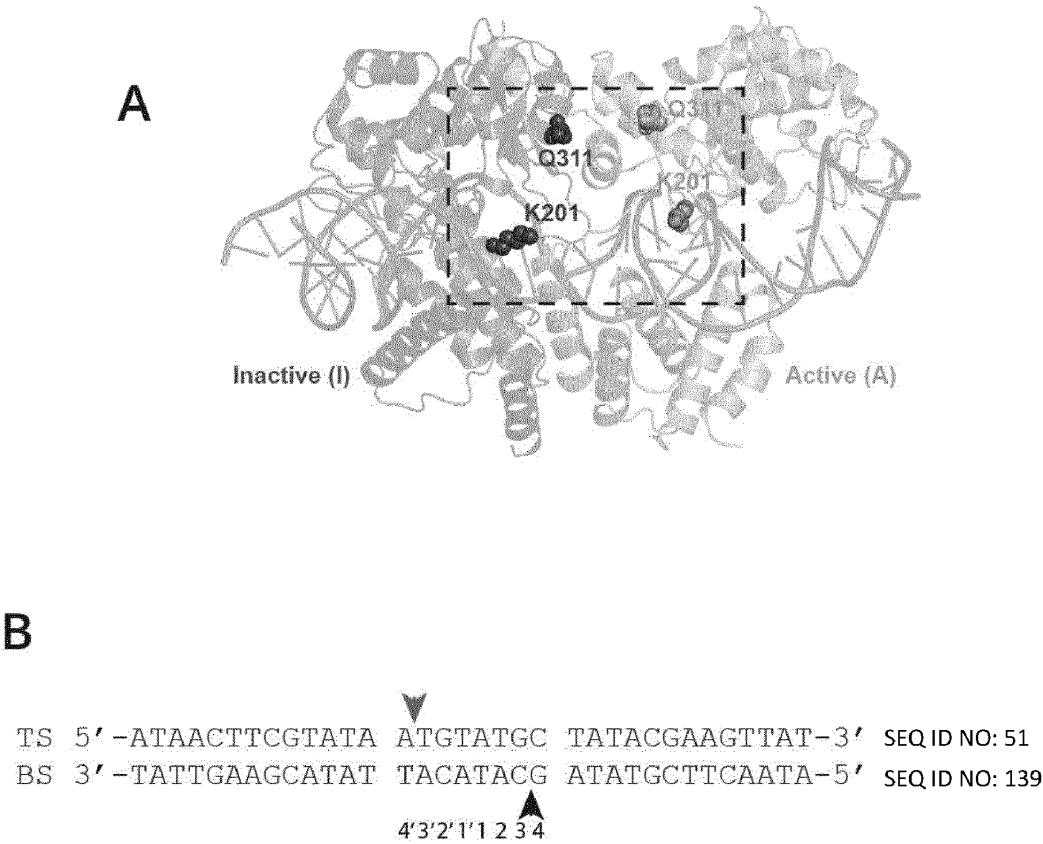


Fig. 5

SUBSTITUTE SHEET (RULE 26)

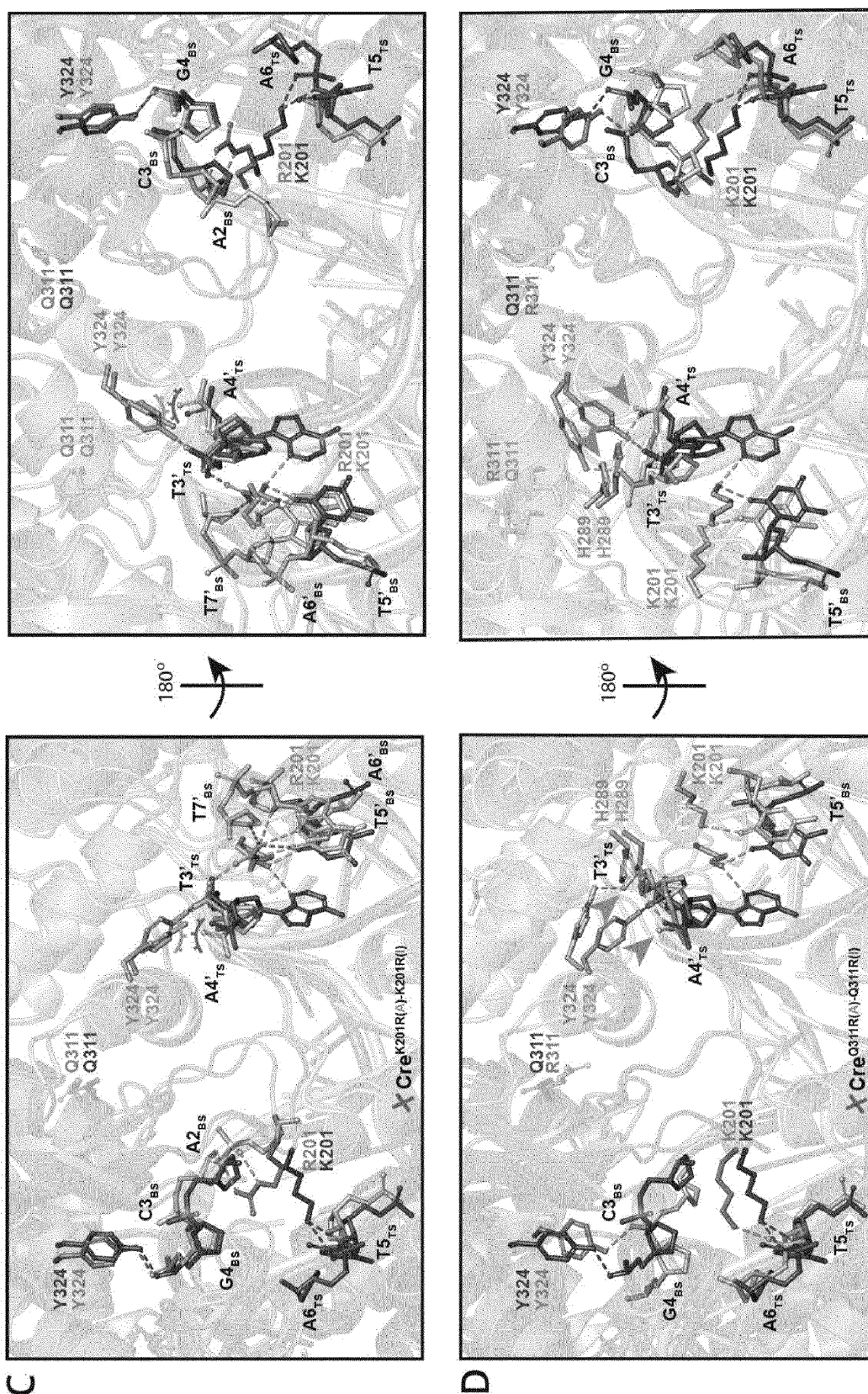


Fig. 5 continued

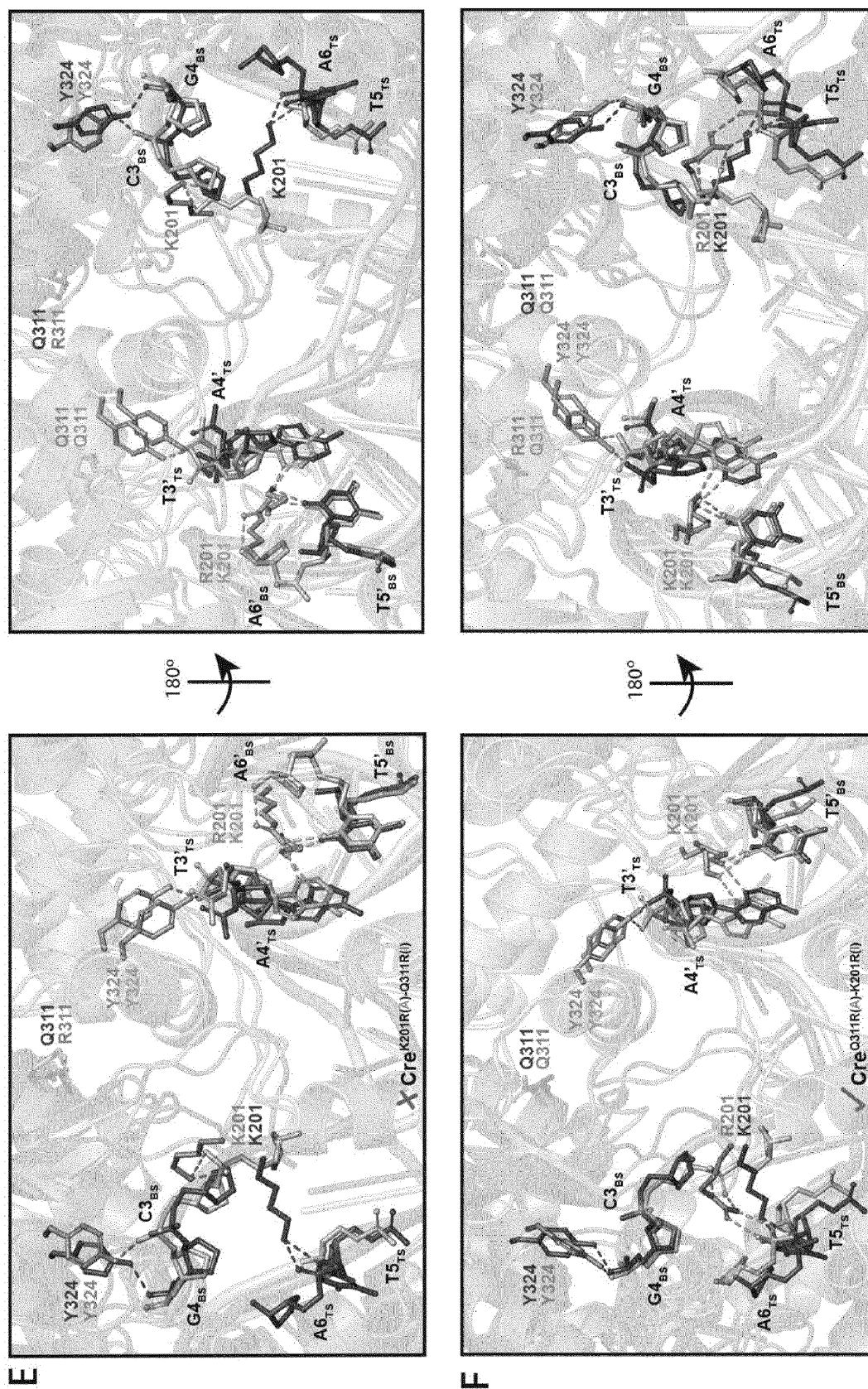


Fig. 5 continued



Fig. 5 continued

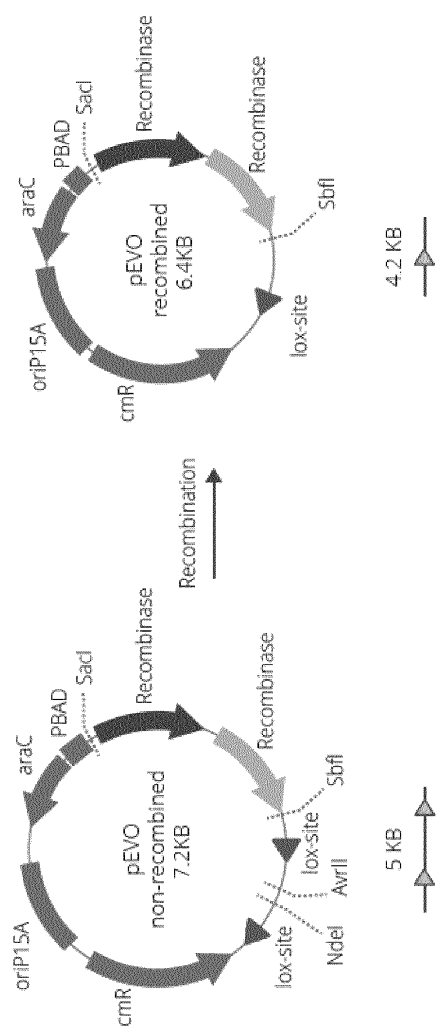


Fig. 6

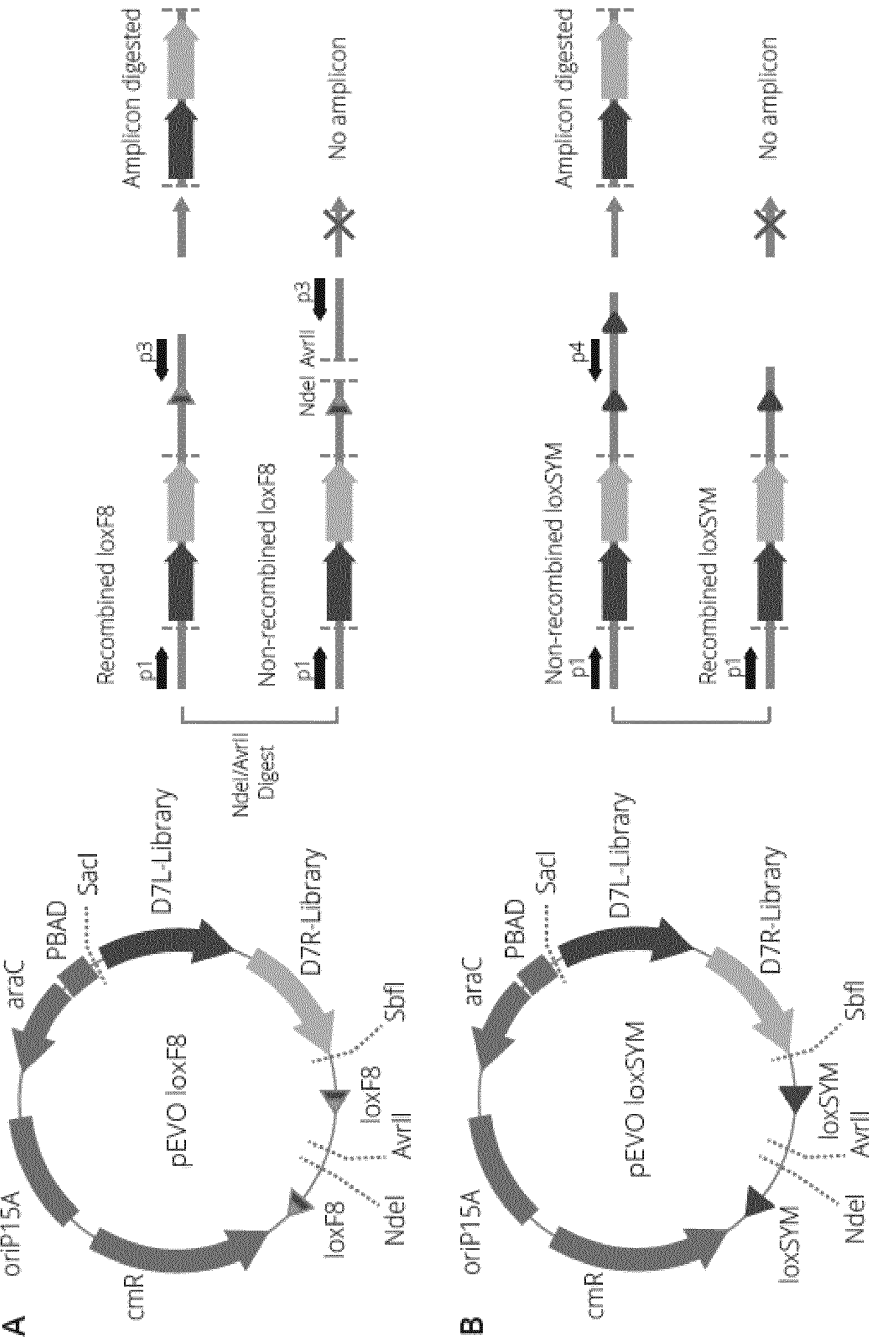


Fig. 7

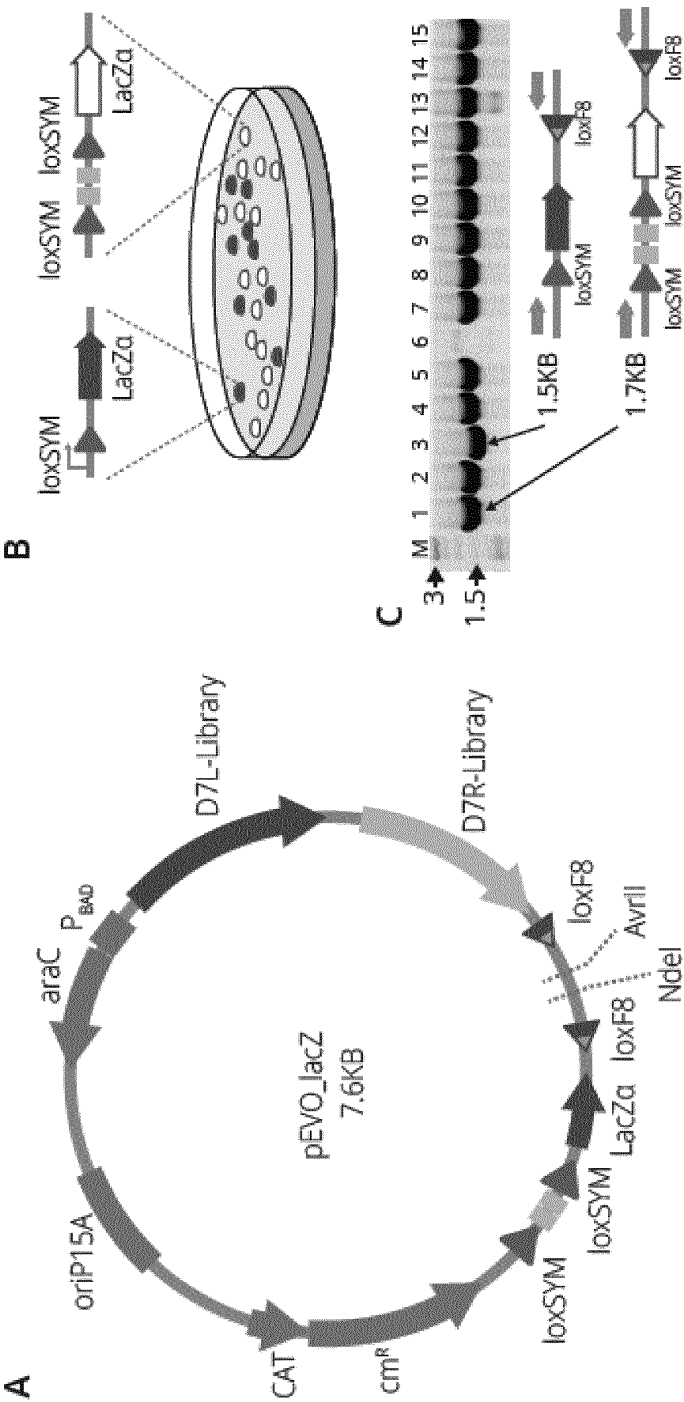


Fig. 8

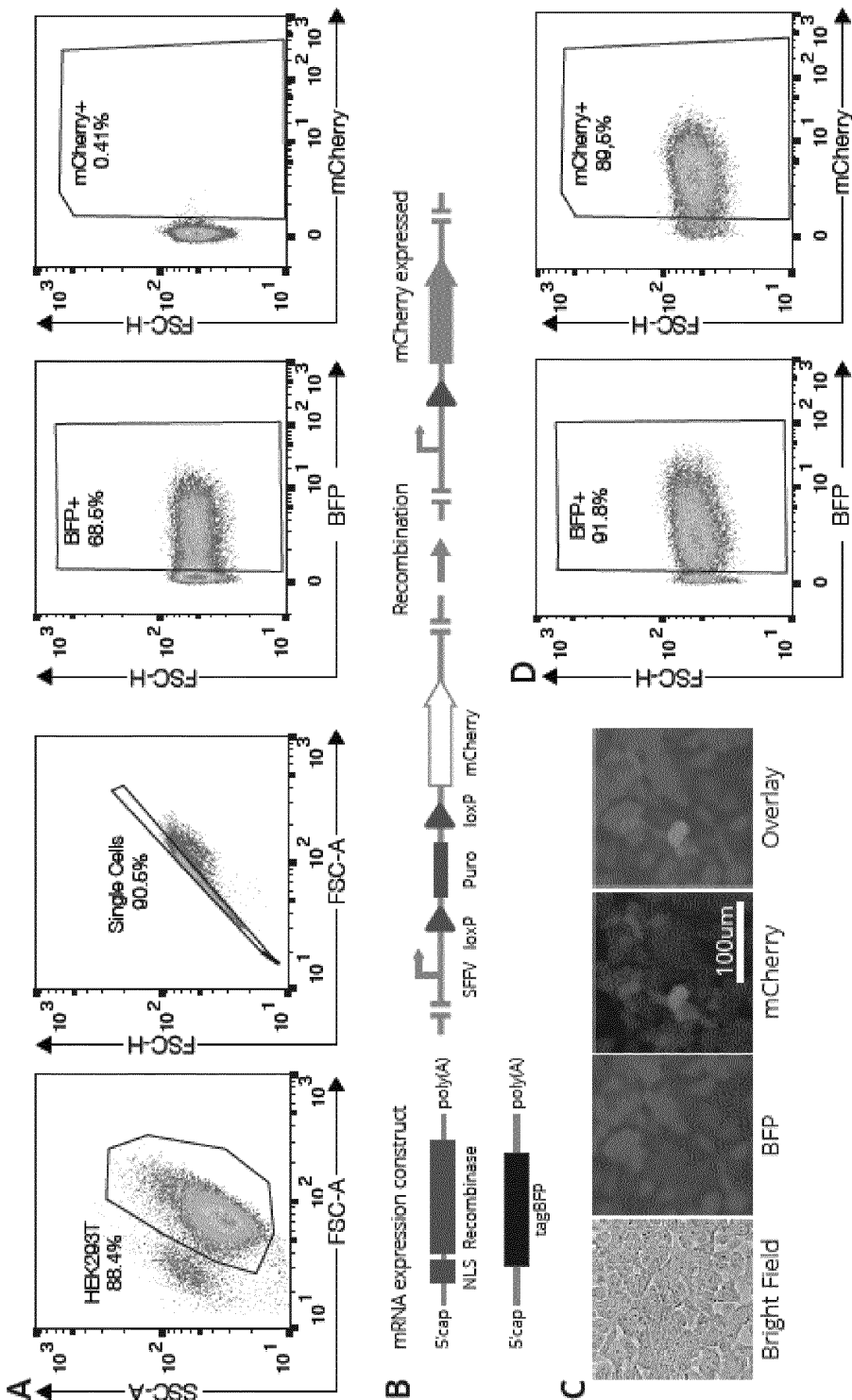


Fig. 9

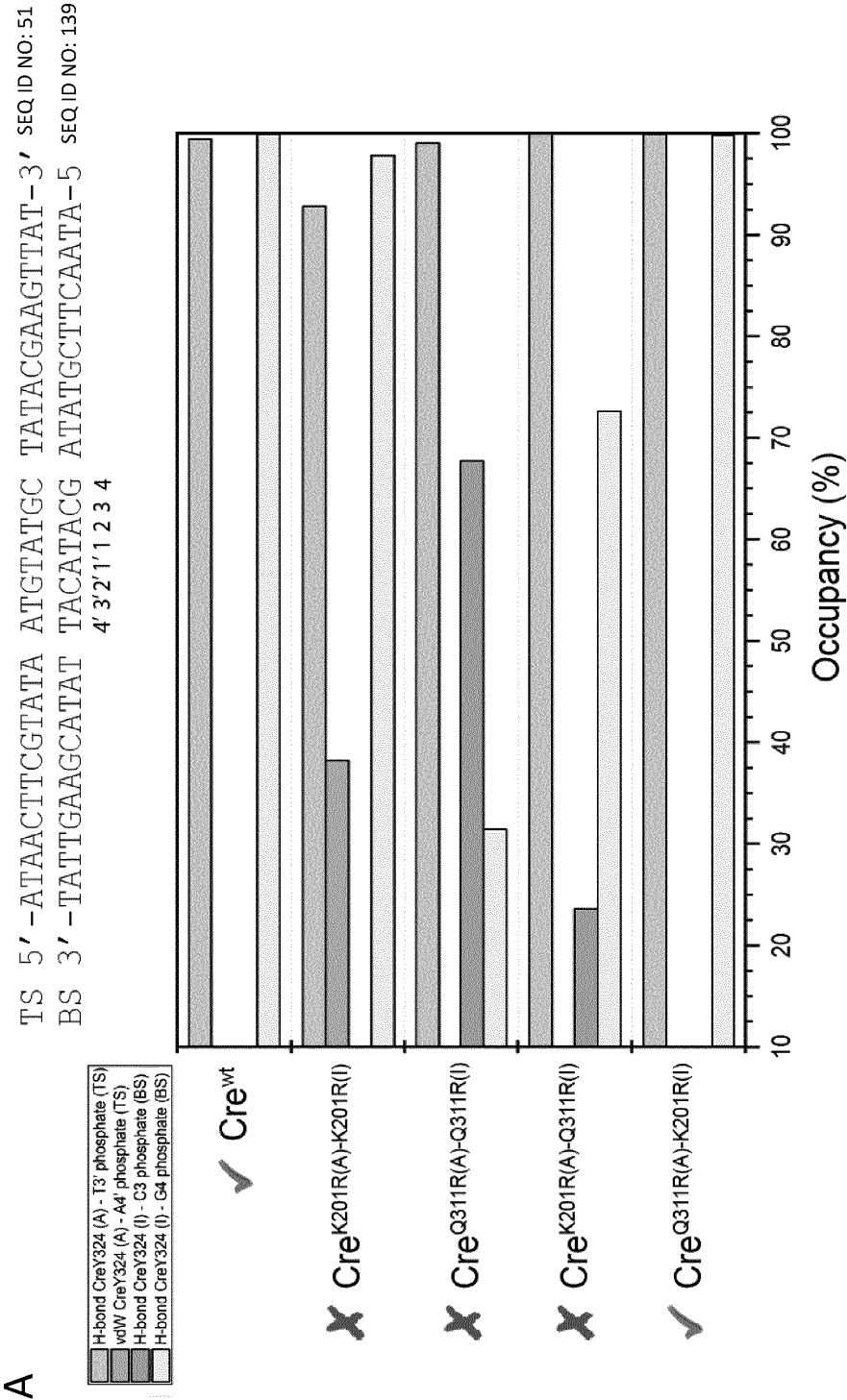
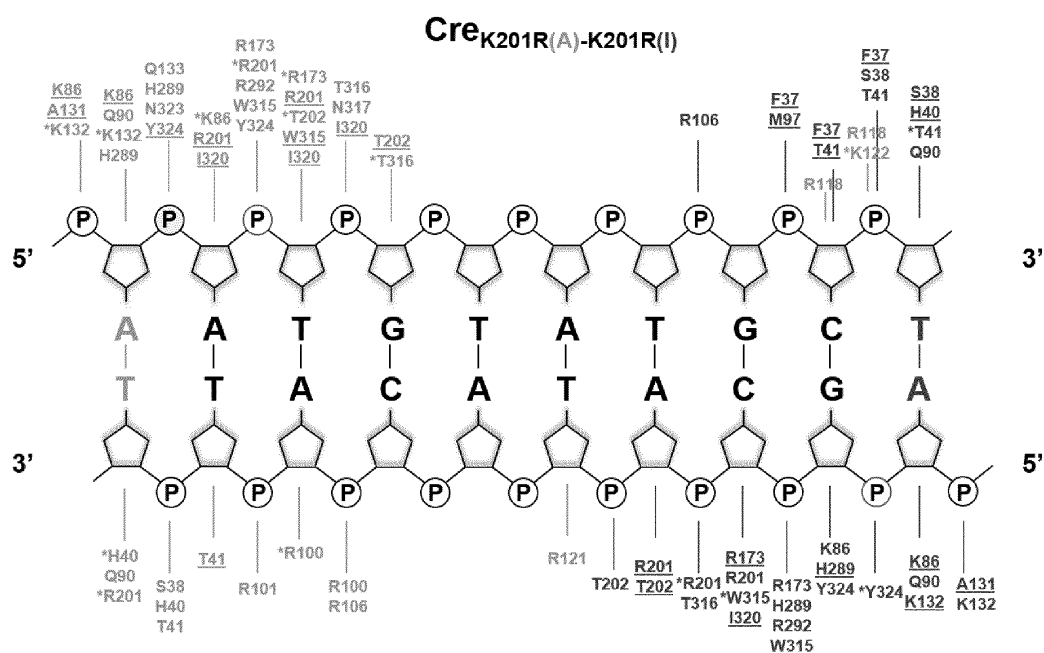


Fig. 10

B



C

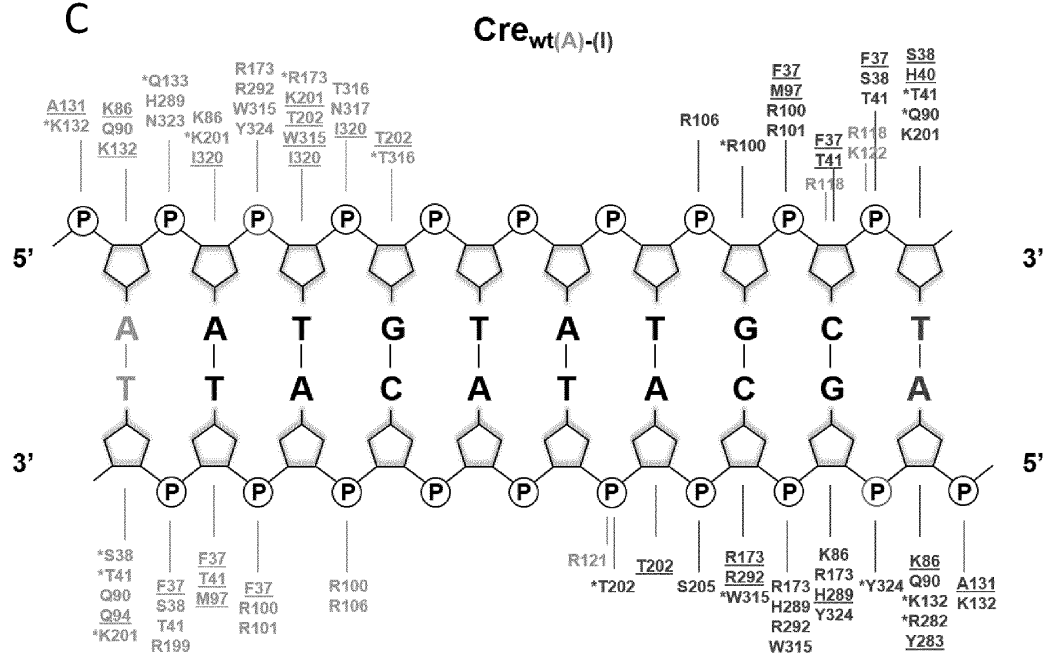


Fig. 10 continued

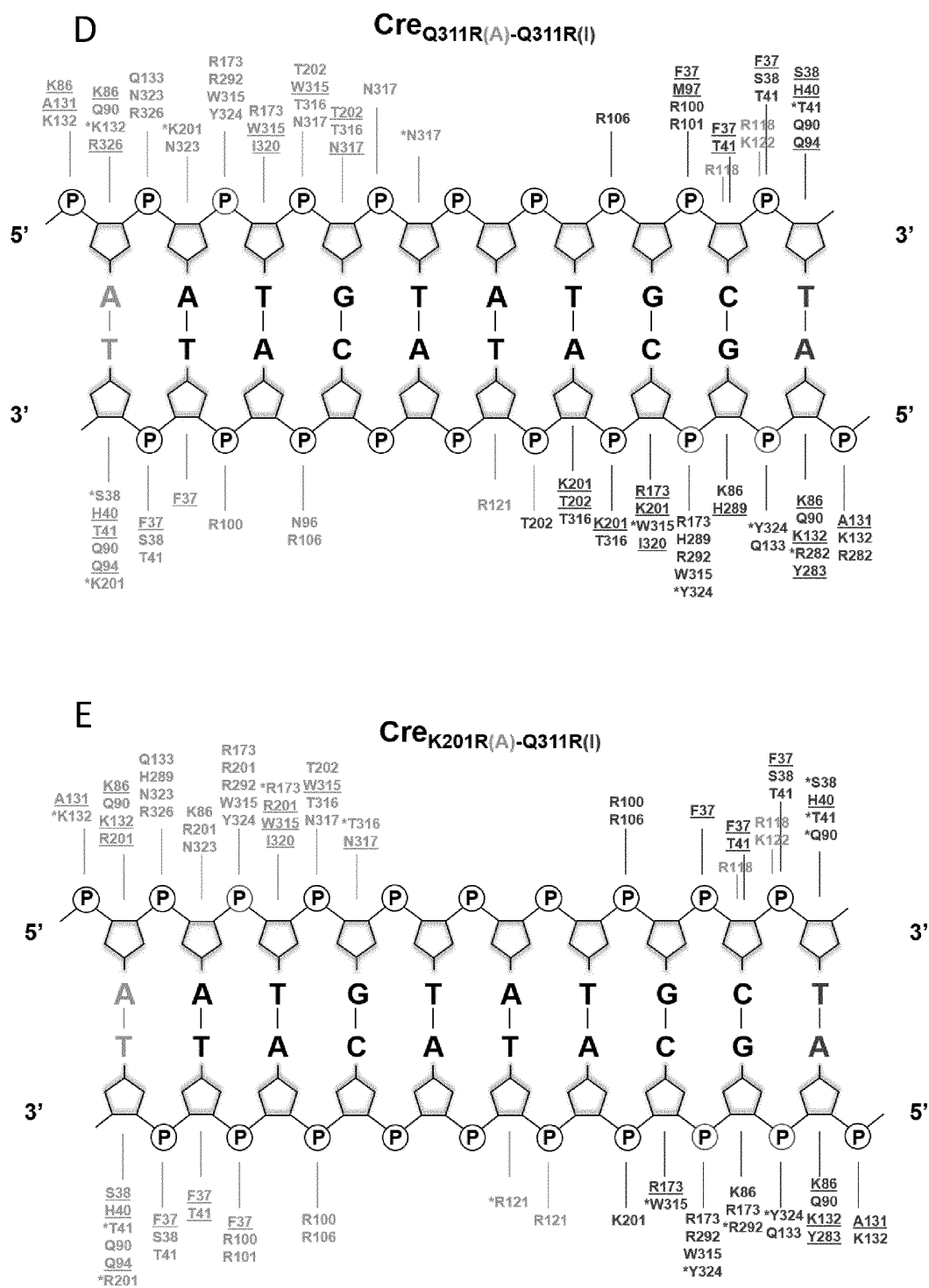


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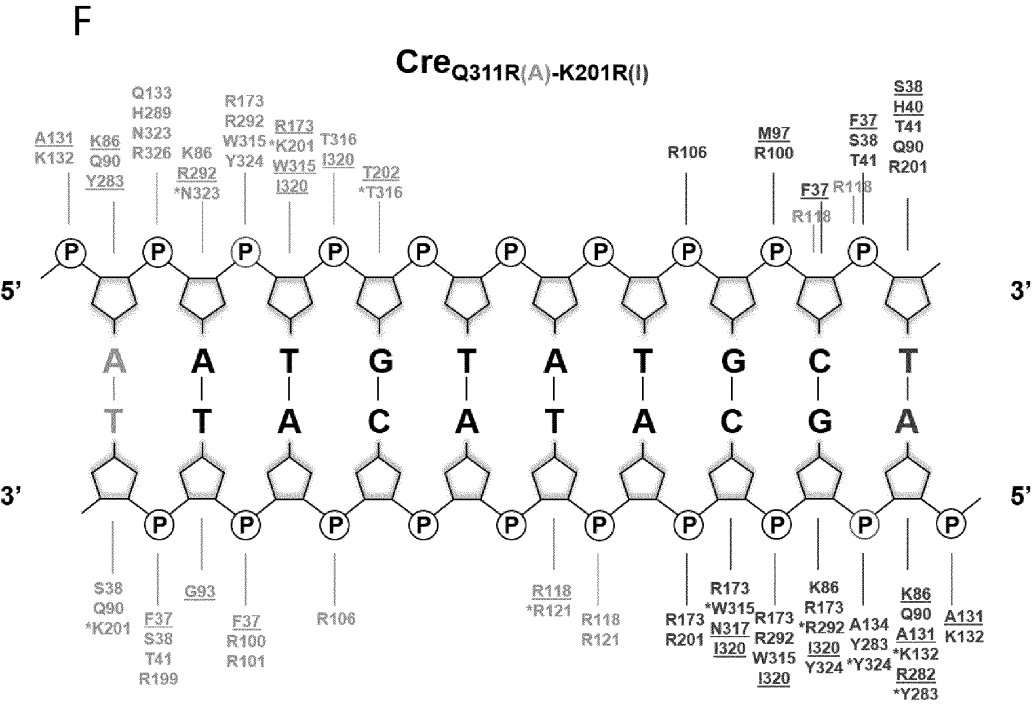


Fig. 10 continued

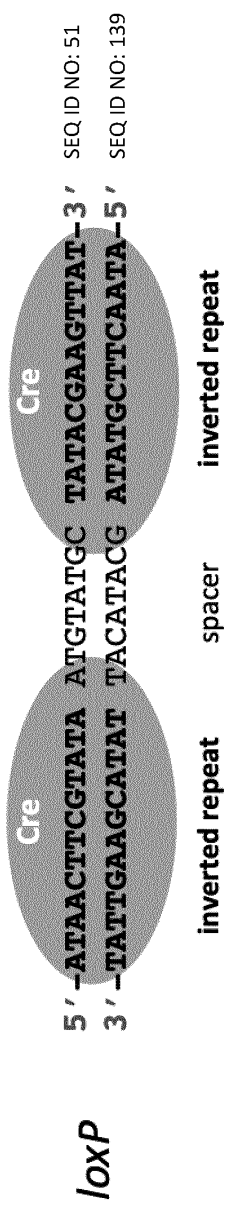


Fig. 11

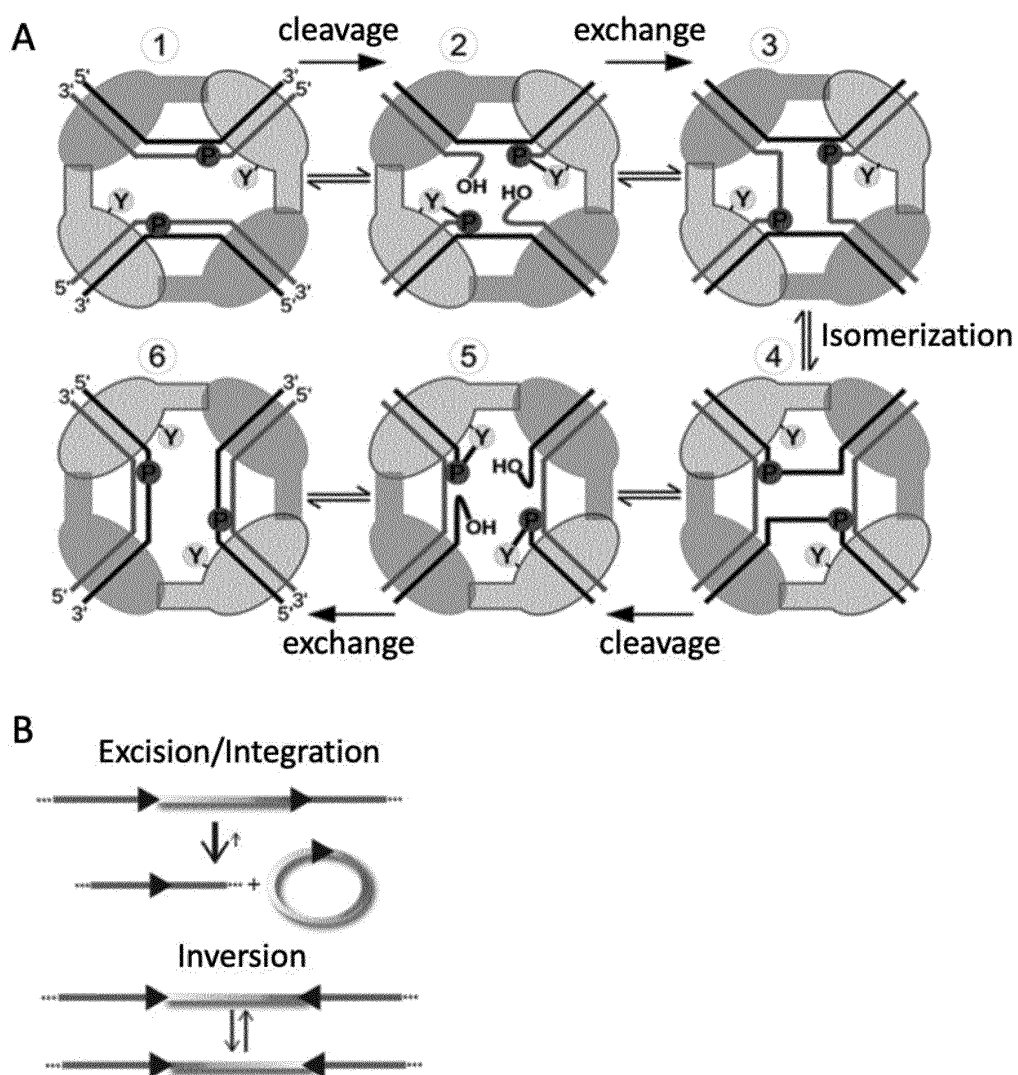


Fig. 12

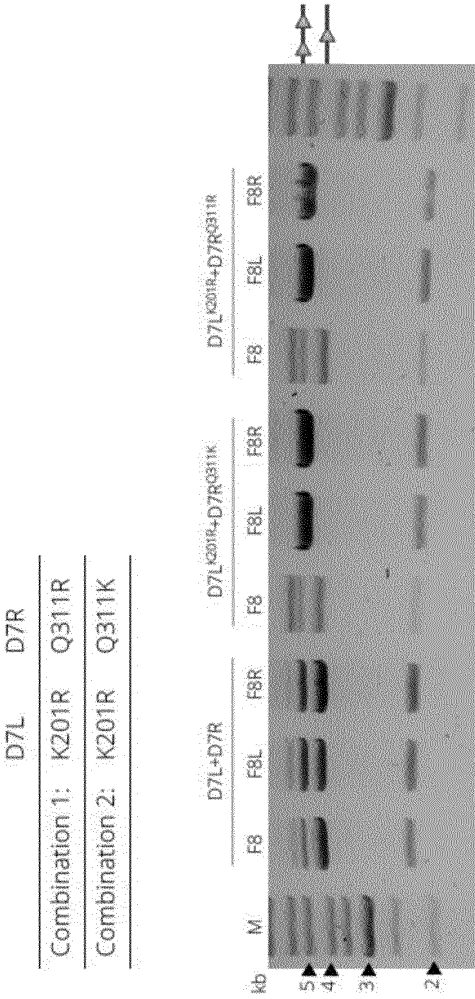


Fig. 13

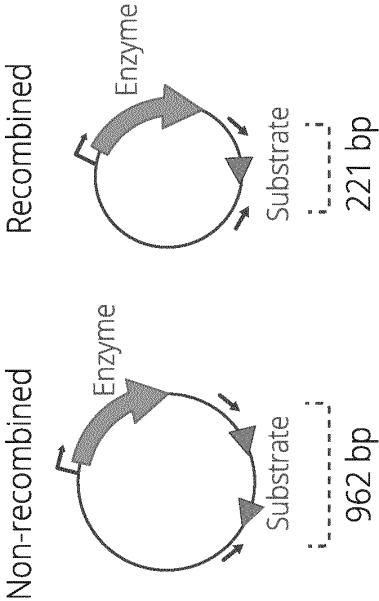
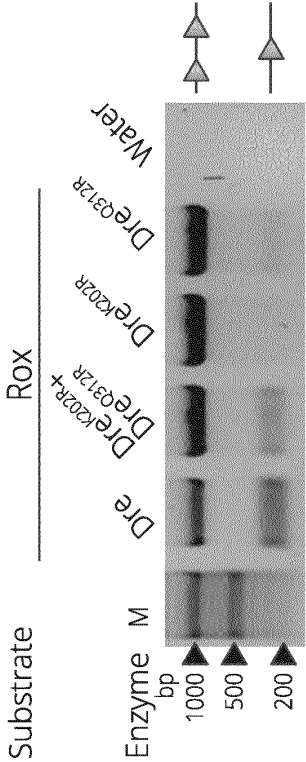


Fig. 14

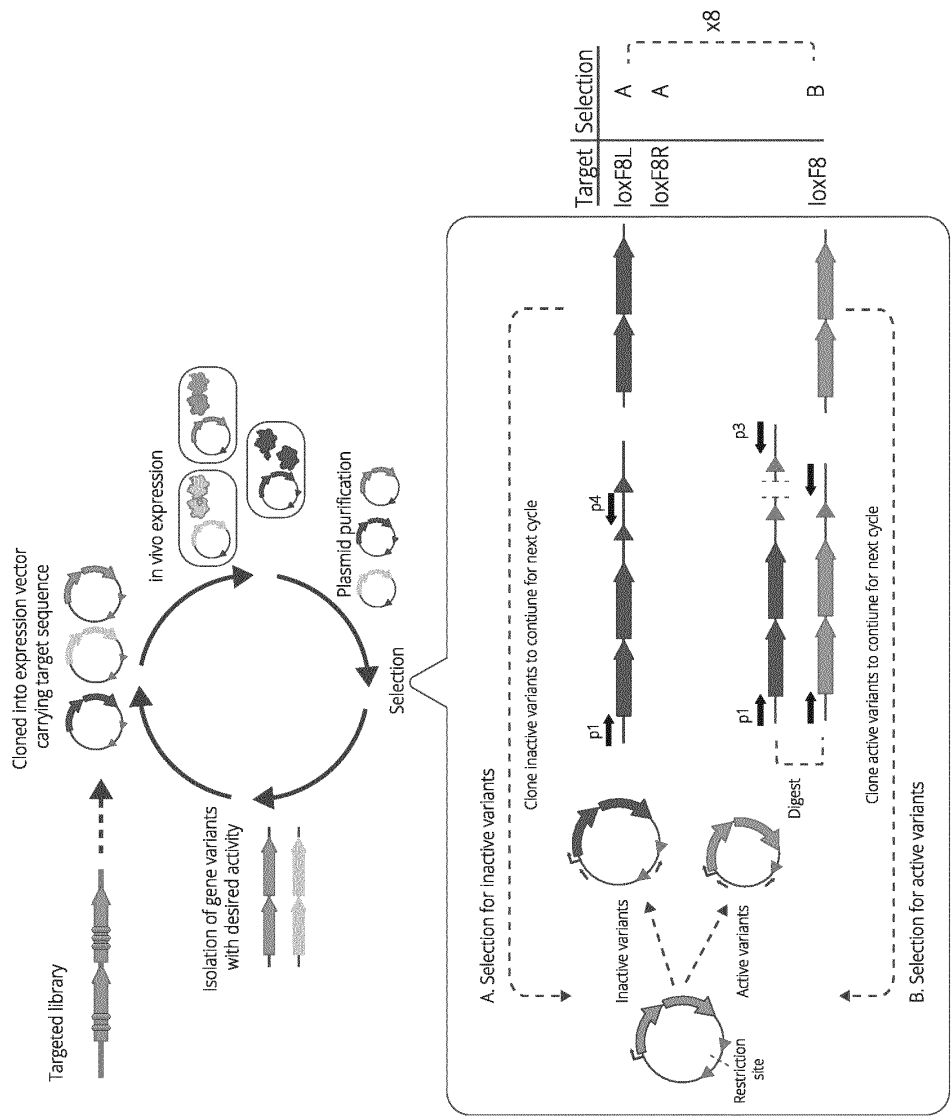


Fig. 15

F8_D7-L	-----MSNLQ--TLHQNL SALL-----	15
F8_D7-R	-----MSNIQ--TPHQSL SALL-----	15
Cre	-----MSNLL--TVHQNL PALP-----	15
Dre	-----MSELIISGSSGGFLRNI-----	17
Panto	-----MKHLA-QIKTGALPAEL-----	16
Nigri	MDKHLLSTRRTAPT DGSDFNSDNVTKNHHAILIERALASALARPGLLLETHFQPIYQRA	60
Vika	-----MTDL-TPFPPLHLEPDEFADLVKKA	25
VCre	-----MTENQL-SLLGDFSGVRPDDVKKAIQSA	27
F8_D7-L	-----ANATSDEARKNLMDVFRDRRAFSEATWKTL SV CRTWAAWCKLNNRKWFPA	66
F8_D7-R	-----TDATSDVTRKNLADMFRDSQAFSEHTWKMLLSVCRSWAAWCELNNRKWLFPV	66
Cre	-----VDATSEVRKNLMDMFRDRQAFSEHTWKMLLSVCRSWAAWCKLNNRKWFPA	66
Dre	-----GKEYQEAAENFMRFMNDQGAYAPNTLRDLRLVFHSHWARWCHARQLAWFPI	67
Panto	-----TQLTPEDIANNLRFIADKAAYSNTFRDLLSVIRRAWFACWNERDVGYLPI	67
Nigri	DRLGVDLSDCPSFFVATQRLLAQHGHQAGLSPRSLEQFHSAVRVFTQWCHVNRRTALPA	120
Vika	IKRDPQAGAHPAIQSAISHFQDEFVRRQGEWQPATLQRLRNAWN VFVRWCTHQGIPALPA	85
VCre	QKKGINVAENEQFKAAFEHLLNEFKKREERYSPNTLRRLSAWTCFVDWCLANHRHSLPA	87
. . . : * * . : *		
F8_D7-L	EPEDVRDYLLHLQVRGLAVNTIQRHLALLNMLHRRSGLPRPGDSSAVSLVMRRIRKENV-	125
F8_D7-R	EPEDVRDYLLHLQTRGLAVKTIQHHLGSLNMLHRRAGLPRPGDSNAVSLVMRRIRKENV-	125
Cre	EPEDVRDYLLYLQARGLAVKTIQQHLGQLNMLHRRSGLPRPGDSNAVSLVMRRIRKENV-	125
Dre	SPEMAREYFLQLHDADLASTTIDKHYAMLNMLSHCGLPPLSDDKSVSLAMRRIRREAA	127
Panto	DPELAREYFLQMAESGLASSTIDKHYAMNMLCRESGLPDLRGSDVKLRSMKRIRREAV-	126
Nigri	SADTFVL FARSNA-PHITLSTLHIYVWAIKRLHLITGLVDPTDSQAVKQHL SRIKKQKIA	179
Vika	RHQDVERYLIERR-NELHRNTLKVHLWAIGKTHVISGLPNPCAHRVYKQMAQI THQKVR	144
VCre	TPDTVEAFFIERA-EELHRNTLSVYRWAI SRVHRVAGCPDCLDIYVEDRLKAI SRKKVR	146
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F8_D7-L	DAGERVRQALAFERTDFDKVRS LMGNSDR CQDIRNLAF LGVAYNTLLRISEIARIRIKDI	185
F8_D7-R	DAGERAQALAFERTDFDQVRS LVENS DR CQDIRNLAF LGVAYNTLLRISEIARIRVKDI	185
Cre	DAGERAKQALAFERTDFDQVRS LMGNSDR CQDIRNLAF LGIAYNTLLRIAEIARIRVKDI	185
Dre	EKGERTGQAIPLRWDDLKLLDVLLSRSERLVDLRNRAFLFVAYNTLMRMSEISRIRVGD	187
Panto	LQGERTGQAVPFRPLDQLLSHLMGRSDRLTDQRNLAF LFVAYNTLCRMSELSRIRVRD	186
Nigri	QFDTAQDQAVPLSDEYRTAMTLLMADDPISWRDATLLGLAYHTMLRQSELVRIQLTHI	239
Vika	ER-ERIEQAPAFRESDLDRLTTELWSATRSVTQQRDLMI VSLAYETLLRKNNLEQMKVGDI	203
VCre	EG-EVVKQASPFEHQHLLKLTSLWYRS DKL LRLRN LALLAVAYESMLRAS ELANIRVSDM	205
* * : . * : : * * : * : . : : .		
F8_D7-L	SRTDGGRM LIHIGRTKTLVSTAGVEKALSLGVTRLVGRWISVSG-VAGDPNNYLF CRVRK	244
F8_D7-R	SRTDGGRM LIHIGRTKTLVSTAGVEKALSLGVTKLVERWISVSG-VADDPNNYLF CRVRR	244
Cre	SRTDGGRM LIHIGRTKTLVSTAGVEKALSLGVTKLVERWISVSG-VADDPNNYLF CRVRK	244
Dre	DQTG-DTVTLHISHTKTIITTAAGLDKVL SRRTAVLNDWLDVSG-LREHPDAVLFPP IHR	245
Panto	DISDSGHVVINLSHTKTMVTAAGVIKHL SRAAAGHLMHWLELSG-LIHHPDAMVFGPVRH	245
Nigri	QPRSDGDWLTLEIPYTKTNKTGRSEYVTLPHYLMPILQRYLSLCGDRTLTDPGYLFVPLTR	299
Vika	EFCQDGSALITIPFSKTNHSGRDDVRWISFPQVANQVHAYLQLPN-IDADPQC FLLQRVKR	262
VCre	ELAGDGTAVLTIPITKTNHSGEPDTCILSQDVVSL LMDYTEAGK-LDMSGDGF LFVGVSK	264
. . : : * * : : : . : : .		
F8_D7-L	NGVAAP-----SATSQ	255
F8_D7-R	YGVAKP-----SATSQ	255
Cre	NGVAAP-----SATSQ	255
Dre	SNKARI-----TT-TP	255
Panto	NNTAGV-----SE-KP	255
Nigri	SGVPRRQRMHVTSTPRAPSGVT PRRKTRGGIQFAPVAPDAVTD SIAAPPDPAPIS EEVQP	359
Vika	SGKALNPESHNTL-----NGHHP	280
VCre	HNTCIKPKKDKDTE-----ELLHKA	284
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Fig. 16

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F8_D7-L      LSTDVLRGVFAAAHRLVYG-TKDDSGQGYLTWSGHSARVGAARDMARAGVSAEIMQAGG 314
F8_D7-R      LSTYALQGIFGAAHRLVYG-AKGD SGQKYLAWSGHSARVGAARDMARAGVPIPEIMQAGG 314
Cre          LSTRALEGIFEATHRLIYG-AKDDSGQRYLAWSGHSARVGAARDMARAGVSIPEIMQAGG 314
Dre          LTAPAMEKIFSDAWVLLNKRDPNKG RYRTWTGHSARVGAAIDMAEKQVSMVEIMQEGT 315
Panto       MSAPATEKIFKDAWDL LGKEPVQDNKG RYAKWSGHSARVGAAMDMAERDATITQIMQEGT 315
Nigri       VAPKLVARTLKKIGERLATHT--SSPQADRAYSGHSARVGRAIHLLLEIGARKEDIVKAGR 417
Vika        VSEKLISR VFERAWRALN-----HET--GPRYTGHSARVGAAQDLLQEGYSTLQVMQAGG 333
VCre        ITTKTVEGVFYSAWQALD-----LERQGVKPFHTAHSARVGAAQDLLKKGYNTLQIQSGR 339
              :           :           :           .           : : . * * * * : *           : : : *

F8_D7-L      WTTVESVMSYLRNLDSETGAMVRLLEDGD----- 343
F8_D7-R      WTTVNSVMNYIRNLDSETGAMVRLLEDSD----- 343
Cre          WTNVNIVMNYIRNLDSETGAMVRLLEDGD----- 343
Dre          WKKPETLMRYLRRGGVSVGANSRLMDS----- 342
Panto       WQDPKTVMRYLRRSESQKGKMSGILDGE----- 343
Nigri       WKSDIMFERYTRQYDVNDGYLAQIRQAED---RHWHQAQTEPPDSTG 460
Vika        WSSEKMVRLRYGRHLHAHTSAMAQKRRQR----- 361
VCre        WSSGTMVARYGRAILARDGAMAHSRVKTRSAFPMNWGSGGG----- 379
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 F8_D7-R = SEQ ID NO: 10
 Cre = SEQ ID NO: 1
 Dre = SEQ ID NO: 20
 Panto = SEQ ID NO: 17
 Nigri = SEQ ID NO: 140
 Vika = SEQ ID NO: 14
 VCre = SEQ ID NO: 23

Fig. 16 continued

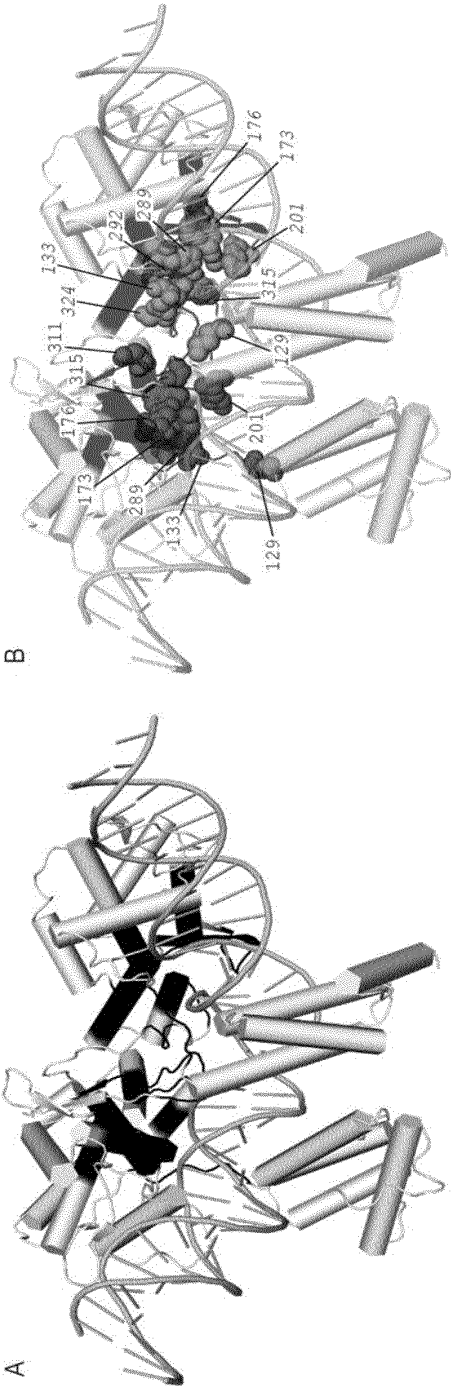
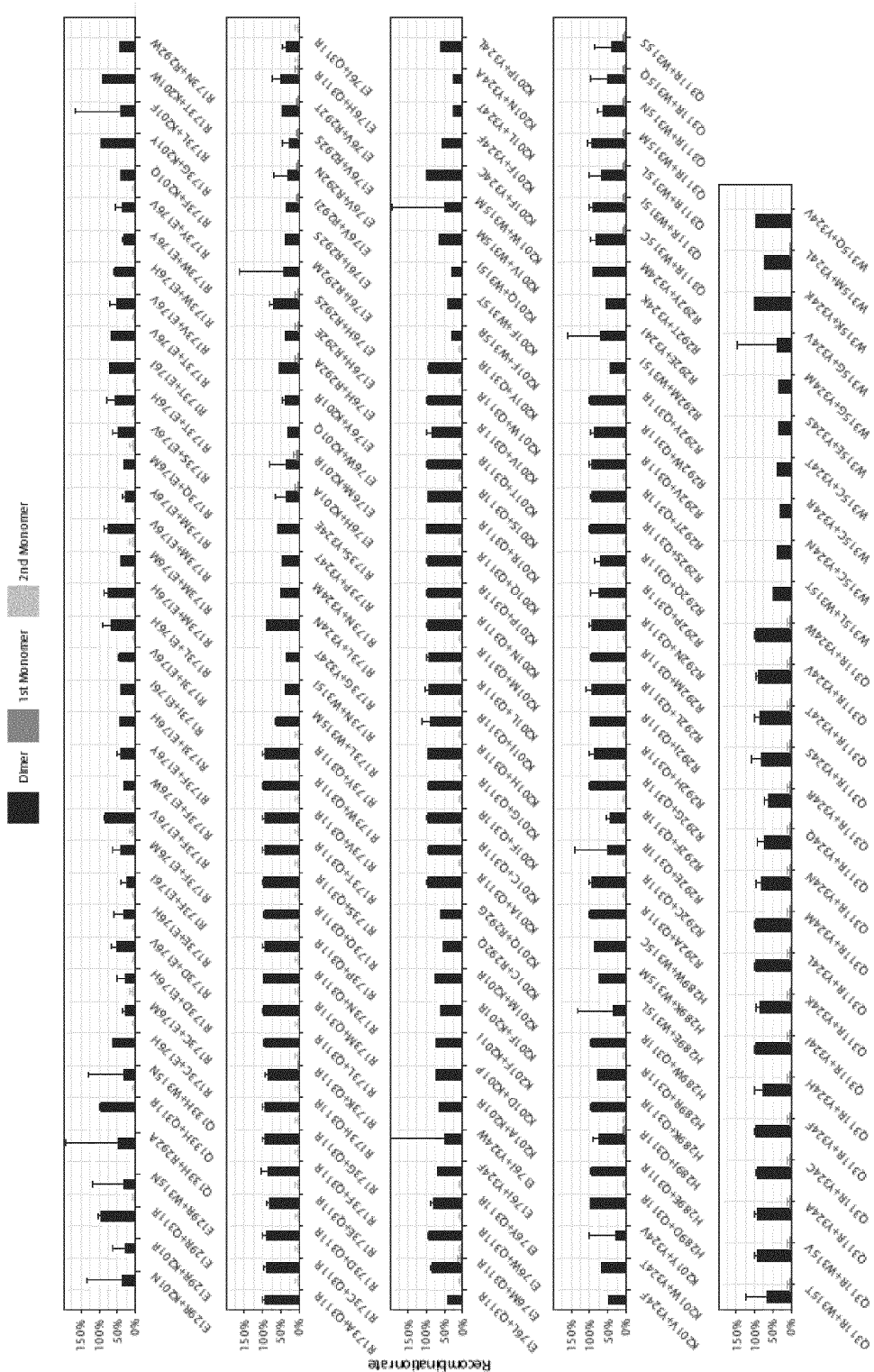


Fig. 17



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Cre  -----MSNLLTVHQNL-PALPVDATSDDEVK-KNLMDFRDRQAFSEHT  41
Vika MTDLTPEFPPELHLEPDEFADLVRKAIKRDPQAGAHPAIQSAISHFQDEFVRRQGEWQPAT  60
Dre  -----MSELIISGSSGGFLRNIGKEYQEAA-ENFMRFMNDQGAYAPNT  42

Cre  WKMLLSVCRSWAAWCKLNNRKWFPAEPEDVRDYLLYLQARGLAVKTIQQHLGQLNMLHRR  101
Vika LQRLRNAWNVVRWCTHQGIPALPARHQDVERYLIER-RNELHRNTLKVHLWAIGKTHVI  119
Dre  LRDLRLVFHSWARWCHARQLAWFPISPEMAREYFLQLHDADLASTTIDKHYAMLNMLLSH  102

Cre  SGLPRPSDSNAVSLVMRRIRKEN-VDAGETRAKQALAFERTDFDQVRSLMENS DRCQDIRN  160
Vika SGLPNPCAHRVYVKAQMAQITHQK-VRERERIEQAPAFRESLDRLTELWSATRSVTQQRD  178
Dre  CGLPPLSDDKSVSLAMRRIRREAATEKGETRTGQAIPLRWDDLKLLDVLLSRSERLVDLRN  162

Cre  LAFLGLIAYNTILRLIAEIAIRIRVKDISRTDGGRM LIHIGRTKTLVSTAGVEKALS LGVTKL  220
Vika LMIVSLAYETILRLKNNLEQMKVGDIEFCQDGSALITIPFSKTNHSGRDDVRWIS PQVANQ  238
Dre  RAFLFVAYNTILRLMSEISRIRVGDLDQT-GDTVTLHISHTKTTITTAAGLDKVL SRRTTAV  221

Cre  VERWISVSGVADDPNNYLFCRVRKNGVAAPS-----ATSQLSTRALEGIFEATHRLIY  273
Vika VHAYLQLPNIDADPQCFLLRVKRSGKALNPESHNTLNGHHPVSEKLISR VFERAWRALN  298
Dre  LNDWLDVSGLREHPDAVLFPPIHRSNKARI-----TTTPLTAPAMEKIFSDAWVLLN  273

Cre  G-AKDDSGQRYLAWSGHSARVGAARDMARAGVSIPEIMQAGGWTNVNIVMNYIRNLDSET  332
Vika HET-----GPRYTGH SARVGAAQDLLQEGYSTLQVMQAGGWSSEKMLVRLYGRHLHAHT  351
Dre  KRDATPNKGRYRTWTGHSARVGAAIDMAEKQVSMVEIMQEGTWKKPETLMRYLRGGVSV  333

Cre  GAMVRLLEDGD* 344 SEQ ID NO: 1
Vika SAMAQKRRQR*- 362 SEQ ID NO: 14
Dre  GANSRLMDS*-- 343 SEQ ID NO: 20

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Fig. 19

INTERNATIONAL SEARCH REPORT

WO 2023/084099

International application No

PCT/EPCT/EP2022/081868

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N9/22 C12N15/10

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Lansing Felix ET AL: "Correction of a Factor VIII genomic inversion with designer-recombinases", bioRxiv, 2 November 2020 (2020-11-02), XP055916921, DOI: 10.1101/2020.11.02.328013 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2020.11.02.328013v1.full.pdf [retrieved on 2022-05-02] the whole document	1-24
X	EP 3 831 939 A1 (UNIV DRESDEN TECH [DE]) 9 June 2021 (2021-06-09) paragraph [0084] - paragraph [0183]; examples 1-9	1-24



Further documents are listed in the continuation of Box C.



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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

8 February 2023

Date of mailing of the international search report

07/03/2023

Name and mailing address of the ISA/

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Fax: (+31-70) 340-3016

Authorized officer

Westphal-Daniel, K

INTERNATIONAL SEARCH REPORT

WO 2023/084099

International application No

PCT/EPCT/EP2022/081868

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 10 017 832 B2 (UNIV WASHINGTON [US]) 10 July 2018 (2018-07-10) cited in the application paragraph [0007] - paragraph [0133] -----	4-7, 13, 17-21
A	LANSING FELIX ET AL: "Wie Designer-Rekombinasen Erbkrankheiten heilen könnten", BIOSPEKTRUM, vol. 27, no. 2, 23 March 2021 (2021-03-23) , pages 139-141, XP037390226, ISSN: 0947-0867, DOI: 10.1007/S12268-021-1549-9 the whole document -----	1-24
A	KARPINSKI JANET ET AL: "Designer-Rekombinasen für präzisesGenome Editing", BIOSPEKTRUM, SPEKTRUM AKADEMISCHER VERLAG, DE, vol. 23, no. 2, 29 March 2017 (2017-03-29) , pages 151-154, XP036199778, ISSN: 0947-0867, DOI: 10.1007/S12268-017-0780-X [retrieved on 2017-03-29] the whole document -----	1-24
A	WO 2018/229226 A1 (UNIV DRESDEN TECH [DE]) 20 December 2018 (2018-12-20) cited in the application page 3, line 13 - page 65, line 9 -----	1-24
A	GRETCHEN MEINKE ET AL: "Cre Recombinase and Other Tyrosine Recombinases", CHEMICAL REVIEWS, vol. 116, no. 20, 10 May 2016 (2016-05-10) , pages 12785-12820, XP055620771, US ISSN: 0009-2665, DOI: 10.1021/acs.chemrev.6b00077 cited in the application the whole document -----	1-24
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INTERNATIONAL SEARCH REPORT

WO 2023/084099

International application No

PCT/EPCT/EP2022/081868

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	HOERSTEN JENNA ET AL: "Pairing of single mutations yields obligate Cre-type site-specific recombinases", NUCLEIC ACIDS RESEARCH , vol. 50, no. 2 25 January 2022 (2022-01-25), pages 1174-1186, XP055916912, GB ISSN: 0305-1048, DOI: 10.1093/nar/gkab1240 Retrieved from the Internet: URL:https://watermark.silverchair.com/gkab1240.pdf?token=AQECAHi208BE49Oan9kKhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAtUwggLRBgkqhkiG9w0BBwagggLCMIICvgIBADCCArcGCSqGSib3DQEHATAeBg1ghkgBZQMEAS4wEQQM4kZE2QKKJS10HV4yAgEQgIICiPk-xky3WniIDSrlK4Pq918GEy59jeVGEHX_F9kb7Qr9-44csYFVC1TqUK1OPSYEn-h3Kg8gdtx_yaao4DtwQ1JQi_ the whole document -----	1-24