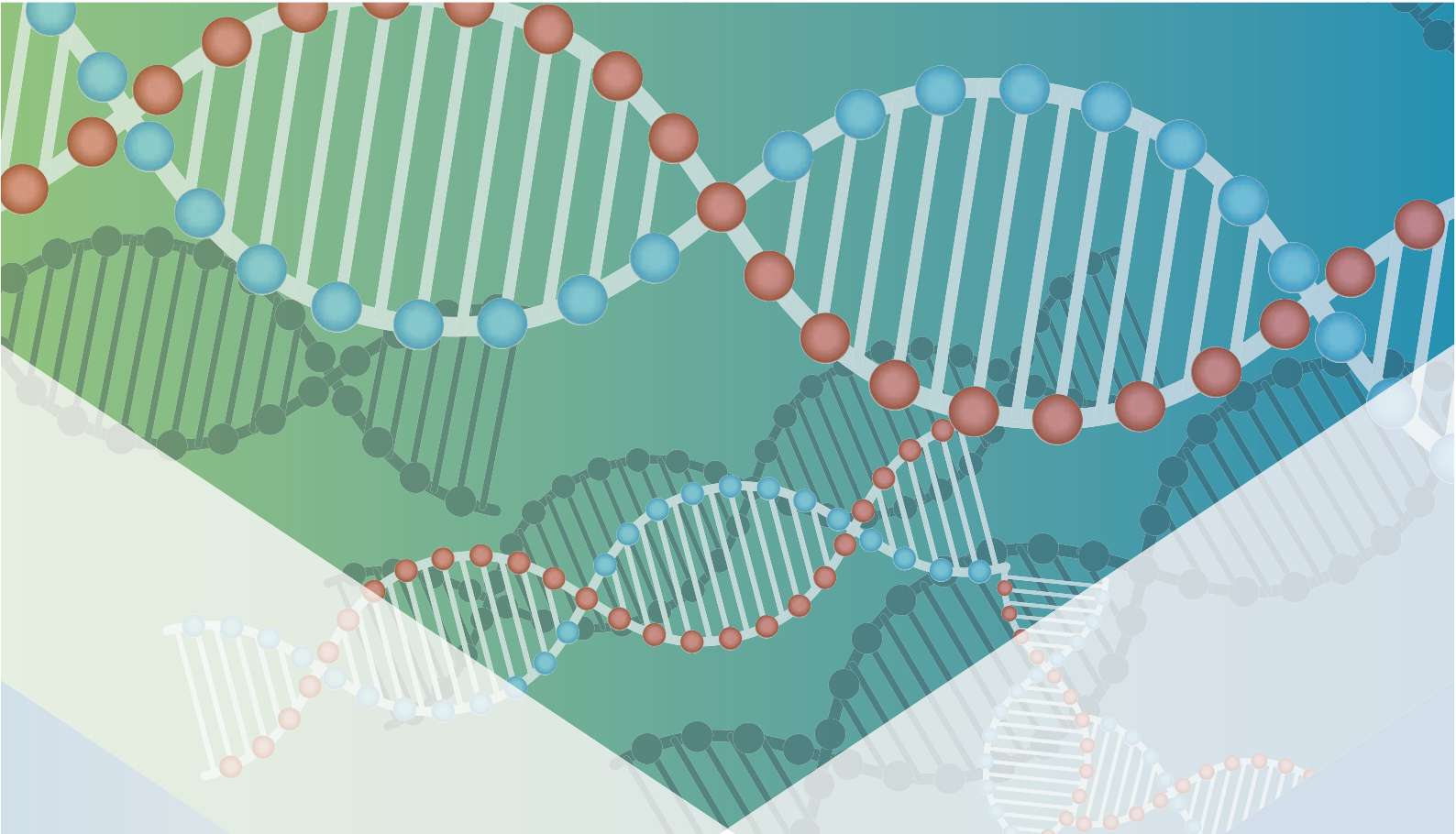


MAXVAL

Technology Landscape Study

On

CRISPR-Cas9

Targeted Genome Editing

info@maxval.com | www.maxval.com

EXECUTIVE SUMMARY

- Although CRISPR was known to have an important role in bacterial immunity for over a decade, it is only in the last 5 years that it has garnered interest as a gene editing tool
- Increasing investment in this field is indicative of global market opportunities for CRISPR-Cas9 over existing alternatives
- Academic and research institutes lead currently in patent filing, indicating that this is an early stage technology
  - The Broad Institute of MIT and Harvard, University of California and their collaborators are among the top filing assignees
  - Intellia Therapeutics, CRISPR Therapeutics, Editas Medicine, ERS Genomics and Caribou
  - Biosciences are among the list of commercialization partners that have broad and exclusive rights to CRISPR technologies
  - Institute of Genetics and Developmental Biology, Institute of Genetics and Developmental Biology takes the lead in research related to gene editing in crops and plants
  - Several industrial players including DowDuPont, Regeneron Pharmaceuticals are carving out their own CRISPR patent estates
- Around one fourth of the total filings in CRISPR-Cas9 is in the classification codes for ribonucleases and nucleic acids that modulate gene expression
  - Significant number of filings are listed under the classification related to vectors for gene editing and introduction of foreign DNA into chromosomes
- PCT filings outnumbered the filings from any single jurisdiction, emphasizing the global market for this technology
- Current clinical trials revolving around CRISPR-Cas9 originate from China
  - A handful number of clinical studies starting from Aug 2016 are identified in which CRISPR-Cas9 is used as an intervention
- Although CRISPR-Cas9 is revolutionizing the field of genome editing, it still remains a stochastic process with a lot of random indels
  - New approaches by researchers at Harvard show promise in solving shortcomings in the technology

INTRODUCTION

Genome Editing and CRISPR

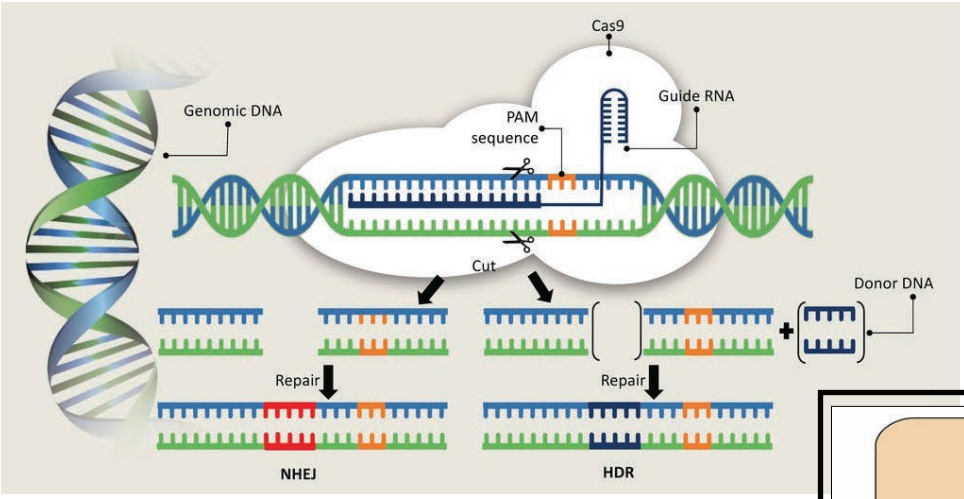
Genetic and epigenetic control of cells with genome engineering technologies allows a broad range of applications from basic biology to biotechnology, medicine and agriculture. It was in 2012 that Jennifer Doudna and Emmanuelle Charpentier first filed for a patent application for the CRISPR-Cas9 gene editing system. The Inventors had re-engineered the Cas9 endonuclease into a more manageable two-component system by fusing the two RNA molecules into a "single-guide RNA" that, when combined with Cas9, could find and cut the DNA target specified by the guide RNA. Several groups including Feng Zhang and colleagues from the Broad Institute of MIT and Harvard followed suit with filings. Fast forward to 2018, the stakes continue to rise with CRISPR being increasingly applied in gene editing and therapeutics. On January 23, 2018 NIH released news declaring that it would launch an effort aimed at removing barriers that slow the adoption of genome editing for treating patients. “Genome editing technologies such as CRISPR/Cas9 are revolutionizing biomedical research”, said NIH Director Francis S. Collins, M.D., Ph.D. Researchers will be awarded with about $190 million over six years beginning 2018, pending availability of funds. Pharmaceutical companies find it increasingly challenging in navigating the evolving and uncertain patent landscape.

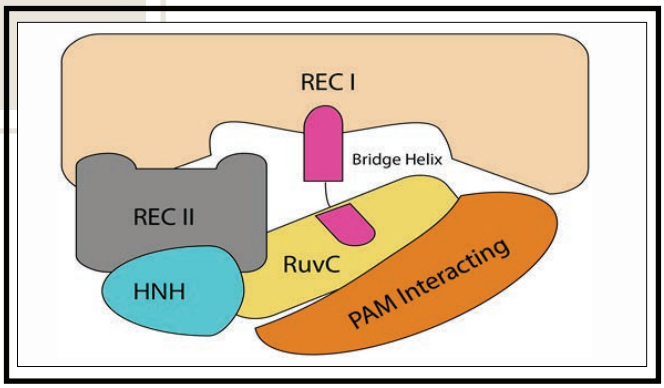
CRISPR-Cas9 allows more precision, ease-of-use, and is inexpensive when compared to other existing techniques such as ZFN, TALEN and Meganuclease for gene editing. For its varied applications, CRISPR was named the Breakthrough of the Year in December, 2015 by Science Magazine. According to a survey conducted by Elsevier, CRISPR has gained scientific momentum among both researchers and corporates in the last few years as shown below:

Technique	Scholarly Output (2011-2015)	Average citations per paper	Average citations per paper with corporate collaborations
CRISPR	2339	26.5	95.3
Meganuclease	132	16.9	2.7
TALEN	783	23.6	30.6
ZFN	1180	11.1	26

The main components of the CRISPR-Cas9 system are two biological macromolecules: i) guide RNA, which guides the endonuclease to the target site and ii) the endonuclease, which causes the nick at the precise location in target DNA.

Gene editing using CRISPR-Cas9 has high specificity because guide RNA molecules can be synthesized for precise homologous binding at target sites. These molecules guide the Cas9 endonuclease to specific sites to perform the nick. Cas9 requires a separate crRNA (CRISPR RNA) and tracrRNA (transactivating CRISPR RNA) that are annealed to each other through homology domains to form a crRNA:tracrRNA guide RNA complex. Sometimes, the crRNA and tracrRNA are combined with a short linker loop into a chimeric single-guide RNA (sgRNA), which is widely used in experiments. The Cas9 protein has 1368 amino acids, and is composed of six domains - REC I, REC II, Bridge Helix, PAM Interacting, HNH and RuvC.





Source: Tufts.edu

One of the shortcomings of the CRISPR-Cas9 system is the occurrence of off-target edits and the reduced efficiency of the gene editing process in the laboratory. Researchers are working to improve the target specific specificity and nicking efficiency of the CRISPR-Cas9 system. New approaches by David Liu and colleagues employ a technology called base editing which uses modified Cas9 nucleases that replace a single nucleotide without the need for a NHEJ or HDR, thereby reducing the chances for errors. These nucleobase editors could lead to the next breakthrough within CRISPR mediated gene editing paving way for CRISPR 2.0

Applications of CRISPR-Cas9

Since its inception, CRISPR-Cas9 has been increasingly applied in therapeutics, diagnostic kits and assays for screening, plant cell modifications, designing vectors for delivery, non-human animal models for experiments including swine, mice among other animals and viruses for gene delivery.

Market Research

The global CRISPR market by application generated revenue was $361 million in 2016, and is anticipated to be several billion in a few years, growing at a CAGR of 36.79% during the forecasted period of 2017-2025. The NIH and other organizations have increased their funding for CRISPR-focused research. On the commercial side, contract research organizations (CROs) have increased their use of the technique to genetically engineer model animals and cell lines for research purposes. The market is extremely fragmented, with numerous smaller companies vying for market share. More than 50% of the market is comprised of companies that hold only 8% or less market share. The growth of the CRISPR-Cas9 market will largely depend on improved funding landscape and overcoming regulatory hurdles.

Funding

Since its announcement as a breakthrough technology, CRISPR mediated gene editing has received ample funding for research and development.

- NIH announced in January 2018 that it is launching an effort to remove barriers that slow down the adoption of genome editing for therapy, the program is funded by NIH's Common Fund. Funding opportunity announcements for this program amount to about $190m
- Inscripta, a CRISPR start-up has raised $55.5m Series C round in February 2018 to create gene-editing tools such as instruments, reagents, and software, and to create a market for these tools
- Beam Therapeutics announced in May 2018 that it has raised up to $87 million in Series A financing and it aims to develop the technology of base editing in the genome with the most promising off-shoot of CRISPR developed so far, called base editor

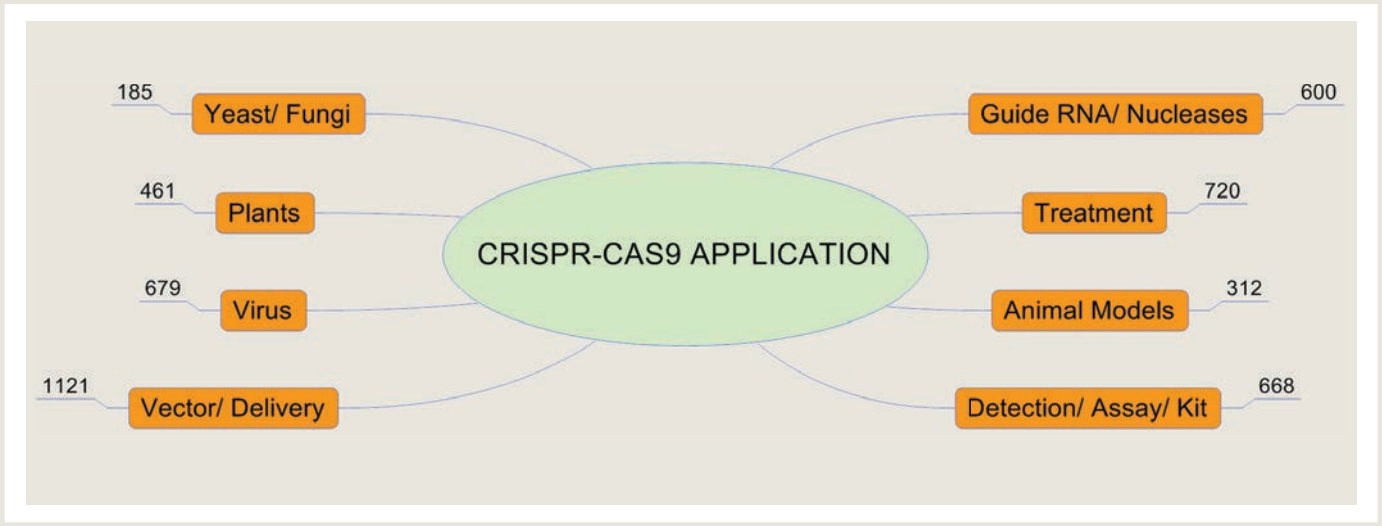
SCOPE & METHODOLOGY

Search & Process

The objective of this study is to explore the market and patenting activity in CRISPR-Cas9 gene editing technology. This study considers issued patents and pending published applications related to CRISPR-Cas9 published since January 1, 2007. Search strategies using various combinations of keywords, classification codes, and prominent assignees resulted in more than 10K patent families. The hits were then refined by semi-automated techniques to arrive at 4800 unique patent applications that spread across ~1750 INPADOC families. These 1750 patent families were analyzed for trends and patterns to identify IP investment, key players, licensing activity and prolific inventors.

Taxonomy

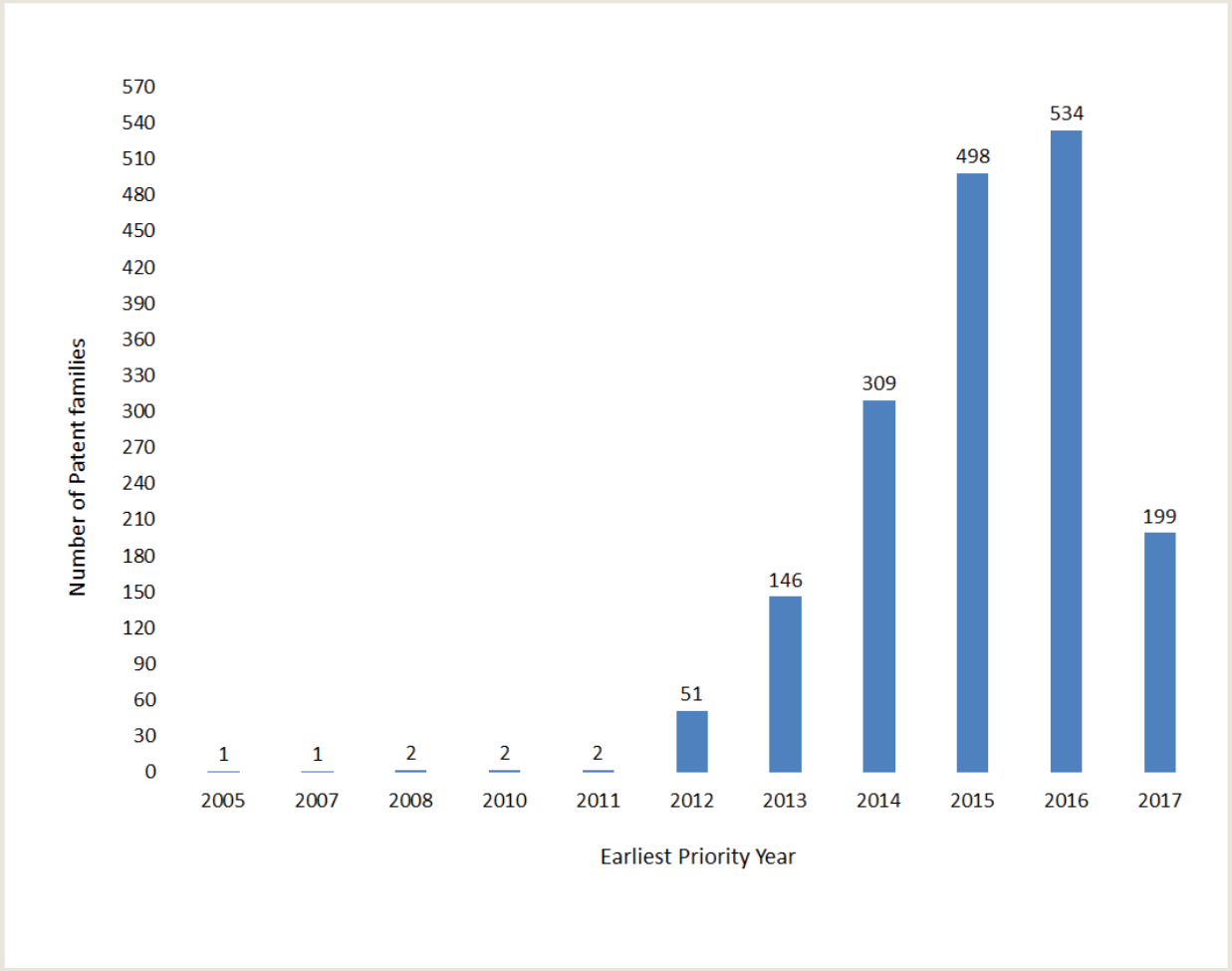
The 1750 patent families were categorized into different clusters as shown in the chart below based on their areas of applications. Categorizing the shortlisted patent documents under these broad applications revealed that a huge percentage of documents disclose vectors and other delivery vehicles to be the leading focus. Apart from these, gene therapy and modification of the guide RNA and nuclease enzyme have been the focus of several studies as well.



* There is some overlap in the categorization as many of the patent families fall in multiple categories.

Investment Trend

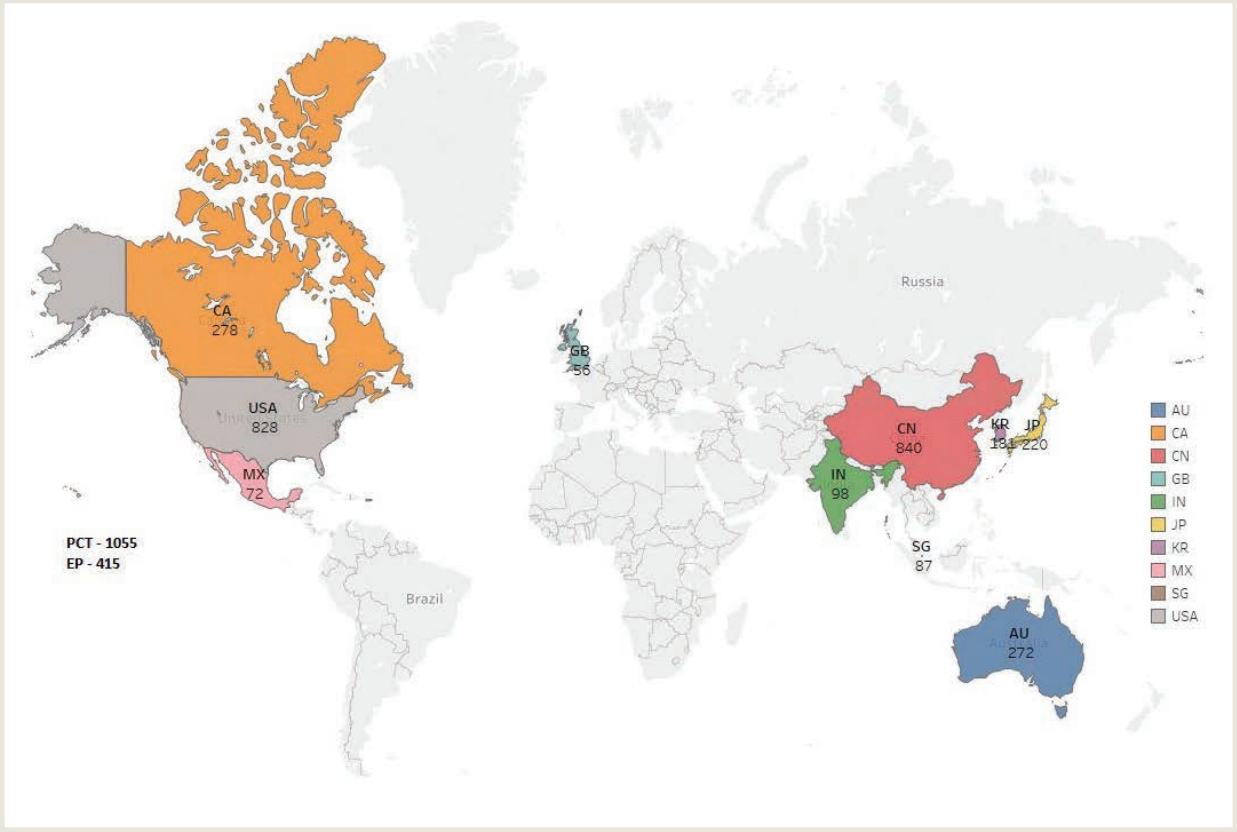
The 1740 patent families were plotted by earliest priority year of any family member



- Publications claiming their priority from 2015 and 2016 account for over 60 percent of all publications, hinting at several upcoming grants in the near future
- The dip in 2017 is likely due to the 18-month publication lag
- Few of the early filings include:
  - US20150283265A1 claiming priority as early as 2005 discloses a method for editing or regulating gene in target cells by administering nanoparticles coated with CRISPR/Cas9
  - US20170157038A1 from 2007 claims a method of treatment by eliminating a gene in the eye using CRISPR Cas9 system
  - US20150218587A1 elaborates on a genetic recombination technique by securing, cutting, transporting and micro-beam welding of genetic material to create a combined genetic material

Geographical Analysis

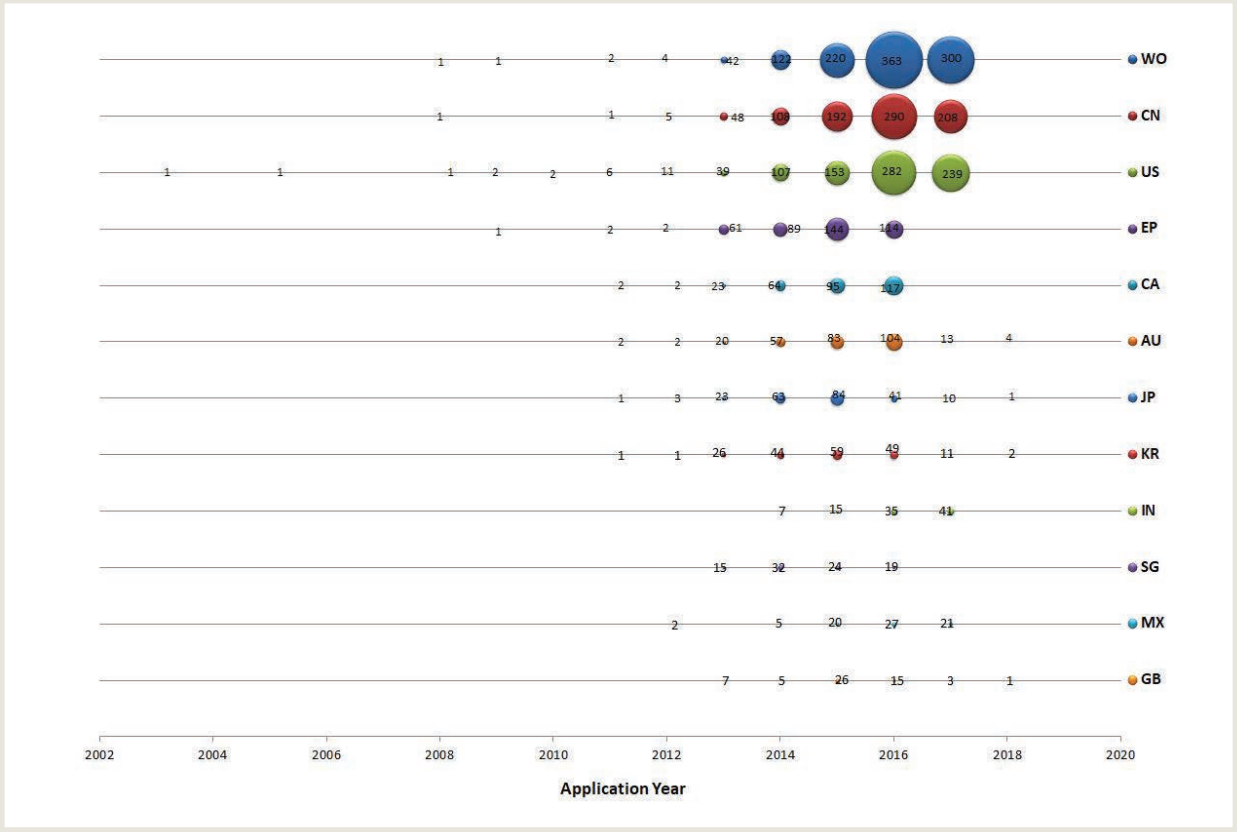
All members of the 1740 patent families were plotted by countries in which patent family members have been filed. The top filers are illustrated in the map below:



- Priority applications primarily originate from US (828) and CN (840)
- Chinese IP activity is mostly restricted to domestic filings
- Though the art has been developed primarily in the US, there is a strong development profile in Asian countries (CN, AU, IN, SG, JP, KR)
- Entities seek multinational patent protection by filing PCT and EP applications

Geographical Filing Trend

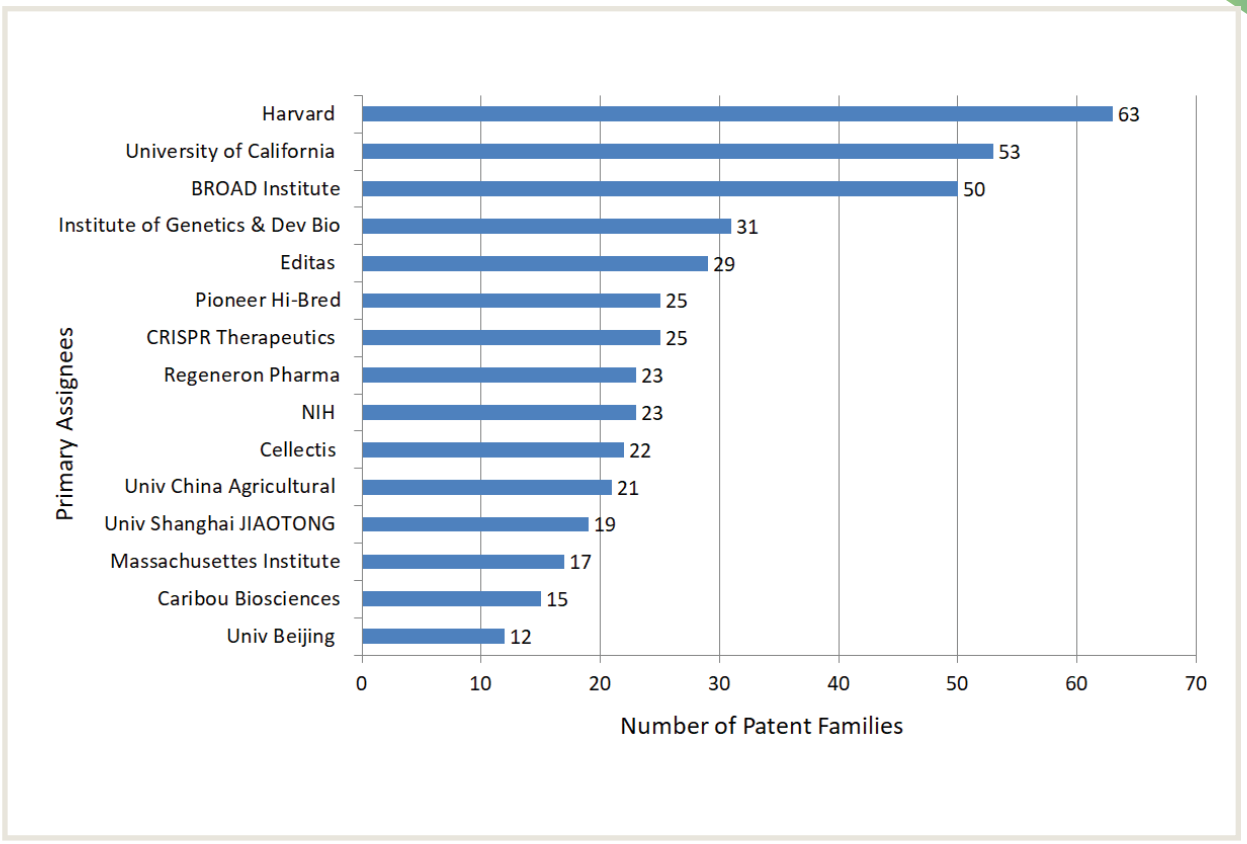
All members of 1740 patent families were plotted by rate of filings in countries against the filing year



- Increased number of filings through PCT in the recent years shows the global market opportunity for CRISPR-Cas9 system
- There is a steady increase in patent filings in the major markets including CN, US and EP

Primary Assignee Analysis

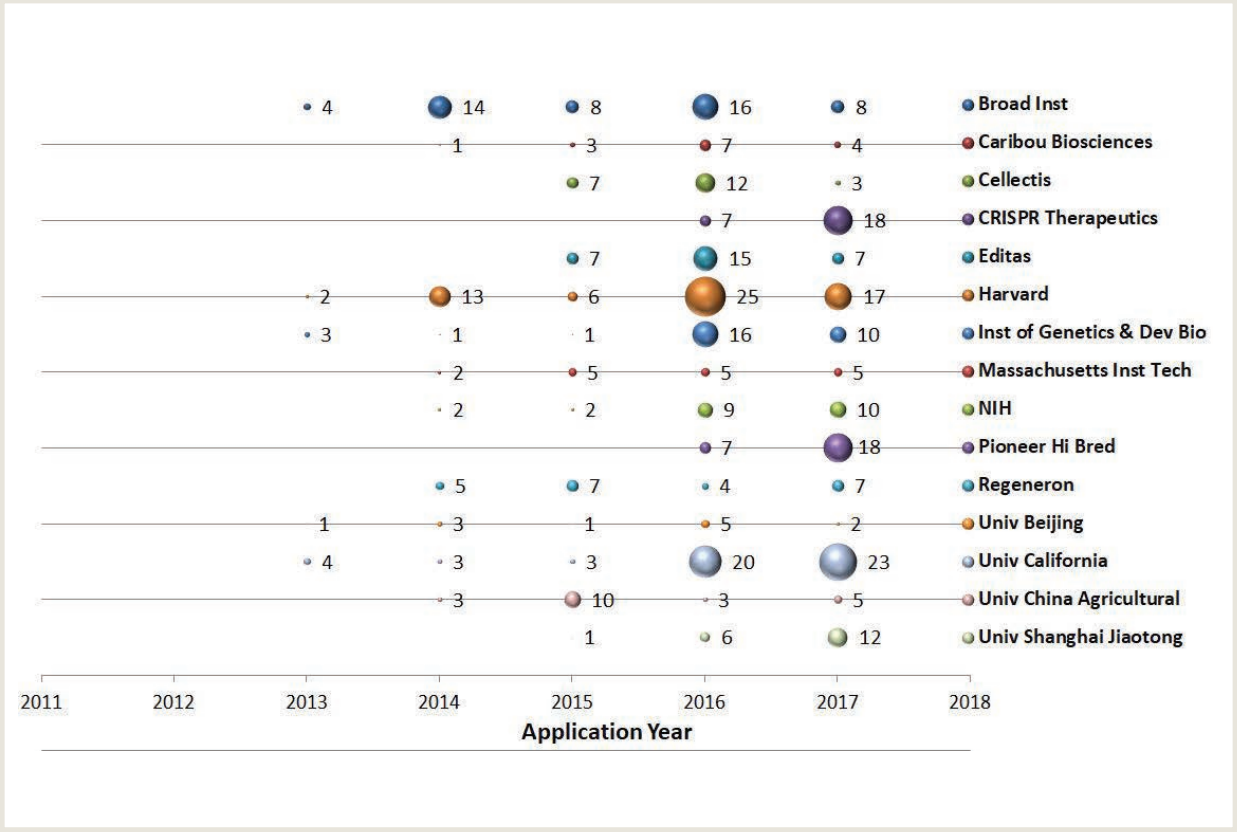
The 1740 patent families were plotted by the assignees



- US and Chinese academic and institutional entities are actively involved in CRISPR research
- Harvard, MIT and the Broad Institute collaborate with one another in many of the filings

Assignee Investment Pattern

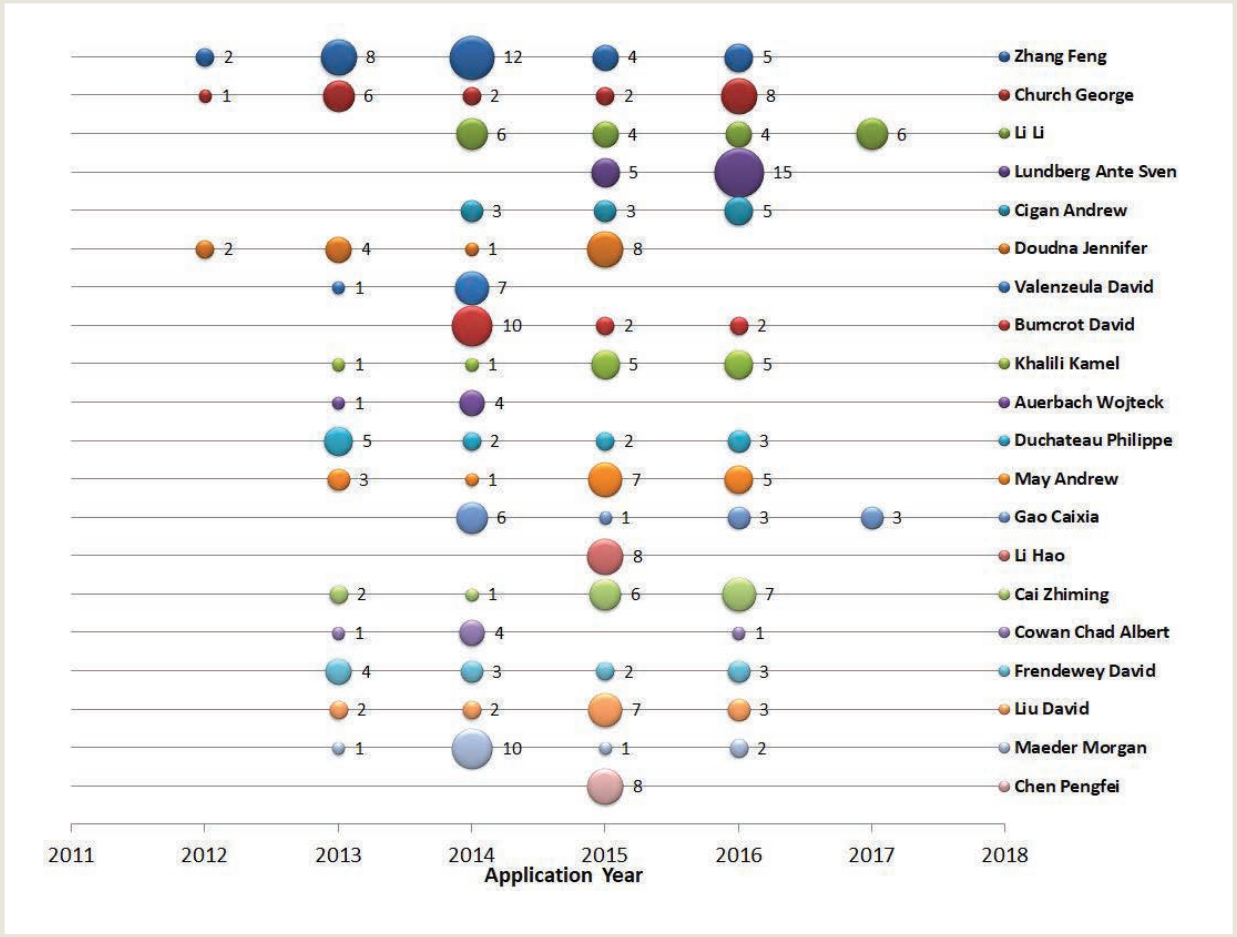
The 1740 patent families were plotted by top assignees vs filing year



- Harvard, Broad institute, University of California, Inst of Genetics & Dev Bio, China and NIH have accelerated their filings in the recent years
- Several new assignees such as Cellectis, CRISPR Therapeutics, Editas, Pioneer Hi-Bred and Univ Shanghai Jiaotong have filed applications in 2015-2017

Prolific Inventors in the Domain

The 1740 patent families were plotted by the top inventors vs filing year



- Among the top inventors in the technology are several researchers from the US including Feng Zhang, George Church, Ante Sven Lundberg, Jennifer Doudna and Andrew Cigan highlighting the patent-friendly research environment in US
- Feng Zhang from the Broad Institute has the most number of patent families
- Emmanuelle Charpentier (not in the top list) has collaborated with Jennifer Doudna in some of the pioneering work related to the CRISPR technology

Legal Disputes

University of California, The Broad Institute and researcher Emmanuelle Charpentier are involved in legal disputes related to the technology. US. PTAB ruled in favor of the Broad Institute in Feb., 2017. US8697359B1 (The Broad Institute) is one of the several patents that was under dispute.

Most of the pioneering patents under CRISPR related gene editing is owned by the following firms, Institutes and Universities: Intellia Therapeutics, University of California, Berkeley, Caribou Biosciences, CRISPR Therapeutics, ERGS Genomics, Editas Medicine and The Broad Institute.

Technology Categorization

The 1740 patent families were categorized as per the taxonomy. There may be overlap as many of the

	Detect/ Diagnose/ Screen	Guide RNA/ Nuclease	Animal Models	Plants	Treatment	Vector / Delivery	Virus	Yeast/ Fungi
Detection/Assay /Kit	668	240	136	116	282	513	294	61
Guide RNA / Nuclease	600	112	156	220	472	248	69	
Animal Models	312	32	103	174	103	20		
Plants	461	76	356	114	99			
Treatment	720	603	437	64				
Vector /Delivery	1121	1396	1343					
Virus	679	80						
yeast/ Fungi	185							

Documents that claim assays or kits include diagnostic, screening and detection kits, buffers used in assays or kits, isolation /screening kits are categorized here

Documents that disclose compositions containing CRISPR/Cas9 systems, modified guide RNA molecules, Cas9 molecules that have been modified, methods of editing genome using guide RNA

Documents disclosing animal models for CRISPR Cas9 applications have been categorized here

Documents disclosing specific genetically modified crops, or CRISPR Cas9 systems used to edit plant genome are categorized here

Treatment of diseases such as HIV, Cancer, Hepatitis, autoimmune disorders and other genetic conditions using CRISPR Cas9 are categorized here

Vectors used in gene editing, delivery of CRISPR/ Cas9 system for treatment of diagnosis are covered here

Viruses used in aiding CRISPR CAS system, Inactivation of viruses using gene editing technologies and other claims pertaining to viruses are covered here

Knock-out of genes in eukaryotes using the expression system of yeast, gene editing in fungi, yeast extracellular vesicles for delivery are covered in this among other documents are covered here

Top Assignees Vs Technology Segmentation

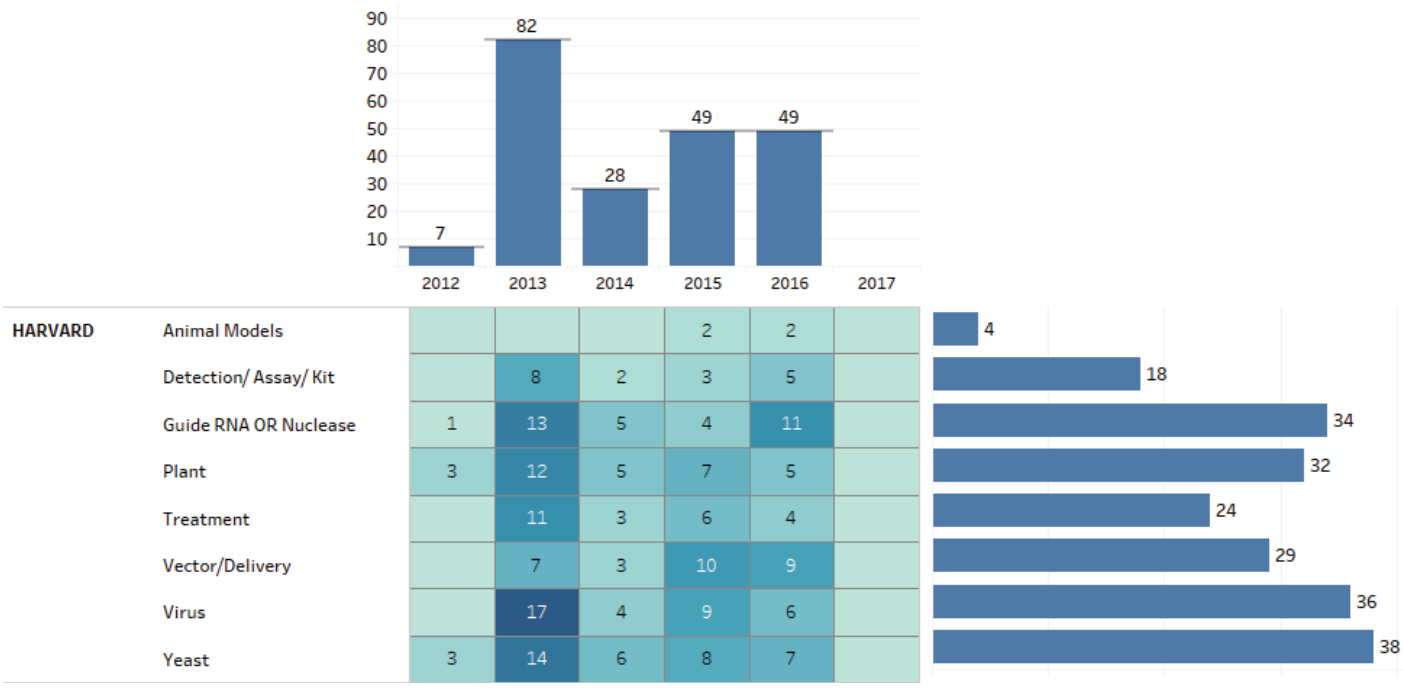
The 1740 patent families were plotted by top assignees vs technology segmentation.

	Detection/ Assay/ Kit	Guide RNA / Nuclease	Animal Models	Plants	Treatment	Vector / Delivery	Virus	Yeast
BROAD INST INC	21	7	12	9	43	49	39	2
CARIBOU BIOSCIENCES	12			2	6	8	8	2
CELLECTIS	6	6		3	16	11	13	
CRISPR THERAPEUTICS		1		1	24	22	18	1
EDITAS	18	24	2	2	25	25	21	3
HARVARD	18	34	4	32	24	29	36	38
INST OF GENETICS & DEV BIO	8	5		31		21	3	
MASSACHUSETTS INST TECH	8	12	1	3	9	14	7	2
NIH	13	11	10	1	14	14	14	2
PIONEER HI BRED	3	9		25	3	4	4	10
REGENERON	9	9	22		8	18	10	
UNIV BEIJING	5	6		2	1	9	4	
UNIV CALIFORNIA	26	11	14	16	21	31	24	6
UNIV CHINA AGRICULTURAL	5	6	13	21		17		
UNIV SHANGHAI JIAOTONG	2	9		5	3	15	4	1

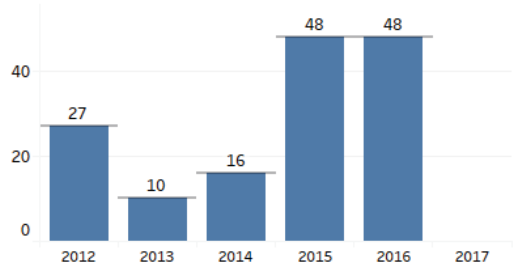
A detailed split of the filing trend of the top assignees across the major technology segmentation is depicted in the following sections.

Top Assignees Vs Technology Segmentation

- **Harvard**

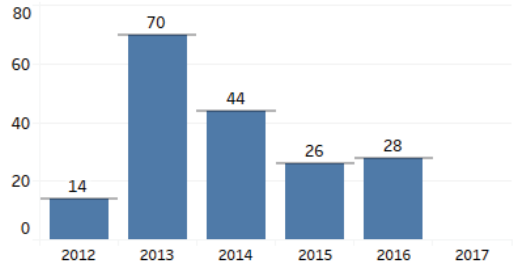


- **University of California**



		2012	2013	2014	2015	2016	2017	
UNIV CALIFORNIA	Animal Models	10		2		2		11
	Detection/ Assay/ Kit	5	4	3	7	7		16
	Guide RNA OR Nuclease		3	2	3	3		24
	Plant	5		3	5	3		6
	Treatment	1	1		9	10		26
	Vector/Delivery	5		2	13	11		14
	Virus	1	2	2	10	9		21
	Yeast			2	1	3		31

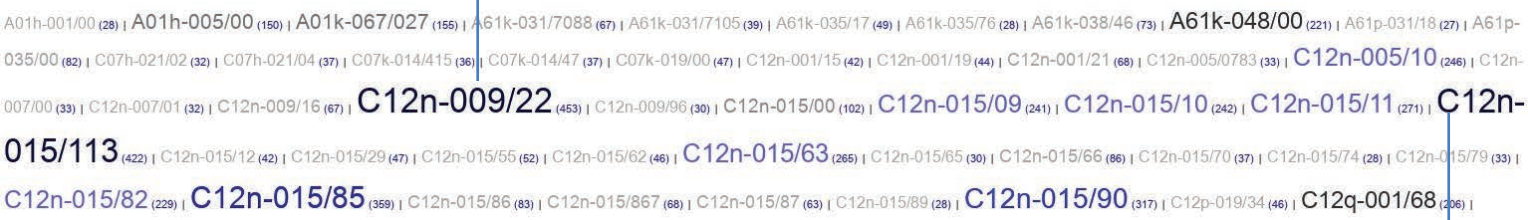
- **Broad Institute**



		2012	2013	2014	2015	2016	2017	
BROAD INST	Animal Models			9	1	2		7
	Detection/ Assay/ Kit	1		8	5	7		9
	Guide RNA OR Nuclease			5	1	1		39
	Plant		4		2	3		2
	Treatment	4	23	6	6	4		21
	Vector/Delivery	5	23	9	7	5		12
	Virus	4	20	7	4	4		43
	Yeast					2		49

Technologies/ Uses Based on IPC Codes

Enzymes, Proenzymes, Compositions thereof, Processes for preparing, activating, inhibiting, separating, or purifying enzymes…Hydrolases…acting on ester bonds…Ribonucleases



Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; Use of hosts therefor … Recombinant DNA-technology… Introduction of foreign genetic material using vectors; Vectors; Use of hosts therefor; Regulation of expression…
Vectors or expression systems specially adapted for eukaryotic hosts…
for animal cells

Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; Use of hosts therefor …Recombinant DNA-technology…Introduction of foreign genetic material using processes not otherwise provided for…Stable introduction of foreign DNA into chromosome

Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; Use of hosts therefor …Recombinant DNA-technology…DNA or RNA fragments; Modified forms thereof…Non-coding nucleic acids modulating the expression of genes, e.g. antisense oligonucleotides

Top Cited US Art

The 1740 patent families were screened for US patents or pending applications with the highest cited-by counts/year.

Publication #	Title	Assignee	Year Issued/ Published	Cited by	Average cites/year
US8697359B1	CRISPR-Cas systems and methods for altering expression of gene products	Massachusetts Institute of Technology | Broad Institute Inc	2014	199	50.97
US20140068797A1	Methods and compositions for RNA-directed target DNA modification and for RNA-Directed modulation of Transcription	Universitaet Wien | University of California	2014	195	48.58
US8993233B2	Engineering and optimization of systems, methods and compositions for sequence manipulation with functional domains	Harvard College | Massachusetts Institute of Technology | Broad Institute Inc	2015	142	48.21
US8771945B1	CRISPR-Cas systems and methods for altering expression of gene products	Massachusetts Institute of Technology | Broad Institute Inc	2014	154	41.91
US8865406B2	Engineering and optimization of improved systems, methods and enzyme compositions for sequence manipulation	Massachusetts Institute of Technology | Broad Institute Inc	2014	139	41.04
US8795965B2	CRISPR-Cas component systems, methods and compositions for sequence manipulation	Massachusetts Institute of Technology | Broad Institute Inc	2014	145	40.3
US8871445B2	CRISPR-Cas component systems, methods and compositions for sequence manipulation	Harvard College | Massachusetts Institute of Technology | Broad Institute Inc	2014	129	38.31
US20140179770A1	Delivery, engineering and optimization of systems, methods and compositions for sequence manipulation and therapeutic applications	Massachusetts Institute of Technology | Broad Institute Inc	2014	93	25.08
US20140186843A1	Methods, systems, and apparatus for identifying target sequences for CAS enzymes or CRISPR-CAS systems for target sequences and conveying results thereof	Massachusetts Institute of Technology | Broad Institute Inc	2014	80	21.69
US20140189896A1	CRISPR-CAS component systems, methods and compositions for sequence manipulation	Harvard College| Rockefeller University | Massachusetts Institute of Technology | Broad Institute Inc	2014	73	19.79

Products in the Market

A web search for CRISPR Cas9 products available for gene editing in the market revealed the following results:

Company Name	Product Name	Product Description
Takara Bio USA, Inc.	Guide-it™ CRISPR/Cas9 System	This product is **a subject of the following patents - US8697359 and US8771945**. The Guide-it CRISPR/Cas9 Systems are kits for the cloning and expression of target single guide RNAs (sgRNAs) for mammalian genome editing using CRISPR/Cas9 technology. The vector in this system simultaneously expresses Cas9 nuclease, a target-specific sgRNA, and an exceptionally bright fluorescent protein for monitoring transfection efficiency and/or for further enriching/isolating transfected cells by flow cytometry (ZsGreen1 and tdTomato versions are available). Generating a plasmid that expresses a sequence-specific sgRNA with this system is simple; a pair of user-provided oligos corresponding to the target genomic sequence of interest are annealed to form a duplex, and the duplexed oligos are inserted into the pre-linearized vector using the included high-efficiency ligation mix. The kit also includes Stellar competent cells to ensure high efficiency transformation.
Integrated DNA Technologies	Alt-R® CRISPR-Cas9 System	The Alt-R® CRISPR-Cas9 System includes all of the reagents needed for successful genome editing based on the natural S. pyogenes CRISPR-Cas9 system. Benefit from the latest improvements in on- and off-target design and chemical modifications, as well as easy ordering of custom or predesigned guide RNAs. Get optimal editing with high on-target potency and reduced off-target activity with Alt-R HiFi CRISPR-Cas9 nuclease. Precisely control editing with efficient delivery of the RNP by lipofection or electroporation
System Biosciences	EF1α-T7-hspCas9-Nickase-T2A-RFP-H1-gRNA All-in-one Cas9 SmartNickase™	All-in-one Cas9 and gRNA plasmids are an excellent way to simplify delivery of your CRISPR/Cas9 Nickase system by providing both Cas9 Nickase and gRNA from a single vector, and the addition of coordinate expression of RFP for monitoring transfection efficiencies helps make genome engineering projects more user-friendly. SBI's EF1α-T7-hspCas9-Nickase-T2A-RFP-H1-gRNA All-in-one Cas9 SmartNickase Plasmid includes a number of additional features that make it a great All-in-one choice for any genome engineering project involving transfectable cells
ThermoFisher Scientific	TrueGuide Synthetic gRNA	Invitrogen TrueGuide Synthetic gRNAs are ready-to-transfect synthetic gRNAs designed and validated to work with the Invitrogen suite of genome editing tools to provide consistent high efficiency editing. Invitrogen is utilizing Synthego's high performance oligo manufacturing to bring you TrueGuide Synthetic gRNAs. Whether you need an economical solution for routine editing tasks or you want to drive maximum editing efficiency, particularly in primary or stem cells, TrueGuide Synthetic gRNAs offer the reagents you require to introduce your specific edit in your cell line.
ThermoFisher Scientific	TrueCut Cas9 Protein v2	Invitrogen TrueCut Cas9 Protein v2, a wild type Cas9 in protein form designed to deliver consistently higher editing efficiency across a range of gene targets and cell types.
Sigma-Aldrich	CRISPR Integration Kit	All-in-one, ready-to-use Cas9 and guide RNA (gRNA) expression plasmids for use with monocots and dicots. CRISPR Plant Cas9 products are intended for Agrobacterium-mediated plant transformation or biolistic microparticle bombardment or protoplast transformation. The products are based on the type IIA CRISPR-Cas9 derived from Streptococcus pyogenes. The native Cas9 coding sequence is codon optimized for expression in monocots and dicots, respectively. The monocot Cas9 constructs contain a monocot U6 promoter for sgRNA expression, and the dicot Cas9 constructs contain a dicot U6 promoter. The plant selection markers include: hygromycin B resistance gene, neomycin phosphotransferase gene, bar gene (phosphinothricin acetyl transferase)
GeneCopoeia	Target site PCR Kit (version 2.0), 200 rxns*	PCR reagents for amplifying region flanking CRISPR/TALEN target site, prior to T7 Endonuclease I digestion*

Clinical Trials

Search on the clinical trials database (www.clinicaltrials.gov) where CRISPR Cas9 is the intervention revealed the following list:

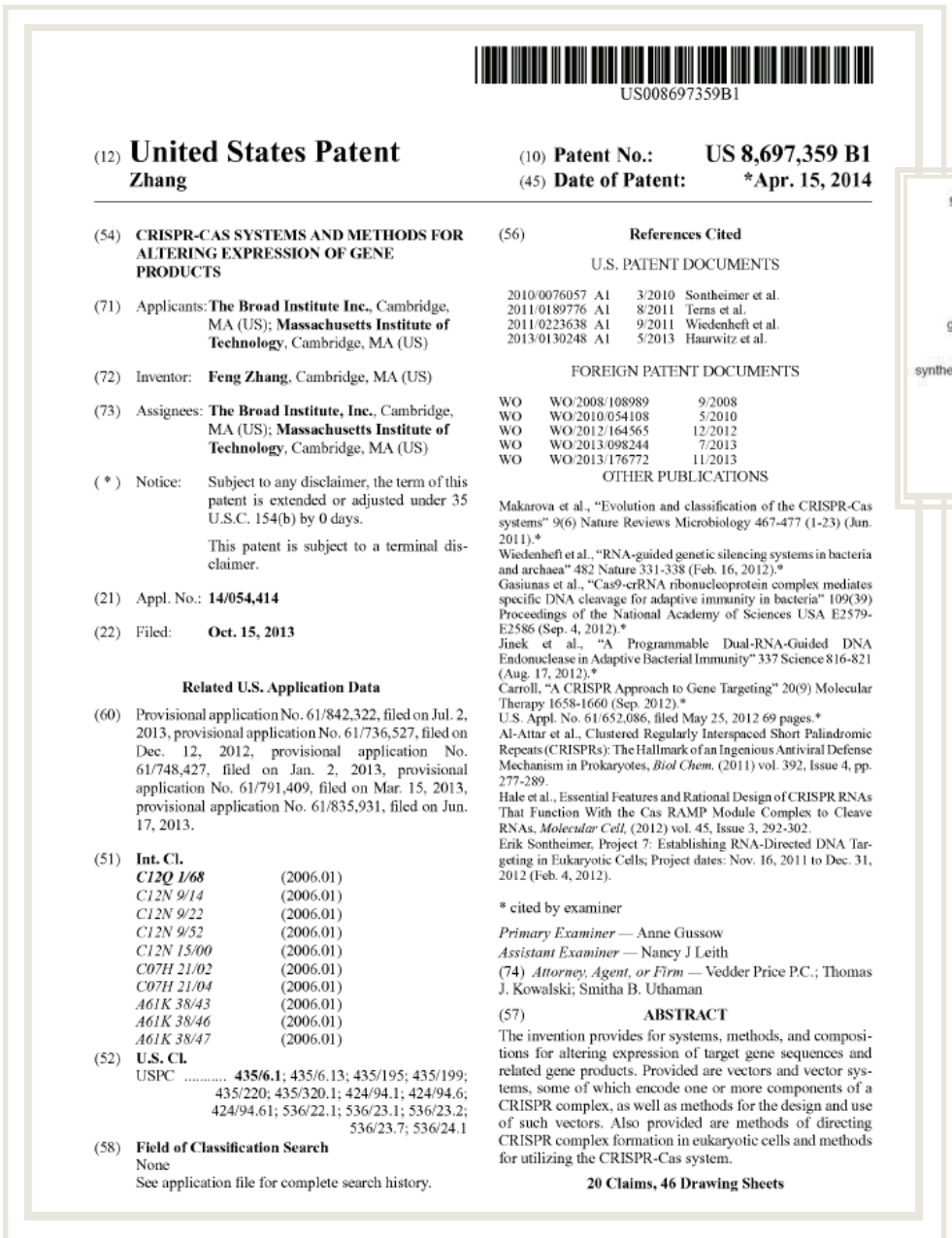
Trial ID	Title	Sponsors	Start Date
NCT03081715	PD-1 Knockout Engineered T Cells for Advanced Esophageal Cancer	Hangzhou Cancer Hospital|Anhui Kedgene Biotechnology Co.,Ltd Location: Hangzhou Cancer Hospital, Hangzhou, Zhejiang, China	20-Mar-2017
NCT03398967	A Feasibility and Safety Study of Universal Dual Specificity CD19 and CD20 or CD22 CAR-T Cell Immunotherapy for Relapsed or Refractory Leukemia and Lymphoma	Chinese PLA General Hospital Location: Biotherapeutic Department and Hematology Department of Chinese PLA General Hospital, Beijing, Beijing, China	02-Jan-2018
NCT03166878	A Study Evaluating UCART019 in Patients With Relapsed or Refractory CD19+ Leukemia and Lymphoma	Chinese PLA General Hospital Location: Biotherapeutic Department and Hematology Department of Chinese PLA General Hospital, Beijing, Beijing, China	01-Jun-2017
NCT02863913	PD-1 Knockout Engineered T Cells for Muscle-invasive Bladder Cancer	Peking University|Cell Biotech Co., Ltd. Location:Department of Urology Peking University First Hospital, Beijing, Beijing, China	01-Sep-2016
NCT02867345	PD-1 Knockout Engineered T Cells for Castration Resistant Prostate Cancer	Peking University|Cell Biotech Co., Ltd. Location:Department of Urology Peking University First Hospital, Beijing, Beijing, China	01-Nov-2016
NCT02867332	PD-1 Knockout Engineered T Cells for Metastatic Renal Cell Carcinoma.	Peking University|Cell Biotech Co., Ltd. Location: -	01-Nov-2016
NCT02793856	PD-1 Knockout Engineered T Cells for Metastatic Non-small Cell Lung Cancer	Sichuan University|Chengdu MedGenCell, Co., Ltd. Location: West China Hospital, Sichuan University, Chengdu, Sichuan, China	01-Aug-2016
NCT03044743	PD-1 Knockout EBV-CTLs for Advanced Stage Epstein-Barr Virus (EBV) Associated Malignancies	Yang Yang|The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School Location:The Comprehensive Cancer Center of Nanjing Drum Tower Hospital, Nanjing, Jiangsu, China|The Comprehensive Cancer Center of Nanjing Drum Tower Hospital, Nanjing, Jiangsu, China	07-Apr-2017
NCT03057912	A Safety and Efficacy Study of TALEN and CRISPR/Cas9 in the Treatment of HPV-related Cervical Intraepithelial Neoplasiaâ…	First Affiliated Hospital, Sun Yat-Sen University|Jingchu University of Technology Location:The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China	15-Jan-2018
NCT03164135	Safety of Transplantation of CRISPR CCR5 Modified CD34+ Cells in HIV-infected Subjects With Hematological Malignances	Affiliated Hospital to Academy of Military Medical Sciences|Peking University|Capital Medical University Location:307 Hospital of PLA (Affiliated Hospital of Academy to Military Medical Sciences), Beijing, Beijing, China	30-May-2017

Licenses

Since the pioneering work in this technology is held by Research institutes and Universities, collaborations and licensing is abundant among the top inventors:

- Broad Institute of Harvard and MIT runs a collaborative research program using an approach they developed called "inclusive innovation" model. Under this model, Broad Institute has exclusively licensed the technology to their commercial partner - Editas Medicine, Inc
- UC Berkeley have exclusively licensed their technology to their commercial partners – Caribou Biosciences, Intellia Therapeutics, and CRISPR Therapeutics
- In 2014, Caribou granted Novartis an option for a non-exclusive, worldwide license. Novartis exercised its option for an internal research license in 2016. Caribou receives maintenance payments for the license to Novartis
- Caribou entered into a multi-year strategic research with Genus PLC in 2016 under which Caribou has provided Genus with exclusive access to technology for the development of new traits in pigs, cattle, and potentially other livestock species.
- Caribou has granted Integrated DNA Technologies, Inc. (IDT) a non-exclusive license agreement in 2016 to commercialize CRISPR-Cas9 reagents. IDT is a producer of custom synthetic oligonucleotide-based technologies
- In 2016 Caribou granted The Jackson Laboratory non-exclusive, worldwide rights to create genetically engineered mice for research purposes.
- Caribou and Pioneer Hi-Bred International, Inc., an affiliate of E.I. du Pont de Nemours and Company, announced a license agreement and multi-year collaboration in 2015, including the cross-licensing of key intellectual property. Pioneer recently entered into an exclusive licensing deal with ERS Genomics for all agricultural uses and applications in plants. With a series of such deals, DowDuPont has now emerged as single biggest owner of CRISPR estate globally
- MPEG LA, LLC initiated a patent pool licensing model for CRISPR-Cas9 patents with the aim of making the technology accessible under a single non-exclusive, transparent license. It remains to be seen if non-exclusive licenses will have any takers amongst those firms working on CRISPR-based human therapeutics which require a significant amount of investment
- In June 2017, in a mail correspondence from The Broad Institute to MPEG LA (a firm that licenses patent pools), The Broad mentioned that CRISPR tools, knowledge and other IP for genome editing tools would continue to be freely available for academic and non-profit communities. CRISPR IP would be non-exclusively licensed to companies for their own commercial research. The Broad Institute also submitted a list of US and EP patents for evaluation of eligibility to participate in discussions.

1. Exemplary Patent



US008697359B1

(12) **United States Patent**
Zhang

(10) **Patent No.: US 8,697,359 B1**
(45) **Date of Patent: *Apr. 15, 2014**

(54) **CRISPR-CAS SYSTEMS AND METHODS FOR ALTERING EXPRESSION OF GENE PRODUCTS**

(71) Applicants: **The Broad Institute Inc.**, Cambridge, MA (US); **Massachusetts Institute of Technology**, Cambridge, MA (US)

(72) Inventor: **Feng Zhang**, Cambridge, MA (US)

(73) Assignees: **The Broad Institute, Inc.**, Cambridge, MA (US); **Massachusetts Institute of Technology**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/054,414**

(22) Filed: **Oct. 15, 2013**

Related U.S. Application Data

(60) Provisional application No. 61/842,322, filed on Jul. 2, 2013, provisional application No. 61/736,527, filed on Dec. 12, 2012, provisional application No. 61/748,427, filed on Jan. 2, 2013, provisional application No. 61/791,409, filed on Mar. 15, 2013, provisional application No. 61/835,931, filed on Jun. 17, 2013.

(51) **Int. Cl.**

C12Q 1/68	(2006.01)
C12N 9/14	(2006.01)
C12N 9/22	(2006.01)
C12N 9/52	(2006.01)
C12N 15/00	(2006.01)
C07H 21/02	(2006.01)
C07H 21/04	(2006.01)
A61K 38/43	(2006.01)
A61K 38/46	(2006.01)
A61K 38/47	(2006.01)

(52) **U.S. Cl.**
USPC **435/6.1**; 435/6.13; 435/195; 435/199; 435/220; 435/320.1; 424/94.1; 424/94.6; 424/94.61; 536/22.1; 536/23.1; 536/23.2; 536/23.7; 536/24.1

(58) **Field of Classification Search**
None
See application file for complete search history.

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Erik Sontheimer, Project 7: Establishing RNA-Directed DNA Targeting in Eukaryotic Cells; Project dates: Nov. 16, 2011 to Dec. 31, 2012 (Feb. 4, 2012).

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Primary Examiner — Anne Gussow
Assistant Examiner — Nancy J Leith
(74) *Attorney, Agent, or Firm* — Vedder Price P.C.; Thomas J. Kowalski; Smitha B. Uthaman

(57) **ABSTRACT**

The invention provides for systems, methods, and compositions for altering expression of target gene sequences and related gene products. 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 and methods for utilizing the CRISPR-Cas system.

20 Claims, 46 Drawing Sheets

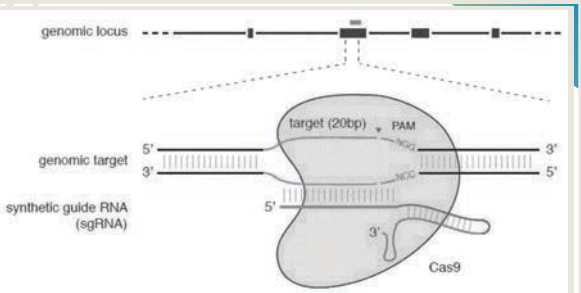
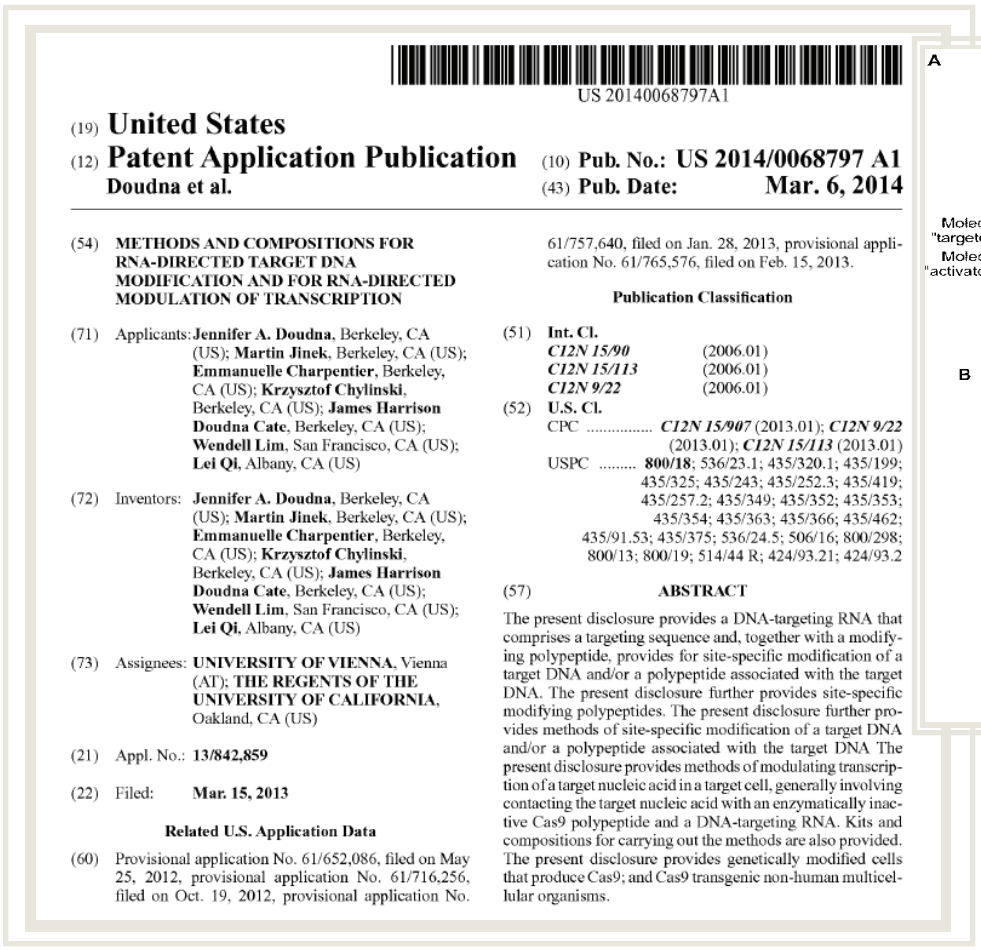


FIG. 1

US8697359B1
Priority Date: 12 Dec, 2012

This patent filed by the Broad Institute and MIT addresses the need for robust systems and techniques for sequence targeting. This patent provides CRISPR CAS related gene editing techniques and acts as one of the foundations on which several inventors have based their work. This technology removes the requirement for the generation of customized proteins to target specific sequences but instead uses a single Cas enzyme that is programmed by a short RNA molecule to recognize a specific DNA target

2. Exemplary Patent Application



US 20140068797A1

(19) **United States**

(12) **Patent Application Publication**

Doudna et al.

(10) **Pub. No.: US 2014/0068797 A1**

(43) **Pub. Date: Mar. 6, 2014**

(54) **METHODS AND COMPOSITIONS FOR RNA-DIRECTED TARGET DNA MODIFICATION AND FOR RNA-DIRECTED MODULATION OF TRANSCRIPTION**

(71) Applicants: **Jennifer A. Doudna**, Berkeley, CA (US); **Martin Jinek**, Berkeley, CA (US); **Emmanuelle Charpentier**, Berkeley, CA (US); **Krzysztof Chylinski**, Berkeley, CA (US); **James Harrison Doudna Cate**, Berkeley, CA (US); **Wendell Lim**, San Francisco, CA (US); **Lei Qi**, Albany, CA (US)

(72) Inventors: **Jennifer A. Doudna**, Berkeley, CA (US); **Martin Jinek**, Berkeley, CA (US); **Emmanuelle Charpentier**, Berkeley, CA (US); **Krzysztof Chylinski**, Berkeley, CA (US); **James Harrison Doudna Cate**, Berkeley, CA (US); **Wendell Lim**, San Francisco, CA (US); **Lei Qi**, Albany, CA (US)

(73) Assignees: **UNIVERSITY OF VIENNA**, Vienna (AT); **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA**, Oakland, CA (US)

(21) Appl. No.: **13/842,859**

(22) Filed: **Mar. 15, 2013**

Related U.S. Application Data

(60) Provisional application No. 61/652,086, filed on May 25, 2012, provisional application No. 61/716,256, filed on Oct. 19, 2012, provisional application No. 61/757,640, filed on Jan. 28, 2013, provisional application No. 61/765,576, filed on Feb. 15, 2013.

Publication Classification

(51) **Int. Cl.**

C12N 15/90 (2006.01)
C12N 15/113 (2006.01)
C12N 9/22 (2006.01)

(52) **U.S. Cl.**

CPC ***C12N 15/907*** (2013.01); ***C12N 9/22*** (2013.01); ***C12N 15/113*** (2013.01)

USPC ..... **800/18**; 536/23.1; 435/320.1; 435/199; 435/325; 435/243; 435/252.3; 435/419; 435/257.2; 435/349; 435/352; 435/353; 435/354; 435/363; 435/366; 435/462; 435/91.53; 435/375; 536/24.5; 506/16; 800/298; 800/13; 800/19; 514/44 R; 424/93.21; 424/93.2

(57) **ABSTRACT**

The present disclosure provides a DNA-targeting RNA that comprises a targeting sequence and, together with a modifying polypeptide, provides for site-specific modification of a target DNA and/or a polypeptide associated with the target DNA. The present disclosure further provides site-specific modifying polypeptides. The present disclosure further provides methods of site-specific modification of a target DNA and/or a polypeptide associated with the target DNA The present disclosure provides methods of modulating transcription of a target nucleic acid in a target cell, generally involving contacting the target nucleic acid with an enzymatically inactive Cas9 polypeptide and a DNA-targeting RNA. Kits and compositions for carrying out the methods are also provided. The present disclosure provides genetically modified cells that produce Cas9; and Cas9 transgenic non-human multicellular organisms.

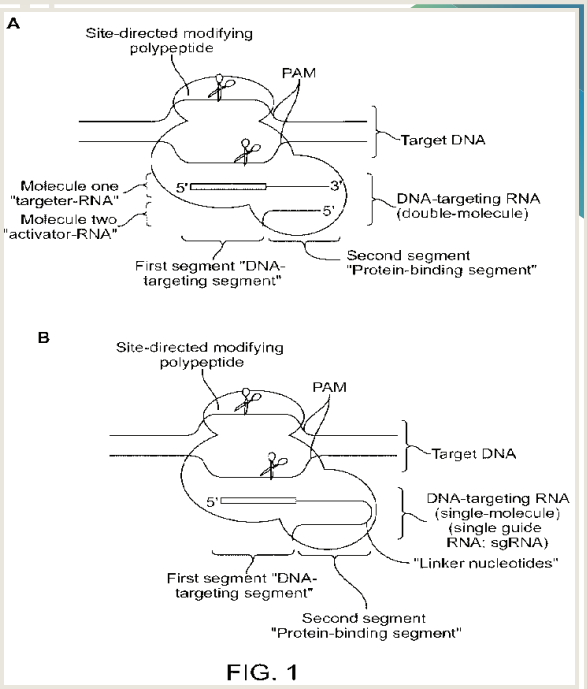
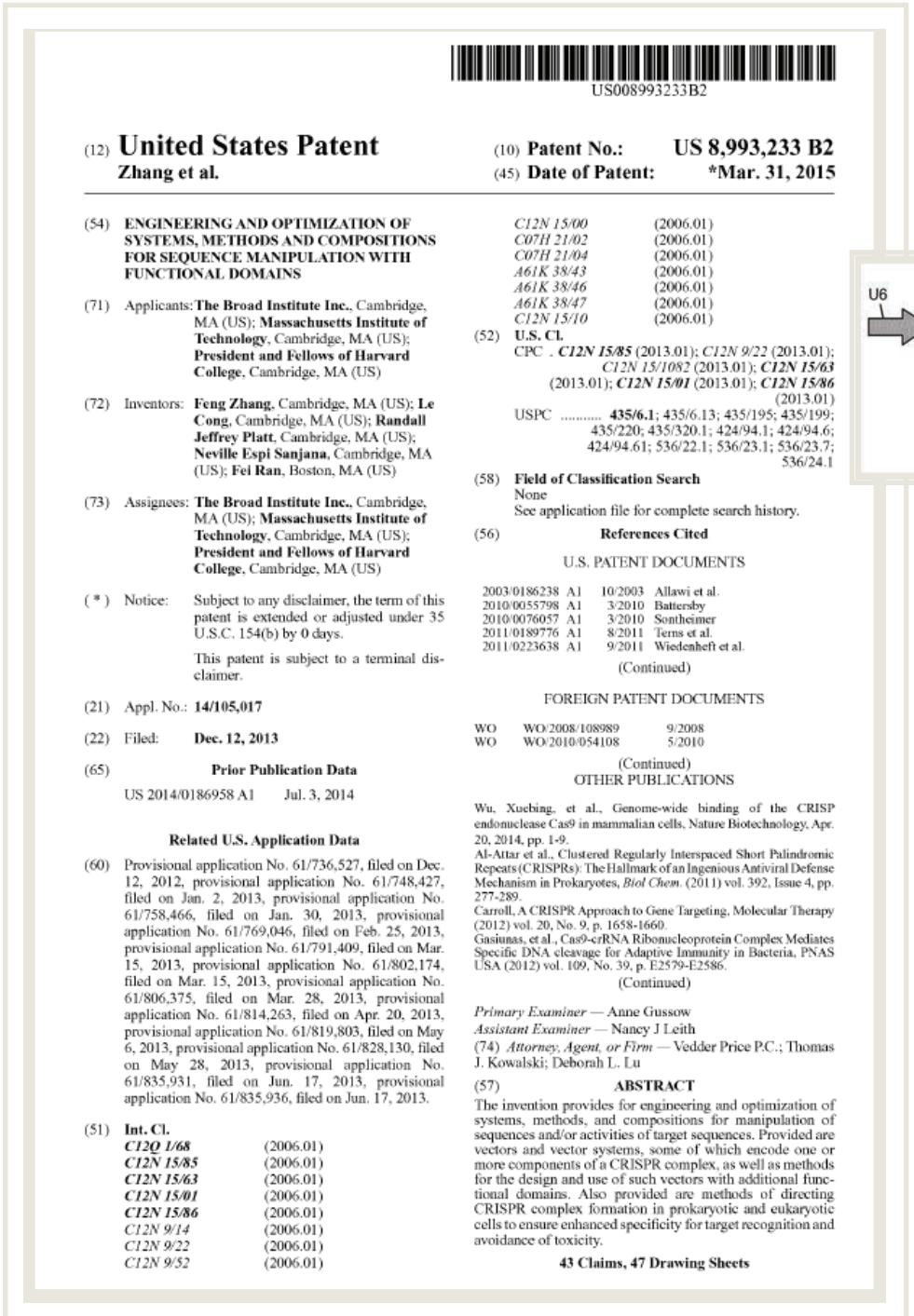


FIG. 1

US20140068797A1
Priority Date: 25 May, 2012

This patent publication discloses a DNA-targeting RNA that comprises a targeting sequence and, together with a modifying polypeptide, provides for site-specific modification of a target DNA and/or a polypeptide associated with the target DNA.

3. Exemplary Patent



US008993233B2

(12) **United States Patent**
Zhang et al.

(10) **Patent No.: US 8,993,233 B2**
(45) **Date of Patent: *Mar. 31, 2015**

(54) **ENGINEERING AND OPTIMIZATION OF SYSTEMS, METHODS AND COMPOSITIONS FOR SEQUENCE MANIPULATION WITH FUNCTIONAL DOMAINS**

(71) Applicants: **The Broad Institute Inc.**, Cambridge, MA (US); **Massachusetts Institute of Technology**, Cambridge, MA (US); **President and Fellows of Harvard College**, Cambridge, MA (US)

(72) Inventors: **Feng Zhang**, Cambridge, MA (US); **Le Cong**, Cambridge, MA (US); **Randall Jeffrey Platt**, Cambridge, MA (US); **Neville Espi Sanjana**, Cambridge, MA (US); **Fei Ran**, Boston, MA (US)

(73) Assignees: **The Broad Institute Inc.**, Cambridge, MA (US); **Massachusetts Institute of Technology**, Cambridge, MA (US); **President and Fellows of Harvard College**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/105,017**

(22) Filed: **Dec. 12, 2013**

(65) **Prior Publication Data**

US 2014/0186958 A1 Jul. 3, 2014

Related U.S. Application Data

(60) Provisional application No. 61/736,527, filed on Dec. 12, 2012, provisional application No. 61/748,427, filed on Jan. 2, 2013, provisional application No. 61/758,466, filed on Jan. 30, 2013, provisional application No. 61/769,046, filed on Feb. 25, 2013, provisional application No. 61/791,409, filed on Mar. 15, 2013, provisional application No. 61/802,174, filed on Mar. 15, 2013, provisional application No. 61/806,375, filed on Mar. 28, 2013, provisional application No. 61/814,263, filed on Apr. 20, 2013, provisional application No. 61/819,803, filed on May 6, 2013, provisional application No. 61/828,130, filed on May 28, 2013, provisional application No. 61/835,931, filed on Jun. 17, 2013, provisional application No. 61/835,936, filed on Jun. 17, 2013.

(51) **Int. Cl.**

C12Q 1/68	(2006.01)
C12N 15/85	(2006.01)
C12N 15/63	(2006.01)
C12N 15/01	(2006.01)
C12N 15/86	(2006.01)
C12N 9/14	(2006.01)
C12N 9/22	(2006.01)
C12N 9/52	(2006.01)
C12N 15/00	(2006.01)
C07H 21/02	(2006.01)
C07H 21/04	(2006.01)
A61K 38/43	(2006.01)
A61K 38/46	(2006.01)
A61K 38/47	(2006.01)
C12N 15/10	(2006.01)

(52) **U.S. Cl.**
CPC . ***C12N 15/85*** (2013.01); *C12N 9/22* (2013.01); *C12N 15/1082* (2013.01); ***C12N 15/63*** (2013.01); ***C12N 15/01*** (2013.01); ***C12N 15/86*** (2013.01)
USPC **435/6.1**; 435/6.13; 435/195; 435/199; 435/220; 435/320.1; 424/94.1; 424/94.6; 424/94.61; 536/22.1; 536/23.1; 536/23.7; 536/24.1

(58) **Field of Classification Search**
None
See application file for complete search history.

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(Continued)

Primary Examiner — Anne Gussow
Assistant Examiner — Nancy J Leith
(74) *Attorney, Agent, or Firm* — Vedder Price P.C.; Thomas J. Kowalski; Deborah L. Lu

(57) **ABSTRACT**

The invention provides for engineering and optimization of systems, methods, and compositions for manipulation of sequences and/or activities of target sequences. 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 with additional functional domains. Also provided are methods of directing CRISPR complex formation in prokaryotic and eukaryotic cells to ensure enhanced specificity for target recognition and avoidance of toxicity.

43 Claims, 47 Drawing Sheets

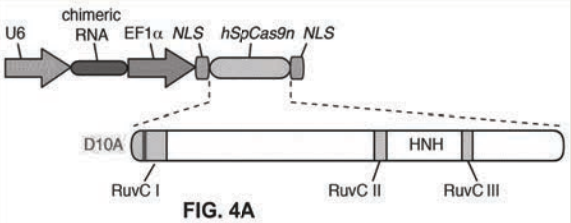
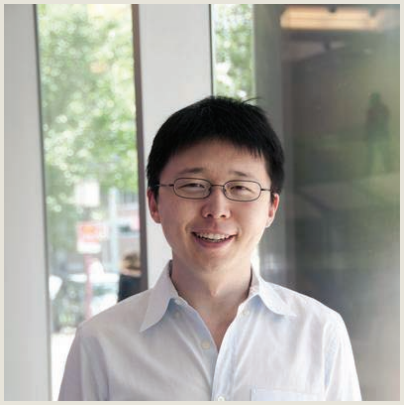


FIG. 4A

US8993233B2
Priority Date: 12 Dec, 2012

This patent discloses 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. To utilize the CRISPR-Cas system effectively for genome editing without deleterious effects, it is critical to understand aspects of engineering and optimization of these genome engineering tools.

NOTABLE INVENTORS BIO



E: zhang_f@mit.edu
P: 617-714-7578

Feng Zhang is a molecular biologist developing and applying novel molecular technologies for studying the molecular and genetic basis of diseases and providing treatment. Zhang has pioneered the development of genome editing tools for use in eukaryotic cells – including human cells – from natural microbial CRISPR systems.
He and his team have adapted multiple CRISPR systems for use as genome engineering tools, including most recently, the RNA-targeting system CRISPR-Cas13a

Co-Founder of Editas Medicine| Founder Beam Therapeutics | Core Institute member of the Broad Institute of MIT | Investigator at the McGovern Institute for Brain Research at MIT

E: gc@harvard.edu
P: 617-432-7562

George Church has co-authored over 480 papers, 130 patent publications and the book Regenesis. He has developed methods used for the first genome sequence (1994), and million-fold cost reductions (via NGS and nanopores). He has pioneered barcoding, DNA assembly from chips, genome editing, writing & recoding.
He co-initiated the BRAIN Initiative (2011), and also the Genome Projects (1984, 2005) that provide & interpret the world's only open-access personal precision medicine datasets.

Co-Founder eGenesis | Co-Founder Editas | Advisor Genome Compiler Corp. | Founder Warp Drive Bio| Founder Gen9, Inc | Founder Knome Inc | Co-Founder Nebula Genomics Founder LS9 Inc | Professor at Harvard & MIT

E: doudna@berkeley.edu
P: 510-643-0113

Jennifer Doudna in collaboration with Dr. Emmanuelle Charpentier, led the team that developed the application of CRISPR/Cas9 and its use as a tool for genome engineering, including editing and repair, in eukaryotes and other organisms. In recognition of this work, she was awarded the 2015 Breakthrough Prize in Life Sciences, the 2014 Dr. Paul Janssen Award for Biomedical Research and the 2014 Lurie Prize in Biomedical Sciences from the Foundation for the National Institutes of Health.

Founder Intellia Therapeutics Inc | Professor and HHMI Investigator at UC Berkeley and Howard Hughes Medical Institute | SAB eFFECTOR Therapeutics & Caribou Biosciences

E: charpentier@mpiib-berlin.mpg.de
P: +49 30 28460-410

Emmanuelle Charpentier is one of the pioneering researchers related to CRISPR Cas9 as a gene editing tool. Emmanuelle Charpentier established her own research group at the Max F. Perutz Laboratories of the University of Vienna in Austria where she habilitated in the field of Microbiology. She was then recruited as an Associate Professor at the Laboratory for Molecular Infection Medicine Sweden (MIMS, Swedish Node of the European Molecular Biology Laboratory (EMBL) Partnership for Molecular Medicine) at Umeå University. In 2012, Emmanuelle Charpentier was appointed Professor at Hannover Medical School (MHH) and head of the department "Regulation in Infection Biology" at the Helmholtz Centre for Infection Research (HZI) in Germany.

Founder CRISPR Therapeutics |Founder and Scientific Advisor ERS Genomics | Director at the Berlin-based Max Planck Institute for Infection Biology

E: liu@chemistry.harvard.edu

P: 617-714-8808

David R. Liu is Professor of Chemistry and Chemical Biology at Harvard University, a Howard Hughes Medical Institute Investigator, a Core Institute Member and Vice-Chair of the Faculty of the Broad Institute of Harvard and MIT, and an Associate Faculty Member of the Wyss Institute for Biologically Inspired Engineering. His major research interests include (i) the evolution of proteins with novel therapeutic potential using methods including phage-assisted continuous evolution (PACE); (ii) the engineering and delivery of genome-editing proteins to study and treat genetic diseases; and (iii) the discovery of therapeutically relevant synthetic small molecules and synthetic polymers through DNA-templated organic synthesis, an approach developed in his laboratory.

Founder Beam Therapeutics | Co-Founder Editas | Scientific Founder Ensemble Therapeutics Scientific Founder Permeon Biologics

Technology Landscape Study on CRISPR-Cas9

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MaxVal Group, Inc.
2251 Grant Road, Suite B
Los Altos, CA 94024
Phone: 650-472-0644
info@maxval.com | www.maxval.com