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GENE EDITING TECHNOLOGY:
MARKET ASSESSMENT AND INTELLECTUAL PROPERTY LANDSCAPE

Primary Authors: Sophie Brayne, Kyriakos Tzafestas, Rebecca Ashton & Bansi Pattni

Sector Lead: Elaine Eggington

IP Pragmatics Ltd.

160 Fleet Street, London, EC4A 2DQ, United Kingdom
www.ip-pragmatics.com
+44 (0)203 176 0252

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EXECUTIVE SUMMARY

The intention of this white paper is to provide an overview of the market developments across the gene editing commercial and patent landscapes. The information contained in this report does not constitute legal advice and should not be interpreted as such.

The market and patent trends show the gene editing industry has experienced rapid growth in the last few years, primarily due to the CRISPR revolution. When compared to the older gene editing technologies, CRISPR has the greatest number of patent filings and publications in recent years, as well as the most collaborations and licensing deals.

Based on the patent portfolios of the key players, there appears to be a single frontrunner in each of the older technologies: Sangamo Biosciences for ZFNs; Cellectis for TALENs and Dow Agrosciences for Meganucleases. In contrast, assignees for CRISPR patent applications appear be more wide spread with four leading organisations. There are several new players in the gene editing field that only own or commercialise CRISPR technologies which has not been the case for Meganuclease, TALEN or ZFN technologies. The existing players in the gene editing field appear to have adopted CRISPR in addition to the older technologies judging from the increase in the number of their CRISPR-related patent filings and licensing deals.

Despite CRISPR's obvious recent dominance in the gene editing industry, the analysis shows that the older technologies are still being used in industry and patents are still being filed in each of the technology areas. However, the steady decrease in the number of deals and patents filings suggests that the commercial focus is moving away from these technologies. This process could be accelerated by the development of novel gene editing technologies that surpass the abilities of CRISPR. For example, Cibus has developed a novel gene editing technology, RTDS™, and more recently, Precision BioSciences has landed its first collaboration for its proprietary technology, ARCUS. Precision BioSciences claim that the technology has advantages over CRISPR, however, it is still a relatively new technology and its full capability is yet to be demonstrated

To date there has been only a few acquisitions in the industry. With the growing number of new CRISPR-based companies and the limited foundational patents, further consolidation in the market would be expected. With these future developments, it is likely that more applications for gene editing will arise in other industry sectors such as the food industry and industrial biotechnology as different companies use their expertise to commercialise products enabled by the underlying technology.

Regulations around gene editing in plants, animals and humans are still in the process of being developed by different countries and regional bodies. The outcome of these decisions and particularly whether animals and plants developed using CRISPR will fall under genetically modified (GM) type regulations or not, will significantly impact on the eventual commercial potential and value of these technologies.

In general, with valuable innovation comes litigation and the gene editing industry is no exception with the Pioneer Hi-Bred vs Cellectis infringement case and the ongoing battle surrounding the ownership of the CRISPR technology. On the whole, there is more collaboration at present than litigation in the field. This may continue given the increase in cross-licensing and collaborations but the creation of a new generation of foundational patents for new technologies may lead to further litigation in the future.

There is great excitement at the possibilities of gene editing coupled with the hesitations of controversial applications of the technology and the environmental and cultural implications of it. Given this potential, innovation in the field is stronger than ever and shows no signs of slowing down.

INTRODUCTION

IP Pragmatics has decided to focus its first white paper on the gene editing industry which has been a popular topic since the invention of the latest gene editing technology, CRISPR. The technology has caught the imagination of the public with the widely broadcasted possibilities of its application in curing fatal diseases, eliminating the threat of diseases transmitted from animals and insects, and even the science fiction notion of 'designer babies'. The new technology is more versatile, faster and more effective than its predecessors and has sparked a rapid growth in research and development in the gene editing industry.

The beginnings of modern genetics can be linked to advances in transgenesis research in the early 1970s, supported by the significant advances in DNA sequencing in the late 1970s and meganucleases in the 1980s which paved the way to nuclease-based gene editing. Technologies based on these advancements allowed for the introduction of genetically modified organisms, now common in agriculture, and the first clinical trials in gene therapy.

Meganucleases and zinc-finger nucleases were the first generation of nucleases and are still being used in academic research as well as in industry. These have been followed by TALE nucleases in 2009 (TALENs) and CRISPR nucleases in 2012. Gene editing now broadly refers to a suite of methods that use site-specific endonucleases to first target a double-stranded break in the genome and then to repair that gene by disrupting it or by rewriting its sequence.

This white paper aims to give an overview of the gene editing industry through a combination of market research and patent landscaping which looks at current and future applications of gene editing in the industry sectors in which IP Pragmatics have their expertise: Life Science Research, Animal Health, Agricultural Biotech and Human Health. The paper also incorporates details of the key organisations, factors affecting the market, licensing and collaborations. The four main gene editing technologies have been compared in each of these instances in order to assess the impact of CRISPR on the older technologies.

MARKET OVERVIEW

The global genome editing market is expected to reach $3,514.08 Million by 2019 from $1,845.25 Million in 2014, growing at a compound annual growth rate (CAGR) of 13.75% (MarketsandMarkets, 2015). The market covers a broad range of sectors including life science research, agriculture, therapeutics, animal health and industrial biotech. This section explores gene editing markets and applications in the first four sectors as the industrial biotechnology is relatively new.

LIFE SCIENCE RESEARCH

Life science research is an important sector for gene editing as the use of the tools and services for research spans over all the downstream commercial sectors. Interest generated from a wide range of application areas such as biomedical research, drug discovery, non-transgenic breeding and clinical therapies is driving a rapid growth in this sector (BCC Research, 2016). The report estimates the following market valuations for the gene editing research market: animal models ($86 million), cell lines ($84 million), gene editing services ($28 million) and gene editing tools ($197 million).

Companies offering gene editing tools as research tools include Sigma Aldrich, Thermo Fisher Scientific, Integrated DNA Technologies and Transposagen. Thermo Fisher Scientific specialises in TALEN technologies whilst the other three focus on CRISPR technologies. Sigma Aldrich also offers tools for ZFN gene editing. In addition to research tools, some companies offer gene editing research services such as Caribou Biosciences. Many companies also use gene editing to create animal models of disease as well as cell models and cell lines.

INDUSTRY APPLICATIONS

Gene editing technologies can carry out many functions that are useful as research tools themselves, or in the generation of other research tools. Such functions include knockouts, knockins, tagging, chromosomal rearrangements, transcriptional interference or activation and genetic screening. Many companies who are already in the life science research space have started to adopt new gene editing technologies across their research tool product lines. The new technologies allow them to offer their clients more efficient and precise solutions.

Knockouts use non-homologous end joining (NHEJ) to inactivate genes by frameshift mutation and can be used to rapidly generate knockout cell lines and animals, analyse loss of function for single-gene knockout and study combinatorial effects, pathway redundancy, and epistatic relationships via multigene knockout. They can also be used to investigate the role of genes in cell processes, disease models, and drug response. Knockins introduce specific nucleotide modifications to genomic DNA via homology-directed repair (HDR). Activities include the rapid generation of cell lines and animals, targeted gene expression and noncoding DNA elements and simultaneously targeting mutations to multiple genomic regions. They can also introduce gain-of-function and loss-off-function mutations in endogenous genes to study the impact of SNPs or somatic mutations on gene function.

Tagging uses HDR to introduce an epitope tag or fluorescent marker at a targeted locus or visualize genomic DNA with a tagged-Cas9 mutant. This can be used to fuse endogenous genes or genomic loci to fluorescent proteins, introduce conditional alleles, e.g. LoxP or FRT, epitope tag (e.g. His or FLAG) targeted genomic sequence to enable downstream analysis and visualize genomic elements in living cells via sgRNA tiling.

Chromosomal rearrangements use two double-stranded breaks to delete intervening genomic regions which can be used to study complete gene knockouts, investigate the function of noncoding regulatory elements and analyse haplo-insufficiency with mono-allelic deletion clones. The rearrangements include deletions, translocations, and other modifications

Transcriptional interference or activation uses target genes to repress expression with CRISPR interference (CRISPRi) or activate expression with CRISPR activation (CRISPRa). This tool can be used to study the effect of gene knockdown or activation in a reversible system and target multiple genes simultaneously to study gene networks and combinatorial effects

Genetic screening systematically identify genes involved in biological processes via high-throughput CRISPR screens. It can be used for genome-wide gene activation and repression screening, systematically identifying genes involved in biological processes and screening to identify genes involved in disease models and drug response.

PLANTS AND AGRICULTURE

In 2015, the global agricultural biotechnology market of gene editing was estimated at $80 million which is almost double the estimate from the year before. The market is expected to reach $315 million by 2020, growing at a CAGR of 31.5% (BCC Research, 2016). While gene editing applications in therapeutics are currently in the spotlight, the figures show that the technology in the agriculture sector has advanced rapidly beyond the laboratory into product development and in some cases even the market. In fact, genome editing technologies already have a more significant impact on agricultural markets in comparison to the human health markets.

INDUSTRY APPLICATIONS

The agricultural biotechnology market for gene editing focuses mainly on the use of the technology for breeding. Plant breeding as an application holds a 20% share of the global market for gene editing and ranks third after drug development and academic research applications.

Conventional breeding technologies such as hybridisation and mutation breeding have allowed in the past for the selection of plants with improved traits. However, traditional breeding relies on natural variation and extensive back-crossing, and as a result is limited by the low frequency of desirable mutations, the long breeding cycles, extensive screenings and the high costs associated with it. Genome editing tools can significantly accelerate that process by introducing precise and predictable modifications, while new advancements like the CRISPR/Cas9 system allow for multiple traits to be modified simultaneously.

The seed genomics industry is using gene editing technology to develop novel germplasm for seeds. The new incorporated traits include increased resistance towards pests, diseases and herbicides. These traits are important since they result in lower tillage and pesticide requirements. Other improvements include plants that tolerate better climate changes, drought-resistant crops that use nitrogen more efficiently, extended shelf life and increased nutrient levels and food quality (e.g. colour and shape of fruits). Plants with targeted insertion of genes for metabolic engineering and molecular farming can also be used for the production of specific metabolites, proteins and other high value chemicals.

ANIMALS

Gene editing in animals has a number of uses, including in laboratories (e.g. to provide models for human disease), for food (e.g. varieties of livestock, including chickens, pigs, cattle, sheep and fish), as resources (including, potentially, tissues and organs for animal-to-human transplantation) and even for companionship. There are also potential applications in wild animal populations, for example to control the vectors of human and animal diseases.

INDUSTRY APPLICATIONS

Animal Health

A number of organisations are using gene editing technologies to reduce the disease burden in animals. This includes the following examples.

Genus Plc has successfully used gene editing CD163 to produces pigs which are resistant to Porcine Reproductive and Respiratory Syndrome Virus ("PRRSv"). PRRSv cost the US pork industry an estimated $664 million per year. This translates into $1.8 million per day or $115 per sow annually. Losses in the breeding herd account for 45% ($302.06 million) and in the growing fattening phase are 55% ($361.85 million) of the total. The annual cost is $114.71 (85.74€) for every sow in the US breeding inventory and for every marketed pig PRRSV costs $4.67 (3.50€). At the European PRRSpective Symposium 2015 it was revealed that in Europe alone PRRS is now believed to be costing more than 1.5 billion euros per year. Inevitably the impact varies widely from one country to another in Europe, but in most cases the cost is estimated between 5 and 10 euros per marketed pig or 100 and 200 euros per sow per year.

Agrivida has entered into collaboration with Precision Bioscience to commercialise Precision's Directed Nuclease Editor™ (DNE) Technology in the area of animal nutrition. The companies plan to alter corn's nutritional characteristics for dairy and ruminant markets.

Researchers at The Roslin Institute in Edinburgh have used CRISPR to alter 3 genes in a pig making them resistant to African Swine Fever (ASF). Scientist have edited the RELA gene based on the knowledge that the ASF immune warthogs and bush pigs carry a different allele of the RELA gene from that found in domestic pigs (The University of Edinburgh, 2016). The National Science Foundation is funding research to create dairy cows that are resistant to sleeping sickness and which could then not act as a reservoir for the parasites to be passed on to humans.

Agriculture/Livestock

Animal applications of gene editing in the agricultural sector are also focussing around the development of livestock with improved food production characteristics.

Recombinetics are using TALENs based gene editing techniques to focus on the biomedical and agricultural markets. Recombinetics has the global exclusive global rights for the uses of TALENs in livestock. The applications currently been actively pursued by the company are as followed:

- Hornless dairy cattle. Recently with the help of TALENs and CRISPR/Cas9, the company tweaked the POLLED gene in cattle cells to make them hornless– preventing the need for the process of dehorning
- Modified DNA in pigs so as the yield more meat with lower food intake
- Pigs that don't have to be castrated – reportedly
- Livestock which is resistant to foot and mouth disease – reportedly
- Another prominent area that Recombinetics is working in is the development of animal models. For example, they are creating genetically edited pigs that could be used for the development of medical devices and drugs (Frost & Sullivan, 2015).

At the Shaanxi Provincial Engineering and Technology Research Center for Shaanbei Cashmere Goats, scientists have just created a new kind of goat, with bigger muscles and longer hair than normal (Larson, 2015). The aim is to use CRISPR to maximise the amount of meat and wool produced by each animal.

Scientists at Seoul National University are using TALENs to create double-muscled pigs through disruption of the myostatin gene (MSTN) that causes muscle cell proliferation. The resulting pigs have higher yield and leaner meat per animal but the changes also cause birthing issues (Cyranoski, 2015).

Human Health

There are a range of applications which use gene editing technologies to modify animals with the hopes of preventing vector borne diseases.

Professor George Church and colleagues at Harvard University and their associated spin out, eGenesis, are working on using CRISPR to develop organs for xenotransplantation. In their published early work, they have used the gene editing technique to eliminate the 62 copies of porcine endogenous retroviruses, dramatically reducing their transmission (Yang, et al., 2015).

Another group is using CRISPR to genetically edit mosquitoes to interrupt female reproduction in the malaria mosquito vector Anopheles gambiae, in order to lower the population such that it does not support malaria transmission (Hammond, et al., 2016).

Researchers in California announced they genetically edited a mosquito so that it could not carry the parasite that causes malaria (Vasich & McDonald, 2015). The mosquito was engineered to carry two DNA modifications. One is a set of genes that send out antibodies to the malarial parasite. Mosquitoes with these genes are resistant to the parasite and so cannot spread malaria. The other modification is a “gene drive” that should propel the malaria-resistance genes through a natural mosquito population. This gene edited mosquito has shown its capability to pass on these malarial resistance traits to close to 99% of its offspring. Scientists have already used CRISPR to modify mosquitoes and the fruit fly Drosophila melanogaster. And in combination with another molecular-biology technique called gene drive, they have found a way to massively increase the efficiency of spreading these transformations to offspring and through the population. Once introduced, these genetic changes are self-propagating (Lunshof, 2015).

Other animal applications

Further applications lie on more ethically questionable ground with gene editing technologies used to breed animals for the purposes of entertainment.

BGI in Shenzhen will soon sell genetically engineered micropigs. The pigs have been engineered using TALENs based technology to disable a growth hormone receptor gene. Whilst being marketed as a companion animal product, the pigs may also be useful as animal models for human disease since the cost of experimentation will be reduced.

The technology is equally applicable to other companion animals, including cats and dogs. Using gene editing technologies may achieve precisely in a short space of time, what is provided by conventional breeding over a matter of years. For example, researchers led by Nanjing University's Xiang Gao used the CRISPR/Cas9 genome editing approach to knock out myostatin in two beagle puppies, creating ones with twice the usual amount of muscle mass (Zou, et al., 2015). The researchers argue that dogs with more muscle with have increased running ability which would be useful for hunting and police applications. The researchers hope to expand into generating dog models for human disease. Other

groups are said to be moving towards commercialisation of gene-edited dogs for companion animals with altered size, intelligence or correct genetic illnesses.

THERAPEUTICS

The advent of research breakthroughs in DNA sequencing, the Human Genome Project and personalised medicine has established several important gene-based therapies. Two key technologies specifically are more advanced than programmable nuclease gene editing discoveries in the development process. These include *gene therapy*, which restores missing gene function by viral transgene expression; and *RNA interference (RNAi)* which mediates repression of defective genes by knocking out the target mRNA. Both have proved to be important steps in the development of gene-based therapies, and indeed for advances in other sectors such as agri-biotechnology and animal health, however as therapeutic applications they have crucial safety challenges and technology hurdles particularly with regards to efficient delivery to cell sites of action.

Gene editing relies on development of protein molecules capable of identifying specific regions of the genome, which will attach and cut in a specific region. It holds huge promise across a range of therapeutic applications. The low hanging fruit is thought to include genes with autosomal function such as autoimmune and blood disorders, cancers and other gene-based diseases. Monogenic diseases are generally regarded as simpler targets, and will likely make up the first to market therapies. Nonetheless, even monogenic diseases have heterogeneity in terms of variation in phenotype. Experts have warned that this may prove to complicate the use of the technology as a therapy. The area of key benefit is in large gene diseases, for example monogenes resulting in gain of function. Additionally, it holds huge promise for multiple allele diseases such as cystic fibrosis. The Gene therapy capabilities are limited primarily to smaller monogenic loss of function genes, although potentially some gain of function genes.

Programmable nucleases are demonstrated as efficient and precise methods for gene alteration across multiple cell and tissue types, making it a step improvement over the previous gene therapy technologies and an exciting platform for both *ex vivo* and *in vivo* applications. The advantage of generating DNA breaks at a specific target location on the genome has a distinct advantage over early, comparatively more random gene editing techniques such as transgenesis and homologous recombination.

The therapeutic application of gene editing technology as a market has not yet come into fruition; however the investment signs and early stage data are extremely promising. It is estimated that approx. $1billion of venture-capital financing was invested in emerging gene editing technologies during the period 2013 to 2015 (Boston Consulting Group (BCG), 2015). Whilst no company has received marketing approval or has fully developed and commercialised any therapeutic or agricultural product based on gene editing thus far, there are certainly key clinical trial milestones being met. In the UK, editing of human germ cells and embryos is highly regulated by the Human Fertilisation and Embryology Authority (HFEA). Currently it is prohibited for therapeutic purposes, and for research can only be undertaken on embryos of up to 14 days of age. The latter requires a specifically approved HFEA licence. The technologies discussed in this report refer only to the editing of somatic cells in a research or clinical context. This is overseen by the Human Tissue Authority (HTA) which regulates the matters relating to human bodies, organs and tissue for research and transplantation. The Medicines and Healthcare Products Regulatory Agency (MHRA) will be responsible for licensing of any clinical application of somatic cell therapies. These fall into the Advanced-therapy-medicinal-product scope.

A key consideration for the success of the technology as a therapeutic platform, will be defining the appropriate end points for clinical trials with the regulatory bodies. The current issue is that a broad, global agreement on what is acceptable has not yet been established. Furthermore there is a need to educate the public and investors that entering phase I or IIa in clinical trial with these candidates does not equate to a definite treatment.

The best indications of market size come from the analysis of the gene therapy market more broadly. According to Boston Consulting Group, among the approx. 500 gene therapy clinical trials approved since 2010, only a small number are using nuclease based gene editing. A recent 2015 study indicates that the global gene therapy market could become a multimillion dollar industry by the end of 2020. Nonetheless it currently has very few marketed products, and there are clinical milestones and regulatory hurdles to overcome. As such the market is currently characterised by research grants, venture investment, government investment and pharmaceutical collaboration investment. The gene therapy market is dominated by therapeutic areas such as oncology, monogenic diseases, and some cardiovascular, infectious disease, diseases affecting the eyes and neurological disease (Research and Markets, 2015). Experts indicate that the future therapy landscape will not be gene therapy or gene editing, but rather gene therapy and gene editing.

INDUSTRY APPLICATIONS

The four classes of programmable nucleases for gene editing has begun to be thought of in categories. The first generation discoveries encompass the meganucleases and the ZFPs. The companies focussing on the development of these therapeutic candidates are generally more established. The second generation nuclease technologies include TALENS and more recently still, CRISPR. Whilst the latter are younger and less well developed, they have made it possible to edit genes in a significantly shorter time period, compared to the months and years of the earlier first generation ZNF and meganucleases. The strength of the CRISPR design is in the use of an RNA molecule for DNA binding, rather than a protein with the RNA an easier structure to design and manipulate than proteins. As such gene editing techniques are now becoming routine in research for the production of cellular and animal models. The technique is showing promising signs of streamlining biological drug research and manufacture in cellular vectors and increasingly showing exciting data in commercial therapeutic experiments and clinical trials.

Ex vivo

Ex vivo approaches involve the removal of cells from the patient to carry out editing in culture conditions before being returned to the patient in a revised form. Delivery has been successful via both electroporation of mRNA encoding the nucleases and RNA or by direct delivery of the purified forms; as well as fusion to cell-penetrating peptides.

Sangamo Biosciences have the most advanced candidate, a ZFN based therapy in phase II trials, where patients' T-cells are collected and the CCR5 gene deleted, as this receptor is needed for HIV to result in infection. Another landmark for human gene editing has been the application of a TALENS nuclease for an ex vivo approach to treatment of leukaemia. Cellectis, along with Great Ormond Street Hospital and UCL Institute of Child Health were granted a special permissions clinical trial in a single patient, refractory to current therapies in the summer of 2015. The treatment focused firstly on modifying donor T-cells against immune rejection by the patient, and subsequently to protect the cells from the anti-cancer drugs with which the patient was being treated.

In the past two years, the hype surrounding the immune-oncology field has been growing. Large players such as Juno Therapeutics and Kite Pharma, who are undergoing CAR-T programs, have invested in partnerships with nuclease-based gene editing companies to combine the technologies with CAR-T cell development approaches (Boglioli & Richard, 2015).

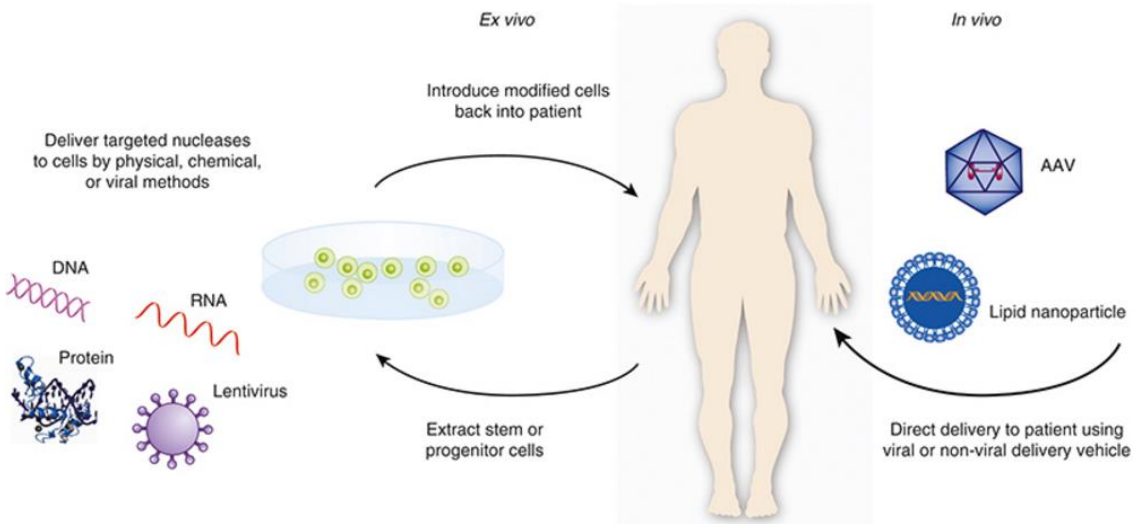
In Vivo

In vivo approaches involve packaging the nuclease for gene editing within a delivery vehicle which is administered directly into the patient. For many genetic-based diseases, the genome needs to be edited in situ, for example if the affected cells are within an organ or tissue type which is more difficult to remove than blood. Arguably the most challenging technology hurdle, as with gene therapy, is this issue of delivery to target tissue. This includes not only successful entry into the cell cytoplasm itself, which can reject exogenous DNA, but to the cell nucleus where the DNA can have an effect. This dual delivery question, around evading defence mechanisms within and outside of the appropriate cells is a complex one. The figure below illustrates the ex vivo and in vivo strategies for genome editing, including delivery vehicles.

Studies are in early stages, but Sangamo Biosciences has reported promising data in monkeys for editing of the factor-IX gene for treatment for haemophilia B. Clinical trials were approved in September 2015 by the US National Institutes of Health. Sangamo also plans to apply for permission to do additional in vivo gene editing trials, including of therapies for the blood diseases haemoglobinopathy and ß-thalassaemia.

Editas Medical is advancing another in vivo approach for the treatment of Leber congenital amaurosis, a form of blindness. Using the CRISPR/Cas9 gene-editing system, the candidate is injected directly into the eyes of patients. The company announced at the end of 2016, that data are promising and plans for a 2017 clinical trial are underway.

Viral vectors are commonly used as delivery vehicles, partly for efficient delivery with minimal toxicity. Adeno-associated virus (AAV) vectors have demonstrated some success for delivery to the liver, eye, nervous system and skeletal and cardiac muscle; both in pre-clinical models and clinical trials (Maeder & Gersbach, 2016). The delivery of smaller nucleases by AAV has proven more successful than for example larger TALENs. Trans-splicing vectors have been investigated, although on the whole are less efficient than single packaged vectors. Lipid nanoparticles have also been tried, however there are ongoing concerns around lipid accumulation in the cell and off target cell uptake resulting in potential toxicity.



Ex vivo and In vivo strategies for genome editing (Maeder & Gersbach, 2016)

The conclusion drawn by several experts indicates that delivery will likely be solved by a toolbox of delivery systems. Largely speaking delivery to the Liver is more commonly successful, and future efforts will be focused on muscle or skeletal tissue.

Cell models – Target Validation

Nuclease based gene editing has proven to be an effective tool in research as a cost effective, fast and relatively simple method for conducting genetic experiments. Genes can be quickly modified to understand their function and cellular or animal models can be generated for preclinical research. This has a promising impact for the drug discovery process.

The recent CRISPR/Cas9 advancements in particular are a stepwise improvement to speed and efficiency. Biogen Idec is using the technology to study amyotrophic lateral sclerosis (Lou Gehrig's disease), which is notoriously difficult to study due to a lack of good animal disease models. Similarly academia have adopted the technology for laboratory research, shortening disease model development from almost 1 year to a couple of months.

US-based Sage Labs produces models for gene editing with applications for preclinical research. The company was acquired at growth stage by Horizon Discovery for £29m in October 2014. Horizon Discovery Group is the leading life science research tool supplier engaged in genomics R&D and the development of personalised medicine. The company supplies a portfolio of genetically defined cell lines, reporter gene assay kits, genomic reference standards and contract research services to organisations involved with biopharmaceutical process optimisation, drug discovery and development, and clinical diagnostics development.

Bioproduction

Research is underway to engineer improved characteristics of cells used for the production of biologic products. Bioproduction is the use of modified organisms or host cells as living factories to produce these therapeutic proteins. Gene editing can be used to increase the yield of therapeutic proteins produced by cell lines. This can simplify manufacturing and decrease costs.

Cells used for such bioproduction include Chinese Hamster Ovary (CHO) cells, and recent research by The University of Manchester has identified critical metabolic check points that control CHO cell growth, as well as the characterised pathways controlling product integrity and yield. Innovate UK awarded a £1.23m grant for a collaboration between the University of Manchester, Horizon Discovery and The Centre for Process Innovation (CPI) to deliver multiple and combinatorial gene edits in CHO cells to produce cells that deliver efficiency and cost gains in the manufacturing process for biotherapeutic products. Where improvements can be made, they will need to be successfully assessed in fermenters before scale up to manufacture ready processes to ensure the improvements are translatable into the manufacturing setting.

DEALS

A combination of internet-based searching and deal information from subscription databases was used to collate information on collaborations, licensing deals and acquisitions in the gene editing industry. The deals were further categorised industry sector, gene editing technology and year of completion in order to analyse the data. Details of the identified deals can be found in the Appendix.

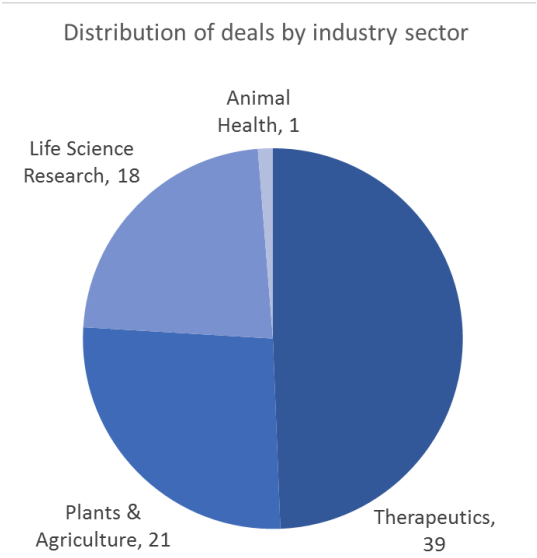
There are multiple deals; venture, licensing and collaborations ongoing between the gene editing biotechnology companies and larger pharmaceutical companies. AstraZeneca is has been involved in

several collaborations with Innovative Genomics Institute, The Broad Institute, The Wellcome Trust Sanger Institute and Thermo Fisher Scientific Inc. and launched an integrated genomics initiative in April 2016 with its global biologics research and development arm, MedImmune (AstraZeneca, 2016). A few other big pharma companies are also active around the CRISPR genome editing space including Novartis and Pfizer (pharmaphorum, 2015). The focus for pharma companies has been on monogenic genetic diseases and this is expected to continue until the technology has been proven.

The deal rate in the sector is picking up pace and since 2014 several of the immune-oncology, CAR-T cell companies such as Juno Therapeutics, Kite Pharma and Novartis are building partnerships with gene editing specialists to utilise nuclease gene editing to engineer CAR-T cells by silencing proteins that activate immune response. The approach has the potential to lead to allogenic CAR-T cell therapies, by creation of a T-cell bank rather than an autologous patient-specific approach. Over the course of 2015, the CRISPR-based companies Editas Medical and CRISPR Technologies have attracted impressive investment sums from elite early-stage venture capital.

For the biotechnology companies themselves, the original, core intellectual property is largely licensed from one of the large academic institutions operating in the gene editing space such as Harvard University and the University of California.

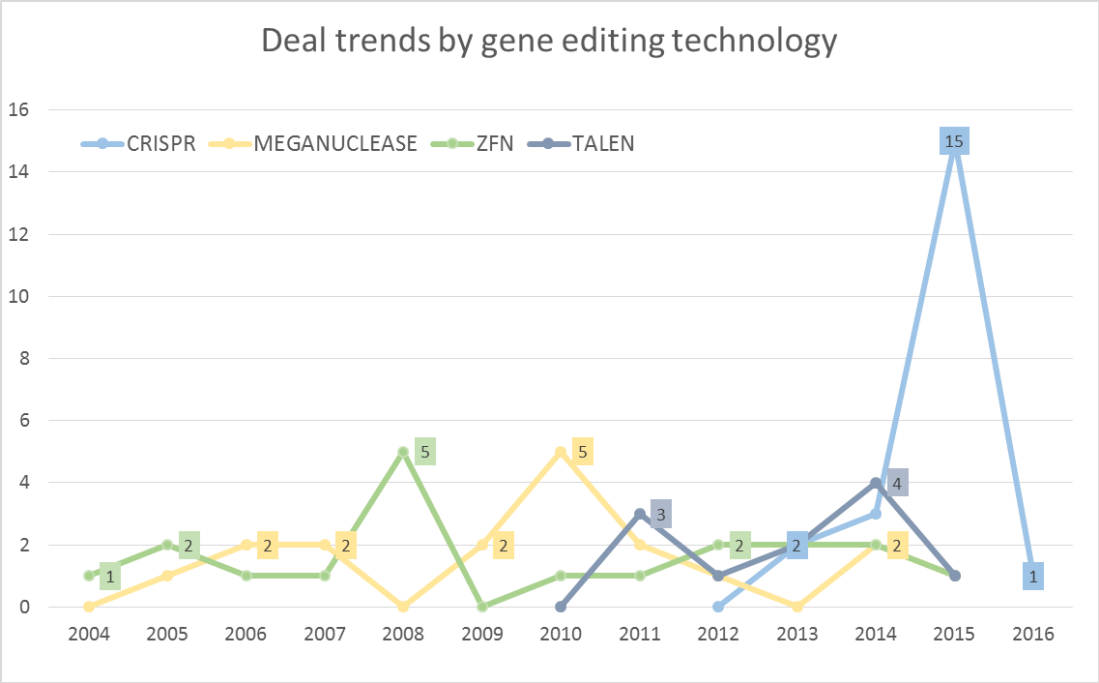
The chart below shows the number of deals in each industry sector. It is clear that the animal health gene editing industry has very little deal activity compared to the other industries. The majority of deals are related to the therapeutics industry while the life science research and plants and agriculture industries have seen less than half the number of deals.



The number of deals in for each gene editing technology are not significantly different though TALEN definitely have the smallest number. The data was analysed further in order to observe how the number of deals in different technology areas changed over the last 10 years. The chart below shows that the CRISPR has had the greatest amount of deals in the shortest period of time. Peaks can be seen for ZFN, Meganucleases and TALEN in 2008, 2010 and 2014 respectively.

From a commercialisation standpoint, experts remain optimistic that good clinical results will push innovation in the manufacturing chain. Indeed in June 2016, Lonza and bluebird bio Inc entered into a strategic manufacturing agreement for two of bluebird bio's candidate therapies. This establishes Lonza as one of the leaders in viral gene and cell therapy manufacturing, an area they are evolving to

service. Despite the deal making excitement, a broad question alongside regulatory standardisation and end point establishment, is around how the current healthcare infrastructure will absorb the costs required to develop these more complex gene and cell therapy based treatments. Particularly in relation to rare diseases, which have potential to be cured by this technology but may not be commercially viable. Work around new models for commercialisation and reimbursement will be critical going forward with the use of these novel technologies in healthcare.



KEY PLAYERS

For the purposes of this white paper, the key players have been compared by following factors which give an indication of the strengths of the companies as well as their strategies:

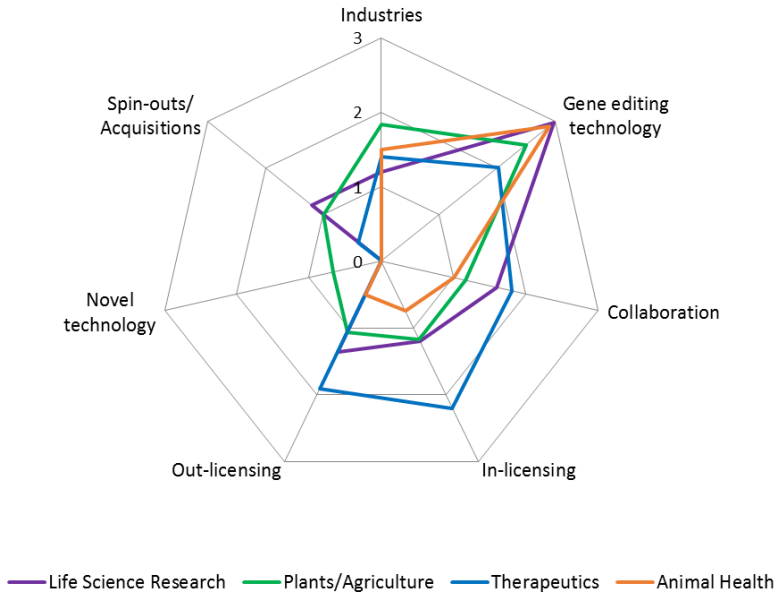
- Number of industry sectors they operate in
- Number of gene editing technologies they specialise in
- Number of collaborations
- Number of in-licenses
- Number of out-licenses
- Number of novel gene editing technologies outside of the main four
- Number of spin-outs or acquisitions

The scores are based on the number of deals, industries or technologies and span from 0 to 5 for each of the factors. The charts for each key player are included in their individual sections.

The average scores of the key players in each industry sector have been plotted on the radial chart below. It can be seen that companies in all three sectors own or commercialise more than one gene editing technology. From the chart it appears that the animal health sector has key players which are

active in the most number of gene editing technologies however, the data is based on two companies at this stage and is less likely to represent the sector as a whole.

Organisations in the plant and agriculture sector are the only ones developing novel technologies at this stage. They also operate in more industry sectors than key players in life science research and therapeutics which means that licensing activity in the sector may increase in the future. Both in and out licensing activity is the lowest in the animal health sector and the highest in the therapeutics sector which lends itself to collaborations and licensing deals given the need for the most cutting edge technology.



LIFE SCIENCE RESEARCH

For life science research tools, key players either offer an improved or branded version of the gene editing technologies as a research tool, and offering products and services around these platform technologies, or are using the technology to create other research tools such as animal models, cell models or cell lines.

Most of these are specialist life science tools companies; however, the list also includes companies from other life science areas. Several companies who were already offering research tools have adopted new gene editing technologies to improve their value propositions. Some new companies have also appeared that are built on the IP of gene editing technologies, and have started offering similar products and services as a way to bring in revenues for their primary applications. Five of the most prominent companies are described here:

- Caribou Biosciences
- Horizon Discovery
- Sigma-Aldrich
- Thermo Fisher Life Sciences
- ToolGen

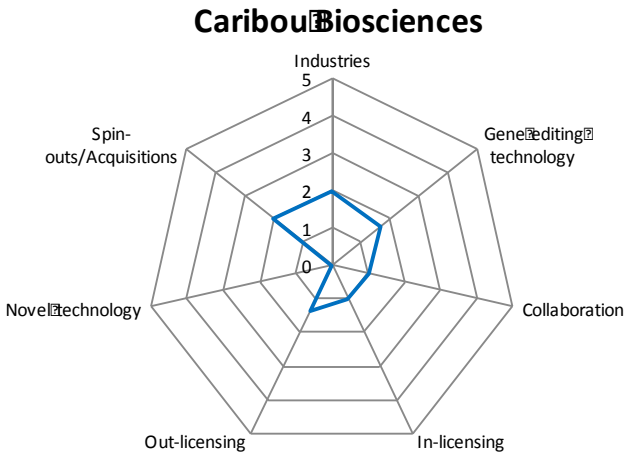
CARIBOU BIOSCIENCES

Caribou Biosciences was founded by scientists from the University of California, Berkeley in 2011 to drive the commercialization of applications based on the nucleic acid modification capabilities found in prokaryotic CRISPR systems. Through its early work and its initial partnerships, Caribou has been a pioneer in the rapidly emerging field of CRISPR-Cas gene editing and has relationships with companies in multiple market sectors. Caribou's aim is to drive the creation and adoption of innovative new medical therapies and bio-based products.

The company offers a broad range of CRISPR gene editing products and services for editing cell models and it recently raised $11 million in a Series A financing round to advance its CRISPR-Cas9 technology platform across the broad spectrum of commercial applications. The platform enables simple, flexible targeting of any site in a genome with applications in human and animal therapeutics, new disease models, genomics, bioproduction cell lines and fermentation strains, functional genomic screens and plants with enhanced traits.

Caribou recently announced a collaboration agreement with Novartis Institutes for Biomedical Research under which the two companies will utilize Caribou's proprietary CRISPR-Cas9 platform to research new CRISPR-based drug target screening and validation technologies. In 2014, Caribou co-founded Intellia Therapeutics, which is utilizing Caribou's technology platform in the discovery, development and commercialization of human gene and cell therapies.

In May 2016 Caribou announced an exclusive partnership with Genus plc, a global pioneer in animal genetics. This involves a multi-year strategic collaboration where Genus receives a worldwide, exclusive license to Caribou's CRISPR-Cas9 platform in certain livestock species.



The chart above suggests that Caribou Biosciences is out-licensing technology more than in-licensing and though it offers products and services in more than one industry, the number of collaborations it is involved in is quite low. It is also primarily focused on one gene editing technology.

HORIZON DISCOVERY

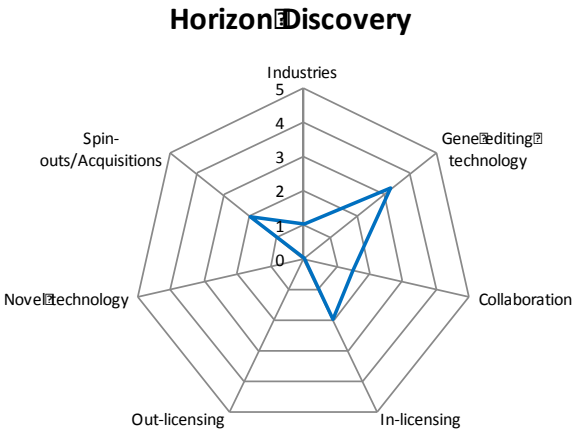
Horizon Discovery Group plc is a UK biotechnology company founded in 2005 that provides products and services to support research into human genetic profiles in health and disease as well as the development of targeted therapeutics, with an emphasis on oncology. Horizon have adopted CRISPR

and ZFN technologies across their range of products and services which include cell lines, in vivo models and research services including functional genomics screening. They supply these products and services to biotechnology, diagnostic and pharmaceutical companies, and academic research institutes.

Using their proprietary genome-editing platform GENESIS, Horizon has created over 500 isogenic X-MAN cell lines. These cell lines are currently being used worldwide in academic and industry settings to understand the effects that individual or compound genetic mutations have on drug activity, patient responsiveness, and resistance, allowing tailoring of new treatments towards specific disease biomarkers and in the design of smaller, faster and more risk-free clinical trials by enabling pre-selection of patients most likely to respond.

Horizon entered into two major collaborations in 2014 with Sigma-Aldrich and Harvard University which allowed them to incorporate the gene editing technologies of the two organisations into their GENESIS platform. The technology licensed from Sigma is a ZFN knockout technology whilst the technology licensed from Harvard is their patented CRISPR RNA-guided gene editing system. The licensed technologies complement their Horizon's recombinant adeno-associated virus (rAAV) genome editing technology which is also incorporate in to the platform.

Horizon's Scientific Advisory Board now includes CRISPR experts Dr. Emmanuelle Charpentier, Dr. J. Keith Joung, and Dr. Feng Zhang (the owner of the patented technology). They also acquired Sage Labs in 2014 which further strengthened their IP portfolio in CRISPR with exclusive rights for in vivo ZFN applications (Horizon Discovery, 2014).



Horizon Discovery specialises in one industry however, it incorporates multiple gene editing technologies. Though it does not appear to licensing out its technology, Horizon may be growing its technology portfolio through in-licensing and acquisition.

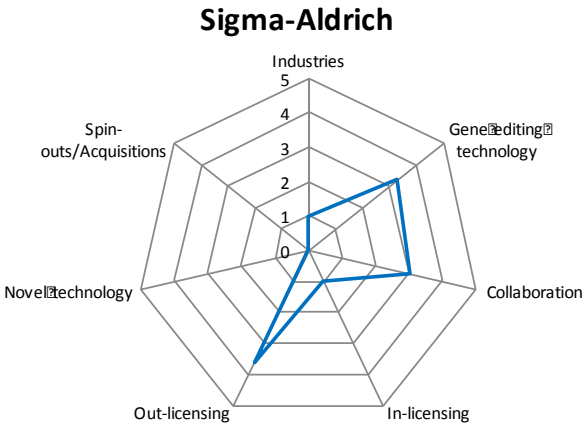
SIGMA-ALDRICH

Sigma-Aldrich Corporation is an American multinational life science and high technology company that was acquired by the German company Merck in 2015. Sigma-Aldrich is the market leader in ZFN gene editing research tools and services and has a licence for their ZFN technology which is subject to 19 patent families controlled by Sangamo BioSciences Inc. Their ZFN technology, CompoZr®, includes two products: Targeted Integration Kits and Knockout ZFNs. The Targeted Integration Kits are designed to rapidly integrate a user-specified gene of interest (GOI) into preferred sites of integration in either the

human, mouse or rat genome. In contrast, the Knockout ZFNs to permanently knockout any human, mouse or rat gene in a quick, simple and target specific manner. They also have a Custom ZFN Service which provides researchers with a functionally validated pair of ZFNs that have been custom designed and assembled to edit a target gene in a highly specific manner. The ZFNs can be used to create stable genetically engineered cell lines or organisms with gene deletions, gene integrations and gene modifications.

Sigma also has a new range of products and services for CRISPR research tools including lentiviral particles, plasmids and paired nickases. These can all be ordered through the Sigma CRISPR Online Design Tool which allows users to browse and select unique, pre-designed CRISPR targets for the coding regions of the human, mouse, and rat genomes.

Sigma has a range of collaborative partners in gene editing including Broad Institute, Sangamo Biosciences, Horizon Discovery, Cellular Dynamics, Cyprotex and Plasticell.



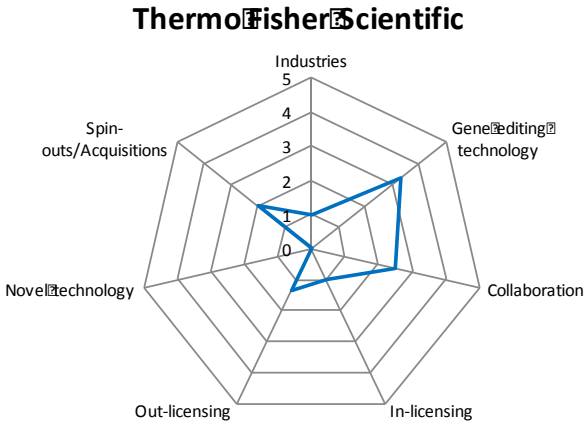
Sigma-Aldrich appears to be a key licensor in the gene editing field with a high level of collaboration and multiple proprietary gene editing technologies in its portfolio. The level of out-licensing suggests that the company is well-established in one industry and is focussing its commercialisation and R&D in that industry whilst licensing out rights to its technology in other industry areas.

THERMO FISHER SCIENTIFIC

Thermo Fisher Scientific is an American multinational with an established life science research tools arm. In April 2013, they acquired Life Technologies Corp for $13.6 billion in a deal that would rank the firm as one of the leading companies in the genetic testing and precision laboratory equipment markets.

They offer a broad range of CRISPR and TALENs solutions to create modified genes, expression systems, and stable cell lines for research. Their products and services including GeneArt CRISPR engineered cell lines/models, GeneArt TALs and CRISPR products and services, genome editing detection and analysis tools, GeneArt CRISPR search and design tool and CRISPR delivery tools.

The Thermo Fisher Scientific TALENs technology intellectual property portfolio includes foundational IP originating from the University of Minnesota, Iowa State University, and Martin-Luther-Universitat Halle-Wittenberg, as well as IP originating from Thermo Fisher Scientific, Cellectis AS, and others. They also have a worldwide license from ToolGen for technology related to their GeneArt platform as well as a more recent license for ToolGen's CRISPR/Cas9 technology.



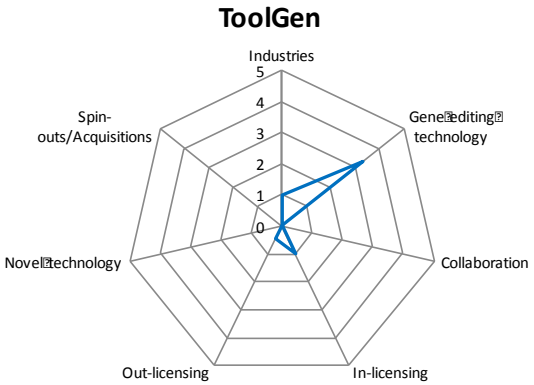
The chart above shows that Thermo Fisher has multiple gene editing technologies and appear to be more focussed on collaboration than on licensing.

TOOLGEN

Founded in 1999, the Korean company ToolGen holds intellectual property rights for essential tools and technologies genome editing technology for editing the genetic information in microbial, plant, animal and human cells. They offer CRISPR/Cas9 services along with a platform which assesses the functionality of gene editing technologies and also owns older patents for ZFN technology.

The Director of ToolGen's Research Center, Seokjoong Kim, says that the company's IP contain important core claims for the use of CRISPR technology for gene editing but also includes a number of unique features such as the ways to modify the RNA for specificity and being the first to show that the CRISPR/Cas system can be used in vivo and in vitro in enzyme form instead of the expression of the CRISPR/Cas9 system in cell.

In 2015, ToolGen granted Thermo Fisher Scientific a worldwide license for research applications including the development and sale of reagents, cell lines, and animal models, as well as rights for high throughput screening, diagnostics, and bioproduction (Thermo Fisher Scientific, 2015).



The chart above suggests that ToolGen is has its own proprietary technologies in multiple gene editing technology fields. At this stage, the company also appears to be less active in licensing and collaboration than other key players.

OTHER COMPANIES

Cellular Dynamics Inc also provides tools for cell models based on TALEN and ZFN technologies. GE Healthcare and ATCC are also worth a mention as they provide CRISPR tools for editing cell lines along with Plasticell that specialise in ZFN tools.

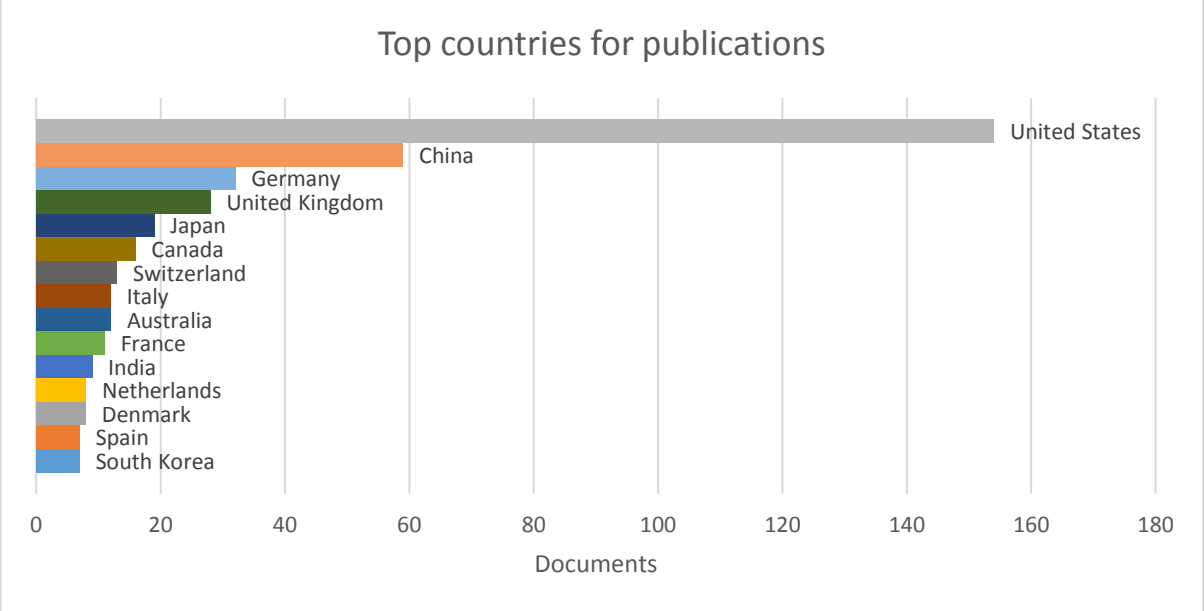
University of Minnesota start-up, B-MoGen Biotechnologies, is a genome editing company that was set up to commercialise proprietary molecular tools used for cutting-edge methods for gene editing and delivery, in the search for novel cancer biomarkers and therapeutics.

RESEARCH LANDSCAPE

To give an indication of the academic institutions contributing to the field, a broad search of academic publications was carried out.

A search of the abstract, title and keywords for (gene* editing) and (research tool*) identified 421 document results, including both peer-reviewed research articles and topic reviews. Sorting the document dataset by affiliation gives a rough indication of the top publishing organisations. The industry is dominated by US and European countries and this is reflected in the results:

All of the top 15 publishing organisations are public sector academic and medical institutions, including universities, hospitals and research institutions. The dataset can also be analysed for top publishing countries, and given that the US-based top institutions are some of the pioneers in gene editing technology it is unsurprising that the top publishing country by a large margin is the USA. The top 15 countries by publishing territory are summarised as follows:



PLANTS AND AGRICULTURE

The agricultural genome editing market is composed of a diverse set of companies, varying in both size and technology platforms. Agricultural biotechnology companies, seed companies, genome editing firms and academic institutes are collaborating to utilise and improve the existing genome editing technologies.

Most of the key players in the field are small private companies with proprietary technologies around which they have been able to build a patent estate. Characteristic examples include Cibus, Caribou Biosciences, Calyxt and Precision Biosciences. All of these firms have developed their own proprietary technology with applications in agriculture.

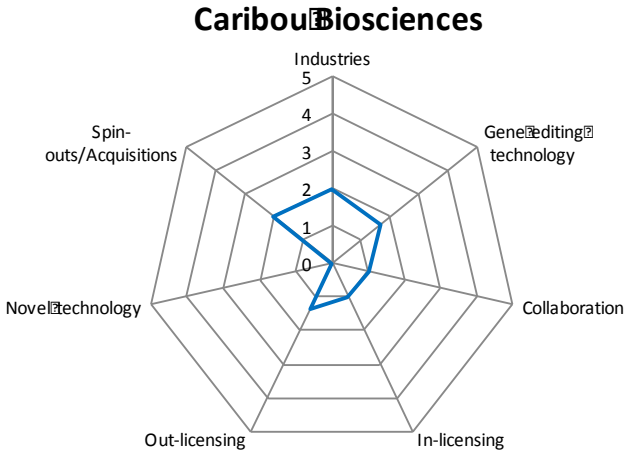
Nevertheless, agricultural biotech giants like Bayer CropScience, BASF, Dow Chemical, DuPont, Monsanto and Syngenta, are actively engaged in strategic alliances to acquire gene editing technologies, mostly through licensing, and to increase their seed development and crop protection capabilities. Indeed these multinational companies play a crucial role by providing, funding, expertise and access to the market. Six of the most prominent key players are described here:

- Caribou Biosciences
- Calyxt
- Cibus
- Dow AgroSciences
- DuPont
- Precision Biosciences

CARIBOU BIOSCIENCES

In addition to being a key player in the gene editing life science research industry, Caribou's proprietary platform has applications that range from human and animal therapeutics, to industrial biotechnology and fermentation. In agriculture, they aim for accelerated precision breeding and generation of new traits such as drought tolerance and disease resistance.

In 2015, the company formed a strategic alliance with DuPont to advance the two companies' respective CRISPR-derived genome editing technology platforms. The multi-faceted agreement includes the cross-licensing of key intellectual property, a research collaboration, and financial investments by DuPont in Caribou (Caribou Biosciences, 2015).



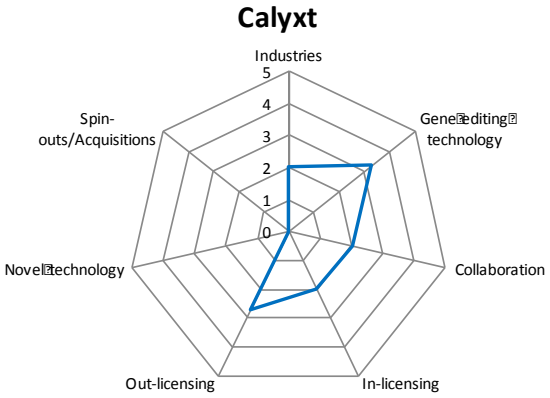
As in the previous section, the chart suggests that Caribou Biosciences is out-licensing technology more than in-licensing and though it offers products and services in more than one industry, the number of collaborations it is involved in is quite low. It is also primarily focused on one gene editing technology.

CALYXT

Founded in 2010, Calyxt, Inc. (previously Cellectis Plant Sciences, Inc.), the plant genome engineering company and subsidiary of Cellectis SA, uses genome editing techniques to develop a novel generation of crops with higher health benefits for the consumers. Their products include: high-oleic/low trans-fat soybean oil, cold-storable potato, gluten reduced wheat and low saturated fat canola oil.

The company uses Meganucleases and TALEN technologies and have collaborated with a number of agriculture companies including Bayer CropScience, SES VanderHave, Limagrain and S&W Seed Company.

The chart on the following page indicates that Calyxt is a quite active in licensing and collaboration for several gene editing technologies. It also appears to be connected to more than one industry.

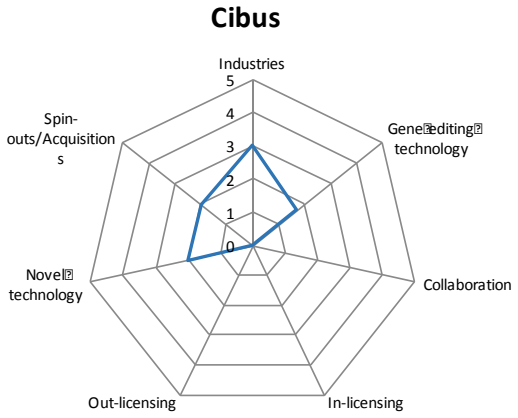


CIBUS

Founded in 2001, Cibus is a leading precision gene editing company with a unique, patented technology for naturally modifying cell functions. The company has over 300 patents and patent applications.

Their proprietary technology (Rapid Trait Development System-RTDS™) is used for non-transgenic breeding for a number of crops. The company currently markets SU Canola™, a non-transgenic canola tolerant to sulfonylurea herbicides in the U.S. that has also received regulatory approval in Canada. They have a worldwide presence, with subsidiaries in both Europe and North America, including Nucelis, its bio-industrials division. While primarily invested in agricultural gene editing, Nucelis applies Cibus' RTDS platform to the production of squalane oil.

The North American regulatory bodies consider RTDS to be a natural form of mutagenesis and as such excluded from the GMO approval process. Cibus is currently working on the development of additional crops, including herbicide-tolerant rice, a potato crop resistant to late blight and glyphosate tolerant Flax.

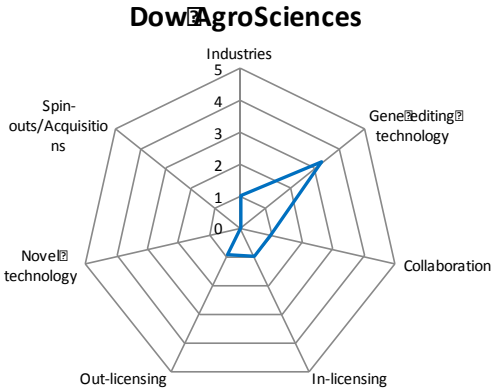


The chart for Cibus is quite different from those of the other key players. They appear to have no licensing or collaboration activity but appear to focus on building their position in the market through novel technology and acquisition. The chart also suggests a diversity in strategy as it active in multiple industries.

DOW AGROSCIENCES

Dow AgroSciences LLC, a wholly owned subsidiary of The Dow Chemical Company, has the exclusive right to use Sangamo's ZFP technology in plants and is marketing ZFP-derived plant products under the trademark EXZACT™ Precision Technology. The Sangamo technology is based on ZFN gene editing.

In August 2015, Dow entered into a collaboration agreement with the Institute of Crop Sciences of the Chinese Academy of Agricultural Sciences (ICS-CAAS). Under the agreement, Dow AgroSciences grants ICS-CAAS a royalty-free, non-transferable research and commercialization license for its proprietary EXZACT™ Precision Genome Editing Technology to be used in rice in China. Dow AgroSciences and ICS-CAAS scientists will collaboratively develop an industry-leading rice genome editing technology platform. This is part of Dow AgroSciences' commitment to providing innovative and sustainable solutions to bolster food security and food safety in China.



The chart for Dow Agrosciences suggests that the company has several different gene editing technologies, both proprietary and through a small amount of in-licensing activity. It appears to be focussed on one industry sector with some collaboration however the level of collaboration appears to be less than that of the majority of key players.

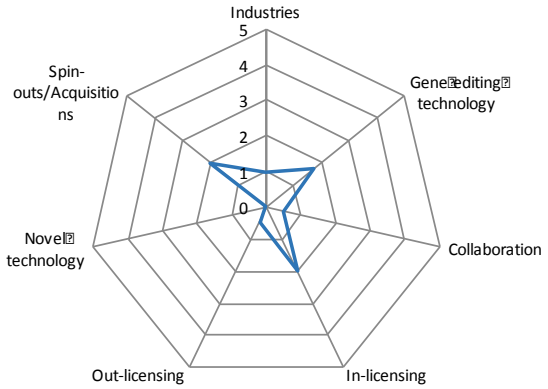
DUPONT PIONEER

DuPont is a world-class science and engineering company. Their products cover agriculture, food & personal care, chemicals, polymers & fibres and industrial biotechnology. In 1999, DuPont acquired crop chemicals and biotech seed business, Pioneer Hi-Bred which is now a part of DuPont's agriculture unit under the name DuPont Pioneer.

The company has acquired an exclusive license for genome-editing technology from Vilnius University, and recently received exclusive intellectual property rights from Caribou Biosciences for CRISPR-Cas technology applications in major row crops, and non-exclusive rights in other agricultural and industrial bioscience applications. DuPont have also invested in Caribou Biosciences.

In October 2015, the company announced that it is already growing corn and wheat plants edited with CRISPR in greenhouses and that field trials will start next spring (Regalado, 2015).

DuPont Pioneer



DuPont is a specialised company with regard to both industry and gene editing technologies. The company has in-licensed some technologies but it does not appear to be particularly involved with many third parties either through out-licensing or collaboration. On the other hand they do appear to be making strategic investments or acquisitions to grow their share of the market.

PRECISION BIOSCIENCES

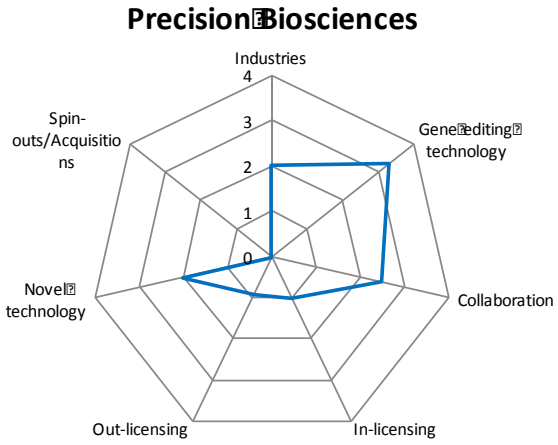
Precision Biosciences is a gene editing firm that aims at developing products for the therapeutics and agriculture industries. The company was founded in 2006 based on technology licensed from Duke University. The company developed a gene-editing technology that can modify genes in the cells of mammals or plant cells. This Directed Nuclease Editor technology (DNE) is based on meganuclease gene editing technology. Since 2000, Precision Biosciences filed an infringement lawsuit against Cellectis over its DNE patents though most of that litigation is now settled.

Their latest proprietary genome editing platform, Arcus, is protected by its own patented R&D, unlike other genome-editing technologies based on intellectual property from third parties (similar to Cibus' RTDS platform). The way Arcus targets genes offers more precision and flexibility compared with CRISPR and TALEN. This combination of flexibility with high site specificity and has been proven to efficiently edit the genes of mammalian and plant cells.

So far the company's strategy is to team up with other companies to develop the products of its partner. Disclosed partners include Ag-Bio startup Agrivida, which is using Precision Bio's DNE technology to improve dairy and beef nutrition and Nova Synthetix which is using the DNE technology to develop ricin-free castor plants. More recently, Syngenta has used Arcus technology to insert "genes of interest" into particular locations of the corn genome (Vinluan, 2015).

Besides uses in therapeutics and agriculture, the company says the technology could have applications in energy, as well as industrial materials.

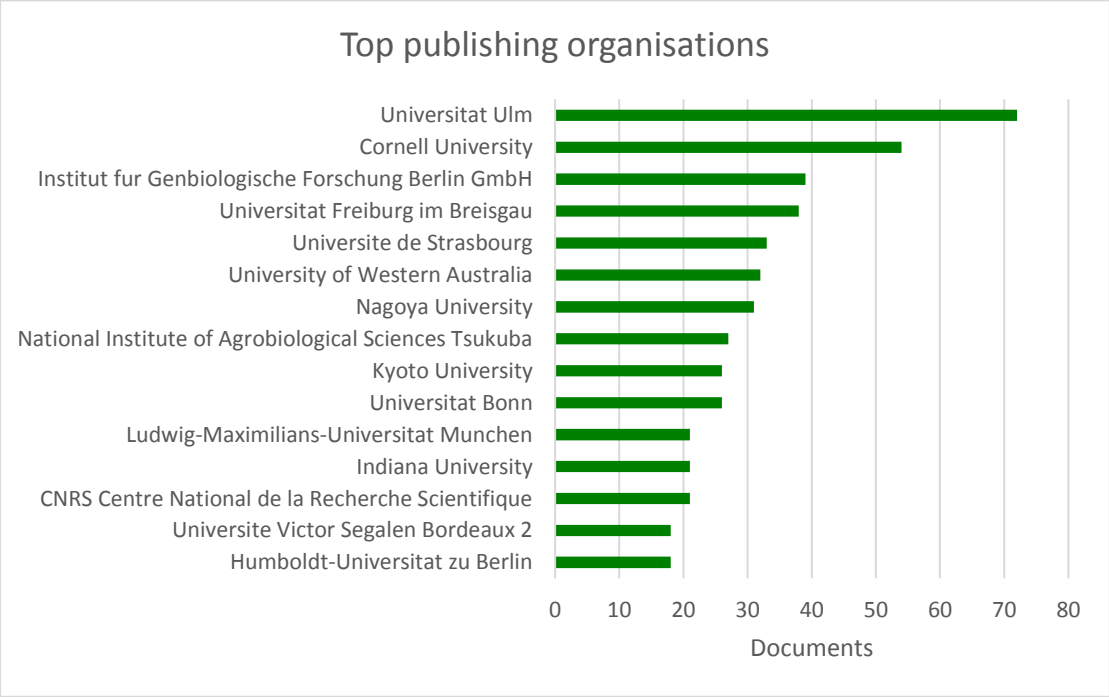
Though there are few licensing deals and no known acquisitions or spin-outs at this stage, Precision Biosciences scores highly for multiple factors. These include the number of collaborations, the number of gene editing technologies and the number of industries in which it is active. Aside from Cibus, it is also the only other company that has developed its own novel gene editing technology.



RESEARCH LANDSCAPE

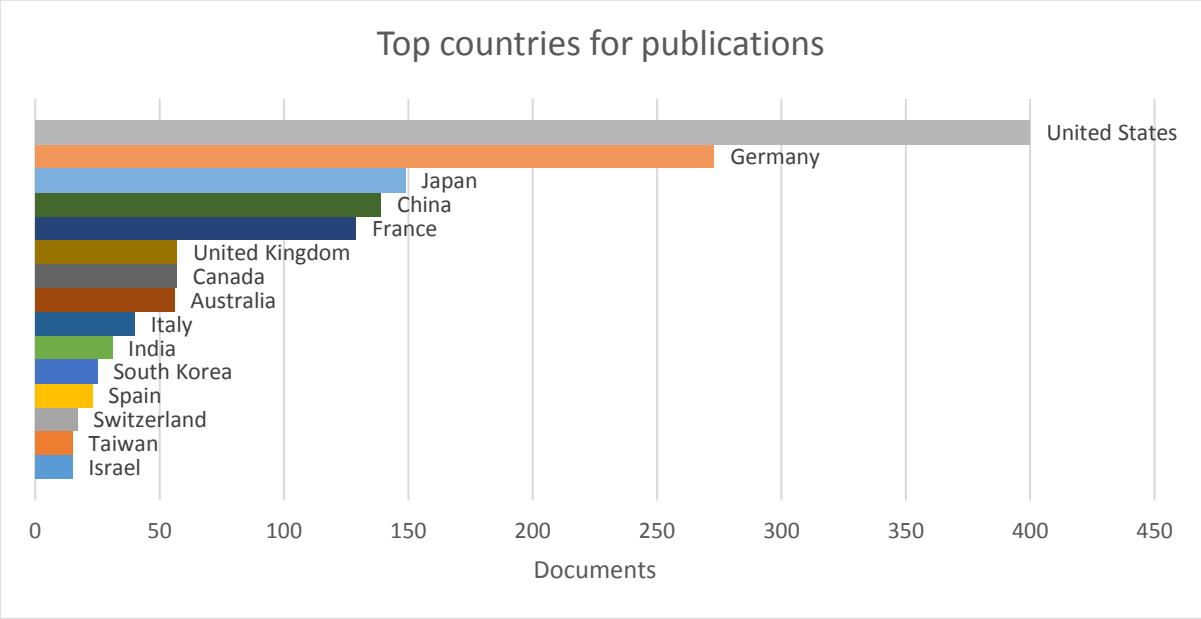
To give an indication of the academic institutions contributing to the field, a broad search of academic publications was carried out.

A search of the abstract, title and keywords for (gene* editing) and (plant* OR agricultur*) identified 1,341 document results, including both peer-reviewed research articles and topic reviews. Sorting the document dataset by affiliation gives a rough indication of the top publishing organisations. The industry is dominated by US and European countries and this is reflected in the results with a significant number of German organisations on the list:



All of the top 15 publishing organisations are public sector academic and medical institutions, including universities, hospitals and research institutions. The dataset can also be analysed for top publishing countries, and given that the US-based top institutions are some of the pioneers in gene editing

technology it is unsurprising that the top publishing country by a large margin is the USA while Germany comes up second. The top 15 countries by publishing territory are summarised as follows:



ANIMALS

To date there are not many major players specifically in the gene editing in the animal sector. The following two companies have successful early-stage technologies; however, they have yet to be commercialised:

- Recombinetics Inc
- Genus Plc

GENUS PLC

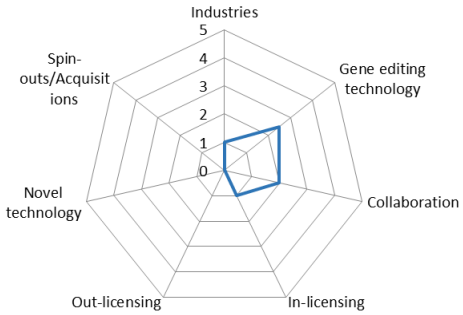
Founded in 1933, Genus plc is a British-based business selling products manufactured using biotechnology to cattle and pig farmers. In 2015, it had worked with the University of Missouri to develop pigs resistant to Porcine Reproductive and Respiratory Syndrome Virus (PRRSv). By using precise gene editing, the team from the University of Missouri was able to breed pigs that do not produce a specific protein necessary for the virus to spread in the animals.

The virus is fatal and costs farmers hundreds of millions of dollars a year which means the development of these resistant pigs is a potential game-changer for the pork industry (Hirschler, 2015).

Genus Chief Scientific Officer Jonathan Lightner said that the work on gene-edited pigs is still at an early stage and said there were several critical challenges ahead to fully develop and commercialize the technology.

In May 2016 the company announced an exclusive partnership with Caribou Biosciences. This involves a multi-year strategic collaboration where Genus receives a worldwide, exclusive license to Caribou's CRISPR-Cas9 platform in certain livestock species. The deal marks a major step forward for the commercial application of gene editing in animals and places Genus at the forefront of the industry for applications of this technology.

Genus



The chart for Genus Plc suggests very little licensing activity and a moderate level of collaboration. The key strength factor for the company appears to be the fact that it commercialises or offers more than one gene editing technology.

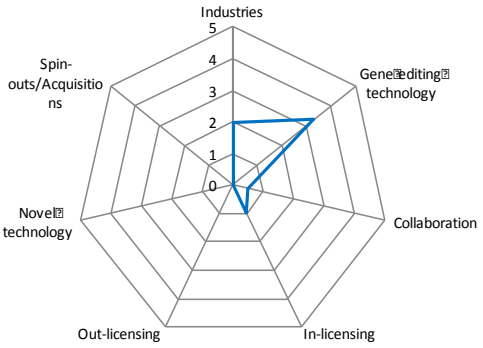
RECOMBINETICS INC

Founded in 2008, Recombinetics' replicates patient disease in large animal models for biomedical research as well as implement precise molecular crossbreeding methods to accelerate the improvement of agricultural genetics. Their technology provides animal breeders a precise, accurate and rapid method of changing specific traits in less time than is possible in a conventional breeding program. The company is targeting traits that impact on productivity, animal health and animal welfare.

Recombinetics' founders and scientific team were actively involved in the development and early application of TALENs and secured the exclusive global rights for Meganuclease and TALENs technologies from Cellectis for TALENs applications in multiple livestock species. The technology originated in the University of Minnesota and was set up for commercial applications by Cellectis for human health applications.

In addition to the licensed technologies, Recombinetics has its own proprietary Passport and Bullseye systems for gene addition and targeted gene modification which is protected in a dozen utility patents covering products and methods for genome engineering of livestock (Recombinetics).

Recombinetics

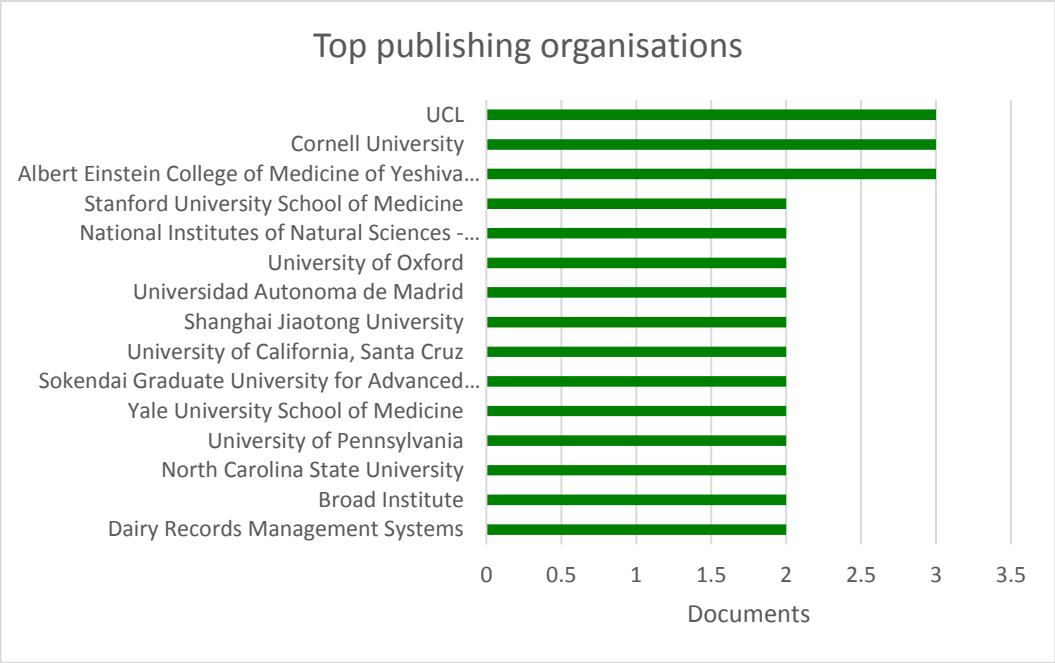


The chart for Recombinetics shows activity in more than one industry with multiple gene editing technologies. Despite this there appears to be very little third-party collaboration and licensing.

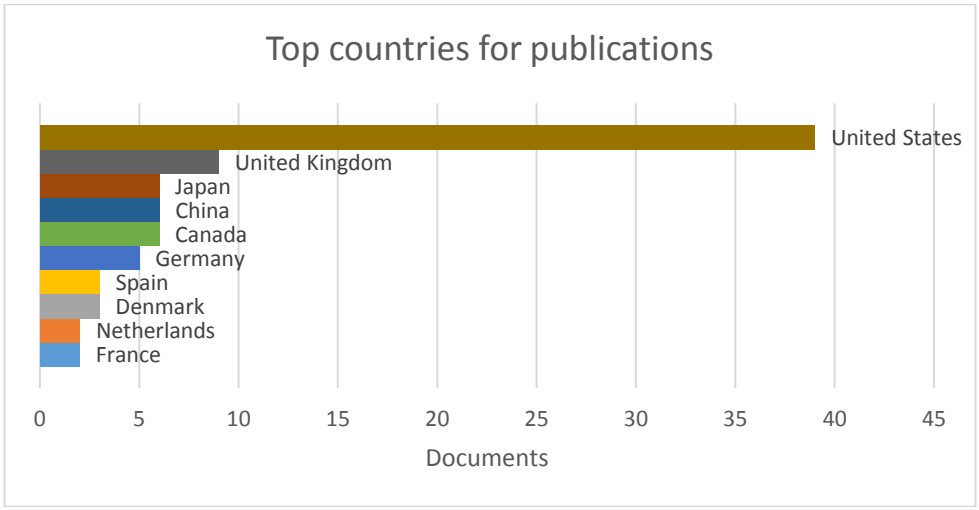
RESEARCH LANDSCAPE

To give an indication of the academic institutions contributing to the field, a broad search of academic publications was carried out.

A search of the abstract, title and keywords for (gene* editing) and (animal* OR livestock) and (health) identified 72 document results, including both peer-reviewed research articles and topic reviews. Sorting the document dataset by affiliation gives a rough indication of the top publishing institutions. The results are a mix of public sector research institutes and universities as well as a few companies:



The dataset can also be analysed for top publishing countries, and as with the equivalent charts in the other sections, USA comes out at the top, followed by UK. The top 10 countries by publishing territory are summarised as follows:



THERAPEUTICS

Gene editing technologies, as with many high risk experimental discoveries, have come to fruition largely by research activities at academic institutions. Subsequent licensing deals and spin-out creation has resulted in the establishment of several biotechnology companies in the gene editing therapeutic sector. Five of the most prominent are described here:

- Sangamo Biosciences
- CRISPR Therapeutics
- Editas Medical
- Intellia Therapeutics
- Cellectis

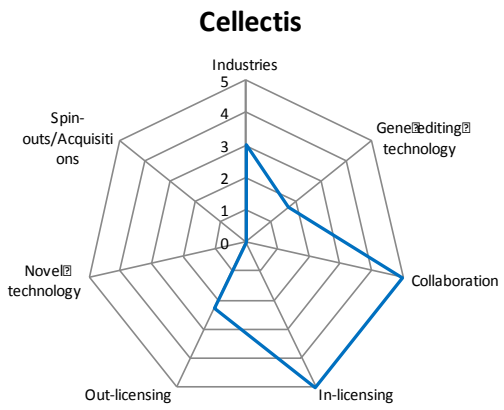
Key indicators such as the cascade of venture funding entering gene editing startups as well as an appetite from pharma to embark on research collaborations, illustrate the market opportunities for gene editing technology in therapeutics. Nonetheless, companies such as Editas Medical and the other gene editing product-focused start-ups are still years or even decades, from bringing a product to market. It remains uncertain that the promise of CRISPR technology will prove suitable for human therapeutics and fundamental challenges are yet to be overcome, such as the degree of specificity and the potential of single-guide RNAs to cause off-target effects in the human genome.

The deal and collaborative activities of some of the companies are described below and summarised in the deals table below.

CELLECTIS

Cellectis are the pioneers of gene editing in CAR-T cells for allogenic therapies. The company is undergoing aggressive patent activity in the TALENS technology area. One core patent family has been licensed from the University of Iowa and Minnesota and a second from Martin Luther University in Germany.

The company is working to provide cancer sufferers accessible, cost-effective, off-the-shelf allogeneic CAR-T therapies. Along with Great Ormond Street Hospital and UCL Institute of Child Health (ICH), the company successfully trialled a CAR-T leukemia treatment in 2015. A phase I/II clinical trial with 10-12 patients for this first gene-edited UCART is scheduled to begin in 2016. The data marks a promising step for a revolution in cancer immunotherapy. The company has ongoing multimillion dollar collaborations and licensing options with Pfizer and Servier.



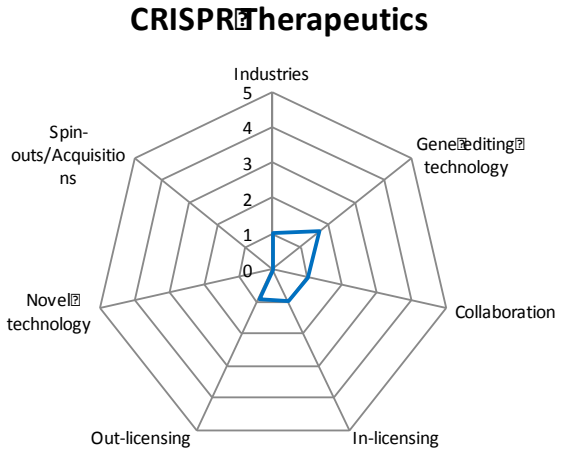
Cellectis appears to have the highest scores for collaboration and in-licensing. The chart also indicates a high level of out-licensing activity and activity in different industry sectors.

CRISPR THERAPEUTICS

In 2009 CRISPR Therapeutics was founded on a CRISPR/Cas9 patent licensed from Dr. Emmanuelle Charpentier at the Max Plank Institute. The company has raised a total of $89 million in Series A and B rounds since April 2014. Investors include SR One, Celgene Corporation, New Enterprise Associates, Abingworth and founding investor, Versant Ventures.

The company has a four-year strategic research collaboration with Vertex Pharmaceuticals to develop potential treatments for genetic disease. As part of the collaboration, Vertex made an up-front commitment of $105 million to CRISPR, including $75 million in cash and a $30 million equity investment. CRISPR is also eligible to receive future development, regulatory and sales milestones and royalty payments on future sales. Therapeutic areas include cystic fibrosis and sickle cell disease. Vertex and CRISPR will share all R&D costs and sales, with CRISPR Therapeutics leading commercialisation efforts in the US. Vertex will have exclusive rights to license up to six new CRISPR-Cas9-based treatments that emerge from the collaboration.

CRISPR Therapeutics and Bayer AG have established a joint venture designed to bring breakthrough therapies to patients suffering from such serious conditions as blood disorders, blindness and congenital heart disease. CRISPR has 50% ownership of the venture, which will be fuelled by $300 million in research and development funding from Bayer over the next five years. Bayer also acquired a minority stake in CRISPR Therapeutics for an additional $35 million investment. CRISPR contributes its proprietary CRISPR-Cas9 gene-editing technology, while Bayer brings protein engineering expertise and experience in the targeted disease areas. CRISPR Therapeutics will have full access to the intellectual property created by the venture at no cost. Newly created know-how from the collaboration around the CRISPR-Cas9 system beyond the three disease areas, will be exclusively made available to CRISPR Therapeutics for human-use, and to Bayer for non-human use, such as agricultural applications. This is the first strategic partnership to make a substantial investment in the development of target delivery systems. The key goal is to develop systemic *in vivo* CRISPR-Cas9 gene editing technology applications for patients.

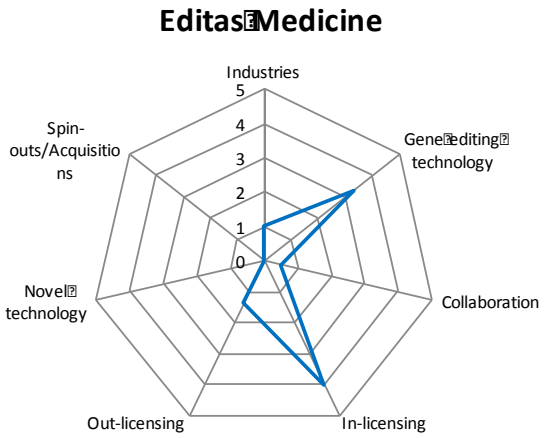


CRISPR therapeutics has conservative scores for the strength factors. The chart suggests that the company specialises in one gene editing technology and one industry and has been involved in some deals.

EDITAS MEDICINE

The company has harnessed CRISPR/Cas9 and TALENS for therapeutic application. Editas was founded in 2013 with $43 million in Series A venture capital financing led by leading health care venture capital funds Flagship Ventures, Polaris Partners and Third Rock Ventures with participation from Partners Innovation Fund. A further $120million was raised in late 2015 and by February 2016 the company went public.

The company's intellectual property is licensed from the Broad Institute, Harvard University, Duke University and Massachusetts General Hospital. The core development candidate is for in vivo application to the eyes of Leber congenital disease patients. The company aims to start a clinical trial in 2017 to treat this rare form of blindness, using CRISPR/Cas9 technology. Proof of concept has been demonstrated thus far by generating genetically engineered monkeys.



The charts suggests that Editas Medicine's key strengths and strategies involve in-licensing and multiple gene editing technologies. Though there is some out-licensing activity and collaboration, it may not be a core part of the company strategy.

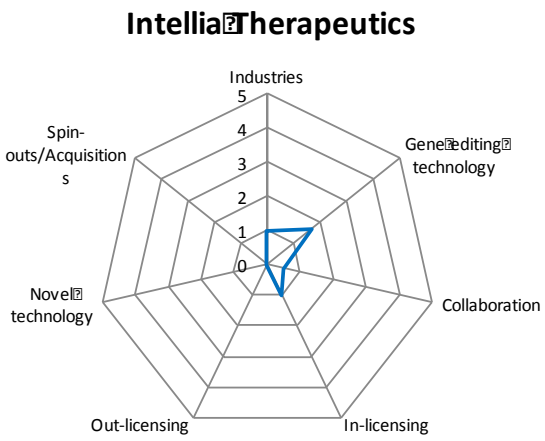
INTELLIA THERAPEUTICS

Intellia Therapeutics is a biotechnology company developing the CRISPR/Cas9 gene editing platform for therapeutic application. The company state that the discovery of the platform in 2012, has led to the publication of 1,500 academic papers, 40 proof of concept publications covering more than 20 potential indications. The technique has so far been used to:

- Cure muscular dystrophy and rare liver disease in mice models
- Immunise human cells against HIV
- Correct sickle cell anaemia
- Alter cancer cells to induce susceptibility to chemotherapy

In November 2014, the company raised $15million at seed stage with Novartis AG venture arm, Atlas Venture. The company was fully launched by Atlas Venture and Caribou Biosciences. In 2015, the relationship with Novartis progressed to a collaboration to develop new cell therapies using the CRISPR/Cas9 technology for chimeric antigen receptor T-cells (CARTs) and hematopoietic stem cells (HSCs). The aim is to harness the immune system to fight blood cancers, as well as inherited disorders such as sickle cell anaemia and beta thalassemia.

In September 2015 the company achieved a Series B investment round of $70million from several investors[1] led by OrbiMed HealthCare Fund Management. The company are pursuing a strategy to accelerate its pipeline development, expand its platforms for gene editing and delivery as well as strengthening its intellectual property portfolio. The company is focusing efforts on *ex vivo* gene editing approaches. In January 2016, it announced the launch of a new division within the company called eXtellia Therapeutics, with the intent of focusing resources and research on *ex vivo* applications of the novel technology. The division will focus on medical needs for immune-oncology, autoimmune and inflammatory diseases using an *ex vivo* approach. The *in vivo* approaches will continue through a dedicated scientific team.



Looking at the chart, Intellia appears to be a very specialised and company with minimal deals involving third parties. This reflects the young age of the company however, the chart may look very different in the near future. The company went public in May 2016 raising $163 million, making it the largest biotech IPO of 2016 so far (Intellia Therapeutics, 2016).

SANGAMO BIOSCIENCES

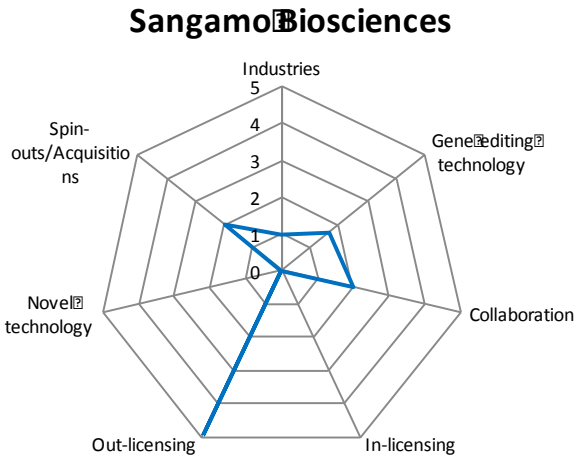
Sangamo Biosciences is a clinical stage biopharmaceutical company. The company's core technology is the use of ZFP nuclease for gene editing solutions. The company has demonstrated efficacy of the compound for treatment of HIV, and are now conducting an ongoing phase II clinical trial (SB-728mR-T-1401). The preliminary data from these studies indicate that the treatment is well tolerated in HIV infected subjects. In addition, the data from Phase I and Phase II clinical trials of the ZFP Therapeutic, SB-509, for diabetic nephropathy and ALS demonstrated it was well tolerated. Additionally a ZFP nuclease candidate is undergoing development for treatment of factor IX disease, and has

[1] Including Fidelity Management and Research Company, Janus Capital Management, Foresite Capital, Sectoral Asset Management, EcoR1 Capital and other leading mutual fund and healthcare investors

demonstrated proof of concept in a cohort of 15 monkeys. The company also have candidates for Haemophilia B where the ZFP targets albumin manufacturing gene in the liver cells.

In 2012, Sangamo acquired Ceregene Inc, a company focussed on developing adeno-associated virus (AAV) gene therapies. Through the acquisition, Sangamo received over 120 issued, pending or in-licensed patents that include patent families covering the AAV vector platform and manufacturing methods, therapeutic transgenes, and technology for direct administration of AAV to the brain.

The company strategy is clearly to license the technology widely across other applications, not in their areas of strategic focus. For example Dow AgroSciences licensed the IP broadly to cover applications to plant cell gene editing. Sangamo also have ongoing collaborations and licensing deals with pharmaceutical companies Shire International and Biogen Idec. The terms of the Shire collaboration state that each company is responsible for expenses associated with its own programs and will reimburse the other for any ongoing services provided. Sangamo has granted Shire a right of first negotiation to license the hemophilia A and B candidate. No milestone payments will be made on any program and each company will pay certain royalties to the other on commercial sales up to a specified maximum cap.

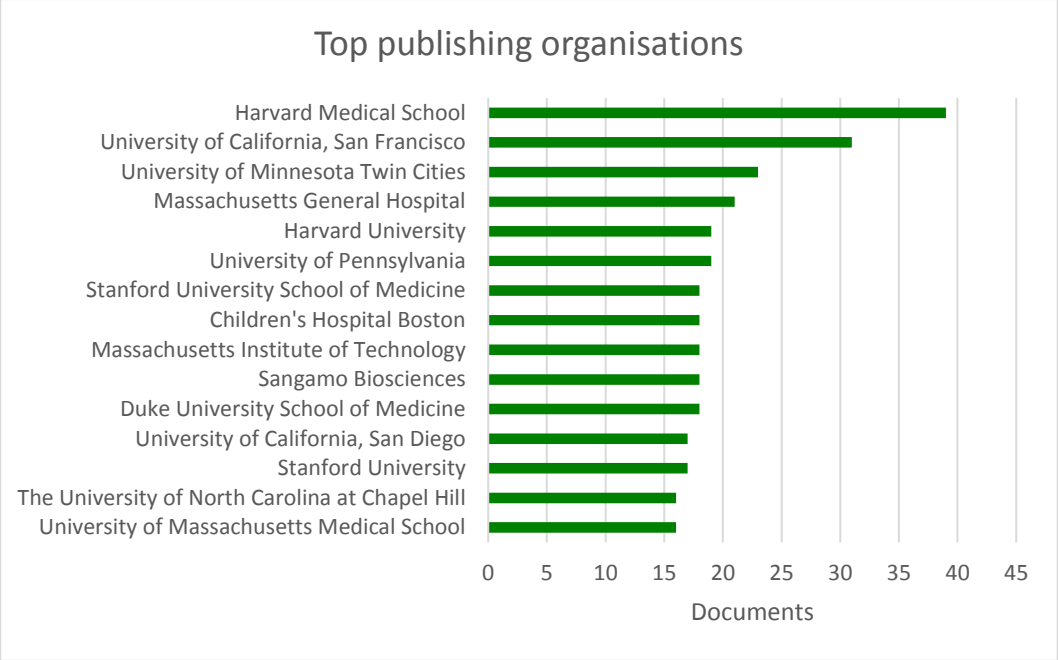


Similar to Sigma-Aldrich, the chart for Sangamo Biosciences suggests that the company is a key licensor in the gene editing industry and most likely holds foundational patents and technology. It also specialises in one field and appears with a moderate level of collaboration and more than one gene editing technology.

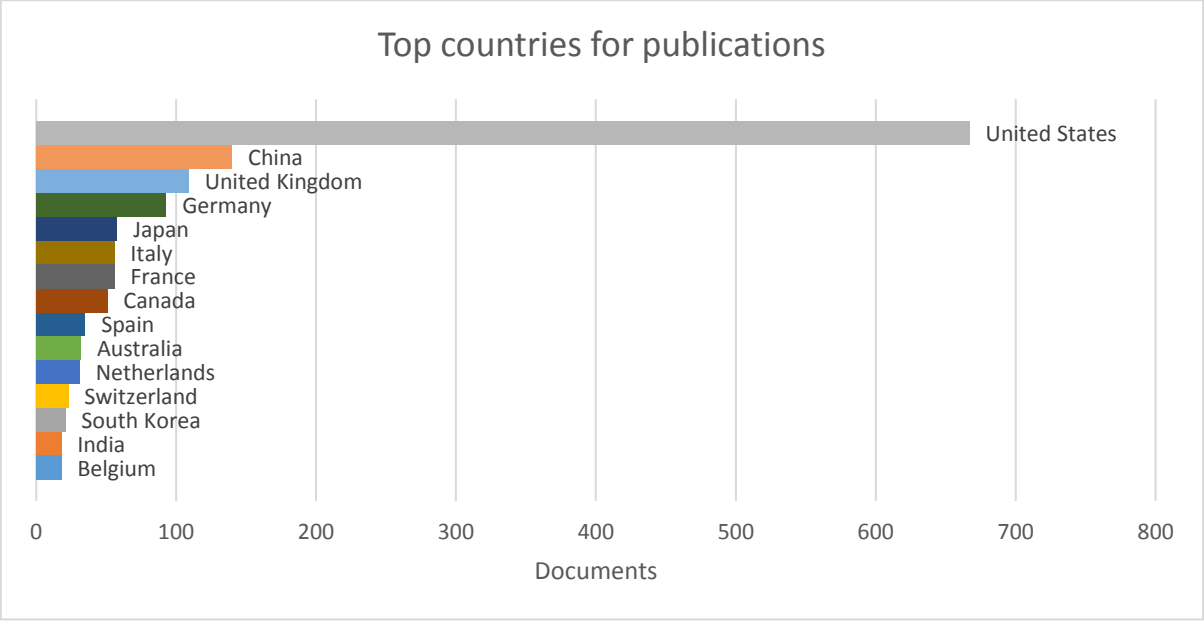
RESEARCH LANDSCAPE

To give an indication of the academic and other institutions contributing to the field, a broad search of research publications was carried out.

A search of the abstract, title and keywords for (gene* editing) and (therap*) identified 1,263 document results, including both peer-reviewed research articles and topic reviews. Sorting the document dataset by affiliation gives a rough indication of the top publishing institutions. It is no surprise that Harvard Medical School, University of California and Sangamo Biosciences come in the top 5 affiliations:



The vast majority (93%) of the top 15 publishing organisations are public sector academic and medical institutions, including universities, hospitals and research institutions. Sangamo Biosciences is the oldest established gene editing therapeutics company as described. The dataset can also be analysed for top publishing countries, and given that the top 10 institutions are US-based it is unsurprising that the top publishing country by a large margin is the USA. The top 10 countries by publishing territory are summarised as follows:



MARKET DRIVERS AND TRENDS

Regardless of the industry sector, the new CRISPR technology is less expensive, faster and offers several technical advantages over the older gene editing technologies and as expected, the adoption of this new technology across all sectors is the primary trend for the gene editing market. Stemming

from this rapid increase in research and development in CRISPR technology field, there has been a surge of new players specialising in the revolutionary technology and a couple that claim to have developed technology whose performance surpasses that of CRISPR.

Academic institutions own a lot of the foundational IP for all four gene editing technologies and there are several companies collaborating with these institutions and licensing the technology in order to commercialise it. Now more R&D is being done within the companies themselves and whilst it is likely that the significant collaboration between industry and academia will continue, new gene editing technologies may have their origins in industry.

There is a fair amount of licensing and cross-licensing as companies develop more proprietary technologies. However, the key players tend to keep within their area of expertise by licensing out technology for applications outside of that expertise. Alternatively, spin out companies are formed to commercialise the technologies in a different sector. This is the case with Nucelis, Calyxt and Intellia, in that the organisations that formed them or hold the core IP operate in different sectors to these new companies.

There have been a few acquisitions in the gene editing industry and the need for new technologies will most likely trigger further consolidation in the gene editing industry. Based on previous acquisitions and the patent portfolio analysis of the key players, the consolidation may be grouped around industry sectors or gene editing technologies rather than the gene editing market as a whole.

LIFE SCIENCE RESEARCH

In the life science research sector, most of the key players focus their products and services around one of the older gene editing technologies: Meganucleases, ZFNs and TALENs. However, these companies are now in-licensing or developing CRISPR technology. As with the overall life science research market, the companies in the gene editing market are increasingly using branding to differentiate their products and services from their competitors. The variety of research tools and gene editing services available are also increasing as companies are starting to specialise in two or more gene editing technologies.

As CRISPR licensing is increasing, there will most likely continue to be more new entrants in the market that are already in the research tools market, but who have yet to take up advanced gene editing technologies. Other new entrants could be ‘gene editing’ companies like those focusing on CRISPR therapeutics but have a side market that can create revenue from the outset as it would take several years to generate revenue from therapeutics.

PLANTS AND AGRICULTURE

The global population is estimated to reach 9 billion by 2050 while per-capita arable land is decreasing and the Food and Agriculture Organisation (FAO) estimates that crop production must increase by 70% just to maintain nutrition at the current levels. As a result, there is a global call for plant seeds with higher yields and better tolerance towards a variety of stresses like pest attacks, viruses, and drought. The need for these will be heightened by rising food prices and the global climate change.

Based on these factors, there will most likely continue to be significant growth in the agricultural biotechnology industry including the plant and agriculture gene editing sector which has already seen plenty of collaboration and cross licensing in recent years and counts a number of established companies amongst its key players. The market is directly affected by the number and mass of

countries that are adopting the novel biotech seed products. As of 2013, 27 countries had planted such crops, while 127 regulatory approvals were recorded for the same year worldwide (BCC Research, 2012). This points to a growing acceptance by several developing and developed countries. However the potential regulatory requirements, environmental and ethical concerns associated with gene editing might stall its growth for a while. That said, federal governments around the world realise the need for higher yields to feed the increasing populations and are becoming more open to funding and adopting gene edited agricultural products. It is likely that gene edited crops will be viewed as natural products by more countries and gain both public and regulatory authorities approval. In the United States, the Agriculture Department (USDA), which is responsible for developing and executing federal government policy on farming, agriculture, forestry, and food, has already passed several plants made using ZFN, TALEN and CRISPR gene-editing techniques as "non-GMOs". However, the plants may still undergo a voluntary review by the US Food and Drug Administration.

The market is also driven by increased R&D expenditure and technological advancements, significantly accelerating the development of novel plant traits. This high growth potential provides opportunities to new players in the gene editing agriculture market.

ANIMALS

Other than Genus plc the majority of the key players in the gene editing market in animals are U.S. based organisations. However, when analysing the key patent assignees in the field as well as the organisations publishing the most research papers and, it appears that Chinese organisations have the greatest increase in R&D and innovation in the space. In particular, China has widely embraced gene editing technologies for animals, with research being supported via grants from the National Natural Science Foundation of China, Ministry of Agriculture, Ministry of Science and Technology as well as provincial governments (Larson, 2015). The level and sophistication of work in China using CRISPR is already "about the same" as in Europe and the U.S., where the technology was co-developed, says George Church, a professor of genetics at Harvard Medical School.

THERAPEUTICS

In the therapeutics sector, the currently unresolved nuclease delivery issues indicate that the first treatments, which have progressed to later stages of development, are the ex vivo approaches and will likely prove to be first to market. Aside from ex vivo treatable diseases, the low hanging fruit for industry will be for diseases resulting from single gene mutations. In particular addition mutations, where the gene simply needs to be knocked out during gene therapy before the nucleic acids are ligated back together. Replacing a mutated gene with a new segment of DNA will be harder to achieve technically (Editas Medical).

Whilst the candidates based on ZFP or meganucleases may be further ahead in development in the therapeutics sector, CRISPR offers a stepwise improvement over these technologies. Current forecasts indicate that CRISPR will become the dominant method of choice for therapeutics. However, in certain indications such as HIV (Sangamo Biosciences) the older technologies will likely have first-to-market advantage or exclusivity for a period of time before competing products are approved.

BARRIERS TO ENTRY

A key barrier to entry in the gene editing industry is ownership of the core technologies. A new entrant would have to license a gene editing technology from one of the key patent holders in one of the ZFN, TALEN or CRISPR fields. Alternatively, they would have to develop proprietary gene editing technology.

Other significant barriers include regulatory and ethical issues that may be interpreted differently in different parts of the world and in different sectors.

LIFE SCIENCE RESEARCH

There are fewer barriers to growth in the life science research sector than for other industry sectors particularly as there are no significant ethical or regulatory issues. Research tools and services also have applications in several sectors and have a diverse customer base. The size and diversity of the market also contributes to the decreasing the barriers to entry.

Barrier	Description
Licensing technologies	Several companies are developing similar research tools using a range of gene editing technologies. To stay competitive, they have sometimes been licensing in more than one gene editing technology. Licensing a gene editing technology from one of the key IP holders in ZFN, TALEN or CRISPR may prove to be difficult given the significant number of existing exclusive licenses.
	The companies developing improved gene editing technologies like Arcus and RTDS may monopolise the market for the new technologies.
	The patent dispute could affect many companies currently licensing IP for their products and services in the research tools application area.
Existing players	New companies may find it difficult to gain market share in the research tools industry, since the well established companies have already adopted the new gene editing technologies and have good distribution channels, large customer bases and strong brands.
Research funding	Research funding limitations would mean that there were fewer researchers taking on gene editing research projects and possibly could reduce the need for certain gene editing research tools as products.

PLANTS AND AGRICULTURE

The main barrier for the agricultural biotechnology market of gene editing lies with the ambiguities regarding the regulatory status of gene edited crops and whether they should be classified as genetically modified organisms (GMOs). The ongoing deliberations show that the level of regulatory scrutiny will likely be based on the type of technology used, the intended use of the resulting phenotype and the regional regulatory restrictions.

Barrier	Description
Regulatory issues	The regulatory status of gene edited crops is yet to be determined and it is not clear whether they will be classed as GMO and have the same challenges faced by GM crops.

	The level of regulatory scrutiny will be based on the type of technology used, the intended use of the resulting phenotype and the regional regulatory restrictions.
	Gene edited crops differ from genetically modified crops in that there is no foreign DNA introduced to the plant species. As a result, a gene edited crop cannot be distinguished from a naturally occurring mutation. This may mean the gene edited crops would not be classed as GMO in some countries.
Regional restrictions	The EU, following from its policy on GMOs, has not embraced genome edited crops and has effectively hindered further product development for European companies. According to EU legislation, a crop shall be classified as GM, and thus banned, if the genetic material has been altered in a not naturally occurring way such as mating and/or natural recombination. It wasn't until recently that the Board of Agriculture in Sweden, an EU member, announced that some plants edited through the CRISPR/Cas9 system do not fall under the European GMO definition.
	In the U.S., the Department of Agriculture (USDA) has recently ruled that mutations caused by Meganucleases, ZFNs and TALEN do not fall under the umbrella of GMOs. Therefore, the costly and time-consuming approval process can be avoided. The USDA is currently evaluating the status of CRISPR technology with the decision expected to be the same as with the previous gene editing technologies.
Improved technologies	Companies developing new technologies may make it difficult for other players depending on the regulations surrounding the new technologies. As an example, U.S. regulatory bodies consider the proprietary technology of ag-bio firm Cibus to be a natural form of mutagenesis so it is excluded from the GMO approval process.

ANIMALS

The primary concern for gene editing in animals is regulatory and environmental biosafety, similar to concerns raised for agricultural applications

Barrier	Description
Biosafety	Once introduced, genetic changes in animals are self-propagating. If released beyond the laboratory, the effects would spread with every new generation and may quickly run out of control. The risk of broader ecosystem disruption is unknown and would require extensive mathematical modelling to estimate.
Public consent	Depending on the purpose or role of the gene edited animals, it may not be accepted by the wider public despite regulatory approval. As with genetically modified foods, consumers may have concerns over the potential health implications of gene editing livestock and fish.
Ethical issues	Consumers may believe gene editing in animals a violation of animal rights or a danger to their welfare. Though some gene editing may have benefits, such as improving resistance to disease, other changes may lead to unforeseen and potentially painful side-effects.

Regulatory barriers	It is unclear at present how major regulators such as the FDA will regulate animals that have been engineered using gene-editing systems such as CRISPR.
	Regulatory approval may be time-consuming and costly to obtain. The genetically modified 'AquAdvantage' salmon was in two decades of regulatory limbo before its approval by the US Food and Drug Administration (FDA) in 2015.

THERAPEUTICS

The key barriers-to-entry for the commercial application of therapeutic gene editing candidates are around safety, efficacy and manufacturing.

In vivo and *ex vivo* programs require different competencies in research, manufacturing and commercialisation which results in several scientific and commercial hurdles before each of the technologies can reach commercial fruition. The hurdles particularly for *in vivo* use of therapies, means that the first gene editing candidates likely to reach the market will involve removing the patients cells, such as blood, treating them *ex vivo* by gene therapy techniques and replacing them back inside the patient.

Barrier	Description
Safety	Therapeutic candidates under development have so far undergone limited testing in humans, and pioneers such as Sangamo Biosciences ZFP candidate or the Great Ormond Street and UCL Institute of Child Health's TALENS candidate may still fail safety studies during upcoming clinical trials.
	Similarly the successes reported in early Phase I and Phase II clinical trials may not be indicative of long term efficacy in later stage clinical trials. Companies in the pharmaceutical and biotechnology industry have frequently suffered significant setbacks in late stage clinical trials even after achieving promising results in earlier stage clinical trials.
	Long term safety studies have not been carried out. For in vivo applications, the nuclease may persist in the cell or body after it has performed the editing procedure. There is potential that given this length of time, the nuclease could generate high levels of off-target cleavage resulting in toxicity.
	Precision refers to the capacity of the designed nuclease candidate to cleave accurately or as closely as possible, to the desired location. Precision is crucial in therapeutic application, where specificity of gene modification is required for efficiency and safety. This is of prime importance in therapeutics. Both in vivo and ex vivo uses of the nucleases could result in cuts and mutations elsewhere in the genome.
	Unforeseen safety effects, such as an immune reaction of the DNA-cutting enzyme could result in toxic immune reaction when tested in humans.

Delivery	Whilst the technology is intrinsically designed to identify the correct gene for editing, for *in vivo* use, it also needs to be guided to the correct diseased cell or tissue. Vectors such as plasmid DNA, DNA encapsulated in viral vectors and RNA have historically been used. There is work underway exploring the use of adeno-associated virus particles and lipid nanoparticles to carry the therapy to the correct cell. Receptor recognition by the particle allows the therapy to be delivered directly to the diseased site.
	Delivery of single nucleases, particularly Cas9, is difficult because of the large size of the DNA sequences encoding the Cas9 nuclease (4,200 bases). Companies are already looking at engineering Cas9 to make it more suitable for delivery via viral vectors.
	The successful commercialisation of an *in vivo* therapy will rely on these delivery systems. Many of the development companies will need to in-license these technologies for the use of the nuclease in both *ex vivo* and in vivo applications, since they may not have developed their own gene transfer technologies in house.
	Additional in vivo concerns around the use of gene editing technology include the delivery vector remaining active and present in the body long after the therapy is complete.
Efficacy	The concerns around immune rejection of the DNA cutting enzyme itself would render it useless for *in vivo* treatment.
	Aside from ex vivo treatable diseases, the low hanging fruit for industry will be for diseases resulting from single gene mutations. In particular addition mutations, where the gene simply needs to be knocked out during gene therapy before the nucleic acids are ligated back together. Replacing a mutated gene with a wild type will be harder to achieve technically.
	Multiplexing, or generating several DNA modifications at a time, for treatment of more complex genetic disorders is currently not on the horizon.
Manufacturing	For therapeutic application of gene editing technology, and cell therapies more generally, manufacturing sufficient amounts of product to current good manufacturing process (cGMP) level is a challenge. Many pharmaceutical and biotechnology companies will outsource this procedure to third party contract manufacturing organisations. The number of third party suppliers with the necessary manufacturing and regulatory expertise and facilities for disruptive technologies such as gene editing and cell therapy is limited.
	Manufacturing costs will be driven in part by the size of the nuclease DNA sequence, when it is larger it will be more difficult to package along with the guide RNA.
Ethical Issues	Adverse public perception in the field of gene therapy may negatively impact regulatory approval of, or indeed the demand for, potential gene editing therapies. Public attitudes may be influenced by claims that gene therapy is unsafe, which has the potential to result in products not gaining acceptance of the public or the medical community. Furthermore, negative public reaction to gene therapy in general could result in greater government

	regulation and stricter labelling requirements. This public sentiment issue extends to the successful commercialisation of genetically modified agricultural products.
	Public concerns around the use of gene editing technology in human embryos is high. Ethical debates about its potential use for non-therapeutic modifications as well as the possible unpredictable effects on future generations are currently underway. There will be public education issues around somatic cell gene editing versus gamete cell editing.
Regulatory issues	The regulatory environment for gene editing technologies, as applied to therapeutics, is likely to have a high level of stringency and complexity throughout the western world.

PATENT ANALYSIS

Thomson Innovation was used to carry out searches for patents and patent applications published in the last 20 years. Separate patent searches were carried out for the following topics:

- Gene editing broad search
- ZFN
- TALEN
- CRISPR
- Meganucleases

The five searches were then combined to provide a comprehensive gene editing patent landscape. The number of patent publications identified in each of the searches is detailed below alongside the number of patent families they are grouped into:

Search subject	Number of families	Number of publications
Gene editing	432	1006
CRISPR	393	1139
TALEN	222	524
ZFN	395	1432
Meganuclease	360	1771
Gene editing combined search	**1309**	**4301**

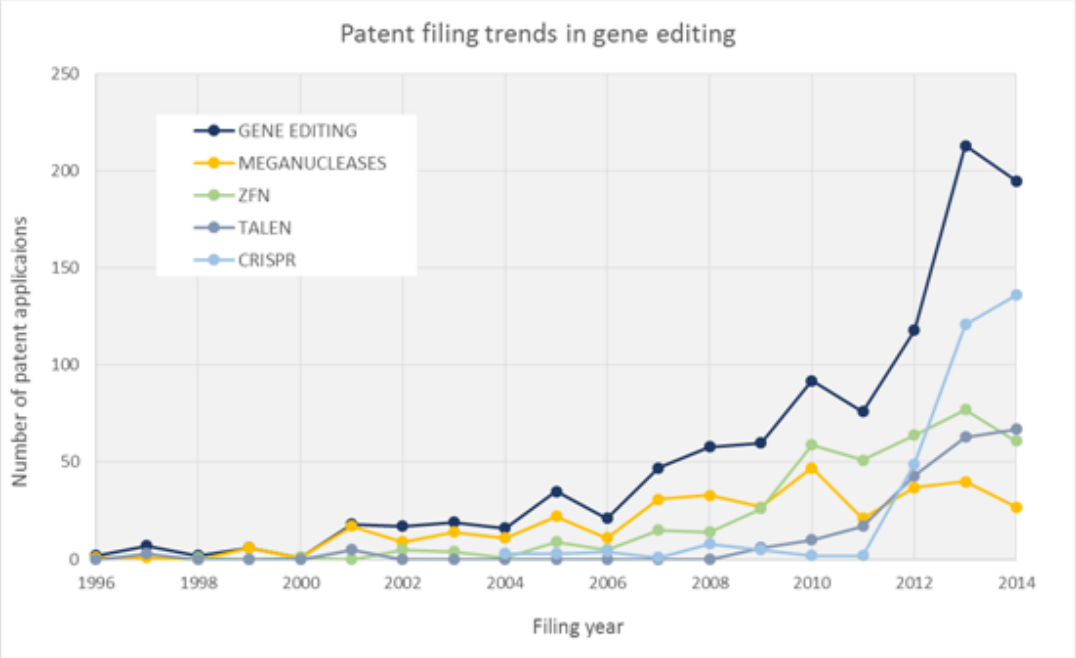
PATENT FILING TRENDS IN GENE EDITING

The graph on the following page shows the number of new priority patent applications being filed by year therefore the data lags 18 months behind the actual filing dates. Analysing the priority filing data gives an indication of the number of new gene editing inventions.

Overall, the numbers of new priority patent filings related to gene editing have grown exponentially since 2008, with a steep rise in 2011 that is most likely associated with the rapid advancement in CRISPR technology. Before 2008, new priority patent filings in gene editing seem to have been primarily dependent on patent applications related to Meganuclease technology. Patent filings for this technology have grown steadily from 1996 to 2010 though appear to have declined fairly rapidly since then. From the graph, this decline may be explained by the rise in filings of newer and potentially more effective technologies: first ZFN, then TALEN and finally CRISPR. The significant increase in patent filings for ZFN and TALEN technologies started in 2009 and 2011, respectively which gives an indication of when each of the technologies were introduced.

Patent filings for Meganuclease, ZFN and TALEN technologies have not stopped after the invention of CRISPR technology, though their rate of increase has fallen. As a general trend, the numbers of filings for older technologies are surpassed by the newer technologies. However, this is not the case for ZFN which continued to have more filings than TALEN up until 2014. This could suggest that ZFN technology appears to be equally as technically effective as TALENs despite being older.

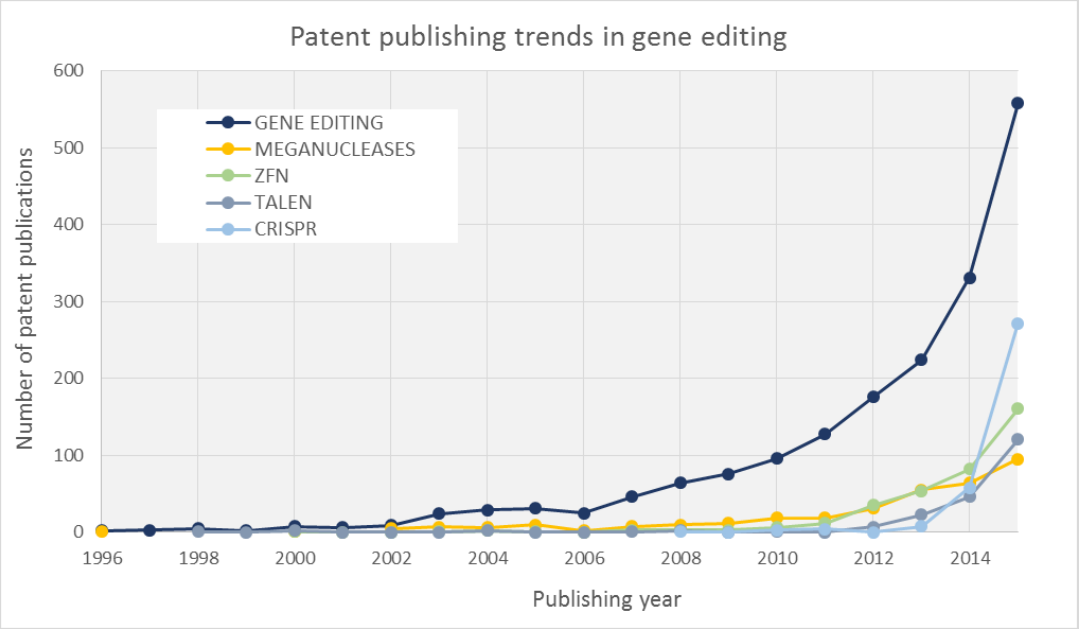
Innovations relating to the application of CRISPR have rapidly overtaken the other technologies. However, the continued filing in the other technologies shows that there is still innovation happening for those technologies.



Note: filing numbers for 2014 may be incomplete as the applications may not have been published as yet.

PATENT PUBLISHING TRENDS IN GENE EDITING

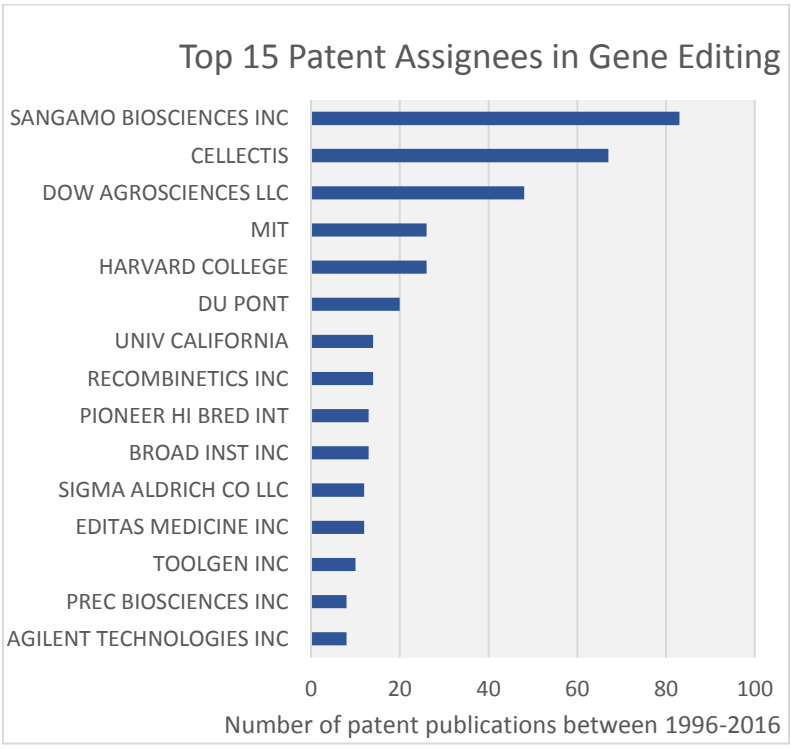
The following graph shows the number of patent publications by year. The numbers include the publication of patents or patent applications for each of the family members in a patent family.



The difference in the overall gene editing patent publications and the publications of the four technologies is significantly greater than the relative difference in patent filings. This suggests that wide geographical protection is sought for gene editing patents as the ratio of publications to filings increases. The number of publications for CRISPR surpassed those of the other three technologies in 2015 despite having the lowest number of publications just two years beforehand. This is consistent with a rapid growth in the number of patent filings.

KEY ORGANISATIONS

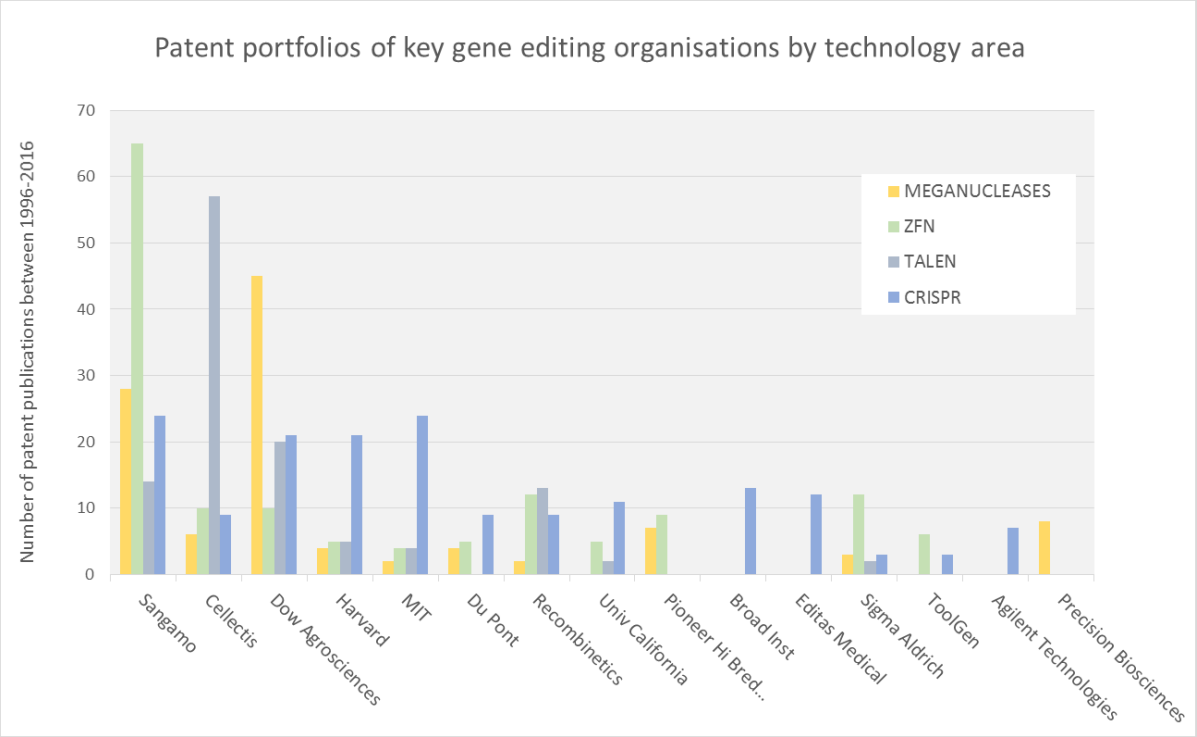
This section focuses on the top fifteen organisations based on the number of patent publications assigned to them in the broad landscape:



Sangamo Biosciences, Cellectis and Dow Agrosciences stand out as having the largest number of gene editing patent publications, followed by MIT, Harvard and Du Pont Pioneer (combination of Du Pont and Pioneer Hi Bred International publications).

The patent publications for each of the key organisations were analysed in more detail and categorised into the four main gene editing technology areas:

1. Meganucleases
2. Zinc Fingered Nucleases (ZFN)
3. TALEN
4. CRISPR



The graph above shows the distribution of patent publications in each of the technology areas for each of the key organisations. The graph indicates that there are seven key organisations that have patents or patent applications in all four technology areas: Sangamo BioSciences, Cellectis, Dow Agrosciences, Harvard, MIT, Recombinetics and Sigma Aldrich.

There appears to be a single frontrunner in each of the older technologies: Sangamo Biosciences for ZFN; Cellectis for TALEN and Dow Agrosciences for Meganucleases. In contrast, assignees for CRISPR patent applications appear be more wide spread with four leading organisations. Three of the key organisations only have patent applications related to CRISPR and not any other gene editing technologies.

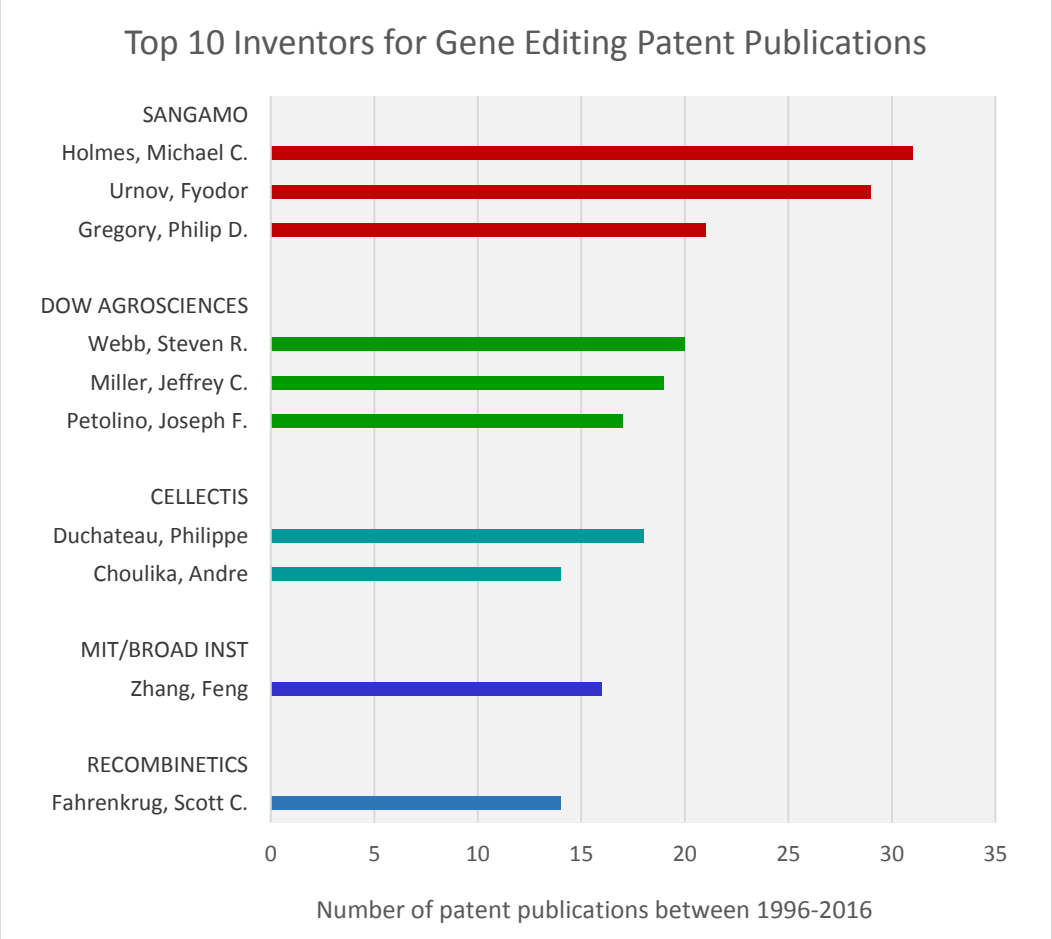
The significant number of companies with sizeable CRISPR technology patent portfolios suggests that the CRISPR market has not yet undergone any major consolidation. Some of these companies seem to be new players specialising in CRISPR technology as they do not appear to have any existing patent applications in other gene editing technology areas.

In December 2015, an expected merger between Dow Chemical and DuPont Pioneer was announced. As Dow Agrosciences is a wholly owned subsidiary of Dow Chemical, the patent portfolios of Dow

Agrosciences and DuPont Pioneer would be also be merged which would change the patent landscape for gene editing in terms of key players.

KEY INVENTORS

As expected, all the top ten inventors come from the key organisations detailed in the previous section. Four of the key inventors are also listed in Thomson Reuters' Highly Cited Researchers 2015 list which represents some of world's most influential scientific minds. This list of top researchers around the globe have earned their distinction by publishing the highest number of articles that rank among those most frequently cited by fellow researchers. The chart below shows the top ten inventors based on the number of patent publications:

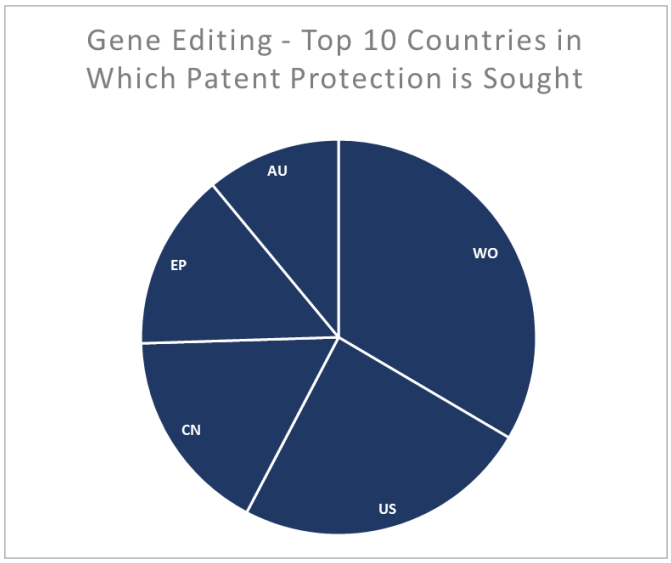


GEOGRAPHICAL ANALYSIS

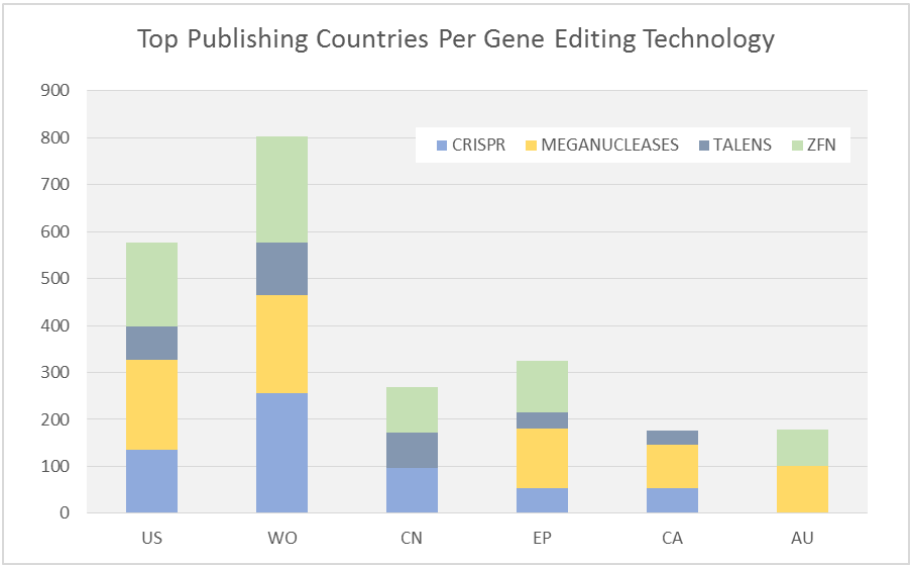
TOP 5 COUNTRIES IN WHICH PATENT PROTECTION IS SOUGHT FOR GENE EDITING TECHNOLOGIES

The top countries for patent publications give some idea on the countries, which players in an industry sector consider the most commercially valuable. Overall, the key countries and regions for the broad

gene editing landscape appear to be US, China, Europe, Canada and Australia. The largest number of publications is PCT applications which suggests a tendency towards broad geographical scope of protection for gene editing patents and also reflects that many of the patent applications are still at an early stage and have yet to progress through to their own national phase country publications.



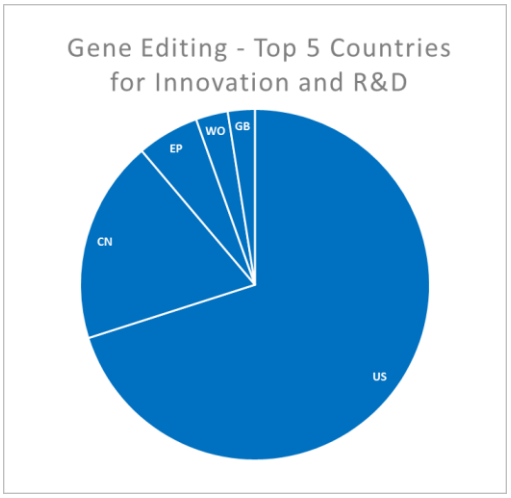
The number of publications in the top publishing countries for each of the gene editing technology searches was combined to give the graph below. Australia is noticeably absent from the list of key publishing countries for CRISPR as well as TALEN. Other absences include China from the top publishing country for meganucleases and Canada for the key publishing countries for ZFN.



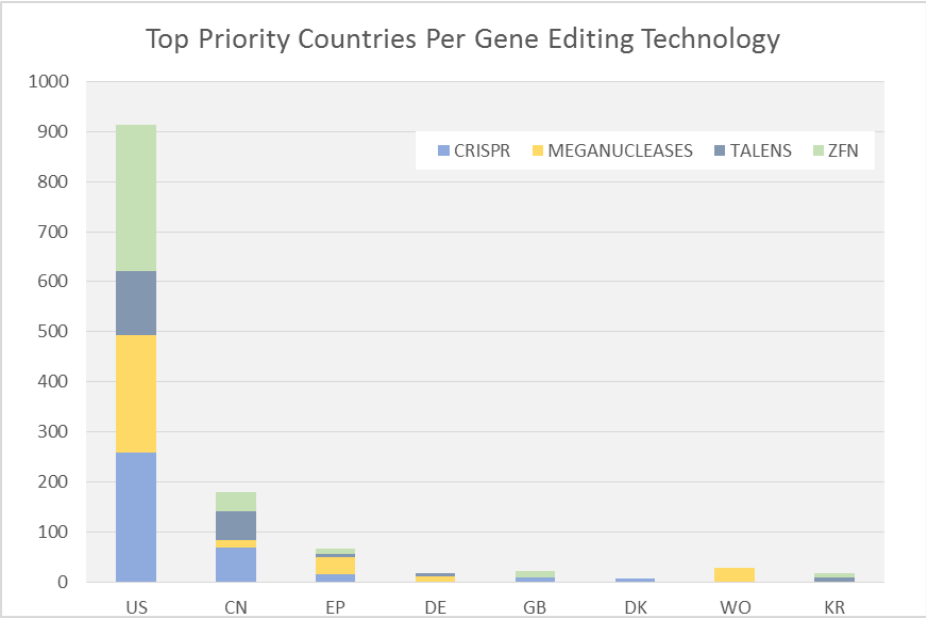
TOP 5 COUNTRIES FOR INNOVATION AND R&D IN GENE EDITING

The top countries for priority patent filings can indicate the most active countries for innovation and research and development. The charts show that almost two thirds of the priority filings for gene editing are from the US. The last third is made up of China, Europe and the UK with some priority

filings also being PCT applications (WO). The presence of PCT filings in the list of top priority countries again suggests tendency towards broad geographical scope of protection.



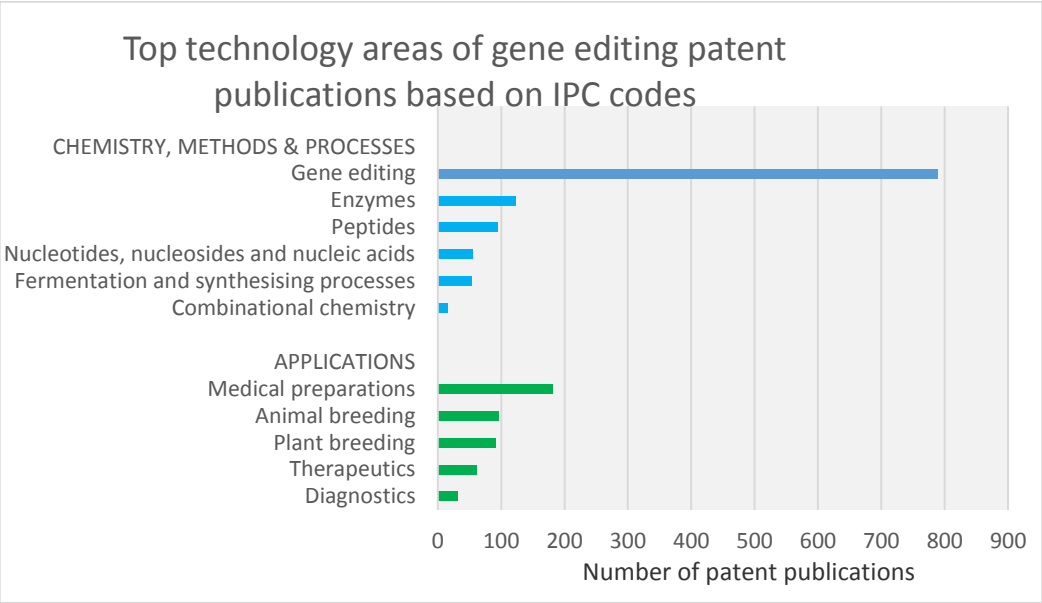
The number of publications in the top priority countries for each of the gene editing technology searches was combined to give the graph below. The US is clearly the dominant country for innovations in all technologies. China and Europe are also key priority countries for all four technologies. PCT applications are only on the list of top countries for Meganucleases which suggests a change in patenting strategy for more recent technologies from a bolder more expensive strategy of filing a PCT directly to a more reserved strategy which starts with a more cost effective national filing.



TECHNOLOGY AREAS

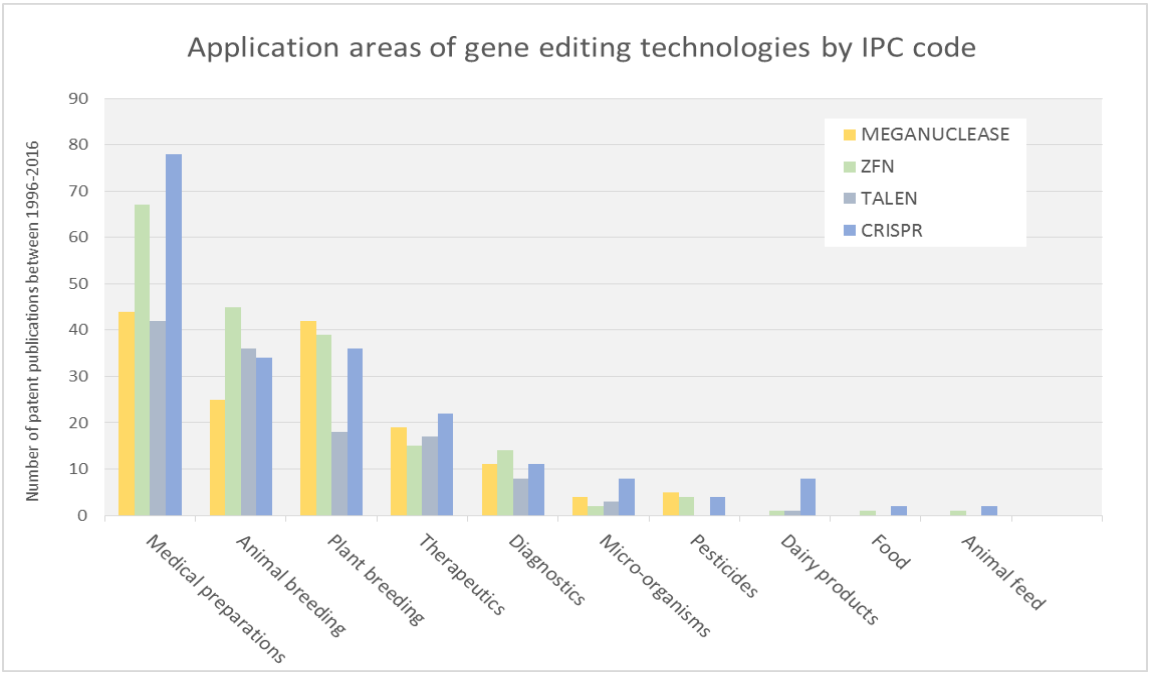
The patent search results were analysed further in order to identify the top IPC codes. These give an indication of the most important technology areas and applications in the gene editing patent landscape. Below is a chart of the top 10 IPC codes grouped into the two key categories covering patent publications related to the chemical compositions, methods and processes and patent

publications related to the applications of the gene editing technologies. The IPC codes corresponding to the technology areas are detailed in the sections below with descriptions.



The chart below shows the distribution of the top application areas based on IPC code for each of the gene editing technologies. Medical preparations, plant and animal breeding, therapeutics and diagnostics appear to be the leading technology areas and include patent publications from all four technologies. For medical preparations, CRISPR appears to be the dominant technology followed by ZFN technologies. ZFN appears to be the most dominant technology in animal breeding and is close second to Meganuclease in plant breeding. The number of TALEN patent publications with IPC codes for plant breeding is significantly smaller than the other gene editing technologies in the area.

CRISPR and ZFN patent publications are present in each of the technology areas whilst TALEN and Meganuclease publications do not appear to cover the less core technology areas such as food and animal feed. `



The tables in the sections below detail the corresponding IPC codes and descriptions for the technology areas.

INDUSTRY APPLICATIONS

Technology area	IPC Code
Medical preparations	**A61K**
Preparations for medical, dental, or toilet purposes	
Animal breeding	**A01K**
Animal husbandry; care of birds, fishes, insects; fishing; rearing or breeding animals, not otherwise provided for; new breeds of animals	
Plant breeding	**A01H**
New plants or processes for obtaining them; plant reproduction by tissue culture techniques	
Therapeutics	**A61P**
Specific therapeutic activity of chemical compounds or medicinal preparations	
Diagnostics	**G01N**
Investigating or analysing materials by determining their chemical or physical properties	
Micro-organisms	**C12R**
Indexing scheme associated with subclasses c12c-c12q, relating to micro-organisms	
Dairy products	**A23C**
Dairy products, e.g. milk, butter, cheese; milk or cheese substitutes; making thereof	
Food	**A23L**
Foods, foodstuffs, or non-alcoholic beverages; their preparation or treatment, e.g. cooking, modification of nutritive qualities, physical treatment; preservation of foods or foodstuffs, in general	
Animal feed	**A23K**
Feeding-stuffs specially adapted for animals; methods specially adapted for production thereof	

GENERAL METHODS, PROCESSES AND CHEMISTRY

Technology area	IPC Code
Gene editing	**C12N**
Micro-organisms or enzymes; compositions thereof; propagating, preserving, or maintaining micro-organisms; mutation or genetic engineering; culture media	

Enzymes	**C12Q**
Measuring or testing processes involving enzymes or micro-organisms; compositions or test papers therefor; processes of preparing such compositions; condition-responsive control in microbiological or enzymological processes	
Peptides	**C07K**
Peptides	
Nucleotides, Nucleosides & nucleic acids	**C07H**
Sugars; derivatives thereof; nucleosides; nucleotides; nucleic acids	
Fermentation & synthesising processes	**C12P**
Fermentation or enzyme-using processes to synthesise a desired chemical compound or composition or to separate optical isomers from a racemic mixture	
Digital data processing	**G06F**
Electric digital data processing	

PATENT LANDSCAPING

The combined gene editing patent search was mapped using Thomson Innovation's proprietary ThemeScape™ mapping tool. ThemeScape uses term frequency and other algorithms to cluster documents based on shared language – in this case the English Title, Abstracts and Claims from the patents together with the DWPI-enhanced Titles and Abstracts were mapped. It uses several algorithms to perform terminology-based clustering. The text from one record is compared with the text from all other patent records within the search collection. The map uses vectors to give each patent record a proximity score to all of its peers. The outcome of this analysis is a visualisation of the patent space with each patent (dot) represented once in the map, with patents in close proximity sharing more phraseology than those located apart. The patents are grouped into map "contours" to show areas of high and low patenting activity organised into common themes. The illustration shows these contour lines, with the "mountain peaks" representing a concentration of patents. Each peak is labelled with the key terminology concepts contained in the patents within the cluster.

Although the landscaping is not a precise tool, it is possible to identify clusters of technology areas on the map and this can be a useful tool for analysing trends. The resulting maps are shown on the following pages.

Overall, the gene editing landscape is divided into several islands of varying sizes. This may be a result of the diverse technology types and application areas but may also hint at a field in which the terminology between organisations varies greatly. As the technologies and the gene editing field mature, the use of well-established terminology may lead to a more cohesive landscape. However, based on the contour labels, there are still some trends that may be seen on the map: patents related to the gene editing processes and proteins appear to be concentrated across the middle of the landscape whilst patents related to the applications of the technologies are generally grouped around the top right and bottom left hand corners of the landscape map.

Separate searches were carried out to identify patents in the landscape that are relevant to the four key gene editing technologies as well as some of the key applications of gene editing technologies. The two sets of searches are shown on separate maps below.

Map 1 shows the distribution of the patents relating to the four different gene editing technologies. It appears that the islands in the top right and bottom left hand corners of the map appear to have patents related to all of the technologies as well as a large number of patents that are related to more than one technology based on the number of white dots. This indicates that patents related to applications of gene editing may not specify the technology required or include several different technologies.

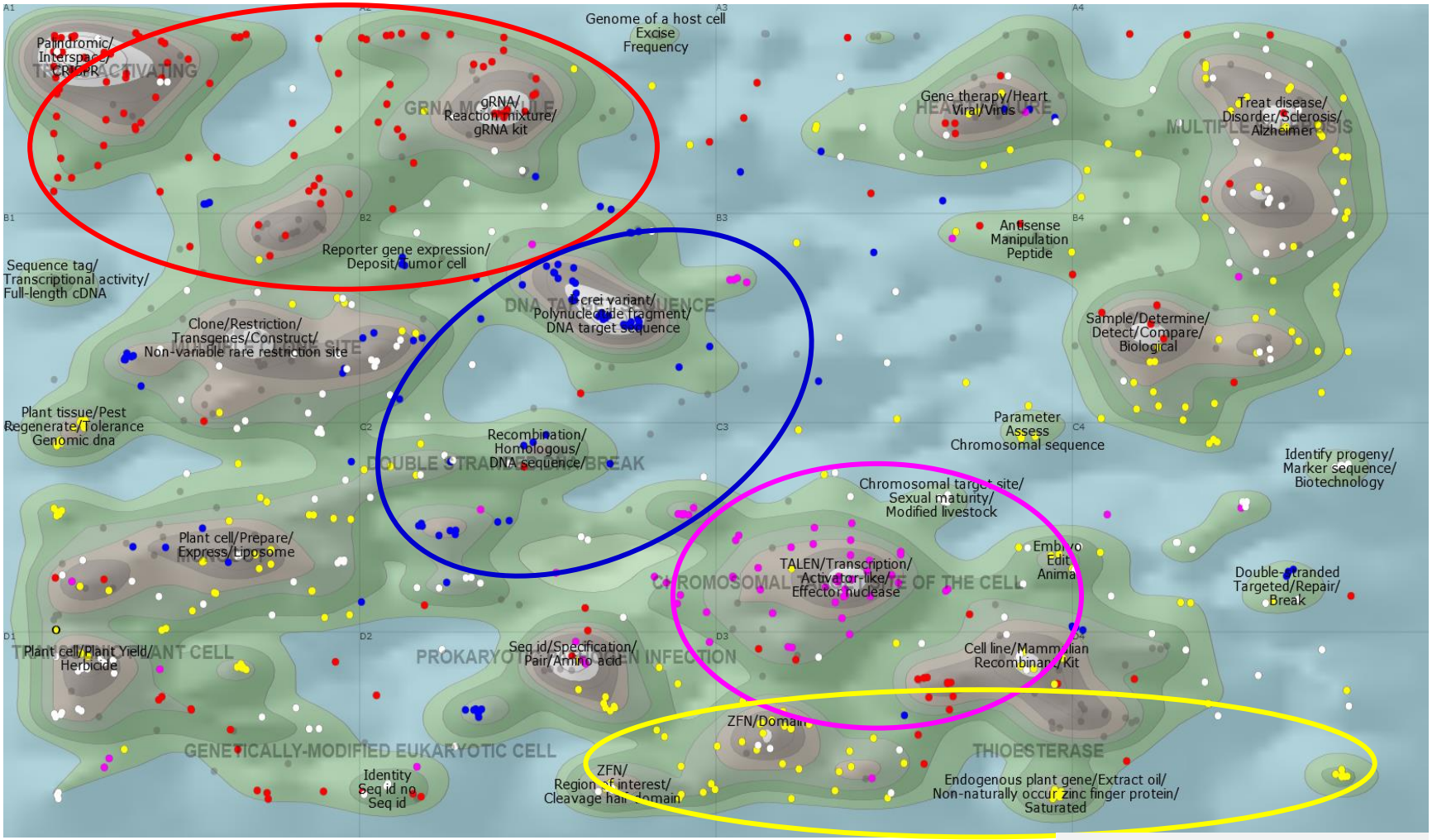
The cluster of CRISPR patents in the red circle appears to cover the largest area compared to the other technology clusters which is in line In line with the number of patent filings for the different technologies. It also sits in one corner of the landscape though this may change over time as CRISPR's dominance over the other technologies increases and it becomes more central to the structure of the landscape.

The second patent landscape map shows the distribution of patents relating to different application areas that can be easily defined with keywords. These areas did not include life science research as the keywords for the industry appear to apply to the majority of patents in the landscape. This shows that the research services and tools are most likely used across all industries and technologies.

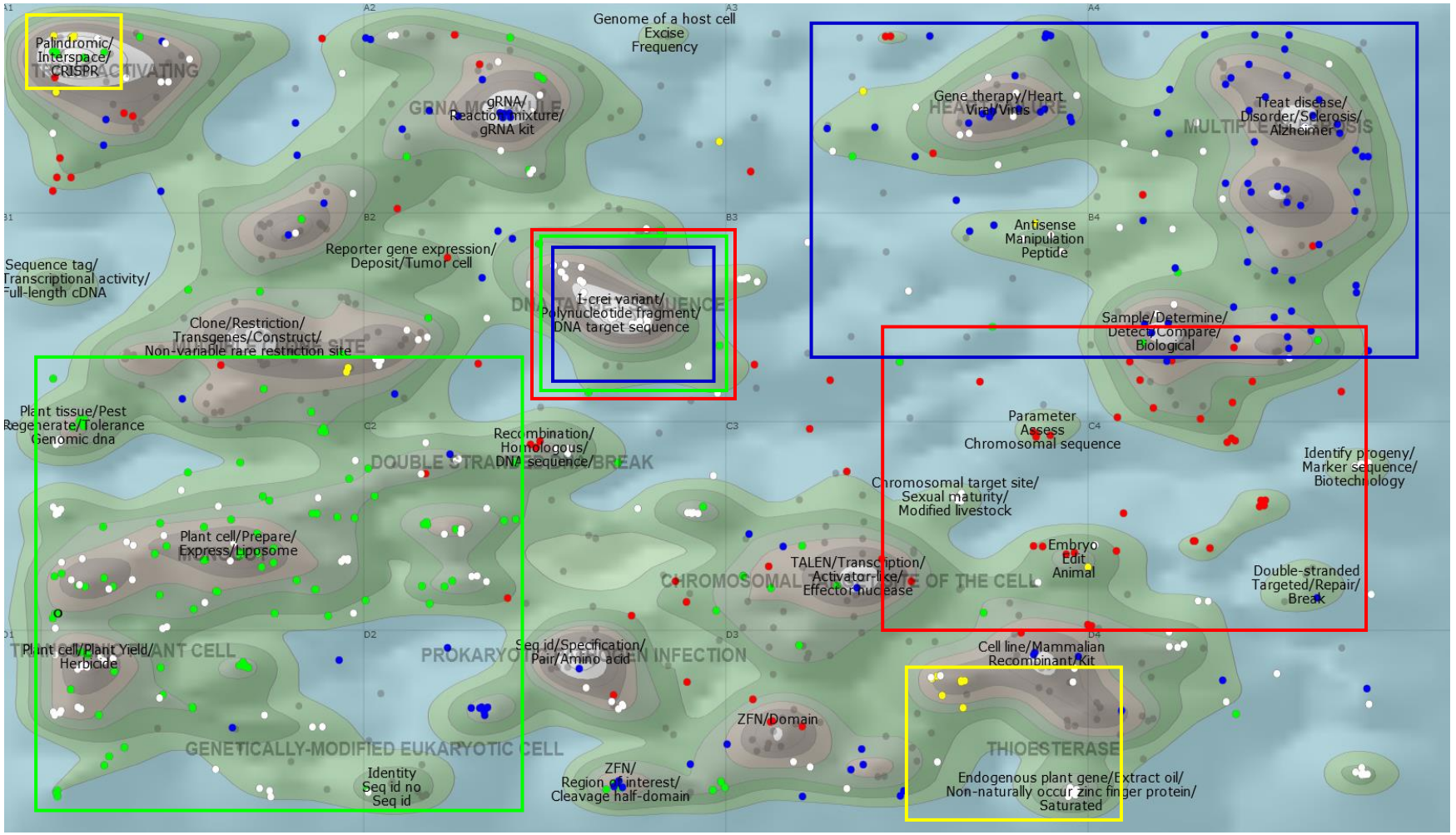
The clusters on Map 2 reinforce the observation of the major application areas being located in the top right and bottom left hand corners of the map. Overall, the clusters of the different applications areas appear to be in separate areas without much overlap. However, in the middle of the map, there is an area with a high number of white dots. Further analysis of this area showed that the patents in this area were related to keywords for plants/agriculture, gene therapy and animal/livestock. This area also overlaps with the area for Meganuclease patents as shown in Map 1.

The areas corresponding to CRISPR, TALENs and ZFN all have little or no clustering which may be related to the versatility of the technologies. Alternatively, this may also indicate the level of maturity of the technologies in that the patents still seek to cover the proteins and processes at this stage and consist of more foundational patents.

Gene editing applications in food and dairy are easy to define and were identified in the IPC analysis in a previous section of the paper. For these reasons, they have been included in the patent landscape map analysis even though the food industry has not been detailed as a key application area. The clustering for this application is minimal however it is clearly present which suggests a potentially upcoming application area.



Map 1: Gene editing patent landscape map identifying patents with keywords relating to gene editing or any of the four technologies in the claims, title or abstract. The dots refer to patents relevant to keywords related to the technologies in the legend. The circles indicate clusters of similar patents. The white dots refer to patents relevant to two or more the searches. (*Source: Thomson Innovation)*



Map 2: Gene editing patent landscape map identifying patents with keywords relating to gene editing or any of the four technologies in the claims, title or abstract. The dots refer to patents relevant to keywords related to the industry sectors in the legend. The squares indicate clusters of similar patents. The white dots refer to patents relevant to two or more the searches. (*Source: Thomson Innovation)*

KEY PATENTS

A citation analysis allows you to identify key patents and patent applications within a set of patent search results. Citations are documents that are linked together when one document mentions another as having related content. There are two reasons why a patent can be cited by another patent: the applicant disclosed it as known prior art, or the examiner found it during the search.

A "backward citation" is the term used for a traditional citation and refers to the document cited in a newer publication. A “forward citation” is a term more common in patent analysis and refers to the citing documents. The number of forward citations refer to citations received by a particular patent by subsequent patents. The frequency may be an indicator of key inventions or patents with high value. Publications with higher numbers of recent backward citations are more likely to be key strategic or defensive patents (Abrams, Akcigit, & Popadak, 2013).

FORWARD CITATIONS ANALYSIS

The table below details the top 10 patent publications with the highest number of forward citations. The DWPI Novelty has been included for each publication which is a summary of the novelty of an invention written by subject experts from Thomson Reuters. The more the recent the application date, the more likely it is for that the publication is a key invention. In this respect, there are two patents of note:

1. **WO2010075424A2** - The University of California’s patent application titled “*Compositions and methods for downregulating prokaryotic genes*” and ranked one.
2. **US20100076057A1** - The University of Northwestern’s patent application titled “Target DNA interference with crRNA” which is ranked four.

	No. of citations	Publication Number	Assignee - DWPI	Application date
1	39	WO2010075424A2	UNIV CALIFORNIA	2009-12-22
	Title: Compositions and methods for downregulating prokaryotic genes			
	Abstract - DWPI Novelty: An isolated polynucleotide comprises a clustered, regularly interspaced short palindromic repeat (CRISPR) array nucleic acid sequence, is new. The spacer of the CRISPR is sufficiently complementary to a portion of at least one prokaryotic gene so as to down-regulate expression of the prokaryotic gene.			
2	30	US20020187508A1	US GENOMICS INC	2002-06-10
	Title: Methods and products for analyzing nucleic acids using nick translation			

	Abstract - DWPI Novelty: Analyzing a nucleic acid molecule (NA), comprises exposing a NA to a sequence specific nicking enzyme, allowing the sequence specific nicking enzyme to introduce nicks into the NA, exposing the NA to a polymerase enzyme and labeled nucleotides, allowing the enzyme to incorporate labeled nucleotides into the molecule, and detecting a signal from the labeled nucleotides incorporated into the NA.			
3	30	US5496714A	NEW ENGLAND BIOLABS INC	1992-12-09
	Title: Modification of protein by use of a controllable intervening protein sequence			
	Abstract - DWPI Novelty: A modified protein (A) comprises a target protein and a controllable intervening protein sequence (CIVPS) capable of excision or cleavage under predetermined conditions.			
4	28	US20100076057A1	UNIV NORTHWESTERN	2009-09-23
	Title: Target DNA interference with crRNA			
	Abstract - DWPI Novelty: Inhibiting the function and/or presence of a target DNA sequence in a eukaryotic cell comprises administering crRNA and one or more clustered, regularly interspaced short palindromic repeat (CRISPR)-associated (cas) proteins, or nucleic acid sequences encoding the cas proteins, to a eukaryotic cell comprising a target DNA sequence, where the crRNA hybridizes with the target DNA sequence, thus interfering with the function and/or presence of the target DNA sequence.			
5	18	WO2004031346A2	HUTCHINSON CANCER RES CENT FRED	2003-09-05
	Title: Methods and compositions concerning designed highly-specific nucleic acid binding proteins			
	Abstract - DWPI Novelty: Creating a modified nuclease with nucleic acid sequence-specificity activity comprises identifying potential contact points between the DNA binding domain and the specific nucleic acid sequence.			
6	16	US6297054B1	UNIV RUTGERS STATE NEW JERSEY	1999-06-01
	Title: Editing-based selectable plastid marker genes			
	Abstract - DWPI Novelty: A novel recombinant chimeric DNA construct (I) useful for selection of plastid transformants, comprises an edited plastid gene segment translationally fused to the coding region of a selectable marker gene, which is expressible following RNA editing of the plastid gene segment.			

7	14	US6933362B1	HEALTH RES INST | RENSSELAER POLYTECHNIC INST	2000-08-17
	Title: Genetic system and self-cleaving inteins derived therefrom, bioseparations and protein purification employing same, and methods for determining critical, generalizable amino acid residues for varying intein activity			
	Abstract - DWPI Novelty: Screening (M1) for enhanced or reduced intein cleavage activity involves subjecting intein DNA to random mutagenesis, expressing the intein DNA with a reporter and screening for elevated or reduced intein cleavage activity using varying growth medium and conditions, or by an assay with a chemical that plays a part in a cell metabolic and/or biochemical cycle, respectively.			
8	12	US7098031B2	CELLECTIS SA	2002-09-13
	Title: Random integration of a polynucleotide by in vivo linearization			
	Abstract - DWPI Novelty: Randomly integrating a polynucleotide into a host cell genome by preparing into the host cell of the linear polynucleotide having free 5' and 3' ends from a vector, is new.			
9	12	US7309605B1	INST PASTEUR | UNIV CURIE PARIS VI	2004-04-09
	Title: Nucleotide sequence encoding the enzyme I-SceI and the uses thereof			
	Abstract - DWPI Novelty: A method to induce ≥ 1 site-directed double strand (ds) break in a cell's DNA comprises: (a) providing cells contg. ds DNA including≥1 I-SceI restriction site; (b) transfecting the cells with at least a plasmid comprising DNA encoding the I-SceI meganuclease; and (c) selecting cells in which ≥1 ds break has been induced.			
10	9	US7736886B2	INST PFLANZENGENETIK & KULTURPFLANZENFOR | SUNGENE GMBH	2004-01-05
	Title: Recombination systems and methods for eliminating nucleic acid sequences from the genome of eukaryotic organisms			
	Abstract - DWPI Novelty: Recombination system comprises, in a eukaryotic cell or organism: a transgenic recombination construct inserted into the chromosomal DNA of a eukaryote; and an enzyme that induces DNA double-strand breaks (or nucelic acid encoding it).			

BACKWARD CITATION ANALYSIS

The table below details the top 10 patent publications with the highest number of backward citations. The DWPI Novelty has been included for each publication which is a summary of the novelty of an invention written by subject experts from Thomson Reuters. Six out of the ten publications are patent applications assigned solely to Harvard College, three to The Broad Institute and one each to Recombinetics and Caribou Biosciences.

The assignees in the section are all organisations that have been identified in deals and analysis in previous sections. Generally they are all actively collaborating, licensing and commercialising gene editing technologies and it is likely that their portfolios would include the following significant strategic and defensive patent applications:

	No. of citations	Publication Number	Assignee - DWPI	Application date
1	213	US9322006B2	HARVARD COLLEGE	2014-06-30
	Title: Evaluation and improvement of nuclease cleavage specificity			
	Abstract - DWPI Novelty: Identifying a target site of a nuclease comprises: (a) providing a nuclease that cuts a double-stranded nucleic acid target site and creates a 5' overhang; (b) contacting the nuclease with a library of candidate nucleic acid molecules; (c) filling in the 5' overhangs of a nucleic acid molecule that has been cut twice by the nuclease and comprises a constant insert sequence flanked by a left half-site and cut spacer sequence on one side, and a right half-site and cut spacer sequence on the other side, thus creating blunt ends; and (d) identifying the nuclease target site cut by the nuclease.			
2	193	US9359599B2	HARVARD COLLEGE	2014-06-30
	Title: Engineered transcription activator-like effector (TALE) domains and uses thereof			
	Abstract - DWPI Novelty: Engineered transcriptional activator-like effectors (TALEs) are versatile tools for genome manipulation with applications in research and clinical contexts. One current drawback of TALEs is their tendency to bind and cleave off-target sequence, which hampers their clinical application and renders applications requiring high-fidelity binding unfeasible. This disclosure provides engineered TALE domains and TALEs comprising such engineered domains, e.g., TALE nucleases (TALENs), TALE transcriptional activators, TALE transcriptional repressors, and TALE epigenetic modification enzymes, with improved specificity and methods for generating and using such TALEs.			
3	192	US20150056177A1	HARVARD COLLEGE	2014-06-30
	Title: Engineered transcription activator-like effector (tale) domains and uses thereof			

	Abstract - DWPI Novelty: Isolated transcription activator-like effector (TALE) domain, is new. The isolated TALE domain is an N-terminal TALE domain and the net charge of the isolated N-terminal domain is less than the net charge of the canonical N-terminal domain (SEQ ID NO: 1 (a 136 amino acid sequence fully defined in the specification)) at physiological pH. The isolated TALE domain is a C-terminal TALE domain and the net charge of the C-terminal domain is less than the net charge of the canonical C-terminal domain (SEQ ID NO: 22 (a 63 amino acid sequence fully defined in the specification)) at physiological pH.			
4	155	US9322037B2	HARVARD COLLEGE	2014-06-30
	Title: Cas9-FokI fusion proteins and uses thereof			
	Abstract - DWPI Novelty: A fusion protein comprising (i) nuclease-inactivated clustered regularly interspaced short palindromic repeat (CRISPR) associated protein 9 (dCas9), and (ii) nuclease, is new.			
5	126	US9163284B2	HARVARD COLLEGE	2014-06-30
	Title: Methods for identifying a target site of a Cas9 nuclease			
	Abstract - DWPI Novelty: Identifying a target site of a RNA-programmable nuclease, comprises: (a) providing the nuclease that cuts a double-stranded nucleic acid target site; (b) contacting the nuclease with a library of candidate nucleic acid molecules, where each nucleic acid molecule comprises a concatemer of a sequence comprising a candidate nuclease target site and a constant insert sequence; and (c) identifying the nuclease target sites cut by the nuclease in (b) by determining the sequence of an uncut nuclease target site on the nucleic acid strand that is cut by the nuclease in step (b).			
6	104	US9260752B1	CARIBOU BIOSCIENCES	2015-01-22
	Title: Compositions and methods of nucleic acid-targeting nucleic acids			
	Abstract - DWPI Novelty: Method for detecting proximity of two complexes with each other, involves (a) contacting a first target nucleic acid with a first complex, where the first complex comprises a first site-directed polypeptide, a first modified nucleic acid- targeting nucleic acid, and a first effector protein, the effector protein is adapted to bind to the modified nucleic acid-targeting nucleic acid, and the first effector protein comprises a non-native sequence that comprises a first portion of a split system, and (b) contacting a second target nucleic acid with a second complex.			
7	97	WO2015089465A1	MASSACHUSETTS INST TECHNOLOGY | UNIV ROCKEFELLER | BROAD INST INC	2014-12-12

	Title: Delivery, use and therapeutic applications of the CRISPR-Cas systems and compositions for HBV and viral diseases and disorders			
	Abstract - DWPI Novelty: Modification of an organism or a non-human organism by manipulation of a target hepatitis B virus (HBV) sequence in a genomic locus of interest comprises delivering a non-naturally occurring or engineered composition comprising: (A) (I) a clustered regularly interspersed short palindromic repeats (CRISPR)-CRISPR-associated (Cas) (CRISPR-Cas) system RNA polynucleotide sequence, and (II) a polynucleotide sequence encoding a CRISPR enzyme, or (B) (I) polynucleotides comprising: (a) a guide sequence capable of hybridizing to a target HBV sequence, and (b) tracr mate sequences.			
8	89	EP3009511A2	HARVARD COLLEGE | MASSACHUSETTS INST TECHNOLOGY | BROAD INST INC	2016-01-07
	Title: Novel CRISPR Enzymes And Systems			
	Abstract - DWPI Novelty: An engineered, non-naturally occurring Clustered Regularly Interspersed Short Palindromic Repeat (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) system comprising Type V CRISPR-Cas polynucleotide sequences, and a Cpf1 effector protein, or nucleotide sequences encoding the Cpf1 effector protein, is new.			
9	84	US9074224B2	RECOMBINETICS INC	2010-08-26
	Title: Methods and compositions for targeted gene modification			
	Abstract - DWPI Novelty: A purified composition for transfection of exogenous DNA into chromosomal DNA of a cell, comprises a nucleoprotein filament of a probe and a proteinaceous fusion molecule, where the probe contains double-stranded denatured DNA complementary to a chromosomal DNA site, and the fusion molecule comprises a recombinase domain and a DNA-binding domain, where the composition is free of DNA sequences that specifically bind to the DNA-binding domain.			
10	83	WO2015089486A2	HARVARD COLLEGE | MASSACHUSETTS INST TECHNOLOGY | UNIV TOKYO | BROAD INST INC	2014-12-12
	Title: Systems, methods and compositions for sequence manipulation with optimized functional CRISPR-Cas systems			
	Abstract - DWPI Novelty: Non-naturally occurring or engineered composition comprises single guide RNA (sgRNA) comprising a guide sequence capable of hybridizing to a target sequence in a genomic locus of interest in a cell.			

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APPENDIX

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Animal health	TALEN	Recombinetics	Cellectis SA	Collaboration & Licensing	2011	$50m in sales-based milestones	Recombinetics' founders and scientific team were actively involved in the development and early application of TALENs and secured the global rights from Cellectis for TALENs applications in multiple livestock species.
Life Science Research	CRISPR	Caribou Biosciences	Novartis	Collaboration	2015		Caribou Biosciences collaboration focused on using CRISPR as a research tool for drug discovery
Life Science Research	CRISPR	Caribou Biosciences	Integrated DNA Technologies	Licensing	2016		Caribou has granted IDT a non-exclusive worldwide license to commercialize CRISPR-Cas9 reagents under Caribou's intellectual property. The license is subject to a research use limited label.
Life Science Research	Meganuclease	Cellectis S.A.	Biogen, Inc	Collaboration & Licensing	2005		Cellectis has entered into a research and co-development agreement with Biogen Idec for the development of a custom Meganuclease Recombination System (c-MRS)
Life Science Research	Meganuclease	Cellectis S.A.	Celonic GmbH	Collaboration & Licensing	2007		Under the agreement, Celonic received a commercial license to the cell line developed with Cellectis' meganuclease recombination system (MRS) technology. Meganucleases are biotechnological tools for performing precise gene insertion, modulation, deletion or substitution in any living cell.
Life Science Research	Meganuclease	Cellectis S.A.	Les Laboratoires Servier SAS	Licensing	2007		Servier signed an agreement with Cellectis for the use of Cellectis' p10 cell platform and meganuclease recombination system (MRS) by Servier for enabling the targeted and reproducible insertion of genes of interest in this cell line and for high-throughput screening
Life Science Research	Meganuclease	Cellectis S.A.	Cedarlane Laboratories Limited	Collaboration	2010		Cellectis bioresearch, a provider of ready- and easy-to-use tools for genome customization, entered into an agreement with Cedarlane Laboratories Limited, a manufacturer and distributor of research reagents, for the distribution of Cellectis bioresearch's research kits in Canada.

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Life Science Research	Meganuclease	Celonic GmbH	Cellectis bioresearch	Licensing	2009		Under the agreement, Cellectis secured rights to Celonic's meganuclease-based CEMAX technology, which will enable Cellectis bioresearch to sell kits using CEMAX technology for research and in vitro screening purposes. Celonic retains the rights to use the technology for the generation of cell-lines in the production of bio-therapeutics.
Life Science Research	Meganuclease	Helix BioService & Consultants Pvt. Ltd.	Cellectis S.A.	Collaboration	2010		Cellectis bioresearch entered into an agreement with Helixfor the promotion of Cellectis bioresearch's meganuclease-based products and services in India.
Life Science Research	CRISPR	Horizon Discovery	Desktop Genetics	Collaboration	2013		Horizon Discovery entered into a co-development agreement with Desktop Genetics for CRISPR design platform. Under the agreement, Desktop Genetics will design and implement algorithms for the new platform based on Horizon's input and CRISPR knowledge. The platform will be used by Horizon to quickly identify the best guide-RNAs in the human genome for each gene editing task, as part of its GENESIS suite of gene editing technologies. This agreement enables Horizon Discovery and Desktop Genetics to provide CRISPR design platform for gene editing to researchers.
Life Science Research	TALEN	Life Technologies Corp (bought by Thermo Fisher)	ToolGen, Inc.	Licensing	2013		ToolGen received sub-license covering nucleic acids encoding Transcription Activator-Like Effector Nuclease fusion proteins (TALENS).
Life Science Research	Meganuclease	Lonza Inc.	Cellectis S.A.	Collaboration	2010		Cellectis Bioresearch,a subsidiary of Cellectis, entered into an agreement with Lonza Ifor the development and commercialization of a bioengineered cell line.
Life Science Research	CRISPR	Sigma-Aldrich Corporation	The Wellcome Trust Sanger Institute	Collaboration	2015		Sigma-Aldrich Corporation has entered into an exclusive agreement with Wellcome Trust to manufacture and distribute Wellcome Trust's arrayed lentiviral clustered regularly interspaced short palindromic repeats (CRISPR) library. The library will be providing researchers with a collection of individual clones designed to knock out every known human and mouse protein-coding gene using the CRISPR system.
Life Science Research	TALEN	Sigma-Aldrich Corporation	Cellular Dynamics International	Licensing	2013		CDI licensed patents cover Life Technologies' GeneArt Precision TALs (TALENs) and Sigma's CompoZr ZFN technologies

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Life Science Research	ZFN	Sigma-Aldrich Corporation	Horizon Discovery	Licensing	2013		Horizon Discovery has a non-exclusive licensing agreement for Sigma's CompoZr ZFN.
Life Science Research	ZFN	Sigma-Aldrich Corporation	Cellular Dynamics International	Licensing	2013		CDI licensed patents cover Life Technologies' GeneArt Precision TALs (TALENs) and Sigma's CompoZr ZFN technologies
Life Science Research	ZFN	Sigma-Aldrich Corporation	Cyprotex	Licensing	2012		Cyprotex obtained license relating to the application of Sigma's exclusive CompoZr ZFN technology to ADME-Tox field to create a range of proprietary cell-based assays for drug candidate screening.
Life Science Research	ZFN	Sigma-Aldrich Corporation	Plasticell	Licensing	2010		Plasticell was licensed rights to CompoZr ZFN technology, to engineer various human stem cell lines that enable tracking of differentiation to specific mature cell types via fluorescent reporters, integrated directly into developmentally expressed genes
Life Science Research	CRISPR	ToolGen	Thermo Fisher Scientific	Licensing	2015		ToolGen and Thermo Fisher announced an agreement under which ToolGen will license its CRISPR/Cas9 intellectual property portfolio to Thermo Fisher Scientific.
Plant/Agriculture	CRISPR	Calyxt Inc (formerly Cellectis SA)	University of Minnesota	Licensing	2015		Cellectis Plant Sciences (now Calyxt, Inc.), signed an exclusive license agreement with the University of Minnesota that grants Cellectis the worldwide rights to use the technology covered by the patent rights of the family WO/2014/144155 entitled "Engineering Plant Genomes Using CRISPR/Cas Systems"
Plant/Agriculture	Meganuclease	Calyxt Inc (formerly Cellectis SA)	Monsanto	Licensing	2009		Monsanto announced a non-exclusive research and commercial license agreement with Calyxt for broad use of its meganuclease technology in plants.
Plant/Agriculture	Meganuclease	Calyxt Inc (formerly Cellectis SA)	BASF Plant Science	Licensing	2010		Cellectis, announced that BASF has just broadened its license to use their meganuclease technology. This agreement extends the license signed by Cellectis and BASF Plant Sciences in January 2006. Under a non-exclusive license, BASF Plant Science will use meganucleases engineered by Cellectis to make targeted modifications of plant genomes.

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Plant/Agriculture	Meganuclease	Calyxt Inc (formerly Cellectis SA)	SESVanderHave	Collaboration	2012		Calyxt announced a research and commercial agreement with SESVanderHave, a world leader in the sugar beet seed industry, on the use of Cellectis technologies in sugar beet. The agreement aims at developing commercial varieties for the sugar beet seed market using new breeding techniques and targeted genetic modifications.
Plant/Agriculture	Meganuclease	Calyxt Inc (formerly Cellectis SA)	Bayer CropScience	Collaboration	2014		Calyxt signed two new agreements with Bayer CropScience on gene editing in plants. The agreements extend the companies' existing partnership to introduce targeted modifications to selected plant genes and genomes. The first aim of this extended partnership is to collaboratively create commercial traits for the canola seed market using new technologies developed by Cellectis Plant Sciences. The second aim is to provide Bayer with access to technologies that enable the directed engineering of plant genome, such as gene stacking and targeted mutagenesis, for the development of improved crops.
Plant/Agriculture	TALEN	Calyxt Inc (formerly Cellectis SA)	2Blades	Licensing	2014		Calyxt and the 2Blades announced the execution of a non-exclusive cross-license agreement relating to TAL nuclease technologies. Pursuant to the agreement, 2Blades receives a license to TALEN™ technology for not-for-profit uses, including use in 2Blades' humanitarian efforts to support subsistence farming, and for certain commercial applications related to the disease resistance programs of 2Blades. In addition, pursuant to the agreement, Calyxt receives a license under 2Blades' TAL Code technology related to nucleases for commercial uses in certain specified crop plants. Calyxt has an option to expand its license to additional crops.
Plant/Agriculture	Unknown	Calyxt Inc (formerly Cellectis SA)	S&W Seed Company	Collaboration	2015		S&W and Calyxt announced they have entered into a collaboration agreement to research, develop, produce, and commercialize alfalfa seed products involving next generation gene editing technology on S&W's industry leading alfalfa seed genetics.
Plant/Agriculture	Unknown	Calyxt Inc (formerly Cellectis SA)	University of Minnesota	Licensing	2015		Calyxt, Inc., announced an exclusive license agreement with the University of Minnesota that grants Calyxt the worldwide rights to use the technology covered by the patent rights of the family PCT/US2013/046495 entitled "Gene Targeting Using Replicating DNA Molecules".

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Plant/Agriculture	Unknown	Calyxt Inc (formerly Cellectis SA)	Plant Bioscience Limited (PBL)	Collaboration & Licensing	2015		Calyxt, Inc., announced a research collaboration and option to exclusive licenses with Plant Bioscience Limited (PBL) for certain new crop plants developed using gene editing by the Institute of Genetics and Developmental Biology (IGDB) of the Chinese Academy of Sciences in Beijing.
Plant/Agriculture	CRISPR	Caribou Biosciences	Fidelity Biosciences, Novartis, Mission Bay Capital, 5 Prime Ventures	Venture	2015	$11m	Caribou raised $11m in a Series A funding round. In addition to the named investors, there was also an undisclosed strategic partner.
Plant/Agriculture	CRISPR	Caribou Biosciences	Intellia Therapeutics	Venture & Licensing	2014		Atlas Venture and Caribou launched Intellia. Caribou provided Intellia with an exclusive license to utilize its technology platform for the discovery, development, and commercialization of human gene and cell therapies.
Plant/Agriculture	RTDS	Cibus	Nucelis Inc	Acquisition	2014		Cibus acquired the remaining interest in Nucelis which has an exclusive license to Cibus' RTDS™ technology in its key product areas of fermentation and bio-based chemicals.
Plant/Agriculture	ZFN	Dow Agro-Sciences LLC	ICS-CAAS (Chinese Academy of Agricultural Sciences)	Collaboration & Licensing	2015		Dow AgroSciences granted ICS-CAAS a royalty-free, non-transferable research and commercialization license for its proprietary EXZACT™ Precision Genome Editing Technology to be used in rice in China.
Plant/Agriculture	ZFN	Dow Agro-Sciences LLC	Sigma-Aldrich	Licensing	2014		Dow entered into an exclusive manufacturing license and supply agreement with Sigma-Aldrich, to provide ZFN kits and reagents for use with Dow's EXZACTTM Precision Technology. Under the terms of the agreement, Sigma-Aldrich will be the exclusive provider of ZFN reagents for use in plants which will be available to Dow, its affiliates and licensees of the EXZACT Precision Technology.
Plant/Agriculture	Meganuclease	Duke University Medical Center	Precision Biosciences, Inc.	Licensing	2006		Precision entered into an exclusive worldwide licensing agreement with Duke University to receive exclusive rights for the directed nuclease editor technology developed at the university, including the patent application and related materials.

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Plant/Agriculture	CRISPR	DuPont	Caribou Biosciences	Collaboration & Licensing	2015		The companies have formed a strategic alliance to advance their CRISPR-derived gene editing technology platforms. This multi-faceted agreement includes the cross-licensing of key intellectual property, a research collaboration, and financial investments by DuPont in Caribou, a developer of CRISPR-Cas technologies.
Plant/Agriculture	Meganuclease	Precision BioSciences Inc.	Duke University Medical Centre	Licensing	2006		Precision BioSciences receives exclusive rights for the directed nuclease editor technology developed at the university, including the patent application and related materials. This agreement enables Precision BioSciences to develop and commercialize the meganuclease design technology.
Plant/Agriculture	Meganuclease	Precision BioSciences Inc.	Calyxt Inc (formerly Cellectis SA)	Licensing	2014		Cross-license and settlement agreement for gene editing technology including the part that settles patent litigation involving engineered I-CreI meganuclease technology. This agreement enables broad commercialization of highly specific engineered meganuclease technology with its full potential to be developed in applications such as bio-production and agricultural biotechnology.
Plant/Agriculture	Unknown	Precision BioSciences Inc.	Fidelity Biosciences, Amgen Ventures, Baxter Ventures, Osage University Partners, the Longevity Fund	Venture	2015	$25.6m	Precision BioSciences, announced the closing of a $25.6 million Series A financing led by venBio. Joining in the oversubscribed financing were Fidelity Biosciences, Amgen Ventures, Baxter Ventures, Osage University Partners, the Longevity Fund, and two well-known public market investors.
Plant/Agriculture	Unknown	Precision BioSciences Inc.	Agrivida	Collaboration	2014		A trait development collaboration based on precise gene modifications generated by Precision's Directed Nuclease Editor™ (DNE) Technology. The collaboration aims to improve the nutritional characteristics of crops and develop a pipeline of agricultural products for the dairy and beef market segments.
Plant/Agriculture	ZFN	Sangamo Biosciences	Dow Agrosciences	Licensing	2005	$21.4m total	Sangamo granted commercial licensing rights to Dow AgroSciences for the use of its zinc finger DNA-binding protein (ZFP) technology to develop products exclusive basis in plant agriculture, industrial products, and non-exclusive basis, animal health and biopharmaceutical products produced in plants. Sangamo also granted an option to Dow for the commercial license to sell products incorporating/derived from plant cells generated using ZFP technology, including agricultural crops, industrial products and plant-derived biopharmaceuticals.

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Therapeutics	CRISPR	AstraZeneca	Innovative Genomics Institute	Collaboration	2015		Under the agreement, both companies will focus on either inhibiting (CRISPRi) or activating (CRISPRa) genes to understand their role in disease pathology. The IGI and AstraZeneca will work closely together to identify and validate gene targets relevant to cancer, cardiovascular, metabolic, respiratory, autoimmune and inflammatory diseases and regenerative medicine to understand their precise role in these conditions.
Therapeutics	CRISPR	AstraZeneca	The Broad Institute	Collaboration	2015		This agreement enables AstraZeneca, Broad Institute and Whitehead Institute to evaluate a genome-wide CRISPR library against a panel of cancer cell lines for identifying new targets for cancer drug discovery.
Therapeutics	CRISPR	AstraZeneca	The Wellcome Trust Sanger Institute	Collaboration	2015		Under the agreement, the both companies will focus on deleting specific genes relevant to cancer, cardiovascular, metabolic, respiratory, autoimmune & inflammatory diseases and regenerative medicine to understand their precise role in these conditions.
Therapeutics	CRISPR	AstraZeneca	Thermo Fisher Scientific Inc	Collaboration	2015		Under the agreement, AstraZeneca will provide cell lines, compounds and will receive RNA-guide libraries that target individual known human genes and gene families.
Therapeutics	Meganuclease	Bluebird Bio	Kite Pharma	Collaboration	2015	Not disclosed	Meganuclease and TALEN hybrid. Collaboration for HPV-related cancer treatments. Companies to share all R&D and commercial costs and split profits 50-50
Therapeutics	TALEN	Bluebird Bio	Kite Pharma	Collaboration	2015	Not disclosed	Meganuclease and TALEN hybrid. Collaboration for HPV-related cancer treatments. Companies to share all R&D and commercial costs and split profits 50-50
Therapeutics	Unknown	Bluebird Bio	Precision Genome Engineering Inc. (Pregenen)	Acquisition	2014	$24m upfront; $140m total	Pregenen were a leader in the development and reprogramming of novel Homing Endonuclease and MegaTAL hybrid enzymes for gene-editing.
Therapeutics	Unknown	Bluebird Bio	Celgene	Collaboration	1905	$225m	CAR-T cancer drug programs. Narrowed to just one in 2015.

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Therapeutics	Meganuclease	Cellectis S.A.	VitamFero SA	Collaboration & Licensing	2011		Cellectis entered into a research, development and licensing agreement with VitamFero for the development of vaccines against parasitic infection, for a period of five years. Under the agreement, Cellectis will provide VitamFero with preselected meganucleases for initial use in the development of vaccines against parasites responsible for toxoplasmosis, neosporosis, and others.
Therapeutics	TALEN	Cellectis S.A.	Pfizer	Collaboration & Licensing	2014	$80m upfront; $185m per product; $2.8bn total.	TALEN for CAR-T cell development. Pfizer has exclusive rights to develop and commercialise CAR-T cancer therapies directed at 15 targets. The companies are working together on pre-clinical research, with Pfizer overseeing development and commercialisation. Cellectis is pioneering the allogenic CAR-T cell approach using gene editing.
Therapeutics	TALEN	Cellectis S.A.	Servier	Collaboration & Licensing	2014	$38.2m upfront; $300m in milestones	TALEN for CAR-T cell development. Servier obtains global rights to the program, and the US rights to Pfizer.
Therapeutics	CRISPR	CRISPR Therapeutics	Celgene & GSK	Venture	2015	$64m upfront. $89m total.	CRISPR for use in CAR-T cell therapy development
Therapeutics	CRISPR	CRISPR Therapeutics	Vertex Pharmaceuticals	Licensing	2015	$75m upfront; $30m equity; $2.6bn total	CRISPR. Up-front commitment of $105 million to CRISPR, including $75 million in cash and a $30 million equity investment
Therapeutics	CRISPR	CRISPR Therapeutics	Bayer	Collaboration	2015	$30m total	Targeting blood disorders, blindness and congenital heart disease. Key goal is in vivo solutions. Bayer also acquired a minority stake in CRISPR Therapeutics for an additional $35 million investment
Therapeutics	CRISPR	Editas Medicine	Polaris, Third Rock and Flagship	Venture	2013	$47m	Venture funding from: Polaris, Third Rock and Flagship

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Therapeutics	CRISPR	Editas Medicine	Juno Therapeutics	Collaboration & Licensing	2015	$25m upfront; $737m total	CRISPR for use in CAR-T immunotherapies.
Therapeutics	CRISPR	Editas Medicine	MIT, Broad Institute & Harvard University	Licensing	2014	Not disclosed	CRISPR/Cas9 licensed for specific gene targets. Non-exclusive licenses for other applications available for other parties; IP is available for the research community.
Therapeutics	CRISPR	Editas Medicine	Massachusetts General Hospital	Licensing	2014	Not disclosed	Exclusive license agreement to access CRISPR/Cas9 and TALENS IP for prevention and treatment of human or animal disease and broad agricultural use
Therapeutics	CRISPR	Intellia Therapeutics	Novartis AG	Collaboration	2015	$15m upfront; remainder undisclosed	CRISPR for CAR-T cell and hematopoietic stem cells. Novartis receives exclusivity for CAR-T programs and right to develop undisclosed number of targets for ex vivo editing of HSCs. Non-exclusive rights for in vivo editing of CRISPR.
Therapeutics	TALEN	Iowa State University	Cellectis S.A.	Licensing	2011		Under the agreement, Cellectis received exclusive world-wide licensing rights related to the use of TAL technologies in any field. Cellectis integrated TALENs into its DNA Nuclease production platform.
Therapeutics	TALEN	Life Technologies Corp (bought by Thermo Fisher)	Cellular Dynamics International, Inc.	Collaboration & Licensing	2012		Under the agreement, Cellular Dynamics received sub-license covering nucleic acids encoding Transcription Activator-Like Effector Nuclease fusion proteins (TALENS)
Therapeutics	ARCUS	Precision BioSciences Inc.	Baxalta Inc.	Collaboration	2016		A collaboration to develop a broad series of allogeneic chimeric antigen receptor (CAR) T cell therapies directed towards areas of major unmet need in multiple cancers. Precision BioSciences' proprietary ARCUS genome editing technology enables the production of CAR T cells derived from healthy donors rather than relying on the patient, thus overcoming the manufacturing-related limitations with existing CAR T therapies
Therapeutics	Meganuclease	Precision Genome Engineering, Inc.	Cellectis S.A.	Collaboration	2011		Cellectis entered into an agreement with Pregenen for the development of Meganucleases, for use in key therapeutic applications.
Therapeutics	Unknown	Sangamo Biosciences	Ceregene	Acquisition	2013	$2.7m	Acquired Cregene Inc, focussed on developing adeno-associated virus (AAV) gene therapies. Sangamo receive 120 patents.

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Therapeutics	ZFN	Sangamo Biosciences	CHDI	Licensing	2011		The companies entered into a collaboration to develop a novel therapeutic for Huntington's disease based on Sangamo's ZFP technology.
Therapeutics	ZFN	Sangamo Biosciences	Hoffman-La Roche	Licensing	2008		Roche obtained a worldwide license for Sangamo's proprierary ZFN technology and also has an option to obtain an exclusive worldwide license for the commercial use of the ZFN-generated transgenic animals in the production of therapeutic and diagnostic products.
Therapeutics	ZFN	Sangamo Biosciences	Genentech Inc	Licensing	2008		Sangamo expanded its April 2007, $0.4m research and license agreement with Genetech for protein pharmaceutical production, to include additional targets for the improvement of production cell lines using Sangamo's ZFN technology.
Therapeutics	ZFN	Sangamo Biosciences	Open Monoclonal technologies	Licensing	2008		Sangamo granted worldwide licensing rights to OMT for the commercial use of their zinc finger DNA-binding protein (ZFP) technology, for generation of transgenic animals.
Therapeutics	ZFN	Sangamo Biosciences	MaxCyte's	Licensing	2006		Under the agreement, Sangamo will receive license to use MaxCyte's proprietary cell loading system for its HIV/CCR5 ZFP Therapeutic program.
Therapeutics	ZFN	Sangamo Biosciences	LifeScan	Collaboration & Licensing	2004		LifeScan received access to use Sangamo's proprietary zinc finger DNA binding proteins (ZFPs) to develop therapeutic cell lines as a potential treatment for diabetes.
Therapeutics	ZFN	Sangamo Biosciences	Pfizer	Licensing	2008	$3m	Pfizer was granted non-exclusive rights for zinc finger nucleases for protein production
Therapeutics	ZFN	Sangamo Biosciences	Pfizer	Collaboration	2005		The companies entered into a research agreement under which Sangamo will provide its ZFP technology to Pfizer for feasibility check in mammalian cell- based protein pharmaceutical production and Pfizer will fund research at Sangamo.
Therapeutics	ZFN	Sangamo Biosciences	Shire	Collaboration & Licensing	2012	$13m upfront; $33.5m for each target; $180m for specified milestones; $213.5m total	Sangamo ZFP technology development for haemophilia, Huntington's disease and other monogenic diseases. Shire terminated involvement with Haemophilia A&B programme; Sangamo continuing to clinical trial.

Industry	Technology	Licensor/Acquirer	Licensee/Acquired	Deal Type	Year	Financials	Details
Therapeutics	ZFN	Sangamo Biosciences	Biogen Idec	Collaboration & Licensing	2014	$20m upfront; $329m total	Sangamo ZFP technology development for treatments targeting sickle cell disease (SCD) and beta thalassemia. Initial upfront payments and ongoing payments tied to development, regulatory, commercialization, and sales milestones; as well as double-digit royalties on product sales.
Therapeutics	ZFN	Sangamo Biosciences	Sigma-Aldrich Corporation	Licensing	2007	$20m upfront; $5m license fees based on %net sales	Sangamo ZFP exclusive rights for development and commercialisation of research reagents, products and services in the research field; ZFP modified cells later included (2009) for commercial production of protein pharmaceuticals and transgenic animal production. Net sales include sublicensing revenue; thereafter Sangamo recieves 10.5% royalty rate
Therapeutics	ZFN	Sigma-Aldrich Corporation	Hoffman-La Roche	Licensing	2008		Roche was obtained a worldwide license for Sigma's proprierary ZFN technology and also has an option to obtain an exclusive worldwide license for the commercial use of the ZFN-generated transgenic animals in the production of therapeutic and diagnostic products.
Therapeutics	TALEN	Thermo Fisher Scientific Inc.	Cellectis S.A.	Licensing	2014		Thermo Fisher granted a worldwide license to Cellectis for TAL nucleases to therapeutic R&D, including rights to grant sub-licenses for therapeutic uses in the fields of T cells and Natural Killer cells.
Therapeutics	TALEN	University of Minnesota	Cellectis S.A.	Licensing	2011		Under the agreement, Cellectis obtained worldwide rights to use inventions covering all uses of the technology in any field related to TAL effector-mediated DNA recognition and cleavage from UM.
Therapeutics	Meganuclease	Vlaams Instituut voor Biotechnologie	Cellectis S.A.	Collaboration	2010		VIB entered into an agreement with Cellectis a biotechnology company, to develop a new approach for the treatment of haemophilia.