TESTBIOTECH Background 29 - 06 - 2018

Genome Editing: Increasing monopolisation in agriculture and breeding

Patents can also impact conventional breeding

Testbiotech e. V.
Institute for Independent Impact Assessment in Biotechnology

Christoph Then & Ruth Tippe

In the discussion concerning new methods of genetic engineering, several experts are of the opinion that these new technologies are cheaper than previous genetic engineering methods and, therefore, more affordable for smaller companies and not just for the biotech giants. However, this overlooks the fact that the new methods using nucleases, such as CRISPR-Cas9, are patented in the same way as manipulated plants and animals.

Patents on the basics of CRISPR technology

Companies, such as Bayer, Monsanto and DuPont, have long since had contracts with the DNA-scissor inventors from the Broad Institute, which cooperates with the Massachusetts Institute for Technology, MIT & Harvard University and the University of California, to use their patents. These US institutions have already filed many more than 100 patent applications on the technology and its applications for plants, animals and humans. Several of them already have been granted in Europe (such as EP2800811 B1, EP3241902 B1).

Table 1: Overview of patent cooperation between seed giants and the developers of CRISPR technology

Company	Cooperation with
Bayer	ERS Genomics and CRISPR Therapeutics
DowDupont	University of California / Caribou
Monsanto	Broad Institute
Syngenta	Broad Institute

Patents on genome editing and applications for food plants

Companies file further patents for specific applications in plant breeding. For example, Bayer, Monsanto and DowDuPont have filed their own patents on nucleases, their uses and the resulting manipulated plants. In many cases, these patent applications reveal that the new methods are just a tool for following old strategies. For example, the nucleases are used simply to produce additional herbicide resistant or insecticidal plants. Such patent applications comprise the majority of those filed by Bayer in this context. Old ideas are being dressed up as inventive innovations through new methods of genetic engineering: Bayer as well as DowDupont and Monsanto have been filing patents on glyphosate- resistant plants that are engineered with the help of CRISPR technology. These patents can be used to build up new patent monopolies to protect the core business of the agrochemical companies i.e. genetically engineered herbicide-resistant soybeans, maize, oilseed rape and cotton. This is a very specific application of the so-called innovation principle and could be seen as an attempt to dress up old ideas in new packaging.

There are also patent applications that are more specific to the new methods of genetic engineering: For example, DowDuPont as well as Monsanto have filed for patents on naturally occurring DNA

sequences in plant genomes that are supposedly particularly suitable for nuclease applications. Other patent applications are for e.g. changed growth, changed plants composition, resistance to plant diseases or specific technical variations in the application of nucleases.
Most of these patents cover the methods as well as the seeds, the plants and in many cases also the harvest.

Bayer in particular has been cooperating with other companies, such as Cellectis (which is closely connected to Calyxt that wants to market some CRISPR plants soon), as well as CRISPR Therapeutics. Bayer has a particular interest here - CRISPR Therapeutic. One of the inventors of CRISPR Cas9 and a founder of CRISPR Therapetic, Emmanuelle Charpentier, will hand over all applications for use on plants and animals in the agricultural sector exclusively to the company for further use.

Table 2: Some examples of patent applications on food plants and applications for CRISPR-Cas

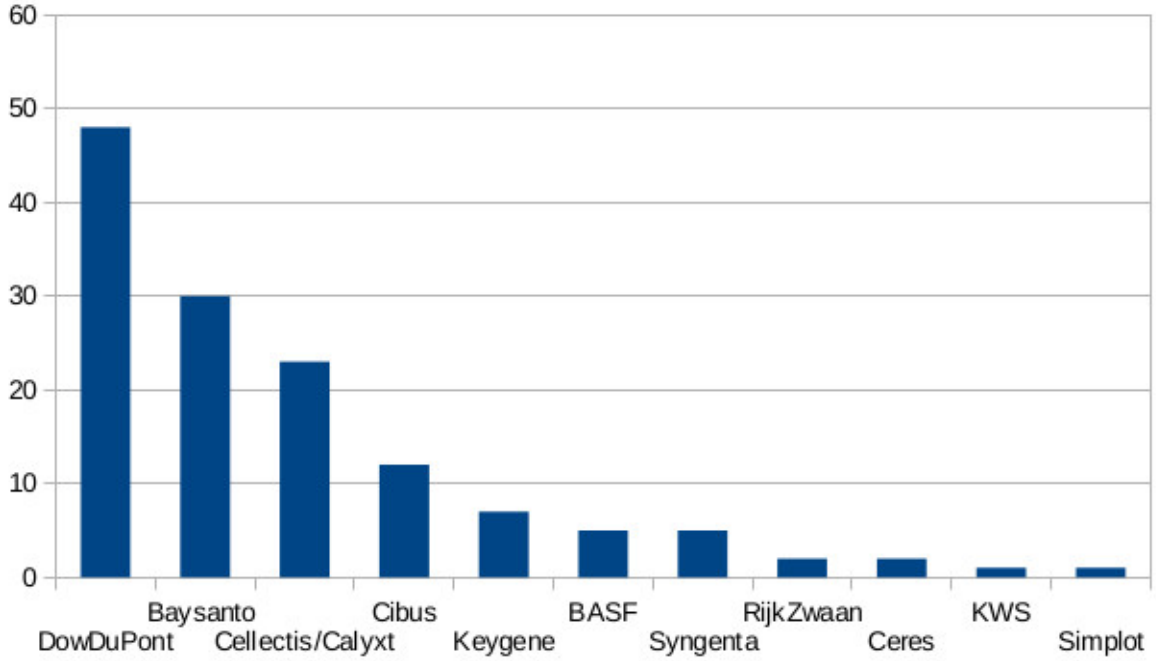
Patent number	Company	Content
WO2014161821	Bayer	Use of nucleases for production of transgenic plants
WO2017158126	Bayer	Male sterility / CMS
WO2018054911	Bayer	Use of nucleases for production of transgenic plants such as those showing glyphosate resistance
WO2017062855	Monsanto	New CRISPR tools and plants and animals (respectively their cells) being engineered with
WO2018035354	Monsanto	Using CRISPR and other tools & methods to bring about changes in structure and growth in order to increase yield.
WO2018064516	Monsanto	Sites in the genome of plants especially suitable for insertion of additional DNA using nucleases.
WO2014039702	DowDuPont	Soybeans with altered oil composition
WO2015066634	DowDuPont	Sites in the genome of soybean plants especially suitable for insertion of additional DNA using nucleases.
WO2017132239	DowDuPont	Maize with changes in quality of starch ('waxy maize')
WO2017222779	DowDuPont	Causing double stranded breaks to promote new recombinations of parts of chromosomes that would not be likely to occur in conventional breeding
WO2014141147	Cellectis / Calyxt	Soybeans with altered oil composition
WO2018035456	Cellectis / Calyxt	Black-spot resistant potatoes
WO2018092072	Cellectis / Calyxt	Changes in composition of amino acids through frameshift manipulation

Impact on the seed market

The patents will allow the influence of the large seed companies to expand further - and also promote concentration in this business sector. Currently, just three companies, Monsanto, DuPont (now merged with Dow AgroSciences) and Syngenta, control around 50% of the international seed market. Of these DowDuPont is leading by around 50 international patent applications for genome editing and plants (filed at the WIPO in Geneva), and is followed by 'Baysanto' with around 30 applications. Cellectis and its subsidiary Calyxt, which cooperated with Bayer, is registered with more than 20 applications. Further applicants are Syngenta and BASF. Very few patents have been filed by traditional breeding companies, such as Rijk Zwaan and KWS.

There was a similar situation around 20 years ago when quite a number of companies attempted to make a profit from the genetic engineering of plants. The only survivors from this era are those companies that had enough money to hire the best patent attorneys and filed numerous patents. Experience shows that in a scenario dominated by patents, small and medium sized breeders cannot survive in the long-term – contrary to situation within plant variety protection law.

Figure: Number of international patent applications (WIPO /WO) in the food plant sector and genome editing per company (2008-June 2018).



Patents on livestock

This development will also affect animal breeding. Genus, one of the largest companies in the livestock breeding sector, has already announced that it intends to use animals produced with gene-editing technology, and is in cooperation with Recombinetics, a company that has already filed around a dozen patents on pigs and cattle.

Table 3: Examples of patents filed by Recombinetics (USA) for livestock genetically engineered with nucleases, such as CRISPR-Cas

Application Number	Claims
WO 2012116274	Methods using nucleases to increase muscle growth in cattle and pigs.
WO 2013192316	Methods using nucleases to increase muscle mass in certain cattle; and produce hornless cattle.
WO 2014070887	Livestock that do not reach sexual maturity and can be fattened for longer. Farmers cannot use these animals for breeding.
WO 2014110552	Hornless cattle for natural and synthetic genetic applications.
WO 2015168125	Animals with multiple genetic changes.
WO2055030881	Applications of nucleases (TALEN) and resulting animals. Amongst others, pigs, cattle, horses, fish, dogs, cats and primates are claimed.
WO 2017062756	Male sterility in livestock as well as wild populations.
WO2017040695	Selection of genetic variants in cattle such as polled, climate adaptation and fertility and other related usages.

Impact on conventional breeding

These developments can have serious implications for conventional breeding: the patents not only cover technical processes, but also plants and animals and their breeding characteristics. The so-called 'absolute product protection' is applied here: these patents cover all plants and animals as described in the patent claims, no matter whether genetic engineering (such as genome editing) or conventional breeding was used to produce them. For example, if a lettuce is made resistant to aphids, such a patent can cover both the plants manipulated with CRSIPR-Cas as well as those derived from conventional breeding. This means that the prohibitions on the patenting of conventional breeding as foreseen by law can be circumvented.

Table 4: Examples of patent applications for genome editing and conventional breeding

Patent number	Company	Content
WO 2014110552	Recombinetics	Hornless cattle for natural and synthetic genetic applications.
WO2017040695	Recombinetics	Selection of genetic variants in cattle such as polled, climate adaption and fertility and related usages.
WO2017044744	Monsanto	Mildew resistance in maize
WO2017106731	Monsanto	Northern leaf blight resistance
WO2018031874	Monsanto	Resistance to 'late wilt' in maize
WO2014006159	Bayer	Changed oil composition in soybean
WO2015000914	Bayer	Changes in flowering times
WO2016176476	Bayer	Changed oil composition in oilseed rape

Interestingly, in their patent applications the companies clearly distinguish between conventional mutation breeding and genome editing in the technical description. Contrary to what the public are being told, Monsanto, for instance, clearly regards CRISPR-Cas applications as a method of genetic engineering and not just plant breeding. For example, in several Monsanto patents applications it states that (see e.g. WO2017044744, page53): „*Exemplary genome engineering techniques include meganucleases, zinc-finger nucleases, TALENs and CRISPR/Cas 9 systems (...). A plant or seed disclosed herein can also be subject to additional breeding using one more known methods in the art e.g., pedigree breeding, recurrent selection, mass selection, and mutation breeding.*“

The distinction made by Monsanto is especially important in regard to the question of how these new technologies should be regulated. In this context, this overview on patent applications provides further evidence that genome editing should be regarded as genetic engineering even if no additional genes are inserted: patents such as WO2017222779 (causing double stranded breaks to promote new recombinations of parts of chromosomes) or WO2018092072 (changes in composition of amino acids through frameshift manipulation) are about processes to circumvent the natural mechanisms of gene regulation to create plants with characteristics that are not likely to result from conventional breeding. Therefore these plants – no matter whether patentable or not – should be subjected to detailed risk assessment.