India

Underweight *(no change)*

Highlighted Companies

UPL Limited

REDUCE, TP Rs754, Rs683 close

Rising raw material prices will hit the company, as they have done for Rallis India. UPL operates in multiple geographies and forex risk is inherent in the business. Given the inherent macro risk in business, we feel UPL can never trade close to other chemical companies like PI Industries on a forward P/E basis.

Rallis India Ltd

REDUCE, TP Rs180, Rs189 close

Business challenges like supply chain and raw material procurement have led to continuous disappointment on the EPS front.

Dhanuka Agritech Ltd

REDUCE, TP Rs704, Rs651 close

We expect gross margin pressure to accentuate in the coming quarters as imported cost of azoxystrobin is on the rise (a key input for the Godiwa product).

Summary Valuation Metrics

P/E (x)	Mar22-A	Mar23-A	Mar24-F
UPL Limited	15.83	14.42	12.28
Rallis India Ltd	22.44	16.42	15.8
Dhanuka Agritech Ltd	15.05	14.25	13.5

P/BV (x)	Mar22-A	Mar23-A	Mar24-F
UPL Limited	2.17	1.89	1.64
Rallis India Ltd	2.17	1.98	1.82
Dhanuka Agritech Ltd	3.24	2.77	2.39

Dividend Yield	Mar22-A	Mar23-A	Mar24-F
UPL Limited	1.66%	1.82%	2.14%
Rallis India Ltd	1.58%	1.71%	1.77%
Dhanuka Agritech Ltd	1.33%	1.4%	1.48%

Chemicals - Overall

Gene editing is at the cusp of a revolution

- On 6 May 2023, China's Ministry of Food and Agriculture approved the safety of gene-edited soyabean, the first gene-edited crop, which is a remarkable and alarming feat for pesticide companies as China is their largest market.
- Gene editing is a revolutionary technology which will help us understand and rewrite the code of life i.e., DNA. However, this was not an easy task with earlier techniques (ZFN & TALENs). CRISPR has changed it all.
- As CRISPR can be used to create seeds that can be protected from various viruses & fungi coupled with relatively easy regulatory oversight, it can sound the death knell for agrochemicals. However, seed companies can benefit from this, especially those with good germplasm repositories.

Gene editing to change agrochemicals industry for the better

Much of the recent optimism that we see in the field of gene editing (GE) has been due to the invention of a technology called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). A significant amount of attention is paid to CRISPR these days involving its potential to make inheritable (germline) edits in humans and plants that will be passed along to all the cells of all future descendants and can alter the species. What clinches the deal for this technology is its simplicity and affordability and that, even you & I, without any scientific background, can easily use it.

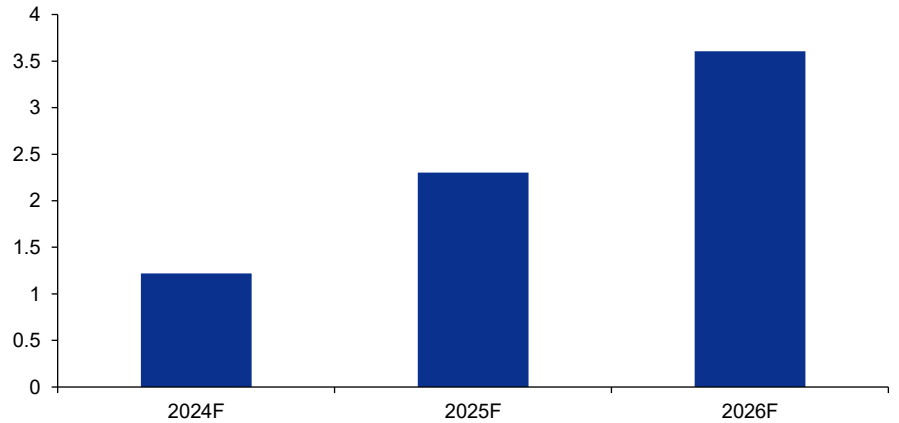
This tech is heavily biased in favour of GE when compared to GMO

GMO or Genetically Modified Organism generally involves the insertion of DNA from a foreign source. The change is, however, less accurate and can take place at a random location in the gene. Moreover, the altercation would not have happened naturally through evolution and requires a longer time frame for product development (8-10 years) compared to GE, which has a shorter timeframe (three-to-five years). GE is highly accurate, and no foreign DNA is inserted in the organism and hence, there is less regulatory oversight.

Generic agrochemical companies to die a slow death

Generic agrochemical companies will have a tough time selling their insecticides and fungicides as the CRISPR technology matures. For instance, let's take azoxystrobin, the fungicide with the largest sales globally. It is manufactured by Syngenta under the brand name Amistar and is used to protect rice, soyabean and cotton from a variety of diseases. One such disease which affects the rice crop is rice blast fungus, and on research, it was found that the gene which weakens the defences of rice against the fungus can be switched off using CRISPR, thereby dramatically improving its resistance. The major beneficiaries of CRISPR are seed companies having large germplasm repositories (Kaveri Seeds), as one needs entire germplasms to make inheritable changes.

Figure 1: Agrochemicals market likely to be replaced by CRISPR (in US$bn)



SOURCES: INCRED RESEARCH, COMPANY REPORTS

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Attack of the mutants

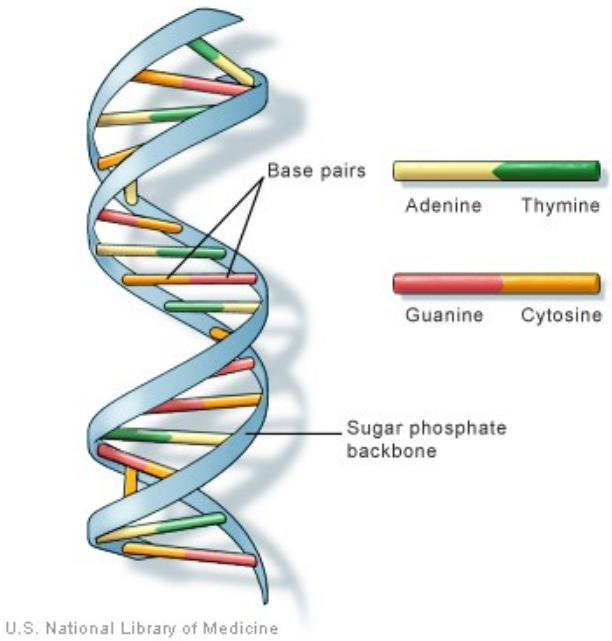
The CRISPR revolution

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. An effective but very simple technology, CRISPR, will hasten the transition to the third great revolution of modern times (the first two being Alfred Einstein's theory of relativity and the information technology era). Children who study digital coding will be joined by those who study genetic code. Back in the days when research was going on in gene editing, scientists were racing to map the genes that are coded by our DNA (deoxyribonucleic acid). However, the trick was about understanding DNA's less-celebrated sibling, RNA (ribonucleic acid). It's the molecule that works in a cell by copying some of the instructions coded by the DNA and using them to build proteins. And proteins are responsible for everything, right from how tall you look to the colour of your eyes. The quest to understand RNA led to the most fundamental question: How did life begin? It was the answer to this question that led to the discovery of CRISPR.

What is CRISPR ➤

Francisco Mojica was a student at Alicante University in Spain, and his PhD research included sequencing the gene of E. coli bacteria. Sequencing effectively means looking at the DNA of the bacteria under the microscope and trying to understand its shape. While doing sequencing, he observed an unusual structure. In the DNA of E. Coli, there were certain sections which were repeats i.e., a section of DNA was repeating itself after regular intervals. Let's understand it a bit more in detail. Human DNA is made of four bases such as adenine (A), thymine(T), guanine(G) and cytosine (C). These bases occur in a sequence i.e., for instance one such sequence could be ATCGCGT (the acronyms denote the bases). Now in the case of this researcher, what was happening was something like this: CAGT, AGTA, CAGT, AGGC, CAGT. So, the sequence CAGT was repeating after regular intervals. This was unique because the order is generally random and does not follow a sequence. Moreover, these sequences were palindromes (for instance, let's say a sequence CAAC) and hence, the name - Clustered Regularly Interspaced Short Palindromic Repeats.

Figure 2: Bases in human DNA



SOURCE: INCRED RESEARCH, COMPANY REPORTS

An ancient enemy back to the fore

When the researcher Mojica took these repeats of DNA sequences of E. coli and ran them through databases, what he found was intriguing: the DNA repeats matched sequences that were in viruses that attacked E. coli. He found the same things when he looked at other bacteria with CRISPR sequences; their sequences matched those of viruses that attacked those bacteria. This led to a very important conclusion; bacteria have an immune system. They can remember what viruses have attacked them in the past and incorporate them.

- What Mojica had stumbled upon was a battlefront in the longest running, most massive and vicious war on the planet; that between bacteria and the viruses that attack them are called 'bacteriophages' or 'phages'.
- Phages are the largest category of viruses in nature. Indeed, phage viruses are by far the most plentiful biological entities on earth. There are 10^{31} of them - a trillion phages for every grain of sand.
- As we humans struggle to fight novel strains of viruses, it's useful to note that bacteria have been doing this for about three billion years. Almost from the beginning of life on this planet, there has been an intense arms race between bacteria, which developed elaborate methods of fighting against viruses.
- Mojica found that bacteria with CRISPR sequences seemed to be immune from infection by a virus that had the same sequence. However, bacteria without the sequence did get infected.
- So, when new viruses came along, the bacteria that survived were able to incorporate some of that virus's DNA and thus create, in its progeny, an acquired immunity to that new virus. They did it with the help of enzymes, called CRISPR-associated enzymes or CAS enzymes.

Enzymes: The root of everything

Enzymes are a type of protein. Their main function is to act as a catalyst that sparks chemical reactions in the cells of living organisms, from bacteria to humans. There are more than 5,000 biochemical reactions that are catalyzed by enzymes. These include breaking down starches and proteins in the digestive system, causing muscles to contract, sending signals between cells and (most important for this discussion) cutting and splicing DNA.

- By 2008, scientists had discovered a handful of enzymes produced by genes that are adjacent to the CRISPR sequences in bacterial DNA. These CRISPR associated enzymes enable the system to cut and paste new memories of viruses that attack the bacteria.
- They also create short segments of RNA, known as CRISPR RNA (crRNA), that can guide a scissors-like enzyme to a dangerous virus and cut up its genetic material. That's how the wily bacteria create an adaptive immune system.
- The notation system for these enzymes was still in flux in 2009, largely because they were being discovered in different labs. Eventually, they were standardized into types such as Cas1, Cas9, Cas12 and Cas13.
- Cas enzymes have a distinct fold, indicating that it is the mechanism that bacteria use to cleave a snippet of DNA from invading viruses and incorporate it into their CRISPR array, thus being the key to the memory-forming stage of the immune system.

The supporting cast

In the years that followed, the CRISPR crowd had coalesced around Cas9 as being the most interesting of the CRISPR-associated enzymes. Researchers had shown that if you deactivate Cas9 in bacteria, the CRISPR system no longer cuts up the invading viruses. They had also established the essential role of another part of the complex: CRISPR RNAs known as crRNAs. These are small snippets of RNA that contain some genetic coding from a virus that had attacked the bacteria in the past. This crRNA guides the Cas enzymes to attack that virus when it tries to invade again. These two elements are the core of CRISPR system: a small snippet of RNA that acts as a guide and an enzyme that acts as a scissor. There is a third element too, called the trans-activating CRISPR RNA or the tracrRNA, which plays a supporting role.

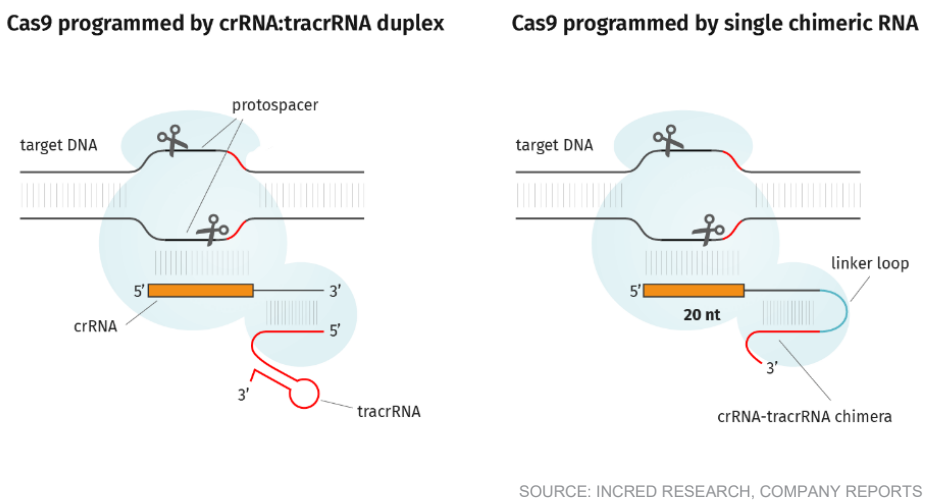
- The tracrRNA performs two important tasks. Firstly, it facilitates the making of crRNA, the sequence that carries the memory of the virus that previously attacked the bacteria. It took long strands of RNA and processed them into small crRNAs that were targeted at specific sequences in an attacking virus.
- Then it serves as a handle to latch on to the invading virus so that crRNA can target the right spot for the Cas9 enzyme to chop.

Together, these three elements combined and formed the CRISPR system, inspired from centuries-old bacteria's defence mechanism against viruses.

The final piece of the puzzle »

This amazing little system, it quickly became clear, had a truly momentous potential application: the crRNA guide could be modified to target any DNA sequence one might wish to cut. It was programmable. It could become an editing tool. In other words, one could add a different crRNA and get it to cut any different DNA sequence he or she chose. These crRNA, also called guide RNAs, became one of the most powerful tools for gene editing. However, this was not the end. The next step was to figure out if the CRISPR system could be made even simpler. If so, it might become not just a gene editing tool but one that would be much easier to program and cheaper than existing methods. So, the CRISPR system had two RNAs, the crRNA and the tracrRNA. These two RNAs could be linked together, fusing the tail of one to the head of the other in a way that could keep the combined molecule functional. This is what ultimately became known as the single-guide RNA or the sgRNA.

Figure 3: Single-guide RNA or the sgRNA



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Gene editing: A brief history

Before we start discussing CRISPR as a gene editing tool, one needs to know a brief history about the same. The road to engineering genes began in 1972 when Professor Paul Berg of Stanford University discovered a way to take a bit of the DNA of a virus found in monkeys and splice it into the DNA of a totally different virus. He had manufactured what he dubbed as 'recombinant DNA'.

- It took another fifteen years before scientists began to deliver engineered DNA into the cells of humans. The goal was similar to creating a drug. There was no attempt to change the DNA of the patient; it was not gene editing.
- Instead, gene therapy involved delivering into the patient's cells some DNA that had been engineered to counteract the faulty gene that caused the disease. This is what happens in GMO crops.
- Instead of treating genetic problems through gene therapy, some medical researchers began looking for ways to fix the problem at source. The goal was to edit the flawed sequences of DNA in the relevant cells of the patient. Thus, was born the endeavour called gene editing.

Gene editing techniques ➤

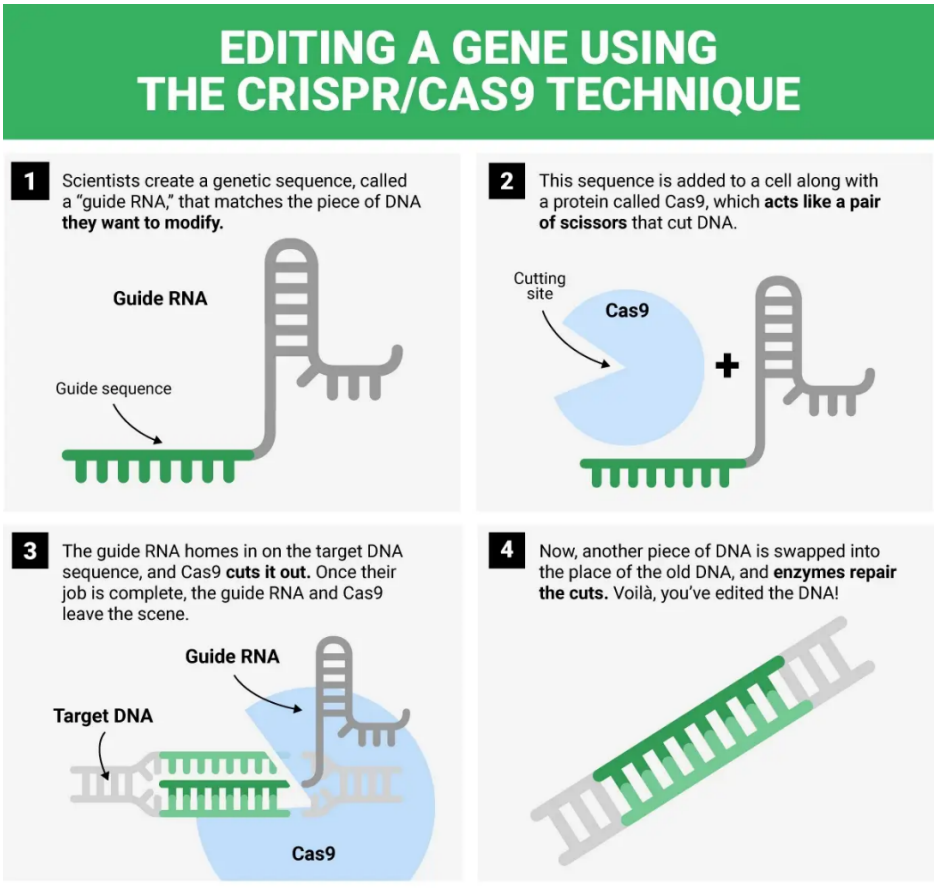
One of the keys to editing a gene is to cause a break in both strands of the DNA double helix, known as double strand break or dsb. When this happens, neither strand can serve as a template to repair the other. So, the genome repairs itself in two ways.

- The first is called 'non-homologous end joining' (homologous comes from the Greek word for matching). In such cases, the DNA is repaired by simply stitching two ends together without trying to find a matching sequence. This can be a sloppy process, resulting in unwanted insertions and deletions of genetic material.
- A more precise process called the 'homology directed repair' occurs when the cut DNA finds a suitable replacement template nearby, i.e., it can repair the DNA based on a template which is close to the target site where the break has occurred.
- The invention of gene editing requires two steps. Firstly, researchers had to find the right enzyme that could cut a double strand break in the DNA. Then they had to find a guide that would navigate the enzyme to the precise target in the cell's DNA where they wanted to make the cut.
- The enzymes that can cut DNA or RNA are called 'nucleases'. In order to build a system for gene editing, researchers needed a nuclease that could be instructed to cut any sequence that the researchers chose to target. By 2000, they had found a tool to do this.
- The FokI enzyme, which is found in some soil and pond bacteria, has two domains: one that serves as a scissor that can cut DNA and another that can serve as a guide telling it where to go.
- Researchers were able to devise proteins that could serve as a guide to get the cutting domain to a targeted DNA sequence. One system, zinc-fingered nucleases (ZFN), came from using the cutting domain with a protein that has little fingers shaped by the presence of a zinc ion, which allows it to grasp on to a specified DNA sequence.
- A similar but even more reliable method, known as TALENs (transcription activator-like effector nucleases), came from fusing the cutting domain with a protein that could guide it to longer DNA sequences.

Why CRISPR is numero uno?

Just when TALENs were being perfected for being more accurate, CRISPR came along. It was somewhat similar: it had a cutting enzyme, which was Cas9, and a guide that led the enzyme to cut a targeted spot on a DNA strand. But in the CRISPR system, the guide was not a protein but a snippet of RNA. This had a big advantage. With ZFNs and TALENs, one had to construct a new protein guide every time one wanted to target a different genetic sequence to cut; it was difficult and time-consuming. But with CRISPR, one merely had to fiddle with the genetic sequence of the RNA guide. A good student could do it quickly in a lab.

Figure 4: CRISPR gene editing process in four simple steps



SOURCE: INCRED RESEARCH, NATURE

GE versus GMO

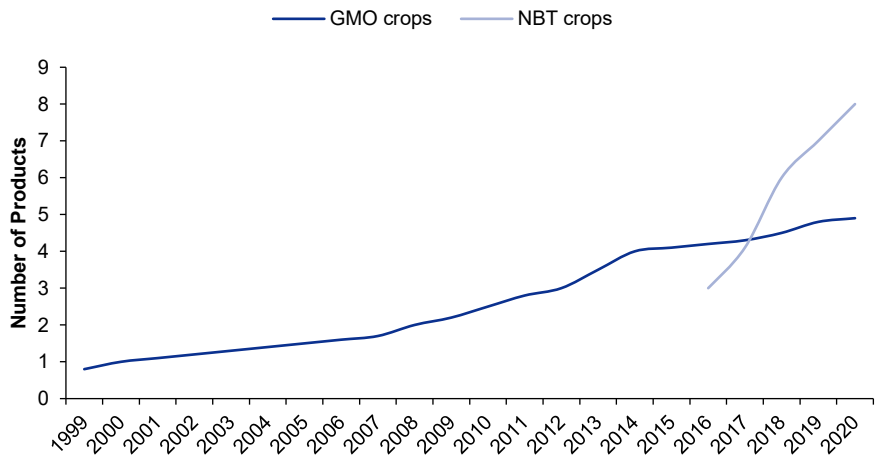
GE or genetically engineered plants are those wherein the host DNA is edited using one of the many gene editing techniques. GMO involves delivering into the plant's cells some DNA that had been engineered to counteract the faulty gene that caused a disease or is resulting in low yield. Instead of treating this using genetic modification, some medical researchers began looking for ways to fix the problem at source. The goal was to edit the flawed sequences of DNA in the relevant cells of the plant. This was gene editing.

- In GMOs, the change is initiated in a random location in the genome, whereas gene editing using CRISPR is highly targeted and occurs at the exact spot required in the genome.
- In GMOs, the DNA can be exotic i.e., they could be taken from another species. In GE, DNA is native or DNA that is already part of the organism is removed or altered.
- In the case of GMO, the change would not have happened naturally through evolution, whereas as we saw in bacteria, for CRISPR the change could happen naturally through evolution.
- The timeline for research, product, and development in the case of GMO is 10-13 years, and the same for GE, particularly CRISPR, is 3-5 years.
- GMO is highly expensive, where only large companies can benefit. GE, on the other hand, is extremely cost-effective and in due course small farmers will be able to utilize this technology.
- GMO is subject to strict regulatory approval because a foreign DNA is inserted into the host DNA. The same is not the case for GE, because no foreign gene insertion takes place and hence, it escapes the regulatory rigmarole, resulting in reduced time for commercialization. It should be noted that though the US treats GE and GMO differently, EU laws treat them similarly, although that may change in the coming years as GE as a technology matures.

What do the numbers indicate? ➤

To understand the numbers behind CRISPR and whether it is beneficial compared to GMO, we need to take a small detour to a South American country, Argentina. Worldwide, the Argentine regulatory framework for contemporary biotechnology used in agriculture is regarded as one of the most established. Being a pioneer in this area, the nation passed a pioneering law for crops produced using the so-called 'new breeding techniques' (NBTs), such as gene (or genome) editing, in 2015. Argentina was the first nation to adopt regulatory standards to determine whether organisms created using new breeding methods (NBTs) should be classified as genetically modified organisms (GMOs). As they have been using these criteria for the past four years, they have seen a sizable number of cases, the majority of which involved gene-edited plants, animals, and microbes used in agriculture. It should be noted that NBTs majorly consist of CRISPR-edited crops.

Figure 5: The timeline of GMO approvals in Argentina and the timeline of crop obtained using different NBTs; the horizontal axis represents the year of the regulatory decision and the vertical axis represents the number of products

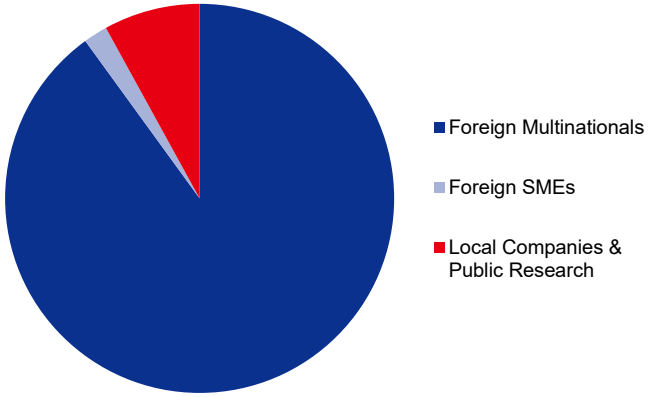


SOURCE: INCRED RESEARCH, FRONTIERS IN BIOENGINEERING AND BIOTECHNOLOGY JOURNAL

The chart above is a moving average based on the period of Argentinean presidential terms of office; this representation was included to help analysing if there is a trend in the noisy data and, at the same time, to explore if there have been changes in public policy that might have influenced that trend. Regarding NBTs, any insight from the very limited number of observations available should be deemed preliminary. Having said that, it seems that NBT products, currently in the founding years, are emerging much faster compared with the foundational (or any other) period of GMOs, and if the trend goes on, NBTs will be significantly higher in number than GMOs soon.

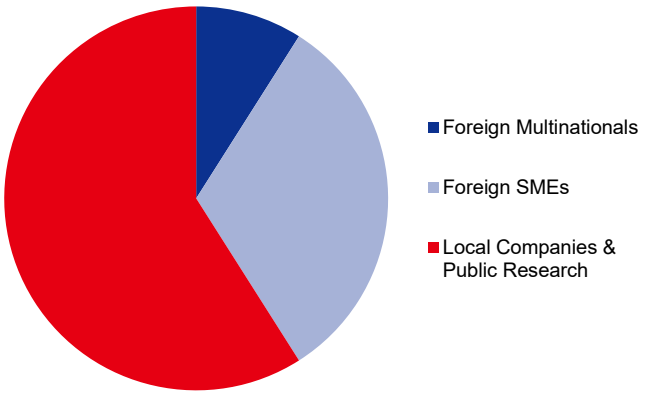
Fig. 6 shows that GMOs are deregulated mostly by MNCs, and such developers were the only group throughout the first two decades of the regulatory system. Only during the last five years has it been feasible that occasionally a local company or a foreign small and medium enterprise or SME is able to deregulate a GM crop. In contrast, Fig. 7 shows that research institutes and/or local SMEs are responsible for about half of NBT products presented to the regulatory authorities, from the very beginning. In these cases, the whole process of product development, deregulation and commercialization is in the hands of such local actors from Argentina, a developing country. Regarding the other half of the cases, most of them correspond to products developed by foreign SMEs, and finally a small proportion was presented by MNCs. This again points to the affordability of NBT techniques. Moreover, it also suggests that NBT can compete with generic agrochemicals, even during the patent period, as they will be less expensive than generic agrochemical molecules.

Figure 6: GMO products by developer profiles



SOURCE: INCRED RESEARCH, FRONTIERS IN BIOENGINEERING AND BIOTECHNOLOGY

Figure 7: NBT (non-GMO products by developer profiles)

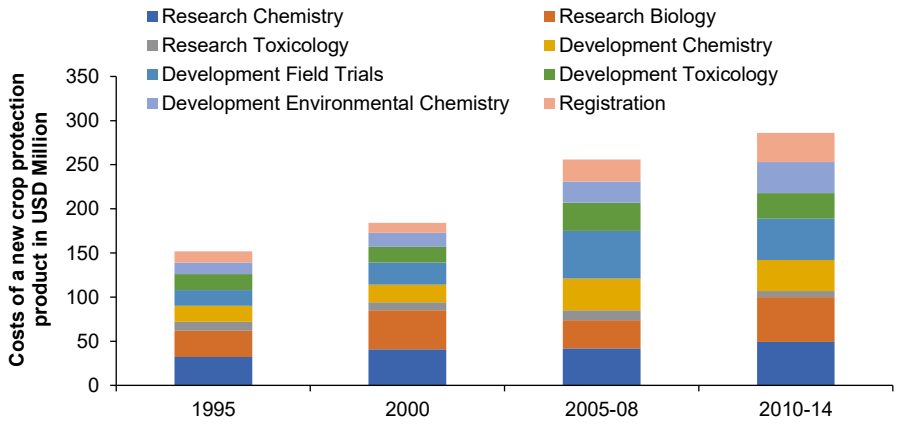


SOURCE: INCRED RESEARCH, FRONTIERS IN BIOENGINEERING AND BIOTECHNOLOGY

Ever-increasing cost of a GMO

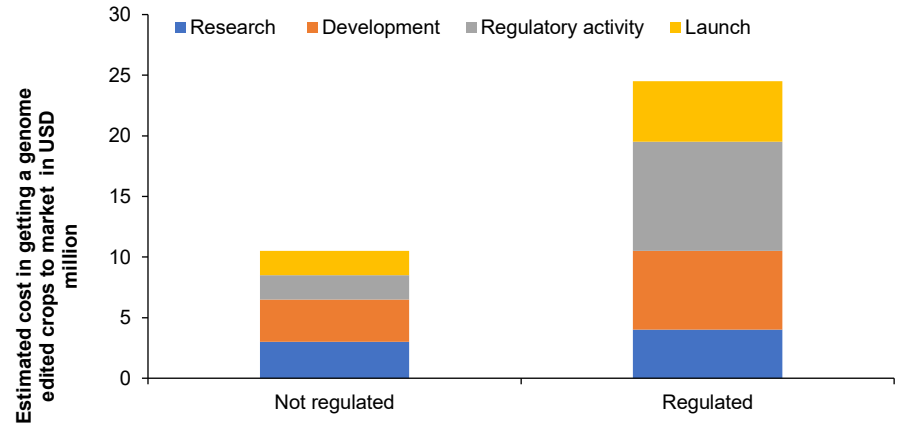
On comparing the cost of a GMO versus a GE, we can see that GE can be done at a fraction of cost of a GMO and in much less time, when there is no regulation.

Figure 8: Cost of development of new agrochemicals is around US$290m and it takes around 9-10 years



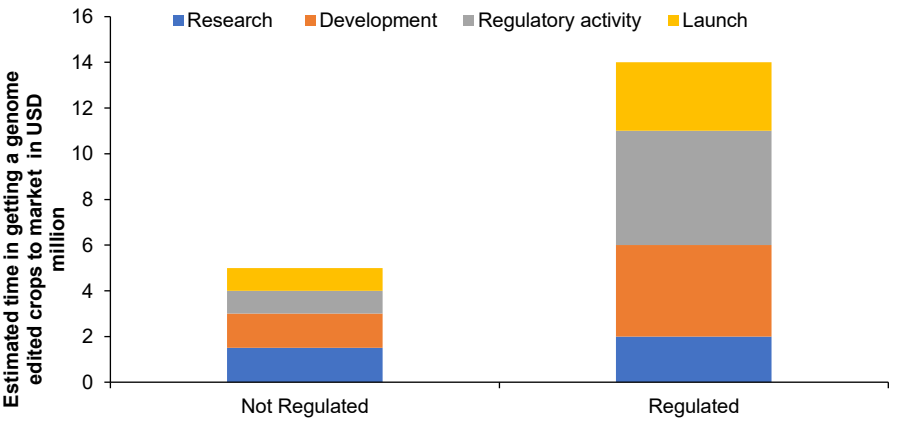
SOURCE: INCRED RESEARCH, PHILLIPS MCDOUGALL

Figure 9: Cost of development of new gene-edited crops is around US$10.5m and US$ 24m in case of no regulation and regulation, respectively



SOURCE: INCRED RESEARCH, RESEARCH BY UNIVERSITY OF SASKATCHEWAN

Figure 10: The time needed for a GE crop to reach the market is five years in case of no regulation (US and Japan) and it will be 14 years in case of likely regulation (Europe); however, as the regulators mature with experience, this number will come down



SOURCE: INCRED RESEARCH, RESEARCH BY UNIVERSITY OF SASKATCHEWAN

Spells doom for the insecticides industry

The United Nations estimates that almost 40% of the world's crop production is currently lost to pests, and plant diseases cost the global economy more than US$220bn every year. A major contributor to the loss of biodiversity, invasive pests cost nations at least US$70bn annually. Due to the warmer environment, species like the autumn armyworm, which feeds on crops like maize, sorghum, and millet, have already expanded. Others, like desert locusts, the most damaging migratory pests in the world, are anticipated to alter their migration paths and geographic distribution. Movements like this undermine food security, and small holder farmers, as well as those in countries where food security is a concern, are among those especially at risk.

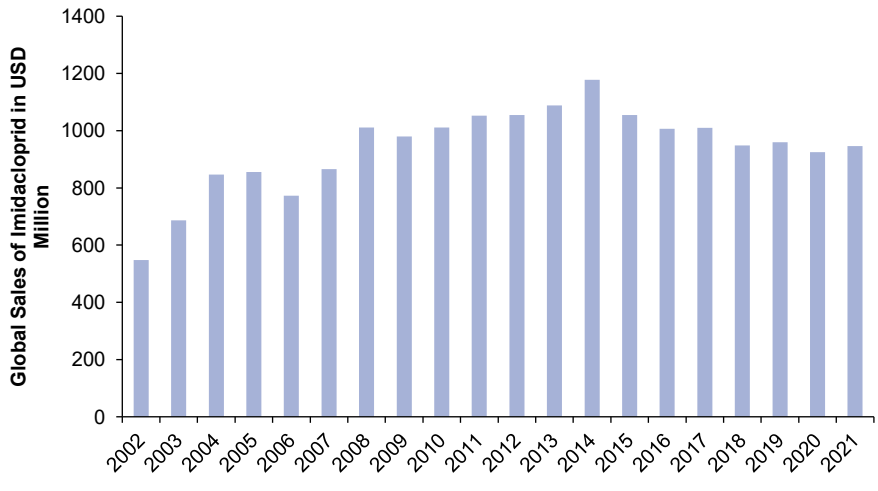
- CRISPR can tackle this problem in two ways, by changing the DNA of the insect which infects the plant. This edit can be made in the germline, so that future progenies of the insects also don't contain the virus. This will be particularly useful when a single species of insects infects a variety of crops, and it's not feasible to edit the germline of each crop individually.
- CRISPR can also work by changing the DNA of the plant and make it more resilient to insects/pests. This edit will also be made in the germline of the plant, making it inheritable in future generations.

Whitefly: A pest of mass destruction ➤

Cotton leaf curl disease is a top-ranked endemic disease to cotton in Pakistan, north western India and Africa, and causes a severe shortfall in the economy of these countries. It is spread by the Whitefly, a pest which regularly causes havoc in Punjab, Rajasthan and other cotton-growing states of India.

- These viruses are of the geminividae family and recently CRISPR Cas 9 has been used to circumscribe the viruses in this family. Please click: https://www.frontiersin.org/articles/10.3389/fpls.2016.00475/full
- Farmers use a variety of insecticides to combat the cotton leaf curl disease, the most famous of all being the insecticide imidacloprid manufactured by Bayer Crop Science. Its other large manufacturers include Rallis, Excel Crop Care, Atul, and Punjab Chemicals.
- A research grant was also awarded by the Government of India or GoI worth Rs4m to the Central University of Punjab, to find a way to combat against cotton leaf curl disease using CRISPR Cas9. Please click: https://www.indiascienceandtechnology.gov.in/node/169297.
- This research suggests that the insecticide used to combat cotton leaf curl disease, imidacloprid, could face an existential crisis in the coming years.

Figure 11: Global sales of imidacloprid - one of the largest-selling insecticides



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 12: A range of insecticides used to control the spread of Whitefly and their manufacturers

Insecticide	Launch Date	Patent Expiry	Key Manufacturer	Other Manufacturers
Acephate	1971	1986	Arysta LifeScience	Orthene, Ortran
Acetamiprid	1996	2011	Nippon Soda	Mospilan
Afidopyropen	2018	2033	Meiji Seika Pharma	Inscalis/Versys
Bifenthrin	1986	2001	FMC	Capture, Talstar, Discipline, Hero
Bistrifluron	2005	2020	FarmHannong	Hanaro, Xterm
Diafenthiuron	1991	2006	Syngenta	Polo, Pegasus
Dinotefuran	2002	2017	Mitsui Chemicals	Starkle, Alubarin, Venom
Fenpropathrin	1980	1995	Sumitomo Chemical	Rody, Danitol
Flometoquin	2018	2033	Meiji Seika Pharma	FineSave Flowable
Fluxametamide	2018	2033	Nissan Chemical	Gracia
Imidacloprid	1991	2006	Bayer Crop Science	CropStar, Confidor, Admire
Lufenuron	1993	2008	Syngenta	Match, Curyom
Nitenpyram	1995	2010	Sumitomo Chemical	Bestguard
Novaluron	1999	2014	ADAMA	Rimon
Omethoate	1959	1974	Arysta LifeScience	Folimat, Le-mat
Pyrifluquinazon	2010	2025	Nihon Nohyaku	Colt
Spiromesifen	2005	2020	Bayer Crop Science	Oberon, Forbid
Spiropidion	2021	2036	Syngenta	n.a.

SOURCE: INCRED RESEARCH, COMPANY REPORTS

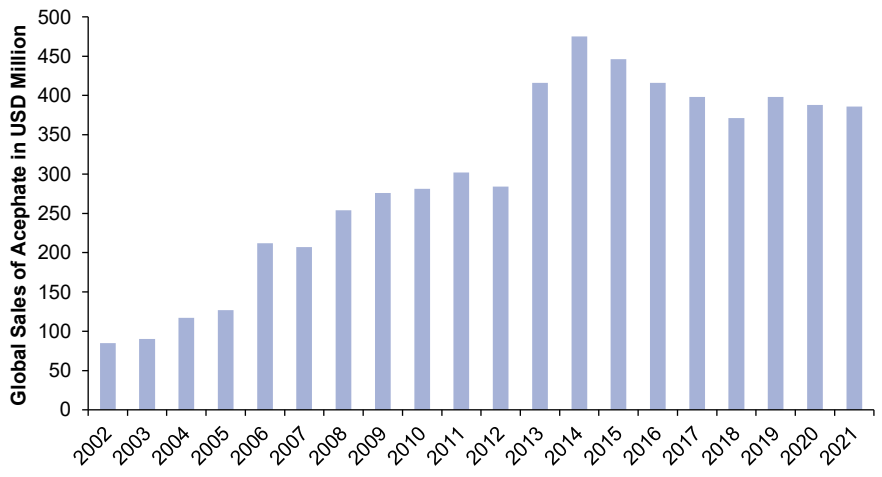
Rice Tungro disease

Tungro is one of the most damaging and destructive diseases of rice in South and Southeast Asia. In severe cases, Tungro-susceptible varieties infected at an early growth stage could have as high as 100% yield loss. Once Tungro is present in the field, it increases rapidly in young rice plants. It is spread by leafhoppers, an insect that prefers to feed on young rice plants. They also acquire Tungro viruses more efficiently from younger infected plants. Tungro infection can occur during all growth stages of the rice plant. It is most frequently seen during the vegetative phase. Plants are most vulnerable at the tillering stage.

- In a series of experiments conducted by the International Rice Research Institute in the Philippines, it was able to develop Tungro-resistant rice through CRISPR.

  Please click: https://onlinelibrary.wiley.com/doi/full/10.1111/pbi.12927
- This variety of rice showed moderate resistance against the Tungro virus. It greatly reduces the use of pesticides required to keep the carrier of this virus i.e., leafhopper at bay.
- A range of pesticides are used to combat the rice Tungro disease, the most notable of which is acephate manufactured by Arysta Lifescience. Other manufacturers include Rallis, Meghmani and Sumitomo Chemicals.

Figure 13: Global sales of acephate (in US$m)



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 14: A range of insecticides used to control the spread of rice Tungro disease and their manufacturers

Insecticide	Launch Date	Patent Expiry	Key Manufacturer	Other Manufacturers
Acephate	1971	1986	Arysta LifeScience	Sumitomo Chemical, Rallis, Meghmani, UPL, FMC, FarmHannong, Sinon, Sabero, Heranba, Amvac, Nortox, Punjab Chemicals, Hubei Sanonda
Dinotefuran	2002	2017	Mitsui Chemicals	n.a.
Ethion	1957	1972	FMC	Rallis, Pesticides India, Bharat Rasayan, Meghmani
Etofenprox	1986	2001	Mitsui Chemicals	n.a.
Fenitrothion	1962	1977	Sumitomo Chemical	FMC, Rallis, Adama, Sinon
Fenpyroximate	1991	2006	Nihon Nohyaku	SePRO
Flupyradifurone	2014	2029	Bayer Crop Science	n.a.
Phenthoate	1961	1976	Nissan	Sumitomo Chemical, Atul, Coromandel
Pymetrozine	1994	2009	Syngenta	Chinese Companies
Triazophos	1970	1985	Bayer Crop Science	Sudarshan, Chinese Companies, Meghmani
Xylyl Methylcarbamate	1968	1983	Sumitomo Chemical	n.a.

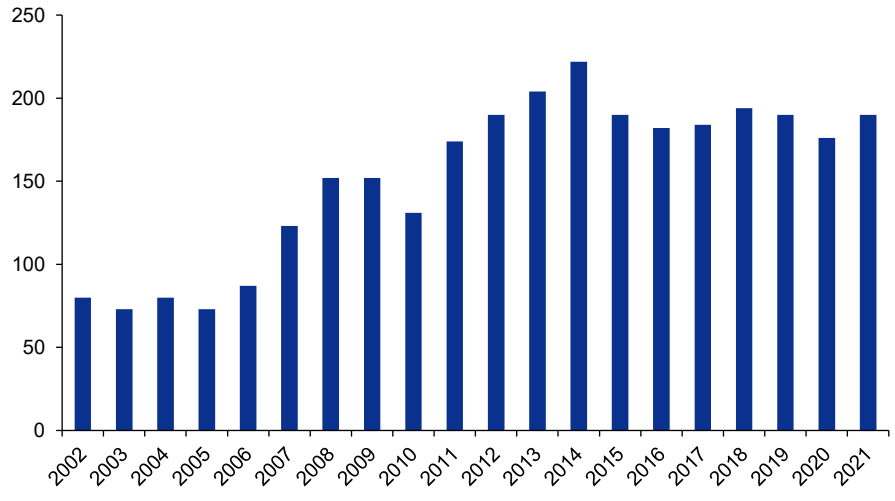
SOURCE: INCRED RESEARCH, COMPANY REPORTS

Rice blast disease

Rice blast disease, caused by magnaporthe oryzae (ascomycota), occurs in about 80 countries in all continents where rice is grown, in both paddy fields and upland cultivation. The extent of the damage caused depends on environmental factors, but worldwide it is one of the most devastating cereal diseases, resulting in losses of 10–30% of the global yield of rice. It is generally considered the most important disease of rice worldwide because of its extensive distribution and destructiveness under favourable conditions. A leaf blast infection can kill seedlings or plants up to the tillering stage. At later growth stages, a severe leaf blast infection reduces leaf area for grain fill, reducing grain yield. Leaf blast can kill rice plants at the seedling stage and cause yield losses in case of severe infection.

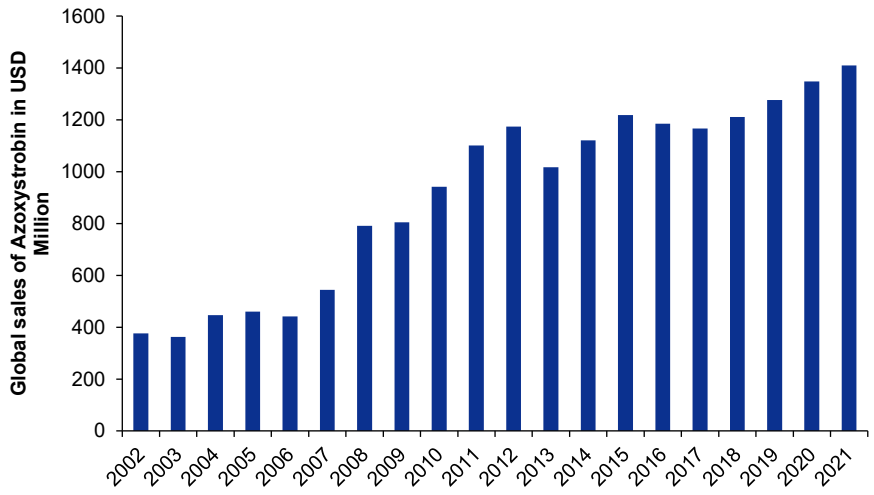
- In research conducted by F. Wang and his team at the College of Agriculture, Nanning, China, they discovered that removing a particular gene from the crop can increase the resistance of rice against the fungus. Please click: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4846023/
- The most important of these fungicides is azoxystrobin which is used to combat rice blast disease, sold by Syngenta. However, azoxystrobin has a very diversified market apart from rice and is used in cereals and soyabean too. However, tricyclazole, manufactured by Corteva, is solely used for rice blast disease and it will see its sales decreasing in the coming years.

Figure 15: Global sales of tricyclazole (in US$m); tricyclazole has been facing a sales decline in recent years and the trend is expected to continue going ahead



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 16: Azoxystrobin, a high-volume molecule, could face sales decline as the GE products moves closer to commercialization



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 17: A range of insecticides used to control the spread of rice blast disease and their manufacturers

Insecticide	Launch Date	Patent Expiry	Key Manufacturer	Other Manufacturers
Carbendazim	1973	1988	BASF	DuPont, Bayer, Gharda, Sinon, Adama, Meghmani, Chinese companies
Fluopyram	2012	2027	Bayer Crop Science	n.a.
Flutriafol	1984	1999	FMC	n.a.
Propiconazole	1980	1995	Syngenta	Corteva, Tagros, Adama, Meghmani, Atul, Chinese companies
Tebuconazole	1988	2003	Bayer Crop Science	Adama, Meghmani, Atul, Punjab Chemicals, Rotam
Tiadinil	2003	2018	Nihon Nohyaku	n.a.
Tolprocarb	2015	2030	Mitsui Chemicals	n.a.
Tricyclazole	1975	1990	Corteva Agriscience	Kumiai, Indofil, Tagros, Chinese Companies, FarmHannong, Heranba, Meghmani
Pyroquilon	1986	2001	Syngenta	n.a.
Tebufloquin	2013	2028	Meiji Seika Pharma	n.a.
Probenazole	1981	1996	Meiji Seika Pharma	FarmHannong, Hokko Chemical
Phthalide	1971	1986	Kureha	Gharda
Orysastrobin	2007	2022	BASF	n.a.
Pefurazoate	1989	2004	Hokko	n.a.
Kasugamycin	1967	1982	Hokko	DongBang Agro, Arysta LifeScience
Iprobenfos	1966	1981	Kumiai Chemical	Pesticides India
Isoprothiolane	1975	1990	Nihon Nohyaku	FarmHannong, Atul
Iminoctadine	1984	1999	Nippon Soda	n.a.
Guazatine	1968	1983	ADAMA	n.a.
Azoxystrobin	1997	2012	Syngenta	FMC, Chinese companies
Carpropamid	1997	2012	Bayer Crop Science	n.a.
Dichlobentiazox	2021	2036	Kumiai Chemical	n.a.
Diclocymet	2000	2015	Sumitomo Chemical	n.a.
Difenoconazole	1989	2004	Syngenta	Atul, Meghmani, Chinese Companies
Edifenphos	1968	1983	Bayer Crop Science	FarmHannong
Fenamistrobin	2008	2023	Shenyang Research Institute	n.a.
Fenoxanil	2001	2016	Nihon Nohyaku	n.a.
Ferimzone	1992	2007	Sumitomo Chemical	n.a.
Fluindapyr	2021	2036	FMC	n.a.

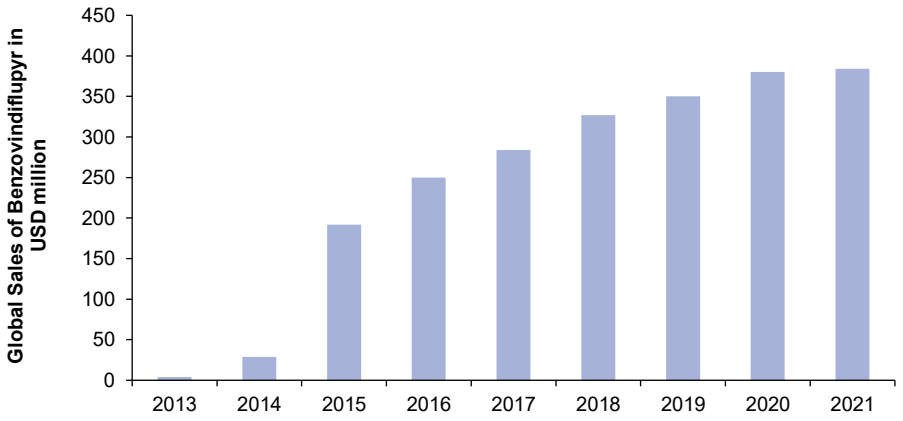
SOURCE: INCRED RESEARCH, COMPANY REPORTS

Powdery mildew disease

Powdery mildews disease ranks among the most important diseases of food and ornamental plants. The damage can result from the death of host tissue (even entire plants), defoliation, cosmetic damage, reduced yields, and lowered quality. The economic and esthetic value of ornamental as well as fruit- and vegetable-bearing species are reduced by the unsightly appearance of powdery mildews. Powdery mildews also can cause losses in yield and quality by enabling decay organisms to enter fruits through damaged tissue. Grapevine, one of the most economically important fruit crops in the world, suffers significant yield losses from powdery mildew.

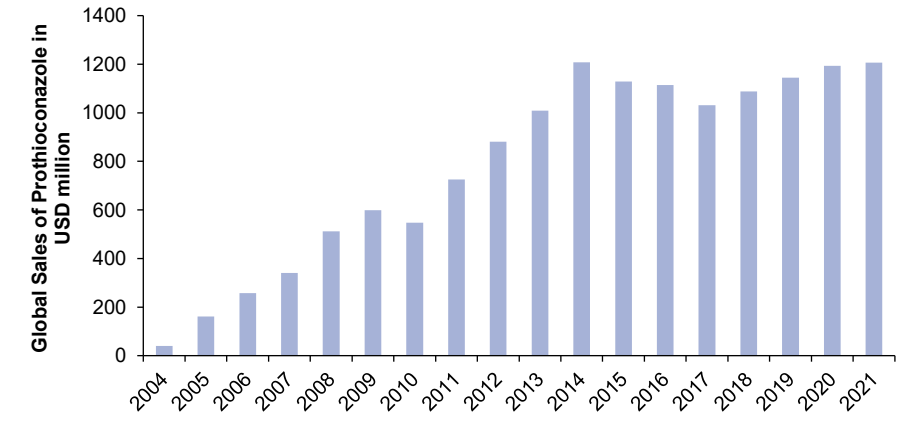
- In a research paper published in Nature journal, it was discovered that CRISPR Cas9 could be used to improve the resistance in grapevine against powdery mildew. Please click: https://doi.org/10.1038/s41438-020-0339-8
- A similar research was conducted for tomatoes, and the results achieved were significant. Tomatoes subjected to CRISPR Cas9 treatment showed enhanced resistance against tomato leaf curl virus and powdery mildew. Please click: https://www.mdpi.com/1422-0067/22/4/1878
- Benzovindiflupyr (Syngenta), epoxiconazole (BASF), prothioconazole (Bayer), pyraclostrobin (BASF) are some of the largest-selling fungicides dealing with powdery mildew.
- Carbendazim is another fungicide, which is manufactured by an Indian company called Meghmani.

Figure 18: Benzovindiflupyr is under patent till 2028, but it could face headwinds in future



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 19: Prothioconazole sales (in US$bn); although its product portfolio is relatively diversified, it will face less pressure in the medium term



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 20: Fungicides dealing with powdery mildew disease

Insecticide	Launch Date	Patent Expiry	Key Manufacturer	Other Manufacturers
Benzovindiflupyr	2013	2028	Syngenta	n.a.
Boscalid	2003	2018	BASF	n.a.
Carbendazim	1973	1988	BASF	DuPont, Bayer, Gharda, Sinon, Adama, Meghmani, Chinese companies
Cyflufenamid	2003	2018	Nippon Soda	n.a.
Cyprodinil	1994	2009	Syngenta	n.a.
Diniconazole	1988	2003	Sumitomo Chemical	n.a.
Dinocap	1959	1974	Corteva Agriscience	Cequisa
Dodemorph	1968	1983	BASF	n.a.
Enestroburin	2006	2021	#N/A	n.a.
Epoxiconazole	1993	2008	BASF	Adama, Sinochem, FMC
Fenarimol	1975	1990	Gowan	n.a.
Fenpropidin	1985	2000	Syngenta	Adama
Fenpropimorph	1980	1995	BASF	n.a.
Fluopyram	2012	2027	Bayer Crop Science	n.a.
Fluquinconazole	1994	2009	BASF	Bayer
Flutianil	2015	2030	OAT Agrio	n.a.
Flutriafol	1984	1999	FMC	n.a.
Fosetyl	1978	1993	Bayer Crop Science	Chimiberg
Harpin	2000	2015	Plant Health Care	n.a.
Imibenconazole	1994	2009	Hokko	n.a.
Isofetamid	2014	2029	Ishihara	n.a.
Isoflucypram	2020	2035	Bayer Crop Science	n.a.
Kresoxim-Methyl	1996	2011	BASF	Adama, Rallis
Mefentrifluconazole	2019	2034	BASF	n.a.
Meptyldinocap	2007	2022	Corteva Agriscience	Gowan
Metrafenone	2004	2019	BASF	n.a.
Myclobutanil	1988	2003	Corteva Agriscience	n.a.
Penconazole	1983	1998	Syngenta	n.a.
Penthiopyrad	2009	2024	Mitsui Chemicals	n.a.
Polyoxin	1970	1985	Kaken	n.a.
Proquinazid	2005	2020	Corteva Agriscience	n.a.
Prothioconazole	2004	2019	Bayer Crop Science	n.a.
Pydiflumetofen	2017	2032	Syngenta	n.a.
Pyraclostrobin	2002	2017	BASF	n.a.
Pyraziflumid	2018	2033	Nihon Nohyaku	n.a.
Pyriofenone	2011	2026	Ishihara	n.a.
Quinoxyfen	1997	2012	Corteva Agriscience	n.a.
Spiroxamine	1997	2012	Bayer Crop Science	n.a.
Sulphur	1880	1895	UPL	Syngenta, BASF, Cuproquim, Sulphur Mills, Excel Crop Care, Meghmani
Triflumizole	1987	2002	Nippon Soda	n.a.
Triticonazole	1992	2007	BASF	n.a.

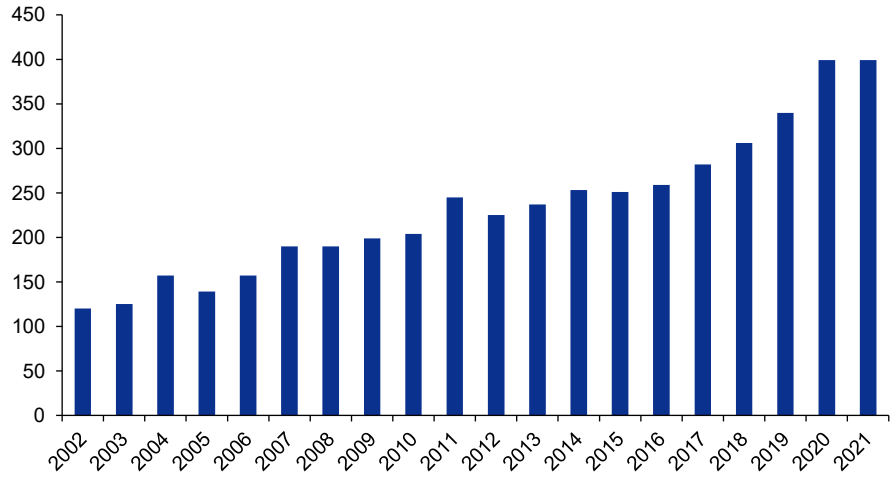
SOURCE: INCRED RESEARCH, COMPANY REPORTS

Spotted-wing drosophila

Spotted-wing drosophila (drosophila suzukii) is an invasive fruit fly species that causes about US$500m in economic damage to fruit crops in the US each year. A native to southeast Asia, it arrived in the US (in Hawaii) in the 1980s and in the continental US (in California) in 2008. It is now widespread through many parts of the US and the world. Several characteristics make spotted-wing drosophila (SWD) difficult to control. It has a high reproductive rate and strong dispersal abilities, and, unlike most fruit flies, a female SWD can pierce the skin of undamaged soft-skinned fruits such as cherries and berries to lay eggs. Also, SWD are highly flexible in their behaviour, physiology, and development, and this allows them to quickly adapt to new environments.

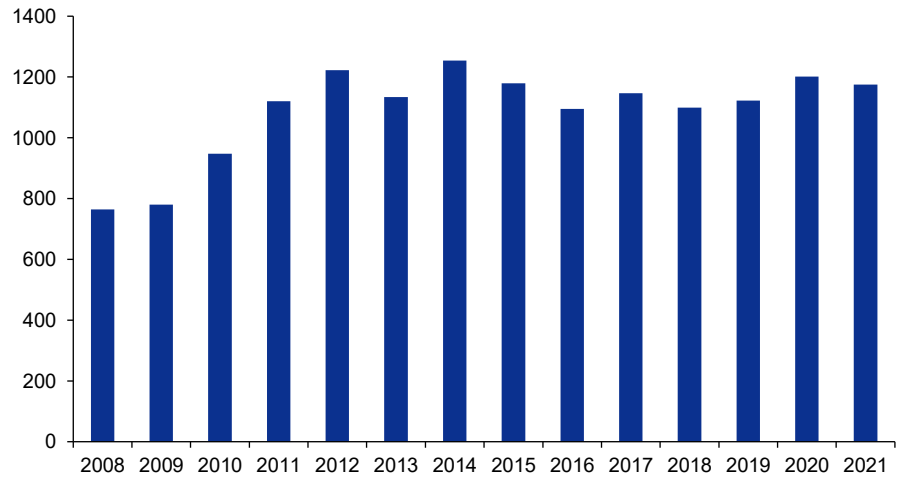
- In research published in the International Journal of Molecular Science, if we disrupt a particular gene in drosophila it results in copulation failure in the insect, or in other words the insect is unable to reproduce. Please click: https://www.sciencedirect.com/science/article/abs/pii/S0022191020302353
- Spinosad and thiamethoxam are two insecticides used extensively against this insect.
- Spinosad is manufactured by Corteva, and thiamethoxam is manufactured by Syngenta, Bharat Rasayan, and Punjab Chemicals.

Figure 21: Global sales of spinosad (in US$m)



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 22: Global sales of thiamethoxam (in US$ m)



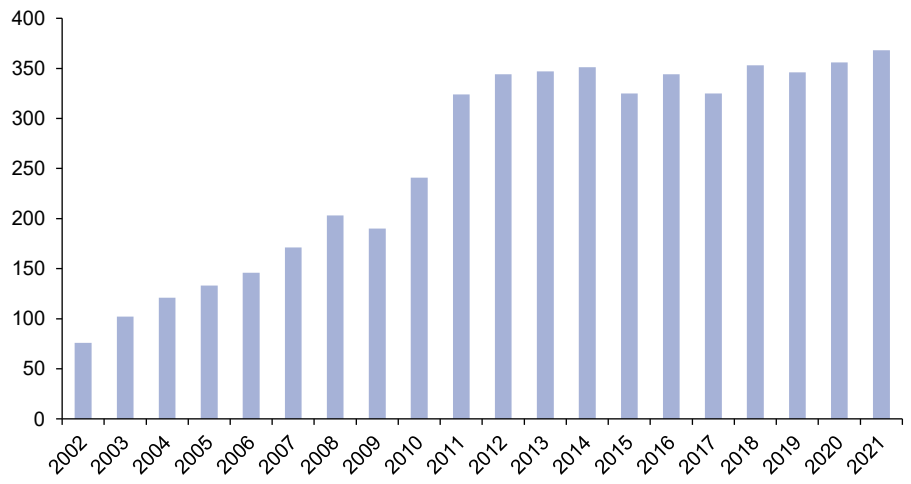
SOURCE: INCRED RESEARCH, COMPANY REPORTS

Grey mould disease

Grey mould disease is a disease caused by the fungus, botrytis cinerea. It normally enters through a wound or infects plants under stress, but will infect healthy plants as well, especially under humid conditions. It can be expected at any time of year. It is common in grapes, strawberries, blackberries, raspberries, gooseberries, beans, cucumber, lettuce and tomatoes. It is also a problem for plants grown under the glass, where conditions can be humid and overcrowded. It can infect chrysanthemum, cyclamen, pelargonium, and primula - in fact, most ornamental plants.

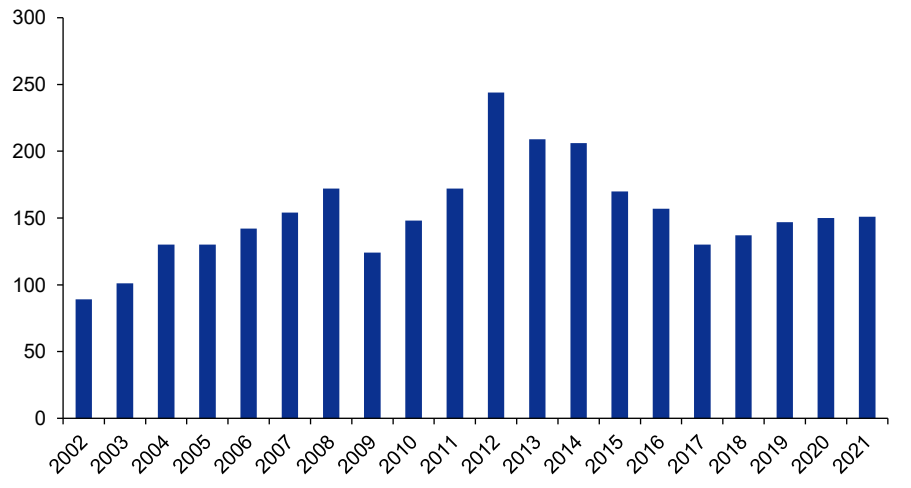
- In research conducted by scientists at the Department of Biology, Kaiserslautern, Germany, using CRISPR technique allowed highly specific genome editing in botrytis cinerea, the fungus which causes grey mould disease. Please click: https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1008326
- Fludioxonil and fluazinam (both manufactured by Syngenta) are the most potent fungicides against gray mould disease.

Figure 23: Global sales of fludioxonil (in US$m); a major part of its portfolio is attributed to grey mould disease



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 24: Global sales of fluazinam (in US$m); it also has grey mould disease as a major part of the product portfolio



SOURCE: INCRED RESEARCH, COMPANY REPORTS

Figure 25: Fungicides dealing with grey mould disease

Insecticide	Launch Date	Patent Expiry	Key Manufacturer	Other Manufacturers
Diethofencarb	1990	2005	Sumitomo Chemical	n.a.
Fenbuconazole	1991	2006	Corteva Agriscience	n.a.
Fenhexamid	1999	2014	Bayer Crop Science	n.a.
Fenpyrazamine	2012	2027	Sumitomo Chemical	n.a.
Fluazinam	1988	2003	Syngenta	Ishihara
Fludioxonil	1994	2009	Syngenta	n.a.
Jun Si Qui	2006	2021	Shenyang Research Institute	n.a.
Mandestrobin	2016	2031	Sumitomo Chemical	n.a.
Mepanipyrim	1995	2010	Kumiai Chemical	n.a.
Procymidone	1977	1992	Sumitomo Chemical	n.a.

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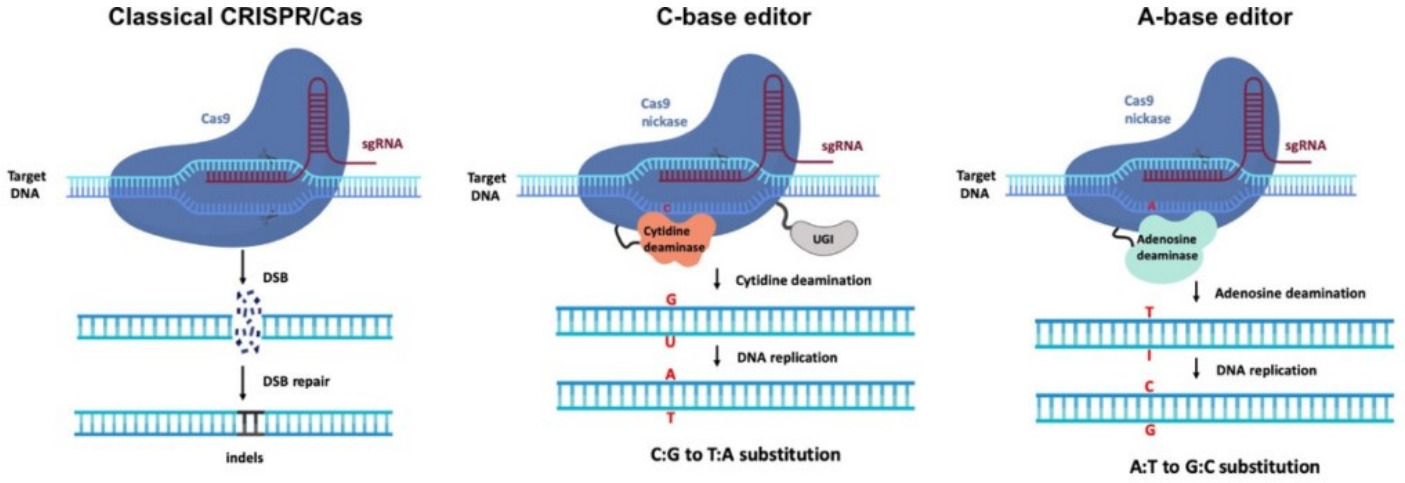
CRISPR is not the end, but the beginning »

As gene editing moves on to uncharted terrains, exciting technologies are coming to the fore. One should note that, even with all its benefits, CRISPR has certain disadvantages. The first one is CRISPR induces double-strand DNA break of the target organism. This has its own problems, as when the DNA is repaired, it can lead to unwanted insertions and deletions, causing loss of genetic material. To avoid this, there is a new technology called base editing. The beauty of it is that it does not require double-strand breaks. In simple terms, it just intends to change the base of the DNA (remember adenine, guanine, cytosine, and thiamine at the beginning of this report). It opens avenues for more targeted gene editing, something which was not even possible with CRISPR Cas9.

Figure 26: A simple diagram explaining the difference between CRISPR and base editing; dsb means double-strand break



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