

# GRIM technology: Bright and grim prospects

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The problem of controlling insect pests attacking crop plants has led scientists to seek solutions through genetic engineering. The widely applied genetic engineering technology in pest control is the introduction of a gene that produces an endotoxin that causes the death of insects that feed on crop plants but is harmless to people. This gene, known as Bt is obtained from the soil bacterium *Bacillus thuringiensis*. Genetically modified crop plants with the Bt gene secrete their own pesticide. A new technology, not yet put into practice has a novel approach in that it introduces a new gene not to the crop but into the bodies of insect pests which can cause their death upon receiving a specific signal. This technology, however, can be used not only against insect pests but has broader applications that can possibly have much wider implications.

This particular genetic engineering technology had been given the patent No. U.S. 5,864,768 on 08.12.1998 and is titled 'Invertebrate apoptosis gene GRIM and methods of producing the protein encoded thereby', and is assigned to the University of Texas (Austin, Texas) in U.S.A. The inventors named are John M. Abrams, Po Chen and William Nardstrom. The term Apoptosis, from the Greek word for 'falling', like the felling away of old leaves in plants, is used to denote cell death or cell-suicide in the bodies of animals. In bodies, cell suicide is the process by which it gets rid of unwanted cells and the destruction of these cells that could become dangerous in the future if retained. This happens when the body gets rid of unwanted nerve cells and old immune cells or those that get damaged, which are in danger of becoming cancerous. According to scientists, those that go through apoptosis have been observed to die and shrink and are absorbed by neighbouring cells and do not swell and burst, spilling their contents on neighbouring cells.

Scientists have, for a long time, thought that this process of cell death is regulated by genes. This assumption was proven in 1972 by the pathologists J.F.R. Kerr, A. H. Wyllie and A. R. Currie. (Ref: Apoptosis: a basic biological phenomenon with wide ranging implications in tissue kinetics, published in the British Journal of Cancer, Volume 26). Since then, a number of genes in various animals that cause cell death have been identified by different scientists. According to Professor Martin Raff of University College, London, a total of 11 genes that causes apoptosis have been identified in human cells and he believes that they may be carrying upto 25 such genes. Three apoptosis genes have been identified in the fruit fly (*Drosophila melanogaster*), a favourite subject in genetic research. Two of these whose functions were explained in 1995 are known as Head Involution Defective gene (HID) and the Reaper (RPR). The third gene, known as GRIM was described in 1996 by a team of scientists led by Po Chen, who is an inventor named in the patent.

The technology described in the patent is based on the GRIM gene. The reason for selecting this gene is that the other two (HID and RPR) cannot cause cell death in the embryo stage of animals. The patent runs into 42 pages and the invention is described and protected under 22 claims. These claims cover the GRIM gene of *Drosophila melanogaster*, the protein (polypeptide) produced by this gene that can cause cell death and

all variations of this polypeptide, all new forms of this gene where the code of the GRIM gene is fused to different promoters (recombinations), insertion of any such recombinated gene to an animal, particularly to insects that change the genome. In addition this patent covers the base sequence, the amino acid sequence and the production of antibodies to the GRIM protein.

The gist of the patented invention is the making of new genes using the code of GRIM and fusing it to a preferred promoter (the promoter is the region of the gene that decides where, when and for how long it should function). The insertion of it to animals and inducing it to function thereby causing death to cells results in the killing of the animal upon receiving a signal. This signal has to be received by the promoter which will then activate the gene resulting in the production of the GRIM protein. The patent has cited a number of examples

so that only those who attack the crop will get killed. Unlike the previous method, this embodiment helps to keep a much tighter control over the insect populations. However, the success will depend on whether the insects get exposed to the chemical. At the same time, it paves the way for chemical companies to create monopolies by designing insects that could be sensitive only to a compound developed by them. Both the heat-sensitive and chemically-sensitive promoters can be used to kill only the developing embryos and not the adults.

The third preferred method in the patent is to have promoters that can be activated only by exposing them to a substance found only in a particular crop plant. A crop specific substance cited in the patent is gossypol, found only in the cotton plant. A promoter sensitive to gossypol will kill only these insects that feed on cotton, but those that feed on

that it gives successful results in mammal cells and cites cells of Chinese Hamster and even human cell line-like He La. They expect that this could be important in developing cures and preventives for human diseases like AIDS, cancer and neurodegenerative diseases. Another aspect mentioned in the patent is the production of antibodies which are said to be useful in the inhibition of apoptosis. They have covered the production of antibodies from sources such as mice, goat, cattle, pig or any other source, including any genetic engineering method. These other uses have been well-known to the inventors and they have taken a broad cover to include all possible uses. The abstract however, gives only the use in controlling insects. But, the field of invention (page 5) states that the invention relates generally to the fields of pest control and molecular biology and in particular to genetic control of programmed cell death or apoptosis in insect and human cells.

Although this technology can be useful in many fields, there has to be a certain amount of caution. Since the patent says that the expression of the protein and the apoptotic functions happens successfully in mammal cells. There is a possibility that the GRIM genes could get transferred to other animals by viruses, basically the same way used by the scientists to transfer this gene to cells. Such unintentional transfers, if they happen, could well be fatal, and should be studied extensively. Such methods could also be used intentionally for destructive purposes.

Like in the use of many other technologies, the ends for which this is used would be determined by the type of uses. This being developed by the University of Texas means that the commercial rights for its exploitation could well be given to others. It is possible that several companies or institutes could enter into agreements to use it in different ways. If used properly, GRIM technology could be of benefit both to agriculture as a means of pest control and in combating diseases that need the destruction of harmful cells as in cancer, or to develop compounds that could stop the suicide of cells, particularly in essential organs, such as cell death in the brain due to Oxygen starvation that happens during strokes. At the same time, regulation and programming of cell death has vast destructive potential if used for immoral and unethical uses.

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for such inducible promoters from the fruit fly, other animals and even viruses. These include those that are sensitive to heat, heavy metals and chemicals. Three types of promoters have been identified as preferred. One type gets activated inside the embryos when the temperature exceeds a certain level. This activation does not kill the insect but makes the eggs sterile. The second type is activated inside the embryos by exposing them to a certain chemical. The third type of promoter is activated by a substance that is specific to a crop plant.

According to the patent, the recombinated GRIM gene can be transferred to the targetted insects by inserting the gene into a virus that can infest the insect and pass it to the insect. These are then reproduced under controlled conditions to build a population. They are then released so that they can breed with wild populations for several generations and distribute the modified GRIM gene to a large percentage of these populations. The patent states that if the gene has a heat-sensitive promoter, the modified animals can be released preferably in winter. This allows the gene to be transferred to others for several generations until summer, when the rising temperature could trigger off the promoter, causing death to a significant portion of the insect population. In this embodiment, it is not necessary, nor possible to provide any external stimulus and the destruction of the modified animals is brought about by the change of season.

The second type involves promoters that have to be activated by exposure to a particular chemical. This particular chemical can be applied only to a crop

other plants would not be affected at all. In the experiment referred to by them, this gene had been used in insects whose larvae feed on cotton and had given them successful results. This method will protect a particular crop, at the same time will not wipe out the insect, and maintain a balance. The expression of the gene is regulated, not by external factors but by the behaviour of the insects.

The use of the GRIM gene is not confined to these but could be made use of for other purposes. The patent states

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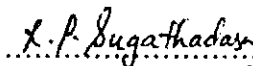
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