The Pharma Innovation Journal 2022; SP-11(2): 1444-1450

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; SP-11(2): 1444-1450

www.thepharmajournal.com
Received: 28-12-2021
Accepted: 30-01-2022

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Terminator technology: Concerns and relevance to seed industry

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Abstract
Transgenic in agriculture is considered as beneficial tool to agriculture. Terminator technology on one hand has been economic for private sector but for farmers end it proved to be fatal. Terminator technology or GURTs are mechanism that restrict the unauthorized use of genetic material by making plants sterile (variety-specific V-GURT) or by hampering the expression of a trait (trait-specific T-GURT) in a genetically modified (GM) plant. In this study the different approaches/mechanisms of GURTs have been emphasized and how the GURTs are related to seed industry and how it affects the same.

Keywords: Agriculture, GURTs, transgenics, seed industry

Introduction

The advances of modern plant technologies, especially genetically modified crops, are considered to be a substantial benefit to agriculture and society (Malav and Gaur, 2017) [36]. However, so-called transgene escape remains and is of environmental and regulatory concern. Genetic use restriction technologies (GURTs), developed to secure return on investments through the protection of plant varieties, are among the most controversial and opposed genetic engineering biotechnological interventions as they are perceived as a tool to force farmers to depend on multinational corporations, seed monopolies (Lombardo, 2014) [34]. (GURTs) are the name given to methods, providing specific genetic switch mechanisms that restrict the unauthorized use of genetic material (FAO, 2001) [16] by hampering reproduction (variety-specific V-GURT) or the expression of a trait (trait-specific T-GURT) in a genetically modified (GM) plant. Both the nicknames 'terminator and 'traitor' were coined by the Canadian-based nongovernment organisation, Rural Advancement Foundation International (RAFI), the former refers to the genetic modification of plants to make them produce sterile seeds at harvest also known as suicide seeds (Bangarwa, 2017) [4]. Terminator alters the expression of certain genes in plants so that plants terminate their reproductive switch, about the embryo and make themselves sterile, such plants then produce seed that cannot germinate (Krishnakumar, 1998) [28]. Terminator technology was patented by U.S Department of Agriculture and the seed company, Delta and Pine Land Company. Terminator has not yet been commercialized or field-tested but tests are currently being conducted in greenhouses. (GURT), refers to methods for restricting the use of genetically modified plants by activating some genes only in response to certain stimuli, especially to cause second-generation seeds to be infertile (Yousuf *et al.*, 2017) [53]. The technology was originally developed under a cooperative research and development agreement between the Agricultural Research Service of the United States Department of Agriculture and Delta and Pine Land company in the 1990s, however, GURT was first reported on by the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) to the UN Convention on Biological Diversity. In India, farmers have hailed the government's decision to notify the Plant Varieties Protection and Farmers' Rights (PVP&FR) Act, 2001 (Eaton *et al.*, 2002) [12]. They said that though the decision is belated, it would solve the farmers' problems to a great extent. The legislation was passed by Parliament way back in 2001 and received Presidential assent in the same year, but was withheld from notification, which prevented its implementation over the past few years. The Act, apart from protecting farm bio-diversity, allows farmers to save, sow, sell and exchange seeds in unbranded form for use in the next crop season. The Act has also banned the registration of seeds containing terminator technology vide section 18 (1) (C) (Sharma, 2015)

[46]. The government has recently constituted Plant Varieties Protection and Farmers' Rights Board under the chairmanship of Dr. S. Nagarajan for implementation of the Act, However, terminator technology leads to trouble for farmers throughout the developing world because they would no longer be able to save seeds to re-use from one harvest to the next (Anonymous, 2005) [2]. Many poor farmers cannot afford to buy seeds each year. Instead, they save, swap and share seeds that have been developed over generations by themselves. If farmers have no choice but to buy new seeds every year, the companies are guaranteed large profits at the expense of poor farmers' food security. The biotech companies argue that Terminator technology will prevent the contamination of non-GM crops with GM-crops. They say that if all GM varieties had the terminator trait they would not be able to spread into the environment, and so biosafety would be ensured (Siddarudh, 2015) [47]. However, like any other GM genes, Terminator genes could spread to other crops by cross-fertilisation and by accidental mixing. So the GM Terminator genes would themselves contaminate non-GM-crops, meaning that these non-GM crops would produce sterile seeds and would no longer be GM-free (Anonymous, 2015) [3].

History of GURTs

The first patent applications related to a biological switch mechanism regulated by external inducers date back to the first years of the 1990s. (Lombardo, 2014) [34]. In 1991, DuPont filed a patent application, granted in 1994 (U.S. 5,364,780), entitled ‘External regulation of gene expression by inducible promoters’ that described a method ‘utilized to transform plants and bring the expression of the gene product under external chemical control in various tissues of monocotyledonous and dicotyledonous plants (Lombardo, 2014) [34]. In 1992, Zeneca (today Syngenta, after the merger with Novartis Agribusiness in 2000) filed a technology application entitled 'Improved plant germplasm' published by WIPO (World Intellectual Property Organization) in February 1994 (WO9403619A2, where the letter A indicates the request for approval), providing 'a gene switch which is inducible by external application of a chemical inducer and which controls expression of a gene product which affects the expression of a second gene in the genome'; the second gene could encode a cytotoxic molecule fatal to the plant or a desirable characteristic that may be excised selectively by applying or withholding chemical application (Lombardo, 2014) [34]. The true watershed was marked when Melvin Oliver, a British researcher, was assigned (1990) by the United States Department of Agriculture (USDA) to develop together with the Delta & Pine Land (DPL) Company a seed-embedded protection technology. (Lombardo, 2014) [34]. The challenge was to create a cultivar that would become sterile only in farmer’s fields through an external stimulus to protect the varieties developed by biotech companies, thus preventing farmers from seed saving. The conception of this 'genetic switch' was realized with the filing of a patent application on 7 June 1995. It was registered at WIPO in 1996 under the number WO 9604393 and finally, on 3 March 1998, the United States Patent and Trademark Office (USPTO) granted the joint application of Delta & Pine Land Corporation and the U.S. Department of Agriculture's Agricultural Research Service and issued the patent U.S. 5,723,765 entitled 'Control of plant gene expression' (Oliver *et al*., 1998) [41].

The adoption of neutral definitions for this new technology did not prevent it from drawing the attention of the whole world. Fierce protests raged worldwide as many saw it as a very disadvantageous and unethical mechanism for poor farmers, especially in developing countries where saving seeds (also known as ‘brown-bagging’) is a common practice, and as an advantage for multinational companies that would have thus increased the dependence of indigenous and rural communities worldwide on their GM seeds. These objections are borne out by the fact that seed saving is estimated to account for between 15% and 20% of the world's food supply, practised by 100 million farmers in Latin America, 300 million in Africa and 1 billion in Asia (IIPTA, 2012) [25]. In June 1999, as a result of the great opposition to this technology by the public opinion, nongovernmental organizations and farmers, Zeneca announced that they would not market terminator seeds. Four months later (October 1999), Monsanto's CEO Robert Shapiro, under the advice of Gordon Conway, president of the Rockefeller Foundation (Vidal, 1999) [50], pledged not to commercialize gene protection systems that render seeds sterile to avoid compromising the public image of the company (technically at that time Monsanto did not possess GURT patents, as it acquired Delta & Pine Land Co. along with its patents only in 2007; however, the announcement that the two companies would merge was made in May 1998). In 2000, D&PL claimed that they would continue trials for commercializing the technology protection system (Collins, 2003) [7], and in 2005, Monsanto opened the possibility of using terminator technology in non-food crops such as cotton and grass.

Application in crop improvement

(GURTs), developed to secure return on investments through the protection of plant varieties, are among the most controversial and opposed genetic engineering biotechnologies (Lombardo, 2014) [34]. GURT may be variety specific (Terminator technology) or trait-specific (Traitor Technology). Traitor technology is the second generation of terminator technology with similar or near to similar mode of action (Fisher, 2002) [17]. Terminator technology on one side controls the plant fertility and the Traitor technology on the other side is designed to switch on or off of a trait, however, without killing the embryo (FAO, 2001) [16]. The genetic modification is activated by chemical treatment or by environmental factors. The main version of the terminator includes a set of three novel genes inserted into one plant. However, there is another version, which divides two or three genes on to two plants that are later to be cross-pollinated (Oliver and Velten, 2001; Gupta 1998) [40, 22]. The outcome is a sterile seed in the following generation. The disrupter protein may or may not be permanently active in the seed depending on the mechanism involved in V-GURT (Lombardo, 2014) [34]. The main goal for which GURTs were designed is the technological protection of genetic resources and innovations; however, their possible application would be further useful for preventing undesired transgene flow and obtaining specific agronomic/economic benefits (Malav and Gaur, 2017) [36]. Some concerns regarding these technologies have been raised. These may have negative impacts on non-target organisms and the environment (Mukherjee and Senthil Kumar, 2014) [38]. Biodiversity and food security especially in developing countries that normally depend on the farm-saved seed is under threat by V-GURT (Malav and Gaur, 2017) [36]. Increased dependency on industrial costly seeds and chemical inducers would create a monopoly of companies over markets. There is a risk of transgene escape (Lemaux, 2009)

[31].

Mechanism of terminator technology

For V-GURTs, essentially three different restriction mechanisms have been proposed. The first mechanism of action is that described in the patent (U.S. 5,723,765) by the USDA and Delta & Pine Land (Bert *et al*., 2001) [5]. The patented method is based on a gene that produces a protein that is toxic to the plant and therefore, does not allow the seed to germinate (Gupta, 1998) [22]. One such gene indicated in the patent is ribosomal inactivating protein (RIP) gene, which if expressed, does not allow protein synthesis to take place. The gene is placed under the control of LEA promoter permitting RIP to express only during late embryogenesis, thus affecting only the embryo development. This gene (RIP gene) will not express in the first generation, because its expression is blocked through the use of a spacer or a blocking sequence between the promoter and the lethal RIP gene (Gupta, 1998) [23]. On either side of the spacer are placed specific excision sequences that are recognized by a recombinase enzyme (CRE/LOX system from a bacteriophage), whose function is to excise the spacer or the blocking sequence. The second gene encoding recombinase is placed behind another promoter/operator, specific for a repressor encoded by the third gene, which is a repressor gene. Before being sold to the consumer (in most cases, to the farmer), these seeds are exposed to the inducer that inhibits the function of the repressor, which causes transcription of the recombinase gene, which produces Cre that recognizes the Cre blocking sequence in the lox sequence and splices lox from the genome, thus placing the ribosomal inactivating protein under the direct control of the late embryogenesis abundant promoter. Thus, the seeds purchased by farmers will be able to germinate in the field. However, the seeds produced in the harvest will be sterile and thus cannot be stored for later cropping. This technology was designed specifically for pure line seed production in self-pollinated crops; the genes introduced into separate transgenic founder lines were then cross-pollinated to provide a genome with the full suite of TPS genes in the target crop (Yousuf *et al*., 2017) [53]. The second mechanism of action of VGURT is based on a reversed process because it is characterized by the presence of a gene encoding a disrupter protein permanently active in the seed, which makes it sterile. The gene promoter is under the control of a specific operator sequence. A further repressor protein, whose gene is under control of a chemically inducible promoter, can bind to the operator, inhibiting the expression of the disrupter protein. In the absence of the exogenous chemical inducer, no repressor protein is expressed; therefore, the breeder must apply the specific chemical inducer throughout the process of seed multiplication to inactivate the disrupter gene that causes sterility, interrupting the application only at the time of selling the seeds. The third strategy is applied to vegetatively reproducing in species, such as tuber and root crops and ornamental plants, or plant's organs such as the cotyledons, leaves and stem, where growth is prevented during the period in which they are stored to increase the „shelf life" of the product. This mechanism patented by Zeneca (Syngenta) in 2001 involves a permanently active gene able to block the vegetative growth of the plant, preventing the multiplication of the seeds. This default-expressed blocking gene can eventually be suppressed by the application of a chemical activating a second gene allowing the plant to develop.

Relevance to seed industry

The main goal for which GURTs were designed is the technological protection of genetic resources and innovations (Garí, 2002) [18]; however, their possible application would be further useful for preventing undesired transgene flow and obtaining specific agronomic/economic benefits.

Intellectual property protection

Although intellectual property protection is granted at the local level in the form of patents or plant varietal protection (PVP), also 'plant breeder's rights' (PBR), and at the international level by the UPOV (International Union for the Protection of New Varieties of Plants) and by the WTO. Moreover, there are several countries where plant varieties and/or biotechnological inventions are not protected or protected with an ineffective or very expensive intellectual property rights (IPR) system. Intellectual property protection analysis is performed by engineering. Team members identify and protect the design elements, features, and other aspects or factors that will make the new product or product improvement successful and provide it with a competitive advantage (Wang and Li-Ying, 2014) [52]. This latter aspect would maintain the relevance for industrial/biotech research as the GURT technology would be protected during the life of the patent (Lombardo, 2014) [34]. Thus, the intellectual property protection granted by GURTs has a double target as it ensures that farmers cannot reuse saved seeds or exploit a valuable trait without purchasing a (patented) chemical and also prevents competitor biotech industries from using seeds in their breeding programmes (Pendleton, 2004) [42]. Eventually, as suggested by Pendleton (2004) [42], a company could use the prospect of the commercial use of GURTs in negotiations with governments or customers as leverage to achieve greater legal protections, better enforcement, or contractual concessions.

A commonly managed form of restriction use is the hybrid seed technology, where the outcrossing occurring in the second and every other generation will produce a significantly lower performance of the plants (insofar as the first rationale of hybridization is to obtain more valuable plants by incorporating desired traits). However, hybridization may be infeasible or ineffective for many self-fertilizing crops such as rice, wheat, soya bean, cotton and horticultural crops (Jefferson *et al*., 1999) [26], whereas GURTs could potentially be applied to all seed-propagated crops (Lehmann, 1998) [29]. Nevertheless, V-GURTs, would not prevent the clonal propagation of plants such as some grass species, shrubs, and trees (Committee on the Biological Confinement of Genetically Engineered Organisms, 2004) [9].

Transgene containment

Genetic use restriction technologies could be used for the environmental containment of transgenic seeds (V-GURT) or transgenes (T-GURT), thus solving or marginalizing one of the greatest concerns associated with GM crops (Collins and Krueger, 2003; FAO, 2001) [7, 16]. According to Dunwell and Ford (2005) [11], seed lethality is the only strategy at present that prevents transgene movement via seeds; however, GURTs may generally prevent unwanted gene flow from transgenic to non-transgenic varieties (including wild relatives) because it is argued that pollen carries the dominant allele of the lethal/inhibiting protein. Accordingly, GURTs may help the breeding companies to address any legal liabilities if the transgenic crop can cross with other commercial varieties or introgress into wild relatives (Hills *et al*., 2007) [24], thus making it particularly attractive in the case of biopharma crops (Oguamanam, 2005) [39].

As an indirect effect, GURTs could reduce or remove the need for buffer zones for gene containment and drastically limit the eventuality of volunteer plants by preventing volunteer seeds from germinating (V-GURTs) or from expressing the GM trait (T-GURTs). Additionally, according to Budd (2004) [6], V-GURTs would be useful to effectively reduce the risk of creating 'super weeds' by reducing the presence of the GM crop in subsequent years. There are several proposed methods for transgene containment in plants, such as physical containment (in greenhouses, growth rooms and bioreactors), partial genome incompatibility, harvesting before flowering, parthenocarpy, stenospermocarpy, reduced shattering, inhibition of seed dormancy, apomixis, plastid transformation (transplastomic approach), cleistogamy, induced triploidy, conditional lethality, male sterility, inducible promoters, complete sterility by nonflowering, transgene excision, transgene mitigation (TM), inteins and auxotrophy (Kausch *et al*., 2010; Liu *et al*., 2013) [27, 32]. Many of these methods including some degree of genetic use restriction; however, none of the strategies currently available blocks all avenues for transgene spread (de Maagd and Boutilier, 2010) [10]. In particular, regarding other gene containment methods based on genetic engineering, several crucial points still need to be overcome.

Benefits to farmers

The implementation of GURTs will lead to improved yield as farmers will use new seeds every year. This will result in stiff competition between the public and private sector institutions and eventually, the farmers will benefit through this technology. Furthermore, incentives to breed new varieties may enhance genetic diversity in many important crops, thereby providing further long-term benefits associated with biodiversity (e.g., pest resistance) to farmers. (Lehmann, 1998) [30]. Apart from long-term yield and biodiversity effects, use of GURTs may offer some short- term practicable applications for farmers as well. Terminator technology could effectively eliminate the problem of genetically modified (GM) crop volunteers in farmers" fields (Pendleton, 2004) [43] and reduce the potential for outcrossing with, and increasing the fitness of, weedy relatives.

Benefits to governments

Governments may benefit from GURTs through reduced investment requirements in breeding and fewer enforcement costs for plant variety protection (Eaton, 2002) [13]. Governments could, thus, use GURTs as justification to decrease funding to agriculture R&D and biosafety/copyright infringement enforcement programs. If the implementation of GURTs results in yield gains and benefits to farmers, then governments can gain politically with policies that support GURTs.

Benefits to breeders

GURTs represent a novel mechanism for capturing returns from innovation in the plant breeding industry, in a similar manner to more conventional hybridizing techniques. The GURT mechanism greatly improves the plant breeder's capacity for rent capture, potentially increasing private investment into agricultural R&D and, hence, a higher rate of innovation in the plant breeding industry (Goeschl and Swanson, 2003) [20]. Breeding companies hope to protect their investments in improved varieties, thus, GURTs may present a better form of insurance (i.e., a biological one) against the free use of genetic innovations than patents, plant breeders" rights or licenses (Burk, 2004) [43]. GURTs would allow better enforcement of property rights15. Apart from the sterile seed technology of GURTs, it is also possible that T-GURTs protecting value-added traits in newly released commercial varieties.

Other possible benefits

The major agronomic benefits deriving from this technology are related to T-GURTs because they could be used to switch the desired trait on or off in favourable or unfavourable situations, such as drought and salt stress or pest attack (FAO, 2001) [16], whereas V-GURTs could be used to prevent preharvest sprouting (Budd, 2004; Pilger, 2002) [6, 44] and, according to Louwaars *et al*. (2002) [35], when combined with apomixis, they could allow seed suppliers to produce seeds with hybrid vigour at a reduced cost while protecting the investment.

Genetic use restriction technologies may increase competition by encouraging private companies to enter the market of self-fertilizing cultivars, especially in countries where seed saving is a common activity (FAO, 2002). Breeders would obtain their economic return through the sale of seeds. The resulting boosted investment in research and development in the plant breeding sector, favoured by the lower costs resulting from cover contracts and intellectual property laws (Smyth *et al*., 2002) [48], could eventually increase productivity and (paradoxically) agricultural biodiversity where the breeders would be able to use a much wider gene pool or develop more varieties (Louwaars *et al*., 2002) [35]. Eaton and van Tongeren (2002) [14] suggested that even governments may benefit from GURTs through reduced investment requirements for breeding and fewer enforcement costs for plant variety protection.

Moreover, against the increased costs to buy seeds (or chemicals to activate the seeds/traits), farmers could profit from the new (improved) varieties providing higher yield potentials and improved pest resistance (Mukherjee and Senthil Kumar, 2014) [38]. These benefits may also have a secondary positive impact on consumers, leading to lower food costs (Eaton and van Tongeren (2002) [14].

Nevertheless, in the forecast realized by Goeschl and Swanson (2003) [21] on the possible outcomes deriving from the application of GURTs in a 20-year horizon, it is suggested that the most developed countries would stand to benefit most, whereas the least developed countries would stand to lose (especially in the short term).

Concerns to Seed Industry

Agrarian sustainability

The main arguments put forward against GURTs, particularly against terminator technology, are the impacts on biodiversity, sustainable agricultural development, and farmers' access to and use of genetic resources through the inability to save and re-sow seeds. Regarding the impact on agrobiodiversity, the first concern is that the introduction of new, uniform, GURT-protected varieties would replace the adapted or selected (possibly less productive) autochthonous cultivars and wild relative species, resulting in the erosion of genetic diversity in fields, adverse effects on local germplasms (or at least the landraces), and effects on the

coevolution of crops at the farm level (FAO, 2001; Visser *et al*., 2001) [16, 51]. Genetic use restriction technologies-transformed crops may also produce low quantities of autotoxic compounds with negative impacts on non-target organisms, induce competition with wild species, and eventually, as food/feed, transfer allergenicity and antibiotic resistance. Similarly, the chemicals used to treat the seeds each year may have negative impacts on the environment where massive use of antibiotics such as tetracyclines, although harmless to humans and plants, may have a detrimental effect on soil ecology, particularly on microflora and fauna, and increase the prevalence of antibiotic-resistant bacteria (Mariani, 2001; Mukherjee and Senthil Kumar, 2014) [37, 38]. Moreover, Giovannetti (2003) [19] suggested that it cannot be excluded that suicide genes could be suddenly activated at different times and in different parts of the plant other than the seed, with disastrous effects on ecosystems and life itself, whereas the application of GURTs that would prevent the formation of pollen in plants could have a detrimental ecological impact on some pollen feeding insects.
From a socio-economic point of view, GURTs would limit the fair and equitable sharing of benefits arising from their utilization provided by the Nagoya Protocol of the Convention on Biological Diversity, because of the increased dependency on ‘industrial’ costly seeds and chemical inducers that would create a companies' monopoly over markets (with an unbalanced distribution of benefits) and a subsequent reduction of the so-called ‘food sovereignty’. Moreover, the 2003 report of the Ad Hoc Technical Expert Group (AHTEG) on the potential impacts of GURTs on smallholder farmers, indigenous and local communities and farmers' rights listed various possible negative impacts including:

1. reduction and limitation of traditional seed exchange practices and participatory plant breeding;
2. reduction of the traditional knowledge and innovation capacity for informal crop genetic improvement, local agro-biodiversity protection and food security;
3. Displacement of local farming systems and the social, cultural and spiritual dimensions associated with them.

A very common issue is that this technology would favour large multinational corporations and would hurt the employment of small farmers (Mukherjee and Senthil Kumar, 2014) [38]. Also, according to Garí (2002) [18], GURTs would tend to concentrate breeding efforts and options, rather than widening them, setting limits to the effective adherence to the international policy framework on plant genetic resources and thus restricting poor farmers' access to new varieties and technologies and preventing them from making crosses to develop valuable and locally adapted varieties.

Risk of transgene escape

Some drawbacks are related to the real effectiveness of GURTs in preventing gene flow, but more generally to the real feasibility of these mechanisms. Whereas partial V-GURT efficiency, that is, causing the reduction of the germination rate, would be enough to force farmers to buy seeds from companies each year (Sang *et al*., 2013) [45], the prevention of flower or seed development and the inducible expression of the GM trait would require a 100% effective application of a chemical inducer to prevent the escape of a non-functioning transgene via both seed and pollen. Some seeds may not respond or may not take up enough inducer to activate the recombinase, thereby producing fertile GM plants (Lemaux, 2009; Van Acker *et al*., 2007) [31, 49] able to transmit the inserted trait and causing exactly the opposite effect to the one intended. Other technical issues have been raised regarding the escape of genes over generations, the mutation of genes, the accidental switching on of sleeper genes, the instability of the promoters and the horizontal flow of genetically modified pollen to non-target organisms (e.g., birds, insects and soil biota) (FAO, 2002).

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