15 The Economics of RNAi-based Innovation: from the Innovation Landscape to Consumer Acceptance

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15.1 Introduction

RNA interference (RNAi) is an innovative technology of gene silencing which offers great opportunities for the development of sustainable solutions for crop protection (Palmgren *et al.*, 2015; Borel, 2017; Limera *et al.*, 2017; Zotti *et al.*, 2018). The most original aspect related to the economics of RNAi is the opening of a completely new innovation scenario consisting of new formulations of RNAi-based products for topical use, which are considered to be able to meet the need to find safer and more effective strategies for pest control and combat agricultural losses (Mitter *et al.*, 2017; Wang and Jin, 2017; Niu *et al.*, 2018). The possibility of substituting agrochemicals with more natural molecules is seen as the major advantage of these new technologies, which provide contributions towards a more sustainable agriculture (Collinge, 2018). In this context, academic interest in the economic aspects of this new technology is growing rapidly, suggesting that this innovative set of technologies is going to reshape the state of the art of the agricultural biotechnology (agbiotech) sector under multiple aspects, including the market structure (Bonny, 2017) and, most probably, public acceptance.

15.2 Market Potential of RNAi Innovation

After decades of debate on genetically modified organisms (GMOs), one of the most controversial ‘science and society’ issues able to divide scientific community and public opinion, a new wave of techniques has replaced the previous transgenic approach to plant breeding, introducing the possibility of imitating natural genetic recombination and thus avoiding the introduction of foreign genetic material. Among them, the economic landscape of RNAi-based innovation has been analysed. Frisio and Ventura (2019) investigated the structure of the global patent landscape of RNAi agricultural applications, identifying significant differences in the role of private and public research and evidencing the specialization of some universities and the rising power of Chinese research. Results revealed that China’s pattern of innovation is able to stay at the forefront in most modern

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agricultural biotechnologies, in stark contrast to the European scenario, where the regulatory landscape continues to impede the exploitation of agbiotech inventions. Mat Jalaluddin *et al.* (2019) provided an analysis of the global trend of RNAi-based product commercialization, using both bibliometric and patent data. They outlined that resistance against viruses, fungi and insect pests are the priorities for research activity and that the global market is rapidly moving toward huge investments in this field, with potential positive impacts on the development of RNAi technologies. These technologies could have very promising opportunities for being developed and applied in a broad range of agrifood products as well as in the formulation of innovative methods for biocontrol.

15.3 The Frontiers of Innovation: RNAi for Biocontrol

A new wave of RNA-based commercial products is ready to reach the market, with the first plant protectant product (to control rootworm) approved in the USA (EPA, 2017). Thus, the identification of the global scenario for RNAi technology innovation applied to biotic control, using patent data as indicators of innovation output, can provide some useful insights about this specific innovation scenario and its future applications (Chi-Ham *et al.*, 2010; Frisio *et al.*, 2010; Lundin, 2011; Egelie *et al.*, 2016)

The analysis has been carried out by mining the Questel-Orbit patent database through specific keywords for the identification of those inventions regarding the use of RNAi technology for plant biotic resistance. For this purpose, a set of keywords related to the term 'RNAi' have been searched in the 'title and abstract' field. The search has been limited to a number of International Patent Classification (IPC) and Cooperative Patent Classification (CPC) classes associated with biopesticides (IPC code A01N and CPC code Y02A-040). Time coverage of data is limited to the past 10 years (2010–2019). The original data set contains information about worldwide innovation in agricultural RNAi-based inventions, amounting to a total of 641 patent families. Then, with the aim of extracting from the data set only those inventions specifically developed for plant protection, a text-mining analysis has been performed through double check in the patent title, abstract, claims and technical concepts, to identify those inventions referring to biotic control for agricultural application. The final data set is composed of 223 patent families, corresponding to 1224 single patents. In some cases, data elaboration has been performed making the distinction between inventions and patents. The term invention relates to the first filing of a patent application, anywhere in the world (usually in the applicant's domestic patent office). The statistics are based on the count of single inventions that provide information on the origin of the invention itself. Conversely, the term patent also refers to the set of patents filed in several countries that are related to the same invention, thus representing the so-called patent family. This variable is more indicative of the spread of innovation and its market, as the size of patent family is considered a proxy for the value of the invention.

Time trends outlined that RNAi technology applied to plant resistance is a field of innovation that has witnessed a good development globally in recent years, with an annual average number of new inventions equivalent to 22, corresponding to 122 patent applications. Nevertheless, Fig. 15.1 shows a peak in the numbers of patent filings in 2014 and a subsequent decline starting from 2015. Since patent applications are normally published after 18 months, data can be considered complete until 2017. The data set is composed of 223 inventions, whose legal status is 'alive' for 96% of cases, while the only nine inventions classified as 'dead' have been at some stage revoked, or lapsed. The analysis of the evolution over time of patent trends based on the nationality of the assignee indicates that, on a global level, the three main countries involved in this innovation sector are China (41.7%), the USA (26%) and the European Union (EU) (20%). The European data are quite surprising, since previous studies focusing on the analysis of the more global patent landscape of RNAi technology for plant improvement (Frisio and Ventura, 2019) revealed the marginal role of European players in producing innovations in this sector. This probably means that, amongst the different applications of RNAi technology, European research and development (R&D) activity shows greater competitiveness in the implementation

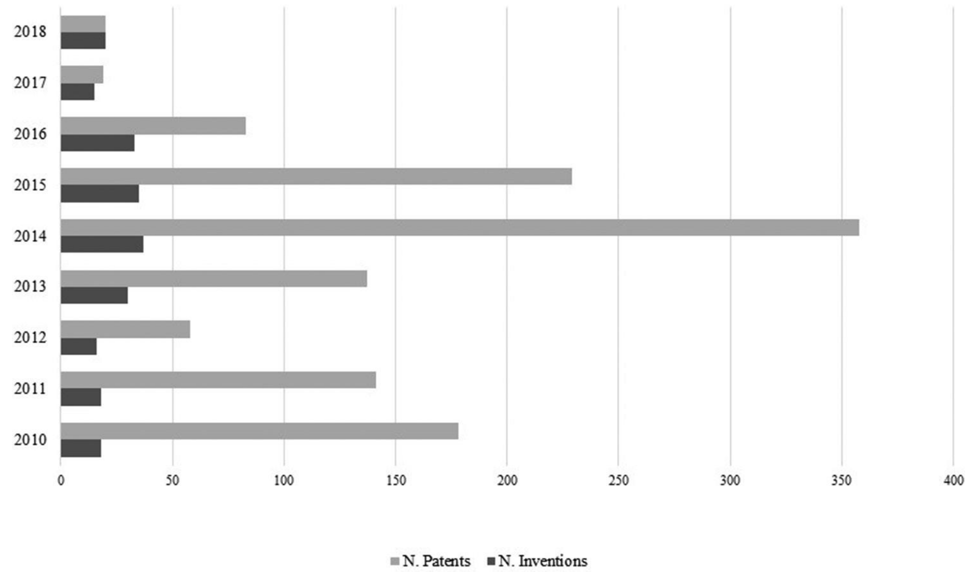

Fig. 15.1. Time trend for plant-RNAi inventions. (Source: own elaboration on Questel-Orbit data.)

of RNAi-based solutions for biotic resistance. The major contribution to the European innovation capacity derives from Germany, accounting for 26% of EU patents, principally applied by the agbiotech firms Bayer and BASF and, for public research, by the Max Planck and the Fraunhofer research institutes. The relevant role of Chinese applicants is most probably due to the massive investments in public research made by a government that considered agbiotech innovation a national priority. Nevertheless, the importance of Chinese applications dramatically decreases when considering the diffusion of inventions, represented by the number of patents filed in foreign patent systems, for which China accounts for only 8% of the total patenting activity.

The analysis of the type of assignee (Table 15.1) reveals that almost 47% of inventions are produced by public research, a value ten points greater than the private sector (35%). Moreover, nearly 18% of inventions derive from collaboration between public and private assignees. However, statistics related to the share of patents show that private players are more capable of exploiting inventions through their protection in different patent systems, as the value of the private sector's contribution moves from 35% of inventions to 55% of patents. It can be deduced that public sector R&D is competitive in producing innovative ideas and products for the application of RNAi technology in agriculture, but misses the opportunity to implement innovations in the form of more

Table 15.1 Analysis of the type of assignee. (Source: own elaboration on Questel-Orbit data.)

		% Share of inventions	% Share of patents
Single Assignee			
	Public	46.6	13.3
	Private	35.4	55.1
Multiple Assignee			
	Public–Private	14.3	29.2
	Public–Public	3.6	2.3

market-oriented solutions. A more detailed classification indicates that the public sector is principally composed of academic institutions, while the private sector is composed of the 'Big Four' agbiotech companies for 35% of the total data set, with an additional 25% represented by other biotech companies.

The top player is Dow Agrosciences (merged with Du Pont in 2017), the seed company most interested in investing in the development of this technology. Notably, this firm shares several patents with three public research institutions, showing a great level of public–private collaboration activity. Apart from the former 'Big Six' agbiotech companies, top assignees (Table 15.2) are small–medium firms specializing in very specific innovation sectors. For example, FuturaGene Ltd focuses on sustainable wood production, Forrest Innovation Ltd aims at providing eco-friendly solutions for mosquito vector control, RNAgri was born as a start-up specifically focused on RNAi-based products for modern agriculture. Considering the content of inventions, the innovative nature of this specific use of RNAi technology emerges from the fact that 65% of patents do not have a single plant as target (30% plant not specified, 25% multiple applications and 10% multiple major crops). The remaining patents have maize as the major target plant (14%), followed by wheat and rice.

As for the analysis of the type of plant resistance, Fig. 15.2 shows that the main trait is insect resistance (79% of inventions), which is an impressive share indicating that this technology is considered to be more effective or even more easily applicable for insect control. Fungal control is included in 6% of patent application and relates to resistance to *Magnaporthe grisea*, *Botrytis*, *Verticillium* and *Zymoseptoria* species. Considering the minor categories, virus resistance accounts for 5% of patents, while nematode resistance (principally to the Heteroderidae family) represents 4% of the applications.

Finally, with regards to the subset of insect resistance, the analysis of the target species (Fig. 15.3) reveals that 32% of inventions relate to Hemiptera. The great majority of these patents derive from China and are intended to confer

Table 15.2 Top players. (Source: own elaboration on Questel-Orbit data.)

Applicant		No. of inventions	No. of patents
Dow Agrosciences llc		24	274
	with Fraunhofer Institute	18	175
	with University of Nebraska	9	147
	with University of Sidney	1	19
Syngenta - DevGen		13	140
BASF		6	50
Bayer CropScience Ag – Monsanto Co		8	62
	with Universitaet Hohenheim	1	9
FuturaGene Ltd		4	32
Forrest Innovations Ltd		1	26
AB Seeds		2	22
University of Queensland		2	20
United States Department of Agriculture		7	17
RNAgri		2	15
Nemgenix Pty Ltd		2	13
Caas (Institute of Crop Sciences)		10	11

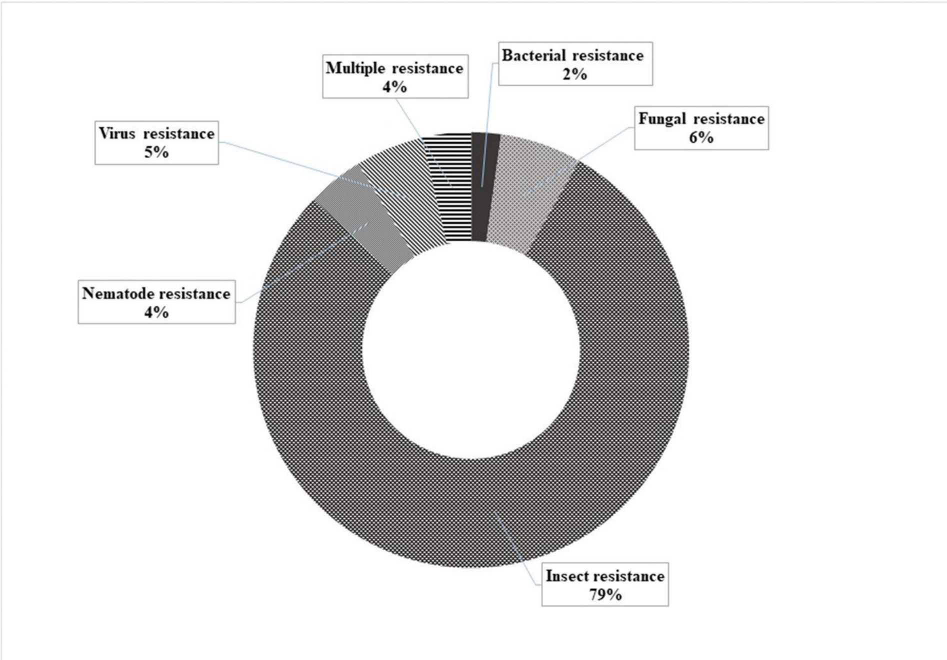

Fig. 15.2. Trait analysis. (Source: own elaboration on Questel-Orbit data.)

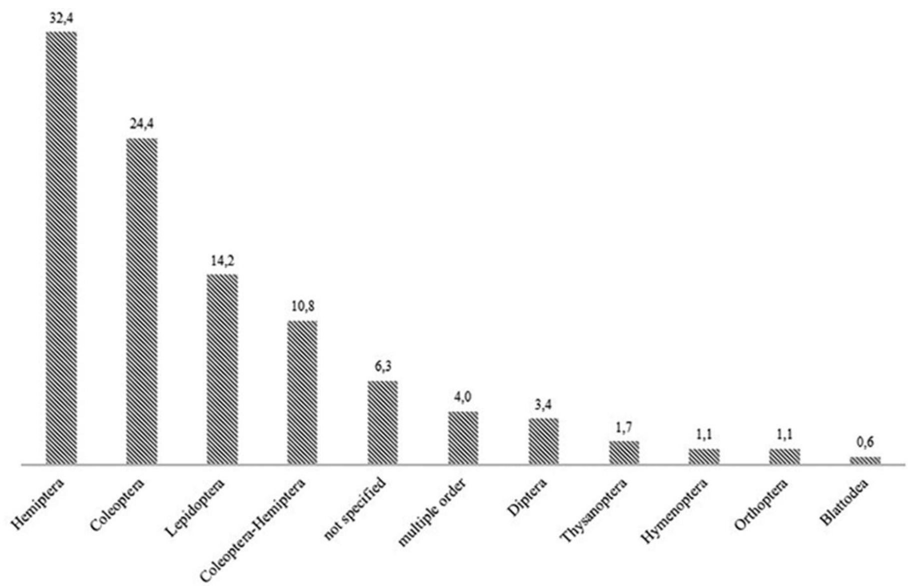

Fig. 15.3. Main targets for insect resistance.

resistance to the Aphididae family. The second type of insect resistance targets Coleoptera, almost entirely represented by the resistance to *Diabrotica* in maize. An additional 10% of patents aim at conferring resistance to both the Hemiptera and Coleoptera, while 14.2% are aimed at resistance to Lepidoptera. With regard to the type of application, the analysis showed that 24% of inventions contain a specific mention of the spray/topical application of the RNAi-based product.

15.4 RNAi: Stakeholder and Consumer Perceptions

Despite the fact that technological innovation plays a crucial role in enhancing the global sustainability of food chains and meeting changing consumers' needs and choices, growing evidence suggests that consumers tend to appreciate technology applications in many fields of their everyday life but tend to reject innovation when applied to the food domain. For this reason, academic research is focusing on the identification of the drivers of consumers' acceptance of innovative products, in order to find the most appropriate tools to mitigate consumer scepticism and resistance to these new technologies. In relation to new breeding techniques for crop improvement, public opinion has always shown one of the highest levels of rejection, principally based on the perceived unnaturalness of crop genetic modification (Mielby *et al.*, 2013; Kronberger *et al.*, 2014). Nevertheless, the literature suggests that not all the biotechnology solutions are perceived as being the same by consumers. Shew *et al.* (2017) showed that respondents valued CRISPR and GM food similarly and substantially less than conventional food, which could be detrimental for meeting future food demand. They also concluded that RNAi may be a better market alternative to more traditional biotechnologies such as GM crops expressing *Bacillus thuringiensis* (Bt) insect resistance. Topical application on plants avoids the need for genetic modification of plants, which could decrease consumer scepticism. Britton and Tonsor (2019) investigated the acceptance of a hypothetical RNAi beef product, concluding that consumers require a discount for buying the innovative product compared with conventional ones. Nevertheless, they also stated that the way RNAi technology is framed in food labels could have an influence on its acceptance. Results could support policy makers in understanding the current determinants of consumer attitudes toward RNAi technologies, in particular the role played by communication. If the information gap represents one of the main barriers to consumer acceptance, policies including information campaigns or educational programmes could be recommended to make consumers more aware and informed during food choice. This aspect has been confirmed by the outcome of a meeting with stakeholders (seed companies, farmer associations, producers) organized by iPlanta in October 2018 in Brussels. The meeting offered the opportunity to exchange knowledge on RNAi technology, biosafety and socio-economic impacts. All stakeholders attending the meeting showed a high interest towards this innovative technology, especially as a potential solution for farmers' needs, but also expressed concerns mostly related to consumer acceptance of RNAi-based products. The meeting outlined the importance of defining common ground to discuss solutions with scientists and stakeholders and for engaging with consumers to reduce the knowledge gaps.

15.5 Conclusions

RNAi for plant biotic resistance is a field of innovation that has been receiving increasing interest in recent years, showing promising future applications and developments. Innovation is being produced by both public and private players. As for the latter category, some emerging small–medium firms are gaining market share by developing tailored solutions for specific problems. In this initial stage of development, insect management is the trait that is receiving the greatest attention in relation to RNAi technology, but new solutions for pest control reveal broad opportunities for the creation of new products for the agbiotech industry. A more comprehensive analysis of the economic costs and benefits for their production in the European Union will have to take into account certain aspects of the innovation supply chain.

Specifically, one of the major issues is how these new highly specific molecules will be classified in the existing EU regulation system (chemicals, bioregulators, biostimulants or biopesticides) (Taning *et al.*, 2019). If properly communicated to consumers, and inserted in the correct legal framework, the economic perspective of RNAi technology in the EU will lead to a growing market, rich in opportunities for all the actors of the agri-food chain.

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