A Model for the Collaborative Development of Agricultural Biotechnology Products in Chile

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ABSTRACT
This chapter presents an operational model used by Fundación Chile to develop commercial biotechnology products. The first section highlights the challenges faced by a developing economy of which the main crops are so-called *orphan crops*. Fundación Chile's experience has shown that establishing public–private collaborations and a solid international network are critical to overcoming obstacles and increasing the probability of success. Indeed, accessing various technology components and managing intellectual property and regulatory issues are serious challenges for a small, export-oriented economy like Chile, and Fundación Chile´s response has been to implement a model that includes the participation of companies and local research organizations with specific expertise at different points along the value chain. International agencies complement the activities and contributions of these local organizations. The chapter's second section gives some specific examples of new products being developed with the new tools of biotechnology.

1. INTRODUCTION
In ten years the area planted with genetically engineered varieties in Chile has grown to more than 81 million hectares.[1] Just four crops—soybean, maize, cotton, and canola/rape—account for almost 100% of this area. Agricultural biotechnology can potentially add significant value to a wide range of crops, but the development of genetically engineered varieties requires a wide range of skills, access to many technologies, and many years of research and development. Because of the lower economic returns for developing products grown in limited areas, such crops have difficulty competing for investors. In fact, the major agribiotechnology companies focus on global *vision crops* that involve large planted areas. Crops covering limited areas can nevertheless be important for specific regions. These crops can be developed by focusing local R&D and leveraging resources through public–private collaborations, which can help to overcome major challenges, such as critical mass in R&D, freedom to operate, and regulatory issues. A similar approach is useful for commercially developing other types of regionally important biotechnology applications.

2. TECHNOLOGY AND IP ISSUES
Developing a commercially viable transgenic plant product requires inputs that include:

- high-quality germplasm
- gene cassettes for the engineering of a specific trait, including appropriate coding sequences and regulatory regions
- a transformation system for the species and genotypes of interest

Materials and technologies in each of the categories may be covered by one or more types of IP (intellectual property) rights, including patents, plant breeders' rights, and copyrights, as well as

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contractual agreements, such as material transfer agreements. IP rights are granted by individual countries and so, can vary from country to country, which often complicates the situation for export-oriented industries (for example, Chile's fruit industry).

Consolidation of the agri-biotechnology industry now means that a few large multinational companies control a large part of the intellectual property related to the genetic engineering of crops.[2] These companies are often reluctant to provide technology for specialty crops or so called *orphan crops* because of liability concerns arising from others' use of the technology.

Public sector laboratories have made, and continue to make, important contributions to agriculture, but they have emphasized the development of novel specific components, without consideration of the IP rights for other components needed to further develop or commercialize complex products such as transgenic crops. As a result, although these public institutions frequently can offer rights to components (for example, a DNA sequence coding for a specific gene of interest or a promoter that drives expression in a particular tissue), the institutions are rarely able to license a complete transgenic plant, or even an entire cassette, for transformation. It is essential to consider IP issues in the R&D program from the outset, because restrictions on freedom to operate can be a barrier to attracting the investment necessary to develop and commercialize products.

Such difficulties have been described for specific cases, such as pro-Vitamin-A containing *golden rice*.[3] Organizations that are attempting to address these issues on a more general level include the International Service for the Acquisition of Agri-biotech Applications (ISAAA),[4] CAMBIA,[5] and the Donald Danforth Plant Science Center.[6] Recently, a group of several leading universities and research institutes in the United States formed the Public Intellectual Property Resource for Agriculture (PIPRA),[7] which has expanded to include a number of nonprofit institutions in other countries, including Fundación Chile.[8] Although a major motivation for such initiatives has been to ensure the availability of biotechnology for humanitarian purposes in developing countries, these organizations are also facilitating the commercial development of minor crops through public–private partnerships.

3. REGULATORY ISSUES

Regulatory issues are currently a major factor when commercializing transgenic plants and the products derived from them. To avoid problems that can prevent or delay commercialization, potential regulatory issues must be considered at the inception of R&D planning and throughout the R&D process. Even during the research phase, it is critical to understand and comply with regulations regarding the handling and movement of genetically modified organisms.

Regulatory issues related to R&D in the genetic engineering of plants can be complex, involving biosafety, environmental impacts, food safety and so on. Transferring materials, especially among international collaborators, can involve phytosanitary regulations and international agreements such as the Convention on Biological Diversity.

Considerations that may affect choices logical of R&D strategies include the source of genes or gene products (allergenic organisms, food crops, nonfood plants, animals), properties of gene products or related proteins (toxicity, allergenicity, antinutritional effects, resistance to digestion), choice of selectable markers, and the design of vectors and transformation procedures, as well as the selection of specific transformation events to minimize the presence of DNA and gene products from other species.

As Chile's agricultural industry is largely export oriented, the policies and regulations of both domestic and major export markets must be taken into account. There are big differences, moreover, between the United States and Europe, and these present significant challenges. Regulations change continuously and must be monitored continually.

4. A COLLABORATIVE MODEL

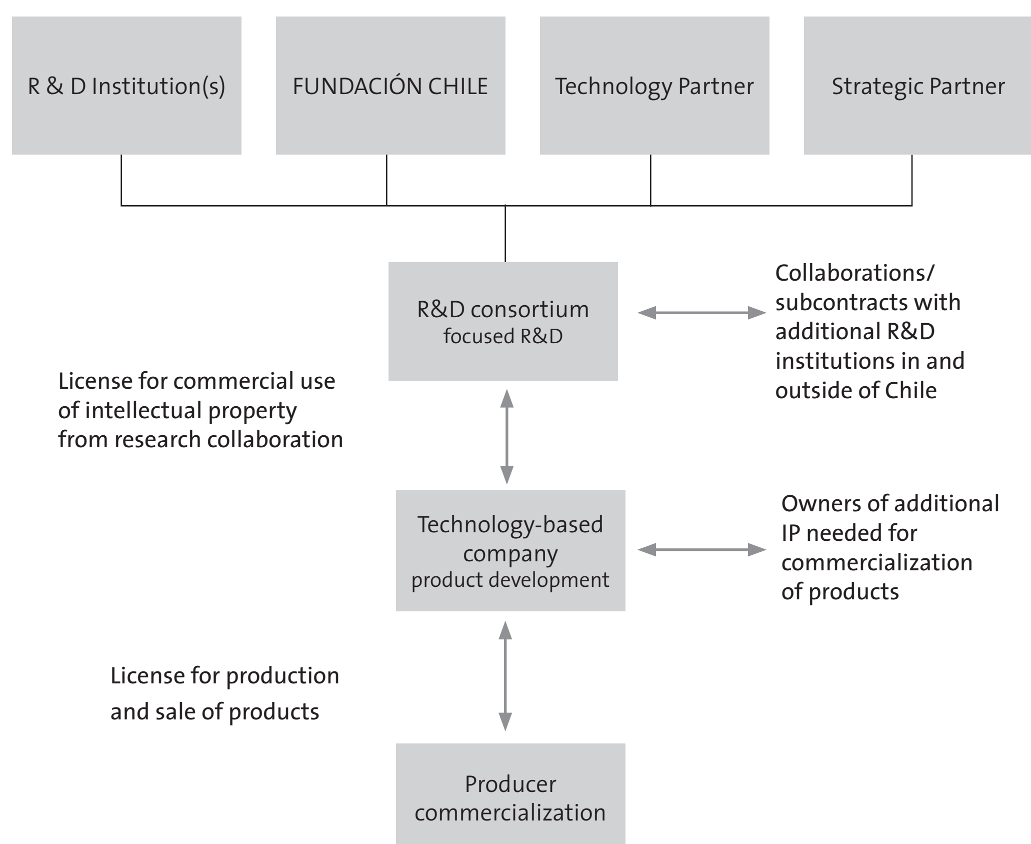
Solving the difficulties requires the participation of many different types of professionals. Indeed, it is difficult for a small biotechnology program with a narrow focus to maintain in-house all the types of expertise required. Fundación Chile's approach has been to develop international networks of parties, with complementary capacities and resources, for the initial development of products. These products are commercialized through new companies with specific commercial foci. The collaborations involve existing companies with strategic positions at different places along the value chain (for example, nurseries with access to germplasm and experience in introducing new varieties to market). The general scheme is illustrated in Figure 1.

4.1 *The R&D consortium*

In this model, the initial task is to form a research and development consortium with a specific focus. Each of the partners in the initial R&D consortium has a largely complementary primary role critical for success:

- **R&D organizations:** research capabilities for the adaptation of technologies to local conditions and the development of products addressing local priorities
- **technology partner:** identification, assessment, and global access to additional appropriate research capabilities and technologies
- **local technology transfer organization:** initial R&D funding, assistance in obtaining grants and other funding, incubation of new technology company
- **strategic private sector partner:** understanding of market demands, ability to

Figure 1: Fundación Chile's Collaborative Model



introduce or use the novel products in the target sector, initial R&D funding

Depending on the specific situation, each of the participants may contribute in additional ways. For example, researchers in the R&D organizations are likely to know about specific technologies of interest and may already have relevant relationships with other R&D centers. The private sector partner may already have rights to some intellectual property useful for developing the new products. The technology consultants may be from an entity that will also contribute to R&D funding.

In the biotechnology programs of Fundación Chile, the R&D consortia have made it possible to leverage investment through public support and the use of existing public research institutions. National agricultural research institutes and universities provide infrastructure (laboratories, green houses, equipment) and human resources to carry out the work.

The consortium is the repository of new intellectual property generated during the project. However, in most cases it is expected that the R&D consortium will not produce final products. In the Fundación Chile model, this is undertaken by a new technology-based company, to which the consortium will license rights to intellectual property in exchange for a royalty or other compensation.

4.2 *The R&D network*

The goal of the consortium is to provide the critical inputs necessary for successful R&D in the specific area. In most cases, achieving significant results in a reasonable time frame requires taking advantage of relevant results from other laboratories. Moreover, licensing and option agreements, research contracts, and collaborative research agreements between the R&D consortium, or its members, and other research institutions and companies are critical to establishing an adequate research network. Whenever possible, Fundación Chile has incorporated provisions for training local personnel as part of such agreements.

4.3 *The channel for commercialization*

Later commercial development usually will require different capabilities and considerable additional resources in the early R&D phase. In general, in Chile there is likely to be a significant gap between the results of projects conducted in public research institutions and industry's ability to use them. The model includes creating one or more new technology-based companies focused on commercially developing specific products. The companies will license the results of the R&D consortium and will be responsible for their commercialization. Achieving the latter will require different partners with different interests and resources. Once development has advanced to a stage at which existing companies can produce or use the product, licensing to a company with an established reputation in the area and with its own existing infrastructure may be most appropriate. In cases where an established company with plant breeders, nurseries and so forth does not exist, a new company may be created to produce and sell the product directly.

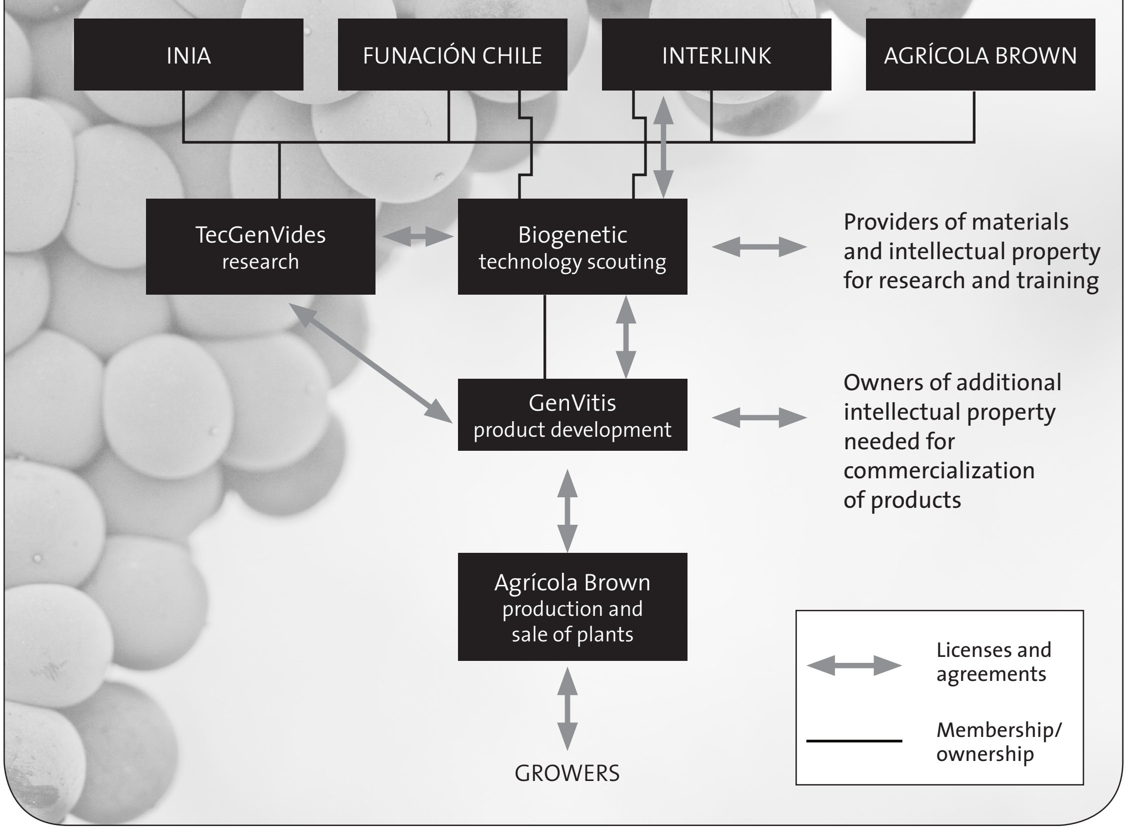
Establishing, early on, a commercial entity with rights to the outputs of the R&D consortium has advantages. Doing so provides a vehicle for licensing any additional rights required for commercialization and for raising additional investments.

5. THE GENETIC ENGINEERING OF GRAPES

A program to genetically engineer grapes was initiated in 2000 by the Chilean Institute for Agricultural Research (INIA),[9] Fundación Chile, InterLink Associates, Inc. (Princeton, U.S.A.), and Agrícola Brown Ltda. (Los Andes, Chile) with support from the FONDEF program of CONICYT.[10] The relationships of the entities involved in the program are summarized in Figure 2.

The program is one of several initiatives in plant biotechnology for which Biogenetic S.A. (Santiago, Chile)—a joint venture formed in 1998 between Fundación Chile and InterLink Associates, Inc.—has contributed to the development and implementation of strategies for applying biotechnology to problems of strategic importance for Chilean agriculture. InterLink provides expertise in technology scouting and

Figure 2: The Grape Genetic Engineering Program



assessment. In addition, it assists in negotiating agreements with a number of different providers of technology components (such as tissue-culture methods and gene candidates) for engineering specific traits in the United States and Europe.

Making use of INIA's existing human resources and infrastructure, the collaboration improved INIA's capacities through the acquisition of additional equipment, construction of new culture rooms and greenhouses, and training of INIA personnel in specific grape-tissue-culture methods at a laboratory in the United States.

The leading producer of grape planting stock in Chile, Agrícola Brown has pioneered the introduction of proprietary varieties of table grapes and also produces and exports grapes. Agrícola Brown's knowledge and experience help to ensure that the grape R&D program addresses the right targets and that any products introduced would be thoroughly evaluated.

The participants in the project formed TecGenVides (Sociedad Tecnológia Genetica en Vides Ltda.) as the entity that would own the results of the initial R&D project. TecGenVides would license intellectual property and materials generated in the project to GenVitis S.A., a new subsidiary of Biogenetic, for further commercial development.

GenVitis would pay a royalty based on its revenues related to the licensed property. In this case, it has been agreed that the major part of the royalty received by TecGenVides will be distributed to the research institution (INIA), with a minor part shared by the other members, who also have the opportunity to benefit from value captured at later stages.

It was agreed at the start of the project that the new technology company, GenVitis, would license the production and sale of transgenic plants in Chile to the strategic partner, Agrícola Brown, which would also participate in the downstream commercial development of products.

More than 1,000 transgenic lines of table grapes have been produced, with most of them containing combinations of candidate genes for increasing tolerance to fungal diseases. The first field trials were planted in 2005. The transformation technology platform developed for this effort also would be used to engineer additional traits.

6. ADDITIONAL EXAMPLES

Programs with similar structures but involving different partners have been established for developing recombinant vaccines for salmon, biotechnology applications for radiata pine (*pinus radiata*), and the genetic engineering of stone fruit trees.

The program for developing novel vaccines to protect salmon is a collaboration between Fundación Ciencia para la Vida and Fundación Chile. The genome of the salmon pathogen *Piscirickettsia salmonis* was sequenced though a contract with a U.S. Department of Energy laboratory. Annotation of the sequence, and identification of protein domains predicted to be highly immunogenic, was carried out by a network of Chilean and foreign researchers. AquaGestión, a company affiliated with Fundación Chile, performed the initial testing of vaccine candidates. Rather than developing production capabilities for a single product, the production and marketing of the vaccine was licensed to Syngenta A.G. (Basle, Switzerland), which was not a participant in the R&D project. A multiple recombinant protein vaccine for *P. salmonis* was expected to be introduced soon thereafter.

The radiata pine biotechnology program includes improvement through clonal selection and genetic engineering. In this case, Fundación Chile established a forestry biotechnology laboratory on the campus of Universidad Austral in space rented from Cefor S.A. (Valdina, Chile), a company affiliated with the university. Some of the investigators were employed directly by Fundación Chile.

The clonal forestry program includes commercialization in Chile by a new company, GenFor S.A. (Talcahuano, Chile). Using somatic embryogenesis and cryopreservation technology developed by CellFor Inc. (Vancouver, Canada), the material was developed by CellFor in collaboration with Bioforest S.A. (Concepción, Chile) and Rayonier Inc. (Jacksonville, U.S.A. and New Zealand). Field tests of clones were initiated in 2000. The initial selection of material for scale-up and commercialization is being made in 2005.

Projects for engineering radiata pine for resistance to insects, for wood composition, and for resistance to fungal diseases have been supported in part by the Fund for Development and Innovation of the Economic Development Corporation (CORFO). The R&D network has included GenFor, Cefor, Universidad Austral, INIA, InterLink, New Zealand Forest Research, New Zealand HortResearch, and Carson Associates Ltd. (Rotorura, New Zealand). A number of additional universities and companies have provided candidate genes.

The structure of the stone-fruit genetic engineering program is very similar to that of the grape program, but the stone-fruit program involves a different strategic partner. With support from CORFO, the program was initiated in 2002 by Fundación Chile, Biogenetic, INIA, and the Andes Nursery Association (ANA; Paine, Chile). ANA is a company focused on developing new fruit varieties that are owned by six nurseries. In addition to an extensive testing program in stone fruit, ANA has initiated a breeding program in peaches and nectarines, in collaboration with the Universidad de Chile, that is focused on improving the fruit's storage life and post-storage quality.

As in the case of the grape program, the products built upon the results of the research consortium will be commercially developed by a new subsidiary of Biogenetic, CaroGen. ANA has a right to license traits developed by CaroGen for commercialization in Chile. The research network includes Okanagan Biotechnology Inc. (Summerland, Canada), which has research collaborations with the Pacific Agri-Food Research Centre of Agriculture and Agri-Food Canada and the U.S. Department of Agriculture Appalachian Fruit Research Station.

Tissue culture and transformation work in the stone-fruit program is being carried out in the same laboratory at which the grape genetic engineering program is based (INIA, La Platina, Chile). This colocation has allowed some synergy among the programs. ■

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2 Graff GD, SE Cullen, KJ Bradford, D Zilberman and AB Bennett. 2003. The Public-Private Structure of Intellectual Property Ownership in Agricultural Biotechnology. *Nature Biotechnology* 21: 989–95.

3 Kryder RD, SP Kowalski and AF Krattiger. 2000. The Intellectual Property and Technical Property Components of Pro-Vitamin A Rice (Golden Rice): A Preliminary Freedom-to-Operate Review. *ISAAA Briefs No. 20*. ISAAA: Ithaca, New York.

4 www.isaaa.org.

5 www.cambia.org.

6 www.danforthcenter.org.

7 www.pipra.org.

8 ww.fundacionchile.cl.

9 www.inia.cl.

10 FONDEF (the Fund for the Promotion of Scientific and Technological Development of Chile) was founded in 1991 as a direct government initiative to improve the level of R&D. CONICYT is the National Commission for Scientific and Technological Research. www.conicyt.cl.