Fundación Chile: Technology Transfer for Somatic Embryogenesis of Grapes

CARLOS FERNANDEZ, *Director, Strategic Studies, Foundation for Agriculture Innovation (FIA), Chile*

ABSTRACT

Fundación Chile is a private, non-profit organization active in developing applications of biotechnology that can improve productivity and add value to existing agricultural and natural resource products of Chile. Fundación Chile seeks to create technology-based companies that would have significant economic and social impact in Chile. This case study details Fundación Chile's initiative in grape biotechnology: globally assessing the availability and priority of different technological components and initiating efforts to access, license, and transfer those key technologies for the initiative.

1. THE INSTITUTION

Fundación Chile[1] is a private non-profit organization. Its mission is to add economic value to Chile's products and services by promoting innovation and technology transfer focused on Chile's natural resources and productive capacity. *Fundación Chile*'s primary strategy is to develop new technology-based companies in Chile that can have a significant economic and social impact. These new companies are generally joint ventures with strategic partners, although other models, such as licensing, are used.

The main activities are focused in the areas of Agribusiness, Marine Resources, Forestry and Forest Products, Environment, Information Technology, Education and Human Resources, and Tourism.

Fundación Chile is unusual in that it is a non-profit institution with active participation in the creation of innovative private companies and involvement in a wide range of activities relevant to different stages in the development of new businesses. These activities include technology services, R&D, creation and incubation of companies, seed capital, scale-up, and financial innovation.

Fundación Chile's activities are focused on increasing the volume and value derived from Chilean production of products that can be exported or can replace imports, but possibilities are also considered for production in other countries.

1.1 *Fundación Chile and biotechnology*

Since 1997 *Fundación Chile* has been active in developing applications of biotechnology that can improve productivity, add value to existing products, and promote introduction of new products in its business areas. Biotechnology activities are mainly focused in forestry, fruit, and aquaculture, with an increasing emphasis on quality and utilization. Biotechnologies used include recombinant proteins, tissue culture, molecular genetics, functional genomics, and genetic engineering.

Strategic alliances in biotechnology in the private sector include

- a licensing agreement for a salmon vaccine with Syngenta

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- a JV in grape biotechnology with Interlink Associates LLC (Princeton, USA)
- an R&D collaboration in stone fruit biotechnology with Okanagan Biotechnology Inc. (Summerland, Canada)
- a strategic alliance in forestry biotechnology with CellFor Inc. (Canada)

Fundación Chile seeks to establish strong Intellectual Property (IP) positions through the licensing of key existing IP and the development of new IP in areas of specific strategic importance in Chile in which it participates in R&D

Fundación Chile's biotechnology activities involve an extensive network of Chilean and foreign research centers and universities, as well as participation in key international consortia. Collaborators in biotechnology R&D in Chile include

- *Fundación Ciencias para la Vida*
- the Chilean National Institute for Agricultural Research
- the University of Chile
- the University of Concepción
- the University of Santiago
- the University of Talca
- University Federico Santa Maria
- Andres Bello University
- Austral University

Alliances with foreign research centers and universities include

- the University of California
- Cornell University
- the University of Florida
- the United States Department of Agriculture
- New Zealand HortResearch
- New Zealand Forest Research

Fundación Chile is a member of PIPRA (Public Intellectual Property Resource for Agriculture) and the California Institute of Food and Agricultural Research, and it is a participant in the ALCUE-Food Specific Support Action funded by the 6th European Framework.

By establishing these networks, Fundación Chile has been able to participate in the development of new product candidates over a relatively short time frame. A recombinant protein vaccine for salmon developed in a collaboration of Fundación Chile and Fundacion Ciencias para la Vida has been licensed to Syngenta and is being introduced into the market. Elite clones of radiata pine developed through somatic embryogenesis in collaboration with CellFor are in advanced stages of testing and are being scaled up for market introduction by a Fundación Chile company, GenFor. Other biotechnology programs of Fundación Chile, including the genetic engineering of grape varieties, peaches, and pine trees are in earlier stages of development.

2. THE CASE: TECHNOLOGY TRANSFER FOR SOMATIC EMBRYOGENESIS OF GRAPES

2.1 *Importance of institutional support for a long-term R&D program*

Agricultural biotechnology R&D programs are long-term, expensive and controversial; it is essential that the institution is committed to the process. In the late 1990s *Fundación Chile* made a strategic decision to invest in development of biotechnology applications in strategic sectors of the Chilean economy: forestry, agriculture, and aquaculture. Genetic engineering was clearly a key technology with a large potential impact, as demonstrated by the rapid adoption of genetically engineered varieties of maize, soybeans, and cotton in some parts of the world. However, these crops play a relatively minor role in Chile. Little effort was being expended anywhere in the world in perennial crop species, such table grapes, which make up an important part of Chilean exports, and in which Chile is a major player.

2.2 *Identification of specific technologies and resources needed to build a foundation for the program*

Typically, three different types of technological components are needed for development of a genetically engineered plant product:

- Germplasm that provides a competitive genetic background
- Specific genes that confer new traits of interest

- Enabling tools such as genetic markers, promoters, tissue culture and regeneration systems, and transformation methods

In addition, human resources, laboratory infrastructure, and financing are needed to carry out the R&D to adapt and combine these components to produce a product.

Laboratory infrastructure existed in Chile, but improvements were needed. There were capable researchers in Chile, but a limited number. Research efforts were spread over many different objectives, and sustained support for a specific program was rare.

In the case of grapes, the foundational technologies were not available in the local R&D institutions at the start of the program, except, to a limited degree, germplasm. A global search led to the identification of sources of technologies and expertise. The availability of different components and priority for access were assessed, and efforts were initiated to access, license, and transfer key components.

2.3 *IP and freedom to operate*

The IP and freedom-to-operate issues were complex, due to the need to address the situations both in Chile and in major export markets, the long and uncertain time frames for development and commercialization of genetically engineered perennial fruit crops, and the concentration of rights to core technologies in companies with little or no interest in "orphan crops." A complete solution was not possible in the short term with the resources available. However, it was possible to establish a position in key technologies that maximized the likelihood of being competitive in a specific niche.

Based on our experience, a critical aspect was the active involvement of personnel with experience in commercial R&D programs and major agribiotech research centers in other countries, and experience in licensing agricultural biotechnologies. Practices vary from country to country and institution to institution within a country. At the time of the initiation of the program there was little experience in Chile with patenting and licensing of technology developed in public research institutions. The ability of partners with international experience to provide appropriate examples drawn from a variety of sources played an important role in bridging gaps in experience and expectations.

The description of our experiences below will, we hope, assist others in similar situations to make significant progress towards obtaining components needed to develop a biotechnology program appropriate for the development of commercial products of interest for their particular situations.

2.4 *Key technologies required for establishment of a grape genetic engineering platform*

At the time the program was initiated there were only a few published reports of transformation of *Vitis vinifera*. In order to be able to obtain R&D funding from public and private sources, and to be considered seriously as a potential licensee by technology providers, it was considered critical to demonstrate the ability to reproducibly transform the target species.

For many transformation systems, an important factor is the availability of a robust tissue culture system that makes it possible to regenerate plants efficiently. In our experience, tissue culture systems involve considerable art and are often difficult to reproduce in other laboratories. Thus, establishment of a strong position in grape tissue culture was selected as the highest initial priority. The process and progress in this area are discussed below.

The second priority was access to specific gene candidates for engineering a trait of commercial interest in the Chilean market. This was carried out in parallel in order to ensure that the tissue culture and transformation platform developed could be applied to production of prototypes with traits of interest with a minimum lag.

2.5 *Identification of leading laboratories with expertise in tissue culture systems suitable for grape transformation*

The search used different and complementary channels, including reviews of research publications, project databases, conference proceedings,

patents and patent applications, news items, and personal contacts. All of them are relevant and provide useful information.

Access to many of these sources has been facilitated by the rapid improvement of the Internet, in terms of content and ease of access. Even for people without good Internet access, the availability of high-quality documents in electronic form has greatly reduced the cost of access.

Open sites such as PubMed (www.ncbi.nlm.nih.gov) and HighWire Press (highwire.stanford.edu) provide convenient access not only to bibliographic information, but to many full papers. An increasing number of full papers are available at no charge, and most others can be downloaded for a fee from sites of journal publishers or specialized clearing houses.

Online databases such as those at the the World Intellectual Property Office (www.wipo.int/ipdl), the European Patent Office (www.espacenet.com), the United States Patent and Trademark Office (www.uspto.gov), and many other national patent offices provide increasingly convenient access to issued patents and published applications.

Less widely appreciated, but valuable due to their more specialized content, are online databases of research projects. These often include information that is otherwise difficult or impossible to find. Examples include the European Union Community Research & Development Information Service (cordis.europa.eu), the Current Research Information System of the USDA (cris.csrees.usda.gov), the FAO-BioDeC database of biotechnology projects in developing countries (www.fao.org/BIOTECH), and the RedBio (*Red de Cooperación Técnica en Biotecnología Vegetal para America Latina y el Caribe*) database of biotechnology activities by member country (www.redbio.org). In Chile the web sites of the major funding agencies for R&D—CONICYT (www.conicyt.cl), CORFO (www.corfo.cl), and FIA (www.fia.cl)—include databases of projects. Many research institutions provide databases of internal research activities and funded projects, which may be useful once specific institutions of interest have been identified.

Advanced Internet search sites such as Google™ have changed the way that most people think about Internet searching. Today it is often an easy way to get started. It is important to remember that searches conducted on such sites generally do not access information stored in specialized databases such as those described above.

All of the above are useful in the identification of potential technology providers, collaborators and competitors. However, direct contacts are critical early in the process to validate the information and to establish a foundation for future relationships. It is important to establish contacts both at the level of the researcher/inventor and at the level of the institution.

2.6 *Negotiation of a research and option agreement*

Once the identification of the laboratory or institution has been made, documents are typically exchanged via electronic mail. Most large private companies and universities have standard forms that are adapted to the specific needs of a given project. Typical research agreements include the following information:

- Date and identification of the parties
- Definitions of terms
- Reports and conferences for proper follow-up of activities
- Costs, payments and other support
- Publications
- Intellectual property
- Grant of rights
- Confidentiality and publicity
- Term and termination
- Insurance and indemnification
- Governing law
- Assignment
- Agreement modification
- Notices
- Counterparts and headings

It is important to emphasize that this standard approach was designed for the United States. Intellectual property laws vary among countries, so it is important that the contents of any agreement are reviewed by a local attorney knowledgeable in intellectual property matters.

Most universities in the United States, and many other public research institutions, will

require that the public institution be able to continue to use the technology for research and education purposes even if exclusive rights for commercial use are granted.

Our general approach has been to negotiate agreements that provide rights to use technologies for R&D and an option for a commercial license. We want to avoid a situation where resources are invested in research if the results cannot be commercialized. Due to the high degree of uncertainty in development and commercialization of agribiotech products, we also want to avoid paying for rights that in the end will not be used. In agreements for access to technology we have generally tried to structure compensation in ways that reduces the up-front cost in favor of sharing of benefits realized from commercialization of products. This is important for making effective use of the resources available, but more importantly, helps to align the interests of the technology provider with our interests. The agreements typically contain modest up-front payments, milestone payments based on successful transfer of the technology, additional milestone payments if a commercial license is entered into and a product is introduced into the market, and royalties based on revenue derived from commercialization of products produced using the technology.

In the case of grape tissue culture, the institution in which the technology had been developed already had agreements with a private company. Thus, we initially had to negotiate an agreement with the third party. Changes in the scope of activities of the company later led to a return of rights to the university and additional negotiations with the university. Similar events have affected other agreements related to the project. Thus, it is important to recognize that management of these agreements is a dynamic process.

2.7 *Material Transfer Agreements (MTA)*

In addition to intellectual property, the transfer of technology in agricultural biotechnology often requires or is facilitated by the transfer of materials. Terms for the use of the materials, their disposal, etc., are generally covered by a material transfer agreement (MTA).

In countries with limited innovation, lawyers have not been exposed or do not have enough experience on matters related to MTAs. If this is the case, the practical approach was to use as a reference form prepared by the technology transfer offices of universities in the United States and other countries with experience on these matters. Some of these offices have sample forms posted on their Web site.[2]

An MTA typically includes the following information:

- Date
- Identification of the provider and recipient
- Definition of the material
- Agreement to be bound by the laws of a specific, legal district
- Recipients agreement to the defined uses and conditions, such as compliance with local laws and regulations regarding the use of the material, limits on individuals with access to the material, limits on import/export of the material
- Conditions of ownership in case of derivatives
- Conditions of exclusivity or non-exclusivity, commercial or non-commercial use, and disposal of the material
- Experimental nature of the material, and no warranty expressed
- Terms if borrower intends commercialization of the material or derivatives
- Terms if borrower intends to publish results or deliver a presentation
- Reporting of observations and results and conditions of use of such information
- Material physical integrity and recordkeeping
- Conditions for termination
- Signatures and agreement to execute the agreement

The MTA should be carefully reviewed. In the past, investigators have sometimes accepted terms that have had critical effects on the value of the R&D they conducted, particularly terms regarding reporting requirements and right of the provider to use information generated by the recipient. It is also critical to consider whether the

material provided incorporates material or technology owned by third parties. If so, it is advisable to request clarification of any restrictions that may be "inherited" with the material.

2.8 *Importation of materials*

Each country has its own regulations regarding the importation of biological materials. In Chile, there are forms and procedures that must be followed. Samples of tissue cultures of grapes were imported following these procedures without major obstacles, although significant time and resources were required.

2.9 *Exchange of professionals between laboratories*

Good communication between the parties is essential for a successful outcome. For transfer of some technologies, the exchange of written information and materials, supplemented by communication via phone calls and e-mail may be sufficient. However, in many cases, successful transfer is greatly facilitated by the active participation of investigators from the provider and recipient laboratories in activities in both laboratories. In the case of the grape tissue culture system, a Chilean investigator first spent time in the laboratory of the inventor to get hands-on experience with the procedures, and then returned to set up the system locally. Several months later, the inventor came to Chile and spent a full week working side by side with the local investigators, reinforcing the training and providing an opportunity to resolve issues that had arisen during the implementation. Some time later, the project leader visited the inventor's laboratory to observe procedures there, with the accumulated experiences in Chile providing a foundation for increased "receptivity." At the end of each exchange, written reports were prepared, disseminated, and discussed.

3. CONCLUSIONS

Currently the lab in Chile has been able to master grape embryogenic tissue culture and regeneration techniques and apply them to genetic engineering. Transformation of these tissue cultures has allowed the production of thousands of transformed grape lines, from which promising lines have been advanced to the field for additional testing. ■

CARLOS FERNANDEZ, *Director, Strategic Studies, Foundation for Agriculture Innovation (FIA), Loreley 1582, La Reina, Santiago, Chile.* carlos.fernandez@fia.gob.cl

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1 See, also in this *Handbook,* Chapter 17.2 by C Fernandez and MR Moynihan.

2 See, for example, F. H. Erbisch. 2005. *Basic Workbook in Intellectual Property Management*. Michigan State University; 156 pages. Available online at http://www.iia.msu.edu/iprworkbook.htm.