Somatic Embryogenesis of Grapes: Fundación Chile

Fundación Chile is a private nonprofit organization. Its mission is to add economic value to Chile's products and services by promoting innovation and technology transfer for Chile's natural resource, agricultural, and manufacturing sectors. 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 area of agribusiness, marine resources, forestry and forest products, environment, information technology, education and human resources, and tourism.

Fundación Chile is unusual as a nonprofit institution that participates in the creation of innovative private companies. In fact the foundation is involved in a wide range of activities relevant to different stages of development of new businesses, including technology services, R&D, incubation, scale-up, seed capital, and financial innovation. Fundación Chile's activities are focused on Chilean production of goods that can be exported or that can replace imports, but possibilities for production in additional territories that can increase the volume and value derived from Chilean production are also considered.

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.[1] Biotechnology activities are mainly focused in forestry, horticulture, and aquaculture, with increasing emphasis on quality enhancement. 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, a strategic alliance in forestry biotechnology with CellFor Inc. (Vancouver, BC, Canada), a collaboration in stone fruit biotechnology with Okanagan Biotechnology Inc. (Summerland, BC, Canada), and a joint venture in grape biotechnology with Interlink Associates LLC (Princeton, NJ, U.S.A.). Fundación Chile seeks to establish strong IP positions through the licensing of key existing IP and the development of new intellectual property in areas of specific strategic importance in Chile.

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 within 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, and Austral University. Alliances with foreign research centers and universities include the University of California, Cornell University, the University of Florida, the U.S. Department of Agriculture (USDA), New Zealand HortResearch, and New Zealand Forest Research. Fundación Chile is a member of PIPRA (the Public Intellectual Property Resource for Agriculture) and the California Institute of Food and Agricultural Research and is a participant in the ALCUE-Food Specific Support Action funded by the 6th European Framework.

As a result of this networking, Fundación Chile has been able to participate in the development of products within a relatively short time frame. A recombinant protein vaccine for salmon, developed in a collaboration of Fundación Chile and Fundación Ciencias para la Vida, has been licensed to Syngenta and is being

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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 the Fundación Chile company GenFor. Other biotechnology programs of Fundación Chile, including genetic engineering of varieties of pine trees, peaches, and grapes, are in earlier stages of development.

THE TECHNOLOGY

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

Agricultural biotechnology R&D programs are long term, expensive and controversial; an institution undertaking such a program must be committed to the process for the long term. In the late 1990s Fundación Chile made a strategic decision to invest in development of biotechnology applications for strategic sectors of the Chilean economy, particularly forestry, agriculture, and aquaculture. Genetic engineering was clearly a key technology with 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 major crops play a relatively minor role in Chile. Little effort was being expended to make improvements in perennial crop species, such table grapes, in which Chile is a major player.

Building 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 required 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 they were limited in number. Research efforts were spread across many different objectives, and sustained support for any one specific program was rare.

In the case of grapes, the foundation 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 and priority of different components were assessed, and efforts were initiated to access, license, and transfer the key components.

IP and freedom to operate

The IP and freedom-to-operate issues confronted were complex, largely due to the need to address the situation in Chile and the situations in Chile's 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 the hands of companies with little or no interest in the development of minor 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 within a specific niche.

A critical aspect was the active involvement of personnel with professional experience in commercial R&D programs and major agri-biotech research centers in other countries, as well as experience in the licensing of agricultural biotechnologies. Practices vary from country to country and from institution to institution within a country. At the initiation of the program there was little experience in Chile with patenting and licensing technologies developed in public research institutions. The involvement of personnel with international experience, providing appropriate examples drawn from a number of sources, played an important part in bridging gaps in experience and expectations.

Establishment of a grape biotechnology 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 given 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 the production of prototypes with traits of interest with a minimum lag.

Identification of suitable laboratories

The search used different and complementary channels, including reviews of research publications, project databases, conference proceedings, patent documents, news items, and personal contacts. All of them are relevant, and each provides unique and useful kinds of information.

Access to many of these sources has been facilitated by the rapid improvement of the Internet, both 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 (highwire.stanford.edu) provide convenient access, not only to bibliographic information, but to many full papers. More and more, full papers are available at no charge, some can be downloaded for a fee from sites of journal publishers or specialized clearinghouses. Even for people without good Internet access, the availability of high-quality documents in electronic form has greatly reduced the cost of access.

Online databases such as those at the World Intellectual Property Office (www.wipo.int/ipdl), the European Patent Office (www.espacenet.com), the U.S. 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/inventory_admin/dep/default.asp), and a database of biotechnology activities, by country, of the Red de Cooperación Técnica en Biotecnología Vegetal para America Latina y el Caribe (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.

Negotiation of a research and option agreement

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

- date
- parties
- definitions of terms such as project, project proposal, sponsor, and joint and recipient intellectual property
- 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 form was designed for use in the United States. Intellectual property laws vary among countries, so, it is important that the content of any agreement is reviewed by a local lawyer knowledgeable in IP 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, along with an option for a future commercial license. We want to avoid situations where resources are invested in research if the results cannot be commercialized. Due to the high degree of uncertainty in the development and commercialization of agri-biotechnology products, we also want to avoid paying at the outset for full commercial rights, if in the end they will not be used. In technology access agreements we have generally tried to structure compensation in ways that reduce the up-front costs in favor of sharing any benefits eventually realized after commercialization. This is important for making effective use of the resources currently available, but, more importantly, it 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 to market, and royalties based on revenue derived from commercialization of products produced using the technology.

In the case of grape tissue culture technology sought by Fundación Chile, the university at which the technology had been developed already had agreements in place with a private company. Thus, initially we had to negotiate a sublicense agreement with that company. Later, changes in the scope of that company's activities led to a return of the IP rights to the university. We then entered into additional negotiations with the university. Similar events affected other agreements related to the project. It is important to recognize that management of such agreements is a dynamic process.

Material transfer agreements (MTAs)

In addition to intellectual property, the transfer of agricultural biotechnologies often requires, or is at least facilitated by, the transfer of actual biological materials such as plant tissue cultures, plasmids, vectors, or reagents. The physical transfer and use of the materials are generally covered by an MTA.

In countries with limited international innovation programs, lawyers have not been exposed to or do not have enough experience on matters related to MTAs. In Fundación Chile's case, the most practical approach was to use, as a reference, MTA forms prepared by the technology transfer offices of universities in the United States and other countries with experience in these matters. Some of these offices have sample forms posted on their Web sites.[2]

An MTA should be carefully reviewed. In the past, investigators have sometimes carelessly accepted terms that could have critical affects on the value of the R&D being conducted, terms such as reporting requirements and rights given to the provider of the material to use information generated by the recipient. It is also critical to consider whether the material provided incorporates materials or technologies already owned by third parties. If so, it is advisable to request clarification of any restrictions that my be "inherited" with those materials.

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 grape tissue culture were imported following these procedures without major obstacles, although significant time and resources were required.

Exchange of professionals between laboratories

Good communication between parties is essential for a successful outcome. For transfer of some technologies, the exchange of written information and materials supplemented by phone calls and e-mails 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 spent a full week working side by side with local investigators, reinforcing the training and providing an opportunity to resolve issues that had arisen during initial implementation. Some time later, the project leader visited the inventor's laboratory to observe the procedures there, with experience accumulated in Chile providing a foundation for increased "receptivity." At the end of each exchange, written reports were prepared, disseminated, and discussed.

CONCLUSIONS

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

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1 Fernandez C and MR Moynihan. 2007. A Model for the Collaborative Development of Agricultural Biotechnology Products in Chile. In *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (eds. A Krattiger, RT Mahoney, L Nelsen, et al.). MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A. Available online at www.ipHandbook.org.

2 The online version of *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* provides many sample forms from a host of different organizations around the world (see www.ipHandbook.org).