Intellectual Asset Management to make available virus resistant papaya to small-scale farmers in Peru

A Case Study

Under Estudio Grau / INIA Peru and CAS-IP NPI Collaboration Project

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Executive Summary

Intellectual Property (IP) management is essential for agricultural R&D activities resulting in products that are intended to become available to farmers. In fact, most of the technologies and materials used to develop these are protected by Intellectual Property Rights (IPRs). Unfortunately, most national research centers and researchers are not fully aware of the legal restrictions associated with these technologies and materials and are not conscious of the future conflicts and possible prohibition to release their products. This is the case of the Peruvian's National Agricultural Innovation Institute (INIA) and their relatively recent R&D activities in biotechnology. The main purpose of the following case study was to analyze how IP is related to one project of INIA in order to make researchers aware that IP is present in their daily activities which eventually will force them to take IP in consideration more systematically in the future. An additional purpose was to trigger, in the near future, a sequence of actions to develop an internal suitable IP Policy for INIA.

The project "Estudios de modificación genética de la papaya para producir plantas resistentes al virus de la mancha anillada"[1] was chosen for the case study as biotechnology is highly concerned with IP. The objective of the said project is to produce in Peru a genetically modified (GM) papaya with resistance to the papaya ring spot virus (PRSV) disease to be distributed among small-scale farmers for local consumption and eventually for export markets. Our work started by identifying all the technologies and materials used in this project. We looked at restrictions arising from contracts and IPRs. While some materials were transferred under very clear agreements that established restriction on uses, others were transferred without any agreements. Regarding IPRs, few patents apparently related to the project technology were found in Peru and other countries. However, after close examination, their scope of protection did not cover any of the project technology in Peru. Where the use of gene sequences to make plants resistant to the ring-spot virus in the US (and some other countries) was identified as a potential a potential infringement for the patent holder, the same use in Peru may not be considered as such. Hence, it appeared clearly that in order to be able to distribute the future product (a GM papaya with resistance to PRSV disease), INIA has to deal only with contractual restrictions. Once contractual issues are solved, INIA will be able to deliver the GM papaya to small-scale farmers in Peru without any legal conflict. However, exporting it to countries where current patents exist may represent a risk and a chance of a plaintiff against the exporter. These results (our IP and contractual assessment of the INIA project) confirmed that an institutional IP Policy need to be developed. Knowing and understanding IP is vital for the institution and its researchers (even from the very early stages of R&D processes). This IP Policy should be a tool for guiding negotiation of contracts, licenses or agreements with third parties (through an IP/Technology Transfer Office) and capacity building to make this possible. It will also allow INIA to decide whether the institution could protect their new technologies and products.

[1] "Studies for the Genetic Modification of the Papaya to develop resistant plants to the 'mancha anillada' (ring spot) virus (PRSV)".

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I. Background

The Instituto Nacional de Innovación Agraria (INIA) promotes a Technological Innovation System which aims to create and improve existing technologies to increase agricultural productivity.

Each year, INIA executes diverse projects involving plant genetic resources and technologies in order to improve crops' production and quality. Improved crops impact on people's lives as they contribute to a better nutrition as well as may represent better prices for farmers.

However, among INIA's activities and projects, Intellectual Property (IP) is not taken into consideration during the development of projects and new crops, although most of the technologies used by INIA are either protected by IP or are related to it in some way.

The main purpose of the following case study is to take one example of a project being executed by INIA and how IP is related to it. This will allow researchers in INIA to be aware that IP is present in their daily activities, and will make them realize that IP is nearer than they may think. An additional purpose of this case study, is to trigger a sequence of actions to develop an internal IP Policy for INIA after complete understanding of the importance of IP for INIA.

INIA is currently executing the project entitled "Estudios de modificación genética de la papaya para producir plantas resistentes al virus de la mancha anillada"[3]. Such project is funded by INCAGRO[4] and technically supported by the International Potato Center (CIP). The objective of said project is to produce in Peru a genetically modified (GM) papaya with resistance to the papaya ring spot virus (PRSV) disease to be distributed among small-scale farmers for local consumption and eventually for export markets.

Therefore, this case study on Intellectual Asset Management has been developed for the following purposes:

i) To identify issues that may affect the development of the technology of interest and its commercialization in Peru and potentially in other countries. Specifically, the issues analyzed will be the contractual matters arisen from the transfer of material and technologies to INIA and the Intellectual Property Rights (IPRs) status concerning them.

[3] "Studies for the Genetic Modification of the Papaya to develop resistant plants to the 'mancha anillada' (ring spot) virus (PRSV)".
[4] INCAGRO stands for "Innovación y Competitividad para el Agro Peruano" which means Innovation and Competitivity for the Peruvian Agricultural sector.

ii) To be ascertain if the new variety of papaya or the procedures that led to its development are subject of IPR protection either through patents or Plant Breeders' Rights (Plant Variety Protection), or both.

iii) To identify –from INIA's experience regarding the development of the GM papaya- the elements that should be taken into consideration to be included in INIA's Intellectual Property (IP) Policy and raise awareness among scientists of the need to assess restrictions on the use of 3rd parties' property in every project developed.

II. Technology and Materials used for the development of the resistant variety

In order to assure that a proper analysis of the restrictions for use of the future product is made, it is important to identify all the technologies, methods and materials used (referred to as "Proprietary elements" hereafter) in the course of its development. In fact, it is important to have an inventory of said elements to identify restrictions on use and potential future conflicts.

INIA expects to produce a ring spot virus resistant papaya through the use of two technologies and proprietary elements as described hereafter.

II.1 Description of the PRSV technology

A. Gene silencing

In simple terms, scientists will introduce new genetic materials into the papaya genome that will produce a portion of the PRSV viral genome. The GM papaya plant recognizes this as an abnormal structure and produces a defense mechanism against this portion of the PRSV viral genome. Hence, the GM papaya plant has this PRSV defense mechanism activated at all time which prevents it from developing the disease when it gets infected.

The details are as follows and illustrated in Annex 1. Engineering virus resistance in papaya will be achieved by post transcriptional gene silencing, also referred to as RNA silencing or small RNA interference, using a hairpin PRSV gene construct (referred to as *hpPRSV* gene hereafter). The transformation vector, which is needed for transferring the genetic modification into the papaya cell, carries two gene expression cassettes: (i) one for the selection of transformed cells containing the *nptII* gene driven by the pNOS promoter which confer kanamycin resistance; and (ii) a gene expression cassette made of an inverted repeat of 400 bp of the PRSV coat protein gene separated by an intron of 190 bp from a catalase gene and driven by the promoter pCaMV35S which confers constitutive

expression. This *hpPRSV* gene allows the production of doubled strand RNA in the papaya cell which mimics the virus genome. This hairpin RNA or hpRNA molecule is recognized in the plant cell as a foreign molecule or abnormal structure and therefore activates a specific plant defense system that will degrade this hpRNA specifically in smaller fragments of 25 bp. Any new invading PRSV virus will be recognized by this activated system because it bears the same 400bp sequence and will be degraded thereby impeding the replication of the virus and hence the disease development.

B. Genetic transformation of papaya using *Agrobacterium tumefaciens*

Papaya plants can be genetically transformed using the *Agrobacterium tumefaciens* ability to transfer DNA into the plant genome (see also Annex 1). To that end, the transformation vector described above is first introduced into a special strain of *A. tumefaciens* (strain EHA105). Secondly, the plant tissues are put in contact with this strain to allow transfer of DNA from the bacteria to the plant cells. By applying then a selection for kanamycin resistance, only the cells that have received and express correctly the kanamycin resistance gene (the *nptII* gene) will be able to grow. After regeneration of a plantlet resistant to kanamycin, other techniques will then be applied to verify the presence and expression of the *hpPRSV* gene. Finally, the transformed plants will be tested for resistance to the virus by a series of tests including field trials.

II.2 Inventory of materials used for the PRSV technology

II.2.A. DNA fragments:

1. Hairpin gene construct:

a. Selectable marker gene:

We will use the neomycin phosphotransferase (*nptII*) gene conferring resistance to kanamycin. CIP has obtained this gene by chemical synthesis from the Germany-based company Entelechon[5].

b. Gene of interest:

i. Promoter sequence: we will use the 35S promoter of the Cauliflower Mosaic Virus (pCaMV35s). Again CIP has obtained it through chemical synthesis from Entelechon.

ii. The virus sequence of 400 bp of the PRSV coat protein gene was obtained by PCR amplification from Peruvian isolates using the sequence information available at GenBank.

[5] Entelechon is a German company offering molecular biology services (www.entelechon.com).

iii. Intron of the catalase gene from the vector pCambia 1305.2 obtained from CAMBIA[6] under a research use license provided to CIP.

iv. Polyadenylation signal sequence, also referred to as terminator: the NOS 3' sequence of the nopaline synthase (*nos*) gene of *Agrobacterium tumefaciens*. This sequence is in the public domain and can be mobilized from several vectors available at CIP (such as CIP 41).

c. **Backbone vector**: we will use a vector developed at CIP deriving from a pCambia vector without the Gus gene and the *nptII* gene.

2. Control vector to monitor transformation:

INIA will use a gene construct to assess the efficiency of genetic transformation of papaya. This is a research activity which will not end up as part of the final product. Hence, only a research license is needed. We will use the reporter (gusA) gene from *Staphylococcus* sp from Cambia transferred to CIP under a research license.

II.2.B. Living biological materials

1. *Agrobacterium tumefaciens* strain EHA105.

This bacterial strain will be used to introduce the genetic modification conferring PRSV resistance in susceptible papaya variety. These plants with new genetic modifications are, referred to as transformation events.,. It is a research tool which will not be part of the final product. Hence, only a research license is needed. CIP has such license for use and can transfer it to INIA.

2. Papaya transferred by IIAP

For the development of the virus resistant papaya, the "Instituto de Investigación de la Amazonía Peruana" (IIAP)[7] transferred to INIA about 100 seeds and 50 papaya plants of the variety chosen to be the recipient of the new genetic modification expected to confer resistance to PRSV disease.

[6] Cambia is an independent non-profit institute creating new technologies, tools and paradigms to promote change and enable innovation (www.cambia.org).

[7] IIAP is a public-private scientific and technologic research institution that seeks for the development and sustainable use of the biodiversity of the Amazon region in Peru.

Upon request to INDECOPI it has been confirmed that said variety of papaya is currently protected by plant breeder's rights entitled to IIAP (See annex 2). According to the Letter 087-2008-IIAP-GG[8], IIAP transfers to INIA the rights to utilize this variety free of restrictions.

3. PRSV strains MB08 and MB02

As part of the project for the development of the ring spot resistant papaya, INIA has isolated from the Junin and Huanuco regions two biological samples representative of this virus, strains MB08 and MB02, respectively, which are subject to the national legislation on access to genetic resources..

III. Proprietary elements of the PRSV technology

III.1 IPR Status

An international patent search was requested to INDECOPI[9] (See Annex 4) for the *Agrobacterium tumefaciens* and the hairpin technologies. Preliminarily results[10] indicate that there are 21 patents worldwide related to such technologies where 10 mention the ring spot virus in papaya. Patents were found in the US (USPTO), the European Patent Office (EPO), the Spanish, Peruvian and Japanese Patent Offices.

Examples of relevant patents are:

- US patent 7,553,668 – Papaya ring spot virus sequences and coat-protein mediated resistance
- US patent 2005/0166289 A1 -- Small interfering RNA (siRNA)-mediated heritable gene manipulation in plants
- US patent 6353155 -- Method for transforming plants

The complete list of results regarding patents worldwide provided by INDECOPI is included in Annex 4.

In Peru, there are three related patents that use genetic transformation using *Agrobacterium* tumefaciens but none of them claim the transformation method in itself or a transformation method for papaya.

[8] See Annex 3.
[9] INDECOPI stands for "Instituto Nacional de Defensa de la Competencia y de la Protección de la Propiedad Intelectual" which is the National IPR Office in Peru.
[10] We use the term "preliminary results" since the information provided does not cover applications that are at the 'confidentiality stage' according to what INDECOPI states.

It is important to note that searches were not made through patent offices in target countries but only international databases[11]. While there may be some countries that have not updated their patent databases onto the international databases, it may be assumed that findings reflect the actual facts.

III.2 Contractual Status

From the legal perspective, restrictions in the commercialization of a new plant variety may have two sources: Intellectual Property Rights and Contracts. In our case, the existing IP protection may not represent an infringement according to national legislation (since IP is mainly territorial), contractual matters must be taken into consideration, especially if parties oblige themselves by contracts or international agreements where they accept to be under jurisdictions different than their own.

Therefore, in the present case study it is essential to analyze all agreements and/or contracts established for the transfer of materials and technologies used by INIA to develop the new variety of papaya.

A. CIP materials

CIP can make available several DNA fragments needed for the project as indicated above through a proprietary technology transfer agreement that will include transfer of liability to INIA and minimize risks of reputational damages. No other restrictions are expected from CIP, leaving to INIA the rights and responsibility to develop GM papaya variety for commercial uses.

B. Cambia Vectors- Material Transfer Agreement

Usage restrictions set in the Cambia MTA explicitly prohibits CIP to transfer CAMBIA vectors including or not the *Staphylococcus* sp gusA genes for any other purposes than research. Therefore, CIP will not be infringing CAMBIA's MTA if transferring material to INIA as it is for research purpose (at this stage) in the present case. However, if or when utilizing such material for commercial purposes, INIA would have to ask CAMBIA for authorization.

C. Entelechon - Terms of Trade

Because several DNA fragments were purchased by CIP from the company Entelechon based in Germany where many of these are protected through patents, it is important to assess whether CIP has the right to transfer these to INIA without putting the institute at risk of inductive patent infringement. We reviewed the Terms of Trade of the company and found that materials provided by this company are solely intended to be used for research purposes. Therefore, there is no infringement at this stage of the project. Nevertheless, it is advisable to confirm this with Entelechon that there will not be any risk for INIA and CIP for commercial uses when required. In addition, it is important to take into consideration that all

[11] This is INDECOPI's regular practice.

liabilities, including those regarding third parties' rights, are assumed by the purchasing party (CIP in this case).

A complete picture of providers, materials transferred and agreements required can be visualized in Box1.

Box 1

Providers, Material and Agreements involved for the development of the GM papaya

Provider	**Material transferred to INIA**	**Transfer Agreement for (Terms and Conditions)**	**Further actions / agreements required**
CIP (materials provided by Entelechon)	*nptII* gene and 35S promoter	Research Purposes Only	Firstly, we need to verify if either of these sequences are patent protected in Germany at the time of synthesis; if it is so, CIP should transfer any liability to INIA and disclose the IP analysis already conducted by CIP concerning this case.
Cambia	Intron (1305.2) *gus*A *staphilococcus*	Research license for use in potato and sweetpotato only	A new agreement CIP-CAMBIA is desirable to extend use for papaya. However, it is not a key element of the technology and can be argued that it has no contribution to the technology.
CIP	Backbone vector without the *gusA* and *nptII* genes *Agrobacterium tumefaciens* strain EHA105	Proprietary Technology Transfer Agreement between CIP and INIA	The PTTA needs to be signed by both parties.
IIAP	Papaya seeds and plants of one susceptible variety	Letter 087-2008-IIAP-GG stating the material can be used by INIA	No, except that we need to verify if the person who signed the letter had the authority to do so.
Strains MB08 and MB02	PRS virus samples collected from Junin and Huanuco regions	No	Access contract for the use of the genetic resource (Decision 391 considers a virus as genetic resource)

IV. Diagnosis

Regarding IPR, the use of gene sequences to make plants resistant to the ring-spot virus existing patents in the US have been identified as a potential infringement. This means that if INIA would like to commercialize the ring-spot virus resistant papaya in the US (or any other country were patents are valid), there may be a conflict with the holder of such patent. On the contrary, since no similar patent has been found registered in Peru, commercialization of the papaya by INIA is feasible without patent infringement. Apparently, regarding transformation of plants utilizing the *Agrobacterium tumefaciens* technology, the existing patents using *Agrobacterium* transformation may not be considered as an infringement in Peru[12].

Regarding contracts, we have observed various contracts governing the use of several materials needed for the development and commercialization of the final product. As seen in Box 1 some of these confer only research use license and no right of distribution to third parties. Although some of them may not be a key element of the technology, this could in an extreme case scenario limit the technology transfer from CIP to INIA and consequently commercialization of the final product. Hence, contractual obligations have to be dealt in priority.

Another contractual issue that must be taken into consideration is if the letter signed by IIAP is sufficient to exempt INIA of any responsibility arisen from the use of a variety that is protected by breeders' rights. Specifically, INIA must verify that the person who signed the said letter, had the authority to transfer the papaya variety without terms or conditions despite the fact that it is a registered variety at INDECOPI and therefore, protected.

Finally, a last contractual element to take into consideration is if INIA must follow the ABS regime set in the Access to Genetic Resources Regulations. Since a virus is considered a genetic resource (according to the Regional Access Regime -Andean Decision 391- and the national Regulations on Access to Genetic Resources -Supreme Decree 003-2009-MINAM), such regime is applicable. Hence, INIA must formalize the accession by having an Access contract[13].

[12] In accordance to the results found in Peru, claims regarding transformation of plants utilizing *agrobacterium tumefaciens* are only referred to transformation with "*isocorismato sintetasa and isocorismato piruvato liasa genes*" and do not include the interference RNA mechanism such as the papaya case. However, further technical analysis is recommended to dismiss any risk to INIA.

[13] It is very interesting however in this particular case if INIA has to adopt an Access Agreement since the same Supreme Decree 003-2009-MINAM has designated INIA as the National Authority responsible for negotiation of these contracts. It is questionable if INIA would be involved in an interests conflict. This would be the first case of this nature and should be solved in a reasonable way, validating perhaps such access before the Ministry of the Environment which is the principal authority for the Access and Benefit Sharing in Peru. .

In conclusion, INIA must address some issues related to contractual agreements. The commercialization of the papaya developed by INIA in those countries where there is currently a patent may be considered an infringement by the holder and represent a legal risk for INIA[14].

If INIA wishes to apply for patent protection of their invention (the GM papaya), it will have to look carefully at the non-obviousness requirement. Nevertheless, INIA could be successful in obtaining Plant Breeders' rights on the GM variety.

V. IP Policy for INIA

From the papaya case study described above (where all contractual and IPR issues have been shown and analyzed) it is obvious that scientists, researchers and managers at INIA need to be aware and understand all the complex relationships that arise from their daily activities.

In fact, asking for material and/or technology transfers has important legal and commercial consequences. Therefore, if INIA is willing to commercialize in-house developed products, it is essential that creators/employees working there understand all the implications of their actions and then decide what the best way to proceed is according to INIA's own interests. Otherwise, it is really easy to infringe agreements or rights granted to third parties with negative consequences for the institution.

For that reason, INIA must look for advice from its Legal Department for review of contracts, agreements, negotiation skills, etc., to establish protocols and proceedings that guarantee safeness to researchers' and scientists' activities. In addition, it is essential to develop an **IP Policy for INIA** assuming that the institution is willing to protect its inventions/innovations and products through IP[15]. Such IP Policy should consider at least the following elements:

1. **Objective of the IP Policy:**

   The Policy's aim must be to encourage high quality and creative research that allows the development of inventions and innovations. IPRs are intended to promote and encourage INIA's mandate and a business strategy that will allow INIA benefit from its IP assets. This objective must lead all IP related activities and actions taken.

2. **Concept of IP**

[14] It would be necessary, however, to analyze the claims according to national legislation in each country independently for a specific infringement analysis.
[15] This certainly would be a change for INIA, since it has not protect its products in the past. IPRs used by INIA in such case would mainly be patents and Plant Breeder's Rights.

Definition of the **concept of IP**, understood as: information, ideas, inventions, innovations, designs, literary text or anything capable of legal protection through IPRs (such as patents, trademarks, industrial designs, tradesecrets,etc.)

3. Terms "Inventor" and "Employee"

Definition and/or interpretation of the terms "inventor" as author or breeder and "**employee**" understood as a person who has a contract of employment with INIA including trainees.

4. Ownership of IPRs

On a general basis, INIA will be the owner of any IP assets created:

4.1 By employees and/or trainees.

4.2 By inventors working on behalf of INIA or by virtue of an agreement with INIA where INIA provides resources, facilities, supervision, logistic support, etc.

4.3 By employees, trainees and/or inventors working jointly at INIA or on behalf of INIA.

4.4 Any other persons established particularly by contracts or agreements.

Ownership of IPRs may be established differently under particular agreements or contracts. However, actual inventors of IP must always appear or be recognized as developers of the IP.

5. Disclosure

Any **disclosure** regarding IP made by employees or inventors shall be previously approved by either the Legal Department or the IP/Technology Transfer Office or its equivalent (previous approval may avoid disclosing key information that could be used in patent applications or plant breeders' rights applications).

There shall be a Group of Experts/Committee in INIA responsible for organizing and conducting meetings on IP activities and actions related to IP that are of interest to INIA.

Such Group/Committee will advice at least on the following matters:

- Convenience of starting patent/plant breeder's rights applications.
- Analysis of the relationships/potential conflict with third parties' rights (either contractual issues or IP issues).
- Negotiations or agreements on behalf of INIA's IP interests.

6. Distribution of Benefits

INIA may negotiate with inventors and employees the distribution of net income even when INIA is the owner of any IP as well as terms and specific conditions.

The elements described above are only preliminary ideas and may not be considered as the only elements included in INIA's IP Policy. At present, there is a plan to establish a Consultant Committee responsible for developing the IP Policy at INIA. As mentioned before, this case study has been developed only as a first step to trigger awareness and development of an IP Policy. Therefore, final components need to be discussed and established by said Committee according to INIA's specific requirements.

VI. Conclusions and Recommendations

The PRSV technology seems to be amenable to freedom for use by INIA. However, contractual restrictions have to be solved one by one to avoid any conflict with third parties' rights. In fact, technology holders should be approached immediately for obtaining a commercial license when needed.

Delivering papaya to small-scale farmers in Peru (once contractual issues are solved) may not raise any legal conflict. However, exporting it to countries where current patents exist may represent a risk and a chance of a plaintiff against the exporter.

Nevertheless, and based on previous experience at CIP on similar cases (where third parties' proprietary elements have been involved in R&D processes) none seems to pose a serious problem.

Knowing and understanding IP is vital for INIA and its researchers. It is essential that INIA develops a suitable IP Policy for its activities. Assuming the PRSV technology will be free for use by INIA, the INIA IP Policy will determine whether the institution should protect this technology. The way of protection (patent law or breeders' right) will be determined when the final product is finalized and a thorough technical analysis made including a complete comparison with the actual state of the art at the date of application.

Commercialization and eventual exportation (including delivery plans) of products developed by INIA to other countries must also be taken into consideration even during first stages of R&D processes. Such issues must also be negotiated with third parties to avoid any future disagreements or disputes.

INIA's IP Policy must be in accordance with its own objectives and should allow that distribution of public goods without posing any risk for the institution on behalf of national interests. To make this happen, the IP policy should be a tool for allowing negotiation of contracts, licenses or agreements with third parties (through an IP/Technology Transfer Office) and capacity building to make this possible.