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A Scorpion's Poison Antivenin R&D+i Project Case from a Mexican Public University.

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Abstract

All over the world there is a huge complex problem caused by the sting of poisonous animals. In many countries all around the orb there are some animal species hazardous for human beings. A case from a Mexican University R&D institute- Private firm innovation project about scorpion's antivenins health area is presented. The scientific-technological allied participant organizations performed a long life cycle innovation project, which includes research and development, knowledge transference, antivenin product development, sales launch and diffusion of the antivenin products to society market contributing with the problem solution within the country overseas.

The scorpion's poison antivenin basic technology was first developed by the Biotechnology Institute (BIT: Instituto de Biotecnología) from The Autonomous National University of Mexico (UNAM, Universidad Nacional Autónoma de México); and it was transferred to a pharmaceutical firm: Silanes* Labs (Laboratorios Silanes) for its commercialization, this Enterprise developed the poison antidote industrial fabrication process through Bioclon*, its research and development Institute. Silanes first launched the antivenin product into the Mexican local market and through the years it developed new markets in some North African countries and in the USA. The R&D trajectories, the market conduit, the intellectual property strategies along the project's life cycles stages and economic social estimation innovation impact are discussed.

Keywords: Innovation project, Health, Antivenin, México.

1. Introduction

As Bawaskar & Bawaskar (1991) pointed out, scorpion sting embittering is a potentially lethal and a particularly dangerous condition. It is a life-threatening emergency and a common public health problem at many regions of the world, particularly in children of developing countries. Developing severe cardiac, respiratory, neurological and cardiac complications are a great risk in sting injured children. (Amitati, et al., 1985; Bawaskar & Bawaskar., 1998; Dudin et al., Bosnak, 2009).

Some scorpion's venom variety is able to cause dramatic cardiovascular and electrocardiographic changes related to heart stimulation by autonomous nervous system. González, Roberto et al., (1991) studied 722 patients that suffered scorpion's sting, founding electrocardiographic changes like first degree atrioventricular block, intraventricular condition disturbances, ventricular repolarization changes and arrhythmias. A major number of patients could normally die unless they receive prompt therapeutic intervention.

Due to its geography characteristics, there are many poisonous animals in México dangerous to human life like spiders, snakes, bees and scorpions among others. Any insect, arachnid or animal's venom has hundreds of different chemical components; the most important of them are the peptic toxins or toxins that show an interesting characteristic: they are specific to animal species.

According to Possani (2005), there are eight dangerous scorpion species in México, distributed among the Pacific Ocean states, Jalisco, Morelos, Guerrero, Nayarit, Guanajuato, Michoacán, Puebla, Durango, Oaxaca and the State of México. Existing species in other states and geographical areas are less dangerous indeed, nevertheless when a scorpion case happens within the known hazardous geographical areas species; it must be attended by the medical service using an antivenin injections treatment. A patient usually requires between 10 to 50 antivenin serum doses depending its severity. The total number of humans presenting scorpion pickets abroad the country was 220,000 in 2002.

Vega-Franco (2007) noted that the first international South America research experiences were related to the production of hyper-immune antivenin serum at the Butantan Institute of São Paulo in Brazil motivated Carlos de la Peña and Isauro Venzor to begin studying the use of the first generation serum in 1926 against scorpion stings at the city of Durango, México. This first generation crude serum contents a great quantity of antigen substances responsible for many patients' adverse reactions producing death in some cases for allergenic reactions. (Tay et al, 2004). In Europe basic R&D antivenin works were done at the well known French Pasteur Institute which abandoned its leadership on poison animal's antivenin R&D after the Second World War. This presented a clear R&D global commercial opportunity for other worldwide organizations.

The antivenin serum is prepared using venom from three dangerous species, inoculating horses with increasing doses until they generate neutralizing antibodies against the venom toxins. The serum of the immunized horses is preparing to be used by humans safely. In México the use of second generation antivenin was performed around the last century fifties

but the serum was not pure enough. Today, the antibodies are processed for purification eliminating strange proteins from it. Now a days we have got the third generation serum characterized by the use of special enzymes on the immunoglobulins permitting the product be packet in bottles as a simple white powder. The commercial name of this product is Alacramyn* and it was developed by R&D teams from the UNAM's Biotechnology Institute (Instituto de Biotecnología de la UNAM) (BTI) located in the Autonomic Morelos University (Universidad Autónoma de Morelos) campus.

The modern Mexican antivenin investigations were first developed by Lourival Possani, at the Biochemical laboratory of the UNAM's Cellular Physiology Institute during middle seventies (Gaceta UNAM, 1979) Some years later the R&D group from the UNAM's Biomedical Research Institute Molecular Biology Department, obtained the complete primary structure characterization of the Mexican *Centruroides noxius* and the Brazilian *Tytus* Scorpions toxins. (Possani, et al., 1985). Afterwards, now at the UNAM's Biochemical Department of the Genetic Engineering and Biotechnology Center (GE&BTC), the group formed by Possani, A. Alagón C., H. S. Guzmán and A. N. Ramírez characterized the two toxins action mechanisms of Mexican Centruroides limpidus Scorpion from the Mexican states of Guerrero and Morelos which is the most dangerous species of all. (Alagón et al, 1988).

In 1991 the UNAM's GE&BTC was attached covered to the UNAM's BTI (Instituto de Biotecnología) located in Cuernavaca Morelos and in 1995 Possani received the National Sciences and Arts Prize for his basic research conducting to the Scorpion's venom action mode understanding, blocking the sodium and potassium channels conducting to the understanding of live cells ions conduction. (Calderón-Aranda et al., 1999 and Pintar et al., 1999). Considering this basic knowledge, the basic-applied scientist Alejandro Alagón Cano developed an advanced serum purification system called Fabotherapy. (Viniegra-González, 2009).

The UNAM'R&D group has dedicated more than 30 years to scorpion venoms study obtaining national and international field experience. (Herrera 1997; Romero, 2007). They also have been able to investigate the dangerous Buthidae arachnids and other spiders from Brazil, Venezuela, Colombia, Africa and Turkey. According to taxonomical and medical statistical data, the Mexican dangerous spider species are light yellow colored; while against empiric suppositions black common spiders living abroad México City are not dangerous for human beings, although, the most dangerous spider is black but it shows a red spot at its abdomen, it lives in Nayarit, a state of México.

In the first decade of the current century UNAM's scientist obtained the titles for the following patents result of their investigations: US2005065331 (A1)-2003-03-24 Recombinant immunogens for the generation of genus Centruroides antivenins, MMX PA04008435A (A) Inmunógeno y antiveneno contra el veneno de la araña violinista. BR PI0514809 (A) imúnogeno e antiveneno contra veneno o veneno de aranha marrom. CL 22232006 (A) Proteína aislada y recombinante del veneno de araña Loxosteles bonetti, etc. US2011177078 (A) Immunogen and antivenin against violinist spider venom.

UNAM-Silanes/Bioclon Scientific-Technological Alliance

By the end of the last century, within a global vision, Laboratorios Silanes, a Mexican pharmaceutical laboratory specialized in diagnostic products showed interest about the R&D level UNAM's antivenin technology and signed with them collaborating and licensing agreements for the technology transference. Since then the referred firm and UNAM celebrated and renewal collaboration agreements continuously. In 1990 the company decided to make an important investment and started Bioclon as their own R&D private Institute to scale the technology at an industrial level developing process of ***Alacramyn*** serum and other antivenins like those for vipers, spiders and bees. According to the investigation results from UNAM's BTI and Bioclon applied research, they submitted in 2005 the widow and violinist spider antivenin to the clinic essay required before to be launched in the market. (De Roodt & Salomon et al, 2005; de Roodt & Estevez et al, 2005; Romero, 2005).

The allied partner's strategies (Zollo et al, 2005; Romero, 2005) have the following sequence: The basic research for all dangerous species antivenin is done by UNAM's BTI after that applied research is done in conjunction by the BTI and Bioclon, including clinic essays. Subsequently Bioclon industrializes the products developed and finally the commercialization and the technology diffusion made by Bioclon and Silanes.

Nowadays Bioclon is producing one million units of ***Alacramyn*** per year and they expect to reach the production of three million pretty soon. During 2011 the price per unit was about $70.00 USD and the sales amount in 2007 was 100 million USD. (Viniegra-González Op. Cit., CCYTEM, 20011).

The diverse Mexican antivenin products developed by UNAM-Bioclon alliance are sold today in México, Central and South America. In all cases they developed specific antidotes for the local poisonous species.

Overseas experience

In 1999 the Health World Organization (HWO) launched a general invitation to the world's scientific community to get a solution for the need of antivenins in Africa. During 2001 UNAM's BTI scientific team formed by Alejandro Alagón, Lourival Domingos Possani and Roberto Pablo Stock developed the project. In 2004 the first essays at the African Republic of Benin were carried on presenting excellent results. (Rodríguez, 2006). Due to successful of ***Alacramyn*** at Sub Saharan Africa, since 2005 the HWO issued an invitation to UNAM's BTI and Bioclon scientists' team to help finding the solution for other notable poison animal's problem existing at the Maghreb zone. They worked together more than four years developing antivenins for North Africa and the Middle East. (Cruz, 2011).

Similarly to what happens in México, there are about 200,000 scorpion stings per year, majorly to children at the Maghreb Zone, 20% corresponding to Morocco. Today ***Alacramyn*** has the certification and approval of the Morocco Pasteur Institute. Responding to international market requirements, ***Alacramyn*** has three relevant characteristics: immediate reaction time, it is safe and easy to conserve owing to it is able to storage bellow 37°C without refrigeration. Medical doctor of some North Africa and Middle East countries as

Senegal, Algeria and Tunisia have also validated the product.

Anascorp FDA 2011 approval

The antivenin research collaboration between UNAM's BTI and Bioclon scientists has also crossed the Mexican border. There are about 800 scorpion stings in Arizona per year and this situation is considered a public health issue.

As result of 12 years collaboration between Alagón Cano and José Lever from Arizona University with Bioclon, they obtained at the second half 2011 the Federal Drugs Administration (FDA) approval for ***Anascorp*** Scorpion antivenin (the USA commercial nomination for the Mexican ***Alacramyn***) performing the testing and clinical evaluation required by the Agency's protocol. (News Medical, 2011; BoletÍn UNAM-DGCS-458 Ciudad Universitaria, 2011). The clinic essays were conducted by Dr. Leslie Boyer, Director of the Venom Immune Chemist, Pharmacology and Emergency Response Institute (VIPER) at the University of Arizona (UA) applying the antivenin antidote to about 2000 patients from Arizona and Nevada who got healthy without secondary effects. Through this field research experience UNAM and Bioclon scientific team guaranteed the fabrication processes required to comply with the USA standards.

Investigation was financed by the Orphan products development Office of the FDA and mainly conducted in the UA's Medical Center and the Tucson's Medical Center. The spectacular results reported by Boyer et al., (2009) showed that using the ***Anascorp*** antivenin in a double blind placebo study, the critical neurological syndrome solved in patients more rapidly among recipients of the antivenin than among recipients of placebo, diminishing the dose of concomitant midazolam for sedation and the quantitative levels of scorpion's venom in plasma, all of these just four hours after administrating the drug.

Today Bioclon is continuously performing biological and pharmaceutical R&D and emerged as a world leader in the research field also, development and production of antivenin for stings and bites of poisonous animals, creating innovations as the main recourse for competitiveness. (Instituto Bioclon, 2011). Bioclon actually has following granted patents: MEXPAT 30257 and USAPAT 6,709,655 (Pharmaceutical composition of antibody fragments F(ab')2 and process for the preparation thereof). Their products include coral snake, pit viper, central and South America snakes, African snakes, scorpion and black widow antivenin.

Table 1. lacramyn Project Stages & Milestones

Product Technology Development					
Project results and key issues	**Stage 1** UNAM's Basic Research	**Milestone 1-2** UNAM-Silanes Collaboration and TT Agreement	**Stage 2** UNAM's Applied Research	**Milestone 3** Bioclon Institute creation	**Stage 3** Silanes-Bioclon-UNAM product development
Research team leader/MOT	Lourival Domingo Possanni	UNAM's Biotechnology Institute TTO	Alejandro Alagón Cano	Jorge Paniagua	Possanni-Alagón/Paniagua
Location	UNAM's Cellular	UNAM's Scientific Research Coordination	UNAM's Biotechnology	Amores St. Col. del Valle,	Bioclon's installations in Mexico City

	Physiology Institute		Institute	Mex City	
Time required/Date	~ 15 years (1970-1985	~ 1.5 years/1980	~ 10 years, (1985-1995)	1990	~ 5 years (1995-2000)
Investment (estimated)	~ 1 MUSD per year	Not available (NA)	~ 1 MUSD per year	NA	~ 2 MUSD per year
Formation of human resources	PhD, MSc, Eng	Not applicable (NA)	PhD, MSc, Eng	PhD, MSc, Eng	PhD, MSc, Eng
Knowledge Prod. Intl. Art. (Scopus)	Possani (21), Alagón (5)	Development and neg. of Collaboration and Technology Transfer Contract	Possani (61), Alagón (9)	International and national articles	Possani (70), Alagón (8)

Technology Diffusion-Economic & Social Impact				
Project results and key issues	**Milestone 4** Alacramyn-Sales launch	**Stage 4** Developing Overseas market Alacramyn-NAMO	**Stage 5** UA-UNAM-Silanes-Bioclon Collaboration for developing Anascorp.	**Milestone 5** Anascorp FDA approval
Research team	Paniagua-Alagón/Possanni & team	Paniagua-Alagón/Possanni/ R. Stock & team	Boyer (UA), Paniagua-Alagón/Possanni & team	Boyer, Paniagua- Alagón-Possanni & team
Location	Mexico City's Health Secretary	Cuernavaca campus UNAM's IBT and Bioclon installations	University of Arizona and Tucson Medical center	University of Arizona and Tucson Medical center
Time required/Date	~ Date: 2000	~ 7 years collaboration (2000-2007)	~ 12 years collaboration (1999-2011)	2011
Sales by year (MUSD estimated)	~ 5 Initially	~ 25	~ 35	100
Formation of human resources	PhD, MSc, Eng	PhD, MSc, Eng	PhD, MSc, Eng	NA
Knowledge Prod. Int Art. +Patents (Scopus)	Possani (10), Alagón (1)	Possani (76), Alagón (11) US2005065331 (A1) Patent Antivenin Immunogens	(2008-2012) Possani (42), Alagón (8) US2009142356 (A1) Patent	"Orphan" drug FDA title

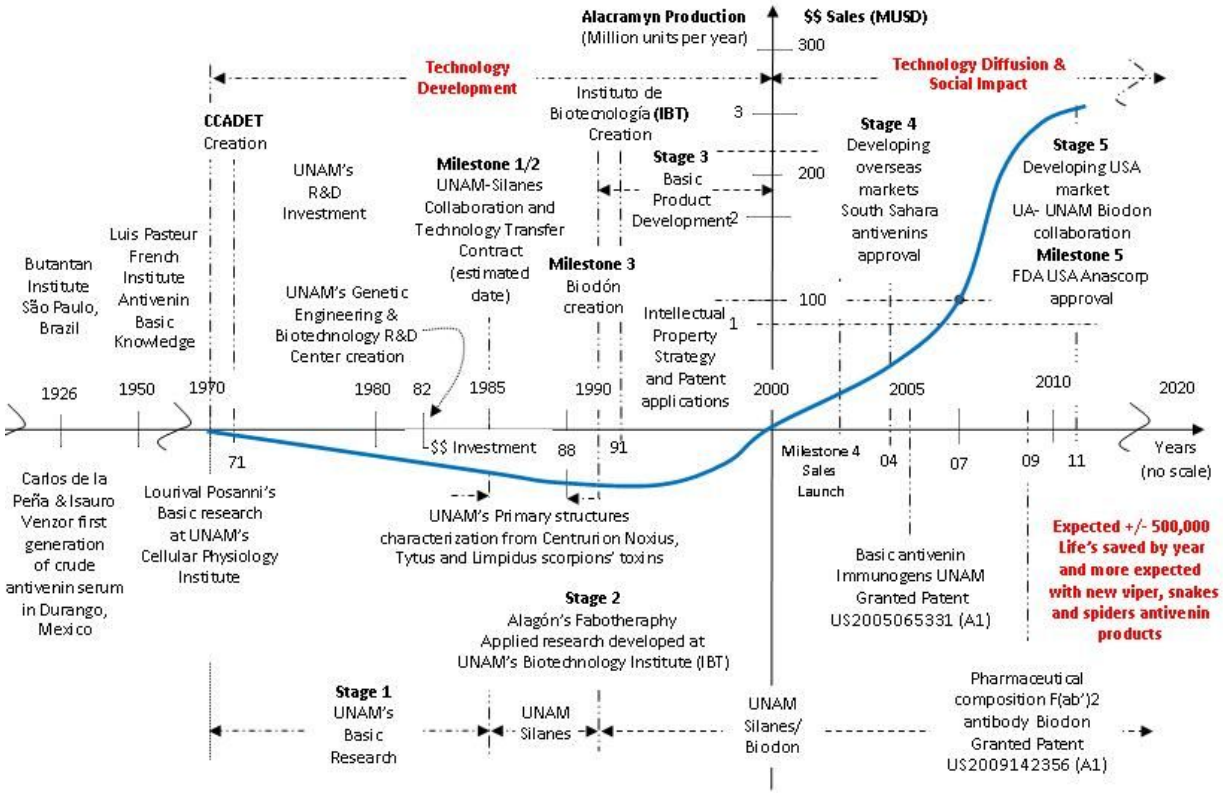

Figure 1. NAM-Silanes/Bioclon Alacramyn R&D+I Project life cycle roadmap

2. Results and Lessons Learned from the Presented Case

Following the description above we can identify up to 5 clearly defined stages grouped in two phases for the innovation project. At the first phase of the pharmaceutical technological product development it has: Stage 1 Basic Research, Stage 2 Applied Research, Stage 3 Product Development and Local Market launch; on the second phase of production it has: Stage 4 Overseas Market Development, finally Stage 5 USA and FDA approval for ***Anascorp*** antivenin.

Undoubtedly behind the project success there are some clearly defined factors, which are: (a) an extraordinary R&D group developed the basic science and technology knowledge; (b) reliable negotiations were done to form the consortium UNAM's BTI, Silanes/Bioclon through the technology transfer; (c) coo-participation of UNAM and Bioclon researchers to develop the final product, (d) effective intellectual property strategy aligned with business strategy, (e) continuous and permanent R&D works done by researchers of both allied organizations to improve their actual antivenin products and to develop new Fabotherapy products against vipers, snakes and spiders; (f) significant efforts to help sting victims from other countries to get healed going over the border and overseas thus extending its market as a result.

Table 1 shows a summary of different innovation project stages key issues, including project milestones and its results. At Figure I it is presented the innovation road map for the entire project's life cycle.

3. Conclusions

R&D public university institutes and centres typically operate in base of projects. Sometimes University allies with external public or private organizations to develop technology and the products obtained are industrially scaled to be launch to the market, driving the project to get the upper innovation level (R&D+i).

Compared with the UNAM`s Mexican technology development projects average, we qualify the R&D+i University ***Alacramyn***'s antivenin as an excellent innovation project.

As proposed by Geisler, (2002) and Choi, (2005), following are some project remarkable successful aspects along its lifecycle:

- Stage 1 Basic Research: extraordinary research team and leadership, developing new scientific knowledge, with high annual international indexed publications and high quality human resources formation.
- Stage 2. Applied research & technological development: they developed integrated laboratory prototypes for the antivenin technologies and patented them.
- Stage 3. Technology transfer and product development: the group pursued a technology transfer and licensing agreement with annual royalties' payment for the UNAM; they also developed a pilot plant for the initial serum production.
- Stage 4. Market launch & technology diffusion: the licensed firm developed a local market of more than 5000 antivenin units per year and overseas market of more than $100 USD million by 2007. The expectation is to double this for 2013.
- Stage 5. High Economic impacts: The expectation is to double the 2007 sales for 2013; high social impacts, saving several hundreds of thousands of injured people all around the world.

According to Vandervert (2003), innovation has to be with the production of new ideas and useful products, including of course pharmaceutical products. Presented case have had great social impact saving the life of hundreds of people in México, north Africa, Middle East and USA while at the same time the firm which produces and sells the products is obtaining good profit in all the markets developed.

Furthermore, in projects like this everybody wins, beginning with starters, people that unfortunately receive a scorpion sting but is properly treated with the antivenin and reacts in less than four hours avoiding extreme pain and saving life without neurological side effects, on the other side the University has been obtaining yearly R&D grants for new BTI's scientist's research collaborations, and annual royalties for the global antivenin sells. Silanes expanded their manufacturing plant facilities in only five years, investing the revenues of the antivenin sells. Besides of that, the Bioclon R&D Institute is in a permanent growing process performing continuous antivenin research in conjunction with their technological partners.

As shown in Figure I the intellectual property strategy has been perfectly aligned with the business strategy, sales expectations will be continuously increasing for the next decades

improving local economy and saving lives in many countries all over the world. Those are the distinctive issues of the innovation project performed by world class technology allied organizations team. UNAM's BTI-Silanes & Bioclon have developed the antivenin product and process technology as their core competences for the 21st century. (Nadler & Tuchman, 1999).

Undoubtedly even though the project time length was very long, the money investment required was very high, and it was required high quality knowledge capital which is scarce and difficult to find, the economic and social benefits of the innovation project presented overcome all the efforts and therefore projects like these must be pursued in Latin America specially those originated in public universities.

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