

Company Portrait:

Newbiotechnic (Seville, Spain)

Genotyping Horses

After ten years of being on a tortuous path, filled with complications, hard work, dreams and disappointments, NBT finally operates on a broad range of business segments, from authenticating fraudulent vegetables to detecting horses' coat colour.



Finally the wind is blowing in the right direction for Newbiotechnic (NBT).

They've got products which are earning them money, they're working on several new and promising projects and they are fully receptive to exciting ideas to further expand their activities. The company looks mature and consolidated, but reaching this point was all but easy. It required ten years of taking a tortuous path filled with complications, hard work, dreams and disappointments, successes and mistakes.

Manuel Rey is the NBT Managing Director and R&D General Manager. His glass-walled office is located on the first floor, at the centre of the NBT building. From this privileged position, he has a general view over the offices, the labs and the processing plant. He recalls, amused, that, "The glass walls were intended to allow a closer control of what was going on out there, but the trick has turned against me. Now I feel as if I am constantly being observed and this makes me work harder".

Rey has been working for the company since its very beginning and knows it quite well inside out. "Looking back", he says, "it is amazing to realise that NBT's complicated path was not exceptional. Most of the other biotech companies created in Spain at that time followed the same general pattern. I believe that this pattern was imposed by the particular circumstances at that time".

Those circumstances produced a genuine kind of biotech company characterised by an amazing capacity for survival and adaptation to hard times. Very often, the fight to keep their original projects alive led these companies to change or diversify their activities. Very few of them closed down, but

most transformed. NBT's recent history illustrates this phenomenon quite well.

Currently, NBT's activity is much wider than that for which the company was created. The company's staff is experienced in molecular biology, microbiology, biomedicine and phytopathology. As a result, they now do business with several research products for agriculture, food, diagnostics and industrial sectors.

Crop protection against fungal diseases

NBT was born in January 1999 as a spin-off promoted by Antonio Llobell and Enrique Monte, two scientists working at Seville University and Salamanca University respectively. They had patented some *Trichoderma* strains showing a particularly effective and broad spectrum fungicidal ability. Their idea was to industrially produce and commercialise Tusal, an original product based on those *Trichoderma* strains. Tusal is a fungicide and growth promoter that was intended for the protection of agricultural crops against fungal diseases in the soil. The project received financial support from the Cajasol Saving Bank. Cajasol contributed €36,000 of initial investment and Llobell and Monte contributed the remaining €24,000.

Parallel to the Tusal venture, the Spaniards promoted an additional project on functional genomics. They aimed to isolate, identify and characterise the *Trichoderma* genes that are biotechnologically interesting. Their final goal was to produce transgenic plants and microorganisms which could be used for the biocontrol of plant pathogens.

"This was pioneering work," says Rey, "the first in the world to tackle the se-

quencing of a whole genus. We sequenced 13 strains and identified more than 35,000 genes. Many of them were patented and a few are being used commercially".

This part of the business very much resembled a basic research project and, in fact, it began to run in this way at the university.

Going back in time

It was exactly this project that attracted Manuel Rey at that time, in 1998. He had just finished his Ph. D. thesis on *Trichoderma* genetics and had acquired a deep and wide knowledge on this fungus. While making up his mind about how to orientate his post doc, he decided to accept a grant to work on the NBT's functional genomics project. They worked hard and successfully and he felt rewarded. He postponed his post doc year after year and he has been employed in the company since its very beginning.

"The creation of NBT", says Rey, "coincided with the Spanish biotech boom. Before 2000, there were very few genuine biotech companies in Spain, and those few were large and well-established companies grounded in traditional disciplines like biochemistry and microbiology. The biotech boom, however, was based on the new and powerful tools of molecular biology".

NBT belonged to this new generation of biotech companies from its very beginning. The company was one of the founding members of the Spanish Association of Bioenterprises (Asebio). Presently, Asebio counts more than 150 members.

"By that time, this fizzing became known as the "bio-enterprising culture", says Rey with some irony, "Well, there cer-

tainly were many projects, initiatives and activity, and I have to admit it was quite an exciting time”.

However, the Spanish biotech boom had one main flaw: its inexperience. The lack of a real and solid biotech culture meant learning the business the hard way. Rey continues, “The typical bio-entrepreneur in those years was a researcher with a solid scientific background and a good and promising idea, but very little knowledge of a company’s management needs. Not only did many investors get dazzled by words like biotechnology, genes and DNA, but in many cases they had no idea of what they were putting their money into. This combination produced disastrous results in more than one case”.

Well, it’s pleasing to hear that Spanish start-ups and investors had the same initial problems as anywhere else in Europe and the USA. The situation in Spain has, of course, changed over the last years. At present, a biotech company cannot be started before it presents a detailed business plan of the project.

(below) Meanwhile, NBT’s staff has increased to 23, most of them with a scientific background.

Always expect the unexpected

A certain lack of experience in commercialised planning was also to take its toll on NBT. The highly technical character of the company had forced it to concentrate most of its energy on setting up the industrial production of the fungicide Tusal, while leaving aside some of the more bureaucratic aspects like the registration of the product. By 2004, when the product was almost ready for marketing, they knew the registration process was going to take longer and be more costly than expected.

Rey tells that, “As you can imagine, that was a hard blow for the company and it was only part of the problem. By that time, transgenic crops were getting a bad reputation in the public opinion and governments were establishing moratoriums on its use and commercialisation. It became evident that our project on *Trichoderma* functional genomics would not bring returns to the company in the short term”.

By 2005, the company was in a delicate situation and measures needed to be taken. The senior members of the company then decided to form an Executive Committee and re-orientate the activity of the company.

“For us, to keep the company running had much of a moral duty towards the investors and ourselves. Giving up would

somehow be like betraying the faith the investors had put in us. Even more, we still believed in our project. We just needed some more time. Fortunately the investors trusted us and gave us the opportunity to demonstrate that to keep on going was the best option,” Rey says.

Changing the course

In countries with a solid biotechnological tradition, this attitude may not make any sense. Very often, if the company’s original idea does not work, the most obvious option is just to close down the company. People get fired, but their merits and experience are recognised and they may find a job in another company. In Spain that also made a big difference. The bio-entrepreneur had also been conditioned by a lack of alternatives. On one hand, there were only a few biotech companies and finding a position in any of them was not an easy task. On the other hand, trying to return to the academic path was not easy either.

“In my case I thought it was too late for dusting off the idea of going abroad for a post doc. My wife had a good permanent position and we already had children. Not only that, somehow, when I left the University to enter the company I already had the feeling that it was going to be a way ►►



▶▶ of no return. It may seem crazy, but in some ways, when I left the department where I did my thesis, I felt as if going into business was like betraying Science. Often, when visiting my old department, I have the feeling that I do not belong to that world any more”.

The new NBT executive committee changed the course radically. They reoriented and diversified the company activities, looking mainly for rapid incomes. A whole set of technical services was set up, ranging from genomics (i.e. DNA sequencing, construction of high density microarrays and genomic libraries) to diagnostics (from plant pathogens to animal and human genetics). These measures brought contracts with other companies, labs, hospitals and insurance companies.

The NBT staff was a young and multi-disciplinary team, with a broad range of experience, and so they decided they could use their scientific background and technological facilities to offer a customised research and development service.

The paprika incident

“We had several external contracts,” Rey reports, “but the paprika one is my favourite as a good example of how biotechnology can offer appropriate solutions to day-to-day problems”.

The region of La Vera in Extremadura (southwest Spain) produces a particular type of smoked paprika with a high reputation for its quality and culinary properties. The paprika from La Vera is under a “Protected Denomination of Origin” (PDO) intended to assure consumers that the product they purchase under this label has been cultivated and processed according to the traditional methods of the region. One day, representatives from the Denomination of Origin rang the NBT bell looking for advice. Year after year, the paprika production in their region had been declining due to a lack in demand. It wasn't up to poor marketing; they were convinced that paprika from different origins was being sold under their “Protected” label. The image of the label was also being damaged because unauthorised additives and colourants like Sudan Red were being added to the product to mask the fraudulent paprika.

At NBT, the team decided to take on the challenge and try to find a method to authenticate this product. “It was an intensive research, but we finally found microsatellite markers that allowed the identification of the local and foreign paprika cultivars and we developed a DNA purification

method to make a genetic analysis possible on samples of the final processed product. Our procedure worked well and tons of adulterated paprika were withdrawn from the markets. I still feel some sort of pride knowing that our work helped to recover the paprika production in La Vera”. Since then, NBT has been analysing many paprika samples and making a profit with their invention. Their success also opened doors to new projects and clients.

Molecular markers for a horse's colour

“Our best client in the area of customised services, however, has been the National Association of Purebred Spanish Horse Breeders (ANCCE). We have maintained a



Manuel Rey, NBT's managing director, coordinates the company's research and development, as well as the framework V European Union project TrichoEST, to identify genes and gene products from *Trichoderma* antagonists with biotechnological value.

quite fruitful and rewarding collaboration with them”.

A horse-breeding project? Well, the Spanish horse does not possess outstanding velocity, agility or resistance; but it is beautiful. It is a horse for riding and showing. Its more valuable characters being its morphology and coat, the latter having an important repercussion on the price of such a horse. More than 20 genes have been identified, which are directly or indirectly responsible for the type, intensity and distribution of horse coat colour. However, only four of them (Gray, Extension, Agouti and Cream) are generally responsible for the

pure Spanish race coat colour breed prototypes. Molecular markers for the alleles of three of those genes were available, but they were lacking for Gray, the dominant and most interesting one. Gray is responsible for the dapple-grey, the most appreciated coat colour in Spanish horses.

“At NBT”, says Rey”, we were able to find specific molecular markers for Gray alleles and, together with the information available on the other genes, an analysis protocol was designed to determine the coat genotype of each horse”. At NBT, the coat genetic study and genotyping of about 30,000 horses have been analysed during the last year. The results of these analyses have been compiled in a data base. NBT developed an internet application (<http://webcapas.lgancce.com>), a database allowing breeders to choose the best mates for their horses, depending on what coat colour they desire their expected offspring.

Jumping the hurdles

Meanwhile, Tusal, the NBT original fungicide product, got its registration and is now in active production. Funny, as it now comes at an opportune moment in which integrated production and sustainability are being promoted in agriculture, and many agrochemicals are being withdrawn from the markets. Multinationals are becoming more and more interested in alternative biological products of this type. In fact, NBT is currently negotiating the commercialisation of Tusal in Europe with a multinational.

In addition, another product, Becan, is being produced. Becan is a biological insecticide based on the fungus *Beauveria bassiana*.

Other long-term research projects have not been abandoned either. Their most ambitious one runs in collaboration with CSIC researchers in Seville. The project's main goal is to identify genetic markers for diagnosing lung cancer, using existing technologies based on small RNA and microRNA phage display libraries. NBT now looks healthier than ever, with a staff of 23 people, including 5 doctors and 11 graduates.

Cajazol Saving Bank has been progressively increasing its share in the company capital. It currently owns 98% of the total €3.1 million capital. Last year, the company yielded revenues of €1.5 million, 50% of which came from services.

“It has been quite a hazardous journey,” says Rey, “I hope at least, that it has made us wiser and more able to tackle whatever is still to come”.

RAFAEL FLORÉS