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From plants to **vaccines**

BSI has further developed its botanical pesticide and ventured into vaccine adjuvants as well. **Andrew Warmington** met with CEO Gaston Salinas

Botanical Solution (BSI) has its origins in work by Chilean academic biologist Gustavo Zúñiga. He found that lab-grown versions of the *Quillaja saponaria* tree, which is native only to Chile, generated specific phenolic compounds with fungicidal activity. The tree itself develops some of these compounds in its bark as it matures, but the amount and precise contents it generates vary considerably.

Together with Gaston Salinas, the firm's CEO, which Zúñiga co-founded in 2013, they patented the technique and continued to refine it by putting the plantlets under different stress conditions, such as varying media culture composition, light exposure, and temperature. This eventually led to the first commercial product, Quilibrium botanical biofungicide.

Quilibrium is a 10% extract from tissue-cultured *Quillaja saponaria* plantlets. They are inoculated into bioreactor systems at 3-60 days of age, so that they grow rapidly and in the right conditions to produce the secondary metabolites responsible for biological activity. Field tests showed Quilibrium to be highly efficacious in the prevention and control of *Botrytis cinerea*, especially for blueberries, vine crops and vegetables.

Aided by a 'soft landing' programme sponsored by the University of California Davis, Salinas moved to the US in 2019. This has given BSI much wider access to talent, because Davis is one of the world centres of agricultural research, as well as to investors who understand the market.

International growth

Next year, the company secured two rounds of funding from multiple banks and 'angel' investors, then reached

an agreement with Syngenta to commercialise Quilibrium in Peru and Mexico. Through this work, it learned that Quilibrium works equally well on powdery mildew, alternaria, sour rot and many other pre- and post-harvest diseases.

After Chile itself, the US was the next big target. At the time registration was simpler and faster to obtain here than in the other regional giant agro market of Brazil. However, this has changed: the EPA is now demanding more documentation, while Brazil has reduced the regulatory hurdles for biologicals and shortened the approval times, sometimes to as little as 9-12 months.

Not only that, the costs per hectare of treating crops with biologicals are now lower than for synthetics, despite the much smaller scale on which the former are manufactured. Biologicals, says Salinas, are now able to compete with synthetics in major crops like corn and soy in Brazil.

For the EU, which has even more stringent requirements than the US,

BSI is putting together a study plan in order to be compliant with regulation there. It expects to submit a first registration in 2025, though this will be a longer, more expensive process than in the Americas.

In 2023 alone, BSI screened 114 different plant species for potential uses in biocontrol. It is now focused on building a pipeline of new products, including bioherbicides, bioinsecticides and bionematicides, all of which are grown using the same technology platform. It will file patents on applications as they come out.

"We are on the path from being a single-product company to becoming a portfolio company," Salinas says. "We are also becoming fully independent from natural sources of raw materials, while other companies continue to rely on them."

Also in 2023, BSI opened two new R&D laboratories at Davis. Its current R&D efforts are based on a molecular breeding programme for *Quillaja saponaria*. "The raw materials that come out of that programme



Quillaja saponaria plantlet

will fuel the future generation of products," says Salinas.

Biopesticide potential

Biopesticides are still a very small part of the overall crop control market, Salinas agrees, but there is not much doubt about their efficacy among growers. Moreover, the world has changed a lot in the last three to five years. Farmers have fewer and fewer options, because many chemical products have been delisted, raising resistance issues.

At the same time, farmers must sometimes transport their products for anything up to 90 days. Biologicals in general play a key part in making that possible and demand continues to grow rapidly every year. And, because they leave no chemical residue, they do not fall foul of increasingly stringent regulations on maximum residue levels.

Salinas believes BSI's value proposition to be unique. The vast majority of biologicals are based on microbial platforms, because they have a proven regulatory pathway to the marketplace that plant extracts currently lack. Historically a bespoke pathway had to be found for each of them and sustainability issues arose. BSI aims to find a pathway to bring more and more plant extracts to the marketplace.

"People always worried about the value chain with raw materials from plant extracts. With our platform, the raw material is plant-free: it can be grown anywhere, it doesn't take a lot of space and it is easily scalable," Salinas says. "The other key factor is quality. When you source from plants, there are big challenges in standardising the raw materials. With this platform, it is easy for them to be made compliant."

Move into pharma

Another major recent change for BSI has been a move into the pharmaceutical sector through the use of *Quillaja saponaria* in the vaccine adjuvant QS-21. This had been studied for over 30 years but was first used in a commercial vaccine in 2017. With the



The BSI team among plantlets growing to make QS-21 vaccine adjuvant

development of Novavax's COVID-19 vaccine, using both QS-21 and QS-7, another biologically active fraction of the tree, demand soared.

BSI's move into pharma came about largely by chance, Salinas relates. He was presenting at a Silicon Valley networking event about the use of QS-21 in controlling botrytis, when the CEO of a pharmaceutical company approached him and asked about sourcing QS-21 from plants. At the time, he knew nothing of it, but tests by Zúñiga established that BSI's in vitro approach could produce QS-21 in practically unlimited quantities and with a ten times higher yield than in saponins concentrated from the tree bark.

Having scaled up the product, BSI has found an industrial partner in Croda International. This will make "all the difference", Salinas says, because there is a very long tail of companies in need of an adjuvant to mix with an antigen to make their vaccines work. QS-21 is rarely used alone but it can add significant value to mixed systems.

In the last few years, Croda has been investing heavily to develop enabling technologies that have helped the vaccine adjuvant space to take off. It first invested in the most basic adjuvant, aluminium hydroxide, and then created a broader portfolio.

The one big challenge in this whole value chain is that it is so difficult to extract these products from their natural source sustainably. In the case of squalene, this is sharks' livers;

monophosphoryl-lipid A (MPLA) is derived from salmonella. Croda wanted to change these value chains and make them more sustainable.

There was an obvious attraction for Croda to BSI's technology because it enables QS-21 to be harvested from plantlets rather than mature trees. These are only found in Chile and are increasingly rare. Likewise, Croda has developed a fermentation route to squalene and a synthetic route to MPLA.

Croda now – uniquely – has access to all the key vaccine adjuvants sustainably and in unlimited quantities. QS-21 is already used in two FDA-approved blockbuster vaccines, Shingrix for shingles and Arexvy for RSV. Looking wider, the company sees this creating a step change in the availability of vaccines, especially for use in poorer countries for less widespread diseases, such as GSK's vaccine for malaria.

BSI's Salinas expects to substantially improve the availability and cost of QS-21, through the company's in-lab approach to extracting a virtually unlimited supply of botanical materials from in-lab grown *Quillaja saponaria* trees. ●

Gaston Salinas

ceo

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