A llama-inspired way to protect crops

most of us will never see a live llama except at a zoo unless we have an opportunity to travel to the South American Andes where they are used as pack animals or they have been adopted as farm animals. They are quite a sight and have become favorites at zoos around the world. With their docile demeanor, sturdy bodies covered in curly wool, banana-shaped ears, long eyelashes, and upturned mouths, they look like creatures that could have walked off the pages of a Dr. Seuss story, delighting children and their parents everywhere.

But soon, they might carry another purpose: as the source for a new class of biological, sustainable crop protection products, which would be designed based on llama antibodies.

Leveraging the llama’s immune system

Like all mammals including humans, llamas have a complex immune system involving two kinds of white blood cells and a collection of specialized proteins called “antibodies” which bind to the “antigens” of disease-causing agents like bacteria, viruses, and fungi. The immune system “learns” to recognize these antigens after the animal is infected and then uses them to ward off future infections. Humans and animals can get that same benefit through vaccinations in which they are exposed just to antigens of an infectious disease or pathogen.

Normal antibodies are large, complicated proteins, and llamas make those. But they and related animals such as camels and alpacas also make a smaller category of antibodies. The antigen binding domain of such simpler antibodies, sometimes called “nanobodies”, are about a tenth of the size of regular antibodies.
Synthetic versions of these proteins are already being developed as targeted human medicines and as treatments to alleviate some of the symptoms of human diseases with no known cures like cystic fibrosis. It is now also possible to produce anti-viral therapies through the advanced fermentation systems that have been developed over the past few decades. Those methods are now used to make everything from human medicines to the soy heme protein in an Impossible Burger. Soon, products inspired by llama antibodies and grown in a sophisticated modern fermentation system could be used to protect fruits and vegetables from fungi.

Biotalys, a Belgium-based company with a US presence in the Research Triangle in Raleigh, is doing just that—developing protein-based biocontrol products that target plant pests and diseases.

**Here’s where the llama comes into play**

Biotalys taps into the llama’s special antibody-generating system. For example, they did a detailed analysis of the biology of a dreaded fungus called *Botrytis cinerea* which creates a fuzzy, gray mold that can rot fruit and vegetables. For growers, this disease can lead to major yield losses and for consumers often causes food waste.
Grapes infected with the fungus Botrytis cinerea

Biotalsys has identified a critical element that the fungus needs in order to infect the plant, but which is unique to that pest. A llama was then injected with some of that material so that it would generate one of its unique, antibodies that can bind to the target antigen of the mold to inactivate it and thus act as a biological fungicide to stop the infection process. The llama fulfilled its role by “suggesting” a sequence of amino acids with that binding capability which Biotalsys then used as a starting point for the design for an even smaller protein that still does the specific binding, but which can be produced through fermentation.

This new category of crop protection agents, “AGROBODYTM biocontrols” could have multiple advantages.

- First, they can be extremely specific, only binding to a unique enzyme or other feature of the pest and not having any “off target” effects.
- Second, they can provide new “modes of action” for pest control; that’s important because fungi and other pests are very good at evolving resistance and so it is important to utilize in “integrated pest management” (IPM) programs. IPM techniques involve mixing and matching agents with different
modes of action, including chemical fungicides, biological control agents and now these antibody-based fungicides.

- Third, proteins like this break down quickly into the amino acids of which they are made and those are just “food” for soil organisms.

Biotalys has developed formulation methods to get as much as seven days of plant protection activity from these proteins, but then they biodegrade and are gone.

Innovative pipeline focusing on biofungicides and bioinsecticides

<table>
<thead>
<tr>
<th>Program</th>
<th>Type</th>
<th>Market</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>EVOCA™ 1st generation</td>
<td>Biofungicide (botrytis, powdery mildew)</td>
<td>High-value fruits &amp; vegetables</td>
<td>Currently under review by regulatory authorities in US and EU</td>
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<td>Developed to have broader application and market penetration</td>
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<tr>
<td>Pipeline</td>
<td>Biofungicides &amp; bioinsecticides (a variety of key diseases and pests)</td>
<td>Fruits &amp; vegetables, legumes, etc.</td>
<td>Targeted discovery approach Partnerships in place or being explored</td>
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Protein-based pest controls are a novel approach, so the Environmental Protection Agency is still working out exactly how to regulate it. But it seems likely that the first of these products could be available to farmers as soon as the second half of next year. Then all of us who love delicious fruits and vegetables will be able to thank a llama.

Steve Savage earned a B.S. in biology at Stanford and pursued an M.S. and Ph.D in Plant Pathology at the University of California, Davis, working on grape diseases. Follow Steve on X @grapedoc