Flystrike vaccine looks promising

Most discussion of vaccines these days seems to relate to Covid-19, but in the CSIRO laboratories, work is progressing on another vaccine of great interest to sheep producers – the sheep blowfly vaccine. By **Jill Griffiths**

It's not time yet to change your fly management strategy to make way for a vaccine, but researchers are making headway and things look promising. Dr Tony Vuocolo, who leads the CSIRO blowfly vaccine project as part of an Australian Wool Innovation (AWI)-funded $2.5 million initiative along with the University of Melbourne, is upbeat about results from antigen studies, but circumspect on the time frame for developing a farm-ready vaccine.

"A potential commercial vaccine is still a way down the track, but we have shown we can produce high antibody levels in sheep against the blowfly," Dr Vuocolo said. "Antibodies are the defence molecules, akin to 'bullets' in general terms, produced by the sheep against the blowfly maggots. The major challenge faced is producing these 'bullets' in a form that will specifically hit the maggots in vulnerable spots and be powerful and plentiful enough to penetrate and ultimately over-run the maggots' armour-like protection.

"Sheep blowfly larvae are incredibly tough and resilient organisms and there is limited opportunity to target the larvae through an immunological approach using a vaccine."

Dr Vuocolo said the larvae are coated in a tough waxy cuticle whilst the foregut and hindgut are lined by a tough impermeable coating. The most susceptible region of the larvae is the midgut, but even that has a protective layer. CSIRO found certain proteins from this protective layer, when used as antigens in a vaccine, produce an immune response in sheep that significantly inhibits larval growth. Eureka!

Vaccine effects: The blowfly larvae on the right have been stunted by exposure to native vaccine antigens. Photo: CSIRO

DEVELOPING A VACCINE

The basic way a vaccine works is by priming the animal's immune system to produce antibodies to a particular disease or parasite. To be effective, a vaccine must initiate the same type of immune response the actual disease would cause, but to a lesser degree. Once the immune system 'learns' how to produce the antibodies the first time, the next time it sees the disease, it can quickly build the antibodies to fight it because it has the basic template filed away.

"Developing a vaccine for an ectoparasite is tricky," Dr Vuocolo said. "It's different to developing a vaccine for a viral or a bacterial pathogen, where it is in constant contact with blood or saliva."

Dr Vuocolo explained that where the disease vector is constantly washed by bodily fluids, it is exposed to a far higher dose of antibodies than in the case of an external parasite (ectoparasite), such as blowfly larvae (maggots), that is only in superficial contact with the animal's antibodies.

Despite this challenge, the CSIRO team has found some potential vaccine candidates that have reduced the size and viability of maggots.

In the past 18 months, the researchers have tested 26 different formulations of vaccine in sheep as well as in a variety of laboratory tests. These vaccine formulations contain blowfly proteins, called antigens, that cause the sheep to produce antibodies to fight them. Identifying, extracting and producing the antigens is challenging and the CSIRO team has tried several approaches. The most successful antigens, as in the ones that have produced the strongest antibody response, have been 'native antigens'. These are antigens that have been isolated directly from blowfly maggots.

However, a big effort is being directed into making recombinant antigens for the vaccine to be as good as or better than the native antigen prototype vaccine. Recombinant antigens are proteins that are engineered in the lab and produced in specialised 'cell factories'. Recombinant antigens are amenable to commercial scale-up and production; a process that will be required to meet demand and be economically viable.

Researchers are making headway on developing a vaccine for flystrike prevention. Photo: CSIRO

MEASURING EFFECTIVENESS

Dr Vuocolo said some native blowfly antigens used in the vaccine are effective in producing an immune response in sheep that stunts maggot growth (Figure 1) and in some cases the immune response of the sheep results in the death of the blowfly maggots when they feed on the sheep serum. Serum is the component of blood that contains the antibodies.

"Obviously we're aiming for 100% effectiveness in the vaccine, but it's probably not realistic to get that," Dr Vuocolo said. "I know that if we start to get 50 per cent or more, we get excited; when we get to 75 per cent, we're getting really, really excited; that's the point where we're tipping the balance.

"At that point you're really having a marked effect on the larvae; they're just not thriving – a strike is something that is thriving. It is a mass of maggots that are thriving. Something that is a tenth of that size is going to be much less of a problem and most likely won't take or develop into viable flies.

"We measure the size of the larvae, their weight, and the total number that survive in our assessment of our prototype vaccines. We know that the smaller larvae are not as viable, so really this is a measure is of viability as well. The smaller larvae may just drop off and not pupate, or if they do pupate, they may not form into viable adult flies."

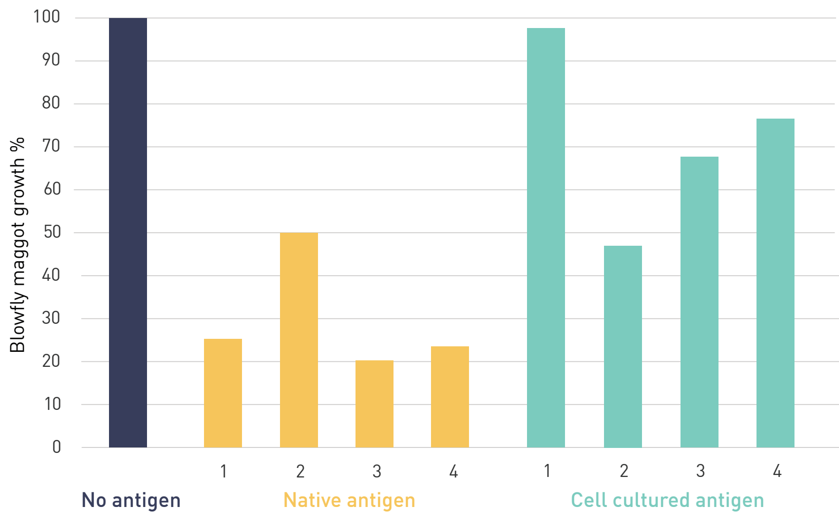
So, while a vaccine that is 100 per cent effective against flystrike might be the gold standard to aim for, a vaccine that is less effective could be very valuable as part of an integrated pest management (IPM) approach to fly control. Dr Vuocolo points out that with increasing chemical resistance, this could be particularly useful in extending the life and effectiveness of existing chemical control methods.

"There is a place for really well managed insecticide use as well," Dr Vuocolo said. "You may only need to apply chemicals at lower rates and strategically. Or we could be really, really lucky and get 100 per cent effective control with a vaccine. Either way, a flystrike vaccine will be a huge step forward in flystrike management and a very valuable weapon to add to the arsenal."

MORE WORK TO DO

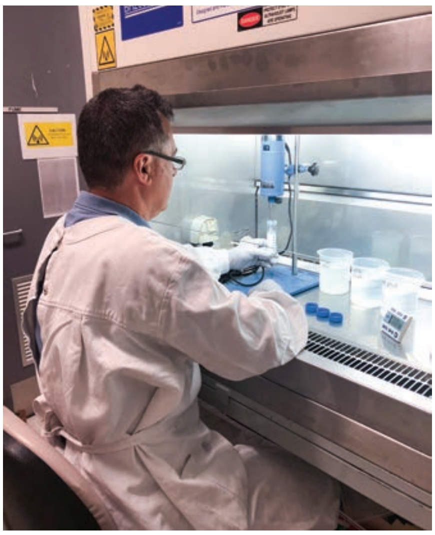
There are some significant hurdles to jump through yet. For one, the approach of using native antigens – the most effective 'bullets' the team so far has in the arsenal – is not commercially applicable at the moment. It's too slow and expensive, however the researchers have ways of possibly making this a viable approach. Another key approach the research team is undertaking is to produce blowfly antigens in bacteria and insect cells, and by chemical synthesis. The cells act as little protein factories and are highly suitable to scaling up to commercial production. To date, these antigens have not produced as strong an antibody response as the native antigens (isolated directly from blowflies and maggots) but that isn't to say it can't be done. CSIRO is looking at novel ways to greatly improve the efficacy of these antigens for use in a vaccine. Dr Vacuolo said the team has a number of exciting leads and several tactics to hopefully outwit and outplay this formidable pest.

Figure 1. Maggot growth on sheep serum



Graph showing maggot growth on sheep serum from sheep vaccinated with (navy blue) no antigen, ie adjuvant only; (yellow) four different maggot derived native antigens; or (aqua) four different cell cultured antigens.
No growth inhibition was shown for no antigen whilst the native antigens have performed the best so far.

Source: Tony Vuocolo, CSIRO



Dr Tony Vuocolo, Project Lead Scientist, formulating a prototype vaccine. Photo: CSIRO

There is also some variation in sheep blowfly genetics across Australia, which is a potential concern but thanks to research being done at University of Melbourne, researchers have the inside running on tackling this issue.

"The University of Melbourne is doing fantastic work on studying blowfly genomes across Australia and it's great that AWI has had the foresight to fund this research," Dr Vuocolo said.

"In collaboration with the University of Melbourne, we've been able to use this genome information to find hotspots in the genome that may potentially effect antigen selection and design for a vaccine. It is great to have this information now during the key phase of vaccine design rather than having to address it in the future. But I'd also like to say that a vaccine and its mode of action allows us to accommodate a number of these specific differences that you see in the different blowfly populations around Australia.

"The vaccines we are developing basically swamp multiple areas across a protein; we're going for whole protein antigens, I don't foresee the genetic differences as a significant problem for our vaccine work. The population variations in the blowfly genome are particularly relevant to chemical resistance will help inform how resistance is occurring and potentially shed light on how new chemicals may need to be produced.

"It's great to know that information. It's much better to have that information now than it would be to get years down the path of developing the vaccine and then discover something that would have been better to know now."

All this points to a lot of things to be positive about in the development of a flystrike vaccine, but there is still a way to go. The scientific world may have produced a number of Covid-19 vaccines in the space of a year, but as devastating as blowflies are to the Australian sheep industry, neither the problem nor the research effort is on anywhere near the scale of the Covid response.

"Generally, it takes around 20 years for a vaccine to come to market," Dr Vuocolo said. "I'd love to say we'll have this one in three to five years, but realistically, it will probably be longer than that. Potentially, 10 years is the ball park. It could be a bit sooner, or it could be a bit longer."

But the data is showing that it may be possible and the numbers are heading in the right direction. FA

More information:

- Vaccine researchers striking back against flystrike: https://bit.ly/3uzKfCo
- 2020 flystrike prevention RD&E program report: https://bit.ly/3yJkfaG
- A vaccine to prevent flystrike on sheep: https://bit.ly/3bULLbF

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