Malaria Drugs Offer New Herbicide Targets

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A relic chloroplast in the malaria parasite opens the prospect of developing a new generation of herbicides from anti-malaria drugs.

New research has found that the evolutionary relationship between malarial parasites and plants is close enough that many antimalarial drugs are also very good herbicides. This finding will spurs new ways of thinking about what new herbicides could be developed, but also offers an opportunity to use plants to study antimalarial drugs.

Malaria: A Military Problem

The original idea for this work was born when I enlisted in the Australian Army Reserve. Although a plant geneticist mostly, as a biochemist of sorts I was admitted to the Army Reserve as a Scientific Officer and assigned to the Army Malaria Institute in Health Service Battalion 2 at Enoggera in Brisbane. Many armies have a malaria wing to them because in recent decades more soldiers have died from malaria than bullets, so investing in malaria expertise is worthwhile for armies. In addition to fitness tests and weapons training I spent time talking to malaria experts and was surprised to hear that malarial parasites (*Plasmodium* spp.) are more closely related to plants than many people would think.

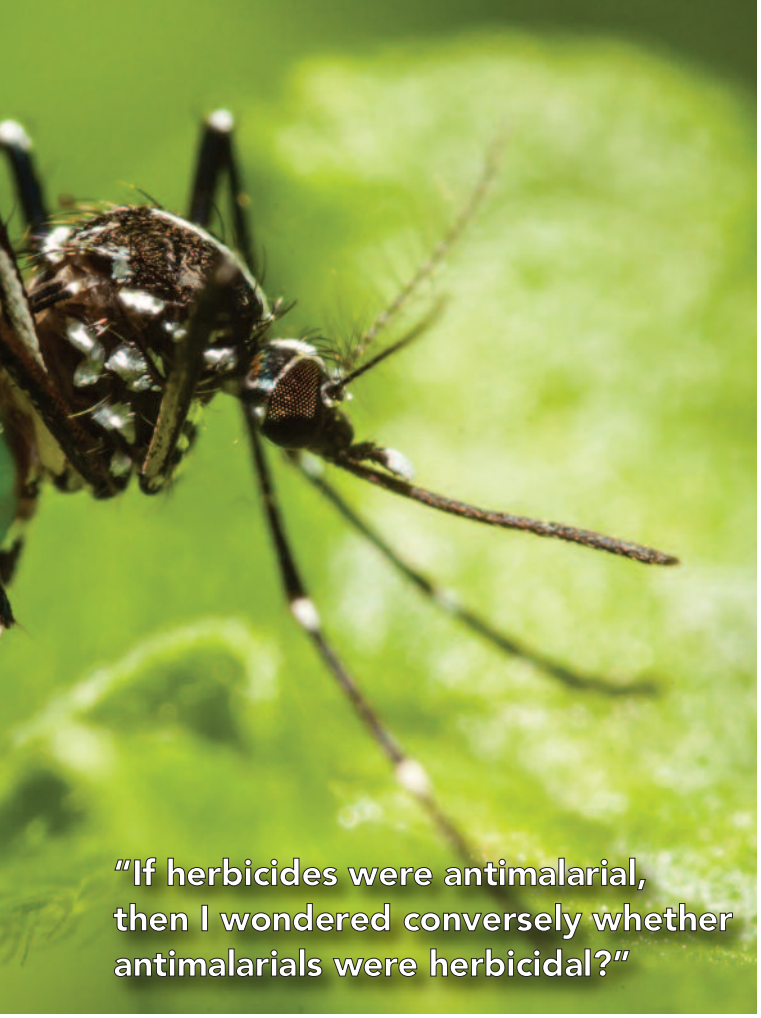
In the 1990s, several groups discovered that *Plasmodium* contains an organelle that looks a lot like a plant chloroplast. Its name is the apicoplast, but it sometimes gets called a relic chloroplast, and it is a visible reminder that the malaria parasite is derived from a single-celled alga like those that currently live in the oceans, catching light and photosynthesising. The apicoplast is not photosynthetic, but it is still essential and responsible for making molecules called isoprenoids that are used to make all sorts of things, including DNA and some amino acids.

One of the ways the apicoplast was shown to be like a plant chloroplast was to use herbicides to disrupt it. After that, several groups attempted to create new antimalarial drugs using herbicides that target chloroplast processes.

I found this relationship between protozoan parasites and plants quite surprising. If herbicides were antimalarial, then I wondered conversely whether antimalarials were herbicidal?

I went fossicking in drawers and chemical cabinets at the Army Malaria Institute and emerged with more than 20 different antimalarial drugs to test. I made a media plate containing each drug and then sowed seeds of the model plant *Arabidopsis* on them to determine which antimalarials were herbicidal and which were not. To my surprise, most were very herbicidal.

There were some notable exceptions. Chloroquine is a very important antimalarial drug that works by interfering with the breakdown of a major blood cell protein called haemoglobin, which is a major food source for the malarial parasite. When digesting haemoglobin, the parasite encounters its toxic and



indigestible haem molecules. To deal with these, it creates insoluble crystals of haem called haemozoin.

Chloroquine interferes with haemozoin formation. As you can imagine, blood proteins and haem crystals don't exist in plants, so it makes sense that chloroquine isn't herbicidal. In fact, I could put so much chloroquine in the media that the gel couldn't set, yet the plants still managed to grow quite nicely.

More detailed analysis comparing antimalarials and known herbicides showed that many of the antimalarial drugs were similarly potent. The research was published this year in *Scientific Reports* (http://www.nature.com/articles/srep45871).

Antimalarials: A Starting Point for Herbicides?

The first and most logical use for this knowledge was to consider antimalarial drugs as lead molecules and develop them into herbicides.

There is certainly a need for new herbicides. Herbicides are an integral part of agricultural practice because weeds have a huge impact on the productivity of a field, even more than diseases and insect predation. However, an overreliance on glyphosate plus the spiralling cost of developing a new compound and taking it to market has meant that many agrochemical companies scaled back their efforts in herbicide discovery. Most of the new herbicides released over the past 20–30 years have been reformulations of existing compounds or ones that work in a similar fashion to past herbicides. This means that no new herbicidal mode of action has been brought to market for more than two decades.

This has consequences. Weeds that are resistant to herbicides are emerging at an alarming rate, so farmers now face the same problem that doctors do with the emergence of antibiotic resistance. Part of the answer is to use the herbicides we have more carefully, but another way to address this problem is to find new modes of action.

Compared with herbicide research, malaria research over the same few decades has advanced rapidly, with chemical drug libraries also becoming publicly available. With the knowledge that many antimalarials are herbicidal, we can apply the knowledge that exists for *Plasmodium* to plants and consider pathways that are not yet targeted by herbicides.

This does not mean spraying fields with antimalarial drugs. There is much development work to be done between finding an active molecule and then developing the compound that gets used as a herbicide in the field.

Making this connection just means thinking about plants and herbicides through the lens of malaria and antimalarial drugs. Thinking in this way, we are examining new potential herbicide targets and attempting to develop new herbicides in collaboration with local organic chemists and agricultural scientists. Our first example was just published in *Angewandte Chemie* (http://tinyurl.com/ydcfu9uz).

Can We Ask Plants How Antimalarials Work?

A more radical application for this close evolutionary relationship could be to use plants to understand how antimalarial drugs work. Some antimalarial drugs have been in use for decades without knowing how they actually work. Perhaps one of the longest-standing mysteries is how the world's most important antimalarial drug, artemisinin, works. This drug is thought to have been used as part of ancient Chinese medicine for more than 2000 years yet how it works remains at best controversial.

Many drugs act by binding an important protein at an important place and stopping it from working. Resistance to drugs often arises when the gene for that important protein mutates so that the drug can no longer bind, but the protein can continue to do its job.

Genetic studies of herbicide-resistant plants often find mutations that provide resistance, and in this way both the protein targeted by the herbicide and the location of its binding are simultaneously revealed. With many antimalarial drugs being herbicidal, if their mode of action is shared with plants then plant genetic approaches could reveal what their targets are. Plants are easy to work with, so we might be able to use plant genetics to reveal how antimalarial drugs work.

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