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The past, present and future of Toxoplasma research: Prof. Geoff Hide

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Why did you choose to focus on parasitology?

Geoff: It all started at when I was at university, I did an undergraduate degree at Edinburgh University in Biological Sciences. In the final year, I specialized in genetics and within the genetics department there, they had a group of people that worked on protozoan genetics which is genetics of single celled organisms but specifically on parasites like the malaria parasite that belong to the genus plasmodium, and another one called trypanosomes or Trypanosoma brucei which is a parasite that causes sleeping sickness in Africa. So, I moved on from my undergraduate degree to doing a PhD with this group of people and so I got interested in single celled parasites.

Most of my initial PhD research and beyond was on trypanosomes and on sleeping sickness I suppose that's where my interest in parasitology came from. It's kind of interesting because I was sort of a geneticist interested in molecular biology and genetic engineering which at the time was new and few people had been doing it in parasites. So, I was able to be at that interface of working with parasites that cause disease and with genetics and molecular biology. It was a combining of two areas which put me in a position that was unique compared to other people at the time.

What interested you in researching Toxoplasma gondii?

Geoff: After I did my PhD and I went to Glasgow and did postdoctoral research on the parasite that causes sleeping sickness, I moved to Salford to take up a lectureship. When you're working as a postdoc, you're working for other people and doing their projects but when you start as a lecturer, you're starting your own independent career and what I wanted to do was to carry on the research I was already doing, which I still do on trypanosomes. But I wanted to develop a new area and toxoplasma was one that I'd been interested in because it's quite an interesting parasite and that was what got me involved with the parasite. It's an interesting parasite and the more you know about it, the more you realize you don't know about it.

Which of your discoveries do you believe to be most important to the future of T. gondii research?

Geoff: Something that's recent and quite exciting was we discovered a parasite which is intracellular and quite common across the globe. What was interesting was we started looking at a group of patients from Wythenshawe Hospital that had lung cancer and I did this in collaboration with Dr Lucy Smyth who is a lung specialist. I was interested to see whether any of the lung tissue that Lucy was getting from these cancer patients had any kind of parasites like toxoplasma in them. It turned out that when we looked at it that in fact, they all did. We had looked at 72 patients, which is quite a large sample size for getting lung tissue as it is a very difficult tissue to get hold of, and we were detecting the parasite in every single one of them. That's quite exciting and frightening because it's unusual.

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What effect on people and animals does the parasite have, that you think we should be more aware of?

Geoff: We need to look at this in the background in the context of the parasite. A striking statistic is that one in three people on the planet have toxoplasma and it varies a bit in different countries. So, in the UK, it's about 1 in 10 and when we're going to big lectures theatres with 200 people in there, 20 people in that room are on average infected with toxoplasma. Also, when you look at other warm-blooded animals, you find that it's very prevalent there as well. So, about 1 in 3 wild animals and wild birds are infected with the parasite as well. So that makes it an interesting parasite, because how has it got to all these different hosts whether they be human hosts, or animal hosts. Another thing that's interesting about it is that it's a parasite where it only completes its full lifecycle in the cat. It's a cat specific parasite and what happens is that it gets ingested by the cat, it develops in the cat, it goes through its sexual cycles in the cat and then infective oocysts are shed from the rear end of the cat and spread into the environment where they infect secondary hosts like us. It's interesting because even sea mammals like whales and dolphins have toxoplasma and yet they don't encounter cats regularly. I almost call it the perfect parasite because it's spread so widely through the human and animal kingdom. It is in a high percentage of people and animals, so it's managed to adapt its way into spreading quite widely. But one of the questions raised out of that is does it cause us any harm? and the short answer is that in most cases, no, it doesn't. When I say 1 in 10 of us in the UK, or 1 in 3 of us in the on the planet are infected with toxoplasma, we may never even know it.

It lodges as a kind of a cyst form in our bodies, and it's held in check by the immune system and there it stays probably for the rest of our lives, and we may never know we've got it. But of course, it does cause some problems and it causes problems in people that are immunocompromised due to a disease like HIV/AIDS where the immune system is compromised by a viral infection, or it could be people that are undergoing cancer treatment where the drug treatment causes the immune system to be depressed and then the parasite can become active, or it could be things like immunosuppressive drugs. It’s also a problem in pregnant mothers if you're a pregnant mother and you become infected with toxoplasma during your pregnancy it can be passed through to your developing baby and cause problems with the baby and sometimes it can cause miscarriage as well. That's a very serious effect to the parasite but in terms of the number of people on the planet infected with the parasite, it's a rare occurrence.

What is the focus of your latest research? Have you gotten any significant results so far?

Geoff: What we're doing at the moment is that we're interested in carrying on this topic of trying to understand these patients with cancer and why they're all infected. So, what happens is we section the tissues, and we can use antibodies to stain the parasites so we can see the parasites very clearly stained in the tissues. We see those cysts stages that I talked about earlier and these are the dormant stages. But we also see which is interesting, in about 90% of the people we looked at, we saw stages, which indicate the parasites in an active stage. So, what the parasite does is it can get into macrophages, and it hides inside the macrophage and reproduces and then infects other macrophages and other cell types. So, we see those active forms present in the lung tissue as well. That suggests that these individuals have got an active infection and not just a historical infection. What we wanted to try and do was to find out what kind of molecules were involved in this process why the parasite active here and what's behind it.

I work in collaboration with a large group of scientists in China on toxoplasma and what we were doing in China was we were looking at the effects of host immunity on parasite. So, if you infect laboratory animals with toxoplasma, what you find is that some of them are more susceptible than others. So, if you infect laboratory mice with toxoplasma, they die very quickly within sometimes a few days, or sometimes a couple of weeks. If you infect rats, they survive much longer because there's something about the rat which makes it more immune or more resistant to the parasite than the mice.

So, what we discovered is that it’s to do with two enzymes arginase and inducible nitric oxide synthase (iNOS). What happens is, both enzymes rely on the same subject substrate, so they metabolize arginase and so you get arginine which goes either to the iNOS or to the arginase.

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When we looked at the rats, we found that the expression of iNOS was very high relative to arginase, so these rats were resistant but when we look to the mice, it was the other way around. So, the iNOS is very low, and the arginase is very high and what iNOS does is it produces a molecule called nitric oxide. Nitric oxide is a powerful killer of intracellular pathogens like toxoplasma and other parasites. So, what's happening is in the rats, we've got the balance of power the iNOS is high and the arginase low so they're resistant, but in the mice, it's the other way around. So, the iNOS is low, and the arginase is high, so the mice don't produce much nitric oxide. So, we were looking at this and we discovered this mechanism that determines resistance or sensitivity to the parasite.

One of the things we're interested in then was then to move from rats to humans and what's happening in the humans. So, what we were interested in doing with these lung samples was then to see if we can detect the expression of iNOS and arginase in the lung tissue and to see what's happening in these human lung's samples. We can do this with antibodies to the iNOS enzyme or antibodies to the arginase enzyme and we label them with coloured fluorescent dyes to see the distribution of these two enzymes in the lung tissue and we can look at it in relation to where the parasite is. So interestingly what we see is that where there's iNOS, there are no parasites, and where there's arginase the parasites more prevalent. So, it supports this theory that when the iNOS is high, the parasites not there and when the arginase is high, the parasites are there.

When we looked at some of these cysts which are the circular dormant stage for the parasites in these lung samples, there's only three we could detect. But when we looked at those three, what we found was that there a ring of iNOS being expressed around the outside of the cyst. So, what we think is that the iNOS the enzyme that produces this nitric oxide is involved in this process of locking the parasite into the cyst. That's what we're doing currently and we're developing that a bit further.

Have you had any further projects as a result of your research on this parasite?

Geoff: There are some things that we've been doing with our colleagues in China. One of the things that we've been able to do over there is we've been able to generate rats in which the gene for the iNOS enzyme has been completely deleted. So, these are what we call iNOS knockout rats. What we've done with those is we've looked at toxoplasma, we've looked at another parasite called leishmania which causes a very serious human and animal disease, and another one called Schistosoma which causes bilharzia in Africa and other diseases. What we've shown is that when you knock out the iNOS gene the rats become very much more susceptible to both the Schistosoma and the leishmania but not the toxoplasma which is what we expected to see. What seems to happen is that when you remove the iNOS protein, the parasite itself triggers another host response against itself. When you lock out the iNOS, we expected the parasite to kill the rats or make them very seriously ill but instead they were protected against the parasite.

It appears the parasite has got something like a feedback loop. It's not being killed by the levels of nitric oxide or the iNOS expression, what it's doing is it's triggering another immune response which is protecting the host from itself. That's interesting because if you're a parasite you don't want to kill your host because then you don't get transmitted on to another host. What we think might be happening here is that the parasite has evolved a mechanism to save its host from itself.

The other thing that we've been doing here in Salford is looking at what's going on in wild animals. So, we collect wild mice from pest control processes, and we also trap wild mice and what we've been looking at is what the expression of iNOS and arginase is in those wild mice. It's interesting because we can look at some genetic markers for expression and what we see is that in the wild mice that are that are not infected, they seem to have higher iNOS than the ones that are infected. So, what we're looking at here is just natural variability within wild animals in terms of the levels of expression of iNOS and arginase. So, so quite complicated. It all comes together to suggest that this balance of iNOS and arginase is important in terms of how resistant we are to parasites like toxoplasma. Looking forward, if we were at the stage where we could measure the levels of iNOS and arginase in people we might be able to determine whether some people are more resistant to parasites like toxoplasma than others and get an understanding of this sort of personal medicines side of understanding about individual resistance and susceptibility to parasites like toxoplasma and a wider range of pathogens.

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Has your work on T.gondii led you to any other research topics that you would like to focus on in the future?

Geoff: There's lots of genetics project, so me being a geneticist what I'm interested in is the control of the genes for things like iNOS and arginase, so if there's one person that's more susceptible than another person, what switches the genes on and off in that person that doesn't happen in the other person.

Another aspect to what we would like to focus on in the future is that one of the things that's interesting about this parasite is it affects behaviour. So, if you infect mice with toxoplasma, they become attracted to cat urine, which uninfected mice are not. That's quite interesting because what it's saying is that the parasites which have lodged in the brain as cysts are having some influence on the behaviour of the mice. There's been some work over the last decade or so that's shown this in humans. If you look at a cohort of people that have schizophrenia and compare them with a cohort of people that don't have schizophrenia, the people with schizophrenia have a higher prevalence of toxoplasma in them than the other population.

These are difficult studies to do because there's lots of different factors that could determine these relationships but there's definitely something there that's happening in humans where the parasite is affecting human behaviour. That's an area I'm quite interested in, and we did a study with my colleagues in China, to see whether there was any kind of linkage between postpartum depression, the kind of depression that mothers get when they've just given birth, to see whether there's any link between that and whether the mothers were infected with toxoplasma or not. In that case, we didn't find any link at all there was no difference between mothers that had postpartum depression and mothers that didn't have it in terms of the prevalence of infection in those two groups. There's a lot of these kinds of neurological diseases out there where maybe a parasite that forms cysts in the brain, that's involved in that. So, I think these are exciting areas to be interested in the future.

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