Speaker: **Patricia Nuttall – Professor of Arborvirology, University of Oxford**

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0:06
Have you even been bitten by a tick? If you have, I bet you didn't feel a thing. I bet you didn't know they were there, and they do tend to get into places that, yeah, can be a bit embarrassing. So, ticks are not like insects, they're not like mosquitos or or sand-flies, they don't have a quick meal, they don't hit you quickly, take a big slurp, go a then you're left with a a red lump on your skin. Inflammation, swelling, itchiness. They really tuck in, ticks when they feed.

0:53
This is a a electro micrograph of a tick feeding in the skin. They really burrow their heads into the skin and and they may be feeding if you don't find them for quite a few days, so how do they do that. How come you haven't noticed they are there? Well they do that because they have some very complicated salivary glands and in those salivary glands, we can see them if we take them back off the tick. Inside there we can see these complex, grape like structures, and in particular these round blobs, these round grape like structures called Acini.

1:35
In the electron microscope, we can see in these Acini staining them with different chemicals, that they are stuffed with lots of amazing molecules. Proteins, peptides, non-peptitick molecules. And this is what we call the tick's pharmacy. So, before I tell you my story about the tick's pharmacy and exploring it. I want to just go back in time a little bit and and say well how on earth id I get to this position. Which might seem a bit odd. And it goes to this is this paper was published in 1987 - it goes back to an experiment, a PHD student of mine was doing. So, we were looking at a virus that was transmitted by ticks. And, one of the problems was when you work with ticks that take a long time to feed - you do have to use animals. And we wanted an animal that was not susceptible to this virus because we wanted to look to see if the virus could be transmitted between infected female ticks, or infected male ticks - vice versa.

2:48
So we wanted to see if we could get trans/transsexual transmission of this particular virus. What happened was the experiment seemed to go wrong. So all the controls which should of stayed negative turned positive. So when the ticks fed, 8-14 days, all those negative ticks had become positive. We called this phenomenon - non - viremic transmission. So viremia means, virus in the blood. And for these kind of virus, viruses, that is the the has been for many type, many years, the dogma that in order to be transmitted via tick or a mosquito - these viruses must get into the blood, there must be lots of them so that when the virus, when the tick or the mosquito feeds; it takes the blood up. With the virus in it. But here we got so called non-viremic transmission.

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So, this was published in a very prestigious journal, but nobody believed it. They thought, this is pretty weird. So obviously we had to find out what, how they how could this happen. And about the same time a group in the states were working on leech mania which is caused by a parasite transmitted by sand-flies. And they found that there was something in the sand-flies saliva that was helping the leech mania to be transmitted. So so we said - OK, let's have a look at the saliva of these ticks. And we didn't know how to do it but I had a colleague in in Canada, Reuben Kauffman, who's the world's expert and still is on making ticks spit. So he came in the lab and we fed up some ticks, and you can see them all laid out on their backs, on these microscope slides. We put these capillaries over their mouth parts, we stimulated with a chemical and then we collected the saliva. And there is a knack in that because they have a horrible habit of spitting out the saliva and then sucking it back. So you really have to be very careful.

5:04
So we looked at the saliva, we mixed it with the virus, we repeated the experiments and hey presto - yes, there's definitely something in the saliva. And that started my research career in trying to understand what these molecules are. And I just want to share with you some of these amazing molecules and convince you that ticks really are amazing creatures. So this is the first molecule we found, it was isolated from this tick and we can prod/we could produce it synthetically. We managed to crystallise it it's a protein you can see a crystal at the top right there - that's the dream of every scientist who's looking at protein structures, get a crystal we could resolve the atomic detail; and this cartoon here is a cartoon of the atomic detail of this particular molecule. So its amino acids making up a protein, their organised in an anti-parallel beta sheets that's these strip like ribbons. And amazingly what we saw inside this molecule were two molecules of histamine. You must of heard of histamine.

6:18
That's the thing that those mosquitos are releasing that's causing your swelling and inflammation when you're bitten by a mosquito. So, how does it work? Well I'll, think again of being pricked by a mosquito or just just a blade a bit of wood. Your finger goes red it swells. And what's happening is that you're activating cells that contain preformed histamine. Things like mast cells. And this histamine which is shown in this figure as 'H', interacts with receptors on the surface of different white blood cells. And there are at least four different receptors and by interacting with those receptors they initiate these processes of constricting the blood vessels of inflammation, reddening and bringing in more cells to try and deal with this invasion. So what does the tick do? Well it also causes this degranulation and release of histamine.

7:34
But this histamine binding protein binds up the histamine and by binding up the histamine its stops the histamine from from binding to the receptors. So it stops, prevents that inflammation, that itching, that swelling. If we think any of you suffer from hay fever or or have skin problems; go to the pharmacy to buy antihistamines. There are all sorts of them. There's a drug for every single one of those different receptors. What the tick has done is said, I don't care what those receptors are. I'm designing, I have designed one molecule that deals with histamine. So, there's one molecule from the tick, there's a whole pharmacy from our pharmaceutical industry. So one message; the first message really about ticks is their pretty smart. This cartoon is an antibody drug. There are a lot of antibody drugs now on the market.

8:46
This particular one is the most expensive drug in the world. So it costs just over $500,000 half a million dollars for one year's treatment. It's for patients with a a an awful disease, a rare disease but a hugely expensive drug. Drawn to scale this molecule here is from a tick. Produced synthetically, it's 9 times smaller than this complicated antibody drug. It does exactly the same thing and more. So, message here is that these drugs from ticks can be highly cost effective. And this one here is a tick anticoagulant. So what does that mean? Well if you look at those ticks up there, that small one actually is the same as the big one. It's the female and yes the females do all the work - so it's the female after she's fed. So the female feeds, and increases her body weight about 100 times. Why does she do that? All that blood that she takes in, is converted into eggs. So the bigger she is - the more eggs she can produce.

10:04
Now if that blood was to coagulated, clot, you know and awful mess; in fact the tick would die. So not surprisingly ticks produce very powe/potent, powerful anticoagulants. This is the this is the sequence, this is the composition of one of those proteins which call a peptide, we've called it variegin. It's very similar to a drug that's been derived from the leech called hirudin and is now marketed as bivalirudin or angiomax. This drug is used in heart disease, so for coronary stenting if you have a constriction of coronary arteries, the technique these days is to put a little tube inside that artery to keep it open. It's a non-invasive procedure, it's becoming used increasingly. And obviously when those when that surgery's done, it's very very important that there's not blood clotting. This drug is used for that purpose.

11:12
The tick equivalent is 15 times more potent. And it's more potent one of the reasons it's more potent is that like the leech drug, it targets a protein at the centre of the blood coagulation cascade. Thrombin. Thrombin is shown here in the crystal structure in yellow and that crimson ribbon there is the tick protein after its been cleaved by Thrombin. It sits in a little canyon on the surface of the Thrombin molecules. And by interacting with the catalytic triad at the heart of this Thrombin molecule, it stops it from working. And it stops it as long as this Thrombin is around. So it's it's a long acting anticoagulant and this very mechanism by which it works has taught us something new about controlling anticoagulation. So that's really the third message about these ticks. They're teaching us new tricks.

12:20
Recently we've heard in the news a lot about immunotherapy. Immunotherapy is having some fantastic results in cancer treatment. It may well be a way of not needing chemotherapy and radiotherapy. Well, ticks are already there. They produce a an imuno - modulator. This is the molecule, it likes to work in pairs. When we got the crystal structure of this one, we found to our surprise, that buried in the heart of the molecule was one molecule of cholesterol. Why is this imuno-modulator carrying cholesterol? Really don't know. We're really scratching our heads about this one. If anyone has any ideas, really interested to know them. But I'm sure once we've worked it out, we will discover yet something else that's new. So nature inspires us in many ways. Usually you know it's a wonderful painting, it's a walk in the park, it's not usual that creatures like these that suck blood inspire us.

13:41
But what I'd like you to do next time your bitten by a tick, is just to pause a moment and think to yourself, what a clever little tick you are.

13:54
Thank you

13:57
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