British Sjögren's Syndrome Association

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All aboard the bandwagon!

By Pete Smith, Senior Lecturer in Oral Biology School of Dental Sciences, The University of Liverpool.

Exciting and well funded research projects in Sjögren's Syndrome have become a bit like the proverbial London bus. You wait for years and then two come along at once. In the last newsletter, Wan-Fai Ng told you all about the UK's Primary Sjögren's Syndrome Registry (UKPSSR) and what it could mean for future research into Sjögren's Syndrome. When he wrote that the blood samples contributed to the Registry *'are useful for the investigating mechanisms that cause Sjögren's Syndrome (and) the development of novel diagnostic tests....'* he was thinking about us and our research at Liverpool. We have been very interested in the UKPSSR ever since we first heard about it, because we think that we can learn an awful lot can from serum samples from well characterised Sjögren's Syndrome sufferers and, just last week, The Arthritis Research Campaign agreed with us and are funding a project to screen serum from the registry so that we can work out how many Sjögren's Syndrome sufferers have autoantibodies for the muscarinic receptor.

What is the muscarinic receptor, and why should we care?

We've written about this before in the newsletter (Summer 2002) so, to avoid too much repetition, I'll be brief. The first stage of saliva production is activation of the salivary gland acinar cells by nerves. In much the same way as your nerves make your muscles work, nerves make salivary gland cells work by releasing a neurotransmitter called acetylcholine. Releasing acetylcholine is the chemical equivalent of shouting WAKE UP or MAKE SALIVA. Muscarinic receptors are the ears of the cells that listen very carefully for the nerves to shout MAKE SALIVA, to which they respond by signalling to the secretory part of the cell, which turns on the tap (salt and water channels mainly) so that saliva is released.

Which bit isn't working in Sjögren's Syndrome then?

We really don't know yet. We're pretty sure that it isn't the salt channels, but some people think that it might be the water channels (the tap). We think the problem is probably with the muscarinic receptors (the ears) or with the signal between the ears and the tap. Or there could be problems with both.

What do you know then?

Over the last few years our experiments have shown that we can stop the salivary gland cells from working with an autoantibody that we have extracted from the serum of people with Sjögren's Syndrome. I'm not going to try and explain what an autoantibody is, you probably know at least as much as I do. We think that this autoantibody stops the muscarinic receptor from working. Think of it as making the cells deaf. You could picture the autoantibody as a giant pair of furry earmuffs; once you put them on, you can't hear anything. Most importantly, your cells never get to hear the nerves shout MAKE SALIVA, so they don't make any. Eventually, like any part of the body that is never used, the gland cells will wither away.

Are You Sure?

No, not yet. What we need to know next is how many Sjögren's Syndrome sufferers make this antibody. So far, we have only been able to try the serum from a few people because it is really, really hard work to detect the antibody. It takes us about a week to tell whether or not one person has the antibody, and that is when everything works first time. We need to test hundreds of Sjögren's Syndrome sufferers to be able know whether or not the antibody could be important in the disease. This is a very slow and very, very expensive process.

You're making me depressed. Is there any good news?

Well yes there is. One of the reasons that detecting the antibody is so slow is that people, even scientists, insist on going home every night, they take days off just because it is a weekend AND they have only two arms and two eyes, which strictly limits the number of experiments that they can do at the simultaneously. What we need is a sort of robotic spider that never takes time off and which has many arms and eyes so that it can perform lots and lots of experiments at the same time. Before you think me completely mad, I must tell you that there is such a thing. It is called a FlexStation III and it is made by a company called Molecular Devices. This machine has just two drawbacks. First, the robot spider has been hidden inside a metal box that looks for all the world like a giant bread maker, which is a shame because I would like to have watched it at work. The second is that it costs a lot, lot more than a bread maker, about 1000 times more, or roughly the same as slightly used Aston Martin Vantage.

The really good news is that the very nice people at The Arthritis Research Campaign (**http://www.arc.org.uk/**) have agreed that we should have one of these devices.

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Tell me again, what exactly are you going to do with the spider inside the bread maker?

It is very, very simple. Do everything faster, much faster.

Instead of taking a week per person, we should be able to test at least 8 people in a week and probably twice that once we are sure what we are doing. With such a high throughput, screening hundreds of people becomes feasible.

We want to test lots and lots of Sjögren's Syndrome sufferers for the antibody. We must also find out how many people without Sjögren's syndrome have the antibody.

The proportion of Sjögren's Syndrome sufferers who show the antibody is called the 'sensitivity' of the antibody for the disease. If all, or even most, Sjögren's Syndrome sufferers have the antibody then it could be very useful for diagnosis. We do look for a couple of antibodies now as part of diagnosis, Ro & La. La, in particular has a quite low "sensitivity" of about 60% (60% of people with Sjögren's syndrome have the antibody). We are going to see if we can do better than this!

Why bother looking for it in people who don't have Sjögren's Syndrome?

To be useful diagnostically the antibody should be present in people with Sjögren's Syndrome and not present in people without. This is called 'specificity'. You must always measure both 'sensitivity' and 'specificity' together. Either one by itself is meaningless. Imagine how excited we would be if 100% of Sjögren's Syndrome sufferers were antibody positive (100% 'sensitivity') and then how disappointed, if everyone else was also positive (0% 'specificity'). To be a good test, which is one that distinguishes between those who have the condition and those who don't, it must be both 'sensitive' and 'specific' for the disease.

Surely you don't really think that everyone has anti muscarinc receptor antibodies?

Frankly no. The few experiments that we have done so far suggest that the antibody is fairly specific for Sjögren's Syndrome. BUT we don't KNOW that this is the case. The only way to find out for sure is to test lots of people who don't have Sjögren's Syndrome. Incidentally, if you are planning to get involved with the UKPSSR then please find a friend of about the same age and sex who has not got Sjögren's Syndrome and who would be prepared to donate a little blood in a good cause. So far as our study is concerned, the blood from a "control" (Someone without Sjögren's Syndrome) is every bit as useful to us as is the blood from a Sjögren's Syndrome sufferer.

Do you only find muscarinic receptors in the salivary glands?

No. You get muscarinic receptors all through the body as part of the parasympathetic branch of the autonomic (automatic) nervous system. There are two branches to the autonomic nervous system. The sympathetic winds you up (increases heart rate, sweating etc.) and the other, the parasympathetic calms you down again.

The answer to your next question is yes, it is possible that anti muscarinic receptor autoantibodies could be the cause of some of the extra-glandular features of Sjögren's syndrome. Perhaps even fatigue. Part of our project is a collaboration with the team at Newcastle to work with a subset of patients where we will measure autonomic dysfunction (how well your automatic nervous system works) and relate these findings both to fatigue (measured by questionnaire) and the presence of anti muscarinic receptor autoantibodies.

Is there anything else interesting going on?

Oh yes!

I haven't got the space to write about:

- Nitric oxide, which probably affects the signal part of secretion
- Ectopic lymphoid germinal centres, which could completely change the way we think about muscarinic receptors.
- 'Pacemaker' cells which is all about cells talking to each other.
- Whether lacrimal (tear) glands are really the same as salivary glands. A very important project which has been funded by the BSSA.

Perhaps another time.

This is a good time for Sjögren's Syndrome research. We have lots of projects, all starting up together, and coordinated through the UKPSSR. The more the merrier. This is a good bandwagon to be on, let us hope we can keep the momentum going.

Can I find out more?

You really are a glutton for punishment. Go to **www.petesmif.org.uk** and click the 'Research' tab. All of out recent publications are available. There are also notes about salivary glands in general under the 'notes' section.

Biography - Pete Smith

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I have been studying transport of salts and water across cell membranes and epithelia for the best part of 30 years. I've studied transport in the intestine and the kidneys and in salivary and lacrimal glands. I am a physiologist and so am very interested in how things work and not very bothered at all in what they look like, something you may have spotted from my diagrams. More specifically, I am an electrophysiologist and I study the movement of ions (salt in solution) across cell membranes by following the electrical currents that they make.

I'm also interested in education and in how students learn, I have an addiction to writing computer software (it is very hard to stop) and I am very fond of gadgets.