Comments by J. C. Spencer

The sugar research of Australian Professor Nicki Packer has led her to put forward a rather fascinating hypothesis: that the glycoproteins found in mammalian fluids such as breast milk, tears and saliva have anti-pathogenic properties. There may be a SUGAR FIX FOR PATHOGENS.

We applaud Nicki Packer and her work in this cutting edge science that is a boost to the Australian and worldwide glycomics sector. Especially commendable is the fact that she has negotiated with Proteome Systems the transfer of a sugar structure database from the company's hands into the public domain. The database was developed during Packer's time with the company to list the sugar structures that have been reported in the literature.

Now today's Glycomics News

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Sugary fix for pathogens

The protein complement of ear fluid might be considered an unusual way to spark an interest in an emerging field, but it has led Nicki Packer to become one of Australia's premier experts in glycomics.

It wasn't the ear fluid that inspired Professor Nicki Packer to take an interest in proteomics per se, more the potential it offered to understand cellular processes at a deeper level.

In the early 90s, when Packer was part of the now-famous lab run by Professor Keith Williams at Macquarie University, a chance visit from Swiss proteomics pioneer Denis Hochstrasser provided the spark for a fascination with a then-emerging field that continues to this day.

Hoschstrasser gave a talk about the proteins in the ear fluid of accident victims. These proteins, found in a tiny amount of fluid exuding from the ear drum, provided a marker as to whether the patient had experienced brain damage or physical injury.

The Williams lab was already protein-oriented, but in those days, as Packer says, analysing a single protein took a whole PhD, and everyone else was into molecular biology.

However, the Williams lab was inspired to begin work in the nascent field of proteomics. It was one of the lab's students, Marc Wilkins, who coined the term itself.

“Basically it came about – this is his story anyway – that because he was sick of writing ‘the protein complement of the genome’ in his thesis he shortened it to proteomics to rhyme with genomics and off we went,” she says.

Off they went indeed. The group, also containing Andrew Gooley, Ben Herbert, Jenny Harry and Brad Walsh, was able to obtain funding from the Major National Research Facilities (MNRF) program to buy the infrastructure and equipment to set up APAF, the Australian Proteomics Analysis Facility.

While this money paid for the bricks and mortar, the researchers’ salaries were another matter, and when an application for a CRC failed at the last minute, part of the group decided to strike out on their own and set up a biotech company, Proteome Systems.

The idea was to concentrate on technology development for proteomics research driven by discovery, Packer says. Projects included investigating tuberculosis as a driver of technology development – the company is still working in this area – and an interesting project funded by Nestle into the differences between the glycosylation of proteins in cow’s milk and human breast milk.

“For obvious reasons they wanted to know the difference, whether the cow’s milk could be supplemented with human factors,” she says. “We found that human breast milk is very different in its glycosylation to cow’s milk, which is fortunate for both species.”

After eight years with Proteome Systems – now re-invented as Tyrian Diagnostics and concentrating on biomarkers and diagnostics rather than instrument technology – Packer returned to Macquarie in 2007, where she now specialises in glycomics.

Her research has led her to put forward a rather fascinating hypothesis: that the glycoproteins found in mammalian fluids such as breast milk, tears and saliva have anti-pathogenic properties.

Protective mechanism

Packer’s hypothesis is that the reason why the glycosylation of human milk is different from cow’s milk is that mother’s milk offers a protective mechanism against the pathogens that infect human babies.

“The cows are probably protecting their babies in a similar way but their sugars are different, their proteins are different and the bugs that infect cows are different.”

Along with the antibodies passed from mother to child in the milk, there are also growth factors and anti-microbial peptides. Packer’s work is investigating the idea that the sugars in breast milk also work to protect the child.

“Bacteria have sugar binding molecules which allow them to essentially dock in the baby’s gut,” she says. “This is one of the initial infective mechanisms of the bacteria –

they grab hold of the baby's mucosa. Our theory is that the milk has very similar sugar epitopes on its glycoproteins.

"It is these sugar epitopes that are able to out-compete the binding of the bacteria – or virus or any other pathogen – to the mucosa. If you look at the sugar epitopes on the milk glycoproteins, they are very similar to those that are on the gastric mucosa. The epitopes bind to the bugs and clear them from the stomach.

"We have evidence that this is true, and our research now involves looking at different bacteria and how they compete."

At the Lorne Proteomics Symposium this weekend, Packer will predominantly talk about the milk research, but as she points out, the theory applies to any mucosal surface that is washed by human fluids, including saliva and tears.
"All of these things are protective of the natural mucosa," she says.

"For example, the eye is sterile – we don't have bacteria in the eyes because we are very good at protecting them as they are constantly being exposed to external pathogens.

"We have lots of elements in tears that are antimicrobial, including these glycoproteins. The sleep in our eyes in the morning is essentially a secretion of these bugs that are trapped by the glycoproteins and are cleared from the eye. It is the glycoproteins that are our overall research focus."

This also extends to cancer. Packer's team has received funding from the NSW Cancer Institute to set up the infrastructure to do glycomics in cancer research, including leukaemia and prostate cancer.

From her point of view, glycoproteins have everything to do with cancer.

"It has been known for decades that cancer produces changes in the glycosylation of proteins," she says. "Currently, the diagnostics that are around – CA125 and CA19-9 for example – are based on changes in glycoproteins.

"How they actually work no one really knows, other than the fact that sugars are only found on the surface of the cells and therefore they are involved in cell-cell interaction.

"You can make a reasonable deduction that in cancer, where cell-cell communication has broken down, there are changes in the glycosylation. There is a lot to study there and it's of increasing interest."

Sugar structure database

In a boost to the Australian and worldwide glycomics sector, Packer has negotiated with Proteome Systems the transfer of a sugar structure database from the company's

hands into the public domain. The database was developed during Packer's time with the company to list the sugar structures that have been reported in the literature.

Sugar structures, as opposed to proteins, cannot be read off the genome, she says. "Protein databases are established from the genome databases but you can't do that for sugars. There's no template, nothing to say you can read the structure of a sugar from the gene or from the protein, nothing that codes for the sugar structure.

"So the only way we could do it at the time – and still – is to actually read the literature to see what was being reported. We did this to match the mass spec data the same way that proteomics does. You do a theoretical fragmentation of the database and match your mass spectra against it."

The database – which is a bit out of date and needs to be updated and new tools developed – is about to be installed on the ExPASy server in Switzerland, maintained by the Swiss Institute of Bioinformatics, which has offered to host it.

At Lorne, Packer will be closely watching the debate about whether to take a gene- or protein-centric approach to the proposed Human Proteome Project. She sits on the scientific advisory council of HUPO's Human Glycoproteome Initiative, and admits to a bias as to which way she'd like the HPP to go.

"I'm coming from the glycomics approach and that comes very much from the protein approach, which is describing what is there under different conditions. I'm a little bit biased but if you only look at the gene, you don't know what is being expressed at any one time in any one cell in any one disease.

"Only by looking at the expression and more importantly the modification – it's not only glycosylation, it's phosphorylation, it's cleavages, it's ubiquination – the protein is being modified amazingly to do its job.

"I'm pretty much firmly in the court that you have to look at the expressed gene."

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Kate McDonald (Australian Life Scientist) 06/02/2009

http://www.biotechnews.com.au/article/275746/sugary_fix_pathogens?pp=1