Campylobacter jejuni, a bacterium that causes severe food poisoning. This will assist both accurate diagnosis of the pathogen, as well as monitoring its evolution over time.

Using the DNA of *C. jejuni* NCTC 11168, the first strain to be sequenced, Champion has already assembled a microarray for this strain, and is now adding individual genes of other *C. jejuni* strains, isolated and donated by research groups worldwide. Different *C. jejuni* strains can vary considerably (e.g. in their content of different virulence factors) according to analysis by Champion's colleague Nick Dorrell. The *C. jejuni* composite chip will better represent the whole species, Champion told delegates attending the *Ordinary Meeting of the Society for General Microbiology* (8–12 April 2002, Warwick, UK).

With approximately 60 microbial genome sequences now deciphered, and an additional 100 or more under way [1], including a second *C. jejuni* strain by The Institute for Genomic Research (TIGR; Rockville, MD, USA), the progress of DNA chip-based diagnostics looks extremely promising. 'In theory it could be used for all sorts of diagnostic applications,' Champion concluded.

Reference

1 Doolittle, R.F. (2002) Biodiversity: microbial genomes multiply. *Nature* 416, 697–700

Bacteria prove gutsy against inflammatory bowel disease

Julie Clayton, freelance writer

A gene responsible for the deadly effects of the bacterium *Yersinia pseudotuberculosis* – a relative of the plague-causing pathogen *Y. pestis* – has a beneficial side. The 'Jekyll and Hyde' gene, which is active in non-pathogenic strains of *Salmonella* bacteria, has been shown to block immune rejection of these non-pathogenic strains in *in vitro* studies. This finding promises to be the first of many new insights into the molecular signaling between gut-dwelling microbes and their hosts, and could lead to more rational treatments for diseases in which this signaling has broken down.

Salmonella strains

Salmonella spp. cause severe diarrhoea in humans by triggering a massive immune reaction in the gut lining. This involves the activation of signalling molecule nuclear factor-κB (NF-κB), which in turn triggers release of the cytokine interleukin-8 (IL-8) to attract neutrophils and other white blood cells to the site of infection.

Andrew Neish and his team at the Emory University School of Medicine's Epithelial Pathobiology Unit (Atlanta, GA, USA) have discovered two *Salmonella* strains that actively inhibit, rather than trigger, NF-κB activation and IL-8 secretion in cultured epithelial cells. These strains are *S. pullorum*, which is non-pathogenic in humans but causes disease in chickens, and a laboratory mutant of *S. typhimurium* NF-κB [1]. Both strains also promote apoptosis, which is normally inhibited by NF-κB.

It has now been shown that the inhibitory effect on NF-κB and IL-8 is caused by a gene called *AvrA*, the *S. typhimurium* homologue of a disease-promoting gene in *Y. pseudotuberculosis*, Neish told delegates at the *Ordinary Meeting of the Society for General Microbiology* (8–12 April 2002, Warwick, UK). The *AvrA* gene product is one of several signalling proteins known as type III secretion systems. These are highly conserved in nature and have homologues in the plant kingdom that trigger the appearance of a protective ring of apoptotic cells around sites of virus infection, according to Neish. He suspects that, by analogy, promoting apoptosis in the gut lining could be protective for other bacteria, particularly the commensal flora that normally inhabit the intestine. He stresses, however, that the *in vivo* relevance of his findings is speculative: 'How that translates to biology in a whole animal is open to interpretation – is that a pathogenic or a non-pathogenic mechanism?'

Martin Maiden, Senior Research Fellow at the Department of Zoology, University of Oxford (Oxford, UK) commented that: 'Neish's work suggests that a lot of these things that people have only studied from the point of view of disease, particularly type III secretion systems, actually are rather more complicated and interesting than that, in that the bacteria are modulating an interaction with the host.'

Other colonization inhibitors

Elizabeth Furrie, a postdoctoral researcher at the University of Dundee (Dundee,

 1359-6446/02/$ – see front matter PII: S1359-6446(02)02334-6

Figure 1. *Salmonella pullorum.* Image courtesy of Peter Holt, Southeast Poultry Research Center, Agricultural Research Service, US Dept of Agriculture, Washington, DC, USA.

UK) added, 'In the intestine, ''friendly'' bacteria might also prevent the colonization of ''non-friendly'' bacteria by competing for receptors on the surface of epithelial and immune system cells.' Working with Sandra MacFarlane, Honorary Lecturer and George MacFarlane, Professor of Bacteriology, both from the MRC Microbiology and Gut Biology Group, University of Dundee Medical School (Dundee, UK), Furrie has found that certain Gram-positive bacteria isolated from normal rectal mucosa induce varying increases in expression of Toll-like receptor-3 (TLR-3) in cultured HT29 human colonic epithelial cells.

TLRs are part of a growing group of at least 25 so-called 'pattern-recognition receptors', which appear to play a key role in the first line of defence against bacteria and viruses. Their ligands are still unknown, but bacterial products such as lipopolysaccharide (LPS), peptidoglycan and lipoteichoic acids are likely candidates. Regulation of these receptors could form the basic crosstalk of an entire microbe–host interaction.

The ultimate eavesdropping device, however, will need to be a precise *in vivo* model that examines the sequential interactions between combinations of organisms and their hosts.

Lora Hooper and Jeff Gordon at Washington University St Louis (MO, USA) are using laser capture technology and DNA microarray analysis to identify genes that are switched on in gut epithelial cells of germ-free mice colonized with selected commensals [2]. By adding inflammation-triggering species to the system, they hope to identify the mechanisms by which bacteria not only promote their own survival, but also protect the host against pathogens.

'If members of our microflora have developed chemical strategies that manipulate host gene expression then it is very important to understand the metabolic potential of these organisms…and whether they might be the source of a new generation of therapeutic agents,' says Gordon.

Clinical potential

One set of patients that might benefit from such drugs in the future is those with inflammatory bowel disease (IBD). IBD is a spectrum of conditions, including Crohn's disease, which mostly affects the small intestine, and ulcerative colitis, which affects the large intestine and rectum. Together these conditions affect one in every thousand people in the USA, and are currently treated using broadly immunosuppressive steroids, and surgical resection of affected areas of the bowel.

Studies with germ-free animals have revealed that inflammation requires the presence of intestinal flora [3], but no one yet knows whether just one type of bacteria triggers the inflammation, or indeed how the normal inhibitory mechanisms could have failed.

Although novel drugs are the long-term goal, in the short-term, researchers could use these findings to develop a more rational approach to the use of probiotics. The practice of consuming drinks or yoghurt containing live cultures of *Lactobacillus* or *Bifidobacter* has long been touted as a cure-all for different ailments, ranging from allergies and IBD to traveller's diarrhoea and arthritis [4].

Aileen Kennedy, a graduate student in MacFarlane's research group at Dundee University, envisages a treatment based on a precisely defined bacterial cocktail for patients with ulcerative colitis, tailored to their individual needs. She has already begun pilot clinical studies, using strains of *Bifidobacterium* that are present in healthy individuals but not in patients with ulcerative colitis. 'It should reduce inflammation, while at the same time colonizing to the exclusion of the considered 'bad' bacteria,' she says.

References

1 Neish, A.S. *et al.* (2000) Prokaryotic regulation of epithelial responses by inhibition of IκB-α ubiquitination. *Science* 289, 1560–1563

2 Hooper, L.V. *et al.* (2001) Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 291, 881–884

3 Bhan, A.K. *et al.* (1999) Colitis in transgenic and knockout animals as models of human inflammatory bowel disease. *Immunol. Rev.* 169, 195–207

4 Hooper, L.V. and Gordon, J.I. (2001) Commensal host–bacterial relationships in the gut. *Science* 292, 1115–1118