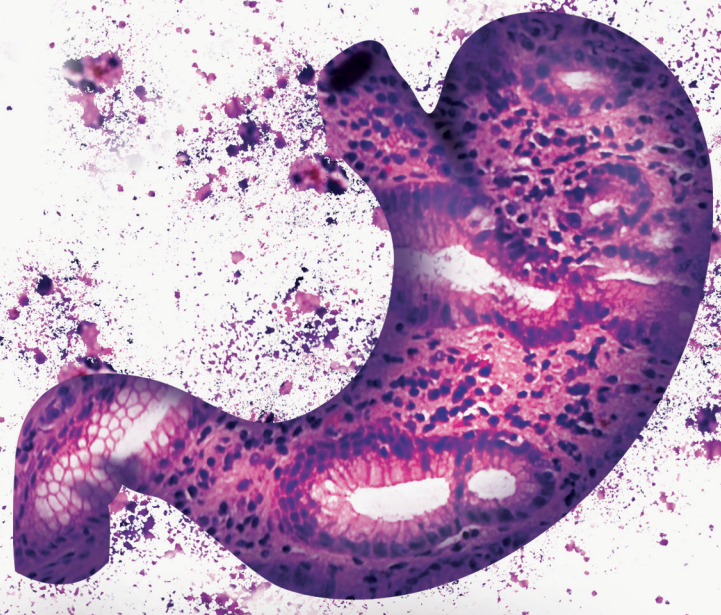
Gut reactions



DR KAREN ROBINSON

Microbiological expert **Dr Karen Robinson** discusses the future of the field, and shares insights into her work on a highly prevalent strain of gastrointestinal bacteria that infects many people from childhood

What prompted your interest in microbiology, specifically the role of *Helicobacter pylori* in stomach infections, gastric and duodenal ulcers, and stomach cancer?

This fascinating organism was only discovered in the 1980s, by the Nobel prize-winning Australian researchers Barry Marshall and Robin Warren. They found that *H. pylori* was virtually always present in the stomach of people suffering from ulcers, and they were the first to isolate it. Famously, Marshall even infected himself with the organism to prove that it caused gastric inflammation. Aside from its fascinating history, the bacterium has adapted in many sophisticated ways so that it can remain (usually silently) in its host for many decades: it is equipped to survive in the harsh acidic conditions of the stomach and is able to avoid being cleared by the immune system. This pathogen has a multitude of very intriguing features.

What is human β-defensin 1 (hβD1)? How does *H. pylori* interfere with its expression, and why is this interaction important to human health?

HβD1 is an antimicrobial peptide produced at epithelial surfaces – such as the eye, respiratory tract, and gut and genital tract – to defend surfaces of the body against infections. In a recent paper, we showed that *H. pylori* is able to act on epithelial cells overlying the stomach lining to make them reduce their production of hβD1. This effect was even more apparent in patients infected with virulent strains that are positive for the *cag* pathogenicity island (*cag*PAI). The *cag*PAI encodes a type IV secretion system, which acts like a molecular syringe to inject bacterial components into human cells. Strains expressing this secretion system are more likely to cause gastric cancer than those that do not, but the relationship is not completely understood.

In what manner can *H. pylori* induce changes within regulatory T cell (T_{REG}) populations?

T_{REG}s are more abundant in the gastric mucosa and peripheral blood of infected patients compared to uninfected controls. These cells secrete cytokines, which suppress inflammation and promote immunosuppression. We proposed that such cells could also inhibit damaging responses at sites outside the gastric mucosa. We therefore wished to understand more about this response, how it is generated and what drives these immunosuppressive cells to accumulate in the gastric mucosa.

You currently collaborate with the Nottingham Digestive Diseases Biomedical Research Unit and the Department of Pathology at the University of Nottingham. How have these partnerships facilitated the study?

We use a variety of approaches in our lab, and we believe it is of paramount importance to understand what is happening in the stomachs of infected people before going on to perform experiments with *in vitro* or *in vivo* models. Because our research is patient-focused, we know that our findings are directly relevant. They provide more information on how the bacteria interact with the cells of the stomach lining, and better inform us about disease mechanisms. We are fortunate to be a part of the National Institute for Health Research-funded Nottingham Digestive Diseases Biomedical Research Unit, as its aim is to facilitate patient-based and translational research in gastroenterology. The facilities and the staff that are employed in this centre are absolutely key to our research. We are extremely grateful to the patients attending the Queen's Medical Centre in Nottingham who donate samples of blood and gastric biopsies for our research.

Microbiology is an ever-evolving discipline. Where do you see it heading?

Technological advances, such as those in gene sequencing, have revolutionised our discipline. I am constantly amazed by the new data characterising microbial gut flora and the diverse effects this has on health and disease. It is incredible that the mixture of microbes in our gastrointestinal tract can have such a strong influence on conditions outside the gut, such as obesity, diabetes, multiple sclerosis, the ageing processes and even our behaviour. I recently helped organise a symposium for the Society for General Microbiology Annual Conference on mind-altering microbes, where speakers showed that organisms in our gut have a major impact on depression, anxiety and even Parkinson's disease. In the future, I envisage that people will be able to manipulate their gut flora, perhaps with probiotics, to become healthier, happier and thinner.

Friend or foe?

A group of researchers at the **University of Nottingham** is examining the molecular effects of bacteria that colonise the human stomach, and it has uncovered statistically significant and surprising results in its investigations

SINCE ITS DISCOVERY around 30 years ago, *Helicobacter pylori* has been identified as one of the most common bacterial infections in the world. *H. pylori* infects the gastric mucosa of humans, and it is highly developed for this purpose; its body, only around 4 µm long, is a helix-shaped rod with a set of beating flagella that endows it with great manoeuvrability. Burrowing into the mucus lining of the stomach, these bacteria express virulence factors that affect host cells and allow them to gain a degree of control over their environment. In most cases, people infected with *H. pylori* remain asymptomatic, and the bacterium usually goes undetected.

Because of this, the bacterium has been able to infect more than half of the world's population: most people are simply unaware they are infected. In some cases, however, this diminutive organism can cause pronounced problems. Between 10 and 15 per cent of those infected will suffer from ulcers in the stomach or duodenum, and in as many as 2 per cent of cases, the result will be gastric cancer. Around a million people every year are diagnosed with stomach cancer, the second-leading cause of cancer-related mortality globally, and 60 per cent of these cases are thought to be attributable to *H. pylori* infection. In the UK alone, medical professionals diagnose 7,000 gastric cancer cases each year, but even with a high standard of healthcare, the five-year survival rate is set at a discouraging 15 per cent.

TIMING IS EVERYTHING

The problem with stomach cancer arising from *H. pylori* – as with many of the most deadly cancers – is with diagnosis. Because the bacterial infection is largely asymptomatic and gastric tumours themselves do not produce observable problems until they are relatively advanced, this form of cancer is difficult to recognise before it becomes life threatening. By achieving a more complete understanding of the interaction between *Helicobacter* and the human body, it may be possible for medical professionals to identify the people the disease is likely to affect earlier. Further, this knowledge could uncover ways to improve the efficiencies of current antibiotic therapies for eradicating the infection.

Dr Karen Robinson at the University of Nottingham's Digestive Diseases Centre, UK, together with Professor John Atherton, leads one research group dedicated to pursuing this valuable information. Using approaches from clinical investigations to longitudinal birth cohort studies, the researchers have revealed a wealth of information about the deleterious microorganism and its interaction with the body of its host. Most of these discoveries have related to the progression of infection towards disease.

MOLECULAR AMELIORATION

One area the Nottingham scientists have been particularly interested in is the mechanism the bacteria use to suppress the production of human β-defensin 1 (hβD1), a protective anti-microbial peptide that human cells express. Using a cell culture model, they showed that the *cag* type IV secretion system, which certain strains of *H. pylori* employ, activates signalling pathways in human gastric epithelial cells that suppress the production of hβD1. This is a surprising result, since the same pathways are also involved in the generation of an inflammatory response in the tissue. This mechanism allows the bacteria to alter their environment to suit their needs, but over time, this causes damage to the affected tissue.

Using samples collected from patients at Queen's Medical Centre in Nottingham, the microbiologists subsequently discovered that people infected with *cag*-positive bacteria had reduced hβD1 levels and therefore larger populations of bacteria surviving in their stomachs. With continued study, they have found methods for identifying the bacterial strains capable of manipulating the human system in this way. Since their research is patient-focused, Robinson and her collaborators feel more certain that their findings will be directly relevant to clinical practice, while informing the scientific understanding of the mechanisms behind the disease.

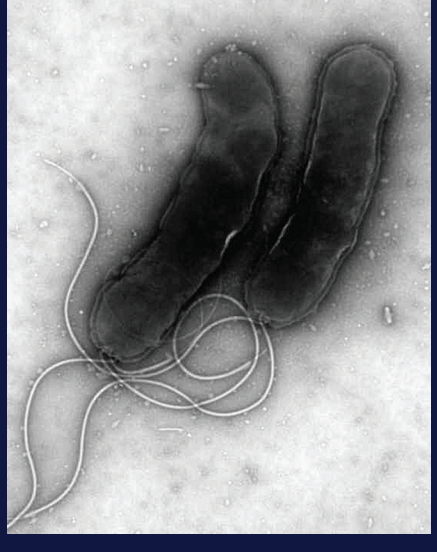
UNLIKELY ALLIES

Robinson and her colleagues have also investigated some protective consequences of infection with *H. pylori*, which are equally fascinating. A particular interest is how the infection stimulates a cell type called regulatory T cells, which dampen inflammation and suppress damaging immune responses, such as in asthma. In a recent paper, Robinson's group demonstrated that most regulatory T cells in the human gastric mucosa express a certain chemokine receptor. This receptor, CCR6, attracts cells towards its ligand, CCL20, which appears in areas of the mucosa with *H. pylori*. Infected patients had larger populations of regulatory T cells in their peripheral blood, and a higher proportion of them expressed CCR6 – indicating, that they might have a more robust and flexible immune system than those who have never been affected.

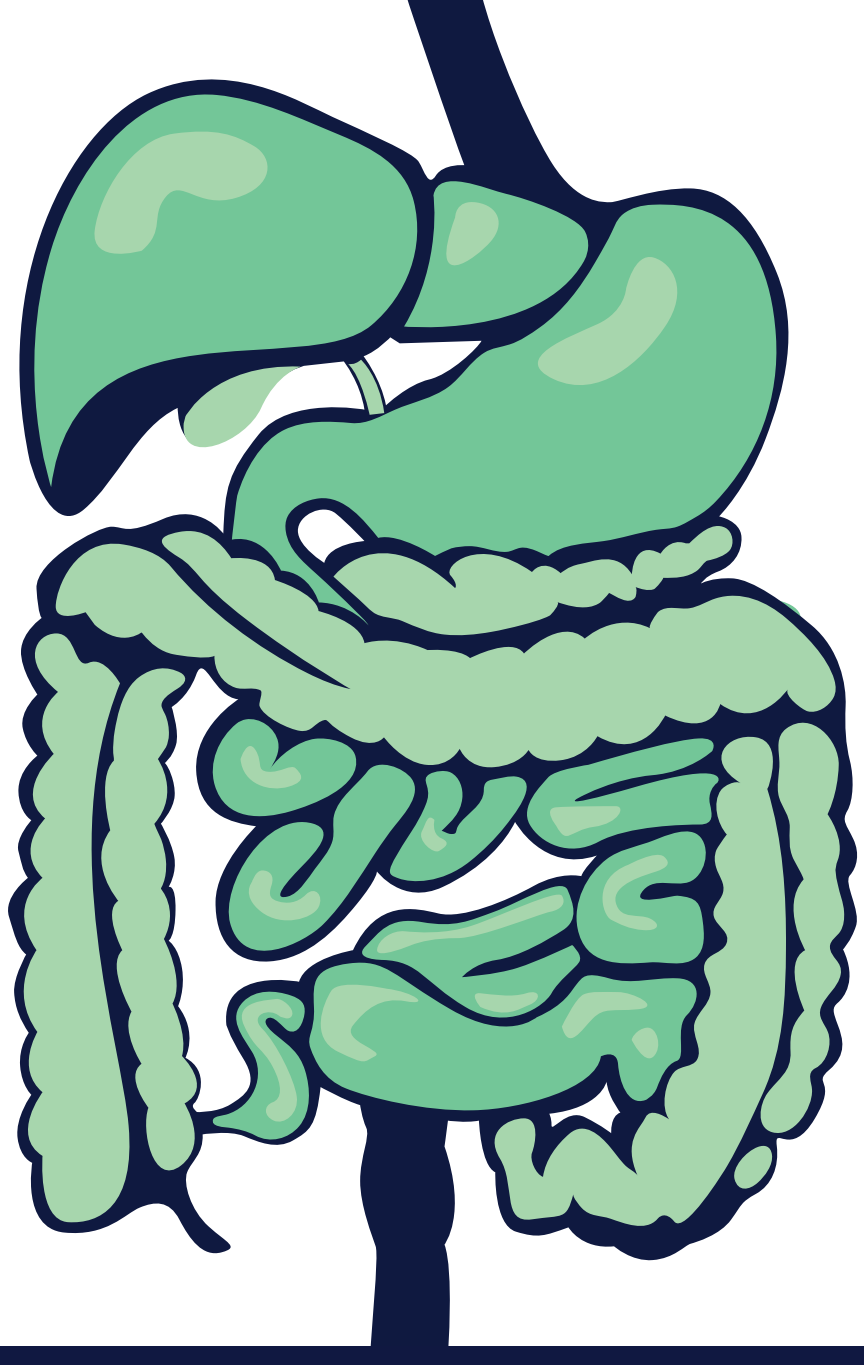
This impact of infection may seem counterintuitive, but in a wider context, it makes perfect sense. For at least 50,000 years, humans have been coevolving with *H. pylori* – and with more than half of the world's population still hosting bacterial populations today, infection is arguably the ancestral state of humans. In other words, the modern human immune system is designed with the presence of bacteria in mind, and its absence may be at the root of the allergies and autoimmune conditions that are exploding in developed countries today. In 1989, immunologist David Strachan was among the first to identify this possibility, referring to it as 'the hygiene hypothesis'. Since then, scientists have identified early exposure to many infectious diseases, including various gastrointestinal parasites and soil mycobacteria, as a possible stimulator of a healthy immune system.

TURNING THE TIDE

Is *H. pylori* among these unlikely medical helpers? The investigations going on in Nottingham suggest it is possible. The prevalence of infection with this bacterium has dramatically declined in developed countries,



Electron micrograph of negatively stained *H. pylori* bacteria.



while the incidence of asthma and allergies has risen exponentially – and the data from Robinson's team suggest that the differences in regulatory T cell populations that *H. pylori* produce are behind this shift. Past studies of the relationship between bacterial infection and allergy, however, have been almost universally cross-sectional – which is not ideal for examining a medical phenomenon that seems to have a profound impact on disease development.

In light of this, the Nottingham researchers joined in a longitudinal birth cohort study to investigate claims of a protective association between infection and childhood asthma. The research focused on the Butarija Birth Cohort in rural Ethiopia, and drew on data collected at four points in the children's lives. The results were striking. The study searched for associations between *H. pylori*, intestinal parasites or intestinal microflora and the risk of wheeze, eczema, hay fever and allergic skin sensitisation in 878 children at ages three and five. The researchers only found statistically significant protective associations present with *H. pylori*.

GOING FORWARD

Building on this intriguing work, Robinson and her team will now begin to investigate these relationships in a more mechanistic way. In order to do this, they plan to work closely with tissue engineers to create an *in vitro* multicellular model of the human gastric mucosa, a physiological model that might yield further information on the interaction between immune, stromal and epithelial cells during bacterial infection. Through ambitious endeavours such as this, the lab will likely retain the position it currently holds as a leading research institution in this area.

INTELLIGENCE

HELICOBACTER PYLORI: ROLE IN GASTRIC CANCER AND EFFECTS ON ASTHMA

OBJECTIVES

- To determine how *Helicobacter pylori* virulence factors interact with host immunity to increase disease risk and to use this information to develop non-invasive diagnostic tests
- To investigate how *H. pylori* stimulates an anti inflammatory regulatory T cell response
- To explore the link between *H. pylori* and a reduced risk of allergy and autoimmune disease

KEY COLLABORATORS

Professor John Atherton; **Dr Darren Letley**; **Dr Andrew Jackson**; **Dr Ian Spendlove**; **Dr William Coward**; **Dr Bruno Gran**; **Professor Cris Constantinescu**; **Mr James Crooks**; **Dr Andrea Venn**; **Dr Andrew Fogarty**; **Professor John Britton**, University of Nottingham, UK • **Dr Jody Winter**, Nottingham Trent University, UK • **Dr Phillip Kaye**; **Professor Abed Zaitoun**, Queen's Medical Centre Campus, UK • **Professor Gail Davey**, University of Brighton, UK • **Dr Girmay Medhin**; **Dr Charlotte Hanlon**, Addis Ababa University, Ethiopia • **Dr Alemayehu Amberbir**, London School of Hygiene and Tropical Medicine, UK • **Dr Georgina Hold**; **Professor Emad El-Omar**, University of Aberdeen, UK • **Dr Vartul Sangal**, University of Northumbria, UK • **Dr Paul Hoskisson**, University of Strathclyde, UK

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