Gastroenterology, Gut Biology & Microbiology

RESEARCH AREA OVERVIEW
Gastroenterology research in Norwich offers a broad portfolio of research covering clinical research with patients, laboratory and epidemiological research. Norwich Medical School is one of the UK's major centres for gastrointestinal research; senior academics in the school and the consultants at NNUH work in close collaboration with the Institute of Food Research, The Genome Analysis Centre and the John Innes Centre. From 2018, clinical gastroenterology research will be concentrated in the new £82m Quadrum Institute (QI) based on Norwich Research Park. This will house the NNUH Endoscopy Facility and provide research facilities for academic scientists working on the biology of the gastrointestinal tract, alongside clinicians and clinician-scientists in NNUH Gastroenterology. We also have strong contacts with major epidemiological databases in the UK and USA to study dietary risk factors for gastrointestinal disease. This gives an excellent teaching environment for research training.

Relevant Links
http://www.uea.ac.uk/medicine/research/research-areas/gastroenterology-and-gut-biology
http://www.ifr.ac.uk/ghfs/GutHealth.htm

Current Research Opportunities
Dietary risk factors for gastrointestinal disease – Professor Andrew Hart
Intestinal failure, disease-related malnutrition and sarcopenia – Professor Alastair Forbes and Dr Cinzia Papadia
Primary sclerosing cholangitis of the liver – Dr Simon Rushbrook
Gastrointestinal pharmacology, therapeutics and education – Dr Ian Beales
Gut microbes in health and disease – Professor Simon Carding
Gut microbes and disease (NHS primary and community care) – Professor Simon Carding
Gut immunology and the microbiota early in life – Dr Lindsay Hall
Autophagy and Crohn's disease – Professor Tom Wileman and Professor Ulrike Mayer
Maintaining intestinal barrier function – Professor Alastair Watson
Generation of organoids from stem cells to study innate immune responses in the GI tract – Dr Penny Powell
Pathogenesis of E.Coli – Dr Stephanie Schuller

Medical Microbiology
Molecular diagnosis of infectious disease – Dr Justin O'Grady
Genomic Microbiology – Professor John Wain
Antibiotic resistance – Professor David Livermore
Emerging infectious disease – Professor Paul Hunter

Tropical Medicine
Parasite virulence – Dr Kevin Tyler
Antimicrobials - Dr Dietmar Steverding
Dietary risk factors for gastrointestinal disease

The aim of my work is to firstly conduct epidemiological aetiological studies in to the causes of inflammatory bowel diseases and cancers of the oesophagus and pancreas, to allow the development of public health interventions to prevent these diseases.

Translational studies will be conducted, invariably clinical trials, to develop novel treatments for patients with these conditions.

We work with large observational databases including the EPIC Study (European Prospective Investigation in to Cancer) and The Clinical Practice Research Database (CPRD).

Inflammation is a valuable defence against infection but chronic inflammation resulting from the sustained production of inflammatory cytokines can contribute to many acute and chronic human diseases. Interestingly, long-chain n-3 polyunsaturated fatty acids (also called PUFAs or omega 3s) found in oily fish can decrease the production of inflammatory cytokines, and are therefore potential anti-inflammatory compounds. In Crohn’s disease and ulcerative colitis we have shown inverse associations between higher intakes of dietary n-3 polyunsaturated fatty acids and the development of both Crohn’s disease and ulcerative colitis. Diets high in these nutrients will be assessed in relation to increasing the proportion of such patients responding to biological therapies. In oesophageal cancer we have reported people prescribed a statin are at a reduced risk of oesophageal adenocarcinoma and feasibility work is now progressing on their role as an adjunctive treatment in cancer patients. In pancreatic cancer, we are using detailed dietary information from food diaries assessing dietary antioxidants, meat and saturated fatty acids in its aetiology. We are investigating the potential role of metformin as a treatment for patients with this invariably fatal malignancy. Members of the research team include junior doctors (clinical lecturer and academic clinical fellow grades) and medical students.

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Intestinal failure, disease-related malnutrition and sarcopenia

Our research focusses on the evaluation and treatment of intestinal failure and disease-related malnutrition. Malnutrition and malabsorption can lead to sarcopenia which affects >50 million people today and will affect >200 million in the next 40 years. We are particularly interested in improving our monitoring of disease-related malnutrition and the responses to its treatment. This is being explored by combining electrophysiology and biochemistry to generate a detailed picture of body composition, and its response to nutritional therapy. This allows analysis of biomarkers (eg citrulline which is of intestinal origin) and electrophysiology to produce composite prognostic scores and practical management tools. We are interested in developing the measurement of plasma citrulline as a reliable quantitative biomarker of enterocyte absorptive capacity and nutritional status, and determine if citrulline can be used as micronutrient for reducing sarcopenia and as a potential modulator of intestinal inflammation ‘in vivo’.

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Primary sclerosing cholangitis of the liver

Primary sclerosing cholangitis (PSC) is one of the archetypal autoimmune liver diseases characterised by biliary inflammation and fibrosis that can lead to both cirrhosis and cholangiocarcinoma. A major focus of our work is to develop a greater understanding of how these genetic loci are associated with the development of PSC by studying the immune system in both the liver and bowel of patients with PSC.

At present PSC is the 5th commonest indication for liver transplantation in the UK. Although the exact pathogenesis remains unclear, PSC is thought to have both environmental and genetic causes, with 16 genetic loci currently identified and further genetic loci undergoing evaluation in an international GWAS meta-analysis of which I am a collaborator.

Current projects include studies of the role played by genetic variation in PSC and analysis of dendritic cell and T-cell subsets in the pathogenesis of the disease.

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Gastrointestinal pharmacology, therapeutics and education

Dr Beales has a wide portfolio of research interests spanning clinical gastroenterology to education and training. In general this focuses on mechanisms of disease processes and in particular the interactions of drugs on the luminal gastrointestinal tract. The current research portfolio includes participation in several international multicentre trials of novel biological and small-molecule inhibitor agents as well as locally delivered hypothesis-driven studies examining the mechanisms of drug and hormone effects particularly in Barrett’s oesophagus and inflammatory bowel disease.

A variety of experimental approaches have been utilised included laboratory cell line studies, immunohistochemistry (collaborating with colleagues in histopathology), case-control methodology, systematic literature review and metaanalysis and interventional studies.
Recent important work has included the seminal original paper describing the mechanisms of the anti-cancer effects of statins in oesophageal adenocarcinoma, subsequently followed with several case-control studies and a systematic review confirming the clinical benefits. A detailed series of studies have illustrated the mechanisms linking acid-reflux, obesity and oesophageal cancer: showing how leptin combined with acid to promote oesophageal adenocarcinoma and how adiponectin may have inhibitor actions. Further studies to unravel these effects are ongoing.

Other studies have explored the safety of cyclo-oxygenase inhibitors in patients with inflammatory bowel disease, in particular showing the safety and efficacy of COX-2 inhibitors as well as the use of novel therapies to treat iron deficiency anaemia and microscopic colitis. Educational projects have examined timing of endoscopy during the day on colonoscopy performance, predictors of publication of abstracts presented at conferences and attitudes to the use of probiotics.

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Gut microbes in health and disease

A major research focus of the group is to understand how microbes (bacteria and viruses) resident in the lower human GI-tract (the microbiome) interact with their host to maintain lifelong health, and how microbial dysbiosis can lead to chronic diseases affecting not only the GI-tract but elsewhere in the body, including the brain. Current projects in the group include:

- The Gut-Brain axis: Identify factors produced by gut microbes that impact on specialised intestinal epithelial cells of the enteric endocrine and nervous systems that can alter signalling in the CNS.
- The role extracellular (outer membrane) microvesicles produced by gut bacteria play in mediating crosstalk between the intestinal microbiota and host cells.
- The role of the intestinal virome and prokaryotic and eukaryotic viruses play in regulating bacterial populations and in promoting dysbiosis and chronic inflammation.
- Development of novel bacteria-based therapies (e.g. probiotics, bacterial products and microbiota transplants) to treat and prevent intestinal inflammation.
- Role of the microbiota in the pathogenesis of myalgic encephalomyelitis/chronic fatigue syndrome.

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Gut microbes and disease (NHS primary and community care)

Evidence is emerging that disturbances in the human gut microbiota can influence a number of diseases including obesity, inflammatory bowel disease (IBD), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CSF), multiple sclerosis (MS), autism spectrum disorder (ASD), Type 1 Diabetes, rheumatoid arthritis, food allergies and gastrointestinal cancers and liver disease. This is an incredibly exciting time in science, when technological advances in DNA sequencing, transcriptomics, proteomics and metabolomics provide an unprecedented opportunity to explore not only the composition, but also the function of the microbial communities that live in the intestinal tract of patients with these diseases. The knowledge gained should provide new and important insights into disease pathogenesis and innovative therapeutic modalities.

We are developing gut-related projects through collaboration with Norfolk and Suffolk primary and community care, with contributions from secondary (NNUH) care, that are suitable for students enrolled in UEA postgraduate degree clinical research masters courses (MSc Clinical Research, MSc Clinical Research (CAT), MRes Clinical Science, MSc Health Research, MSc Advanced Practitioner).

- **Obesity.** Student research projects we are developing include the identification of the best and safest follow-up care following discharge after bariatric surgery. Development of new dietary interventions for early intervention in obesity, and analysis of behavioural and environmental factors that predispose to obesity.

- **Food allergy in children.** Food protein-induced enterocolitis syndrome (FPIES) and food protein-induced proctocolitis are non-IgE-mediated gastrointestinal allergies. FPIES causes changes in the intestinal architecture in response to chronic exposure to a trigger such as milk. Avoiding milk results in normalization, and its reintroduction results in a recurrence of partial villous atrophy. While this is similar to coeliac disease, the two conditions differ in pathophysiology. Student projects will focus on literature reviews of the incidence, presentation, likely mechanisms, diagnosis and management of FPIES accompanied by case histories of patients in primary care diagnosed with FPIES and discussions with their families. A greater understanding of the mechanisms may lead to development of diagnostic tests and management strategies for non-IgE-mediated gastrointestinal allergies.

- **Gastrointestinal Symptoms in Adult Eczema Patients.** Food allergy is a multisystem disease. Infants present with a combination of symptoms predominantly in the skin, the gut and the respiratory system. Some adult patients with food related atopic eczema and may also have gastrointestinal symptoms suggestive of both IgE or non IgE mediated food allergy which can go unrecognised. Student projects will to look further into the links between eczema and gastrointestinal symptoms in a cohort of adult patients. They will conduct a literature review of bowel symptoms associated with adult eczema and non IgE mediated gastrointestinal disease,
and develop questionnaires for use in the dermatology clinic to identify gastrointestinal symptoms in patients with atopic eczema. Students may also search the primary care database for adults with eczema that have been referred with GI symptoms.

- **Gut microbes and mental health (neurodegenerative disease).** By 2025 it has been estimated that there will be more than 1 million patients in the UK suffering from dementia, more than 10% of which will be attributed to East Anglia cases. Age-associated decline in mental health is associated with striking changes in the make-up and activity of the intestinal microbiota with animal studies suggesting a direct causal link between the production of toxic metabolites in the gut and brain pathology. The implications of altered host-microbiome interactions in neurological disease would be far-reaching as they may underpin the development of more effective therapeutic management of neurological diseases. Student projects will be to look further into evidence for intestinal microbial dysbiosis contributing to chronic degenerative diseases such as dementia and Alzheimer’s Disease through literature reviews and discussions with gut microbiologists at IFR and dementia diagnosis and care experts within the NNUH and practitioners in primary and community care.

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**Gut immunology and the microbiota early in life**

Complex microbial communities (microbiota) colonise the body after birth. These beneficial bacteria shape immune defence, limiting infection by gut pathogens through a process of colonisation resistance. However, disturbances such as preterm delivery, caesarean sections and antibiotic exposure in early colonisation events can lead to increased susceptibility to pathogens, as well as allergic and chronic inflammatory diseases in later life. The Hall group work on building our knowledge of the contribution of specific bacterial species during early-life development, and how microbiota disturbances increase susceptibility to gut infection, focusing on Bifidobacterium. Current goals are:

- To understand the effects of Bifidobacterium on critical colonisation resistance
- Determine the short- and long-term impact of early life antibiotic-induced disturbances
- Characterise and develop strategies for restoring a disturbed early-life microbiota to control gut infection, for use in infectious-disease settings.
- Determine how a probiotic treatment strategy in at-risk preterm neonates alters the microbiota.

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Autophagy and Crohn’s disease

Autophagy is a membrane trafficking pathway that generates autophagosomes which deliver cytosol to lysosomes for degradation. Autophagy provides a powerful means of removing intracellular pathogens and is an important arm of innate immunity to infection. Recent genome wide association screens have identified autophagy gene Atg16L1 as a risk allele for Crohn’s disease, an inflammatory disease of the bowel. Susceptibility to Crohn’s disease is also linked to mutations in NOD2, a microbial sensor that activates autophagy during infections. We are using mouse models to investigate whether the inflammation seen in Crohn’s disease is caused by defects in the control of microorganisms by autophagy in gut epithelial cells.

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Maintaining intestinal barrier function

The Watson group have a long-standing interest in the regulation of cell death in intestinal epithelial cells. Specifically, intestinal epithelial cell shedding, a special form of cell death which leaves a “gap” in the epithelial barrier. Under normal conditions the “gap” is short lived and barrier function is maintained at sites of cell shedding. However, during inflammation cell shedding is increased, resulting in loss of barrier integrity and creating sites for the potential entry of microorganisms and luminal antigens. Importantly, increasing evidence predicts that certain species within the gut microbiota (probiotics) can reduce intestinal inflammation.

On-going studies are focused on determining how the microbiota and probiotics can regulate epithelial integrity and thus critical barrier function. Current projects in the lab include:

- Determining to what extent the microbiota plays in modulating the intestinal barrier
- Characterise the host cell molecules involved in microbiota signalling and epithelial barrier integrity
- Identification and development of probiotic therapies that would protection against chronic inflammation
- The role of mucins in prevention of intestinal inflammation

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Generation of organoids from stem cells to study innate immune responses in the GI tract

We are interested in the innate immune response in gut following viral infection which may explain the pathogenesis of human diseases.

Innate immune responses to infection include apoptosis, autophagy and inflammation. When cells are infected with viruses these pathways are activated, the major pathway being production of interferon and interferon-stimulated genes (ISGs) triggered by dsRNA produced during viral replication. We are investigating this in primary cell cultures and gut organoids developed from small intestinal stem cells. In addition, we have used viruses to deliver exogenous genes to organoids to study innate immune pathways. The project will mainly involve bioimaging with confocal microscopy.

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Pathogenesis of E.coli

*E. coli* bacteria are usually known as harmless commensals in the human gut. However, several subsets of *E. coli* have acquired genetic elements which make them pathogenic to humans.

Research in our laboratory is focused on pathogenesis of enteropathogenic (EPEC) and enterohaemorrhagic *E. coli* (EHEC). While EPEC is a major cause of infant diarrhoea in developing countries, EHEC is associated with bloody diarrhoea and kidney disease (Haemolytic Uraemic Syndrome/HUS) in children in the developed world. Both EPEC and EHEC share the ability to adhere to the gut epithelium and use a type III secretion system to inject bacterial effector proteins into the host cell which ultimately lead to the development of diarrhoea. EHEC also produce Shiga toxins which cause HUS by killing kidney cells. By using advanced model systems which mimic the environment in the human gut (polarised cell culture, biopsy organ culture) we aim to elucidate the interactions of EPEC and EHEC with human intestinal epithelium. This should lead to a better understanding of the early events during EPEC and EHEC pathogenesis and enable the design of more efficient treatment strategies.

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Medical Microbiology

Molecular diagnosis of infectious disease

Current research interests are in the molecular diagnosis of infectious diseases with a particular focus on the utility of next generation sequencing (NGS) for the diagnosis of complex clinical syndromes such as sepsis and respiratory tract infections.

Currently, NGS is being used in centralised national reference laboratories to type referred bacteria but is not yet available for routine diagnostic laboratories. Technologies under development will radically change this landscape, reducing cost and removing the need for expert operators. Oxford Nanopore are developing one NGS technology, the MinION device, which is expected to be available in 2014 and will work through the USB port of a computer. Such technological advancements will move NGS from being a research and reference laboratory technology to being something that can be used for the rapid, routine profiling of pathogens in clinical samples, possibly at the point of care. The challenges to implementation are sample preparation and data analysis. NGS platforms are not optimised for the enrichment of tiny amounts of pathogen nucleic acid from a vast excess of human nucleic acid, as applies, for example, in the investigation of bloodstream infection. We intend to facilitate this leap in technology by developing methods for preparing routine biologicals.

Key references:


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Genomic microbiology

Our research is centred on the use of bacterial genomic data in clinical and public health microbiology; in particular the development of sequence based tools for the diagnosis and molecular epidemiology of infectious disease. We are establishing an evidence base for the association of a bacterial species (or sub-species) with any given infection. Our current Norwich based research projects include the linking of *Staphylococcus* to prosthetic joint infection, *Clostridium* to outbreaks of antibiotic associated diarrhoea and specific strains of *Pseudomonas aeruginosa* to antibiotic resistant biofilm associated respiratory infection.

We have a very active collaboration with Public Health England to develop the use of metagenomic DNA sequencing for pathogen discovery and outbreak detection, as well as with the Jos University, Nigeria to look at *Salmonella* epidemiology and antibiotic resistance.

For MRes students we offer specific experimental plans within each project that can be carried out to completion within the one year time frame; the work adds incremental information towards publication. We also encourage undergraduates to be part of our research effort and MRes students are expected to help with their supervision.

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Antibiotic resistance

The main research focus of the Livermore lab is antibiotics and pathogen resistance. Research is centred on β-lactamases, their activity and bacterial resistance strategies including studies on hyper-resistant β-lactamase-hyper-producing mutants of Enterobacter.

Other research relates to resistance epidemiology: leading teams investigating the molecular biology behind rises in MRSA, ciprofloxacin-resistant gonococci, carbapenemase-resistant Acinetobacter spp., cephalosporin-resistant E. coli and, latterly, carbapenemase-producing Enterobacteriaceae. Other current interests centre on the rapid detection of resistant bacteria in clinical samples and how this information can be used to improve patient treatment and antibiotic stewardship.

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Emerging infectious disease

The epidemiology of emerging infectious disease especially regarding outbreaks and epidemics linked to environmental factors.

Research in the Hunter group has been focussed in the spread of infection by drinking water and insect vectors, the role of recreational water contact and food, climate conflict and other causes of rapid change. But a broader interest in zoonotic diseases, disease reservoirs and transmission pathways has developed during recent years working with SGOs like WHO and NGOs including MSF. Currently conducting case-control and other epidemiological studies in the UK, Europe and the developing world. Particular interest in risk assessment and risk communication.

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Tropical Medicine

Parasite virulence

Infectious disease remains the major cause of illness and mortality especially of infants worldwide but disproportionately affect those in tropical regions the developing world. At UEA we are particularly interested in interventions to diagnose and prevent waterborne and vector borne diseases which are often most prevalent in the tropical areas but which continue to represent a threat to the UK population.

Protozoan parasites cause many of the most widespread infections; most are benign, but many are deadly.

Virulence factors determine what makes one infection deadly, while another is asymptomatic, as well as the extent and type of symptoms and pathology observed. We are interested in determining which parasite proteins are virulence factors and how we can exploit their identification for diagnosis of virulent strains, therapy and prevention. Current projects are directed towards understanding which virulence factors are associated with host range for cryptosporidiosis and trichomoniasis, with cell invasion for leishmaniasis and with enteric pathology for giardiasis.

Opportunities exist for students to identify virulence factors from genomic analyses, to culture and transfet parasites and host cells and to evaluate the function of the proteins they identify and their role in pathogenesis.

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Antimicrobials

My research aims to identify synthetic and natural compounds with anti-microbial activity against neglected tropical diseases (e.g. human African trypanosomiasis or sleeping sickness) and fungal infections (e.g. candidiasis).

My work focusses on the anti-microbial activity of compounds that inhibit cysteine proteases, proteasomes or topoisomerase. We test antimicrobial activity using bloodstream forms of Trypanosoma brucei, the causative agent of human African sleeping sickness, and Candida albicans, a causative agent of superficial fungal infection of the mucosa and skin. Compounds are tested in cell culture and the effect of the compounds on parasite and fungal cells are monitored by cell counting and/or spectrophotometrically by measuring absorbance. The effect of inhibitors on the targeted enzyme is determined by activity assays using substrate specific for the enzyme.

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